Supplementary Online Content

Krysko KM, Rutatangwa A, Graves J, Lazar A, Waubant E. Association between breastfeeding and postpartum multiple sclerosis relapses: a systematic review and meta-analysis. *JAMA Neurol*. Published online December 9, 2019. doi:10.1001/jamaneurol.2019.4173

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable. Characteristics of included studies.

Source	Study design	Study setting	Total N	MS diagnostic criteria & types	Mean age	Mean disease duration	Pre- & pregnancy ARR	Baseline EDSS	Pre-pregnancy DMT	Definition of BF exposure groups	Definition of relapse outcome	Time period PP	Group differences BF vs non-BF	PP DMT use BF vs non-BF
Achiron 2004[1,a]	Retrospective cohort	Israel	108	Poser criteria; RRMS	28 +/- 3.3 y	5.1 +/- 2.4 y	1 y pre: 0.94 Preg: 0.48	1.70	96%	BF: ≥ 3 weeks, non-exclusive NBF: < 3 weeks or none	≥ 48 hrs with ≥1.0 increase EDSS	3 mo	N/A	None; all had IVIG
Airas 2010[2]	Prospective cohort	Finland	61	N/A	30.5 y (range 23-42)	5.7 y (range 0-17.5)	1 y pre: 0.82 +/- 0.98 T3: 0.4 +/- 1.2	1.33 +/- 1.17	N/A	BF: ≥2 mo exclusive NBF: Non-exclusive, < 2 mo or none	N/A	6 mo	BF less if active MS pre-pregnancy	BF: 1 IFN β; NBF: 5 IFN β; 1 IVIG but unclear which group
Benoit 2016[3,a]	Prospective cohort	France & Italy Multi-center	93 but 78 for BF analysis	Poser criteria or 2005 McDonald criteria; all MS types	32.1 +/- 4.1 y	9.1 +/- 3.9 y	1 y pre: 0.53 +/- 0.69 Preg: 0.32 +/- 0.6	1.9 +/- 1.5	34%[b]	BF: Any BF NBF: No BF	≥ 24 hrs, no EDSS requirement	3 mo	N/A	N/A
Confavreux 1998[4,a]	Prospective cohort	12 European countries	227 but 209 for BF analysis	Poser criteria; all MS types	30 +/- 4 y	6 +/- 4 y	1 y pre: 0.7 +/- 0.9 T3: 0.2 +/- 1.0	1.3 +/- 1.4	N/A	BF: Any BF NBF: No BF	≥ 24 hrs, no EDSS requirement	3 mo	BF lower pre-pregnancy ARR (0.6 vs 0.8) & lower pregnancy ARR (0.3 vs 0.5)	4 azathioprine, 1 mitoxantrone but unclear which group
De Las Heras 2007[5,a]	Retrospective cohort	Spain Multi-center	88 but 62 for BF analysis	Poser criteria; RRMS & SPMS	30.5 +/- 4.2 y	5.5 +/- 2.5 y	1 y pre: 0.61 Preg: 0.31	1.70	100 %	BF: Any BF NBF: No BF	N/A	3 mo	N/A	69% resumed DMT shortly after delivery; Longer time to start DMT PP in BF

