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Breastfeeding, ovulatory years, and risk of multiple sclerosis

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ABSTRACT

Objective: To determine whether women who breastfeed their infants longer or have fewer ovulatory years are at lower risk of developing multiple sclerosis (MS).

Methods: We recruited women with newly diagnosed MS or its precursor, clinically isolated syndrome (CIS) (n = 397), and matched controls (n = 433) into the MS Sunshine Study from the membership of Kaiser Permanente Southern California. A structured in-person questionnaire was administered to collect the behavioral (pregnancies, breastfeeding, hormonal contraceptive use) and biological (age at menarche and menopause, amenorrhea) factors to make up ovulatory years.

Results: Among women who had live births, a cumulative duration of breastfeeding for ≥15 months was associated with a reduced risk of MS/CIS (adjusted odds ratio [OR] 0.47, 95% confidence interval [CI] 0.28–0.77; $p = 0.003$ compared to 0–4 months of breastfeeding). Being ≥15 years of age at menarche was also associated with a lower risk of MS/CIS (adjusted OR 0.56, 95% CI 0.33–0.96; $p = 0.035$). Total ovulatory years and the remaining factors that determine it, including gravidity, parity, episodes of amenorrhea, and hormonal contraceptive use, as well as age at first birth, showed no significant association with the risk of MS/CIS.

Conclusions: Mothers who breastfeed longer may be at lower subsequent risk of developing multiple sclerosis. This is consistent with the other known maternal health benefits of breastfeeding and with our previous observation that women with MS who breastfeed exclusively are at lower risk of postpartum relapses. ***Neurology*® 2017;89:1–7**

GLOSSARY

CIS = clinically isolated syndrome; **EHR** = electronic health record; **ICD-9** = *International Classification of Diseases, 9th revision*; **KPSC** = Kaiser Permanente Southern California; **MS** = multiple sclerosis.

Multiple sclerosis (MS) is a chronic autoimmune disease with a susceptibility and disease course that are influenced by reproductive factors. The few published studies of reproductive risk factors for MS have focused on parity,[1–8] gravity,[1] age at menarche or first birth,[1,2,9–11] or oral contraceptive use[3,5,8,12,13] and produced conflicting results. None examined the duration of breastfeeding or amenorrhea or considered total ovulatory years. Breastfeeding is particularly interesting because it is a modifiable factor with other reported maternal health benefits[14] and appears to reduce the risk of postpartum MS relapses.[15,16]

MS affects predominantly women during their childbearing years; the onset is rare before menarche or after menopause, and the risk of MS relapses is significantly diminished during pregnancy[17] and exclusive breastfeeding.[15] While many experts attributed these observations to sex hormone levels, we previously postulated that anovulation may be the unifying explanation.[15,16]

The primary objective of the analyses presented herein was to determine whether a longer duration of breastfeeding or fewer total ovulatory years is associated with a reduced risk of MS.

METHODS

Study population. Participants in the MS Sunshine Study were recruited from the Kaiser Permanente Southern California (KPSC) membership between December 2011 and December 2014 via mailings and telephone contact. KPSC is a large, prepaid

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health maintenance organization with >4 million members representative of the general population in Southern California.[18] KPSC uses an integrated electronic health record (EHR) system that includes all inpatient and outpatient encounters, diagnostic tests, diagnoses, and medications, as well as some demographic and behavioral characteristics. Data were collected from the EHR, and after informed consent was obtained, a structured in-person interview was conducted.

Standard protocol approvals, registrations, and patient consents. The study protocol was approved by the KPSC institutional review board.

Case identification. Incident cases with MS or clinically isolated syndrome (CIS) were identified with methods similar to those described previously.[19,20] Briefly, we searched EHRs monthly for first mention of ICD-9 diagnostic codes for MS or CIS. Diagnoses were confirmed by an MS specialist (A.L.-G.) according to diagnostic criteria/consensus definitions for MS[21] or CIS.[22,23] Eligibility required diagnosis of MS or CIS within the past 1.5 years or symptom onset within the past 3 years and age ≥18 years.

