

Supplement

Effects of maternal smoking on body size and proportions at birth: A register-based cohort study of 1.4 million births

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1 Data cleaning

1.1 Study population

The MATEX cohort was identified from the Finnish Medical Birth Register (MBR). The register contains perinatal outcomes, pregnancy characteristics and sociodemographic information for all live births and stillbirths after the 22nd gestational week or with a birth weight of at least 500 g.

This work focuses on the effects of maternal smoking on singleton pregnancies born between 1st January 1991 and 31st December 2016. From initial 1.75 million children born in this period, 1.38 million were included in the analyses after exclusion of multiple births, congenital malformations and newborns with missing information on maternal smoking status or co-variables. Information on head circumference and maternal weight and height, and maternal co-morbidities were available only for the years 2004 to 2016, reducing the cohort size to 659,157 mother-child pairs (Figure S1).

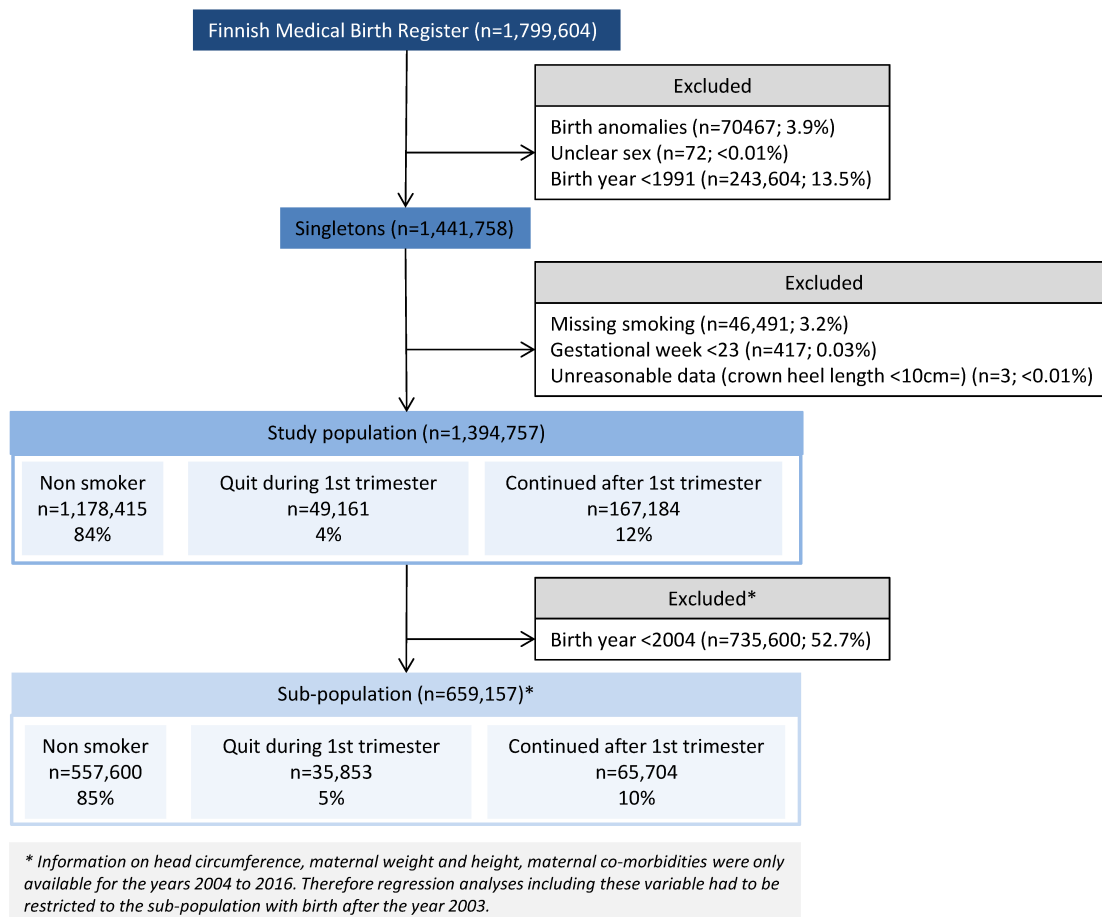


Figure S1. Data cleaning process with exclusion criteria and number of excluded children

2 Results

2.1 Study Power

The smallest detectable RR>1 (similar to OR at expected levels) was estimated using a 95% Confidence Interval (CI) and a study power of 90%. The calculations were done using R Statistical Software epiR package.