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Fernández Liguori 2009[6,a]	Retrospective cohort (Cross-sectional survey & record review)	Argentina Multi-center	103	McDonald criteria; all MS types	30.5 +/- 5.2 y	7.3 y	1 y pre: 0.22 (95% CI 0.12-0.31); T3: 0.04 (95%CI -0.04-0.12)	N/A	30%	BF: Any BF ≥ 1 day NBF: None or <1 day	≥ 24 h, require objective finding on neuro exam	12 mo	N/A	Prophylaxis with IVIG (3) & steroids (3), not separated by BF group; 16 NBF due to DMT
Fernández Liguori 2012[7] **[Abstract]**	Retrospective cohort	Argentina 3 centers	40	McDonald criteria; all RRMS	41.7 +/- 8.8 (at time of study)	Median 16.4 (at time of study)	1 y pre: 0.02 Preg: 0.005	N/A	N/A	BF: Exclusive for ≥2mo NBF: Non-exclusive BF, <2mo, or none	≥ 24 h, require objective finding on neuro exam	6 mo	NBF higher ARR pre-pregnancy (NBF 0.03 vs BF 0.02), but similar age, disease duration, pregnancy ARR	N/A
Gulick 2002[8]	Prospective cohort with mailed questionnaires	US and Canada	175	N/A; all MS types	32.7 +/- 4.2 y	5.0 +/- 3.9 y	1 y pre: 0.58; Preg: 0.18	N/A	N/A	BF: Any BF for all or part of 12 mo PP, non-exclusive NBF: None or ≤2 d	≥ 24 hrs, no EDSS requirement, neurology confirmed	12 mo (also 6 mo)	BF group 2 y older, 6 mo longer MS, fewer with relapse in pregnancy	More DMT in NBF (0-3 mo PP BF 16.4% vs NBF 65.7% DMT); BF: 7 DMT concurrent (6 IFN β, 1 GA)
Haas 2007[9,a]	Prospective cohort, RCT of IVIG	9 European countries	163	N/A; RRMS w/ ≥1 relapse in 2 y prior	29.6 +/- 4.0 y	6.5 +/- 4.4 y	2 y pre: 1.0 +/- 0.7; Preg: 0.4 +/- 0.6	1.6 +/- 1.3	48%	BF: Divided into <3mo and ≥3 mo, non-exclusive NBF: None	≥24h, no EDSS requirement, neurology confirmed	3 mo	N/A	All received IVIG in both groups

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Hanulíková 2013[10,a]	Retrospective cohort	Czech Republic Single center	76 but 73 for BF analysis	N/A; all RRMS	31 y (range 21-40)	N/A	Pre N/A Preg: 0.08	1.4	N/A	BF: Any BF, non-exclusive NBF: None	Chart documented relapse	6 mo	N/A	93.4% PP IVIG, not listed by group
Hellwig 2009[11] **[Correspondence]**	Retrospective cohort with some prospective	Germany Multicenter	213	N/A	31.2 +/- 4.0 y	N/A	N/A	N/A	N/A	BF: Exclusive ≥4 mo NBF: Did not exclusive BF ≥4 mo	N/A	3 mo	BF older & less likely on DMT pre-pregnancy; no difference in disease duration, pre-pregnancy ARR	NBF group more likely on DMT
Hellwig 2015[12]	Prospective cohort	Germany Multicenter	201	2005 McDonald criteria; all RRMS	31.3 +/- 4.2 y	Median 4.5 y	2 y pre: 0.63; 42 had pregnancy relapse	N/A	89%	BF: Intent to BF ≥2 mo exclusively NBF: BF with supplemental feeding <2 mo (for reasons other than relapse) or none	≥24h, no EDSS requirement, neurology confirmed	6 mo (also 12 mo)	BF older, less likely on DMT pre-pregnancy, & less likely relapse in pregnancy; no difference in disease duration or ARR pre-pregnancy	BF less likely to start DMT in first 30 d PP. 2 started DMT within 30 d and BF some (1 exclusive BF). NBF 29 resumed DMT within 30 d.

