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# BMJ Open

## Maternal smoking alters body proportions at birth: A register-based cohort study of 1.4 million births

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3 **Maternal smoking alters body proportions at birth: A register-based cohort study of 1.4**  
4 **million births**  
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## Altered body proportions at birth after maternal smoking during early pregnancy

### ABSTRACT

**Objectives:** In this work our aim was to study the effect of growth restriction on body proportions at birth in newborns exposed to maternal smoking at different time points during pregnancy.

**Design:** Register-based cohort study

**Setting:** Finnish Medical Birth Register

**Participants:** All singletons birth singleton births without congenital anomalies and missing data (1.34 million) born in Finland between 1st January 1991 and 31st December 2016

**Methods:** We examine the effects of self-reported, register recorded, smoking during early pregnancy in contrast to smoking in late pregnancy utilising the MATEX birth cohort. Logistic regression was used to quantify the effect of maternal smoking on the outcomes.

**Outcome measures:** Outcomes included reduced body size (birth weight, body length, and head circumference) and altered body proportions (indicated by high ponderal index (PI), low brain-to-body ratio (BBR), and high head-to- length ratio (HLR)) at birth.

**Results:** Smoking during pregnancy was associated with an increased risk for smaller body size and altered body proportions, as indicated by high PI (OR 1.26, 95% CI 1.23-1.28), low BBR (1.11, 1.07-1.15) and high HLR (1.22, 1.19-1.26). The effects were slightly more pronounced for smoking throughout pregnancy than for smoking only during early pregnancy.

**Conclusions:** Growth restriction in newborns associated with maternal smoking was found to change body proportions at birth with larger reduction of length and head circumference in comparison to weight. The effect by smoking only during early pregnancy or throughout pregnancy was similar, suggesting the importance of early pregnancy as a sensitive exposure window.

**KEYWORDS**

smoking, register research, growth restriction, prenatal, low birth weight, small for gestational age, pregnancy

**ABBREVIATIONS**

OR Odds ratio

PI Ponderal index (birth weight/length<sup>3</sup>)

BBR Brain: body ratio (indicator calculated using head circumference and birth weight)

HLR Head: length ratio (indicator calculated using head circumference and length)

SGA Small for gestational age (10<sup>th</sup> smallest percentile)

PTB Preterm birth

LBW Low birth weight

MBR Medical Birth Register

SES Socioeconomic status

IUGR Intrauterine growth restriction

CI Confidence interval

**STRENGTH AND LIMITATIONS OF THIS STUDY**

- The register-based design of this study provides a big study size to detect small risks and minimises risks for recall bias.
- In sensitivity analyses the results were shown to be robust when stratified by socioeconomic status and birth year, as well as additional adjustment models for sociodemographic factors and co-morbidities.
- Smoking status was self-reported during antenatal visits, leading to possible reporting bias.
- The register-based design restricted available information on lifestyle-related confounders.

## INTRODUCTION

Smoking during pregnancy increases the risk for adverse pregnancy outcomes. Adverse pregnancy outcomes are not only associated with complications in the neonatal period, but also long term, potentially throughout well into late adulthood.[1] Tobacco smoke contains thousands of chemicals, which can potentially cross the placental barrier and enter fetal circulation. Among them nicotine has a multitude of adverse effects on the development of organs including brain.[2] Other well-known fetotoxic chemicals of tobacco smoke include carbon monoxide, which can interfere with oxygen supply of the unborn child, and genotoxic and carcinogenic polycyclic aromatic hydrocarbons and tobacco-specific nitrosamines, which are teratogenic in animal studies.[3]

The association between maternal smoking and low birth weight, commonly defined as weight below 2,500g, is well established. In addition the susceptibility of anthropometric indices, such as body length, head size and abdominal circumference to maternal smoking is emerging.[4] Low birth weight as such does not hold information whether the reduction of weight is due to reduction due to loss of lean or fat body mass. Similarly, reduction in any other anthropometric indices alone, fails to identify altered in body proportions. Symmetrical in utero growth restriction (IUGR) is a stronger risk factor for later life morbidity and mortality than asymmetrical growth restriction with decreased amount of fat tissue.[5] Small for gestational age, used as a substitute for IUGR at birth, is not an optimal proxy.[6] This clearly demonstrates the importance of body proportions for future health in the newborn.

The effects of early smoking cessation on body size are less well studied. Smoking only during early pregnancy has been shown to be less harmful than continued smoking during late pregnancy. Previous, small studies indicated anthropometric indices in newborns only exposed during early pregnancy similar to those of non-smoking mothers [7], while current, bigger studies report increased risk for growth restriction even in foetuses exposed only during the 1<sup>st</sup> trimester.[8] There is insufficient data about anthropometric indices, other than birth weight, in those exposed only during early pregnancy in comparison with the newborn of non-smokers.[9]

The aim of our work was, using a register-based approach, to compare the effect of early or continued smoking during pregnancy on body proportions at birth associated with growth restriction induced by smoking. Additionally, we investigated the possibility of mechanistic interpretations of possible alterations in body proportions in newborns of smoking mothers.

## MATERIALS & METHODS

### Study design

To study the effect of maternal smoking on body size at birth we conducted a register-based cohort study utilising the Finnish MATEX cohort. The MATEX cohort was identified from the Finnish Medical Birth Register (MBR) described in more detail elsewhere.[10] This register contains perinatal outcomes, pregnancy characteristics and sociodemographic information for all live births and stillbirths after the 22<sup>nd</sup> gestational week or with a birth weight of at least 500g. The MBR receives information from standardised forms filled out by nurses and midwives during antenatal care visits and after the delivery of the baby.

This work focuses on the effects of maternal smoking on singleton pregnancies between 1<sup>st</sup> January 1991 and 31<sup>st</sup> December 2016. From initial 1.75 million mother-children pairs 1.38 million were included in the analyses after exclusion of multiple births, newborns with congenital anomalies and newborns with missing information on maternal smoking status or co-variables (Supplement, Figure S1).

We analysed the effect of maternal smoking on four groups of outcomes: (i) preterm birth (PTB); (ii) low birth weight (LBW); (iii) small anthropometric indices for gestational age, and (iv) body proportions. We analysed the effect of smoking during the 1<sup>st</sup> trimester only and smoking during later pregnancy separately with no smoking during pregnancy as a reference.

### Exposure

Maternal smoking data is recorded in the MBR during antenatal care visits as reported by the expectant women. In the MATEX cohort, smoking status is assigned as three categories: (1) non-smoker, (2) quit smoking during the 1<sup>st</sup> trimester, and (3) continued smoking after the 1<sup>st</sup> trimester. The trends in smoking during the study period have been described in detail elsewhere. [11]

### Outcomes

Term birth was defined as birth during gestational week 37 or later. Preterm birth (PTB) was categorised as all preterm (<37 weeks), late preterm (34-36 weeks), moderately preterm (28-33 weeks), extremely preterm (<28 weeks).

Low birth weight (LBW) was categorized in accordance with ICD10 diagnosis criteria as generally low (<2,500g), low (1,000-2,500g), and extremely low (<1,000g). As reference



category normal weight was defined as 2,500-4,500g, excluding high birth weight according to ICD10 definition.

In this work we use “small for gestational age” (SGA) as a general expression to describe the measurement of each anthropometric index below a cut-off at 10<sup>th</sup> percentile. It was included as an endpoint to take into account the impact of gestational age on body size. It was defined based on sex- and parity-specific mean and standard deviation for the corresponding gestational week as reported in the Finnish standard reference population.[12] SGA was defined separately for three anthropogenic indices: Birth weight, crown-heel length and head circumference.

Body proportionality was assessed by putting all three anthropometric indices into relation to each other using ponderal index (PI), brain: body ratio (BBR) and head: length ratio (HLR).

PI was calculated using birth weight in grams and crown-heel length in cm (Equation 1). It was categorized normal (10-90<sup>th</sup> percentile, used as the reference) and high (>90<sup>th</sup> percentile) of the study population. The lowest 10<sup>th</sup> percentile was excluded.

*Equation 1.*

$$PI = 100 \times \frac{\text{birth weight [g]}}{\text{crown heel length [cm]}^3}$$

BBR was calculated based on head circumference in cm and birth weight in grams (Equation 2). It was categorized as low (<10<sup>th</sup> percentile) and normal (10-90<sup>th</sup> percentile, reference) of the study population. The 90<sup>th</sup> percentile was excluded.

*Equation 2.*

$$BBR = 100 \times \frac{0.037 \times \text{head circumference [cm]}^{2.57}}{\text{birth weight [g]}}$$

BBR is an indicator of head-to-body proportionality, and is defined as the percentage of the infant's birth weight that is estimated to reside in the brain. The nominator of the formula is the estimation of the brain weight according to the National Institute of Neurological and Communicative Disorders and Stroke's Collaborative Perinatal Project.[13]

HLR was calculated using head circumference in grams and crown-heel length in cm (Equation 3). It was categorized normal (10-90<sup>th</sup> percentile, reference) and high (>90<sup>th</sup> percentile) of the study population. The lowest 10<sup>th</sup> percentile was excluded.

### Equation 3.

$$HLR = \frac{\text{head circumference [cm]}}{\text{crown - heel length [cm]}}$$

HLR is a second indicator of head-to-body proportionality, and is defined as ratio between head circumference and crown-heel length in order to estimate the proportionality between head size and body length.

Percentiles of indices for body proportionality were calculated for each gestational week separately.

### Covariates

Maternal age and gestational age in weeks were used as continuous variables in the regression models. Parity was defined as null- or multiparous. Sex was defined as male or female. Socioeconomic status (SES) was categorized as upper white collar (upper level employees with administrative, managerial, professional and related occupations), lower white collar (lower level employees with administrative and clerical occupations), blue collar (manual workers) and others (farmers, self-employed, students, pensioners, no information) based on the Finnish national classification of occupations.[14] An additional category (information missing) was added to this classification.

### Statistical analyses

Multiple logistic regressions were performed to estimate ORs with 95% confidence intervals (CI). The regression models were adjusted for potential confounders (Table 1). The data were analysed using R Statistical software (version 3.4.3). The smallest detectable was estimated using a 95% CI and a study power of 90%. The calculations were done using R Statistical Software epiR package (Supplement, Table S1).

### Ethics approval and register data permit

In accordance with the Finnish Medical Research Act (1999/488) the MATEX study including the birth cohort identified from the MBR has been evaluated and approved by the ethics committee of the Northern Ostrobothnia Hospital District (EETTMK 44/2016; issued

18th April 2016). The right to use of register data held by the National Institute for Health and Welfare was granted under the document number THL/838/6.02.00/2016 (issued 22nd June 2016). Due to the full register-based design of the study, no informed consent is required from the study participants according to the Finnish Personal Data Act 1050/2018.

### Patient and Public Involvement

No patients were involved in the design, recruitment or conduct of the study. The utilised register data are routinely collected.

### RESULTS

Of all women with singleton births included in this study (n=1 376 778), 84.5% were non-smokers, 3.5% quit smoking during the 1<sup>st</sup> trimester and 12.0% continued smoking after the 1<sup>st</sup> trimester. Smoking pregnant women tend to be younger and nulliparous (Supplement, Table S2).

Any maternal smoking was associated with an increased risk for SGA and altered body proportions, while PTB was only associated with smoking throughout pregnancy (Table 1, Fig 1).

**Table 1.** Summary of studied association of maternal smoking and preterm birth, anthropogenic indices and indices for altered body proportions and possible interpretations of change

Endpoint	Definition	Smoking	No. of mother-child pairs included in the regression	OR (95%CI)	Adjustment	Interpretation
<b>Preterm birth</b>	Gestational age < 37 weeks	quitted	1 210 410	1.00 (0.95-1.04)	maternal age, sex, parity, SES	born earlier than peers
		continued	1 286 667	1.38 (1.35-1.42)		
<b>Low birth weight</b>	Weight <2500g	quitted	1 170 187	1.10 (1.02-1.19)	maternal age, sex, parity, gestational weeks, SES	overall small (symmetrical growth restriction) or thin (asymmetrical growth restriction) child
		continued	1 328 221	2.22 (2.14-2.30)		
<b>Small for gestational age</b>						
<b>Weight</b>	<10 <sup>th</sup> percentile of weight at	quitted	1 210 048	1.04 (1.01-1.07)	maternal age, sex, parity,	lower weight than peers

	corresponding gestational week	continued	1 327 783	2.06 (2.03-2.09)	SES	
<b>Crown heel length</b>	<10 <sup>th</sup> percentile of length at corresponding gestational week	quitted	1 210 048	1.16 (1.12-1.20)	maternal age, sex, parity, SES	shorter than peers
		continued	1 327 783	2.26 (2.22-2.30)		
<b>Head circumference</b>	<10 <sup>th</sup> percentile of head circumference at corresponding gestational week	quitted	573 343	1.03 (0.99-1.06)	maternal age, sex, parity, SES	smaller head than peers
		continued	601 407	1.64 (1.60-1.68)		
<b>Body proportions</b>						
<b>Ponderal index</b>	>90 <sup>th</sup> percentile of weight:length ratio at corresponding gestational week	quitted	1 088 451	1.19 (1.15-1.23)	maternal age, sex, parity, SES, weight z-score	more weight for lengths (chubby) than peers
		continued	1 196 479	1.26 (1.23-1.28)		
<b>Brain:body ratio<sup>a</sup></b>	<10 <sup>th</sup> percentile of weight:head circumference ratio at corresponding gestational week	quitted	518 704	1.08 (1.04-1.12)	maternal age, sex, parity, SES, weight z-score	more weight for head size (small head) than peers
		continued	541 549	1.11 (1.07-1.15)		
<b>Head:length ratio<sup>a</sup></b>	>90 <sup>th</sup> percentile of head circumference:length ratio at corresponding gestational week	quitted	521 420	1.09 (1.05-1.13)	maternal age, sex, parity, SES	bigger head for length (shorter) than peers
		continued	547 597	1.22 (1.19-1.26)		

<sup>a</sup> Available 2004-2016

quitted: Quitted smoking during 1<sup>st</sup> trimester

continued: Continued smoking after the 1<sup>st</sup> trimester

SES Socioeconomic status

Maternal smoking increased the risk for low birth weight (LBW, <2,500g). Smoking throughout pregnancy doubled the risk for LBW (OR 2.22, 95% CI 2.14-2.30). Smoking cessation during early pregnancy is associated with an increased risk for LBW (OR 1.10, 95% CI 1.02-1.19), albeit not as strong as with continued smoking.

Smoking during pregnancy was associated with an increased risk for SGA (<10<sup>th</sup> percentile) in the weight and crown-heel dimension. Mothers who quitted smoking during early pregnancy were at elevated, but not statistically significant risk for giving birth to a child with a small head circumference. Among the mothers who continued smoking throughout pregnancy the risk for small head circumference was clearly increased with an OR of 1.64 (95% CI 1.60-1.68).

The risk for altered body proportions was significantly increased by maternal smoking. A stronger increase in risk was observed for high PI and high HLR than for low BBR. ORs were consistently higher for continued smoking after the 1<sup>st</sup> trimester than among those who quitted

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3 smoking during the 1<sup>st</sup> trimester. Nevertheless, smoking only during early pregnancy was  
4 associated with statistically significantly increased risks for altered body proportions.  
5 Especially the risk for BBR was almost similar in those exposed only during the 1<sup>st</sup> trimester  
6 and those exposed throughout pregnancy (Fig 1).  
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13 **Fig 1** Adjusted Odds Ratio for preterm birth, low birth weight, small for gestational age and  
14 altered body proportions; adjusted for maternal age, sex, parity, socioeconomic status; marker  
15 + error bar: OR (95% CI), grey bars: number of cases included in the regression  
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22 We stratified the analysis by socioeconomic status (SES) in order to investigate the influence  
23 of lifestyle factors and health behaviours that correlate with SES. Stratification by SES did  
24 not show statistically significant differences in the risk estimates (Supplement, Figure S2).  
25 We stratified the data by birth year to investigate potential influence of changes in tobacco  
26 composition and social acceptability of smoking during the study period on the risk estimates.  
27 Stratification by birth year did not indicate a clear temporal pattern in any of the analysed  
28 endpoints (Supplement, Figure S3). Sensitivity analysis was performed to test the robustness  
29 of results against choice of adjustment factors in the regression model. Different adjustment  
30 models did not significantly alter the risk estimates for any of the reported endpoints  
31 (Supplement, Figure S4).  
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## 42 **DISCUSSION**

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44 In this work we investigated the effect of smoking during early and late pregnancy on body  
45 size and proportions at birth. The most important finding of our study is that although the risk  
46 for low birth weight decreases by smoking cessation during the first trimester, brain size and  
47 crown-heel length in relation to body weight seem not to catch up. All anthropometric indices  
48 showed signs of growth restriction and body proportions were altered in newborns exposed to  
49 maternal smoking only during the 1<sup>st</sup> trimester.  
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55 This work indicated a difference in susceptibility for growth restriction between the  
56 anthropometric indices. The association with PI suggests a stronger reduction in length than in  
57 weight. Similarly, the association with low BBR suggests reduction rather in brain size than in  
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3 weight. However, the association of maternal smoking with high HLR suggests a stronger  
4 reduction in length than in head size. It is in line with previous research showing that smoking  
5 during pregnancy predominantly affect lean body mass and not fat body mass.[4] Although  
6 risks are lower in newborns whose mothers quit smoking during the 1<sup>st</sup> trimester than in those  
7 who continued smoking, suggest a direct effect of maternal smoking on cell proliferation  
8 during organogenesis in early prenatal development. Insults during this period are persistent  
9 throughout life.[5] This stresses the importance of smoking cessation before pregnancy since  
10 even smoking only during very early pregnancy has potentially a devastating effect on the  
11 long term health of the unborn child.

