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Supplementary Information for

Population-based neuroimaging reveals traces of childbirth in the maternal brain

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Brain age analyses using brainageR

The brain age values obtained using brainageR were corrected for age using Equation 1, and outliers with a value of < 0 and > 90 were removed (n = 14). The brain age that was estimated using brainageR and the brain age that was estimated using our current approach showed a correlation of $r = 0.61$, $p =< 0001$, CI = [0.60, 0.62]. When using the brain age values from the brainageR estimation, a negative correlation was found between number of childbirths and brain age gap $r = -0.05$, $p = 6.73 \times 10^{-9}$, CI = [-0.06, -0.02]), and the group differences showed 0.72 (SD = 6.35) years for > 1 births ($t = 4.98$, $p = 6.52 \times 10^{-7}$, $d = 0.11$), 0.54 (SD = 6.35) years for 1 birth ($t = 2.65$, $p = 8.12 \times 10^{-3}$, $d = 0.08$), 0.63 (SD = 6.36) years for 2 births ($t = 4.06$, $p = 4.94 \times 10^{-5}$, $d = 0.10$), 0.94 (SD = 6.38) years for 3 births ($t = 4.98$, $p = 6.68 \times 10^{-7}$, $d = 0.15$), 0.79 (SD = 6.46) years for 4 births ($t = 2.45$, $p = 0.01$, $d = 0.12$), and 2.50 years (SD = 6.48) for 5-8 births, $t = 4.18$, $p = 3.00 \times 10^{-5}$, $d = 0.38$), relative to nulliparous women, respectively.

