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Miscellaneous

Exposure to breastfeeding and risk of developing multiple sclerosis

Elisa Baldin [1,2,3]* Anne Kjersti Daltveit,[4,5] Marianna Cortese,[4,6] Trond Riise[4,7] and Maura Pugliatti[1,8]

[1]Department of Biomedical and Specialty Surgical Sciences, University of Ferrara, Ferrara, Italy, [2]INSERM, University of Limoges, CHU Limoges, UMR 1094, Tropical Neuroepidemiology, Institute of Epidemiology and Tropical Neurology, GEIST, Limoges, France, [3]IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy, [4]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway, [5]Department of Health Registry Research and Development, Norwegian Institute of Public Health, Bergen, Norway, [6]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, USA, [7]The Norwegian Competence Centre for MS, Haukeland University Hospital, Bergen, Norway and [8]Research Center for Neuroinflammation and Neurodegeneration, University of Ferrara, Ferrara, Italy

*Corresponding author. Department of Biomedical and Specialty Surgical Sciences, University of Ferrara, Ferrara, Italy; Epidemiology and Statistics Unit, IRCCS Istituto delle Scienze Neurologiche di Bologna, Via Altura 3, 40139 Bologna, Italy. E-mail: e.baldin@gmail.com

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Abstract

Background: Early-life factors are reported to modulate the risk of developing multiple sclerosis (MS) among adults. The association between exposure to breastfeeding and the risk of MS is debated. We aimed to disclose whether past exposure to breastfeeding and its duration are associated with the risk of developing MS.

Methods: We used a cohort design linking prospectively collected information on breastfeeding from the Cohort of Norway community-based surveys on health status (CONOR) with the Norwegian MS Registry and the population-based Medical Birth Registry of Norway that includes information on all births in Norway since 1967. MS clinical onset was collected throughout 2016. A total of 95 891 offspring born between 1922 and 1986 to mothers participating in CONOR were included. We identified 215 offspring within this cohort who developed adult-onset MS. Associations between breastfeeding and MS risk were estimated as hazard ratios using Cox proportional hazard models adjusting for maternal factors including education.

Results: We found no association between having been breastfed for $\geq$4 months and MS risk, also after adjusting for various maternal factors (hazard ratio = 0.90; 95% confidence interval 0.68–1.19). The estimates did not change for different durations of breastfeeding. The results were similar when adjusting for other perinatal factors.

Conclusion: Our study could not confirm previous findings of an association between breastfeeding and risk of MS. Breastfeeding information was less likely to be biased by knowledge of disease compared with case–control studies.

Key words: Multiple sclerosis, breastfeeding, early-life risk factors

Key Messages

- Early-life factors may modulate the risk of developing multiple sclerosis (MS).
- In a community-based cohort of Norwegian individuals, there was no association between breastfeeding and risk of MS in adulthood.
- The use of previously collected information on breastfeeding in this study reduces the risk of bias.

Introduction

Whereas it is likely that genetics contributes to the overall population susceptibility to multiple sclerosis (MS), specific epidemiological patterns of MS, such as an increasing incidence documented during the last decades, suggest an important role of lifestyle factors in disease initiation and modulation.[1,2] Some of these factors (e.g. Epstein-Barr virus infection, low vitamin D levels, cigarette smoking, obesity) could play an important role during early life (from the perinatal phase to adolescence) in predisposing to MS.[3]

Among early-life exposures, breastfeeding and early nutrition deserve particular attention for MS risk. The protective effect of human milk towards immune-mediated diseases is related to the role of some of its components (e.g. enzymes, antimicrobial proteins, growth factors, chemokines, antioxidants, etc.)[4] and to its anti-inflammatory properties (e.g. stimulation of IL-10).[5,6] The World Health Organization currently recommends that infants should be exclusively breastfed for $\leq$6 months, with continued breastfeeding along with appropriate complementary foods up to 2 years of age or beyond.[7] Breastfeeding has been of interest as a potential protective factor against MS. A beneficial effect would be in line with evidence suggesting a protective effect of breastfeeding against other autoimmune diseases (i.e. inflammatory bowel disease, celiac disease, type-1 diabetes).[8–11] However, the association between having been breastfed and the risk of developing adult-onset MS is not fully elucidated. Case–control studies have been performed in different populations with inconsistent findings.[6,12–15]

We therefore aimed to investigate the association between exposure to breastfeeding and the occurrence of MS in adulthood using prospectively collected community-based data on the exposure of interest.