Source	Study design	Study setting	Total N	MS diagnostic criteria & types	Mean age	Mean disease duration	Pre- & pregnancy ARR	Baseline EDSS	Pre-pregnancy DMT	Definition of BF exposure groups	Definition of relapse outcome	Time period PP	Group differences BF vs non-BF	PP DMT use BF vs non-BF
Horvat Ledinek 2013[13,a] **[Abstract]**	Cohort (unclear follow-up)	Slovenia single center	67	N/A	34.5 +/- 4.3 y	7.9 +/- 4 y	2 y pre: 0.48; Preg: 0.16	1.47 +/- 1.37	60%	N/A	N/A	24 mo	N/A	All received IVIG prophylaxis PP
Iorio 2009[14] **[Correspondence]**	Cohort (unclear follow-up)	Italy single center	23	N/A	31.5 +/- 3.8 y	5.0 +/- 3.4 y	Pre: 0.88 +/- 0.69; Preg N/A	N/A	70%	BF: Exclusive for ≥2mo NBF: Non-exclusive BF, <2mo, or none	N/A	12 mo	No difference age or pre-pregnancy ARR; longer disease duration & more pre-pregnancy DMT in NBF	N/A
Jesus-Ribeiro 2017[15]	Retrospective cohort	Portugal single center	111	2010 McDonald criteria; all RRMS	31.9 +/- 4.9 y	4.9 +/- 2.7 y	1 y pre: 0.6 +/- 0.8; Preg 0.3 +/- 0.6	1.6 +/- 0.7	80%	BF: Any duration, non-exclusive NBF: None	≥24 h with objective worsening on neuro exam	12 mo	BF longer disease duration, lower ARR pre-pregnancy (BF 0.5 vs NBF 0.7) & in pregnancy (BF 0.2 vs NBF 0.3)	BF group started DMT PP later than NBF. 99 started DMT in 12 mo PP, not reported by group.
Langer-Gould 2009[16]	Prospective cohort	US 2 centers	29	Poser criteria; 28 RRMS, 1 SPMS	32.8 +/- 4.1 y	Median 5.1 y (range 1.6-20.8)	2 y pre: 0.71; Preg: 0.18	27 EDSS ≤2; 2 EDSS ≥4	76%	BF: Exclusive ≥2mo NBF: Non-exclusive BF, <2mo, or none	≥48 h, no EDSS requirement, neurology confirmed	12 mo	NBF more on DMT pre-conception, but age,	NBF more likely to resume DMT in 12 mo PP (NBF 80% vs BF 43%) &

Source	Study design	Study setting	Total N	MS diagnostic criteria & types	Mean age	Mean disease duration	Pre- & pregnancy ARR	Baseline EDSS	Pre-pregnancy DMT	Definition of BF exposure groups	Definition of relapse outcome	Time period PP	Group differences BF vs non-BF	PP DMT use BF vs non-BF
								(1 BF, 1 NBF)					disease duration, pre or pregnancy relapses, EDSS similar	shorter time to DMT PP
Langer-Gould 2019[17] **[Abstract]**	Cohort (prospective EHR & retrospective survey)	US population-based with Kaiser EHR data	466	N/A	N/A	N/A	1 y pre: 0.39; Preg: 0.14 to 0.07	N/A	62%[b]	BF: Exclusive ≥2mo NBF: Non-exclusive BF, <2mo, or none	N/A	12 mo	N/A	BF: 28% DMT while BF exclusively (mostly GA/IFN β) vs 49% NBF
Nelson 1988[18]	Retrospective cohort with interview	US multi-center	191	Schumacher criteria; non-progressive MS	N/A	N/A	Pre N/A Preg: 0.13	N/A	N/A	BF: Any BF reported, non-exclusive NBF: None	Self-reported	9 mo	N/A	N/A
Nikseresht 2017[19,a] **[Abstract]**	Retrospective cohort with survey	Iran single center	75	N/A	33.2 +/- 4.5 y	N/A	1y pre: 24% ≥1 relapse Preg:13% ≥1relapse	N/A	N/A	BF: Any BF NBF: No BF	Self-reported	9 mo	N/A	N/A
Perez-Sanchez 2014[20] **[Abstract]**	Retrospective cohort with interview	Spain single center	79	N/A; all RRMS	31.5 y	N/A	N/A	N/A	N/A	BF: Any BF NBF: No BF	Self-reported	N/A	No difference disease duration, EDSS, ARR pre or pregnancy	NBF shorter time to restart DMT PP

