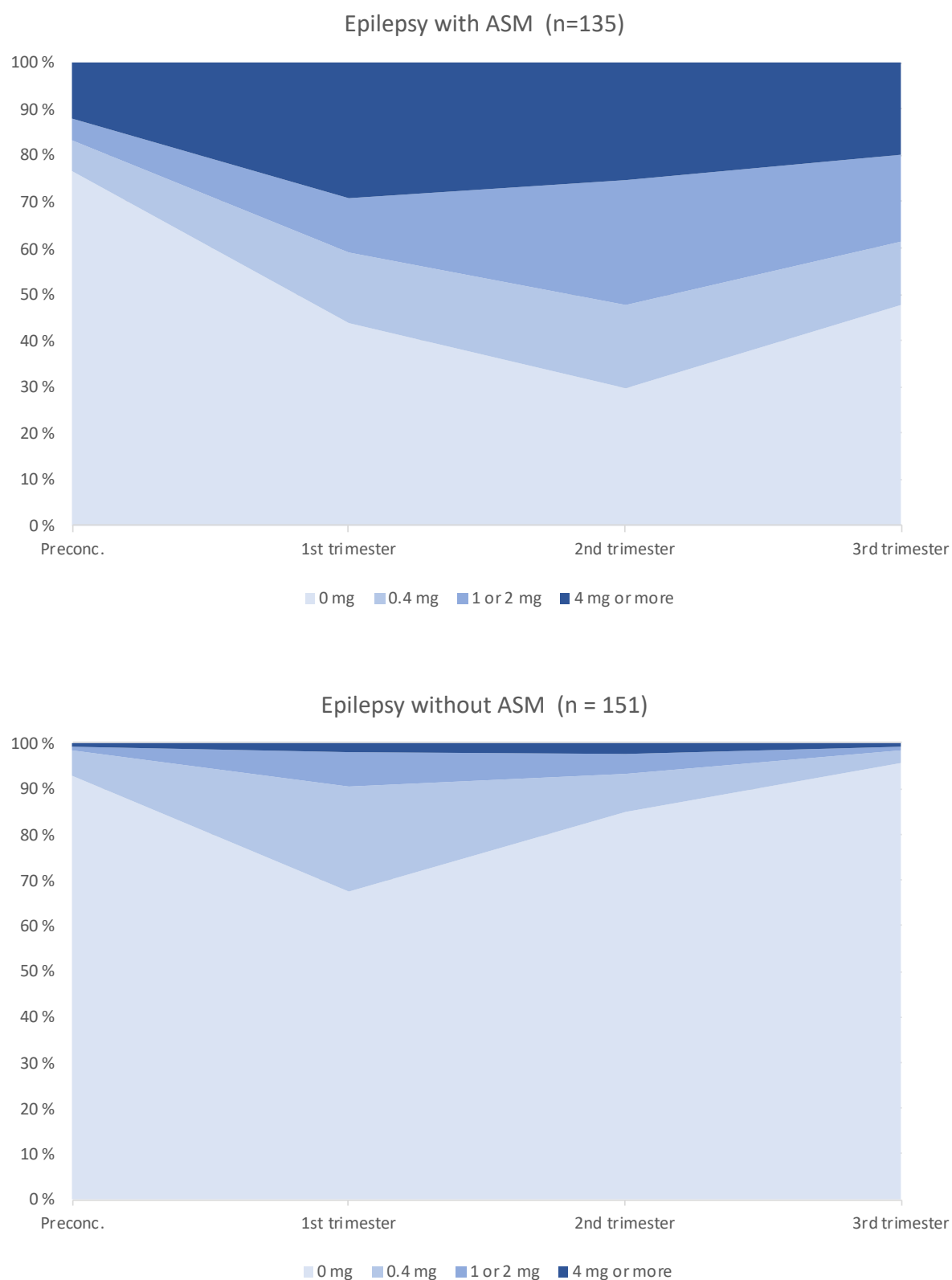