Control selection. Once a case interview was completed, at least one control participant from the KPSC population, matched to the case on race/ethnicity, date of birth (within 2 years), sex, and home KPSC facility (a surrogate measure for socioeconomic status), was identified from the EHR and recruited. The controls were assigned the same index date as their matched case (symptom onset date).

Data collection. Reproductive details, including age at menarche, gravidity, parity, date and outcome of each pregnancy, menstrual cycle length, episodes of amenorrhea (≥3 months without menses while not on hormonal contraceptive, pregnant, or breastfeeding), hormonal contraceptive use, breastfeeding, and age at menopause (if applicable), were obtained during an in-person interview with a previously validated interviewer-administered questionnaire.[24]

Other covariates obtained from the interview included smoking (never/ever), education (less than college degree/college degree or higher), annual household income defined by the California median (<US $65,000 vs ≥US $65,000), and self-identified race/ethnicity of the participant and 4 grandparents. White non-Hispanics were classified as white; any black race regardless of ethnicity was classified as black; and those who identified themselves as white Hispanics were classified as Hispanics. Age was defined as age at index date.

Statistical analyses. The final analysis cohort included 830 (99.4%) of the 835 black, Hispanic, or white women who had completed the study protocol by June 2, 2015. Women were excluded from the final analysis because of missing variables needed to calculate ovulatory years (n = 3) or congenital absence of a uterus (n = 2).

Total cumulative duration of breastfeeding for each participant with at least one live birth was calculated by adding the duration of breastfeeding for each live birth, similar to previous studies.[25,26]

Total ovulatory years was determined by the same method as previously described.[27] First, total menstrual years was calculated as the age at menarche subtracted from the age at the index date for women with premenopausal onset and from the age at menopause for women with postmenopausal onset. Then, anovulatory years was calculated for periods due to pregnancies, breastfeeding, hormonal contraceptive use, and episodes of amenorrhea before menopause. In this equation, breastfeeding was truncated at 6 months for each pregnancy for women who reported >6 months of breastfeeding, the assumption being that anovulation due to lactation does not persist >6 months postpartum. Next, lifetime ovulatory cycles was determined from total years of anovulation subtracted from total menstrual years and multiplied by the number of cycles per year based on the participant's cycle length (365.25/cycle length). Finally, total ovulatory years was calculated from dividing lifetime ovulatory cycles by 13 (the average cycles per year, 365.25/28).

A priori–defined, hypothesis-driven multivariate unconditional logistic regression was used to estimate the risk of MS/CIS associated with cumulative duration of breastfeeding, total ovulatory years, and the variables that it comprises. Non-normally distributed variables were categorized into tertiles based on the distribution among controls. Breastfeeding was defined as 0 to 4 months (the time at which table food is usually introduced), 4 to 15 months, and >15 months (tertile cutoff in controls). To allow comparison with previous studies, we also examined the association of gravidity, parity, or age at first birth with MS/CIS. Age at menarche, gravidity, and parity were categorized similarly to the Ausimmune study for comparison.[1] Age at first birth was categorized into tertiles based on distribution of controls.

Because many reproductive factors vary by race/ethnicity, we tested for multiplicative interaction of each variable with race/ethnicity, with the intent of running analyses in each racial/ethnic group if a significant interaction ($p < 0.05$) was detected. No significant interactions were detected; thus, all models were adjusted for race/ethnicity in addition to age and smoking. The effect of breastfeeding was also adjusted for parity. Education and income were examined as potential confounders (change in β coefficient by ≥20%) but were not found to meet these criteria in any model and therefore not retained in the final models.

To assess whether the association between breastfeeding and MS/CIS among women with live births could be due to reverse causality (i.e., presymptomatic MS influences a woman's ability or desire to breastfeed), the analysis was stratified by time since last birth (<5, 5–10, >10 years).[4]

A 2-sample *t* test was used to compare means; the Wilcoxon-Mann-Whitney test was used for nonnormally distributed variables; and the χ^2 or Fisher exact test was used to compare frequencies between 2 groups. Statistical significance was set at $p < 0.05$. All analyses were conducted with SAS version 9.3 software (SAS Institute, Inc, Cary, NC).