Table S1. Study power (lowest detectable OR>1) of the MATEX cohort (1991-2016) and sub-cohort (2004-2016) for endpoint studied in this work*

Incidence rate	Endpoint(s)	Complete MATEX cohort		Sub-cohort*	
		Quit smoking	Continued smoking	Quit smoking	Continued smoking
10%	Small for gestational age, body dis-proportionality	1.06	1.03	1.07	1.05
5%	Preterm birth (<37 weeks)	1.08	1.04	1.10	1.07
3%	Low birth weight (<2500 g)	1.11	1.06	1.29	1.10
1%	Moderately preterm birth (<28-33 weeks)	1.20	1.10	1.23	1.17
0.2%	Extremely preterm birth (<28 weeks), extremely low birth weight, (<1000 g)	1.47	1.24	Not analysed	Not analysed

* Head circumference available only for sub cohort; Sensitivity analyses (adjustment models) conducted only for sub-cohort due to data availability

Study power estimations have shown that the present cohort is large enough to detect RRs (similar to ORs in the present range) for the incidence levels and exposure levels in this work. The study size is sufficient for the evaluation of the association of continued maternal smoking and all endpoints including the rare endpoints (extremely low birth weight, extremely preterm birth) in the total MATEX cohort (1991-2016). Additionally, the study size of the sub-cohort (2004-2016) is sufficient to study the effects of continued maternal smoking.

2.2 Main Analyses

Of all women with singleton births included in this study (n=1,376,778), 84.5 % (n=1,163,225) were non-smokers, 3.5 % (n=47,819) quit smoking during the 1st trimester and 12.0 % (n=165,734) continued smoking after the 1st trimester. Smoking pregnant women tend to be younger and nulliparous, and prenatally exposed children tend to be born lighter (Table S2).

Table S2. Pregnancy and birth characteristics among all children and their mothers born in singleton births in Finland during 1991-2016 (n=1,376,778) according to maternal smoking status.

	All		Non smoker		Quit smoking during 1st trimester		Continued smoking after 1st trimester	
	n [^]		n [^]		n [^]		n [^]	
Mother	1,376,778		1,163,225	84 % (1,163,225)	47,819	3 % (47,819)	165,734	12 % (165,734)
		mean (SD)		mean (SD)		mean (SD)		mean (SD)
Age (years)	1,376,775	29.39 (5.34)	1,163,223	29.78 (5.16)	47,819	27.18 (5.43)	165,733	27.3 (5.83)
Pre-pregnancy weight (kg)*	631,504	66.82 (14.09)	533,712	66.65 (13.79)	35,156	67.81 (15.08)	62,636	67.72 (15.87)
Length (cm)*	634,743	165.53 (6.04)	536,266	165.64 (6.05)	35,386	165.32 (5.96)	63,091	164.76 (5.97)
Parity (nulliparous)	1,376,030	59.5 (818294)	1,162,606	39.4 (458010)	47,806	58.8 (28097)	165,618	43.2 (71629)
Socioeconomic status	1,376,778	% (count)	1,163,225	% (count)	47,819	% (count)	165,734	% (count)
Upper white collar worker		14.9 (205,770)		16.8 (195,402)		6.4 (3,081)		4.4 (7,287)
Lower white collar worker		36.4 (501,780)		37.4 (435,623)		30.9 (14,786)		31 (51,371)
Blue collar worker		15.1 (207,962)		13.2 (153,567)		19.2 (9,189)		27.3 (45,206)
Other		16.8 (231,481)		16.3 (189,157)		17.2 (8,229)		20.6 (34,095)
Missing		16.7 (229,785)		16.3 (189,476)		26.2 (12,534)		16.8 (27,775)
Socio demographics		% (count)		% (count)		% (count)		% (count)
Marital status (married or partnership)	1,366,007	62 (846,557)	1,154,817	66.8 (771,065)	47,514	35.9 (17,039)	163,676	35.7 (58,453)
Cohabiting (yes)	1,362,636	90.7 (123,6296)	1,153,511	92.5 (1,067,242)	47,470	84 (39,881)	161,655	79.9 (129,173)
Previous abortion (yes)	1,331,370	10.2 (135,153)	1,131,045	8.2 (92,580)	46,907	19.6 (9,172)	153,418	21.8 (33,401)
Previous stillbirth (yes)	1,376,136	0.7 (10,190)	1,162,685	0.7 (8,701)	47,808	0.5 (224)	165,643	0.8 (1,265)
Assisted pregnancy		% (count)		% (count)		% (count)		% (count)
Intrauterine insemination (yes)	1,376,778	0.3 (4,643)	1,163,225	0.4 (4,334)	47,819	0.3 (156)	165,734	0.1 (153)
Ovulation induction (yes)	1,376,778	1.0 (13,586)	1,163,225	1.1 (12,902)	47,819	0.7 (336)	165,734	0.2 (348)
Embryotransfer (yes)	1,376,778	0.5 (6,955)	1,163,225	0.6 (6,480)	47,819	0.5 (251)	165,734	0.1 (224)
Co-morbidities*		% (count)		% (count)		% (count)		% (count)
Pre-existing hypertension (ICD10 O10)	659,157	0.9 (5,922)	557,600	0.9 (5,117)	35,853	0.8 (279)	65,704	0.8 (526)
Pre-eclampsia superimposed on chronic hypertension (ICD10 O11)	659,157	0.04 (287)	557,600	0.4 (243)	35,853	0.04 (16)	65,704	0.04 (28)
Gestational oedema and proteinuria without hypertension (ICD10 O12)	659,157	0.4 (2,383)	557,600	0.3 (1,844)	35,853	0.5 (197)	65,704	0.5 (342)
Gestational hypertension (ICD10 O13)	659,157	2.9 (18,820)	557,600	2.8 (15,746)	35,853	3.7 (1,321)	65,704	2.7 (1,753)
Pre-eclampsia (ICD10 O14)	659,157	1.9 (12,264)	557,600	1.9 (10,446)	35,853	2.2 (801)	65,704	1.5 (1,017)
Unspecified maternal hypertension (ICD10 O16)	659,157	0.1 (686)	557,600	0.1 (558)	35,853	0.2 (81)	65,704	0.1 (47)
Diabetes mellitus in pregnancy (ICD10 O24)	659,157	10.2 (67,556)	557,600	10 (55,933)	35,853	12.6 (4,508)	65,704	10.8 (7,115)
Child		mean (SD)		mean (SD)		mean (SD)		mean (SD)
Gestational age (days)	1,376,778	278.66 (12.05)	1,163,225	278.74 (11.85)	47,819	279.34 (12.11)	165,734	277.87 (13.29)
Birth weight (g)	1,376,778	3549.45 (542.2)	1,163,225	3573.19 (536.38)	47,819	3540.62 (535.37)	165,734	3385.36 (556.1)
Crown-Heel length (cm)	1,376,778	50.21 (2.43)	1,163,225	50.32 (2.4)	47,819	50.12 (2.39)	165,734	49.5 (2.59)
Head circumference (cm)*	636,818	34.94 (1.64)	538,290	34.99 (1.62)	35,225	34.91 (1.65)	63,303	34.55 (1.71)
Preterm birth		% (count)		% (count)		% (count)		% (count)
Any preterm birth (<37 weeks)	1,376,778	4.3 (58,828)	1,163,225	4.1 (47,775)	47,819	4.3 (2,040)	165,734	5.4 (9,013)
Late preterm birth (34-36 weeks)	1,361,992	3.2 (44,042)	1,151,538	3.1 (36,088)	47,298	3.2 (1,519)	163,156	3.9 (6,435)
Moderately preterm birth (28-33 weeks)	1,329,578	0.9 (11,628)	1,124,641	0.8 (9,191)	46,204	0.9 (425)	158,733	1.3 (2,012)
Extremely preterm birth (<28 weeks)	1,321,108	0.2 (3,158)	1,117,946	0.2 (2,496)	45,875	0.2 (96)	157,287	0.4 (566)