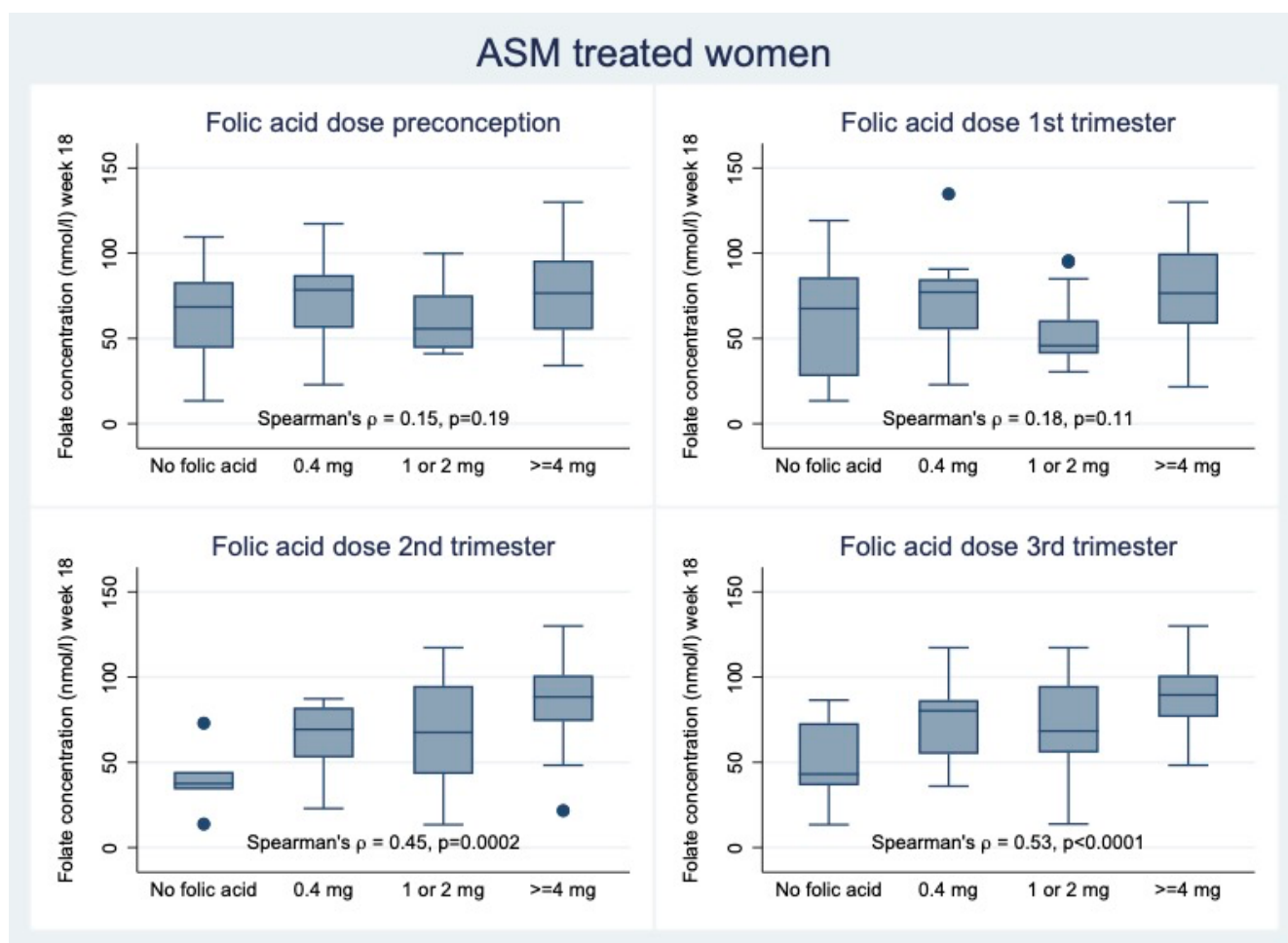