RESULTS Table 1 shows selected demographic and clinical characteristics in cases and controls. Socioeconomic status and the proportion of women who were postmenopausal by the symptom onset/index date were similar between cases and controls. Only smoking differed between the 2 groups. The median time from diagnosis to interview among cases was 11.1 months (interquartile range 7.0–21.9 months).

Among women who had live births, a cumulative duration of breastfeeding for ≥15 months was associated with a reduced risk of MS/CIS (figure). The magnitude and direction of this effect was similar regardless of when a woman's last baby was born, although it was no longer statistically significance when broken down into these smaller subgroups (table 2).

Younger age at menarche was also associated with a higher risk of MS/CIS (table 3) among all women.

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Table 1 Selected characteristics at symptom onset/index date of incident female MS/CIS cases and controls

	Cases (n = 397)	Controls (n = 433)	*p* Value
Age, mean (SD), y	36.9 (12.2)	36.6 (12.2)	0.736
Race/ethnicity, n (%)			0.995
White	163 (41.1)	177 (40.9)	
Hispanic	138 (34.8)	152 (35.1)	
Black	96 (24.2)	104 (24.0)	
Education, n (%)			0.282
Some college or less	232 (58.4)	237 (54.7)	
College or more	165 (41.6)	196 (45.3)	
Income,[a] n (%)			0.645
≤$65,000	169 (42.6)	179 (41.3)	
>$65,000	205 (51.6)	232 (53.6)	
Declined to answer	23 (5.8)	22 (5.1)	
Ever smoker, n (%)	118 (29.7)	104 (24.0)	0.061
Postmenopausal, n (%)	70 (17.6)	75 (17.3)	0.906

Abbreviations: CIS = clinically isolated syndrome; MS = multiple sclerosis.
[a] Annual household income.

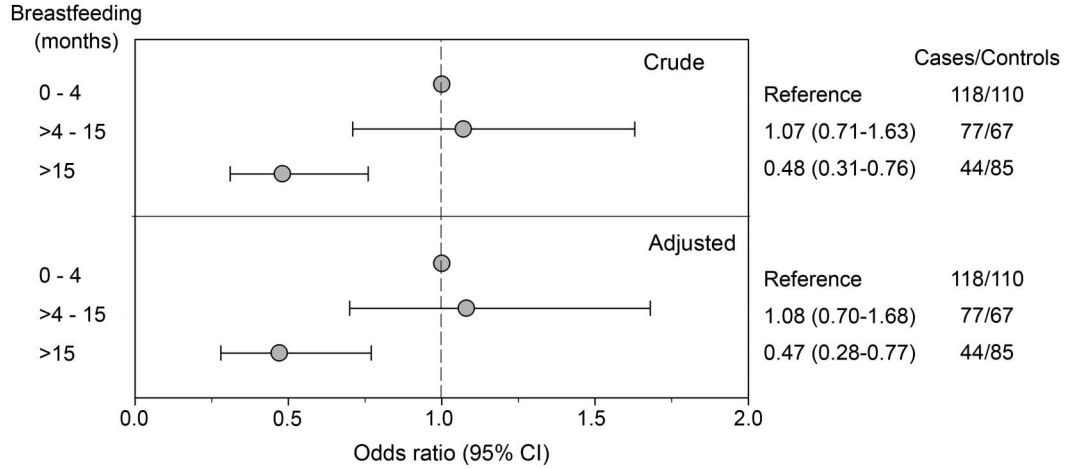
Total ovulatory years, gravidity, parity, age at first birth, hormonal contraceptive use, and having experienced any episodes of amenorrhea showed no significant associations with MS/CIS in either crude or adjusted analyses (table 3). Total menstrual years and cumulative duration of amenorrhea for reasons other than pregnancy, breastfeeding, or hormonal contraceptive use during menstrual years also showed no significant association with MS/CIS (data not shown).