Methods

Previously collected data from a set of Norwegian community-based surveys were accessed. These surveys are part of the Cohorts of Norway consortium (CONOR) and were carried out during the period 1994–2002.[16,17] CONOR allowed us to identify mothers and link them to their offspring recorded in the Medical Birth Registry of Norway (MBRN) at the Norwegian Institute of Public Health. The MBRN provides, among others, information related to birth such as birthweight, gestational age at birth, mode of delivery and pregnancy complications such as pre-eclampsia, for all individuals born in 1967 or later in Norway. Permission to use information from the National Population Register to link mothers with children born before 1967 was obtained from The Norwegian Tax Administration. The linkage was performed by the MBRN. The study population was characterized by children with information on breastfeeding and born between 1922 and 1986, in order to have $\geq$30 years of follow-up. In order to link the different data sets, we used the national identification number unique to every Norwegian citizen and resident.

Outcome

Offspring who developed MS were identified by linking the cohort data set with the National MS Registry of Norway (Norwegian Competence Center for Multiple Sclerosis, Bergen), where MS patients are recorded up to 2016. The registry contains information on age at diagnosis and clinical course, and covers >70%[18] of the cases of MS in the country. The percentage of coverage is estimated using the data of the Norwegian National Patient Registry. This database contains MS codes according to the International Statistical Classification of Diseases, 10th edition (ICD-10) assigned to every inpatient or outpatient and partly to patients treated at private practices in Norway.[19]

Exposure and covariates

The primary exposure of interest was 'breastfeeding'. In the CONOR surveys, mothers were asked how many

children they gave birth to and for how many months they breastfed each of them. Duration of breastfeeding was considered as a categorical variable according to different cut-offs: ≥1 month vs <1 month; ≥3 months vs <3 months; ≥4 months vs <4 months; ≥6 months vs <6 months. Possible confounders and/or effect modifiers of the association between breastfeeding and risk of MS were offspring sex, year of birth by 5-year categories, offspring birth order, level of education of the mother (mandatory, high school, college/university, missing), cigarette-smoking habits of the mother (ever vs never smoked) and mother's age at delivery. Among the offspring born in 1967 or later, additional factors were evaluated as possible confounders: pre-eclampsia during the pregnancy, mode of delivery, offspring birthweight (low: <2500 g, medium: 2500–3499 g, high: ≥3500 g) and gestational age (preterm: <37 weeks vs full-term: ≥37 weeks).

Statistical analyses

The frequency of breastfeeding varied according to other potential risk factors; we tested this difference using the χ^2 test or Fisher's exact test for categorical variables (offspring sex, maternal smoking) and Wilcoxon rank-sum test for continuous variables (mother's education and offspring birth order). Cox proportional hazard regression models were used to estimate the association between the exposures and the risk of MS onset during the observation period given as hazard ratios (HRs). Follow-up started at birth and subjects were censored at death or the end of the study period, whichever came first. Different models were used considering different cut-offs for duration of breastfeeding.

Each factor was examined in univariate models. All multivariable Cox models were adjusted for infant sex, birth order and year of birth by 5-year categories, as well as mother's age at delivery, mother's cigarette-smoking habit (ever vs never smoker) and mother's education level (mandatory, high school, college/university, missing data).

These covariates were those considered clinically relevant and those that showed an association with MS risk with a p-value <0.05 in the univariate analyses (Table 1).

We considered as potential effect modifiers the factors of sex, age at MS onset (<30 years vs ≥30 years) and year of birth (born before 1971 vs born in 1971 or after), and estimated their effects in regression models with different cut-offs for breastfeeding duration (test of interaction term).

In order to account for a possible correlation between siblings, all analyses were performed also using 'VCA (cluster option)' in STATA to model the correlation.

Moreover, to check for any possible recall bias, we repeated all analyses including only cases whose mothers reported about breastfeeding prior to disease onset in their offspring.

We further conducted a sub-analysis for individuals born after 1967 including also the following perinatal factors into the multivariable models: mode of delivery, birthweight (low, medium, high) and gestational age (preterm vs full-term birth).

We used a two-sided significance level of 0.05 for all analyses. All analyses were conducted using SPSS® software, v.25 and STATA software, v 16.1.

Results

The study included 50 069 mothers who participated in at least one CONOR survey between 1994 and 2002, and for whom information on breastfeeding duration was available for each of their children. If the mother participated in more than one survey, we used information from the first survey. Based on this cohort of mothers, the analyses were performed on 95 891 children (78.4%) with information on breastfeeding and born between 1922 and 1986. Of these, 6231 (6.5%) had never been breastfed, whereas 89 660 (93.5%) had been breastfed for ≥1 month.