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19 The importance of body proportions at birth has been demonstrated by Zanelli and co-  
20 workers.[15] They showed that newborns with high ponderal index are more likely to develop  
21 coronary heart disease as obese adults than their peers, who were born small but not thin. It is  
22 not possible to infer from our study whether the high PI and higher risk for shorter crown-heel  
23 length is comparable to stunting due to malnutrition and infections. Mechanistic studies of the  
24 overserved effects are needed to extrapolate the risk to later life.

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31 Additionally, it was shown that the smaller head circumference directly translates into a  
32 smaller brain.[16, 17] The insults during early development of the brain result in differences  
33 in DNA methylation, altered gene expression of regulatory genes of brain structure and  
34 function by maternal smoking,[18] and neuronal content of the brain,[19] as well as  
35 neurophysiological functions and overall brain function are altered due to prenatal  
36 smoking.[20] The smaller brain volume observed in newborns has been shown to be  
37 persistent into young adulthood.[21]

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43 Overall our results are in line with previously reported studies by other groups (Supplement,  
44 Table 4).[22-25] Smoking cessation during the 1<sup>st</sup> trimester has a weaker effect on reduction  
45 in weight or length measures, whereas smoking especially at the end of pregnancy reduces  
46 femur length, abdominal circumference and biparietal diameter.[26] A clear dose response of  
47 cigarettes per day and low birth weight and ponderal index has been demonstrated.[17, 27]  
48 Previous studies examining the effect of smoking cessation during pregnancy consistently  
49 reported a reduction in harm compared with continued smoking.[4]

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60 There is increasing evidence from animal studies of nicotine as a causative agent for  
reproductive toxicity, including detrimental effects on brain.[28, 29] In a large  
epidemiological study, among the few existing ones, aberrations in lung development due to

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3 nicotine replace product (NCP) use during pregnancy has already been suggested.[30]  
4 Epidemiological studies on the effects of nicotine products, other than cigarettes, are needed  
5 in order to give informed recommendations to pregnant women who wish to quit smoking.  
6 We recommend the inclusion of information on the use of nicotine products in the MBR. This  
7 would allow detecting pregnancies at risk more reliably and facilitating epidemiological  
8 research on nicotine exposure during pregnancy beyond maternal smoking.  
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14 This work is solely based on routinely collected register data, which dictates the data  
15 availability. We tested our results for sensitivity to different adjustment models and our  
16 results were shown to be robust against maternal co-morbidities, maternal anthropometric  
17 indices, social background and reproductive history. Smoking and socioeconomic status have  
18 been shown to correlate well with other lifestyle related factors and they are a reliable marker  
19 for the unaccounted factors.[31] It was not possible to analyse the impact of timing of  
20 smoking cessation in more detail or possible dose response relationships due to lack of data.  
21 In addition, we lack information on paternal and household smoking. Second hand tobacco  
22 smoke exposure during pregnancy has been shown to increase the risk for low birth weight  
23 and growth restriction.[32]. We cannot exclude the possibility that some observed effects are  
24 partly attributable to second hand tobacco smoke exposure, especially in those women who  
25 ceased smoking during their 1<sup>st</sup> trimester.  
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36 Strength of this work is the register-based design with, to our knowledge, the biggest study  
37 population. Overall, the MBR data, including the smoking information, have been shown to  
38 be reliable.[33-35] SES was assigned solely on maternal occupation and no information about  
39 the father's occupation was available. For a high proportion of mothers (18%) the occupation  
40 was not available. Previous studies applied the same SES categorization and showed that the  
41 missing information did not bias the proportions in the other SES categories.[24] Overall,  
42 occupation is well correlated with education and income in Finland and it can be used as an  
43 indicator for socioeconomic health differences.[33]  
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## 52 CONCLUSIONS

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54 This study shows that growth restriction by maternal smoking during pregnancy is not  
55 proportional. Maternal smoking was associated with a stronger reduction in crown-heel length  
56 and head circumference than weight. It seems that especially brain is suffering as judged by  
57 the more extensive reduction of head circumference than weight. The effects were more  
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3 pronounced for smoking throughout pregnancy than for smoking only during early pregnancy.  
4 Although quitting smoking during early pregnancy reduced the risk for preterm birth to  
5 background level, the association with generalized reduction in all anthropometric indices and  
6 changed body proportions stresses the importance of the period of early prenatal development  
7 and the limited potential to repair damages induced in early pregnancy.  
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12 Animal studies suggest nicotine as a potential causative agent, which questions the safety of  
13 nicotine replacement therapy during pregnancy. It is highly important to study the association  
14 of growth restriction and other adverse effects with the use of nicotine therapy products. Until  
15 their safety has been proven, caution should be taken and nicotine therapy products should not  
16 be recommended for pregnant women as safer alternative to active smoking. Routine  
17 collection of information on the use of nicotine replacement products in the Medical Birth  
18 Register is needed for more careful follow-up of risk pregnancies and to facilitate scientific  
19 research on specific effects associated with nicotine replacement products.  
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#### 44 **CONTRIBUTORS**

45 IKR, OH, KV and MV conceived the research question and designed the study. IKR  
46 conducted statistical analysis, interpreted the results and wrote the first and subsequent drafts  
47 of the manuscript with support of OH. KV, MV, MG and HdR contributed to data  
48 interpretation and revisions of the manuscript. MV, OH, KV and IKR obtained funding. All  
49 authors approved the final version of the submitted manuscript.  
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#### 58 **COMPETING INTERESTS**



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3 Kirsi Vähäkangas is currently the chair of the scientific committee of the Savuton Suomi  
4  
5 (Smoke-free Finland) 2030 initiative. Other authors declare no competing interests.  
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#### 33 **DISCLAIMER**

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35 None of the funding agencies had a role in n the study design; in the collection, analysis and  
36 interpretation of the data; in the writing of the report; and in the decision to submit the paper  
37 for publication.  
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#### 45 **DATA SHARING STATEMENT**

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47 Data may be obtained from a third party and are not publicly available. The Finnish National  
48 Institute of Health and Welfare is controller of the Medical Birth Register. Data may be  
49 obtained from the register controller ([https://thl.fi/en/web/thlfi-en/statistics/information-on-](https://thl.fi/en/web/thlfi-en/statistics/information-on-statistics/register-descriptions/newborns)  
50 [statistics/register-descriptions/newborns](https://thl.fi/en/web/thlfi-en/statistics/information-on-statistics/register-descriptions/newborns) accessed 29 May 2019).  
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#### 57 **PATIENT CONSENT**

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59 Not required.  
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## ETHICAL APPROVAL

The study was approved by the ethics committee of the Northern Ostrobothnia Hospital District (EETTMK 44/2016; issued 18th April 2016). The right to use of register data held by the National Institute for Health and Welfare was granted under the document number THL/838/6.02.00/2016 (issued 22nd June 2016).

## WORD COUNT

3210 words (Introduction to Conclusions)

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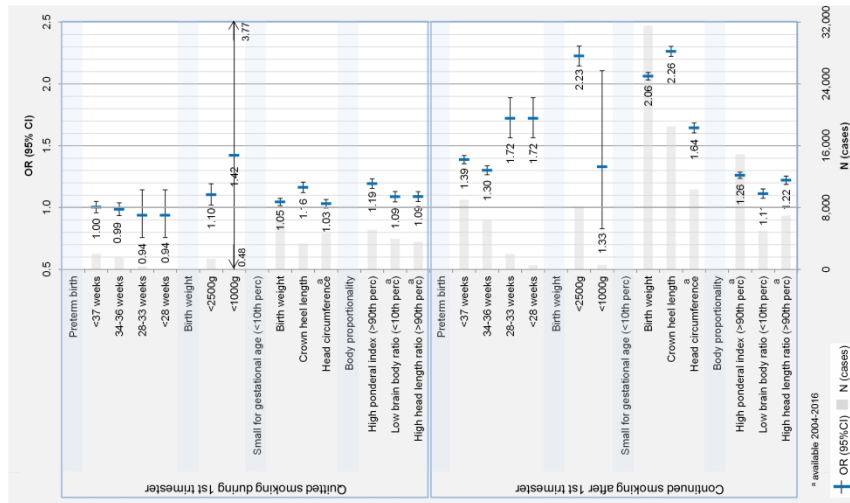
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**TABLE**

**Table 1.** Summary of observed association of maternal smoking and preterm birth, anthropogenic indices and indices for body proportionality and possible interpretations of change

**FIGURE LEGEND**

**Fig 1** Adjusted Odds Ratio for Preterm birth, low birth weight, small for gestational age and body proportionality; adjusted for maternal age, sex, parity, socioeconomic status; marker + error bar: OR (95% CI), columns: number of cases included in the regression



254x190mm (300 x 300 DPI)

# Supplement

## Maternal smoking alters body proportions at birth: A register-based cohort study of 1.4 million births

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## 1 Abstract

**Background:** Association of low birth weight with maternal smoking is well established. Moreover, symmetrical intrauterine growth restriction of children has been shown to increase susceptibility for complications later in life. In this work our aim was to study the effect of growth restriction on body proportions at birth in newborns exposed to maternal smoking at different time points during pregnancy.

**Methods:** In this register-based cohort study we examine the effects of self-reported smoking during early pregnancy in contrast to smoking in late pregnancy utilising the MATEX birth cohort (n=1.4 million singleton births). Outcomes included reduced body size (birth weight, body length, and head circumference) and altered body proportions (indicated by high ponderal index (PI), low brain-to-body ratio (BBR), and high head-to-length ratio (HLR)) at birth. Logistic regression was used to quantify the effect of maternal smoking on the outcomes.

**Results:** Smoking during pregnancy was associated with an increased risk for smaller body size and altered body proportions, as indicated by high PI (OR 1.26, 95% CI 1.23-1.28), low BBR (1.11, 1.07-1.15) and high HLR (1.22, 1.19-1.26). The effects were slightly more pronounced for smoking throughout pregnancy than for smoking only during early pregnancy.

**Conclusions:** Growth restriction in newborns associated with maternal smoking was found to change body proportions at birth with larger reduction of length and head circumference in comparison to weight. The effect by smoking only during early pregnancy or throughout pregnancy was similar, suggesting the importance of early pregnancy as a sensitive exposure window.

## 2 Data cleaning

### 2.1 Study population

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

This work focuses on the effects of maternal smoking on singleton pregnancies born between 1<sup>st</sup> January 1991 and 31<sup>st</sup> 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 (Figure S1).

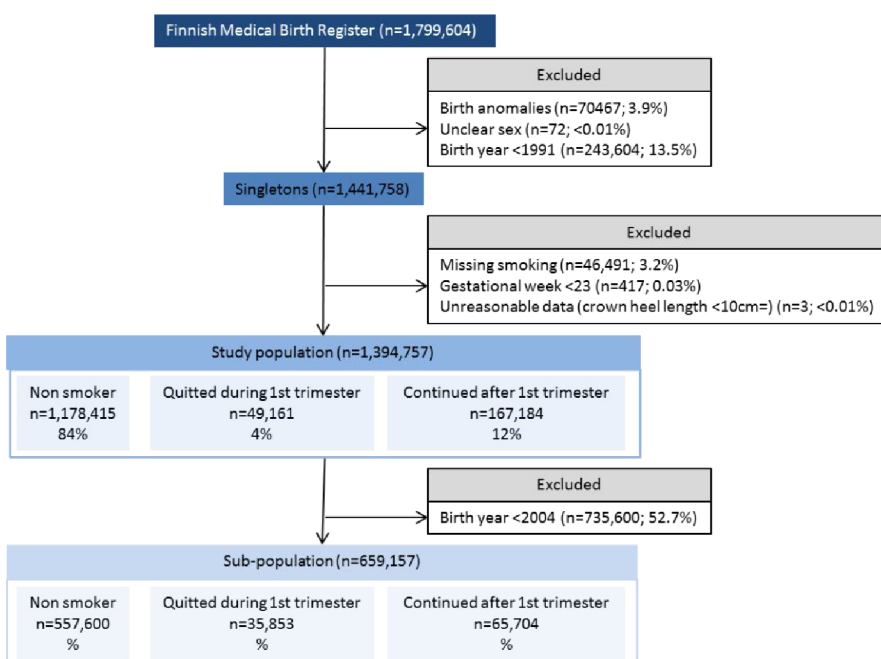


Figure S1. Data cleaning process with exclusion criteria and number of excluded children

### 3 Results

#### 3.1 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*	
		Quitted smoking	Continued smoking	Quitted 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 (<2500g)	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, (<1000g)	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.

### 3.2 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 1<sup>st</sup> trimester and 12.0% (n=165,734) continued smoking after the 1<sup>st</sup> 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	mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)
<b>Mother</b>		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)

Cont. Table 2

Child	All		Non smoker		Quitted smoking during 1st trimester		Continued smoking after 1st trimester	
	n	mean (SD)	n	mean (SD)	n	mean (SD)	n	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)
Low/High birth weight		% (count)		% (count)		% (count)		% (count)
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)
Proportionality		% (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: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:length ratio*	573,5638	9.6 (60,358)	483,613	9.8 (49,830)	31,979	8.9 (3,560)	58,063	8.3 (6,960)

\* 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 1<sup>st</sup> trimester) (Table S3).

*Table S3. Singleton births Odds ratio and 95% Confidence interval for logistic regression (adjusted for maternal age, parity, sex, socioeconomic status and gestational age (for birth weight outcomes))*

	Crude		Adjusted	
	Quitted smoking OR (95%CI)	Continued smoking OR (95%CI)	Quitted smoking OR (95%CI)	Continued smoking OR (95%CI)
<b>Preterm birth</b>				
<b>Preterm birth (&lt;37 weeks)</b>	1.04 (0.99-1.08)	1.34 (1.31-1.37)	1.00 (0.95-1.04)	<b>1.38 (1.35-1.42)</b>
<b>Late preterm birth (34-36 weeks)</b>	1.02 (0.97-1.08)	1.26 (1.23-1.30)	0.98 (0.93-1.03)	<b>1.30 (1.26-1.33)</b>
<b>Moderately preterm birth (28-33 weeks)</b>	0.93 (0.75-1.14)	1.61 (1.47-1.76)	0.93 (0.75-1.14)	<b>1.72 (1.56-1.88)</b>
<b>Extremely preterm birth (&lt;28 weeks)</b>	0.93 (0.75-1.14)	1.61 (1.47-1.76)	0.93 (0.75-1.14)	<b>1.72 (1.56-1.88)</b>
<b>Low/High birth weight</b>				
<b>Low birth weight (&lt;2500g)</b>	1.10 (1.04-1.16)	1.89 (1.85-1.94)	<b>1.10 (1.02-1.19)</b>	<b>2.22 (2.14-2.30)</b>
<b>Low birth weight (1000-2500g)</b>	1.12 (1.05-1.18)	1.92 (1.87-1.97)	<b>1.10 (1.02-1.19)</b>	<b>2.22 (2.14-2.30)</b>
<b>Extremely low birth weight (&lt;1000g)</b>	0.93 (0.76-1.13)	1.58 (1.44-1.73)	1.42 (0.48-3.77)	1.32 (0.82-2.10)
<b>High birth weight (&gt;4500g)</b>	0.85 (0.81-0.90)	0.48 (0.47-0.50)	0.99 (0.94-1.05)	<b>0.50 (0.48-0.52)</b>
<b>Small for gestational age (10th percentile)</b>				
<b>Birth weight</b>	1.35 (1.31-1.38)	2.02 (2.00-2.05)	<b>1.04 (1.01-1.07)</b>	<b>2.06 (2.03-2.09)</b>
<b>Crown heel length</b>	1.38 (1.33-1.43)	2.31 (2.27-2.35)	<b>1.16 (1.12-1.20)</b>	<b>2.26 (2.22-2.30)</b>
<b>Head circumference*</b>	1.36 (1.32-1.40)	1.74 (1.70-1.78)	1.03 (0.99-1.06)	<b>1.64 (1.60-1.68)</b>
<b>Body proportionality</b>				
<b>High ponderal index (&gt;90th percentile)</b>	1.06 (1.03-1.10)	0.89 (0.87-0.91)	<b>1.19 (1.15-1.23)</b>	<b>1.26 (1.23-1.28)</b>
<b>Low brain:body ratio (&lt;10th percentile)*</b>	1.13 (1.09-1.17)	0.79 (0.77-0.82)	<b>1.08 (1.04-1.12)</b>	<b>1.11 (1.07-1.15)</b>
<b>High head:length ratio (&gt;90th percentile)*</b>	1.11 (1.07-1.15)	1.20 (1.17-1.23)	<b>1.09 (1.05-1.13)</b>	<b>1.22 (1.19-1.26)</b>