DISCUSSION We found that a cumulative duration of breastfeeding of >15 months among women who had children is associated with a lower risk of developing MS later in life. This finding adds to the growing literature of other delayed maternal health benefits of breastfeeding, including reduced risk of type 2 diabetes mellitus, breast and ovarian cancer,[14] metabolic syndrome,[25] and myocardial infarction, particularly with longer duration of breastfeeding.[25,26,28]

The maternal effects of prolonged breastfeeding, episodes of amenorrhea, and total menstrual or ovulatory years on MS risk are unknown. Few studies have examined reproductive factors and MS/CIS risk; most focused on parity,[1–8] and none previously collectively considered all the biological and behavioral factors that make up total menstrual or ovulatory years.

Of the previously studied factors, our findings are largely consistent with the existing literature. This includes our findings that older age at menarche appears to be associated with a reduced risk of MS/CIS[10,11] (or younger age at menarche is associated with an increased risk of MS/CIS) and duration of hormonal contraceptive use[3,5,8,12,13] is not associated with MS/CIS risk. We, like others, found no association with age at first birth,[1,2] although one large Danish data linkage study reported a small protective association with younger age at first birth in men and women, implying a nonbiological association.[9]

Figure Duration of breastfeeding and MS



Depicted are the crude (top) and adjusted (bottom) odds ratios (ORs) and 95% confidence intervals (95% CIs) of the association between the cumulative duration of breastfeeding among women with live births before symptom onset (cases) or index date (controls) and multiple sclerosis (MS)/clinically isolated syndrome (CIS). The numbers of cases and matched controls in each analysis are listed in the right column. The cumulative duration of breastfeeding is represented in tertiles based on the distribution among the controls. ORs are adjusted for age, smoking, race/ethnicity, and parity. Cumulative duration of breastfeeding for >15 months was associated with a significantly lower risk of MS/CIS in both crude and adjusted analyses ($p = 0.001$ and 0.003 for trend, respectively).

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Table 2 Association of breastfeeding duration and MS/CIS stratified by time since last live birth

Time since last birth, y	Breastfeeding duration, mo	Cases, n (%)	Controls, n (%)	Adjusted OR[a] (95% CI)	p Value
<5	0–4	26 (43.3)	37 (40.2)	Reference	
	>4–15	26 (43.3)	26 (28.3)	1.41 (0.65–3.10)	0.386
	>15	8 (13.3)	29 (31.5)	0.46 (0.16–1.31)	0.145
	Trend				0.092
5–10	0–4	23 (46.9)	20 (43.5)	Reference	
	>4–15	16 (32.7)	8 (17.4)	1.64 (0.50–5.30)	0.413
	>15	10 (20.4)	18 (39.1)	0.30 (0.09–1.07)	0.064
	Trend				0.05
>10	0–4	69 (53.1)	53 (42.7)	Reference	
	>4–15	35 (26.9)	33 (26.6)	0.84 (0.45–1.57)	0.586
	>15	26 (20.0)	38 (30.7)	0.51 (0.25–1.04)	0.063
	Trend				0.176

Abbreviations: CI = confidence interval; CIS = clinically isolated syndrome; MS = multiple sclerosis; OR = odds ratio.
[a] Adjusted for age at index date, race/ethnicity, smoking, and parity.

Four of the previous 8 studies that examined parity as an MS risk factor found no association,[3,5,6,8] as did we, and 4 studies[1,2,4,7] reported a protective effect of parity. However, an elegant analysis[4] showed that this association was detected only when the last live birth was within 5 years of MS symptom onset and was found in men as well. The authors of this study concluded that an association between increased parity and reduced MS risk was more likely due to subclinical MS impairing fertility or increasing early miscarriages (i.e., reverse causality).[4] There is some biological plausibility to this because other female-predominant autoimmune diseases have been associated with impaired fertility and recurrent miscarriages, although there is no strong signal that this is true in women with MS. Our findings indicate that another possible explanation for the conflicting results of parity and MS in women may be unmeasured confounding by cumulative duration of breastfeeding.

In contrast, we did not find any evidence for reverse causality as a possible explanation of the association of breastfeeding with MS/CIS risk. This is not surprising because breastfeeding is primarily a behavior that is unlikely to be influenced by as-yet unknown future events.

