

Appendix e-1. Propensity score matching methodology and results.

Logistic regression was used to generate propensity scores based on the characteristics of individual subjects (see below). MS mothers were then matched by propensity score to control subjects with the exact or closest propensity score in a ratio of 1:2 using the caliper method. If none of the control subjects had a propensity score within 25% of the standard deviation of an MS subject's propensity score, then the MS case went unmatched and was discarded. Likewise, any unmatched controls were also discarded. The propensity score matched groups were then compared using the generalized estimating equation (GEE) approach, allowing adjustment for clustering (i.e. the potential dependence among multiple singleton births to the same mother). For the analysis of maternal hospitalization, initially cesarean section, diabetes, hypertension, maternal age, number of antenatal visits and parity were used to generate the propensity scores. This approach paralleled the main analyses where these same characteristics were considered (see methods). Of the 432 births to MS mothers and 2,975 births in the general population from the original cohorts, 32 births MS mothers and 174 births in the general population were excluded from the matching process due to missing values for some variables used in generating the propensity score. Among the 400 included births to MS mothers, 369 (92%) were each matched to two births in the general population. The characteristics of those selected after propensity score matching are shown in table e-1 and the results from the subsequent GEE analysis in table e-5. Although findings from this analysis were very similar to the main analysis, it was clear from table e-1 that BMI and birth weight of the newborn remained statistically significantly different between the MS and general population mothers. These two factors were additionally included in the generation of new propensity scores. The resulting propensity score matched groups did not differ statistically on any

characteristics (see table e-2). The subsequent GEE results were very similar to the initial non-propensity score matched findings, see table e-5.

The same approach was used when considering the newborn hospitalization. Variables initially incorporated into the propensity score included: 5-minute Apgar score, alcohol use during pregnancy, birth weight, cigarette use during pregnancy, congenital anomaly, drug use considered as harmful during pregnancy, diabetes, hypertension and maternal age. Of the 432 births to MS mothers and 2,975 births in the general population from the original cohorts, 1 birth to an MS mother and 25 births in the general population were excluded from the matching process due to missing values in some variables used in generating the propensity score. Among the 431 included births to MS mothers, 383 (89%) were each matched to two births in the general population. Characteristics of the initial propensity score matched groups are shown in table e-3. The final propensity score additionally included the number of antenatal visits and duration of the second stage of labor; characteristics of these two groups did not differ from each other (table e-4). From the GEE analysis, findings were again very similar to the original analysis, see table e-5.

Table e-1. Maternal and newborn characteristics in British Columbia (April 1998-March 2009) after propensity score matching (factors considered: cesarean section, diabetes, hypertension, maternal age, number of antenatal visits and parity).

Characteristic	MS	General Population	p value
	n=369	n=738	
Maternal age (year)			0.95 ^a
Median (range)	32 (19-44)	32 (19-44)	
Maternal BMI (kg/m ²) - n (%)			0.04 ^a
Underweight (<18.5)	14 (5)	34 (6)	
Normal (18.5 to <25)	152 (56)	336 (63)	
Overweight (25 to <30)	68 (25)	95 (18)	
Obese (≥30)	36 (13)	66 (12)	
Median (range)	23.4 (16.1-46.9)	22.7 (14.4-48.2)	
Gravidity			0.62 ^a
Median (range)	2 (1-11)	2 (1-11)	
Parity			0.86 ^b
Nullipara – n (%)	170 (46)	336 (46)	
Multipara – n (%)	199 (54)	402 (54)	
Number of antenatal visits			0.90 ^a
n	369	738	
Median (range)	10 (1-19)	10 (1-19)	
Lone parent status			0.17 ^b
n (%)	13/340 (4)	40/683 (6)	
Exposure to alcohol during pregnancy			0.29 ^c
n (%)	1 (<1)	8 (1)	
Exposure to drug considered as harmful for			0.61 ^b

pregnancy	7 (2)	11 (1)	
<i>n</i> (%)			
Cigarette use during pregnancy			0.25 ^b
<i>n</i> (%)	47 (13)	77 (10)	
Hypertension during pregnancy			0.79 ^b
<i>n</i> (%)	22 (6)	47 (6)	
Abnormal glucose level or diabetes during pregnancy			0.91 ^b
<i>n</i> (%)	14 (4)	29 (4)	
Duration of the second stage of labor (hour)			0.94 ^a
<i>n</i>	264	550	
Median (range)	0.6 (0-6.6)	0.6 (0-7.0)	
Assisted vaginal delivery (forceps and/or vacuum use)			0.39 ^b
<i>n</i> (%)	32/256 (13)	77/521 (15)	
Cesarean section			0.68 ^b
<i>n</i> (%)	113 (31)	217 (29)	
Birth weight – live birth only (gram)			0.004 ^a
<i>n</i>	369	736	
Median (range)	3,403 (1,985-5,770)	3,508 (900-5,513)	
Gestational age – live birth only (week)			0.07 ^a
<i>n</i>	369	735	
Median (range)	39 (32-42)	39 (23-43)	
5-minute Apgar score – live birth only (10-point scale)			0.76 ^a
<i>n</i>	368	732	
Median (range)	9 (5-10)	9 (5-10)	
Congenital anomalies diagnosed within first 28 days			0.27 ^b
<i>n</i> (%)	17 (5)	46 (6)	