Cont. Table S2

	All		Non smoker		Quit smoking during 1st trimester		Continued smoking after 1st trimester	
		% (count)		% (count)		% (count)		% (count)
Low/High birth weight								
Any low birth weight (<2500g)	1,333,851	3.0 (40,006)	1,124,351	2.7 (30,443)	46,458	3.0 (1,387)	163,042	5.0 (8,176)
Moderately low birth weight (1000-2500g)	1,330,491	2.8 (36,646)	1,121,691	2.5 (27,783)	46,355	2.8 (1,284)	162,445	4.7 (7,579)
Extremely low birth weight (<1000g)	1,297,205	0.3 (3,360)	1,096,568	0.2 (2,660)	45,174	0.2 (103)	155,463	0.4 (597)
High birth weight (>4500g)	1,334,899	3.1 (41,054)	1,131,073	3.3 (37,165)	46,384	2.8 (1,313)	157,442	1.6 (2,576)
Small for gestational age (<10th percentile)		% (count)		% (count)		% (count)		% (count)
Weight	1,375,578	11.5 (158,817)	1,162,258	10.4 (120,800)	47,792	13.6 (6,483)	165,528	19.1 (31,534)
Crown-Heel length	1,375,578	6.0 (81,869)	1,162,258	5.2 (60,003)	47,792	7.0 (3,345)	165,528	11.2 (18,521)
Head circumference (cm)*	636,620	10.9 (69,350)	538,130	10.1 (54,321)	35,213	13.3 (4,675)	63,277	16.4 (10,354)
Abnormal body proportions		% (count)		% (count)		% (count)		% (count)
High ponderal index	1,239,427	11.0 (136,918)	1,048,672	11.1 (116,902)	43,235	11.8 (5,111)	147,520	10.1 (14,905)
Low brain-to-body ratio*	573,360	11.1 (63,520)	487,052	11.2 (54,554)	31,731	12.5 (3,968)	54,577	9.2 (4,998)
High head-to-length ratio*	573,655	9.6 (60,358)	483,613	9.8 (49,830)	31,979	8.9 (3,560)	58,063	8.3 (6,960)

n[^] number of mother-child pairs with available information

* Available 2004-2016

Any maternal smoking was associated with an increased risk for SGA and body dis-proportionality (especially with small BBR), while preterm birth was only associated with smoking throughout pregnancy (did not quit smoking during the 1st trimester) (Table S3).

