

Supplementary Online Content

Roth C, Magnus P, Schjølberg S, et al. Folic acid supplements in pregnancy and severe language delay in children. *JAMA*. 2011;306(14):1566-1573.

eTable 1. Parental characteristics by severe language delay^a

eTable 2. Risk of having a child with severe language delay according to maternal supplement use (boys and girls shown separately)

eTable 3A. Risk of having a child with severe language delay according to maternal supplement use, adjusted for all potential confounders in Table 1 (missing excluded list wise)

eTable 3B. Risk of having a child with severe language delay according to maternal supplement use, adjusted for all potential confounders in Table 1 (categories for missing included for breastfeeding, alcohol and paternal education)

eTable 4. Risk of having a child with severe language delay according to maternal supplement use, with “other supplements, but no folic acid” as reference group

eTable 5. Risk of having a child with severe language delay according to maternal supplement use, with plural births, preterm, low birth weight, children with hearing problems included in the sample for analysis^a

eTable 6. Risk of having a child with severe language delay according to maternal supplement use, with inclusion of children with “no words” at age 3 in the severe language delay group (adjusted for all potential confounders in Table 1)

eTable 7. Use of folic acid in the period 4 weeks before to 8 weeks after conception and risk of severe language delay stratified by maternal education

eTable 8. Proportion of age 3 questionnaires returned by four combinations of maternal folic acid use and maternal education level^a

eTable 9. Risk of delay in gross motor skills, at age 3, by maternal supplement

eFigure. Box plots comparing language delay based on maternal report with Vineland Adaptive Behavior Scales at age 3^a

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

eTable 1. Parental Characteristics by Severe Language Delay^a

		Severe language delay			
		N	%	N	%
Maternal education					
	<12	6 671	17.1	63	0.9
	12	4 656	12.0	29	0.6
	13-16	17 189	44.1	62	0.4
	17+	9 576	24.6	44	0.5
	Missing	862	2.2	6	0.7
Paternal education					
	<12	12 845	33.0	93	0.7
	12	3 894	10.0	25	0.6
	13-16	10 879	27.9	37	0.3
	17+	8 951	23.0	34	0.4
	Missing	2 385	6.1	15	0.6
Maternal age					
	<25	3 741	9.6	18	0.5
	25-29	13 140	33.7	69	0.5
	30-34	15 423	39.6	74	0.5
	35+	6 650	17.1	43	0.6
	Missing	0	.	.	.
Paternal age					
	<25	1 537	3.9	5	0.3
	25-29	8 774	22.5	45	0.5
	30-34	15 632	40.1	72	0.5
	35-39	9 122	23.4	55	0.6
	40+	3 809	9.8	26	0.7
	Missing	80	0.2	1	1.3
Planned pregnancy					
	No	6 674	17.1	45	0.7
	Yes	31 852	81.8	154	0.5
	Missing	428	1.1	5	1.2
Smoking^b					
	No	35 840	92.0	193	0.5
	Yes	2 840	7.3	10	0.4
	Missing	274	0.7	1	0.4
Alcohol^c					
	No	30 664	78.7	160	0.5
	Yes	4 812	12.4	21	0.5
	Missing	3 478	8.9	23	0.6
BMI^d					
	<25	26 211	67.3	119	0.5
	25-29	8 354	21.4	49	0.6
	30-34	2 549	6.5	20	0.8
	35+	905	2.3	7	0.8
	Missing	935	2.4	9	1.0
Parity^e					
	0	18 575	47.7	77	0.4
	1	13 674	35.1	74	0.5
	2+	6 705	17.2	53	0.8
	Missing	0	.	.	.
Maternal height^f					
	<1.65	9 910	25.4	71	0.7
	1.65-1.68	10 008	25.7	48	0.5
	1.69-1.72	9 518	24.4	42	0.4
	>1.72	9 115	23.4	41	0.4
	Missing	403	1.0	2	0.5

Marital status^g				
Married/living with partner	23 345	62.5	131	0.5
Single	11 869	30.5	53	0.4
Other	1 825	4.7	15	0.8
Missing	915	2.3	5	0.5
Type of milk at 6 months				
Breast milk	22 588	58.0	104	0.5
Infant formula	4 844	12.4	43	0.9
Breast/Infant formula	7 693	19.7	31	0.4
Missing	3 829	12.3	26	0.7

Abbreviations: BMI, body mass index.

^a p<.001 for all variables, Chi Square, 2-sided, to test for associations: sample for this analysis n=38,954.