Supplemental material

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eFigure 1 Distribution of folic acid supplement dose

Dose of folic acid supplement in women with epilepsy. Percentage of women who are using the specified dose category in different pregnancy periods. ASM: anti-seizure medication. Precon.: preconception period (the last 4 weeks prior to pregnancy). Median dose (interquartile range) for “Epilepsy with ASM” and “Epilepsy without ASM” groups respectively: 0 mg (0-0) vs. 0 mg (0-0) in preconceptional period; 0.4 mg (0-4) vs. 0 mg (0-0.4) in 1st trimester; 1 or 2 mg (0-4) vs. 0 mg (0-0) in 2nd trimester; 0.4 mg (0- 2) vs. 0 mg (0-0) in 3rd trimester. Wilcoxon rank sum test for the difference between groups: $p < 0.0001$ for all periods.

eFigure 2 Association between folate concentration and folic acid supplement dose in women using ASM in pregnancy

Folate concentrations as measured in blood samples in gestational week 17-19 in women using ASM. Self-reported dose of folic acid supplement. Number of observations included in the Spearman's rank-order correlation analysis (ρ , p): $n = 79$ preconception (the last 4 weeks prior to pregnancy), $n = 76$ in 1st trimester, $n = 65$ in 2nd trimester, $n = 75$ in 3rd trimester.

eMethods

Laboratory analysis

Plasma folate analysis included the biologically active 5-methyltetrahydrofolate (mTHF) and the degradation product 4-alfa-hydroxy-5-methyltetrahydrofolate (hmTHF). mTHF is unstable in blood samples kept at room temperature but is largely recovered as hmTHF. The plasma concentration of maternal folate is therefore given as the sum of the mTHF and hmTHF concentrations.

Validation of folic acid supplement data

The present study includes data from both the Medical Birth Registry of Norway (MBRN) and the MoBa study. In MBRN, doctors or midwives are recording the use of folic acid supplement by checking a box if it was used *prior to*, and another box if used *during* pregnancy. According to MoBa data on the same women, the information from MBRN on folic acid supplement *during* pregnancy includes supplement that was started both early (1st trimester) and late in pregnancy (from the 2nd trimester). In the current study we found that the effect of folic acid supplement on the risk of preterm birth was evident if supplementation was started periconceptionally. When we performed sensitivity analyses based on the folic acid supplement data from MBRN alone, we could not find this effect. There was a 75% agreement between MoBa and MBRN on the use of folic acid *before* pregnancy, with a kappa of 0.40. There was a 69% agreement between MoBa and MBRN on the use of folic acid *during* pregnancy, with a kappa of 0.28.

Regression models in Table 2:

Some covariates were omitted in some regression analyses due to groups with zero or few observations. The fully adjusted regression models include the following covariates:

Preterm birth

- Epilepsy with ASM: maternal age, socioeconomic status, parity, anxiety/depression score, BMI, smoking during pregnancy, alcohol during pregnancy, unplanned pregnancy, pre-pregnancy diabetes, ASM polytherapy
- Epilepsy without ASM: maternal age, socioeconomic status, parity, anxiety/depression score, BMI, smoking during pregnancy, alcohol during pregnancy, unplanned pregnancy
- No epilepsy: maternal age, socioeconomic status, parity, anxiety/depression score, BMI, smoking during pregnancy, alcohol during pregnancy, unplanned pregnancy, pre-pregnancy diabetes, pre-pregnancy hypertension, and pre-pregnancy renal disease

Small for gestational age:

- Epilepsy with ASM: maternal age, socioeconomic status, parity, anxiety/depression score, BMI, smoking during pregnancy, unplanned pregnancy, and ASM polytherapy
- Epilepsy without ASM: maternal age, socioeconomic status, parity, anxiety/depression score, BMI, smoking during pregnancy, unplanned pregnancy, and pre-pregnancy hypertension
- No epilepsy: maternal age, socioeconomic status, parity, anxiety/depression score, BMI, smoking during pregnancy, alcohol during pregnancy, unplanned pregnancy, pre-pregnancy diabetes, pre-pregnancy hypertension, and pre-pregnancy renal disease

Preeclampsia:

- Epilepsy with ASM: maternal age, socioeconomic status, parity, anxiety/depression score, BMI, smoking during pregnancy, unplanned pregnancy, pre-pregnancy diabetes, and ASM polytherapy
- Epilepsy without ASM: logistic regression analysis not possible due to zero observations of preeclampsia in the group without folic acid supplementation