Table S3. Odds ratios and 95% confidence intervals for logistic regressions (adjusted for maternal age, parity, sex, socioeconomic status and gestational age (for birth weight outcomes), singletons only

	Crude		Adjusted	
	Quit smoking OR (95% CI)	Continued smoking OR (95% CI)	Quit smoking OR (95% CI)	Continued smoking OR (95% CI)
Preterm birth				
Preterm birth (<37 weeks)	1.04 (0.99-1.08)	1.34 (1.31-1.37)	1.00 (0.95-1.04)	1.38 (1.35-1.42)
Late preterm birth (34-36 weeks)	1.02 (0.97-1.08)	1.26 (1.23-1.30)	0.98 (0.93-1.03)	1.30 (1.26-1.33)
Moderately preterm birth (28-33 weeks)	0.93 (0.75-1.14)	1.61 (1.47-1.76)	0.93 (0.75-1.14)	1.72 (1.56-1.88)
Extremely preterm birth (<28 weeks)	0.93 (0.75-1.14)	1.61 (1.47-1.76)	0.93 (0.75-1.14)	1.72 (1.56-1.88)
Low birth weight				
Low birth weight (<2500 g)	1.10 (1.04-1.16)	1.89 (1.85-1.94)	1.10 (1.02-1.19)	2.22 (2.14-2.30)
Low birth weight (1000-2499 g)	1.12 (1.05-1.18)	1.92 (1.87-1.97)	1.10 (1.02-1.19)	2.22 (2.14-2.30)
Extremely low birth weight (<1000 g)	0.93 (0.76-1.13)	1.58 (1.44-1.73)	1.42 (0.48-3.77)	1.32 (0.82-2.10)
Small for gestational age (<10th percentile)				
Birth weight	1.35 (1.31-1.38)	2.02 (2.00-2.05)	1.04 (1.01-1.07)	2.06 (2.03-2.09)
Crown heel length	1.38 (1.33-1.43)	2.31 (2.27-2.35)	1.16 (1.12-1.20)	2.26 (2.22-2.30)
Head circumference*	1.36 (1.32-1.40)	1.74 (1.70-1.78)	1.03 (0.99-1.06)	1.64 (1.60-1.68)
Abnormal body proportions				
High ponderal index (>90th percentile)	1.06 (1.03-1.10)	0.89 (0.87-0.91)	1.19 (1.15-1.23)	1.26 (1.23-1.28)
Low brain-to-body ratio (<10th percentile)*	1.13 (1.09-1.17)	0.79 (0.77-0.82)	1.08 (1.04-1.12)	1.11 (1.07-1.15)
High head-to-length ratio (>90th percentile)*	1.11 (1.07-1.15)	1.20 (1.17-1.23)	1.09 (1.05-1.13)	1.22 (1.19-1.26)

* Available for years 2004-2016

The results supplement previously published risk estimates from the Finnish population with ORs for small for gestational age and body proportionality. (Table S4).