^bSmoking in this pregnancy.

^cUse of alcoholic unit(s) per week. One unit equals 1.5 cl. pure alcohol.

^dBody mass index is calculated as weight in kilograms divided by height in meters squared.

^eParity including abortion after week 22.

^fMaternal height in meters.

^gMarital status from age 3 questionnaire.

eTable 2. Risk of Having a Child With Severe Language Delay According to Maternal Supplement Use (Boys and Girls Shown Separately)

Supp use-4 to 8 weeks ^a	Boys (n=19,956)								Severe language delay								Girls (n=18,998)			
	N ^b	% ^b	N ^c	% ^c	OR ^d	(95 % CI)	OR ^e	(95 % CI)	N ^f	% ^f	N ^g	% ^g	OR ^h	(95 % CI)	OR ⁱ	(95 % CI)				
no supp (ref.)	4 587	24.1	62	1.4					4 465	23.9	19	0.4								
other supp	1 295	6.8	17	1.3	0.97	(0.56-1.66)	1.05	(0.59-1.87)	1 185	6.4	5	0.4	0.99	(0.36-2.66)	0.95	(0.31-2.85)				
folic acid only	3 559	18.7	24	0.7	0.49	(0.30-0.79)	0.61	(0.37-1.00)	3 568	19.1	4	0.1	0.26	(0.08-0.77)	0.36	(0.12-1.10)				
folic acid+	9 574	50.3	56	0.6	0.42	(0.29-0.61)	0.55	(0.37-0.82)	9 431	50.6	17	0.2	0.42	(0.21-0.81)	0.56	(0.27-1.15)				

Abbreviations: OR, odds ratio; CI, confidence interval.

^aFour categories of supplement use in the period 4 weeks to before to 8 weeks after conception: a) no supplements (ref), b) other supplements, but no folic acid, c) folic acid only, d) folic acid together with other supplements.

^bNumber and percentage of boys by maternal supplement use.

^cNumber and percentage of boys with severe language by maternal supplement use.

^dUnadjusted, boys with moderate language delay excluded (n=941): sample for this analysis 19,015.

^eAdjusted for maternal education, maternal BMI, parity and marital status, boys with moderate language delay (n=941) and missing confounder data (n=1,270) excluded from analysis: sample for this analysis 17,745.

^fNumber and percentage of girls by maternal supplement use.

^gNumber and percentage of girls with severe language by maternal supplement use.

^hUnadjusted, girls with moderate language delay excluded (n=349): sample for this analysis 18,649.

ⁱAdjusted for maternal education, maternal BMI, parity and marital status, girls with moderate language delay (n=349) and missing confounder data (n=1,259) excluded from analysis: sample for this analysis 17,390.

eTable 3A. Risk of Having a Child With Severe Language Delay According to Maternal Supplement Use, Adjusted for All Potential Confounders in Table 1 (Missing Excluded List Wise)

Supplement use -4 to 8 weeks	N ^a	% ^a	N ^b	% ^b	Severe Language Delay	
					OR ^c	(95 % CI)
No supplements (ref.)	6 232	22.8	48	0.8		
Other supplements, no folic acid	1 735	6.3	14	0.8	1.11	(0.61-2.04)
Folic acid only	5 175	18.9	18	0.3	0.50	(0.29-0.87)
Folic acid together with other supplements	14 215	52.0	51	0.4	0.56	(0.37-0.85)

Abbreviations: OR, odds ratio; CI, confidence interval.

^aNumber and percentage of children by maternal supplement use.

^bNumber and percentage of children with severe language delay by maternal supplement use.

^cAdjusted for maternal education, maternal BMI, parity, marital status, paternal education, maternal age, planned pregnancy, maternal smoking, maternal alcohol use, maternal height, paternal age, breastfeeding at 6 months. Children with moderate language delay (n=1,290) and children with missing confounder data (n=9,607) were excluded from analysis: sample for this analysis n=27,357.

eTable 3B. Risk of Having a Child With Severe Language delay According to Maternal Supplement Use, Adjusted for All Potential Confounders in Table 1 (Categories for Missing Included for Breastfeeding, Alcohol and Paternal Education)

Supplement use -4 to 8 weeks	N ^a	% ^a	N ^b	% ^b	Severe Language Delay	
					OR ^c	(95 % CI)
No supplements (ref.)	8 110	23.4	67	0.8		
Other supplements, no folic acid	2 249	6.5	17	0.8	1.00	(0.58-1.71)
Folic acid only	6 568	18.9	27	0.4	0.57	(0.36-0.90)
Folic acid together with other supplements	17 712	51.1	68	0.4	0.57	(0.40-0.81)

Abbreviations: OR, odds ratio; CI, confidence interval.