Why breastfeeding may reduce the risk of developing MS is unclear. We previously reported that the risk of postpartum MS relapses was reduced in women who breastfeed exclusively, which seemed to be related to inducing lactational amenorrhea.[15,16] Thus, we proposed a unifying hypothesis that anovulation, a state common to pregnancy, prolonged breastfeeding, and being premenopausal or postmenopausal, may be a key protective factor for MS susceptibility and disease activity.[15] However, we carefully measured ovulatory years in this study and found no association with MS/CIS risk, nor did we find any reduced risk of MS with other anovulatory states, including pregnancy or prolonged hormonal contraceptive use. In light of these findings, lactational amenorrhea is still an excellent surrogate measure of the duration and intensity of breastfeeding but most likely is not an important mediator of the potentially protective effect on MS/CIS.

Whether breastfeeding can have sustained effects on immune homeostasis as it does on mediators of cardiovascular health[25] is unknown. We previously reported that prolonged breastfeeding results in a decrease in proinflammatory CD4+ tumor necrosis factor-α–producing cells in both healthy women and women with MS, but cell counts increased again after menses resumed.[29]

Limitations of this study include the possibility of recall bias as a result of the case-control design, although it is unlikely that this would significantly influence the breastfeeding results because we saw very similar magnitudes of effect even when the last live birth was >10 years ago. We also have no reason to think that recall bias would be differential between cases and controls because it is not thought of as a risk factor for MS. For calculation of total ovulatory years, it is possible that recall error of precise durations of hormonal contraceptive use and episodes of amenorrhea would bias the results toward the null. Therefore, we cannot exclude the possibility that total ovulatory years could have a small effect on MS/CIS risk. Another limitation is that we did not directly ascertain why women did not breastfeed or breastfed only briefly. However, it is unlikely that any of biological factors that could influence this such as

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Table 3 Association of reproductive characteristics with MS/CIS

	Cases (n = 397)	Controls (n = 433)	Crude OR (95% CI)	p Value	Adjusted OR[a] (95% CI)	p Value
Age at menarche, n (%)						
≤11 y	131 (33.0)	120 (27.7)	Reference		Reference	
12–14 y	239 (60.2)	269 (62.1)	0.81 (0.60–1.10)	0.183	0.81 (0.60–1.10)	0.173
≥15 y	27 (6.8)	44 (10.2)	0.56 (0.33–0.96)	0.036	0.56 (0.33–0.96)	0.035
Trend				0.094		0.091
Gravidity, n (%)						
0	126 (31.7)	140 (16.9)	Reference		Reference	
1	62 (15.6)	54 (12.5)	1.28 (0.82–1.98)	0.275	1.23 (0.78–1.92)	0.374
2	78 (19.7)	89 (20.6)	0.97 (0.66–1.44)	0.893	0.93 (0.61–1.40)	0.718
3	57 (14.4)	72 (16.6)	0.88 (0.58–1.34)	0.552	0.84 (0.53–1.33)	0.461
≥4	74 (18.6)	78 (18.0)	1.05 (0.71–1.57)	0.796	0.98 (0.63–1.53)	0.929
Trend				0.688		0.693
Parity, n (%)						
0	158 (39.8)	171 (39.5)	Reference		Reference	
1	73 (18.4)	70 (16.2)	1.13 (0.76–1.67)	0.545	1.08 (0.72–1.63)	0.7
2	93 (23.4)	105 (24.3)	0.96 (0.67–1.37)	0.815	0.91 (0.62–1.33)	0.621
3	48 (12.1)	58 (13.4)	0.90 (0.58–1.39)	0.624	0.87 (0.54–1.39)	0.551
≥4	25 (6.3)	29 (6.7)	0.93 (0.52–1.66)	0.814	0.86 (0.47–1.60)	0.641
Trend				0.912		0.894
Age at first birth, n (%)						
0–21 y	77 (32.2)	85 (32.4)	Reference		Reference	
>21–26 y	80 (33.5)	89 (34.0)	0.99 (0.64–1.53)	0.972	0.96 (0.61–1.50)	0.846
>26 y	82 (34.3)	88 (33.6)	1.03 (0.67–1.58)	0.898	0.96 (0.59–1.57)	0.879
Trend				0.985		0.98
HC use, n (%)						
0–<6 mo	120 (30.2)	143 (33.0)	Reference		Reference	
6 mo–5 y	135 (34.0)	155 (35.8)	1.04 (0.74–1.45)	0.828	1.02 (0.73–1.43)	0.911
>5 y	142 (35.8)	135 (31.2)	1.25 (0.89–1.76)	0.191	1.23 (0.87–1.75)	0.245
Trend				0.367		0.426
Amenorrhea,[b] n (%)	52 (13.1)	56 (12.9)	1.02 (0.68–1.52)	0.944	1.00 (0.67–1.51)	0.992
Menstrual years, n (%)						
0–17	132 (33.3)	145 (33.5)	Reference		Reference	
>17–29	142 (35.8)	153 (35.3)	1.02 (0.73–1.42)	0.908	0.95 (0.63–1.43)	0.794
>29	123 (31.0)	135 (31.2)	1.00 (0.71–1.41)	0.996	0.85 (0.45–1.59)	0.606
Trend				0.992		0.865
Total ovulatory years, n (%)						
0–10	125 (31.5)	133 (30.7)	Reference		Reference	
>10–20	133 (33.5)	160 (37.0)	0.88 (0.63–1.24)	0.473	0.89 (0.63–1.27)	0.528
>20	139 (35.0)	140 (32.3)	1.06 (0.75–1.48)	0.751	1.07 (0.68–1.69)	0.772
Trend				0.554		0.597