Table S4. MATEX study results and previously published Finnish results

	MATEX		Previous studies in Finland	
	Quit OR (95% CI)	Continued OR (95% CI)	Quit OR (95% CI)	Continued OR (95% CI)
Preterm birth				
Preterm birth (<37 weeks)	1.00 (0.95-1.04)	1.38 (1.35-1.42)	1.01 (0.95-1.07) [1] 1.03 (0.95-1.12) [2]	1.39 (1.36-1.43) [1] 1.36 (1.29-1.43) [2] 1.29 (1.27-1.34) [3]; <35years] 1.73 (1.61-1.85) [3]; >35years]
Late preterm birth (34-36 weeks)	0.98 (0.93-1.03)	1.30 (1.26-1.33)	1.0 (0.95-1.05) [4]	1.15 (1.11-1.18) [4]
Moderately preterm birth (28-33 weeks)	0.93 (0.75-1.14)	1.72 (1.56-1.88)	1.18 (1.02-1.36) [4]	1.23 (1.33-1.34) [4]
Extremely preterm birth (<28 weeks)	0.93 (0.75-1.14)	1.72 (1.56-1.88)	0.98 (0.8-1.19) [4]	1.21 (1.12-1.54) [4]
Low birth weight				
Low birth weight (<2500 g)	1.10 (1.02-1.19)	2.22 (2.14-2.30)	1.09 (1.02-1.16) [1]	2.02 (1.97-2.07) [1] 1.74 (1.68-1.80) [3]; <35years] 2.60 (2.43-2.78) [3]; >35years]
Low birth weight (1000-2499 g)	1.10 (1.02-1.19)	2.22 (2.14-2.30)		
Extremely low birth weight (<1000 g)	1.42 (0.48-3.77)	1.32 (0.82-2.10)		
Small for gestational age (10th percentile)				
Birth weight	1.04 (1.01-1.07)	2.06 (2.03-2.09)	1.16 (1.09-1.23) [1] 1.07 (1.00-1.15) [5] 0.96 (0.88-1.05) [2]	2.47 (2.41-2.53) [1] 2.34 (2.28-2.42) [5] 2.47 (2.35-2.59) [2] 2.14 (2.09-2.19) [3]; <35years] 2.38 (2.27-2.51) [3]; >35years]
Crown heel length	1.16 (1.12-1.20)	2.26 (2.22-2.30)		
Head circumference	1.03 (0.99-1.06)	1.64 (1.60-1.68)		
Abnormal body proportions				
High ponderal index (>90th percentile)	1.19 (1.15-1.23)	1.26 (1.23-1.28)		
Low brain-to-body ratio (<10th percentile)	1.08 (1.04-1.12)	1.11 (1.07-1.15)		
High head-to-length ratio (>90th percentile)	1.09 (1.05-1.13)	1.22 (1.19-1.26)		

1. Raisanen, S., U. Sankilampi, M. Gissler, M. R. Kramer, T. Hakulinen-Viitanen, J. Saari, and S. Heinonen. 2014. "Smoking Cessation in the First Trimester Reduces most Obstetric Risks, but Not the Risks of Major Congenital Anomalies and Admission to Neonatal Care: A Population-Based Cohort Study of 1,164,953 Singleton Pregnancies in Finland." *Journal of Epidemiology and Community Health* 68 (2): 159-164. doi:10.1136/jech-2013-202991 [doi].
2. Raisanen, S., M. R. Kramer, M. Gissler, J. Saari, and S. Heinonen. 2014. "Unemployment at Municipality Level is Associated with an Increased Risk of Small for Gestational Age Births--a Multilevel Analysis of all Singleton Births during 2005-2010 in Finland." *International Journal for Equity in Health* 13 (1): 1. doi:10.1186/s12939-014-0095-1 [doi].
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4. Raisanen, S., M. Gissler, J. Saari, M. Kramer, and S. Heinonen. 2013. "Contribution of Risk Factors to Extremely, very and Moderately Preterm Births - Register-Based Analysis of 1,390,742 Singleton Births." *PloS One* 8 (4): e60660. doi:10.1371/journal.pone.0060660 [doi].
5. Raisanen, S., M. Gissler, U. Sankilampi, J. Saari, M. R. Kramer, and S. Heinonen. 2013. "Contribution of Socioeconomic Status to the Risk of Small for Gestational Age Infants--a Population-Based Study of 1,390,165 Singleton Live Births in Finland." *International Journal for Equity in Health* 12: 28. doi:10.1186/1475-9276-12-28 [doi].

3 Sensitivity analyses

3.1 Stratification

We stratified the analyses by socioeconomic status and birth year to test the robustness of results. Socioeconomic status is correlated with general health behaviour, which may lead to differences in susceptibility for effects. We stratified by birth year because the chemical composition of cigarettes changed since 1991 with less nicotine and tar allowed.

3.2 Additional adjustment model

Maternal weight (kg) and height (m) have been included as continuous variables in the additional adjustment model. As binary (yes/no) variables have been included in the additional adjustment model: previous abortions, marital status (married or partnership), cohabiting, fertility treatment with embryo transfer (IVF: in vitro fertilisation, ICSI: intracytoplasmic sperm injection, FET: frozen embryo transfer), intrauterine insemination, ovulation induction. Maternal co-morbidities, which have been included in the confounding analyses are hypertension (ICD10 codes O10, O13 and O16), pre-eclampsia (ICD10 codes O11 and O14) and diabetes (ICD10 code O24).

We performed sensitivity analyses by including additional adjustment factors into the regression model for the years 2004 to 2016, for which additional confounding variables were recorded in the MBR.