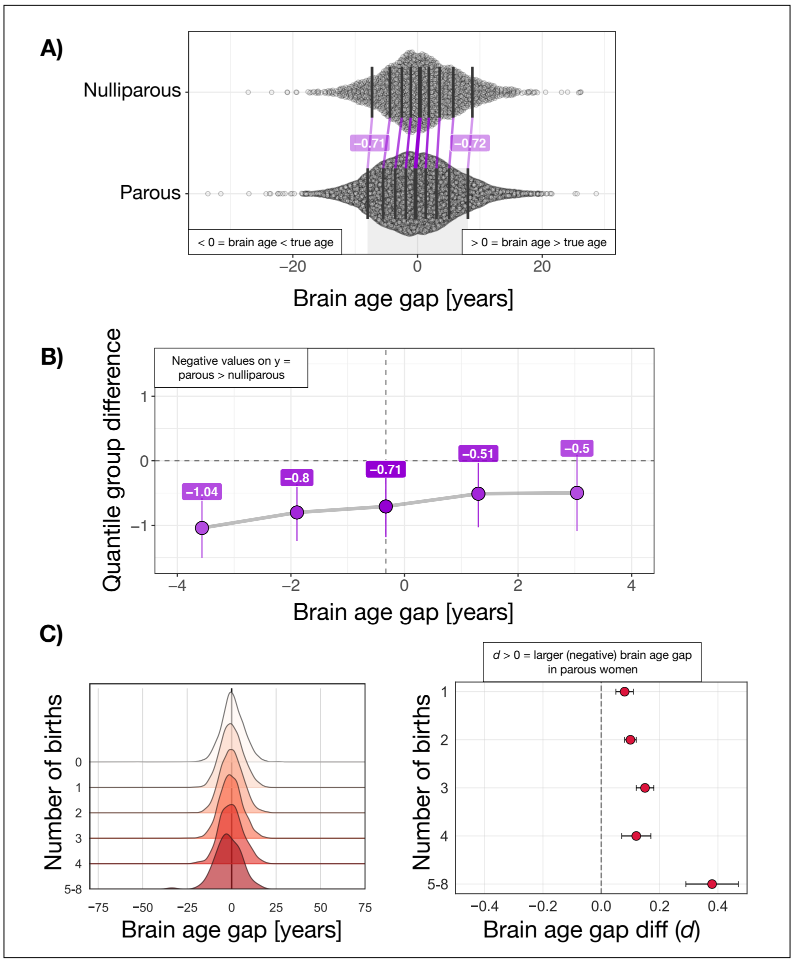

Fig. S1. Results based on the brain age values using brainageR A) The distributions of bias corrected brain age gap in nulliparous and parous women. Negative values indicate a predicted brain age that is lower than chronological age, i.e. a 'younger-looking' brain. The plot shows a uniform, negative shift in the group of parous women. B) The y-axis shows the differences between deciles (parous group minus nulliparous group), while the x-axis shows the deciles of the parous group. C) Left plot: The distribution of estimated brain age gap in subgroups of women based on number of childbirths. The plot shows a negative shift in the distribution with a larger number of births. Darker color indicates a larger number of births. Right plot: Difference in brain age gap between each of the subgroups and nulliparous women as indexed by Cohen's d. The error bars represent the standard deviation of the effect size. Higher values on the x-axis indicate a larger effect size. The dashed line indicates 0 on the y-axis. Number of subjects in each group: Nulliparous women = 2452, 1 birth = 1625, 2 births = 5311, 3 births = 2020, 4 births = 475, and 5-8 births = 124.

Linear and quadratic fits

As a follow-up analysis, the following polynomial fits were run for number of births and brain age gap:

$$\text{BrainAgeGap} = a + b \times N_{\text{births}}, \quad [1]$$

$$\text{BrainAgeGap} = a + b \times N_{\text{births}} + c \times N^2_{\text{births}}, \quad [2]$$

where the coefficient a represents the intercept, b represents the coefficient of the linear term, and c represents the coefficient of the quadratic term. The value of b obtained from the simple linear model was -0.19 ± 0.02 ($t = -8.12, p = 5.00 \times 10^{-16}$). The corresponding value of b obtained from the model including the quadratic term was -0.36 ± 0.06 ($t = -6.56, p = 5.78 \times 10^{-11}$), and the value of c was 0.05 ± 0.01 ($t = 3.41, p = 6.55 \times 10^{-4}$). A comparison of the two models indicated that the inclusion of the quadratic term provided a better fit ($F = 11.62, p = 6.55 \times 10^{-4}$). As a cross check, the fits were re-run with orthogonal polynomials. The results were consistent with the main results (b obtained from the simple linear model: -24.27 ± 2.99 ($t = -8.12, p = 5.00 \times 10^{-16}$), b obtained from the model including the quadratic term: -24.27 ± 2.99 ($t = -8.12, p = 5.00 \times 10^{-16}$), c: 10.18 ± 2.99 ($t = 3.41, p = 6.55 \times 10^{-4}$)). In order to assess the robustness of the parameter estimates, we performed bootstrapping with 10,000 iterations and compared the resulting distributions with an empirical null distribution generated with 10,000 permutations. Bootstrapping was performed with replacement, using samples of equal size to the dataset. Permutation testing was performed by randomly exchanging labels (number of births) on the data points when running the fits. The bootstrapped results from the simple linear model showed a mean ± SD of -0.19 ± 0.02 for b. Using 10,000 permutations, the number of permuted results from the null distribution that exceeded the bootstrapped mean was 0 ($p < 1.00 \times 10^{-4}$). Similarly, the mean ± SD of b obtained from the model including the quadratic term was -0.36 ± 0.05, where 0 permuted results exceeded the bootstrapped mean ($p < 1.00 \times 10^{-4}$). The mean ± SD of c was 0.05 ± 0.01, where 5 permuted results exceeded the bootstrapped mean ($p = 5.00 \times 10^{-4}$).