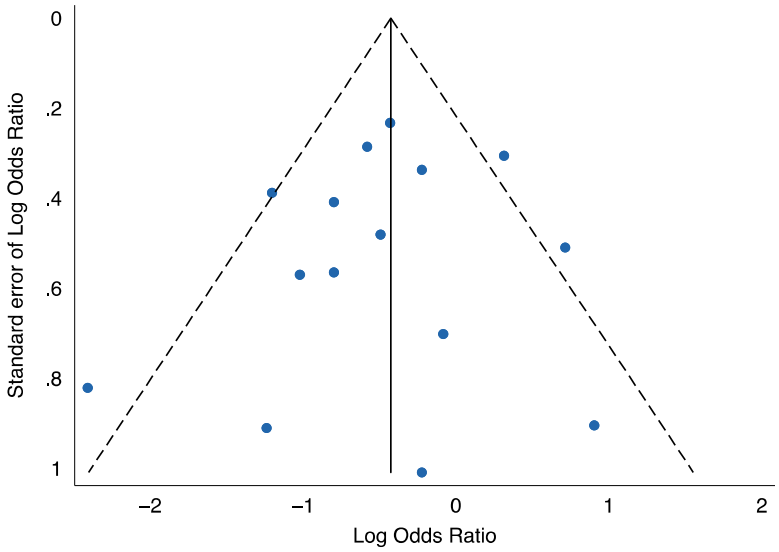
Source	Study design	Study setting	Total N	MS diagnostic criteria & types	Mean age	Mean disease duration	Pre- & pregnancy ARR	Baseline EDSS	Pre-pregnancy DMT	Definition of BF exposure groups	Definition of relapse outcome	Time period PP	Group differences BF vs non-BF	PP DMT use BF vs non-BF
Portaccio 2014[21]	Prospective cohort	Italian multi-center	350	McDonald criteria 2001; all types of MS	31.8 +/- 4.7 y	7.2 +/- 4.8	1 y pre: 0.37 +/- 0.71 Preg: 0.11 +/- 0.35	1.5 (IQR 1-2)	50%	BF: Exclusive ≥2mo NBF: Non-exclusive BF, <2mo, or none	≥ 24 h with objective worsening neurologic exam	12 mo	NBF higher EDSS (NBF 1.6 vs BF 1.3). No difference age, disease duration, ARR pre-pregnancy	BF 11% vs NBF 27% resumed DMT within 3 mo & before a relapse
Runia 2015[22]	Prospective cohort	Netherlands single center	43	McDonald criteria 2001; all RRMS	31.5 +/- 3.8 y	5.5 +/- 6.0 y	1 y pre: 0.47; T3: 0.09	Median 1.5 (IQR 1-2)	N/A	BF: Non-exclusive and any duration NBF: None	≥ 24 h, no EDSS requirement	3 mo	N/A	3 IVIG PP (group not listed); no DMT use 0-3 mo PP
Sahebi Vaighan 2017[23] **[Abstract]**	Prospective cohort	Iran single center	39	N/A; all RRMS	30.6 +/- 5.1 y	N/A	Pre N/A; Preg: 0	N/A	N/A	BF: Exclusive ≥ 3 mo NBF: Non-exclusive, < 3 mo, none	N/A	6 mo, 36 mo	N/A	N/A
Worthington 1994[24,a]	Prospective cohort	United Kingdom single center	15	Poser criteria; all types of MS	30.0 +/- 3.1	9 +/- 3.6 y	1 y pre: 0.57; Preg: 0.48	Median 4.5 (range 3.5-6.0)	N/A	BF: Required ongoing BF, non-exclusive NBF: None or stopped before relapse	≥ 24 h, no EDSS requirement	6 mo	N/A	N/A