^aMann-Whitney U test

^bChi-Square test

^cFisher's Exact test

Table e-2. Maternal and newborn characteristics in British Columbia (April 1998-March 2009) after propensity score matching (factors considered: birth weight of live births, BMI, cesarean section, diabetes, hypertension, maternal age, number of antenatal visits and parity).

Characteristic	MS	General Population	p value
	n=263	n=526	
Maternal age (year)			0.46 ^a
Median (range)	32 (21-44)	32 (16-44)	
Maternal BMI (kg/m ²) - n (%)			0.60 ^a
Underweight (<18.5)	15 (6)	21 (4)	
Normal (18.5 to <25)	151 (57)	338 (64)	
Overweight (25 to <30)	67 (25)	104 (20)	
Obese (≥30)	30 (11)	63 (12)	
Median (range)	23.2 (16.1-46.9)	22.8 (15.1-45.1)	
Gravidity			0.83 ^a
Median (range)	2 (1-8)	2 (1-11)	
Parity			0.55 ^b
Nullipara – n (%)	123 (47)	258 (49)	
Multipara – n (%)	140 (53)	268 (51)	
Number of antenatal visits			0.83 ^a
n	263	526	
Median (range)	10 (2-19)	10 (3-19)	
Lone parent status			0.62 ^b
n (%)	8/241 (3)	20/491 (4)	
Exposure to alcohol during pregnancy			0.67 ^c

<i>n</i> (%)	1 (<1)	5 (1)	
Exposure to drug considered as harmful for pregnancy	4 (2)	6 (1)	0.74 ^c
<i>n</i> (%)			
Cigarette use during pregnancy			0.58 ^b
<i>n</i> (%)	32 (12)	57 (11)	
Hypertension during pregnancy			0.83 ^b
<i>n</i> (%)	16 (6)	30 (6)	
Abnormal glucose level or diabetes during pregnancy			0.89 ^b
<i>n</i> (%)	9 (3)	19 (4)	
Duration of the second stage of labor (hour)			0.89 ^a
<i>n</i>	194	412	
Median (range)	0.6 (0-4.3)	0.6 (0-7.2)	
Assisted vaginal delivery (forceps and/or vacuum use)			0.22 ^b
<i>n</i> (%)	25/188 (13)	67/387 (17)	
Cesarean section			0.50 ^b
<i>n</i> (%)	75 (29)	138 (26)	
Birth weight – live birth only (gram)			0.88 ^a
<i>n</i>	263	526	
Median (range)	3,465 (1,985-5,770)	3,455.5 (1,480-5,513)	
Gestational age – live birth only (week)			0.54 ^a
<i>n</i>	263	526	
Median (range)	39 (32-42)	39 (29-43)	
5-minute Apgar score – live birth only (10-point scale)			0.14 ^a
<i>n</i>	263	526	
Median (range)	9 (5-10)	9 (6-10)	

Congenital anomalies diagnosed within first 28 days

0.61^b

n (%)

15 (6)

35 (7)

^aMann-Whitney U test

^bChi-Square test

^cFisher's Exact test

Table e-3. Maternal and newborn characteristics in British Columbia (April 1998-March 2009) after propensity score matching (factors considered: 5-minute Apgar score of live births only, alcohol use during pregnancy, birth weight of live births only, cigarette use during pregnancy, congenital anomaly, drug use considered as harmful during pregnancy, diabetes, hypertension and maternal age).