\* 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	
	Quitted OR (95%CI)	Continued OR (95%CI)	Quitted OR (95%CI)	Continued OR (95%CI)
<b>Preterm birth</b>				
<b>Preterm birth (&lt;37 weeks)</b>	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]
<b>Late preterm birth (34-36 weeks)</b>	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]
<b>Moderately preterm birth (28-33 weeks)</b>	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]
<b>Extremely preterm birth (&lt;28 weeks)</b>	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]
<b>Low/High birth weight</b>				
<b>Low birth weight (&lt;2500g)</b>	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]
<b>Low birth weight (1000-2500g)</b>	1.10 (1.02-1.19)	2.22 (2.14-2.30)		
<b>Extremely low birth weight (&lt;1000g)</b>	1.42 (0.48-3.77)	1.32 (0.82-2.10)		
<b>Small for gestational age (10th percentile)</b>				
<b>Birth weight</b>	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]
<b>Crown heel length</b>	1.16 (1.12-1.20)	2.26 (2.22-2.30)		
<b>Head circumference</b>	1.03 (0.99-1.06)	1.64 (1.60-1.68)		
<b>Body proportionality</b>				
<b>High ponderal index (&gt;90th percentile)</b>	1.19 (1.15-1.23)	1.26 (1.23-1.28)		
<b>Low brain:body ratio (&lt;10th percentile)</b>	1.08 (1.04-1.12)	1.11 (1.07-1.15)		
<b>High head:length ratio (&gt;90<sup>th</sup> percentile)</b>	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 Sensitivity analyses

### 4.1 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.

### 4.2 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:**
  - o *Preterm birth*: maternal age (cont), sex, parity (nulli/multi), SES
  - o *Birth weight (<2500g)*: maternal age (continuous), sex, parity (nulli/multi), gestational weeks (continuous), SES
  - o *Small for gestational age (weight/length/head <10th percentile)*: maternal age (continuous), sex, parity (nulli/multi), SES
  - o *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



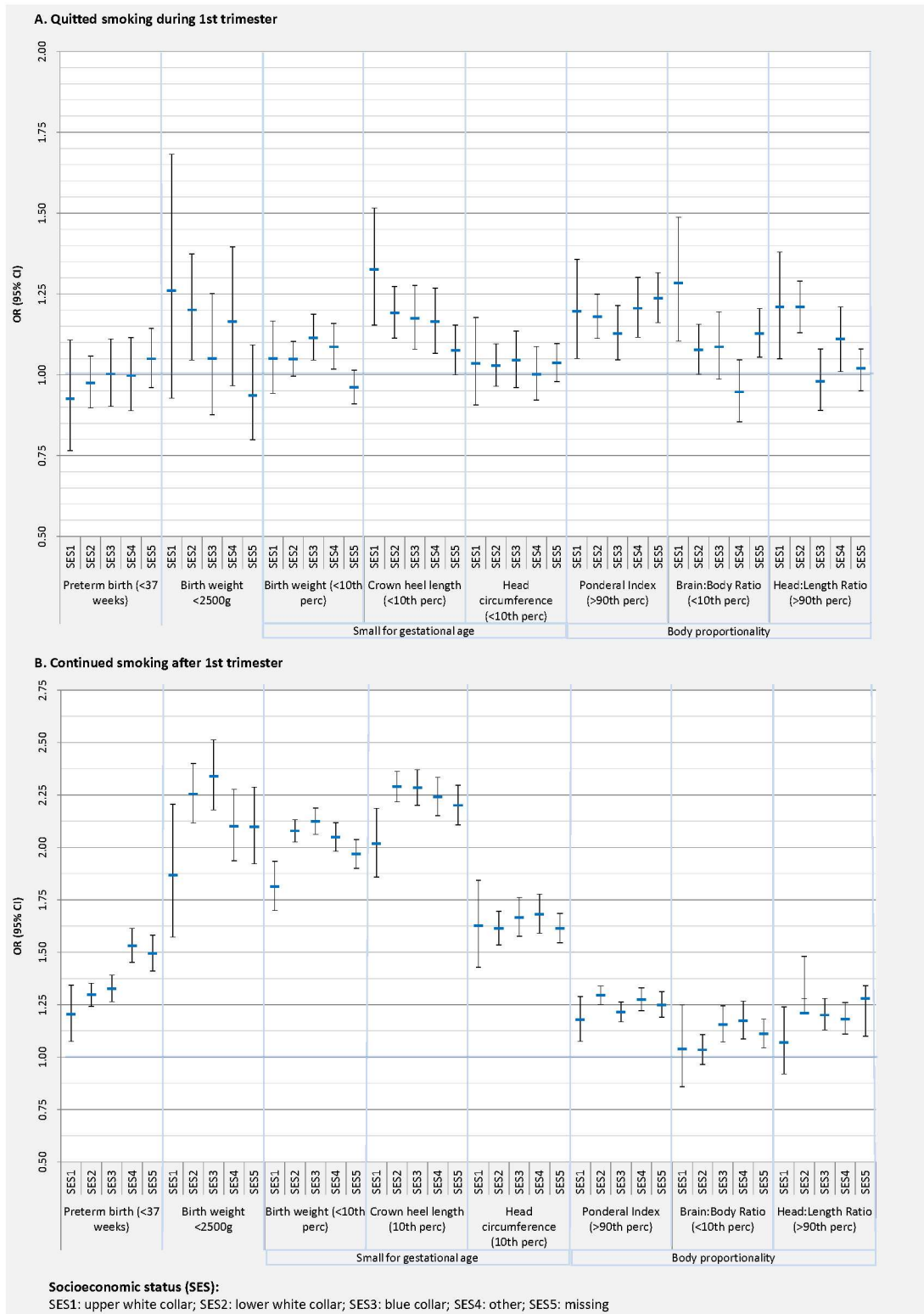
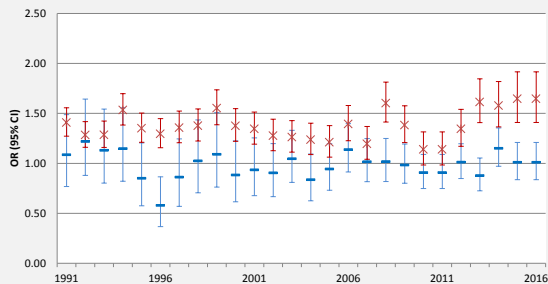
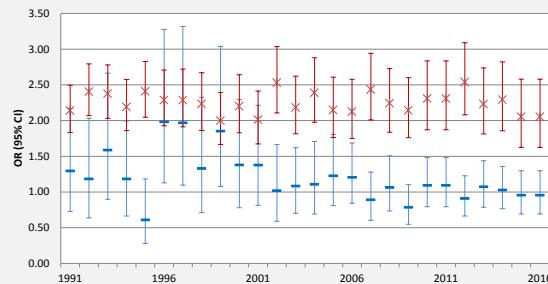


Figure S2. Association of maternal smoking and birth outcomes stratified by socioeconomic status. Pane A: quitted smoking during 1<sup>st</sup> trimester; panel B: continued smoking after 1<sup>st</sup> trimester.

A. Preterm birth (<37 weeks)



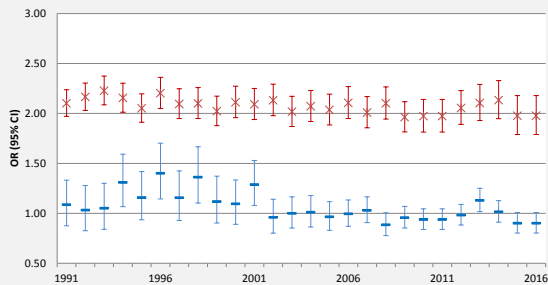
B. Low birth weight (<2,500g)



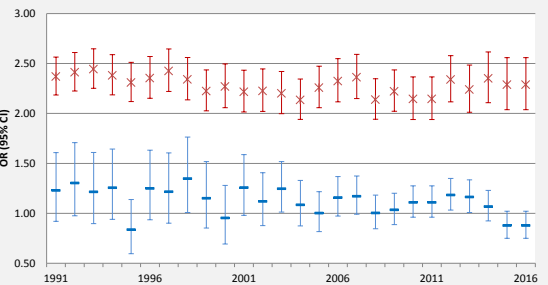
— Quitted smoking during 1st trimester  
 × Continued smoking after 1st trimester  
 \* Not available for years 1991-2003

C. Small for gestational age (<10th percentile)

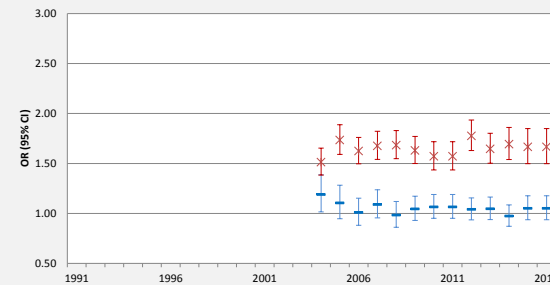
C.1. Weight



C.2. Crown heel length

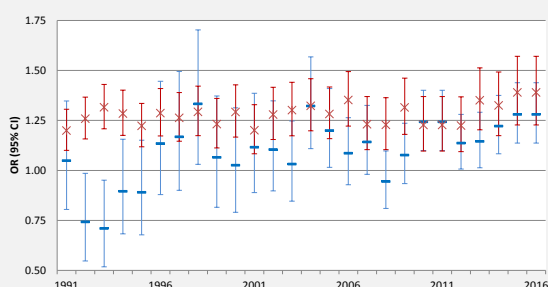


C.3. Head circumference \*

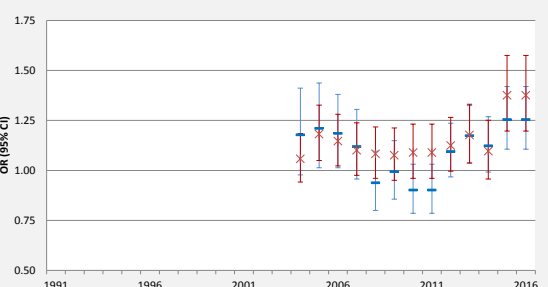


D. Body proportionality

D.1. Ponderal Index (>90th percentile)



D.2. Brain:Body Ratio (<10th percentile) \*



D.3. Head:Length Ratio (>90th percentile) \*

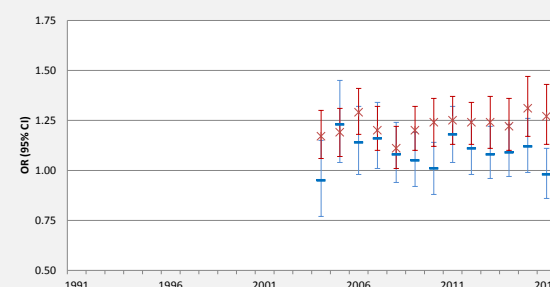


Figure S3. Association of maternal smoking with preterm birth (panel A), low birth weight (panel B), small for gestational age (panel C) and body proportionality (panel D) stratified by birth year

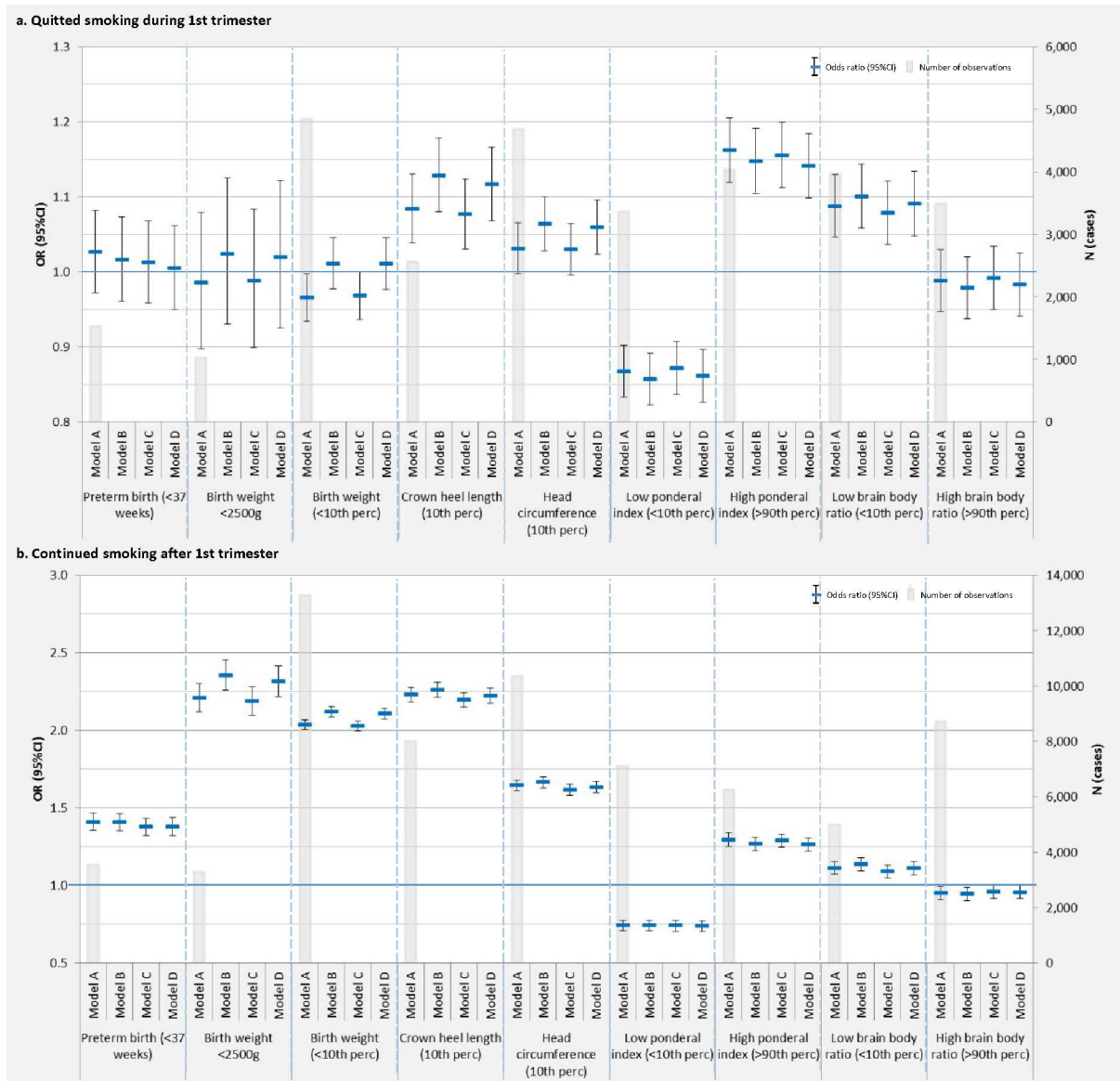


Figure S4. Results for a sensitivity analyses for additional adjustment models for regression on singletons births 2004-2016. Upper panel (a): quitted smoking during 1<sup>st</sup> trimester, lower pane (b): continued smoking after 1<sup>st</sup> trimester:

### 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].

1. Schneider, S. and J. Schutz. 2008. "Who Smokes during Pregnancy? A Systematic Literature Review of Population-Based Surveys Conducted in Developed Countries between 1997 and 2006." *The European Journal of Contraception & Reproductive Health Care: The Official Journal of the European Society of Contraception* 13 (2): 138-147. doi:10.1080/13625180802027993 [doi].
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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(b) For matched studies, give matching criteria and number of exposed and unexposed	na
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5ff
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5ff
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	5ff
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5ff
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7
		(b) Describe any methods used to examine subgroups and interactions	7
		(c) Explain how missing data were addressed	5, 7
		(d) If applicable, explain how loss to follow-up was addressed	na
		(e) Describe any sensitivity analyses	11
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5, supplement Figure S1
		(b) Give reasons for non-participation at each stage	5, supplement Figure S1
		(c) Consider use of a flow diagram	Supplement Figure S1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8, supplement Table S3
		(b) Indicate number of participants with missing data for each variable of interest	Supplement Table S3, Figure S1
		(c) Summarise follow-up time (eg, average and total amount)	na

Outcome data	15*	Report numbers of outcome events or summary measures over time	8, supplement Table S3
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8, supplement Table S3 5ff na
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11, supplement p 9ff, Figures S2, S3, S4
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12f, supplement p 13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12f
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14f

\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

# BMJ Open

## Maternal smoking alters body proportions at birth: A register-based cohort study of 1.4 million births

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Secondary Subject Heading:	Epidemiology, Paediatrics, Smoking and tobacco
Keywords:	PUBLIC HEALTH, EPIDEMIOLOGY, Smoking, pregnancy, growth restriction, register-based

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3 **Maternal smoking alters body proportions at birth: A register-based cohort study of 1.4**  
4 **million births**  
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## Altered body proportions at birth after maternal smoking during early pregnancy

### ABSTRACT

**Objectives:** The aim of our work was, using a register-based approach, to compare the effect of smoking quitted during the 1<sup>st</sup> trimester or continued after the 1<sup>st</sup> trimester on body size and body proportions at birth, and preterm birth associated with smoking.