Of the 95 891 children, 58 803 (61.3%) were born in 1967 or later and, for these, additional information on pre- and perinatal factors was available from the MBRN.

During follow-up, 215 offspring had a clinical onset of MS during adulthood. The mean age at onset was 31.2 years [standard deviation (SD) 8.9] and the mean age at diagnosis was 35.2 years (SD 9.2). The majority of the cases were women (73%).

There were marked differences in exposure to breastfeeding according to maternal education and smoking, as well as offspring birth order and sex (Table 1).

We found no association between breastfeeding and MS onset in adulthood, also when considering different durations of breastfeeding (at ≥1 month vs <1 month, ≥4 months vs <4 months and ≥6 months vs <6 months) (Table 2) and continuous duration (data not shown). Adjusting the models for offspring year of birth, sex, birth order, mother's age at delivery, level of education and smoking habits did not modify the results (Table 2). Taking into account the correlation between siblings did not change the results (data not shown).

In analyses stratified by sex, median age at MS onset (<30 vs ≥30 years) or median year of birth (born before 1971 vs born in 1971 or after), there was no evidence of an effect modification by these variables (test of interaction term, data not shown).

Table 1. Characteristics of study participants and their mothers by different cut-offs for breastfeeding duration

Characteristic	Never BF ($N = 6231$) N (%)	Ever BF ($N = 89\,660$) N (%)	P	BF <4 months ($N = 35\,399$) N (%)	BF ≥4 months ($N = 60\,492$) N (%)	P	BF <6 months ($N = 49\,732$) N (%)	BF ≥6 months ($N = 46\,159$) N (%)	P
Multiple sclerosis	18	197	0.269	85	130	0.439	120	95	0.221
Sex			0.002			0.01			0.04
Male	3328 (53.4)	46 031 (51.3)		18 411 (52.0)	30 948 (51.2)		25 760 (51.8)	23 599 (51.1)	
Female	2903 (46.6)	43 629 (48.7)		16 988 (48.0)	29 544 (48.8)		23 972 (48.2)	22 560 (48.9)	
Mother's education*			<0.001			<0.001			<0.001
Mandatory (≤13 years)	4307 (69.1)	57 749 (64.4)		24 816 (70.1)	37 240 (61.6)		34 568 (69.5)	27 488 (59.6)	
High school (≤13 years)	360 (5.8)	5531 (6.2)		2003 (5.7)	3888 (6.4)		2810 (5.7)	3081 (6.7)	
College (≥14 years)	738 (11.8)	16 710 (18.6)		4438 (12.5)	13 010 (21.5)		6582 (13.2)	10 866 (23.5)	
Missing	826 (13.3)	9670 (10.8)		4142 (11.7)	6354 (10.5)		5772 (11.6)	4724 (10.2)	
Mother's smoking habits			<0.001			<0.001			<0.001
Never	2508 (40.3)	41 914 (46.7)		13 857 (39.1)	30 565 (50.5)		20 088 (40.04)	24 334 (52.7)	
Ever	3723 (59.7)	47 746 (53.3)		21 542 (60.9)	29 927 (49.5)		29 644 (59.6)	21 825 (47.3)	
Birth order			0.002			<0.001			<0.001
1	2665 (42.8)	36 592 (40.8)		15 727 (44.4)	23 530 (38.9)		21 096 (42.4)	18 161 (39.3)	
2	1991 (32.0)	30 079 (33.5)		11 360 (32.1)	20 710 (34.2)		16 279 (32.7)	15 791 (34.2)	
3	962 (15.4)	14 740 (16.4)		5288 (14.9)	10 414 (17.2)		7810 (15.7)	7892 (17.1)	
4	405 (6.9)	5473 (6.1)		2030 (5.7)	3848 (6.4)		3015 (6.1)	2863 (6.2)	
5	140 (2.2)	2003 (2.2)		702 (2.0)	1441 (2.4)		1115 (2.2)	1028 (2.2)	
6	68 (1.1)	773 (0.9)		292 (0.8)	549 (0.9)		417 (0.8)	424 (0.9)	

BF, breastfeeding; *$N = 58\,722$. $P = P$-values corresponding to χ^2 tests.