- No epilepsy: maternal age, socioeconomic status, parity, anxiety/depression score, BMI, smoking during pregnancy, alcohol during pregnancy, unplanned pregnancy, pre-pregnancy diabetes, pre-pregnancy hypertension, and pre-pregnancy renal disease

eTable 1. Pregnancy complications in women with and without periconceptual folic acid supplementation

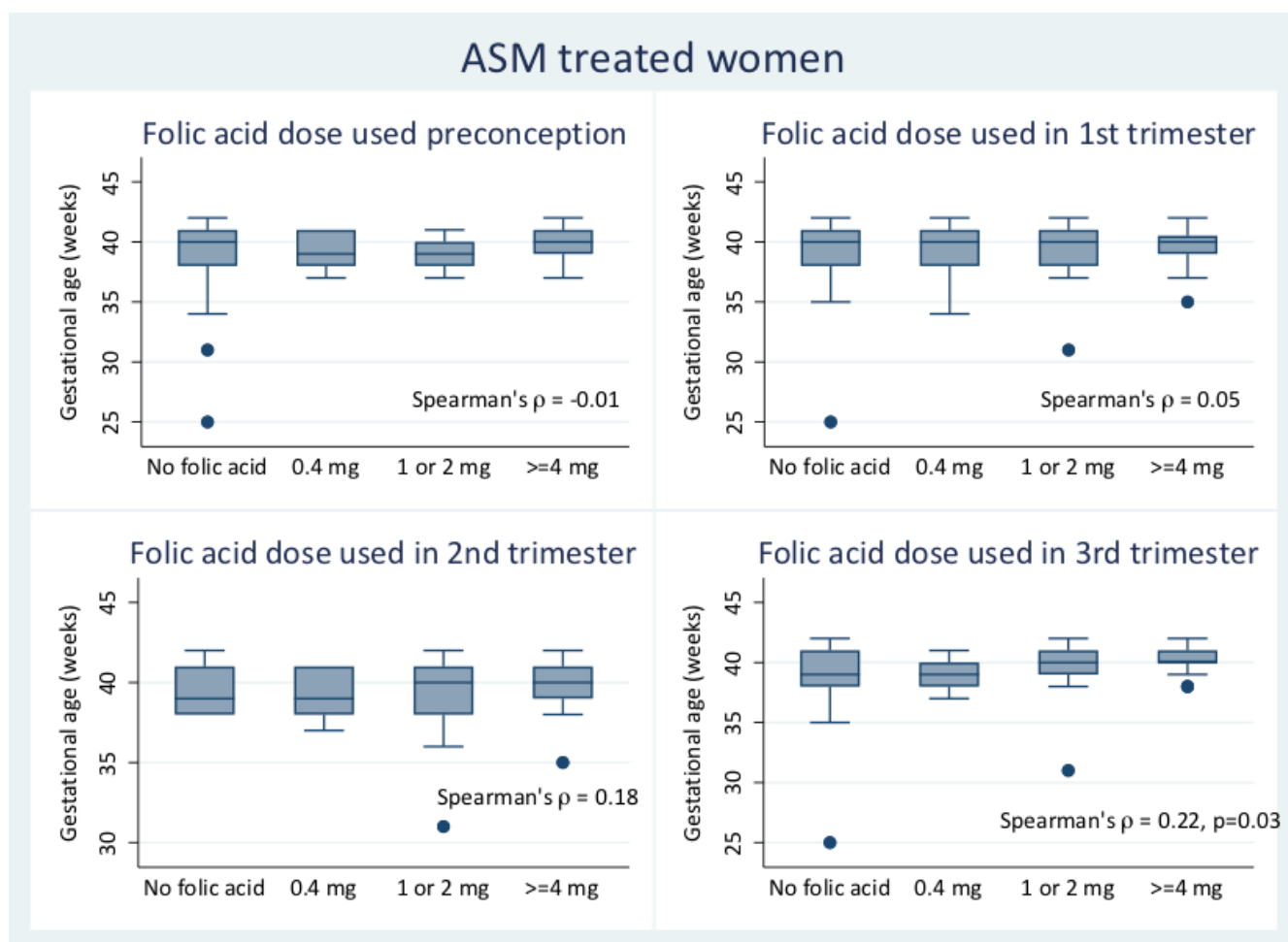
Women with epilepsy and ASM exposure			
	Periconceptual folic acid		OR (95% CI)
	No n (%)	Yes n (%)	
Lamotrigine			
Preterm birth	2 of 26 (8%)	4 of 101 (4%)	1.4 (0.1-22.3)
SGA	2 of 26 (8%)	4 of 102 (4%)	0.8 (0.0-28.1)
Preeclampsia	0 of 26 (0%)	6 of 102 (6%)	-
Carbamazepine			
Preterm birth	5 of 22 (23%)	7 of 64 (11%)	3.7 (0.9-14.8)
SGA	5 of 22 (23%)	7 of 64 (11%)	2.6 (0.4-15.3)
Preeclampsia	3 of 22 (14%)	4 of 64 (6%)	4.9 (0.8-30.6)
Valproate			