^aNumber and percentage of children by maternal supplement use.

^bNumber and percentage of children with severe language delay by maternal supplement use.

^cAdjusted for maternal education, maternal BMI, parity, marital status, paternal education, maternal age, planned pregnancy, maternal smoking, maternal alcohol use, maternal height, paternal age, breastfeeding at 6 months. Children with moderate language delay (n=1,290) and children with missing confounder data (n=3,025) were excluded from analysis: sample for this analysis n=34,639.

eTable 4. Risk of Having a Child With Severe Language Delay According to Maternal Supplement Use, With “Other Supplements, but No Folic Acid” as Reference Group

Supplement use -4 to 8 weeks	N ^a	% ^a	N ^b	% ^b	OR ^c	Severe Language Delay		
						(95 % CI)	OR ^d	(95 % CI)
Other supplements, no folic acid (ref.)	2 480	6.6	22	0.9				
No supplements	9 052	24.0	81	0.9	1.09	(0.62-1.61)	0.95	(0.57-1.59)
Folic acid only	7 127	18.9	28	0.4	0.44	(0.25-0.77)	0.52	(0.29-0.95)
Folic acid together with other supplements	19 005	50.5	73	0.4	0.43	(0.26-0.69)	0.53	(0.31-0.88)

Abbreviations: OR, odds ratio; CI, confidence interval.

^aNumber and percentage of children by maternal supplement use.

^bNumber and percentage of children with severe language delay by maternal supplement use.

^cUnadjusted, excluding moderate language delay (n=1,290): sample for this analysis n=37,664.

^dAdjusted for maternal education, maternal BMI, parity and marital status. Children with moderate language delay (n=1,290) and children with missing confounder data (n=2,529) were excluded from analysis: sample for this analysis n=35,135.

eTable 5. Risk of Having a Child With Severe Language Delay According to Maternal Supplement Use, With Plural Births, Preterm, Low Birth Weight, Children With Hearing Problems Included in the Sample for Analysis^a

Supplement use -4 to 8 weeks	N ^b	% ^b	N ^c	% ^c	OR ^d	Severe Language Delay		
						(95 % CI)	OR ^e	(95 % CI)
No supplements (ref.)	10 023	24.0	100	1.0				
Other supplements, no folic acid	2 743	6.6	30	1.1	1.09	(0.72-1.65)	1.15	(0.74-1.80)
Folic acid only	7 931	19.0	43	0.5	0.54	(0.37-0.77)	0.63	(0.43-0.92)
Folic acid together with other supplements	21 098	50.5	108	0.5	0.51	(0.38-0.67)	0.61	(0.45-0.83)

Abbreviations: OR, odds ratio; CI, confidence interval.

^aWithout removing plural births, gestation<32, birth weight<2500g, children with hearing problems: sample for this analysis n=41,795.

^bNumber and percentage of children by maternal supplement use.

^cNumber and percentage of children with severe language delay by maternal supplement use.

^dUnadjusted, children with moderate language delay excluded (n=1,570) and children with no word production excluded (n=91).

^eAdjusted for maternal education, BMI, parity and marital status, children with moderate language delay (n=1,570) and children with missing confounder data (n=3,226) were excluded from analysis: sample for this analysis n=38,569.

eTable 6. Risk of Having a Child With Severe Language Delay According to Maternal Supplement Use, With Inclusion of Children With “No Words” at Age 3 in the Severe Language Delay Group (Adjusted for All Potential Confounders in Table 1)

Supplement use -4 to 8 weeks	Severe Language Delay					
	N ^a	% ^a	N ^b	% ^b	OR ^c	(95 % CI)
No supplements (ref.)	6 243	22.8	59	0.9		
Other supplements, no folic acid	1 737	6.3	16	0.9	1.03	(0.59-1.80)
Folic acid only	5 182	18.9	25	0.5	0.57	(0.35-0.92)
Folic acid together with other supplements	14 237	52.0	73	0.5	0.63	(0.44-0.91)

Abbreviations: OR, odds ratio; CI, confidence interval.

^aNumber and percentage of children by maternal supplement use.

^bNumber and percentage of children with severe language delay by maternal supplement use.