- **Model A:**
 - *Preterm birth*: maternal age (continuous), sex, parity (nulli/multi), SES
 - *Birth weight (<2500g)*: maternal age (continuous), sex, parity (nulli/multi), gestational weeks (continuous), SES
 - *Small for gestational age (weight/length/head <10th percentile)*: maternal age (continuous), sex, parity (nulli/multi), SES
 - *Proportionality (ponderal index, brain:body ratio, head:length ratio)*: maternal age (continuous), sex, parity (nulli/multi), SES, weight z-score (not in head-length ratio)
- **Model B:** Basic model (Model A) plus maternal weight & maternal height, hypertension, pre-eclampsia and diabetes
- **Model C:** Basic model (Model A) plus marital status (married /partnership vs others), cohabiting, previous abortions, intrauterine insemination, in vitro fertilization and ovulation induction
- **Model D:** Model A + Model B + Model C

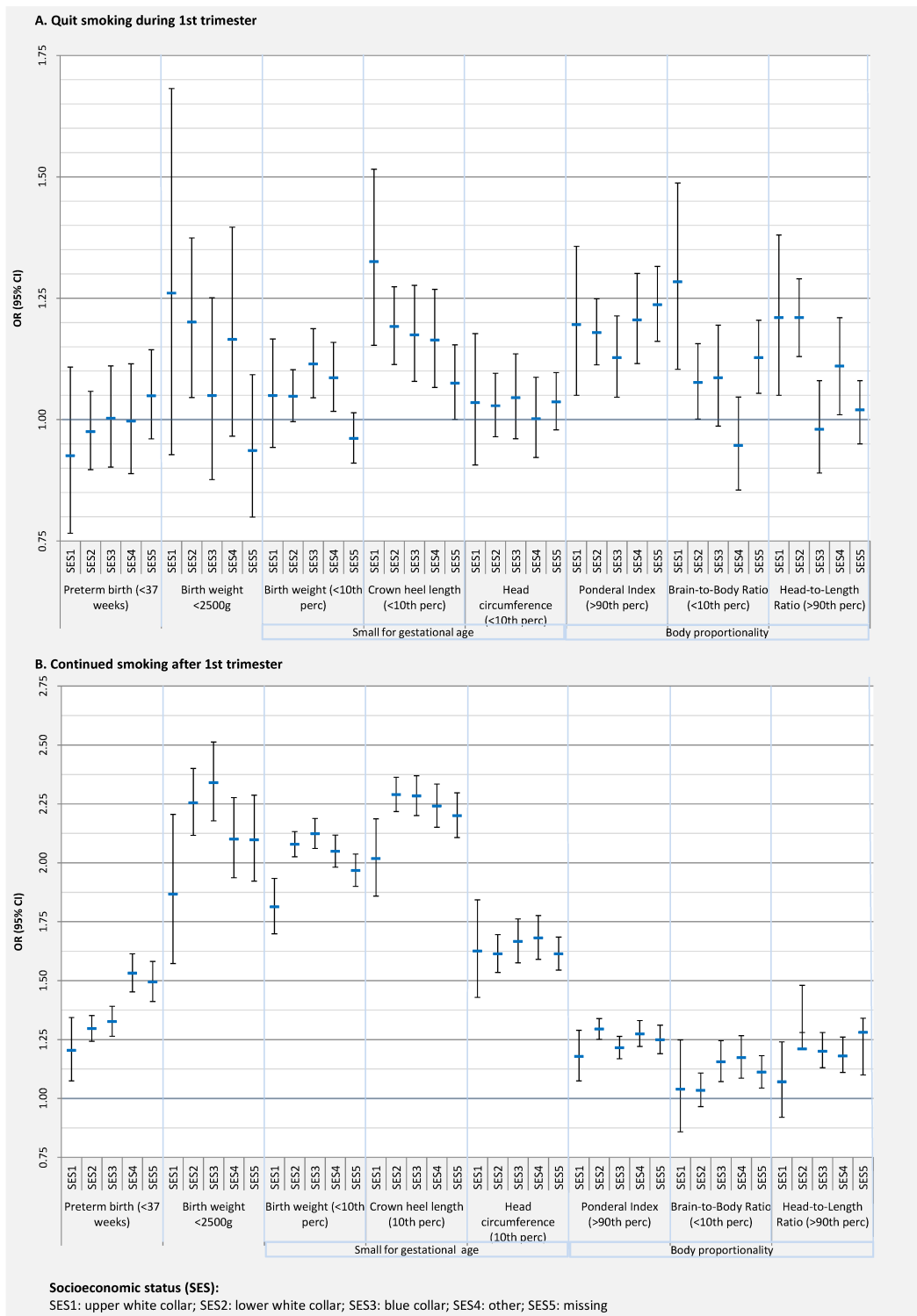


Figure S2. Association of maternal smoking and birth outcomes stratified by socioeconomic status. Pane A: quit smoking during 1st trimester; panel B: continued smoking after 1st trimester.