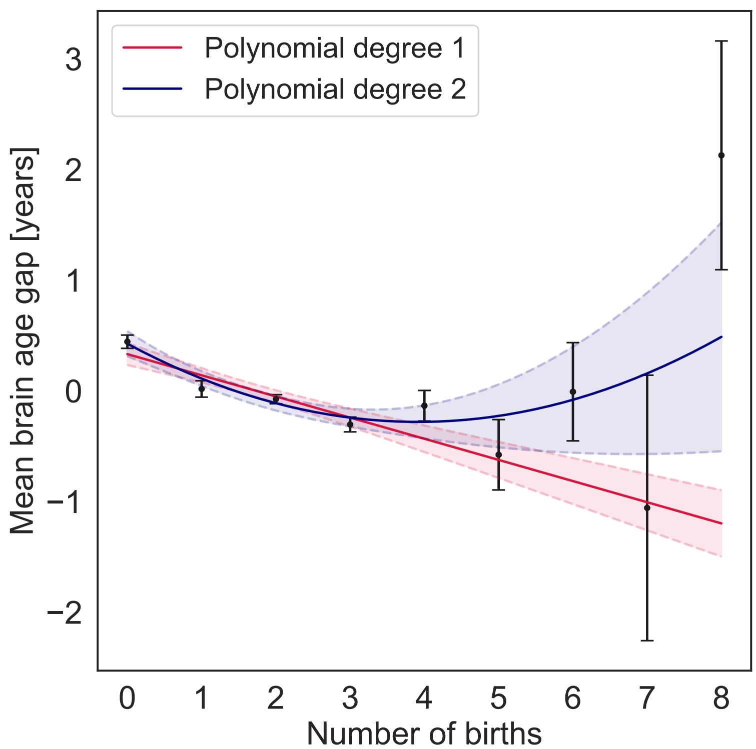

Fig. S2. The results from first and second degree polynomial fits to brain age gap and number of births. The black points show the mean brain age gap value for the groups of women within each birth category, where the error bars indicate the standard error on the means. The solid lines represent the results of the fits, and the shaded areas indicate the $\pm 95\%$ confidence intervals for each fit. Number of subjects in each group: 0 births = 2453, 1 birth = 1630, 2 births = 5315, 3 births = 2021, 4 births = 476, 5 births = 85, 6 births = 31, 7 births = 6, and 8 births = 4.

Births	N	Age at first birth | Years since first birth
>1	7935	26.72 (5.05) | 28.51 (9.58)
1	1630	29.76 (6.27) | 24.06 (10.08)
2	5313	26.81 (4.54) | 28.42 (9.23)
3	2020	24.94 (4.09) | 31.00 (8.91)
4	476	23.78 (4.05) | 33.01 (8.62)
5-8	126	22.94 (3.70) | 33.38 (7.24)

Table S1. Age at first birth and years since first birth (M $\pm$ SD) for each group, including only subjects with available data.

Classifier probability score and number of childbirths						
Pearson's *r* (within the parous group)			Logistic regression			
r	*p*	95% CI	β	SE	z	*p*
0.01	0.66	-0.03, 0.05	2.14	0.70	3.09	2.02×10^{-3}
Brain age gap and number of childbirths						
Pearson's *r*			Logistic regression			
r	*p*	95% CI	β	SE	z	*p*
-0.07	7.90×10^{-16}	-0.09, -0.06	-0.06	0.01	-8.38	5.25×10^{-17}

Group differences in brain age gap				
Group	Mean diff (SD)	*t*	*p*	Cohen's *d*
> 1 birth	0.58 (3.06)	8.43	3.82×10^{-17}	0.19
1 birth (n = 1630)	0.45 (3.07)	4.57	5.05×10^{-6}	0.15
2 births (n = 5315)	0.56 (3.05)	7.51	6.45×10^{-14}	0.18
3 births (n = 2021)	0.73 (3.04)	7.92	2.98×10^{-15}	0.24
4 births (n = 476)	0.65 (3.07)	4.26	2.16×10^{-5}	0.21
5-8 births (n = 126)	0.77 (3.07)	2.73	6.34×10^{-3}	0.25

Table S2. Correcting for Euler numbers to control for data quality. The classification and brain age prediction analyses were re-run using MRI data that were residualized with respect to the Euler numbers in addition to the other covariates using linear models. Outliers were identified and removed using the procedure described in Materials and Methods. The top 100 variables from a PCA were included in the analyses. The table shows the results from correlation analyses and logistic regression, and differences in brain age gap between each group of parous women compared to nulliparous women, respectively. The estimated brain age was corrected for age using Equation 1 in the Materials and Methods. Number of women with > 1 birth = 9568, nulliparous women = 2453.