Table 2. Association between duration of breastfeeding (BF) and development of multiple sclerosis in 95 891 individuals. Crude and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs)

	Multiple sclerosis cases (215) *N* (%)	*N* (%)	HR_{crude} (95% CI)	*P*	HR_{adj}[a] (95% CI)	*P*
Model 1						
No BF	18 (8.4)	6231 (6.5)	1.0		1.0	
BF ≥1 month	197 (91.6)	89 658 (93.5)	0.77 (0.47–1.24)	*0.277*	0.74 (0.46–1.20)	*0.220*
Model 2						
BF <4 months	85 (39.5)	35 398 (36.9)	1.0		1.0	
BF ≥4 months	130 (60.5)	60 491 (63.1)	0.94 (0.71–1.23)	*0.644*	0.90 (0.68–1.19)	0.476
Model 3						
BF <6 months	120 (55.8)	49 730 (51.9)	1.0		1.0	
BF ≥6 months	95 (44.2)	46 159 (48.1)	0.92 (0.70–1.2)	*0.521*	0.89 (0.67–1.17)	0.384

[a]HR_{adj} adjusted for offspring year of birth (categorized by 5 years), sex, birth order, mother's age at birth, mother's smoking habit, mother's level of education.

More than 50% of the mothers whose children developed MS (120 of 215) provided information on breastfeeding before knowledge of disease outcome. When we repeated the analysis including only cases whose mothers reported about breastfeeding prior to disease onset in their offspring, there were no major changes in the results {cf. Table 2, for model 1 [cut-off 1 month] the HR was 0.84 [95% confidence interval (CI): 0.43–1.67], for model 2 [cut-off 4 months] the HR was 1.08 [0.73–1.57] and for the third model [cut-off 6 months] the HR was 1.05 [0.72–1.51]}.

The results also did not change in a sub-analysis that was limited to the 58 803 subjects born after 1967 and therefore with available data from the MBRN, considering perinatal factors (mode of delivery, pre-eclampsia, gestational age, birthweight) (data not shown).

Discussion

To our knowledge, this is the first study on breastfeeding as a potential protective factor for the development of MS using data from community-based health and disease registries with ascertainment of breastfeeding exposure before disease occurrence in most cases. In this cohort of individuals followed from the perinatal phase, there was no association between breastfeeding and development of MS, considering different cut-offs for duration (1, 4 and 6 months), based on the available literature and current international health authorities' indications.

Human milk has a direct protective effect on the still immature immune system of the offspring due to some of its multifunctional components (as enzymes, antimicrobial proteins/peptides, such as immunoglobulins).[4]

The influence of human milk can also act indirectly by stimulating the production of immunomodulatory peptides with anti-inflammatory properties (e.g. IL-10, TGF-β).[5,6]

Moreover, feeding habits during early life are correlated with the composition of gut microbiota and the components of human milk might thus be involved in the development of the immune system also by affecting the composition of the gut microbiota.[20,21] However, after 4 months, infants are often no longer exclusively fed with breast milk, but introduced to other nutriments (e.g. infant formula, other food).[22] This may alter the possibility of finding actual associations between breastfeeding and risk of MS, since exclusive breastfeeding was not measured in our study.[14] However, even considering a minimum breastfeeding duration of 1 month, more likely to be exclusive, our findings did not show an association between breastfeeding and MS onset.

In some previous studies, breastfeeding was reported to influence the risk of developing adult-onset MS.[6,13,14] Pisacane *et al.* found that having been breastfed for ≤6 months was associated with a higher probability of MS.[13] Similar results were reported by Conradi *et al.*[6] in another case–control study of German individuals with clinically isolated syndrome and MS, but considering as the cut-off a duration of breastfeeding of 4 months. More recently, Ragnedda *et al.* reported that having been breastfed for <4 months might be associated with adult-onset MS in both Italian and Norwegian male participants in an international multicentre case–control study.[14] In our study population, we did not find any sex differences.

A recent hospital-based study of Italian patients showed a dose–response relationship between duration of breastfeeding and onset of disease, with the latest onset of disease among those who were breastfed for >6 months.[15] Similar results were reported for paediatric MS. Findings from a hospital-based case–control study in children with MS[23] suggest that having been breastfed for at least 1 week compared with never may protect against the development of paediatric MS. However, other case–control studies did not suggest any protective effect.[12,24]

One of the main methodological issues in these studies is recall bias. In most retrospective studies, the information on breastfeeding is collected from the mother only years later and after disease onset in their offspring, thus increasing the risk of differential misclassification of the exposure. The exposure is also more likely to be misclassified when not assessed directly from the mothers, but from the offspring. In our study, breastfeeding information was collected directly from the mothers, mostly during surveys unrelated to the present research, and in >50% of cases before any knowledge of an MS diagnosis of their offspring.