**Design:** Register-based cohort study

**Setting:** Finnish Medical Birth Register

**Participants:** All singletons birth singleton births without congenital anomalies and missing data (1.34 million) born in Finland between 1st January 1991 and 31st December 2016

**Methods:** We examine the effects of self-reported, register recorded, quitted smoking during 1st trimester in contrast to smoking continued after 1<sup>st</sup> trimester utilising the MATEX birth cohort. Logistic regression was used to quantify the effect of maternal smoking on the outcomes.

**Outcome measures:** Outcomes included preterm birth, low birth weight, small body size for gestational age (birth weight, body length, and head circumference) and altered body proportions (indicated by high ponderal index, low brain-to-body ratio, and high head-to-length ratio at birth).

**Results:** Smoking during pregnancy was associated with an increased risk for smaller body size and altered body proportions, as indicated by high ponderal index (OR 1.26, 95% CI 1.23-1.28), low brain-to-body ratio (1.11, 1.07-1.15) and high head-to-length ratio (1.22, 1.19-1.26). The effects were slightly more pronounced for smoking throughout pregnancy than for smoking only during early pregnancy.

**Conclusions:** Growth restriction in newborns associated with maternal smoking was found to change body proportions at birth with larger reduction of length and head circumference in comparison to weight. The effect by smoking quitted during 1<sup>st</sup> trimester or continued after the 1<sup>st</sup> trimester pregnancy was similar, suggesting the importance of early pregnancy as a sensitive exposure window.

**KEYWORDS**

smoking, register research, growth restriction, prenatal, low birth weight, small for gestational age, pregnancy

**ABBREVIATIONS**

OR	Odds ratio
SGA	Small for gestational age (10 <sup>th</sup> smallest percentile)
PTB	Preterm birth
LBW	Low birth weight
SES	Socioeconomic status
CI	Confidence interval

**STRENGTH AND LIMITATIONS OF THIS STUDY**

- The register-based design of this study provides a big study size to detect small risks and minimises risks for recall bias.
- In sensitivity analyses the results were shown to be robust when stratified by socioeconomic status and birth year, as well as additional adjustment models for sociodemographic factors and co-morbidities.
- Smoking status was self-reported during antenatal visits, leading to possible reporting bias.
- The register-based design restricted available information on lifestyle-related confounders.

## INTRODUCTION

Smoking during pregnancy increases the risk for adverse pregnancy outcomes. Adverse pregnancy outcomes are not only associated with complications in the neonatal period, but also long term, potentially well into late adulthood.[1] Tobacco smoke contains thousands of chemicals, which can cross the placental barrier and enter fetal circulation. Among them nicotine has a multitude of adverse effects on the development of organs including brain.[2] Other well-known fetotoxic chemicals of tobacco smoke include carbon monoxide, which can interfere with oxygen supply of the unborn child, and genotoxic and carcinogenic polycyclic aromatic hydrocarbons and tobacco-specific nitrosamines, which are teratogenic in animal studies.[3]

The association between maternal smoking and low birth weight, commonly defined as weight below 2,500g, is well established. In addition the susceptibility of anthropometric indices, such as body length, head size and abdominal circumference to maternal smoking is emerging.[4] Low birth weight as such does not hold information whether the reduction of weight is due to loss of lean or fat body mass. Similarly, reduction in any other anthropometric indices alone fails to identify altered body proportions. Symmetrical in utero growth restriction is a stronger risk factor for later life morbidity and mortality than asymmetrical growth restriction with decreased amount of fat tissue.[5] Small for gestational age, used as a substitute for in utero growth restriction at birth, is not an optimal proxy.[6] This clearly demonstrates the importance of body proportions for future health in the newborn.

The effects of early smoking cessation on body size are less well studied. Smoking only during early pregnancy has been shown to be less harmful on body size than continued smoking during late pregnancy. Previous, small studies indicated anthropometric indices in newborns only exposed during early pregnancy similar to those of non-smoking mothers [7], while current, bigger studies report increased risk for growth restriction even in foetuses exposed only during the 1<sup>st</sup> trimester.[8] There are insufficient data about anthropometric indices, other than birth weight, in those exposed only during early pregnancy in comparison with the newborns of non-smokers.[9]

The aim of our work was, using a register-based approach, to compare the effect of smoking quitted during 1st trimester with smoking continued after the 1<sup>st</sup> trimester on body size and body proportions at birth, and preterm birth. Additionally, we investigated the possibility of

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3 mechanistic interpretations of possible alterations in body proportions in newborns of  
4 smoking mothers.  
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## 9 10 **MATERIALS & METHODS**

### 11 **Study design**

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13 To study the effect of maternal smoking on body size and proportions at birth we conducted a  
14 register-based cohort study utilising the Finnish MATEX cohort. The MATEX cohort was  
15 identified from the Finnish Medical Birth Register described in more detail elsewhere.[10]  
16 This register contains perinatal outcomes, pregnancy characteristics and sociodemographic  
17 information for all live births and stillbirths after the 22<sup>nd</sup> gestational week or with a birth  
18 weight of at least 500g. The Medical Birth Register receives information from standardised  
19 forms filled out by nurses and midwives during antenatal care visits and after the delivery of  
20 the baby.  
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28 This work focuses on the effects of maternal smoking on singleton pregnancies between 1<sup>st</sup>  
29 January 1991 and 31<sup>st</sup> December 2016. From initial 1.75 million mother-children pairs 1.38  
30 million were included in the analyses after exclusion of multiple births, newborns with  
31 congenital anomalies and newborns with missing information on maternal smoking status or  
32 co-variates (Supplementary Material, Figure S1). Information on head circumference and  
33 maternal weight and height, and maternal co-morbidities were available only for the years  
34 2004 to 2016, reducing the cohort size to 659,157 mother-child pairs (Supplementary  
35 Material, Figure S1).  
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42 We analysed the effect of smoking quitted during the 1<sup>st</sup> trimester and smoking continued  
43 after the 1<sup>st</sup> trimester separately with no smoking during pregnancy as a reference on four  
44 groups of outcomes: (i) preterm birth (PTB); (ii) low birth weight (LBW) (as a crude measure  
45 of small body size); (iii) small body size for gestational age, and (iv) body proportions (Table  
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### 51 **Exposure**

52 Maternal smoking data is recorded in the Medical Birth Register during antenatal care visits  
53 as reported by the expectant women. In the MATEX cohort, smoking status is assigned as  
54 three categories: (1) non-smoker, (2) quitted smoking during the 1<sup>st</sup> trimester, and (3)  
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3 continued smoking after the 1<sup>st</sup> trimester. The trends in smoking during the study period have  
4 been described in detail elsewhere. [11]  
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### 7 **Outcomes**

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9 Term birth was defined as birth during gestational week 37 or later. Preterm birth (PTB) was  
10 categorised as all preterm (<37 weeks), further divided into late preterm (34-36 weeks),  
11 moderately preterm (28-33 weeks), and extremely preterm (<28 weeks).  
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15 Low birth weight (LBW) was categorized in accordance with ICD10 diagnosis criteria as  
16 generally low (<2,500g), further divided into low (1,000-2,500g), and extremely low  
17 (<1,000g). As reference category normal weight was defined as 2,500-4,500g, excluding high  
18 birth weight according to ICD10 definition.  
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23 In this work we use “small for gestational age” (SGA) as a general expression to describe the  
24 measurement of each anthropometric index below a cut-off at 10<sup>th</sup> percentile. It was included  
25 as an endpoint to take into account the impact of gestational age on body size. It was defined  
26 based on sex- and parity-specific mean and standard deviation for the corresponding  
27 gestational week as reported in the Finnish standard reference population.[12] SGA was  
28 defined separately for three anthropogenic indices: Birth weight, crown-heel length and head  
29 circumference.  
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35 Body proportionality was assessed by three anthropometric indices in relation with each  
36 other: ponderal index, brain: body ratio and head: length ratio.  
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40 Ponderal index was calculated using birth weight in grams and crown-heel length in cm  
41 (Equation 1). It was categorized normal (10-90<sup>th</sup> percentile of the study population, used as  
42 the reference) and high (>90<sup>th</sup> percentile). The lowest 10<sup>th</sup> percentile was excluded.  
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#### 45 *Equation 1.*

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$$48 \text{ Ponderal Index} = 100 \times \frac{\text{birth weight [g]}}{\text{crown heel length [cm]}^3}$$
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$$50$$

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52 Brain-to-body ratio was calculated based on head circumference in cm and birth weight in  
53 grams (Equation 2). It was categorized as low (<10<sup>th</sup> percentile of the study population) and  
54 normal (10-90<sup>th</sup> percentile, reference). The 90<sup>th</sup> percentile was excluded.  
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#### 57 *Equation 2.*

$$\text{Brain – to – Body Ratio} = 100 \times \frac{0.037 \times \text{head circumference [cm]}^{2.57}}{\text{birth weight [g]}}$$

The nominator of the formula is the estimation of the brain weight according to the National Institute of Neurological and Communicative Disorders and Stroke's Collaborative Perinatal Project.[13]

Head-to-length ratio was calculated using head circumference in cm and crown-heel length in cm (Equation 3). It was categorized normal (10-90<sup>th</sup> percentile of the study population, reference) and high (>90<sup>th</sup> percentile). The lowest 10<sup>th</sup> percentile was excluded.

*Equation 3.*

$$\text{Head – to – Length Ratio} = \frac{\text{head circumference [cm]}}{\text{crown – heel length [cm]}}$$

Percentiles of indices for body proportionality were calculated for each gestational week separately.

### Covariates

Maternal age and gestational age in weeks were used as continuous variables in the regression models. Parity was defined as null- or multiparous. Sex was defined as male or female. Socioeconomic status (SES) was categorized as upper white collar (upper level employees with administrative, managerial, professional and related occupations), lower white collar (lower level employees with administrative and clerical occupations), blue collar (manual workers) and others (farmers, self-employed, students, pensioners, no information) based on the Finnish national classification of occupations.[14] An additional category (information missing) was added to this classification.

**Table 1.** Summary of the definitions of endpoints and adjustments in the regression model used to study the association of maternal smoking and preterm birth, low birth weight, small for gestational age and altered body proportions at birth.

Endpoint	Definition	Smoking <sup>a</sup>	No. of mother-child pairs included in the regression	Adjustment in stratified multiple logistic regression
Preterm birth	Gestational age < 37 weeks	quitted	1 210 410	maternal age, sex, parity, SES
		continued	1 286 667	

<b>Low birth weight</b>	Birth weight <2500g	quitted	1 170 187	maternal age, sex, parity, gestational weeks, SES
		continued	1 328 221	
<b>Small for gestational age</b>				
<b>Weight</b>	<10 <sup>th</sup> percentile of weight at corresponding gestational week	quitted	1 210 048	maternal age, sex, parity, SES
		continued	1 327 783	
<b>Crown heel length</b>	<10 <sup>th</sup> percentile of length at corresponding gestational week	quitted	1 210 048	maternal age, sex, parity, SES
		continued	1 327 783	
<b>Head circumference</b>	<10 <sup>th</sup> percentile of head circumference at corresponding gestational week	quitted	573 343	maternal age, sex, parity, SES
		continued	601 407	
<b>Altered body proportions</b>				
<b>Ponderal index</b>	>90 <sup>th</sup> percentile of weight-to-length ratio at corresponding gestational week	quitted	1 088 451	maternal age, sex, parity, SES, weight z-score
		continued	1 196 479	
<b>Brain-to-body ratio<sup>b</sup></b>	<10 <sup>th</sup> percentile of weight-to-head circumference ratio at corresponding gestational week	quitted	518 704	maternal age, sex, parity, SES, weight z-score
		continued	541 549	
<b>Head-to-length ratio<sup>b</sup></b>	>90 <sup>th</sup> percentile of head circumference-to-length ratio at corresponding gestational week	quitted	521 420	maternal age, sex, parity, SES
		continued	547 597	

<sup>a</sup> quitted: Quitted smoking during 1st trimester; continued: Continued smoking after the 1st trimester

<sup>b</sup> available 2004-2016

SES: socioeconomic status

### Statistical analyses

Multiple logistic regressions were performed to estimate ORs with 95% confidence intervals (CI). The regressions were stratified by exposure status with no smoking as reference. The regression models were adjusted for potential confounders (Table 1, Supplementary Material, Chapter 3.2). The confounders were selected based on a combination of available data and previously published confounding variables. The data were analysed using R Statistical software (version 3.4.3). The smallest detectable was estimated using a 95% CI and a study power of 90%. The calculations were done using R Statistical Software epiR package (Supplementary Material, Table S1).

### Ethics approval and register data permit

In accordance with the Finnish Medical Research Act (1999/488) the MATEX study including the birth cohort identified from the Medical Birth Register has been evaluated and



approved by the ethics committee of the Northern Ostrobothnia Hospital District (EETTMK 44/2016; issued 18th April 2016). The right to use of register data held by the Finnish Institute for Health and Welfare was granted under the document number THL/838/6.02.00/2016 (issued 22nd June 2016). Due to the full register-based design of the study, no informed consent is required from the study participants according to the Finnish Personal Data Act 1050/2018.

### Patient and Public Involvement

No patients were involved in the design, recruitment or conduct of the study. The utilised register data are routinely collected.

## RESULTS

Of all women with singleton births included in this study (n=1 376 778), 84.5% were non-smokers, 3.5% quitted smoking during the 1<sup>st</sup> trimester and 12.0% continued smoking after the 1<sup>st</sup> trimester. Smoking pregnant women tend to be younger and nulliparous (Table 2, Supplementary Material, Table S2).

**Table 2.** Baseline characteristics by smoking status for all singleton births in the MATEX cohort (1991-2016).

	All	Non-smoker	Quitted smoking during 1st trimester	Continued smoking after 1st trimester
	<b>1,376,778</b>	<b>84% (1,163,225)</b>	<b>3.5% (47,819)</b>	<b>12% (165,734)</b>
<b>Mother</b>				
	mean (SD)	mean (SD)	mean (SD)	mean (SD)
Age (years)	29.39 (5.34)	29.78 (5.16)	27.18 (5.43)	27.3 (5.83)
Parity (nulliparous)	59.5 (818294)	39.4 (458010)	58.8 (28097)	43.2 (71629)
Marital status (married or partnership)	62 (846,557)	66.8 (771,065)	35.9 (17,039)	35.7 (58,453)
Socioeconomic status	% (count)	% (count)	% (count)	% (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)
<b>Child</b>				
	mean (SD)	mean (SD)	mean (SD)	mean (SD)
Gestational age (days)	278.66 (12.05)	278.74 (11.85)	279.34 (12.11)	277.87 (13.29)
Birth weight (g)	3549.45 (542.2)	3573.19 (536.38)	3540.62 (535.37)	3385.36 (556.1)
Crown-Heel length (cm)	50.21 (2.43)	50.32 (2.4)	50.12 (2.39)	49.5 (2.59)
Head circumference (cm)*	34.94 (1.64)	34.99 (1.62)	34.91 (1.65)	34.55 (1.71)
Preterm birth	% (count)	% (count)	% (count)	% (count)
Any preterm birth (<37 weeks)	4.3 (58,828)	4.1 (47,775)	4.3 (2,040)	5.4 (9,013)
Late preterm birth (34-36 weeks)	3.2 (44,042)	3.1 (36,088)	3.2 (1,519)	3.9 (6,435)
Moderately preterm birth (28-33 weeks)	0.9 (11,628)	0.8 (9,191)	0.9 (425)	1.3 (2,012)
Extremely preterm birth	0.2 (3,158)	0.2 (2,496)	0.2 (96)	0.4 (566)

( $<28$ weeks)				
Low/High birth weight	% (count)	% (count)	% (count)	% (count)
Any low birth weight ( $<2500$ g)	3.0 (40,006)	2.7 (30,443)	3.0 (1,387)	5.0 (8,176)
Moderately low birth weight (1000-2500g)	2.8 (36,646)	2.5 (27,783)	2.8 (1,284)	4.7 (7,579)
Extremely low birth weight ( $<1000$ g)	0.3 (3,360)	0.2 (2,660)	0.2 (103)	0.4 (597)
High birth weight ( $>4500$ g)	3.1 (41,054)	3.3 (37,165)	2.8 (1,313)	1.6 (2,576)
Small for gestational age ( $\leq 10$ th percentile)	% (count)	% (count)	% (count)	% (count)
Weight	11.5 (158,817)	10.4 (120,800)	13.6 (6,483)	19.1 (31,534)
Crown-Heel length	6.0 (81,869)	5.2 (60,003)	7.0 (3,345)	11.2 (18,521)
Head circumference (cm)*	10.9 (69,350)	10.1 (54,321)	13.3 (4,675)	16.4 (10,354)
Altered body proportions	% (count)	% (count)	% (count)	% (count)
High ponderal index	11.0 (136,918)	11.1 (116,902)	11.8 (5,111)	10.1 (14,905)
Low brain-to-body ratio*	11.1 (63,520)	11.2 (54,554)	12.5 (3,968)	9.2 (4,998)
High head-to-length ratio*	9.6 (60,358)	9.8 (49,830)	8.9 (3,560)	8.3 (6,960)

\* available only 2004-2016

Any maternal smoking was associated with an increased risk for SGA and altered body proportions, while PTB was only associated with smoking continued after the 1<sup>st</sup> trimester (Fig. 1; Supplementary Material, Table S3).

