

Supplemental Table SII Mediation analysis, in the crude model, showing that a significant part of the effect of smoking on fetal growth parameters and birth weight can be explained by a delayed embryonic morphology.

Model 1 ^a	Total effect estimate (β), 95% CI	Direct effect estimate (β), 95% CI	Indirect effect estimate (β), 95% CI	Mediated proportion (%), 95% CI
Head circumference (N = 635)	-0.015 (-0.053; 0.023)	0.017 (-0.053; 0.023)	-0.033 (-0.045; -0.011)	- ^c
Abdominal circumference (N = 634)	-0.046 (-0.088; -0.004)	-0.018 (-0.057; 0.021)	-0.028 (-0.039; -0.009)	61.1 (22.4; 295.0)
Femur length (N = 634)	-0.091 (-0.133; -0.048)	-0.053 (-0.090; -0.016)	-0.037 (-0.052; -0.012)	41.3 (19.4; 73.4)
Birth weight (N = 667)	-0.147 (-0.197; -0.097)	-0.138 (-0.197; -0.097)	-0.009 (-0.014; -0.002)	6.3 (2.0; 14.5)
Model 2 ^b	Total effect estimate (β), 95% CI	Direct effect estimate (β), 95% CI	Indirect effect estimate (β), 95% CI	Mediated proportion (%), 95% CI
Head circumference (N = 635)	-0.009 (-0.080; 0.061)	-0.002 (-0.066; 0.061)	-0.008 (-0.040; 0.024)	80.2 (15.5; 176094.0)
Abdominal circumference (N = 634)	-0.033 (-0.113; 0.046)	-0.026 (-0.100; 0.048)	-0.007 (-0.038; 0.024)	21.2 (-319.0; 377.0)
Femur length (N = 634)	-0.047 (-0.128; 0.034)	-0.038 (-0.111; 0.035)	-0.009 (-0.046; 0.029)	18.2 (-473.0; 190.0)
Birth weight (N = 667)	-0.164 (-0.214; -0.115)	-0.157 (-0.206; -0.107)	-0.008 (-0.012; 0.001)	4.8 (-0.8; 7.6)

The bold values indicate significant associations. Growth parameters are expressed as Z-scores, which are corrected for gestational age. Birth weight is expressed as Z-score, which is corrected for gender and gestational age.

¹Crude model.

²Model adjusted for alcohol use, educational level, folic acid supplement use, maternal age, mode of conception, ethnicity, fetal sex, maternal BMI, parity and vitamin use. The total effect of smoking on fetal growth parameters and birth weight is reported as effect estimates (β) with 95% CIs and is decomposed into a direct effect and an indirect effect mediated by Carnegie developmental stages. The mediated proportion is calculated as the indirect effect divided by the total effect and represents the proportion of the total effect mediated by smoking during pregnancy. CIs were obtained by non-parametric bootstrapping with 5000 replications.

^cNot interpretable due to opposing direct and indirect effect estimates.