Abbreviations: CI = confidence interval; CIS = clinically isolated syndrome; HC = hormonal contraceptive; MS = multiple sclerosis; OR = odds ratio.
[a] All analyses adjusted for race/ethnicity, age at index date, and smoking; age at first birth was additionally adjusted for parity.
[b] At least 3-month unexplained episode of amenorrhea (not related to pregnancy, breastfeeding, HC use, or perimenopause).

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breast reduction/augmentations or use of medications that preclude breastfeeding could explain our findings because none have been shown to be associated with the risk of MS/CIS. In addition, the frequency of such exposures is very low. We did not specifically ascertain whether mothers who smoked stopped smoking during breastfeeding. We cannot examine whether such a brief cessation of smoking can influence the association between prolonged breastfeeding and MS/CIS. The findings from this study require validation in a separate cohort, particularly to estimate the expected effect size in other states and countries.

The strengths of this study include that it is hypothesis driven, used a previously validated questionnaire to obtain complete measures of reproductive factors, and calculated ovulatory years with the methods used in ovarian cancer research. Other strengths include the relatively large number of incident cases and matched controls recruited over a relatively short period of time from a population that is representative of its source population.

Taken together with the existing literature, this study provides more evidence that women who are able to breastfeed their infants should be supported to do so. Among other maternal and infant health benefits, breastfeeding may reduce the mother's future risk of developing MS and may even reduce the risk of MS in child.[30–32]

AUTHOR CONTRIBUTIONS

Annette Langer-Gould's contributions include study design, data collection, and drafting and revising the manuscript of content, including study concept and interpretation of data. She had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the analysis. Jessica Smith contributed to the data analysis, interpretation of data, and revision of the manuscript for content. Kerstin Hellwig contributed to revision of the manuscript for content. Edlin Gonzales and Samantha Haraszti contributed to the data collection and revision of the manuscript for content. Corinna Koebnick contributed to drafting and revision of the manuscript for content. Anny Xiang contributed to the study design, interpretation of data, and revision of the manuscript for content.

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DISCLOSURE

A. Langer-Gould has been site principal investigator for 2 industry-sponsored phase 3 clinical trials (Biogen Idec, Hoffman-LaRoche). She receives grant support from the NIH, National Institute of Neurological Disorders and Stroke, and National MS Society. J. Smith reports no disclosures relevant to the manuscript. K. Hellwig has received speaker honoraria and funding from Biogen Idec, Teva Sanofi Aventis, Novartis, Bayer Healthcare, and Merck Serono. E. Gonzales, S. Haraszti, C. Koebnick, and A. Xiang report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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