Strengths

This is a community-based cohort study in which information on breastfeeding for the majority of the mothers was collected prior to the diagnosis of MS in the offspring, thus reducing the risk of recall bias. The exposure of interest was available for a large population and was collected directly from the mothers. We further had information on a series of other potential maternal and perinatal confounders similarly recorded.

Limitations

Not the entire Norwegian population was included in the original surveys (CONOR) and all mothers that did not report information on breastfeeding, and consequently their offspring, were excluded from our study. However, the question on breastfeeding was included in each survey conducted in different years across different regions in the country. Moreover, the MS cases were those identified by the Norwegian MS Registry, which at the time of linkage for this study had a coverage of ~70%.[18,19]

The incomplete coverage of the MS registry might have led to bias. However, the lack of registration was related to regional and hospital compliance to the registration process. Therefore, a systematic differential registration depending on disease or patient characteristics is unlikely. The possible bias would have affected the results towards the null, masking any effect of breastfeeding.

Breastfeeding habits were derived over a long period (1922–1986). During this time cultural habits, historical context, and political and societal rules involved in orienting towards a suggested duration of breastfeeding might have changed.[25–27] In order to control for time trends, all analyses were adjusted for offspring year of birth. Moreover, breastfeeding information in our study did not refer to exclusive breastfeeding, which is difficult to capture, and therefore includes any combination of breastfeeding with other feeding habits. However, the variable composition of nutrition during this period might have altered the effect on the microbiota and thus the possible association with MS. Thus, in order to cover different possible combinations, we considered different cut-offs for duration of breastfeeding, according to the literature and current suggestions from the World Health Organization.

Norway is among the countries with highest rates of breastfeeding (recently reported: 71% at 6 months and 46% at 12 months)[22,25,26,28] thanks to longer and remunerated maternity and paternity leave and a generalization of the findings could be difficult. Given the use of previously recorded data, we were not able to evaluate all potentially important confounding factors [i.e. socioeconomic status (SES) of the offspring in adulthood]; however, we used maternal education as a proxy for SES, although the possible confounding role is complex, since maternal SES would be more closely related to breastfeeding than to the onset of MS in the adult offspring.[29]

The mother's smoking habits were used as a proxy for offspring exposure to smoke, even though we were not able to define whether the individual was exposed prenatally or through passive smoking during infancy/childhood/adolescence.

During the data collection, the information related to these variables could have been misclassified, possibly for social acceptance. However, the surveys were conducted before and unrelated to the study, so a misclassification would have been applied to the whole sample of mothers, regardless of the exposure and the outcome (and possibly diluting any true effects). However, despite the effort to use proxy variables, some important factors were not available given the data characteristics, such as the maternal and paternal history of MS.

Another aspect, related to the long observation period, is the increased incidence and prevalence of MS over the years, partly associated with better care for people with MS and with changes in MS diagnostic criteria.[30] Over the last two decades, the new criteria developed and applied have made an early diagnosis more likely in less symptomatic cases compared with the previous criteria available. However, considering the improved survival of people with MS, also more severe cases would be alive and included as well in the registry. All cases in the MS registry have a neurologist-verified diagnosis of MS, thus increasing the validity of the outcome measure. The possible effect was considered by adjusting and stratifying the analyses by year of birth.

Another limitation that could have affected our findings is the sample size in our study, considering the small expected effect size. Given the study population, the smallest detectable effect would have been ≥0.7 (HR), which, however, would be too big for the kind of exposure considered. Therefore, even though we cannot confirm an

association with this study, should there be a protective effect of having been exposed to breastfeeding, the effect size would, however, be small.

Conclusion

Our study could not confirm previous findings of an association between longer duration of breastfeeding and reduced risk of developing MS in adulthood. In contrast to studies in which such an association has been observed, our study was based on previously collected data linking community-based health and disease registries.

Author contributions

E.B., A.K.D., T.R. and M.P. conceived of the study idea and designed the study. E.B. and A.K.D. carried out the analyses of the data. E.B. organized the writing and wrote the initial draft. All authors participated in the discussion and interpretation of the results. All authors critically revised the manuscript for intellectual content and approved the final version before submission.

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Conflict of interest

None declared.

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