Preterm birth	2 of 11 (18%)	2 of 41 (5%)	4.9 (0.5-51.9)
SGA	0 of 11 (0%)	3 of 41 (7%)	-
Preeclampsia	1 of 11 (9%)	4 of 41 (10%)	0.9 (0.0-17.6)
Levetiracetam			
Preterm birth	0 of 5 (0%)	1 of 29 (3%)	-
SGA	0 of 5 (0%)	2 of 29 (7%)	-
Preeclampsia	0 of 5 (0%)	2 of 29 (7%)	-
Oxcarbazepine			
Preterm birth	1 of 7 (14%)	0 of 13 (0%)	-
SGA	1 of 7 (14%)	1 of 13 (8%)	-
Preeclampsia	0 of 7 (0%)	1 of 13 (8%)	-
Topiramate			
Preterm birth	1 of 3 (33%)	1 of 14 (7%)	-
SGA	1 of 3 (33%)	3 of 14 (21%)	-
Preeclampsia	0 of 3 (0%)	1 of 14 (7%)	-
Monotherapy			
Preterm birth	6 of 45 (13%)	8 of 202 (4%)	3.9 (1.2-13.1) ^a
SGA	6 of 45 (13%)	18 of 203 (9%)	1.1 (0.3-3.4)
Preeclampsia	2 of 45 (4%)	12 of 203 (6%)	0.8 (0.2-3.9)
Polytherapy			
Preterm birth	3 of 18 (17%)	4 of 41 (10%)	2.1 (0.2-20.8)
SGA	3 of 18 (17%)	3 of 41 (7%)	1.4 (0.1-23.1)
Preeclampsia	1 of 18 (6%)	3 of 41 (7%)	0.7 (0.1-11.0)