N sample size; MS multiple sclerosis; ARR annualized relapse rate; EDSS Expanded Disability Status Scale; BF breastfeeding; non-BF non-breastfeeding; PP postpartum; DMT disease-modifying therapy; RRMS relapsing remitting MS; Preg pregnancy; mo months; N/A not available; RCT randomized controlled trial; IVIG intravenous immunoglobulin; T3 third trimester; IFN β interferon β; SPMS secondary progressive MS; CI confidence interval; h hour; d day; EHR electronic health record; GA glatiramer acetate

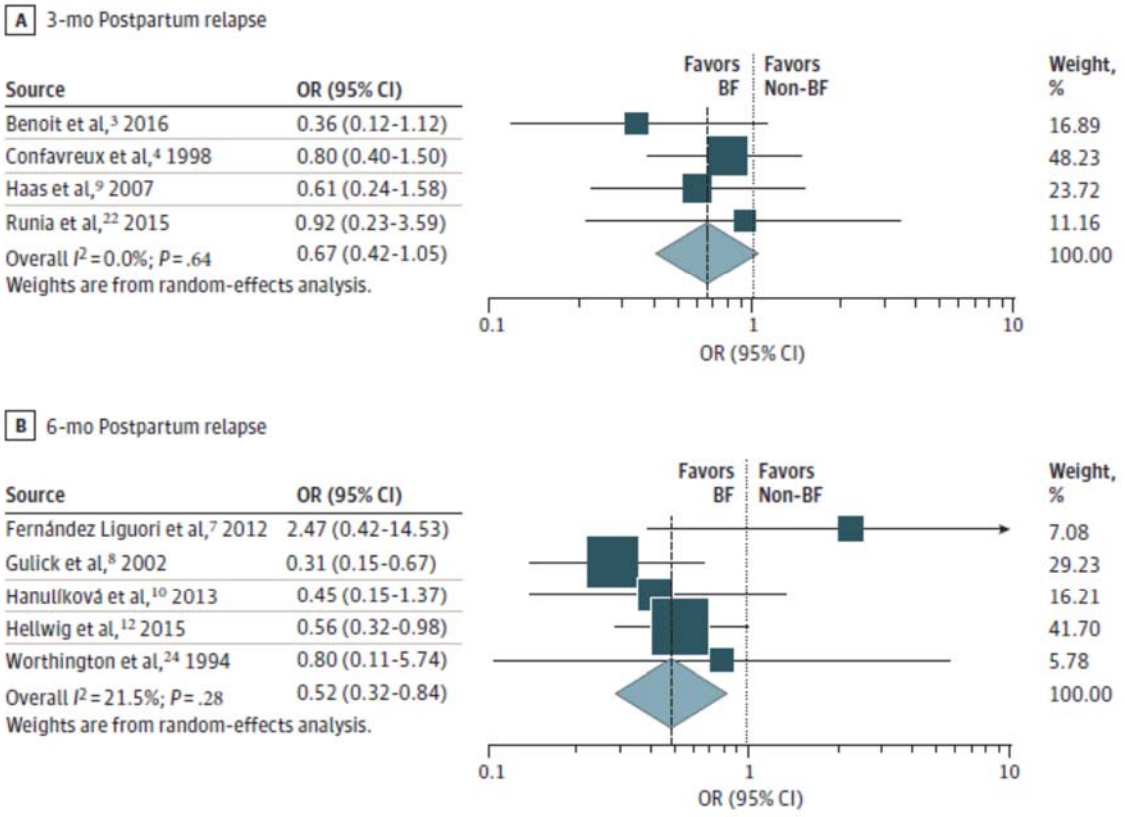
[a]A main study goal was not to evaluate BF.

[b]DMT use only reported for within 1 year prior to pregnancy.

eFigure 1. Funnel plot evaluating for publication bias with no publication bias demonstrated.



eFigure 2. Stratified Data on Association of Breastfeeding (BF) With Postpartum Multiple Sclerosis Relapses in Studies Reporting 3-Month and 6-Month Postpartum Relapse Outcomes



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