### [Figure 1]

Maternal smoking increased the risk for low birth weight (LBW,  $<2,500$ g). Smoking continued after the 1<sup>st</sup> trimester doubled the risk for LBW (OR 2.22, 95% CI 2.14-2.30). Smoking quit during the 1<sup>st</sup> trimester was associated with an increased risk for LBW (OR 1.10, 95% CI 1.02-1.19), albeit not as strong as with continued smoking (Fig. 1A).

Smoking during pregnancy was associated with an increased risk for SGA ( $<10$ <sup>th</sup> percentile) in the weight and crown-heel dimension. Mothers who quit smoking during the 1<sup>st</sup> trimester were at elevated, but not statistically significant risk for giving birth to a child with a small head circumference. Among the mothers who continued smoking after the 1<sup>st</sup> trimester the risk for small head circumference was clearly increased with an OR of 1.64 (95% CI 1.60-1.68) (Fig. 1A).

The risk for altered body proportions was significantly increased by maternal smoking. A stronger increase in risk was observed for high ponderal index and high head-to-length ratio than for low brain-to-body ratio. ORs were consistently higher for smoking continued after the 1<sup>st</sup> trimester than among those who quit smoking during the 1<sup>st</sup> trimester. Nevertheless, smoking quit during the 1<sup>st</sup> trimester was associated with statistically significantly

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3 increased risks for altered body proportions. Especially the risk for brain-to-body ratio was  
4 almost similar in those exposed only during the 1<sup>st</sup> trimester and those exposed throughout  
5 pregnancy (Fig 1B).  
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9 We stratified the analysis by socioeconomic status (SES) in order to investigate the influence  
10 of lifestyle factors and health behaviours that correlate with SES. Stratification by SES did  
11 not show statistically significant differences in the risk estimates (Supplementary Material,  
12 Figure S2). We stratified the data by birth year to investigate potential influence of changes in  
13 tobacco composition and social acceptability of smoking during the study period on the risk  
14 estimates. Stratification by birth year did not indicate a clear temporal pattern in any of the  
15 analysed endpoints (Supplementary Material, Figure S3). Sensitivity analysis was performed  
16 to test the robustness of results against choice of adjustment factors in the regression model.  
17 Different adjustment models did not significantly alter the risk estimates for any of the  
18 reported endpoints (Supplementary Material, Figure S4).  
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## 30 DISCUSSION

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32 In this work we investigated the effect of smoking quit during the 1<sup>st</sup> trimester and  
33 continued after the 1<sup>st</sup> trimester on preterm birth, body size and body proportions at birth. The  
34 most important finding of our study is that although the risk for low birth weight decreases by  
35 smoking cessation during the first trimester, brain size and body length in relation to body  
36 weight seem not to catch up. Among the newborns exposed to maternal smoking only during  
37 the 1<sup>st</sup> trimester all three measurements of body size (birth weight, body length and head  
38 circumference) showed signs of growth restriction. In addition, body proportions were altered.  
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45 Our work indicates a difference in susceptibility for growth restriction between weight, body  
46 length and head circumference. The association with ponderal index suggests a stronger  
47 reduction in length than in weight. Similarly, the association with low brain-to-body ratio  
48 suggests reduction rather in brain size than in weight. However, the association of maternal  
49 smoking with high head-to-length ratio suggests a stronger reduction in length than in head  
50 size. It is in line with previous research showing that smoking during pregnancy  
51 predominantly affect lean body mass and not fat body mass.[4] Although risks are lower in  
52 newborns whose mothers quit smoking during the 1<sup>st</sup> trimester than in those who continued  
53 smoking, the results suggest a direct effect of maternal smoking on cell proliferation during  
54 organogenesis in early prenatal development. Insults during this period are persistent  
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3 throughout life.[5] This stresses the importance of smoking cessation before pregnancy since  
4 even smoking only during very early pregnancy has potentially devastating effects on long  
5 term health of the unborn child.  
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9 The importance of body proportions at birth has been demonstrated by Zanelli and co-  
10 workers.[15] They showed that newborns with high ponderal index are more likely to develop  
11 coronary heart disease as obese adults than their peers, who were born small but not thin. It is  
12 not possible to infer from our study whether the high ponderal index and higher risk for  
13 shorter crown-heel length is comparable to stunting due to malnutrition and infections.  
14 Mechanistic studies of the overserved effects are needed to extrapolate the risks to later life.  
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20 Additionally, smaller head circumference has been shown to directly translate into a smaller  
21 brain.[16, 17] I Insults, such as maternal smoking, during early development of the brain have  
22 been shown to result in differences in DNA methylation, altered expression of genes  
23 regulating brain structure and function [18] and reduce neuronal content of the brain,[19].  
24 Also, neurophysiological functions and overall brain functions are altered due to prenatal  
25 smoking.[20] The smaller brain volume observed in newborns has been shown to persist into  
26 young adulthood.[21]  
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33 Overall, our results are in line with previously reported studies by other groups  
34 (Supplementary Material, Table S4).[22-25] Smoking quitted during the 1<sup>st</sup> trimester had a  
35 weaker effect on reduction in weight or length measures, whereas smoking especially at the  
36 end of pregnancy reduced femur length, abdominal circumference and biparietal  
37 diameter.[26] A clear dose response of smoking (number of cigarettes per day) on reduction  
38 of birth weight and increase in ponderal index has been demonstrated.[17, 27] Previous  
39 studies examining the effect of smoking cessation during pregnancy consistently reported a  
40 reduction in harm compared with continued smoking.[4]  
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48 There is increasing evidence from animal studies of nicotine as a causative agent for  
49 reproductive toxicity, including detrimental effects on brain.[28, 29] In a large  
50 epidemiological study, among the few existing ones, aberrations in lung development due to  
51 nicotine replacement products use during pregnancy has already been suggested.[30]  
52 Epidemiological studies on the effects of nicotine products, other than cigarettes, are still  
53 needed.. We recommend the inclusion of information on the use of nicotine products in the  
54 MBR. This would allow detecting pregnancies at risk more reliably and facilitating  
55 epidemiological research on nicotine exposure during pregnancy beyond maternal smoking.  
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3 This work is solely based on routinely collected register data, which dictates the data  
4 availability. We tested our results for sensitivity to different adjustment models and our  
5 results were shown to be robust against maternal co-morbidities, maternal anthropometric  
6 indices, social background and reproductive history. Smoking and socioeconomic status have  
7 been shown to correlate well with other lifestyle related factors and they are a reliable marker  
8 for the unaccounted factors.[31] It was not possible to analyse the impact of timing of  
9 smoking cessation in more detail or possible dose response relationships due to lack of data.  
10 In addition, we lack information on paternal and household smoking. Second hand tobacco  
11 smoke exposure during pregnancy has been shown to increase the risk for low birth weight  
12 and growth restriction.[32]. We cannot exclude the possibility that some observed effects are  
13 partly attributable to second hand tobacco smoke exposure, especially in those women who  
14 ceased smoking during their 1<sup>st</sup> trimester.  
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25 Strength of this work is the register-based design with, to our knowledge, the biggest study  
26 population so far. Overall, the Medical Birth Register data, including the smoking  
27 information, have been shown to be reliable.[33-35] SES was assigned solely on maternal  
28 occupation and no information about the father's occupation was available. For a high  
29 proportion of mothers (18%) the occupation was not available. Previous studies applied the  
30 same SES categorization and showed that the missing information did not bias the proportions  
31 in the other SES categories.[24] Overall, occupation is well correlated with education and  
32 income in Finland and it can be used as an indicator for socioeconomic health differences.[33]  
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## 41 **CONCLUSIONS**

42  
43 This study shows that growth restriction by maternal smoking during pregnancy is not  
44 proportional. Maternal smoking was associated with a stronger reduction in crown-heel length  
45 and head circumference than weight. It seems that especially brain is suffering as judged by  
46 the more extensive reduction of head circumference than weight. The effects were more  
47 pronounced for smoking continued after 1<sup>st</sup> trimester than for smoking quitted during 1<sup>st</sup>  
48 trimester. Although quitting smoking during 1st trimester reduced the risk for preterm birth to  
49 background level, the association with generalized reduction in all anthropometric indices and  
50 changed body proportions stresses the importance of the period of early prenatal development  
51 and the limited potential to repair damages induced in early pregnancy.  
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3 Animal studies suggest nicotine as a potential causative agent, which questions the safety of  
4 nicotine replacement therapy during pregnancy. It is highly important to study the association  
5 of growth restriction and other adverse effects with the use of nicotine therapy products. Until  
6 their safety has been proven, caution should be taken when advising pregnant women.  
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8 Routine collection of information on the use of nicotine replacement products in the Medical  
9 Birth Register is needed for more careful follow-up of risk pregnancies and to facilitate  
10 scientific research on specific effects associated with nicotine replacement products.  
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24 essential support from the Register Holder by Jouni Meriläinen.  
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### 32 **CONTRIBUTORS**

33  
34 IKR, OH, KV and MV conceived the research question and designed the study. IKR  
35 conducted statistical analysis, interpreted the results and wrote the first and subsequent drafts  
36 of the manuscript with support of OH. KV, MV, MG and HdR contributed to data  
37 interpretation and revisions of the manuscript. MV, OH, KV and IKR obtained funding. All  
38 authors approved the final version of the submitted manuscript.  
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### 47 **COMPETING INTERESTS**

48  
49 Kirsi Vähäkangas is currently the chair of the scientific committee of the Savuton Suomi  
50 (Smoke-free Finland) 2030 initiative. Other authors declare no competing interests.  
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### 23 **DISCLAIMER**

24  
25 None of the funding agencies had a role in n the study design; in the collection, analysis and  
26 interpretation of the data; in the writing of the report; and in the decision to submit the paper  
27 for publication.  
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### 35 **DATA SHARING STATEMENT**

36  
37 Data may be obtained from a third party and are not publicly available. The Finnish Institute  
38 of Health and Welfare is controller of the Medical Birth Register. Data may be obtained from  
39 the register controller ([https://thl.fi/en/web/thlfi-en/statistics/information-on-statistics/register-](https://thl.fi/en/web/thlfi-en/statistics/information-on-statistics/register-descriptions/newborns)  
40 [descriptions/newborns](https://thl.fi/en/web/thlfi-en/statistics/information-on-statistics/register-descriptions/newborns) accessed 29 May 2019).  
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### 47 **PATIENT CONSENT**

48  
49 Not required.  
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### 53 **ETHICAL APPROVAL**

54  
55 The study was approved by the ethics committee of the Northern Ostrobothnia Hospital  
56 District (EETTMK 44/2016; issued 18th April 2016). The right to use of register data held by  
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9  
10 3210 words (Introduction to Conclusions)  
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**TABLE**

**Table 1.** Summary of the definitions of endpoints and adjustments in the regression model used to study the association of maternal smoking and preterm birth, low birth weight, small for gestational age and altered body proportions at birth.

**Table 2.** Baseline characteristics by smoking status for all singleton births in the MATEX cohort (1991-2016).

**FIGURE LEGEND**

**Fig 1** Adjusted odds ratios (OR) for association of maternal smoking with (A) traditional birth outcomes (preterm birth, low birth weight and small for gestational age); and with (B) altered body proportions; adjusted for maternal age, sex, parity, socioeconomic status, and gestational week (for low birth weight) and weight z-score (in regressions with weight included in the dependent variable); marker + error bar: OR (95% CI).

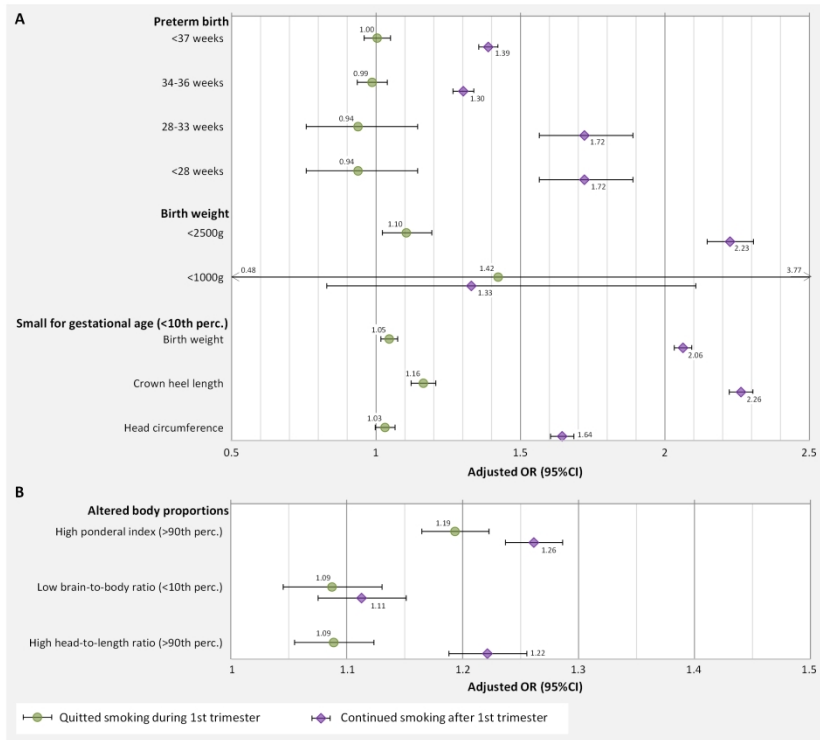


Fig 1 Adjusted odds ratios (OR) for association of maternal smoking with (A) traditional birth outcomes (preterm birth, low birth weight and small for gestational age); and with (B) altered body proportions; adjusted for maternal age, sex, parity, socioeconomic status, and gestational week (for low birth weight) and weight z-score (in regressions with weight included in the dependent variable); marker + error bar: OR (95% CI).

254x190mm (300 x 300 DPI)

# Supplement

## Maternal smoking alters body 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 22<sup>nd</sup> gestational week or with a birth weight of at least 500g.

This work focuses on the effects of maternal smoking on singleton pregnancies born between 1<sup>st</sup> January 1991 and 31<sup>st</sup> 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-variates. 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).