Characteristic	MS	General Population	p value
	n=383	n=766	
Maternal age (year)			0.47 ^a
Median (range)	32 (19-44)	32 (16-44)	
Maternal BMI (kg/m ²) - n (%)			0.25 ^a
Underweight (<18.5)	12 (4)	23 (4)	
Normal (18.5 to <25)	166 (57)	343 (65)	
Overweight (25 to <30)	81 (28)	95 (18)	
Obese (≥30)	30 (10)	70 (13)	
Median (range)	23.3 (16.1-46.9)	23.0 (14.4-56.8)	
Gravidity			0.26 ^a
Median (range)	2 (1-8)	2 (1-11)	
Parity			0.13 ^b
Nullipara – n (%)	179 (47)	322 (42)	
Multipara – n (%)	204 (53)	444 (58)	
Number of antenatal visits			0.002 ^a
n	359	734	
Median (range)	10 (1-22)	9 (0-18)	
Lone parent status			0.22 ^b
n (%)	10/352 (3)	31/704 (4)	
Exposure to alcohol during pregnancy			1.00 ^c

<i>n</i> (%)	1 (<1)	2 (<1)	
Exposure to drug considered as harmful for pregnancy	6 (2)	14 (2)	0.75 ^b
<i>n</i> (%)			
Cigarette use during pregnancy			1.00 ^b
<i>n</i> (%)	30 (8)	60 (8)	
Hypertension during pregnancy			0.48 ^b
<i>n</i> (%)	15 (4)	37 (5)	
Abnormal glucose level or diabetes during pregnancy			1.00 ^b
<i>n</i> (%)	13 (3)	26 (3)	
Duration of the second stage of labor (hour)			0.05 ^a
<i>n</i>	279	553	
Median (range)	0.6 (0-6.6)	0.5 (0-7.9)	
Assisted vaginal delivery (forceps and/or vacuum use)			0.13 ^b
<i>n</i> (%)	33/271 (12)	86/531 (16)	
Cesarean section			0.68 ^b
<i>n</i> (%)	112 (29)	233 (30)	
Birth weight – live birth only (gram)			0.30 ^a
<i>n</i>	383	766	
Median (range)	3,435 (1,985-5,770)	3,454.5 (1,205-5,513)	
Gestational age – live birth only (week)			0.96 ^a
<i>n</i>	382	764	
Median (range)	39 (32-42)	39 (30-43)	
5-minute Apgar score – live birth only (10-point scale)			0.18 ^a
<i>n</i>	383	766	
Median (range)	9 (5-10)	9 (5-10)	

Congenital anomalies diagnosed within first 28 days

0.86^b

n (%)

22 (6)

46 (6)

^aMann-Whitney U test

^bChi-Square test

^cFisher's Exact test

Table e-4. Maternal and newborn characteristics in British Columbia (April 1998-March 2009) after propensity score matching (factors considered: 5-minute Apgar score of live births only, alcohol use during pregnancy, birth weight of live births only, cigarette use during pregnancy, congenital anomaly, drug use considered as harmful during pregnancy, diabetes, hypertension, maternal age, number of antenatal visits and the duration of the second stage of labor).

Characteristic	MS	General Population	p value
	n=251	n=502	
Maternal age (year)			0.38 ^a
Median (range)	31 (19-44)	31 (16-44)	
Maternal BMI (kg/m ²) - n (%)			0.14 ^a
Underweight (<18.5)	8 (4)	18 (5)	
Normal (18.5 to <25)	113 (59)	233 (65)	
Overweight (25 to <30)	47 (25)	80 (22)	
Obese (≥30)	23 (12)	29 (8)	
Median (range)	23.2 (16.1-43.2)	22.7 (14.4-44.2)	
Gravidity			0.39 ^a
Median (range)	2 (1-11)	2 (1-10)	
Parity			0.53 ^b
Nullipara – n (%)	117 (47)	222 (44)	
Multipara – n (%)	134 (53)	280 (56)	
Number of antenatal visits			0.98 ^a
n	251	502	
Median (range)	10 (1-20)	10 (1-17)	
Lone parent status			0.09 ^b
n (%)	6/235 (3)	25/471 (5)	

Exposure to alcohol during pregnancy			---
<i>n</i> (%)	0 (0)	0 (0)	
Exposure to drug considered as harmful for pregnancy			0.29 ^c
<i>n</i> (%)	1 (<1)	8 (2)	
Cigarette use during pregnancy			0.60 ^b
<i>n</i> (%)	22 (9)	50 (10)	
Hypertension during pregnancy			1.00 ^b
<i>n</i> (%)	8 (3)	16 (3)	
Abnormal glucose level or diabetes during pregnancy			0.57 ^b
<i>n</i> (%)	10 (4)	16 (3)	
Duration of the second stage of labor (hour)			0.55 ^a
<i>n</i>	251	502	
Median (range)	0.6 (0-6.6)	0.5 (0-8.0)	
Assisted vaginal delivery (forceps and/or vacuum use)			0.28 ^b
<i>n</i> (%)	29/241 (12)	71/473 (15)	
Cesarean section			0.40 ^b
<i>n</i> (%)	10 (4)	27 (5)	
Birth weight – live birth only (gram)			0.86 ^a
<i>n</i>	251	502	
Median (range)	3,455 (1,985-4,886)	3,470 (1,610-4,770)	
Gestational age – live birth only (week)			0.46 ^a
<i>n</i>	251	502	
Median (range)	39 (32-42)	39 (30-42)	
5-minute Apgar score – live birth only (10-point scale)			0.63 ^a
<i>n</i>	251	502	