The analyses were performed separately for each ASM (both mono- and polytherapy). Pearson's chi squared test or Fisher exact test were used to compare categorical variables. Odds ratios (OR) with 95% confidence intervals (CI) were calculated by logistic regression analysis and adjusted for age, parity, socioeconomic status, maternal smoking and alcohol use during pregnancy, unplanned pregnancy, pre-pregnancy BMI, and depression, as well as clustering effects between siblings (some covariates omitted in some analyses because of collinearity or lack of events in some subgroups).

ASM: anti-seizure medication. Periconceptional folic acid: use of folic acid supplement 4 weeks before conception and/or during the first trimester. Preterm birth: gestational age <37 weeks. SGA, small for gestational age: <10 percentile. Preeclampsia: preeclampsia, HELLP, and eclampsia combined.

a) Significantly different when comparing women *without* periconceptional folic acid supplement to those *with* folic acid supplement, $p=0.03$

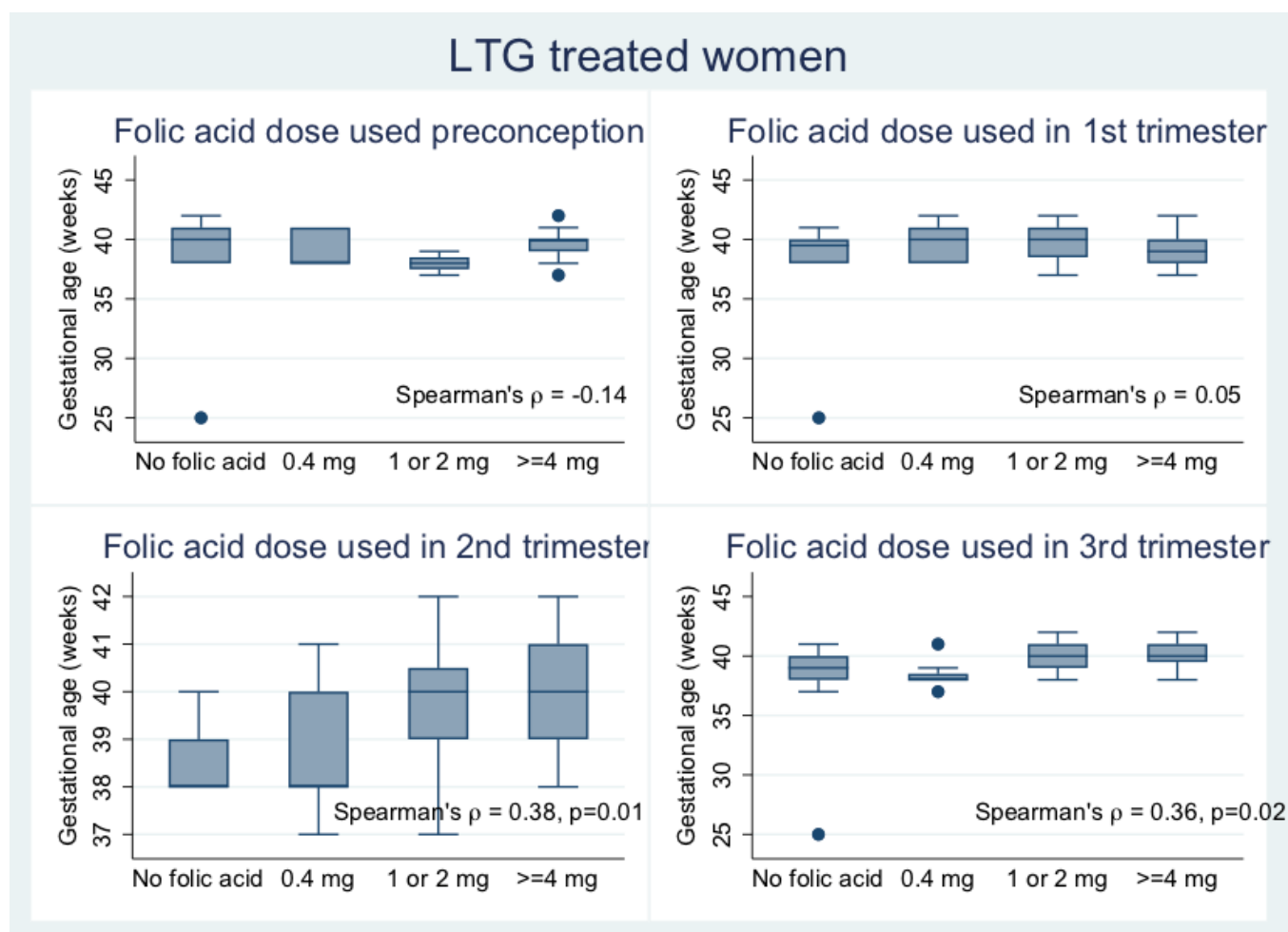
-) Number of observations too small to perform statistical tests

eFigure 3 Association between gestational age and folic acid supplement dose in women using ASM in pregnancy

Self-reported dose of folic acid supplement. Number of observations included in the Spearman's rank-order correlation

analysis (ρ , p): $n = 111$ preconception (the last 4 weeks prior to pregnancy), $n = 108$ in 1st trimester, $n = 90$ in 2nd trimester,