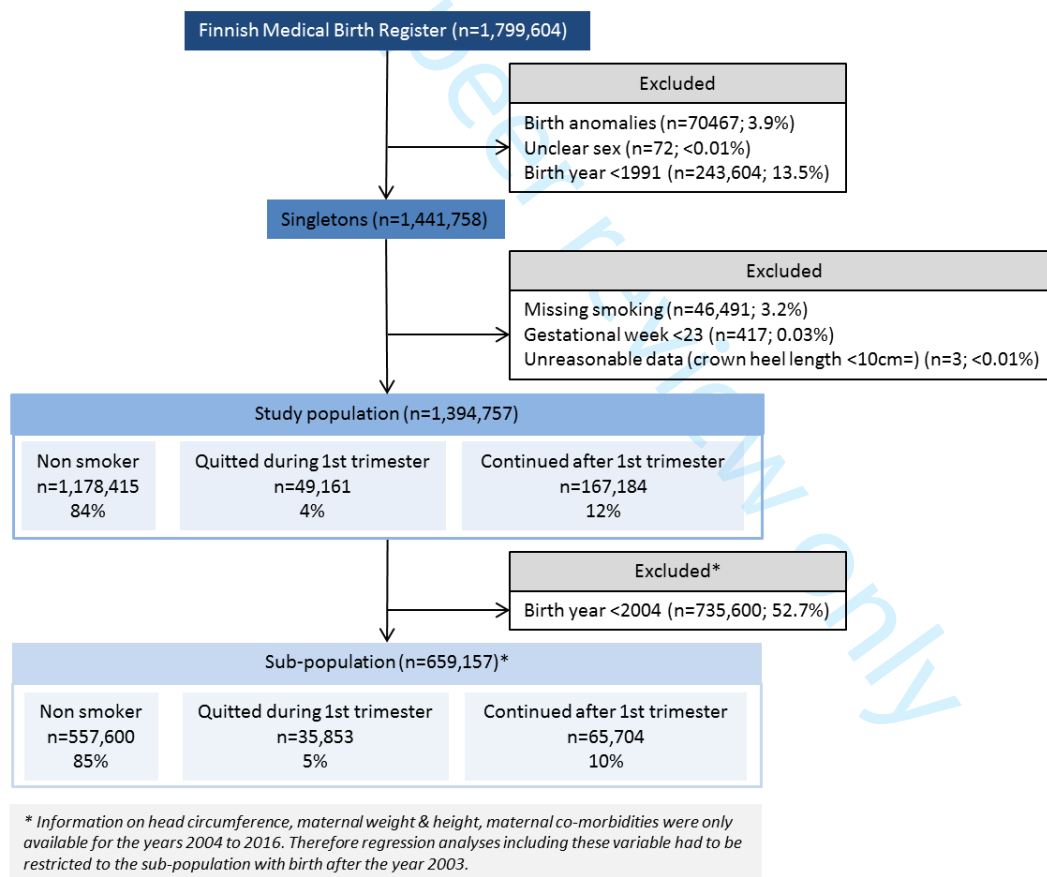


Figure S1. Data cleaning process with exclusion criteria and number of excluded children

## 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*	
		Quitted smoking	Continued smoking	Quitted 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 (<2500g)	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, (<1000g)	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 1<sup>st</sup> trimester and 12.0% (n=165,734) continued smoking after the 1<sup>st</sup> 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		Quitted smoking during 1st trimester		Continued smoking after 1st trimester	
	n^		n^		n^		n^	
Mother	1,376,778		84% (1,163,225)		3% (47,819)		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)

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Cont. Table S2

	All		Non smoker		Quitted 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)
Altered 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<sup>^</sup> 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 1<sup>st</sup> 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	
	Quitted smoking OR (95%CI)	Continued smoking OR (95%CI)	Quitted smoking OR (95%CI)	Continued smoking OR (95%CI)
<b>Preterm birth</b>				
Preterm birth (<37 weeks)	1.04 (0.99-1.08)	1.34 (1.31-1.37)	1.00 (0.95-1.04)	<b>1.38 (1.35-1.42)</b>
Late preterm birth (34-36 weeks)	1.02 (0.97-1.08)	1.26 (1.23-1.30)	0.98 (0.93-1.03)	<b>1.30 (1.26-1.33)</b>
Moderately preterm birth (28-33 weeks)	0.93 (0.75-1.14)	1.61 (1.47-1.76)	0.93 (0.75-1.14)	<b>1.72 (1.56-1.88)</b>
Extremely preterm birth (<28 weeks)	0.93 (0.75-1.14)	1.61 (1.47-1.76)	0.93 (0.75-1.14)	<b>1.72 (1.56-1.88)</b>
<b>Low birth weight</b>				
Low birth weight (<2500g)	1.10 (1.04-1.16)	1.89 (1.85-1.94)	<b>1.10 (1.02-1.19)</b>	<b>2.22 (2.14-2.30)</b>
Low birth weight (1000-2500g)	1.12 (1.05-1.18)	1.92 (1.87-1.97)	<b>1.10 (1.02-1.19)</b>	<b>2.22 (2.14-2.30)</b>
Extremely low birth weight (<1000g)	0.93 (0.76-1.13)	1.58 (1.44-1.73)	1.42 (0.48-3.77)	1.32 (0.82-2.10)
<b>Small for gestational age (&lt;10th percentile)</b>				
Birth weight	1.35 (1.31-1.38)	2.02 (2.00-2.05)	<b>1.04 (1.01-1.07)</b>	<b>2.06 (2.03-2.09)</b>
Crown heel length	1.38 (1.33-1.43)	2.31 (2.27-2.35)	<b>1.16 (1.12-1.20)</b>	<b>2.26 (2.22-2.30)</b>
Head circumference*	1.36 (1.32-1.40)	1.74 (1.70-1.78)	1.03 (0.99-1.06)	<b>1.64 (1.60-1.68)</b>
<b>Altered body proportions</b>				
High ponderal index (>90th percentile)	1.06 (1.03-1.10)	0.89 (0.87-0.91)	<b>1.19 (1.15-1.23)</b>	<b>1.26 (1.23-1.28)</b>
Low brain:body ratio (<10th percentile)*	1.13 (1.09-1.17)	0.79 (0.77-0.82)	<b>1.08 (1.04-1.12)</b>	<b>1.11 (1.07-1.15)</b>
High head:length ratio (>90th percentile)*	1.11 (1.07-1.15)	1.20 (1.17-1.23)	<b>1.09 (1.05-1.13)</b>	<b>1.22 (1.19-1.26)</b>

\* Available for years 2004-2016

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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	
	Quitted OR (95%CI)	Continued OR (95%CI)	Quitted OR (95%CI)	Continued OR (95%CI)
<b>Preterm birth</b>				
<b>Preterm birth (&lt;37 weeks)</b>	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]
<b>Late preterm birth (34-36 weeks)</b>	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]
<b>Moderately preterm birth (28-33 weeks)</b>	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]
<b>Extremely preterm birth (&lt;28 weeks)</b>	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]
<b>Low birth weight</b>				
<b>Low birth weight (&lt;2500g)</b>	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]
<b>Low birth weight (1000-2499g)</b>	1.10 (1.02-1.19)	2.22 (2.14-2.30)		
<b>Extremely low birth weight (&lt;1000g)</b>	1.42 (0.48-3.77)	1.32 (0.82-2.10)		
<b>Small for gestational age (10th percentile)</b>				
<b>Birth weight</b>	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]
<b>Crown heel length</b>	1.16 (1.12-1.20)	2.26 (2.22-2.30)		
<b>Head circumference</b>	1.03 (0.99-1.06)	1.64 (1.60-1.68)		
<b>Altered body proportions</b>				
<b>High ponderal index (&gt;90th percentile)</b>	1.19 (1.15-1.23)	1.26 (1.23-1.28)		
<b>Low brain:body ratio (&lt;10th percentile)</b>	1.08 (1.04-1.12)	1.11 (1.07-1.15)		
<b>High head:length ratio (&gt;90<sup>th</sup> percentile)</b>	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].
3. Lamminpaa, R., K. Vehvilainen-Julkunen, M. Gissler, and S. Heinonen. 2013. "Smoking among Older Childbearing Women - a Marker of Risky Health Behaviour a Registry-Based Study in Finland." *BMC Public Health* 13: 1179. doi:10.1186/1471-2458-13-1179 [doi].
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:**
  - o *Preterm birth*: maternal age (continuous), sex, parity (nulli/multi), SES
  - o *Birth weight (<2500g)*: maternal age (continuous), sex, parity (nulli/multi), gestational weeks (continuous), SES
  - o *Small for gestational age (weight/length/head <10th percentile)*: maternal age (continuous), sex, parity (nulli/multi), SES
  - o *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

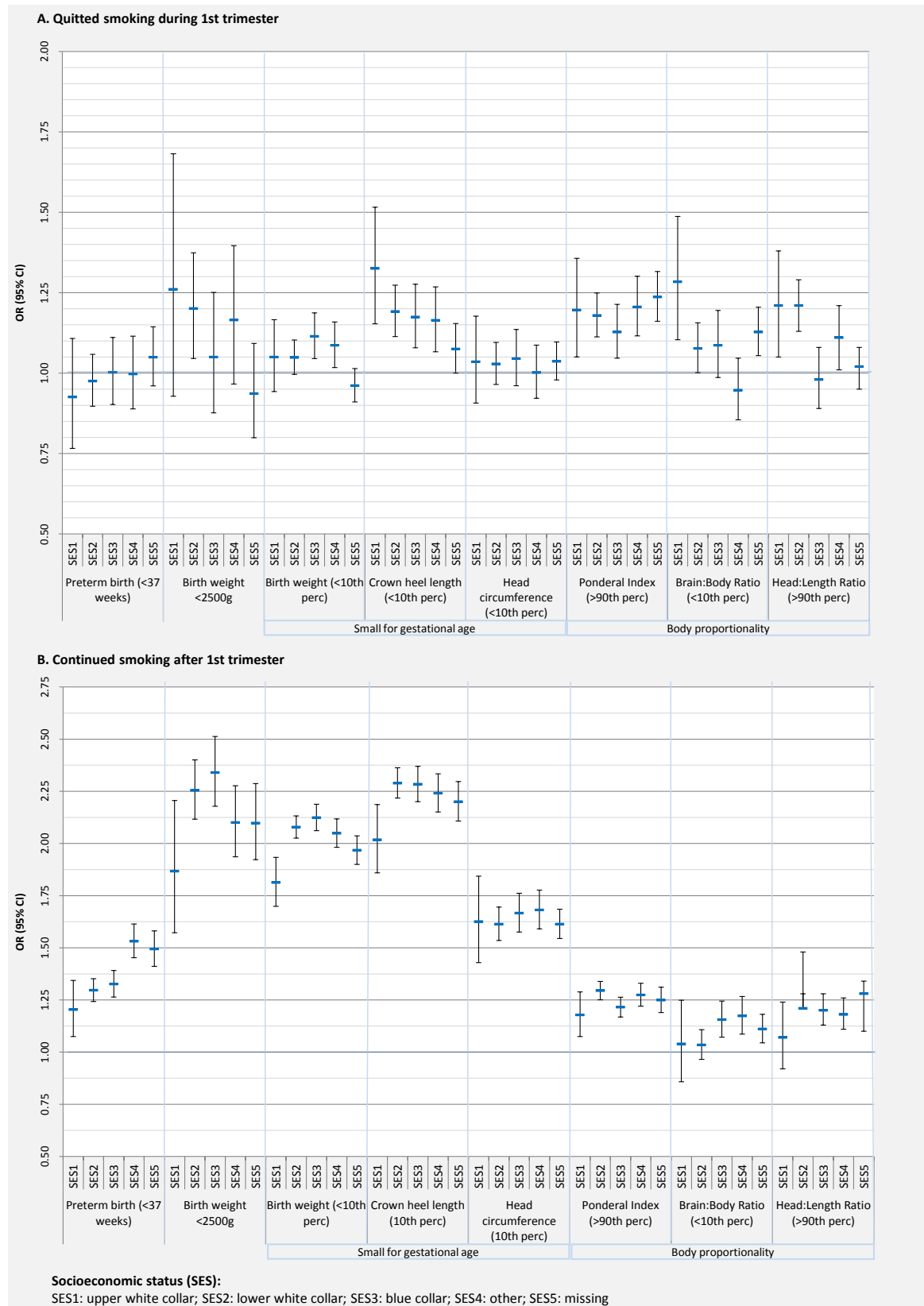


Figure S2. Association of maternal smoking and birth outcomes stratified by socioeconomic status. Pane A: quitted smoking during 1<sup>st</sup> trimester; panel B: continued smoking after 1<sup>st</sup> trimester.

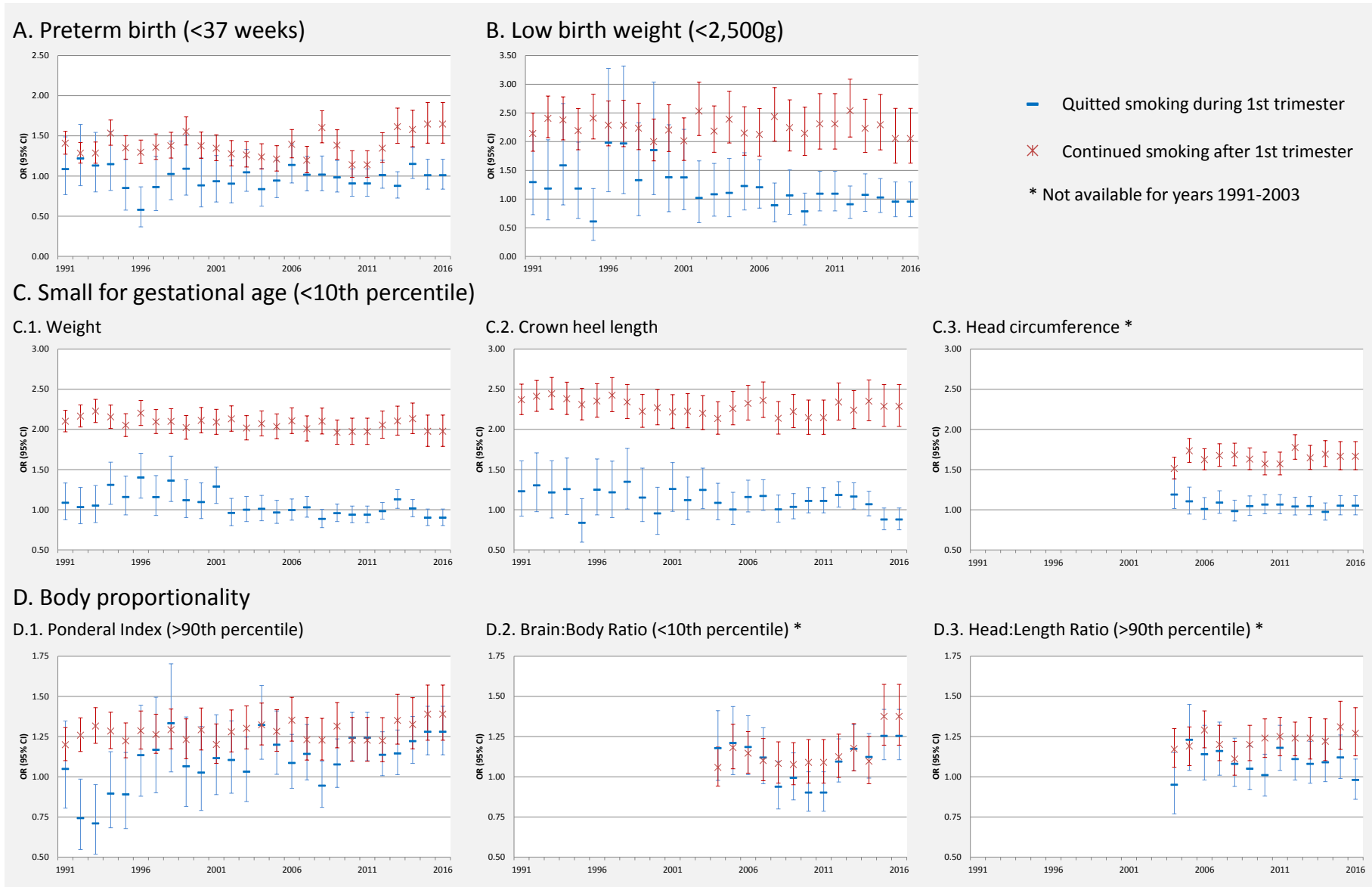


Figure S3. Association of maternal smoking with preterm birth (panel A), low birth weight (panel B), small for gestational age (panel C) and body proportionality (panel D) stratified by birth year