Brain age gap and number of childbirths						
Pearson's *r*			Logistic regression			
r	*p*	95% CI	β	SE	z	*p*
-0.07	2.34×10^{-14}	-0.09, -0.05	-0.06	0.01	-7.73	1.06×10^{-14}

Group differences in brain age gap				
Group	Mean diff (SD)	*t*	*p*	Cohen's *d*
> 1 birth	0.53 (3.77)	7.77	8.31×10^{-15}	0.14
1 birth (n = 1579)	0.38 (2.98)	3.94	8.14×10^{-5}	0.13
2 births (n = 5200)	0.51 (2.97)	6.90	5.80×10^{-12}	0.17
3 births (n = 1966)	0.70 (3.00)	7.67	2.09×10^{-14}	0.23
4 births (n = 462)	0.56 (2.99)	3.70	2.19×10^{-14}	0.19
5-8 births (n = 123)	0.73 (2.98)	2.67	7.71×10^{-3}	0.25

Table S3. Ethnic background. The brain age analysis was re-run on white subjects only. Outliers were identified and removed using the procedure described in Materials and Methods. The top 100 variables from a PCA were included in the regressor. The estimated brain age was corrected for age using Equation 1 in the Materials and Methods. The table shows the results from correlation analyses and logistic regression for the white subsample. Number of women with > 1 birth = 9330, nulliparous women = 2378.

University/college. N = 3877 parous and 1273 nulliparous women						
Brain age gap and number of childbirths						
Pearson's *r*			Logistic regression			
r	*p*	95% CI	β	SE	z	*p*
-0.07	2.00×10^{-6}	-0.9, -0.04	-0.05	0.01	-4.28	1.86×10^{-5}
A level. N = 1353 parous and 333 nulliparous women						
Brain age gap and number of childbirths						
Pearson's *r*			Logistic regression			
r	*p*	95% CI	β	SE	z	*p*
-0.09	2.86×10^{-4}	-0.14, -0.04	-0.07	0.02	-3.63	2.84×10^{-4}
O level or equivalent. N = 2640 parous and 591 nulliparous women						
Brain age gap and number of childbirths						
Pearson's *r*			Logistic regression			
r	*p*	95% CI	β	SE	z	*p*
-0.07	1.29×10^{-4}	-0.10, -0.03	-0.06	0.01	-4.02	5.90×10^{-5}
Other professional (NVQ or similar). N = 942 parous and 177 nulliparous women						
Brain age gap and number of childbirths						
Pearson's *r*			Logistic regression			
r	*p*	95% CI	β	SE	z	*p*
-0.01	0.70	-0.07, 0.05	-0.03	0.03	-1.01	0.31

Table S4. Education. A higher level of education was related to a lower number of childbirths ($r = -0.10, p = 3.32 \times 10^{-26}$, CI = [-0.11, -0.08]). The brain age analysis was re-run within groups of women with a) university or college level education, b) A levels, c) O levels or equivalent, and d) other professional qualifications (NVQ or similar). Outliers were identified and removed using the procedure described in Materials and Methods. The top 100 variables from a PCA were included in the regressor. The estimated brain age was corrected for age using Equation 1 in the Materials and Methods. The table shows the results from correlation analyses and logistic regression within each of the educational categories.

BMI < 18.5. N = 53 parous and 12 nulliparous women						
Brain age gap and number of childbirths						
Pearson's *r*			Logistic regression			
r	*p*	95% CI	β	SE	z	*p*
-0.04	0.74	-0.28, 0.20	0.002	0.10	0.02	0.99
BMI 18.5 - 25. N = 3086 parous and 790 nulliparous women						
Brain age gap and number of childbirths						
Pearson's *r*			Logistic regression			
r	*p*	95% CI	β	SE	z	*p*
-0.06	6.40×10^{-5}	-0.10, -0.03	-0.07	0.01	-5.33	9.96×10^{-8}
BMI 26 - 30. N = 3076 parous and 842 nulliparous women						
Brain age gap and number of childbirths						
Pearson's *r*			Logistic regression			
r	*p*	95% CI	β	SE	z	*p*
-0.08	7.79×10^{-7}	-0.11, -0.05	-0.06	0.01	-4.82	1.43×10^{-6}
BMI > 30. N = 2351 parous and 563 nulliparous women						
Brain age gap and number of childbirths						
Pearson's *r*			Logistic regression			
r	*p*	95% CI	β	SE	z	*p*
-0.06	1.58×10^{-3}	-0.09, -0.02	-0.05	0.02	-3.29	1.66×10^{-3}

Table S5. Body mass index (BMI). The general relationship between brain age gap and number of births persisted when correcting for BMI ($r = -0.07, p = 5.73 \times 10^{-16}$, CI = [-0.09, -0.06]). To further investigate the influence of BMI, the brain age analysis was re-run within groups of women with BMI values of a) < 18.5, b) 18.5 - 25, c) 26 - 30, and d) > 30. Outliers were identified and removed using the procedure described in Materials and Methods. The top 100 variables from a PCA were included in the regressor. The estimated brain age was corrected for age using Equation 1 in the Materials and Methods. The table shows the results from correlation analyses and logistic regression within each of the BMI categories. 65 women had BMI below 18.5 (minimum BMI = 15), constituting a group that was too small to run with PCA. In this group, all the MRI variables were included.