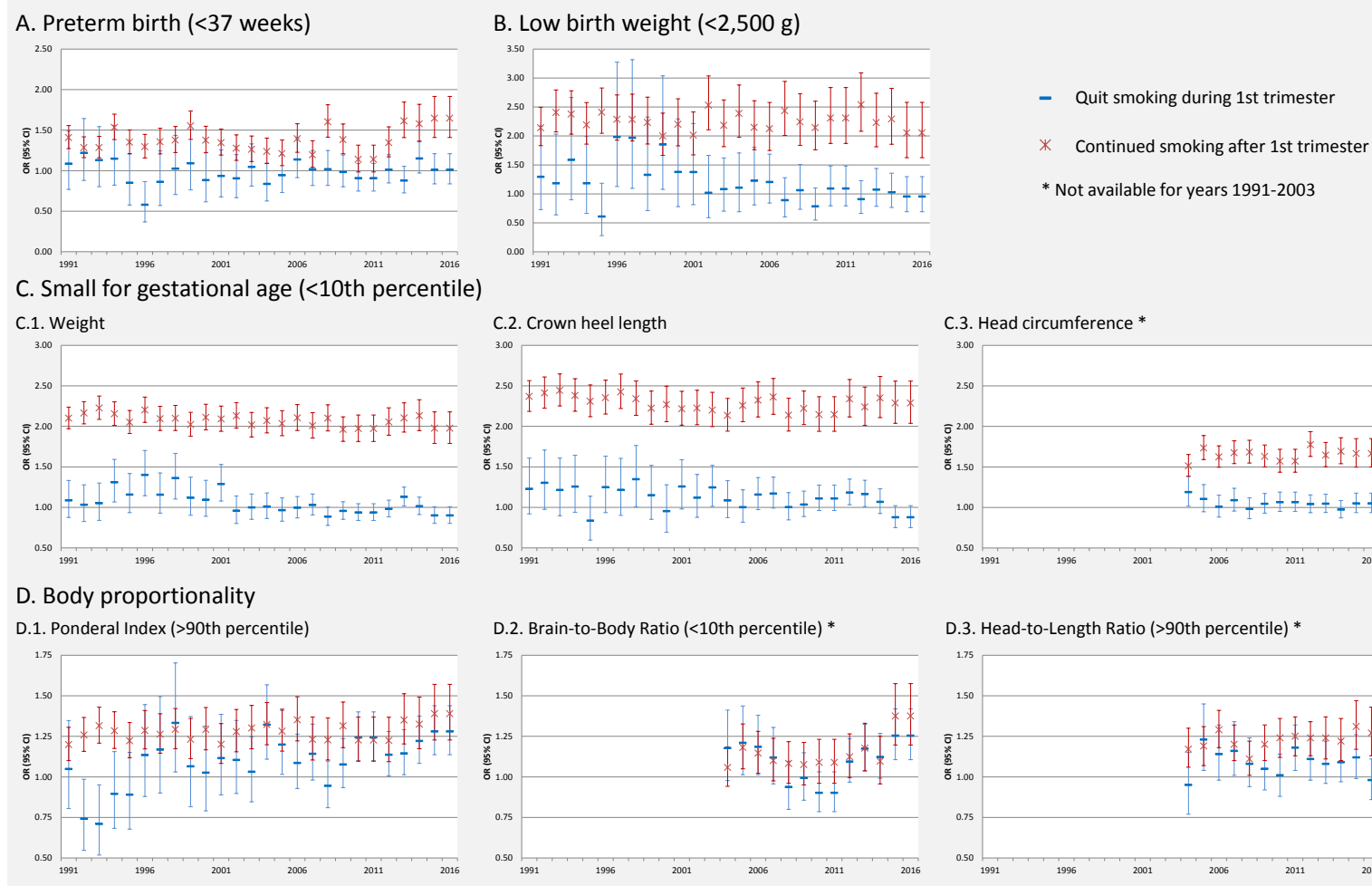


Figure S3. Association of maternal smoking with preterm birth (panel A), low birth weight (panel B), small for gestational age (panel C) and body proportionality (panel D) stratified by birth year