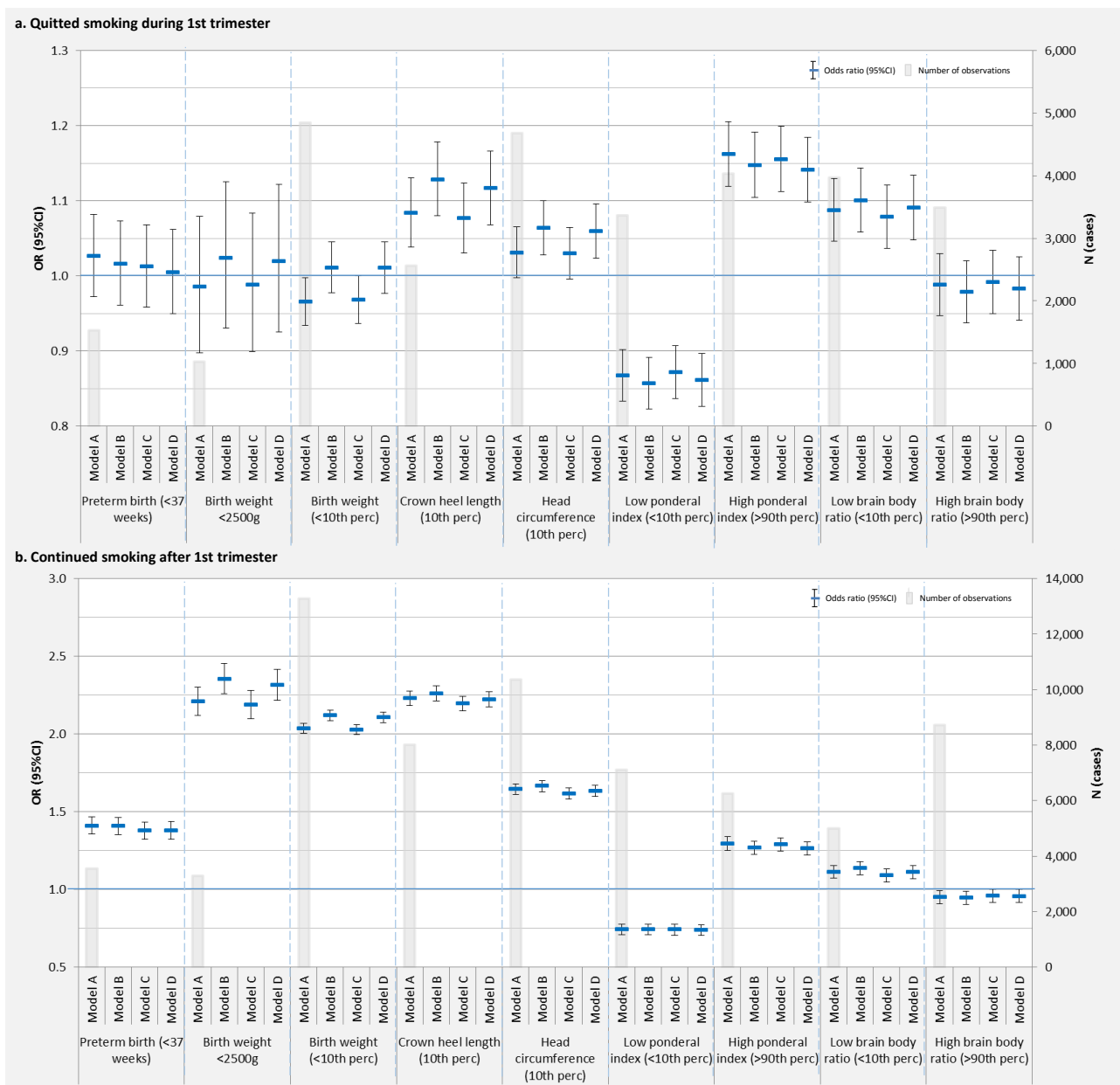


Figure S4. Results for a sensitivity analyses for additional adjustment models for regression on singletons births 2004-2016. Upper panel (a): quitted smoking during 1<sup>st</sup> trimester, lower pane (b): continued smoking after 1<sup>st</sup> trimester:



### 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].

1. Schneider, S. and J. Schutz. 2008. "Who Smokes during Pregnancy? A Systematic Literature Review of Population-Based Surveys Conducted in Developed Countries between 1997 and 2006." *The European Journal of Contraception & Reproductive Health Care: The Official Journal of the European Society of Contraception* 13 (2): 138-147. doi:10.1080/13625180802027993 [doi].
2. Gissler, M., J. Merilainen, E. Vuori, and E. Hemminki. 2003. "Register Based Monitoring shows Decreasing Socioeconomic Differences in Finnish Perinatal Health." *Journal of Epidemiology and Community Health* 57 (6): 433-439.
3. Gissler, M., O. Rahkonen, A. Arntzen, S. Cnattingius, A. M. Andersen, and E. Hemminki. 2009. "Trends in Socioeconomic Differences in Finnish Perinatal Health 1991-2006." *Journal of Epidemiology and Community Health* 63 (6): 420-425. doi:10.1136/jech.2008.079921 [doi].
4. Erickson, A. C. and L. T. Arbour. 2012. "Heavy Smoking during Pregnancy as a Marker for Other Risk Factors of Adverse Birth Outcomes: A Population-Based Study in British Columbia, Canada." *BMC Public Health* 12: 102. doi:10.1186/1471-2458-12-102 [doi].

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(b) For matched studies, give matching criteria and number of exposed and unexposed	na
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5ff
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5ff
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	5ff
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5ff
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7
		(b) Describe any methods used to examine subgroups and interactions	7
		(c) Explain how missing data were addressed	5, 7
		(d) If applicable, explain how loss to follow-up was addressed	na
		(e) Describe any sensitivity analyses	11
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5, supplement Figure S1
		(b) Give reasons for non-participation at each stage	5, supplement Figure S1
		(c) Consider use of a flow diagram	Supplement Figure S1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8, supplement Table S3
		(b) Indicate number of participants with missing data for each variable of interest	Supplement Table S3, Figure S1
		(c) Summarise follow-up time (eg, average and total amount)	na

Outcome data	15*	Report numbers of outcome events or summary measures over time	8, supplement Table S3
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8, supplement Table S3 5ff na
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11, supplement p 9ff, Figures S2, S3, S4
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12f, supplement p 13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12f
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14f

\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

# BMJ Open

## 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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Secondary Subject Heading:	Epidemiology, Paediatrics, Smoking and tobacco
Keywords:	PUBLIC HEALTH, EPIDEMIOLOGY, Smoking, pregnancy, growth restriction, register-based

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3 **1 Effects of maternal smoking on body size and proportions at birth: A register-based**  
4 **2 cohort study of 1.4 million births**  
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3 32 **Effects of maternal smoking on body size and proportions at birth: A register-based**  
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9 35 **ABSTRACT**

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11 36 **Objectives:** The aim of our work was to analyse the effect of maternal smoking on body size  
12  
13 37 and body proportions of newborns when the mother had smoked only during the 1<sup>st</sup> trimester,  
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15 38 in comparison with continued smoking after the 1<sup>st</sup> trimester. Furthermore, we have evaluated  
16  
17 39 how growth restriction associated with maternal smoking contributes to changes in body  
18  
19 40 proportions.

20 41 **Design:** Register-based cohort study

21 42 **Setting:** MATEX cohort identified from the Finnish Medical Birth Register

22 43 **Participants:** Singleton births without congenital anomalies and missing data (1.38 million)  
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24 44 from 1<sup>st</sup> of January 1991 to 31<sup>st</sup> of December 2016.

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26 45 **Methods:** Logistic regression was used to quantify the effect of maternal smoking, stratified  
27  
28 46 by the maternal smoking status.

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30 47 **Outcome measures:** Body proportions indicated by low brain-to-body ratio (defined as <10<sup>th</sup>  
31  
32 48 percentile); high ponderal index and high head-to-length ratio (defined as >90<sup>th</sup> percentile);  
33  
34 49 small body size for gestational age at birth (defined as weight, length, or head circumference  
35  
36 50 <10<sup>th</sup> percentile); and preterm birth (<37 weeks) and low birth weight (2,500 g).

37 51 **Results:** Continued smoking after the 1<sup>st</sup> trimester was associated with high ponderal index  
38  
39 52 (OR 1.26, 95% CI 1.23-1.28), low brain-to-body ratio (1.11, 1.07-1.15) and high head-to-  
40  
41 53 length ratio (1.22, 1.19-1.26), corresponding with absolute risks of 22%, 10% and 19%  
42  
43 54 respectively). The effects were slightly lower when smoking had been quit during the 1<sup>st</sup>  
44  
45 55 trimester. Similar effects were seen for the body size variables and low birth weight. Preterm  
46  
47 56 birth was not associated with smoking only during 1<sup>st</sup> trimester.

48 57 **Conclusions:** Maternal smoking, independent of smoking duration during pregnancy, was  
49  
50 58 associated with abnormal body proportions resulting from larger reduction of length and head  
51  
52 59 circumference in comparison to weight. The effects of having quit smoking during the 1<sup>st</sup>  
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54 60 trimester and having continued smoking after the 1<sup>st</sup> trimester were similar, suggesting the  
55  
56 61 importance of early pregnancy as a sensitive exposure window.  
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3 64 **KEYWORDS**  
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5 65 smoking, register research, growth restriction, prenatal, low birth weight, small for gestational  
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7 66 age, pregnancy  
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11 68 **ABBREVIATIONS**  
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13 69 OR Odds ratio  
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15 70 SGA Small for gestational age (10<sup>th</sup> smallest percentile)  
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17 71 PTB Preterm birth  
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19 72 LBW Low birth weight  
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21 73 SES Socioeconomic status  
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23 74 CI Confidence interval  
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26 76 **STRENGTHS AND LIMITATIONS OF THIS STUDY**  
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- 28 77 - The register-based design of this study provided a big study size to detect small risks  
29 78 and minimises risks for recall bias.  
30  
31 79 - The register-based design of this study allowed for sensitivity analyses including  
32 80 stratification by socioeconomic status and birth year, as well as testing of additional  
33 81 adjustment models for sociodemographic factors and co-morbidities.  
34  
35 82 - The data content of the Finnish Medical Birth Register has been validated for accuracy  
36 83 and completeness.  
37  
38 84 - Smoking status was self-reported during antenatal visits, leading to possible reporting  
39 85 bias.  
40  
41 86 - The register-based design restricted availability of information on confounders. Thus  
42 87 lifestyle related confounders, such as alcohol consumption and exposure to second  
43 88 hand tobacco smoke, could not be adjusted for.  
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## 91 INTRODUCTION

92 Smoking during pregnancy increases the risk for adverse pregnancy outcomes. Adverse  
93 pregnancy outcomes are not only associated with complications in the neonatal period, but  
94 also much later, potentially in late adulthood.[1] Tobacco smoke contains thousands of  
95 chemicals, which can cross the placenta and enter fetal circulation. Among them nicotine has  
96 a multitude of adverse effects on the development of organs including brain.[2] Other well-  
97 known toxic chemicals in tobacco smoke include carbon monoxide, which can interfere with  
98 oxygen supply of the unborn child, as well as genotoxic and carcinogenic polycyclic aromatic  
99 hydrocarbons and tobacco-specific nitrosamines, which are teratogenic in animal studies.[3]

100 The association between maternal smoking and low birth weight, commonly defined as  
101 weight below 2,500 g, is well established. In addition, data on the susceptibility of  
102 anthropometric indices, such as body length, head size and abdominal circumference to  
103 maternal smoking is emerging.[4] Low birth weight as such does not hold information  
104 whether the reduction of weight is due to loss of lean or fat body mass. Similarly, reduction in  
105 any anthropometric index alone fails to identify abnormal body proportions. Symmetrical  
106 growth restriction in utero is a stronger risk factor for later life morbidity and mortality than  
107 asymmetrical growth restriction with decreased amount of fat tissue.[5] Small for gestational  
108 age, used as a substitute for in utero growth restriction, is not an optimal proxy.[6] This  
109 clearly demonstrates the importance of body proportions for future health of the newborn.

110 The effects of early smoking cessation on body size are not well understood. Smoking only  
111 during early pregnancy has been shown to be less harmful on body size than continued  
112 smoking during late pregnancy. Previous, small studies have indicated that anthropometric  
113 indices in newborns exposed only during early pregnancy are similar to those in newborns of  
114 non-smoking mothers [7]. On the other hand, current, bigger studies report increased risk for  
115 growth restriction even in fetuses exposed only during the 1<sup>st</sup> trimester.[8] There are  
116 insufficient data about anthropometric indices, other than birth weight, in newborns exposed  
117 only during early pregnancy in comparison with newborns of non-smokers.[9]

118 The aim of our work was to analyse the effect of maternal smoking on body size and body  
119 proportions of newborns when the mother had smoked only during the 1<sup>st</sup> trimester, in  
120 comparison with newborns of mothers having continued smoking after the 1<sup>st</sup> trimester.  
121 Furthermore, we studied how growth restriction associated with maternal smoking contributes  
122 to abnormal body proportions. For this, we used the MATEX cohort identified from the  
123 Finnish Medical Birth Register. [10] Additionally, we discuss the possibility of mechanistic

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3 124 interpretations of differences in body proportions in newborns of smoking mothers compared  
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5 125 to non-exposed newborns.  
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## 9 127 **MATERIALS & METHODS**

### 11 128 **Study design**

13  
14 129 To study the effects of maternal smoking on body size and proportions at birth we conducted  
15  
16 130 a register-based cohort study utilising the Finnish MATEX cohort. The MATEX cohort was  
17  
18 131 identified from the Finnish Medical Birth Register. It is described in more detail  
19  
20 132 elsewhere.[10] The Finnish Medical Birth register contains perinatal outcomes, pregnancy  
21  
22 133 characteristics and sociodemographic information for all live births and stillbirths after the  
23  
24 134 22<sup>nd</sup> gestational week or with a birth weight of at least 500 g. The Medical Birth Register  
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26 135 receives information from standardised forms filled out by nurses and midwives during  
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28 136 antenatal care visits and after the delivery of the baby.

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30 137 This work focused on the effects of maternal smoking on singleton pregnancies delivered  
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32 138 between the 1<sup>st</sup> of January 1991 and the 31<sup>st</sup> of December 2016. From initial 1.75 million  
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34 139 mother-child pairs, 1.38 million were included in the analyses after exclusion of multiple  
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36 140 births, newborns with congenital anomalies and newborns with missing information on  
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38 141 maternal smoking status or the co-variates (Supplementary Material, Figure S1). Within the  
39  
40 142 MATEX birth cohort, information on head circumference and maternal weight and height, as  
41  
42 143 well as maternal co-morbidities was available only for the sub-population born between 2004  
43  
44 144 and 2016. The sub-population included 659,157 mother-child pairs (Supplementary Material.  
45  
46 145 Figure S1). Thus, the analyses of endpoints related to head size (small head circumference,  
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48 146 brain-to-body ratio and head-to-length ratio), as well as sensitivity analyses, were limited to  
49  
50 147 the smaller sub-population.

### 51 148 52 149 **Exposure**

53  
54 150 Maternal smoking data is recorded in the Medical Birth Register during antenatal care visits  
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56 151 as reported by the pregnant women. In the MATEX cohort, smoking status during pregnancy  
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58 152 was assigned as three categories: (1) non-smoker, (2) quit smoking during the 1<sup>st</sup> trimester,  
59  
60 153 and (3) continued smoking after the 1<sup>st</sup> trimester. The trends in smoking during the study  
154  
155 154 period have been described in detail elsewhere. [11]

## 155 **Outcomes**

156 Four groups of outcomes were included: (i) preterm birth (PTB); (ii) low birth weight (LBW)  
 157 (as a crude measure of small body size); (iii) small body size for gestational age, and (iv)  
 158 body proportions (Table 1).

159 Preterm birth (PTB) was defined as a birth before gestational week 37, and term birth as birth  
 160 during gestational week 37 or later.

161 Low birth weight (LBW) was categorized in accordance with the ICD10 diagnostic criteria as  
 162 weight below 2,500 g. As the reference category normal weight was defined as 2,500-4,500 g,  
 163 excluding high birth weight according to ICD10 definition (>4,500 g).

164 In this work we use “small for gestational age” (SGA) as a general expression to describe the  
 165 small size of the newborn. It was defined as measurement of body weight, body length or  
 166 head circumference below a cut-off at 10<sup>th</sup> percentile, while the normal range defined as  
 167 above the 10<sup>th</sup> percentile. Percentiles were defined based on sex- and parity-specific mean and  
 168 standard deviation for the corresponding gestational age (in weeks) at birth as reported in the  
 169 Finnish standard reference population.[12] It was included as an endpoint to take into account  
 170 the impact of gestational age on body size.

171 Body proportionality was assessed by three anthropometric indices in relation with each  
 172 other: ponderal index, brain: body ratio and head: length ratio. Percentiles of each ratio have  
 173 been separately estimated for each gestational age (in weeks) at births in the study population.  
 174 The 10-90<sup>th</sup> percentiles were categorized as normal and used as reference, while the tails of  
 175 the distribution (<10<sup>th</sup> percentile and >90<sup>th</sup> percentile) were categorized as abnormal

176 Ponderal index was calculated using birth weight and body length (Equation 1). It was  
 177 categorized normal (10-90<sup>th</sup> percentile of the study population, used as the reference) and high  
 178 (>90<sup>th</sup> percentile). Newborns below the 10<sup>th</sup> percentile were excluded.

$$179 \quad \text{Ponderal Index} = 100 \times \frac{\text{birth weight [g]}}{\text{body length [cm]}^3} \quad (\text{Equation 1})$$

180 Brain-to-body ratio was calculated based on head circumference and birth weight (Equation  
 181 2). It was categorized as low (<10<sup>th</sup> percentile of the study population) and normal (10-90<sup>th</sup>  
 182 percentile, reference). Newborns above the 90<sup>th</sup> percentile were excluded.

$$183 \quad \text{Brain - to - Body Ratio} = 100 \times \frac{0.037 \times \text{head circumference [cm]}^{2.57}}{\text{birth weight [g]}} \quad (\text{Equation 2})$$

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3 184 The nominator of the formula is the estimation of the brain weight according to the National  
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5 185 Institute of Neurological and Communicative Disorders and Stroke's Collaborative Perinatal  
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7 186 Project.[13]

8  
9 187 Head-to-length ratio was calculated using head circumference and body length (Equation 3).  
10  
11 188 It was categorized normal (10-90<sup>th</sup> percentile of the study population, reference) and high  
12  
13 189 (>90<sup>th</sup> percentile). Newborns below the 10<sup>th</sup> percentile were excluded.