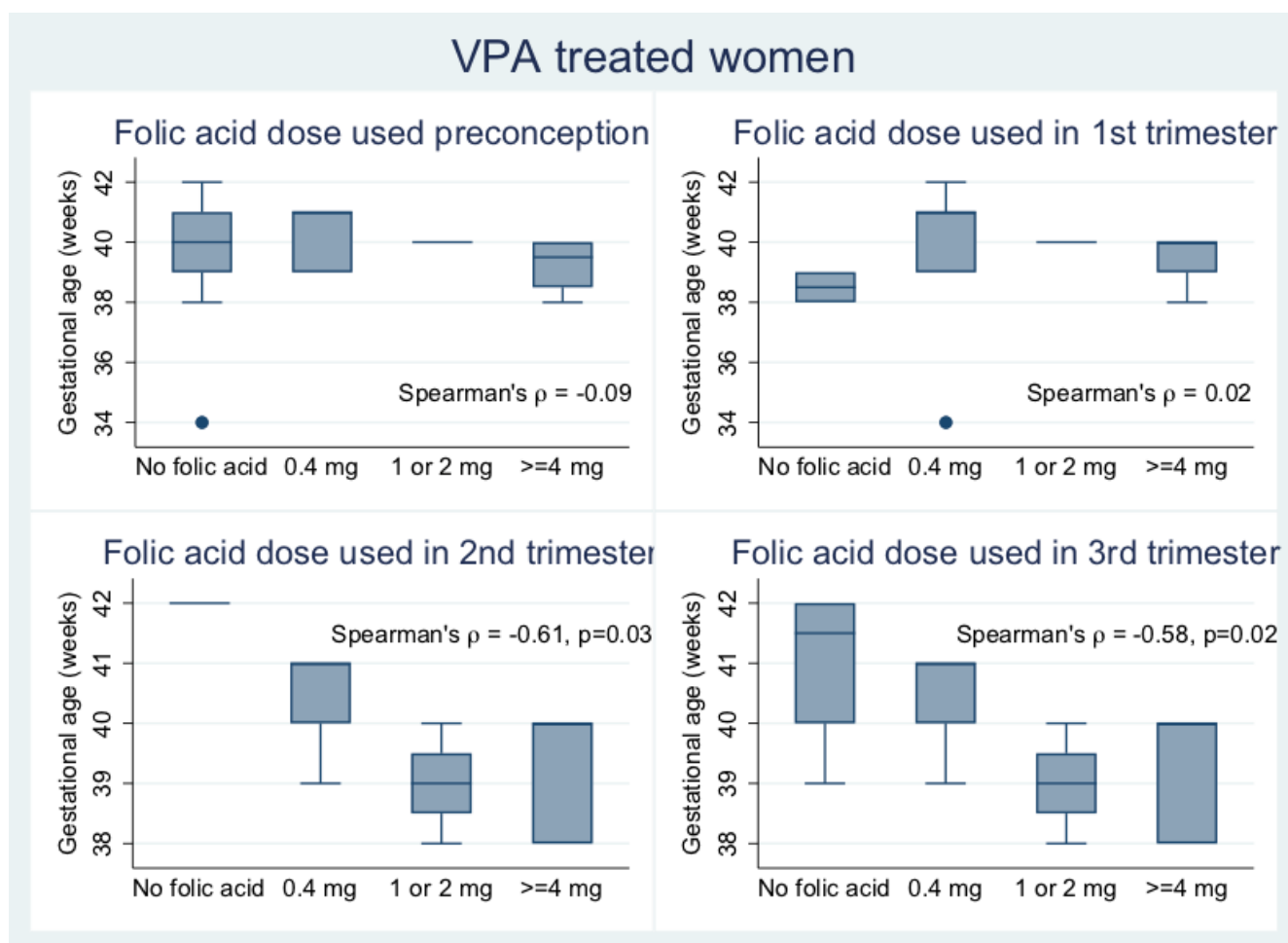
$n = 100$ in 3rd trimester. Exact p -values are given when $p < 0.05$.

eFigure 4 Association between gestational age and folic acid supplement dose in women using lamotrigine in pregnancy

Self-reported dose of folic acid supplement. Number of observations included in the Spearman's rank-order correlation

analysis (ρ, p): $n = 51$ preconception (the last 4 weeks prior to pregnancy), $n = 52$ in 1st trimester, $n = 43$ in 2nd trimester, $n =$