Median (range)	9 (7-10)	9 (6-10)
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Congenital anomalies diagnosed within first 28 days		0.89 ^b
<i>n</i> (%)	10 (4)	19 (4)

^aMann-Whitney U test

^bChi-Square test

^cFisher's Exact test

Table e-5. Length of birth hospitalization in hours between births to mothers with MS and the general population.‡

Factor	n	Length of hospitalization (mean ± SD; median [range])	Propensity-Score Matched [§] and		
			Adjusted for Clustering Effect		
			Beta	95% CI	p value
Maternal Hospitalization					
			Reference level		
Non-MS	738	58.4 ± 39.5; 53.2 [2.9-713.9]			
MS	369	57.3 ± 30.1; 52.1 [1.7-184.1]	<0.01	-0.04 – 0.03	0.94
Newborn Hospitalization					
			Reference level		
Non-MS	526	56.8 ± 28.2; 51.2 [1.6-229.8]			
MS	263	57.0 ± 30.1; 52.3 [1.7-184.1]	-0.01 ^a	-0.05 – 0.03 ^a	0.63 ^a
			Reference level		
Non-MS	502	54.1 ± 58.7; 42.3 [<0.1-726.4]			
MS	251	53.5 ± 56.3; 42.3 [3.4-571.4]	<0.01 ^b	-0.04 – 0.05 ^b	0.87 ^b

‡length of birth hospitalization was logarithmically transformed

§Maternal hospitalizations were matched by: cesarean section, diabetes, hypertension, maternal age, number of antenatal visits and parity. Newborn hospitalizations were

matched by: 5-minute Apgar score of live births only, alcohol use during pregnancy, birth weight of live births only, cigarette use during pregnancy, congenital anomaly, drug use considered as harmful during pregnancy, diabetes, hypertension and maternal age.

^aMaternal hospitalizations were additionally matched by: BMI and birth weight of live births only.

^bNewborn hospitalizations were additionally matched by: number of antenatal visits and the duration of the second stage of labor.

Table e-6. Sensitivity analysis of the association between MS disability (EDSS) and length of birth hospitalization (hours) in births to mothers with MS.‡ EDSS scores closest to the delivery date were considered (± 1 year).

Factor	n	Length of hospitalization (mean \pm SD; median [range])	Unadjusted			Adjusted for Clustering and Confounding Effects*		
			Beta	95% CI	p value	Beta	95% CI	p value
Maternal Hospitalization								
Disability (± 1 year) – EDSS score								
0	47	54.7 \pm 30.9; 46.9 [3.4-144.4]	Reference level			Reference level		
1 or 1.5	81	56.0 \pm 31.5; 48.1 [1.9-162.7]	0.01	-0.10 – 0.11	0.90	-0.02	-0.11 – 0.08	0.72
2 or 2.5	71	60.3 \pm 45.0; 54.4 [9.5-360.7]	0.04	-0.06 – 0.15	0.42	0.01	-0.08 – 0.10	0.82
≥ 3	51	57.9 \pm 37.4; 53.0 [3.4-182.1]	0.03	-0.09 – 0.14	0.67	0.02	-0.08 – 0.12	0.71
Newborn Hospitalization								
Disability (± 1 year) – EDSS score								
0	47	63.3 \pm 51.2; 47.9 [3.4-303.2]	Reference level			Reference level		
1 or 1.5	81	64.2 \pm 53.6; 49.3 [1.9-335.4]	<0.01	-0.11 – 0.12	0.99	-0.05	-0.16 – 0.06	0.36
2 or 2.5	71	65.2 \pm 59.9; 54.8 [9.5-388.8]	0.02	-0.10 – 0.14	0.70	0.03	-0.09 – 0.14	0.67
≥ 3	51	99.5 \pm 160.4; 58.6 [5.8-973.4]	0.09	-0.04 – 0.21	0.18	0.01	-0.11 – 0.14	0.83

‡length of birth hospitalization was logarithmically transformed

*Maternal hospitalizations were adjusted for: cesarean section, diabetes, hypertension, maternal age, number of antenatal visits and parity. Newborn hospitalizations were adjusted for: 5-minute Apgar score of live births only, alcohol use during pregnancy, birth weight of live births only, cigarette use during pregnancy, congenital anomaly, drug use considered as harmful during pregnancy, diabetes, hypertension and maternal age.