AFB < 22 years. N = 1470 parous and 2453 nulliparous women						
Brain age gap and number of childbirths						
Pearson's *r*			Logistic regression			
r	*p*	95% CI	β	SE	z	*p*
-0.09	1.07×10^{-8}	-0.12, -0.06	-0.06	0.01	-5.12	3.01×10^{-7}
Group differences in brain age gap						
Group		Mean diff (SD)		*t*	*p*	Cohen's *d*
> 1 birth		0.51 (2.98)		5.16	2.65×10^{-7}	0.17
1 birth (n = 190)		-0.02 (2.92)		-0.07	0.94	0.01
2 births (n = 649)		0.52 (2.97)		3.94	8.50×10^{-5}	0.17
3 births (n = 432)		0.60 (2.96)		3.90	1.00×10^{-4}	0.20
4 births (n = 148)		0.61 (2.92)		2.46	0.01	0.21
5-8 births (n = 51)		1.22 (2.93)		2.96	3.15×10^{-3}	0.42
AFB 22-29 years. N = 5620 parous and 2453 nulliparous women						
Brain age gap and number of childbirths						
Pearson's *r*			Logistic regression			
r	*p*	95% CI	β	SE	z	*p*
-0.08	3.74×10^{-14}	-0.11, -0.06	-0.07	0.01	-8.48	2.21×10^{-17}
Group differences in brain age gap						
Group		Mean diff (SD)		*t*	*p*	Cohen's *d*
> 1 birth		0.62 (3.00)		8.56	1.36×10^{-17}	0.21
1 birth (n = 607)		0.58 (3.02)		4.22	2.50×10^{-5}	0.19
2 births (n = 3297)		0.57 (2.97)		7.25	4.67×10^{-13}	0.19
3 births (n = 1356)		0.79 (3.00)		7.85	5.57×10^{-15}	0.27
4 births (n = 290)		0.45 (3.00)		2.44	0.02	0.15
5-8 births (n = 70)		0.54 (2.97)		1.48	0.14	0.18
AFB > 30 years. N = 2475 parous and 2453 nulliparous women						
Brain age gap and number of childbirths						
Pearson's *r*			Logistic regression			
r	*p*	95% CI	β	SE	z	*p*
-0.06	1.30×10^{-5}	-0.09, -0.03	-0.04	0.01	-4.39	1.20×10^{-5}
Group differences in brain age gap						
Group		Mean diff (SD)		*t*	*p*	Cohen's *d*
> 1 birth		0.37 (2.91)		4.40	1.09×10^{-5}	0.13
1 birth (n = 833)		0.30 (2.92)		2.60	9.28×10^{-3}	0.10
2 births (n = 1367)		0.36 (2.94)		3.64	2.81×10^{-4}	0.12
3 births (n = 232)		0.58 (2.91)		2.92	3.57×10^{-3}	0.20
4 births (n = 38)		0.65 (2.94)		1.34	0.17	0.22
5-8 births (n = 5)		-0.95 (2.94)		-0.72	0.47	0.32

Table S6. Age at first birth (AFB). The correlation between brain age gap and number of childbirths was $r = -0.04, p = 4.10 \times 10^{-4}$, CI = [-0.06, -0.02]) when correcting for AFB in an analysis including only the parous women. To further investigate the influence of AFB, the brain age analysis was re-run within groups of women with AFB at a) < 22 years, b) 22 - 29 years, and c) > 30 years, as compared to nulliparous women, respectively, in a subsample including the nulliparous women and the parous women who had data on AFB (N = 9565). Outliers were identified and removed using the procedure described in Materials and Methods. The top 100 variables from a PCA were included in the regressor. The estimated brain age was corrected for age using Equation 1 in the Materials and Methods. The table shows the results from correlation analyses, logistic regression, and differences in brain age gap between each of the groups of parous women compared to nulliparous women, respectively, within each of the AFB categories.