^cAdjusted for maternal education, maternal BMI, parity, marital status, paternal education, maternal age, planned pregnancy, maternal smoking, maternal alcohol use, maternal height, paternal age, breastfeeding at 6 months. Children with moderate language delay (n=1,290) and missing confounder data (n=10,328) were excluded from analysis: sample for this analysis n=27,399.

eTable 7. Use of Folic Acid in the Period 4 Weeks Before to 8 Weeks After Conception and Risk of Severe Language Delay Stratified by Maternal Education

Maternal education in years	Folic acid -4 to +8 ^a	N ^b % ^b		N ^c % ^c		Severe language delay			
						OR ^d	(95 % CI)	OR ^e	(95 % CI)
< 12	No (ref.)	3 056	45.8	45	1.6				
	Yes	3 615	54.2	18	0.5	0.32	(0.19-0.57)	0.38	(0.21-0.66)
12	No (ref.)	1 881	40.4	18	1.0				
	Yes	2 775	59.6	11	0.4	0.40	(0.19-0.86)	0.37	(0.17-0.82)
13-16	No (ref.)	4 720	27.5	24	0.5				
	Yes	12 469	72.5	38	0.3	0.59	(0.35-0.99)	0.69	(0.40-1.18)
17+	No (ref.)	2 052	21.4	11	0.6				
	Yes	7 524	78.6	33	0.4	0.80	(0.40-1.60)	0.86	(0.42-1.77)

Abbreviations: OR, odds ratio; CI, confidence interval.

^aMaternal use of folic acid in the period 4 weeks before to 8 weeks after conception as no/yes.

^bNumber and percentage of children by maternal supplement use in each maternal educational category, children with moderate language delay (n=1,290) and children missing data on maternal education (n=862) excluded: sample for this analysis n=36,832.

^cNumber and percentage of children with severe language delay by maternal supplement use in each maternal educational category.

^dUnadjusted: sample for this analysis n=36,832.

^eAdjusted for BMI, parity and marital status, children with moderate language delay (n=1,290) and children with missing confounder data (n=1,667) excluded from analysis: sample for this analysis n=35,165.

eTable 8. Proportion of Age 3 Questionnaires Returned by Four Combinations of Maternal Folic Acid Use and Maternal Education Level^a

	N ^c	% ^c	Returned age 3 questionnaire ^b	
			N	%
a.No folic acid and <17 years education ^a	18 087	30.7	9 867	54.6
b.No folic acid and 17+ years of education	3 285	5.6	2 013	61.3
c.Folic acid and <17 years education	30 375	46.7	18 766	61.8
d.Folic acid and 17+ years education	11 039	17.0	7 219	65.4

^aMaternal use of folic acid use (yes/no) in the period 4 weeks before to 8 weeks after conception. Low education defined as less than 17 years, high education defined as 17 years or more.

^bIncludes all pregnancies (n=64,453) in which the offspring had reached age 3 by the time MoBa Data version 5 was released; 1,667 had missing information on educational level: sample for this analysis n=62,786.

^cNumber and percentage of women in the four different combination of education level and maternal folic acid use (a,b,c,d)

eTable 9. Risk of Delay in Gross Motor Skills, at Age 3, by Maternal Supplement

Supplement use -4 to 8 weeks	N ^b	% ^b	N ^c	% ^c	Delay in gross motor skills ^a			
					OR ^d	(95 % CI)	OR ^e	(95 % CI)
No supplements (ref.)	9 073	24.3	234	2.6				
Other supplements, no folic acid	2 473	6.6	77	3.1	1.21	(0.93-1.57)	1.17	(0.89-1.53)
Folic acid only	7 044	18.9	194	2.8	1.07	(0.88-1.29)	1.00	(0.82-1.22)
Folic acid together with other supplements	18 735	50.2	593	3.2	1.23	(1.05-1.43)	1.08	(0.91-1.27)

Abbreviations: OR, odds ratio; CI, confidence interval.

^aDelay in gross motor skills defined as 'not yet' attained either of; 'Can your child kick a ball by swinging his/her leg forward without holding onto anything for support?' and 'Can your child catch a large ball with both hands?'