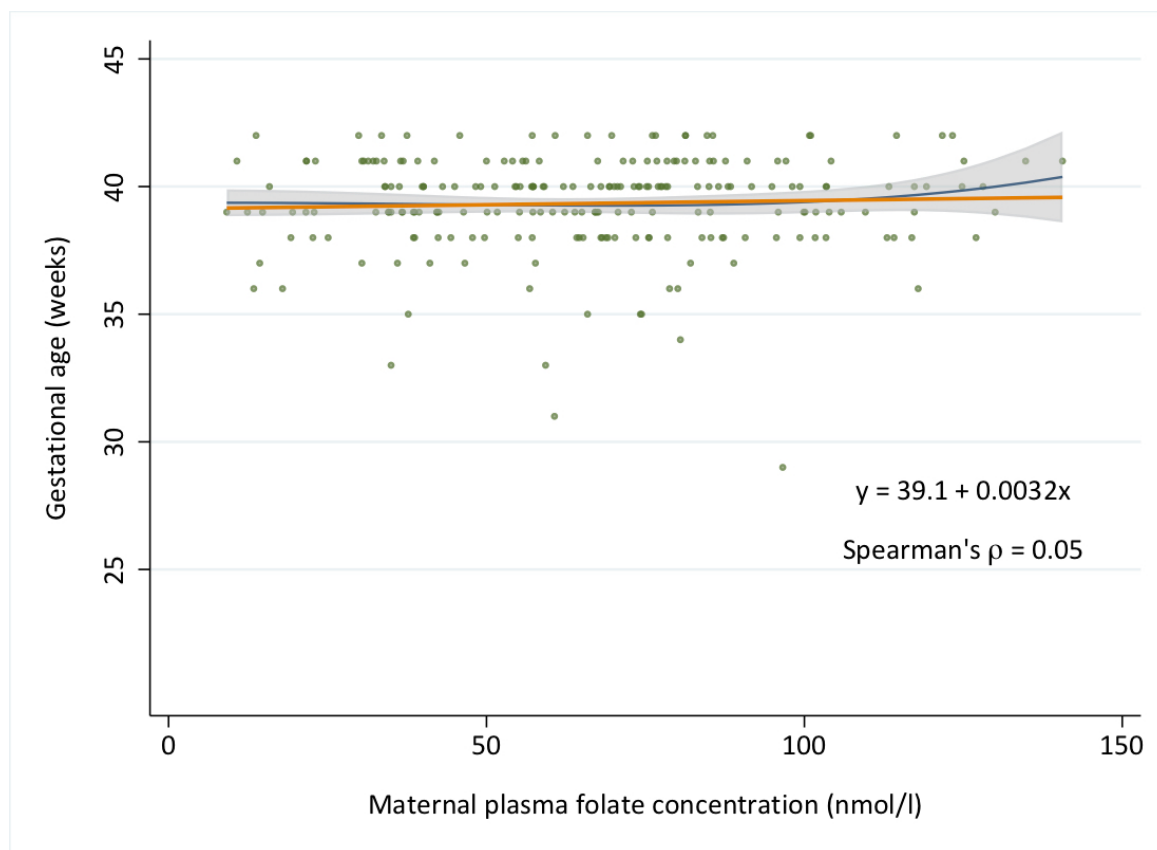
45 in 3rd trimester. Exact p-values are given when $p < 0.05$.

eFigure 5 Association between gestational age and folic acid supplement dose in women using valproate in pregnancy

Self-reported dose of folic acid supplement. Number of observations included in the Spearman's rank-order correlation

analysis (ρ, p): $n = 17$ preconception (the last 4 weeks prior to pregnancy), $n = 14$ in 1st trimester, $n = 13$ in 2nd trimester, $n =$

16 in 3rd trimester. Exact p -values are given when $p < 0.05$.

eFigure 6 Association between gestational age and folate concentration in women using ASM in pregnancy

Folate concentrations as measured in blood samples in gestational week 17-19 in women using ASM. The straight orange line represents linear regression analysis. The curved blue line is a two-way fractional-polynomial prediction plot and the grey area represents the corresponding 95% confidence intervals.