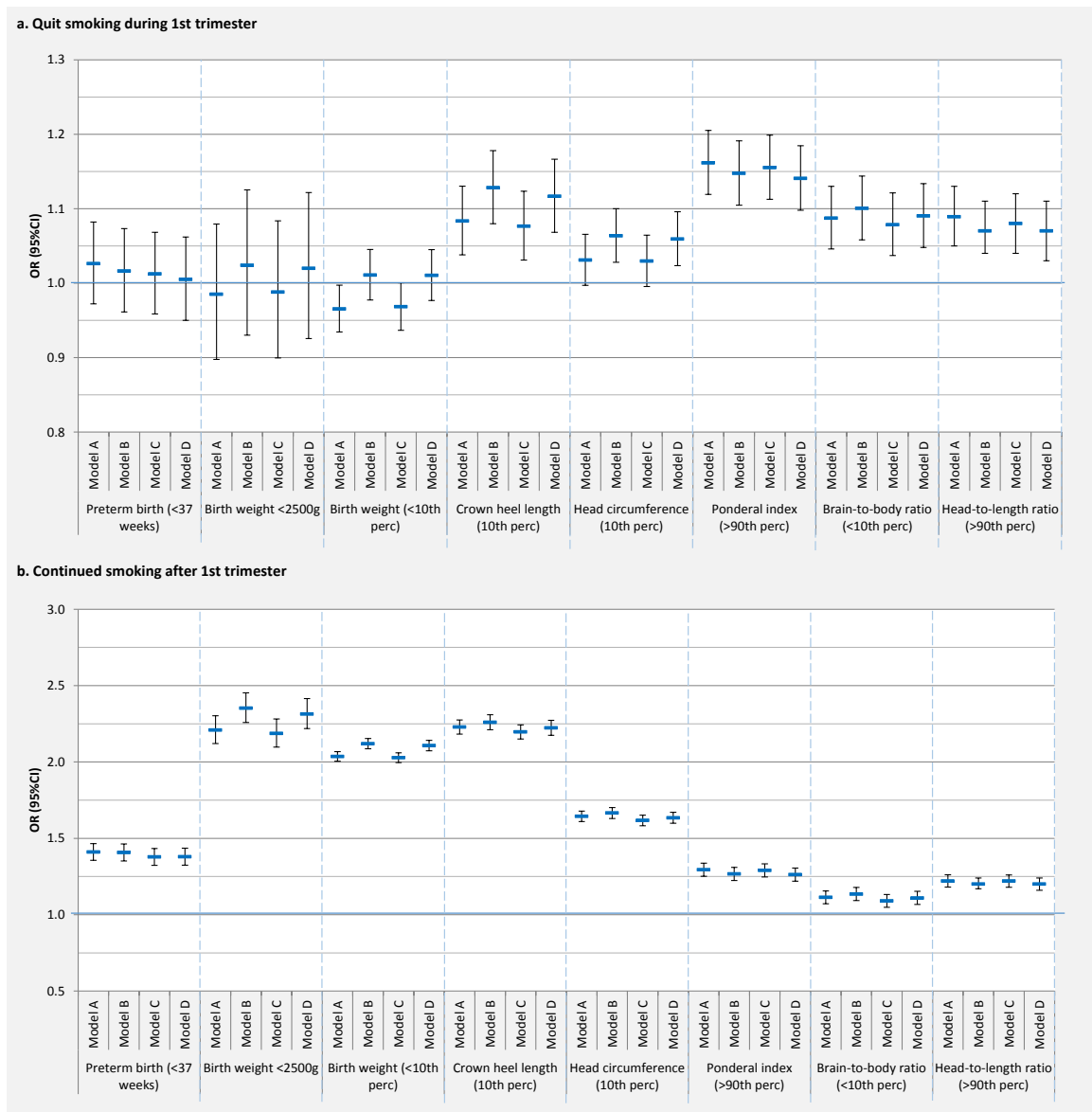


Figure S4. Results for a sensitivity analyses for additional adjustment models for regression on singletons births 2004-2016. Upper panel (a): quit smoking during 1st trimester, lower pane (b): continued smoking after 1st trimester:

3.3 Discussion

It has been shown that women, who smoke during pregnancy, are more likely to be deficient in prenatal care [1]. This may be a contributing factor for poorer pregnancy outcome in smoking women since complications may not be detected and treated as easily as in prenatal care compliant mothers. Furthermore, health discrepancies between the higher and lower socioeconomic groups leave the latter more vulnerable to pregnancy complications. Although the discrepancies decreased until 2000, they stayed stable for the last 15 years [2, 3]. However, maternal smoking was shown to be a good marker for other risk factors during pregnancy [4]. Stratification by socioeconomic group did not reveal significant differences in risk estimates between the socioeconomic groups, indicating that smoking during pregnancy itself was a good marker for overall unhealthy behaviour during pregnancy in the MATEX cohort.

The Finnish Tobacco Act (549/2016) has been updated during our study period, to limit tobacco advertisement and availability as well as restrict the non-private spaces where smoking is permitted. Additionally, the allowed tar, nicotine and carbon monoxide content of cigarettes has been reduced. Stratification by birth year did not reflect these legislative changes. For none of the endpoints a trend in the risk estimates was observed. This suggests that the amount of tobacco related chemicals, especially nicotine, inhaled by the pregnant women did not change substantially despite legislative efforts.

This work is solely based on routinely collected register data, which dictates the data availability. We tested our results for sensitivity to different adjustment models and our results were shown to be robust against maternal co-morbidities, maternal anthropometric indices, social background and reproductive history. We could not adjust for other factors of health behaviour (alcohol consumption, diet, physical activity), but we do not expect that adjustment for these factors would change our risk estimates. Smoking and socioeconomic status have been shown to correlate well with other lifestyle related factors and they are a reliable marker for the unaccounted factors [4].

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