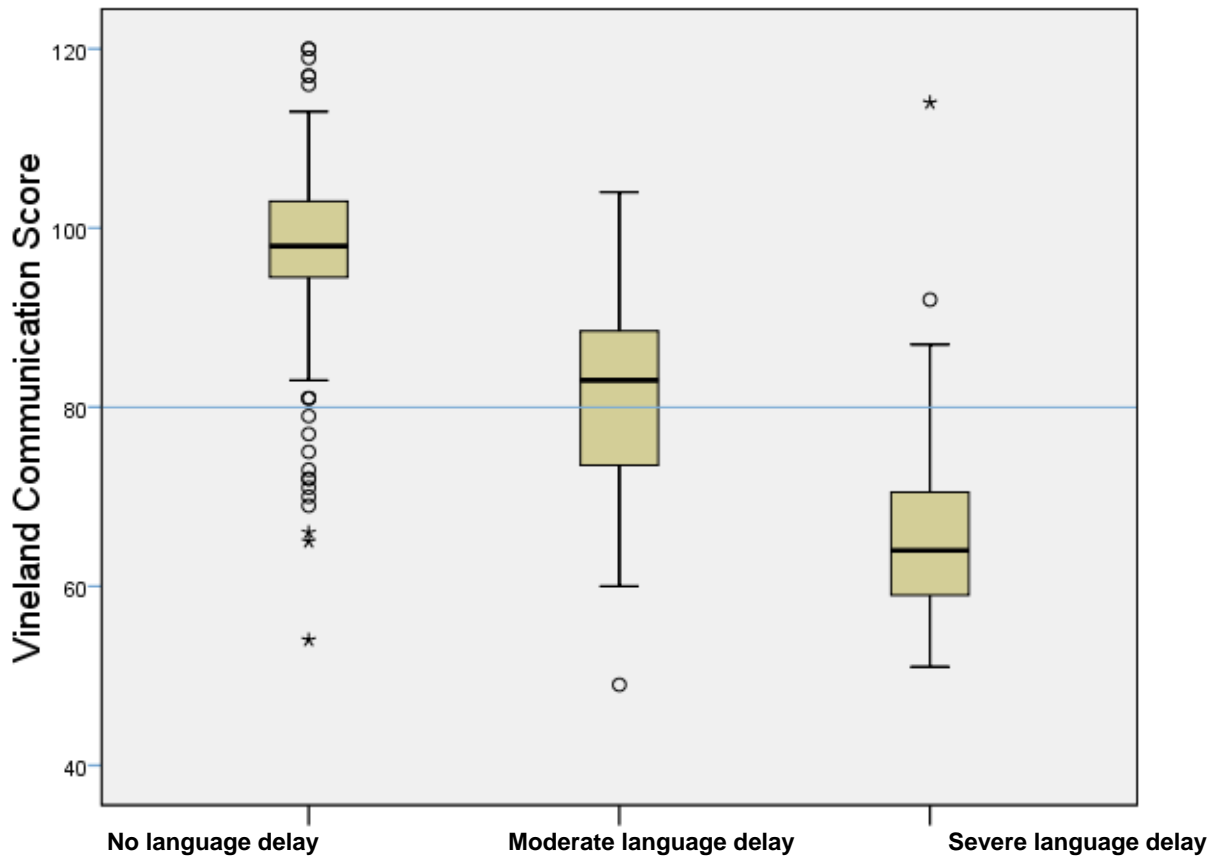
^bNumber and percentage of children by maternal supplement use.

^cNumber and percentage of children with delay in gross motor skills by maternal supplement use.

^dUnadjusted, missing data (2,787) excluded from analysis: sample for this analysis n=36,167.

^eAdjusted for maternal education, maternal BMI, parity and marital status, children with missing confounder data (n=5,219) were excluded from analysis: sample for this analysis n=33,735.

eFigure. Box plots comparing language delay based on maternal report with Vineland Adaptive Behavior Scales at age 3^a



^aThe box plots compare categories of language rating (X-axis) based on mother's report with scores on the clinician administered communication domain of the Vineland Adaptive Behavior Scales at age 3. In this sub-set of 425 children 307 (72.2%) had no language delay; 71 (16.7%) had moderate language delay and 47 (11.0%) had severe language delay. Boxes indicate the interquartile range (ie 25th percentile to 75th percentile) with median shown as the thick horizontal bar. Y-axis indicates range in Vineland score from 40 to 120. The ends of the whiskers are the most extreme observed data values within the interval [Q1 - 1.5 IQR, Q3 + 1.5 IQR]. The box is [Q1,Q3], and the line within the box is the median (i.e., Q2). Here IQR = Q3-Q1 is the interquartile range. Circles indicate mild outliers, stars indicate extreme outliers.