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15 190 
$$\text{Head - to - Length Ratio} = \frac{\text{head circumference [cm]}}{\text{body length [cm]}} \quad (\text{Equation 3})$$
  
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18 191 **Covariates**

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20 192 Maternal age and gestational age in weeks were used as continuous variables in the regression  
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22 193 models. Parity was defined as nulli- or multiparous. Sex was defined as male or female.  
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24 194 Socioeconomic status (SES) was categorized as upper white collar (upper level employees  
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26 195 with administrative, managerial, professional and related occupations), lower white collar  
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28 196 (lower level employees with administrative and clerical occupations), blue collar (manual  
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30 197 workers) and others (farmers, self-employed, students, pensioners), based on the Finnish  
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32 198 national classification of occupations.[14] An additional category (information missing) was  
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34 199 added to this classification.

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201 **Table 1.** Summary of the definitions of endpoints and adjustments in the regression model  
 202 used to study the association of maternal smoking and preterm birth, low birth weight, small  
 203 for gestational age and abnormal body proportions at birth.

Endpoint	Definition case	Definition control	No. of mother-child pairs included in the regression <sup>b</sup>		Adjustment in stratified multiple logistic regression
			Quit during 1st trimester <sup>c</sup>	Continued after 1st trimester <sup>d</sup>	
<b>Preterm birth</b>	Gestational age <37 weeks	Gestational age ≥37 weeks	1 210 410	1 286 667	maternal age, sex, parity, SES
<b>Low birth weight</b>	Birth weight <2500 g	Birth weight 2,500-4,500 g	1 170 187	1 328 221	maternal age, sex, parity, gestational weeks, SES
<b>Small for gestational age</b>					
<b>Weight</b>	<10 <sup>th</sup> percentile of weight for gestational age (weeks) birth	≥10 <sup>th</sup> percentile of weight for gestational age (weeks) birth	1 210 048	1 327 783	maternal age, sex, parity, SES
<b>Body length</b>	<10 <sup>th</sup> percentile of length for gestational age (weeks) birth	≥10 <sup>th</sup> percentile of length for gestational age (weeks) birth	1 210 048	1 327 783	maternal age, sex, parity, SES
<b>Head circumference</b>	<10 <sup>th</sup> percentile of head circumference for gestational age (weeks) birth	≥10 <sup>th</sup> percentile of head circumference for gestational age (weeks) birth	573 343	601 407	maternal age, sex, parity, SES
<b>Abnormal body proportions</b>					
<b>Ponderal index</b>	>90 <sup>th</sup> percentile of weight-to-length ratio for gestational age (weeks) birth	10-90 <sup>th</sup> percentile of weight-to-length ratio for gestational age (weeks) birth	1 088 451	1 196 479	maternal age, sex, parity, SES, weight z-score
<b>Brain-to-body ratio <sup>a</sup></b>	<10 <sup>th</sup> percentile of weight-to-head circumference ratio for gestational age (weeks) birth	10-90 <sup>th</sup> percentile of weight-to-head circumference ratio for gestational age (weeks) birth	518 704	541 549	maternal age, sex, parity, SES, weight z-score
<b>Head-to-length ratio <sup>a</sup></b>	>90 <sup>th</sup> percentile of head circumference-to-length ratio for gestational age (weeks) birth	10-90 <sup>th</sup> percentile of head circumference-to-length ratio for gestational age (weeks) birth	521 420	547 597	maternal age, sex, parity, SES

204 <sup>a</sup> available for the years 2004-2016

205 <sup>b</sup> The number of mother-child pairs is the sum of non-exposed and exposed pregnancies; the number  
 206 varies for outcomes due to exclusion of mother-child pairs with missing information on the exposure,  
 207 outcome or any of the confounding factors included in the multivariate regression

208 <sup>c</sup> Comparison Quit smoking during the 1<sup>st</sup> trimester with no smoking during pregnancy

209 <sup>d</sup> Comparison Continued smoking after the 1<sup>st</sup> trimester with no smoking during pregnancy

210 SES: socioeconomic status

211

## 212 **Statistical analyses**

213 Multiple logistic regressions were performed to estimate odds ratios (ORs) with 95%  
214 confidence intervals (CI). The regressions were stratified by exposure status with no smoking  
215 as reference, i.e. smoking after the 1<sup>st</sup> trimester was compared to no smoking, and separately  
216 smoking only during the 1<sup>st</sup> trimester was compared to no smoking. The regression models  
217 were adjusted for potential confounders (Table 1; Supplementary Material, Chapter 3.2). The  
218 potential confounding factors were selected based on a combination of available data and  
219 previously published factors that could affect both maternal smoking and the outcome  
220 measures. The data were analysed using R Statistical software (version 3.4.3). The study  
221 power was estimated as the smallest detectable risk ratio. The calculations were done using R  
222 Statistical Software epiR package with assumed 95% CI and a study power of 90%.  
223 (Supplementary Material, Table S1).

## 224 **Ethics approval and register data permit**

225 In accordance with the Finnish Medical Research Act (1999/488) the MATEX study  
226 including the birth cohort identified from the Medical Birth Register has been evaluated and  
227 approved by the ethics committee of the Northern Ostrobothnia Hospital District (EETTMK  
228 44/2016; issued 18th of April, 2016). The right to use register data held by the Finnish  
229 Institute for Health and Welfare was granted under the document number  
230 THL/838/6.02.00/2016 (issued 22<sup>nd</sup> of June, 2016). Due to the full register-based design of  
231 the study, no informed consent was required from the study participants according to the  
232 Finnish Personal Data Act 1050/2018.

## 233 **Patient and Public Involvement**

234 No patients were involved in the design, recruitment or conduct of the study. The utilised  
235 register data are routinely collected in Finland.

## 237 **RESULTS**

238 Of all women with singleton births included in this study (n=1 376 778), 84.5 % were non-  
239 smokers, 3.5 % quit smoking during the 1<sup>st</sup> trimester and 12.0 % continued smoking after the  
240 1<sup>st</sup> trimester. Smoking pregnant women were younger and more likely to be nulliparous  
241 (Table 2, Supplementary Material, Table S2).

242



243 **Table 2.** Baseline characteristics by smoking status for singleton births in the MATEX cohort  
 244 (1991-2016).

	All	Non-smoker	Quit smoking during 1st trimester	Continued smoking after 1st trimester
	1,376,778	84.5 % (1,163,225)	3.5 % (47,819)	12 % (165,734)
<b>Mother</b>				
	mean (SD)	mean (SD)	mean (SD)	mean (SD)
Age (years)	29.39 (5.34)	29.78 (5.16)	27.18 (5.43)	27.3 (5.83)
Parity (nulliparous)	59.5 (818294)	39.4 (458010)	58.8 (28097)	43.2 (71629)
Marital status (married or partnership)	62 (846,557)	66.8 (771,065)	35.9 (17,039)	35.7 (58,453)
Socioeconomic status	% (count)	% (count)	% (count)	% (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)
<b>Child</b>				
	mean (SD)	mean (SD)	mean (SD)	mean (SD)
Gestational age (days)	278.66 (12.05)	278.74 (11.85)	279.34 (12.11)	277.87 (13.29)
Birth weight (g)	3549.45 (542.2)	3573.19 (536.38)	3540.62 (535.37)	3385.36 (556.1)
Body length (cm)	50.21 (2.43)	50.32 (2.4)	50.12 (2.39)	49.5 (2.59)
Head circumference (cm)*	34.94 (1.64)	34.99 (1.62)	34.91 (1.65)	34.55 (1.71)
Preterm birth	% (count)	% (count)	% (count)	% (count)
Preterm birth (<37 weeks)	4.3 (58,828)	4.1 (47,775)	4.3 (2,040)	5.4 (9,013)
Low/High birth weight	% (count)	% (count)	% (count)	% (count)
Low birth weight (<2500 g)	3.0 (40,006)	2.7 (30,443)	3.0 (1,387)	5.0 (8,176)
High birth weight (>4500 g)	3.1 (41,054)	3.3 (37,165)	2.8 (1,313)	1.6 (2,576)
Small for gestational age (<10th percentile)	% (count)	% (count)	% (count)	% (count)
Weight	11.5 (158,817)	10.4 (120,800)	13.6 (6,483)	19.1 (31,534)
Body length	6.0 (81,869)	5.2 (60,003)	7.0 (3,345)	11.2 (18,521)
Head circumference (cm)*	10.9 (69,350)	10.1 (54,321)	13.3 (4,675)	16.4 (10,354)
Abnormal body proportions	% (count)	% (count)	% (count)	% (count)
High ponderal index	11.0 (136,918)	11.1 (116,902)	11.8 (5,111)	10.1 (14,905)
Low brain-to-body ratio*	11.1 (63,520)	11.2 (54,554)	12.5 (3,968)	9.2 (4,998)
High head-to-length ratio*	9.6 (60,358)	9.8 (49,830)	8.9 (3,560)	8.3 (6,960)

\* available since 1 January 2004

Any maternal smoking was associated with an increased risk for small for gestational age (SGA) and abnormal body proportions, while preterm birth (PTB) was only associated with smoking continued after the 1<sup>st</sup> trimester (Fig. 1; Supplementary Material, Table S3).

### [Figure 1]

Any maternal smoking increased the risk for low birth weight (LBW, <2,500 g). Smoking continued after the 1<sup>st</sup> trimester in comparison to no smoking was associated with twice as high a risk for LBW (OR 2.22, 95% CI 2.14-2.30). Smoking only during the 1<sup>st</sup> trimester was also associated with an increased risk for LBW compared to non-smokers (OR 1.10, 95% CI 1.02-1.19), albeit not as strong as with continued smoking (Fig. 1A).

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3 257 Any smoking during pregnancy was associated with an increased risk for weight or body  
4  
5 258 length at birth being below the 10<sup>th</sup> percentile. Mothers who quit smoking during the 1<sup>st</sup>  
6  
7 259 trimester were at elevated, but not statistically significant risk for giving birth to a child with a  
8  
9 260 small head circumference. Among the newborns of the mothers who continued smoking after  
10  
11 261 the 1<sup>st</sup> trimester the risk for small head circumference was clearly increased with an OR of  
12 262 1.64 (95% CI 1.60-1.68) (Fig. 1A).

13  
14 263 The risk for abnormal body proportions of newborns was significantly increased by any  
15 264 maternal smoking. A stronger increase in risk was observed for high ponderal index and high  
16 265 head-to-length ratio than for low brain-to-body ratio. ORs were consistently higher if smoking  
17 266 was continued after the 1<sup>st</sup> trimester than when the mothers quit smoking during the 1<sup>st</sup>  
18 267 trimester. Nevertheless, smoking only during the 1<sup>st</sup> trimester was associated with statistically  
19 268 significantly increased risks for abnormal body proportions in newborns. Especially the risk  
20 269 for brain-to-body ratio was almost similar in those exposed only during the 1<sup>st</sup> trimester and  
21 270 those exposed also after the 1<sup>st</sup> trimester (Fig 1B).

22  
23 271 We stratified the analysis by socioeconomic status (SES) in order to investigate the influence  
24 272 of lifestyle factors and health behaviours that correlate with SES. Stratification by SES did  
25 273 not result in statistically significant differences in the risk estimates between the SES groups  
26 274 (Supplementary Material, Figure S2). We stratified the data by birth year to investigate  
27 275 potential influence of changes in the composition of tobacco (e.g. use of additives and  
28 276 changes in tar and nicotine content) and decreased social acceptability of smoking during the  
29 277 study period on the risk estimates. Stratification by birth year did not indicate a clear temporal  
30 278 pattern in risk estimates for any of the analysed endpoints (Supplementary Material, Figure  
31 279 S3). Sensitivity analysis was performed to test the sensitivity of risk estimates to choice of  
32 280 adjustment factors in the regression model. Alternative multivariate adjustment models,  
33 281 including co-morbidities or additional socio-economic factors, did not significantly alter the  
34 282 risk estimates for any of the reported endpoints (Supplementary Material, Figure S4).

35 283

## 36 284 **DISCUSSION**

37 285 In this work we investigated the effect of maternal smoking during pregnancy, categorized as  
38 286 quit during the 1<sup>st</sup> trimester and continued after the 1<sup>st</sup> trimester on preterm birth, on body size  
39 287 and body proportions at birth. The most important finding of our study is that although the  
40 288 risk for low birth weight decreases by smoking cessation during the first trimester, brain size



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3 289 and body length in relation to body weight seem not to catch up. Among the newborns  
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5 290 exposed to maternal smoking only during the 1<sup>st</sup> trimester all three measurements of body size  
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7 291 (birth weight, body length and head circumference) showed signs of growth restriction. In  
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9 292 addition, body proportions were abnormal.

10  
11 293 Our work indicates a difference in susceptibility for growth restriction between weight, body  
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13 294 length and head circumference. The observed positive association of maternal smoking with  
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15 295 ponderal index suggests a stronger reduction in length than in weight. Similarly, the  
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17 296 association with low brain-to-body ratio suggests reduction rather in brain size than in weight.  
18  
19 297 However, the association of maternal smoking with high head-to-length ratio suggests a  
20  
21 298 stronger reduction in length than in head size. It is in line with previous research showing that  
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23 299 smoking during pregnancy predominantly affects lean body mass and not fat tissue.[4] While  
24  
25 300 the associations with reduced body size and abnormal body proportion were stronger in  
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27 301 newborns of mothers who continued smoking after the 1<sup>st</sup> trimester, there was a clear  
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29 302 association also in newborns exposed only during the 1<sup>st</sup> trimester. This can be interpreted as  
30  
31 303 an effect of maternal smoking on cell proliferation during organogenesis in early prenatal  
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33 304 development. Insults during this period have been shown to persist throughout life.[5] This  
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35 305 stresses the importance of smoking cessation before pregnancy since even smoking only  
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37 306 during early pregnancy has potentially devastating effects on long term health of the unborn  
38  
39 307 child.

37  
38 308 The importance of body proportions at birth has been summarised by Zanelli and co-  
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40 309 workers.[15] Children born small and thin were shown to be more likely to develop coronary  
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42 310 heart disease as obese adults than their peers, who were born small but not thin. It is not  
43  
44 311 possible to infer from our study whether the high ponderal index and higher risk for shorter  
45  
46 312 body length is comparable to stunting due to malnutrition and infections. Mechanistic studies  
47  
48 313 of the observed effects are needed to extrapolate the risks to later life.

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49 314 Additionally, smaller head circumference has been shown to directly translate into a smaller  
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51 315 brain.[16, 17] Insults during early development of the brain, such as maternal smoking, have  
52  
53 316 been shown to result in differences in DNA methylation, altered expression of genes  
54  
55 317 regulating brain structure and function [18] and reduction in neuronal content of the  
56  
57 318 brain,[19]. Also, neurophysiological functions and overall brain functions are altered due to  
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59 319 prenatal smoking.[20] The smaller brain volume observed in newborns has been shown to  
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320 persist into young adulthood.[21]

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3 321 Overall, our results are in line with previously reported studies by other groups  
4 322 (Supplementary Material, Table S4).[22-25] Smoking quit during the 1<sup>st</sup> trimester had a  
5 323 weaker effect on reduction in weight or length measures, whereas smoking especially at the  
6 324 end of pregnancy reduced femur length, abdominal circumference and biparietal  
7 325 diameter.[26] A clear dose response of smoking (number of cigarettes per day) on reduction  
8 326 of birth weight and increase in ponderal index has been demonstrated.[17, 27] Previous  
9 327 studies examining the effect of smoking cessation during pregnancy have consistently  
10 328 reported a reduction in harm compared with continued smoking.[4]

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17 329 There is increasing evidence from animal studies of nicotine as a causative agent for  
18 330 reproductive toxicity, including detrimental effects on brain.[28, 29] In a large  
19 331 epidemiological study, among the few existing ones, aberrations in lung development due to  
20 332 nicotine replacement products used during pregnancy has already been suggested.[30]  
21 333 Epidemiological studies on the effects of nicotine products, other than cigarettes, are still  
22 334 needed. We recommend the inclusion of information on the use of nicotine products in the  
23 335 Medical Birth Register. This would allow detecting pregnancies at risk more reliably and  
24 336 facilitating epidemiological research on nicotine exposure during pregnancy beyond maternal  
25 337 smoking.

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34 338 This work is solely based on routinely collected register data, which dictates the data  
35 339 availability. We tested our results for sensitivity to different adjustment models. Our results  
36 340 were robust against inclusion of maternal co-morbidities, maternal anthropometric indices,  
37 341 social background and reproductive history as confounders in the statistical model. Smoking  
38 342 and socioeconomic status have been shown to correlate well with other lifestyle related  
39 343 factors and they are reliable markers for the unaccounted factors.[31] The smoking  
40 344 information was self-reported by the mother during antenatal care visits. Thus, reporting bias  
41 345 cannot be excluded. It was not possible to analyse the impact of timing of smoking cessation  
42 346 in more detail or possible dose response relationships due to lack of data. In addition, we lack  
43 347 information on paternal and household smoking. Second hand tobacco smoke exposure during  
44 348 pregnancy has been shown to increase the risk for low birth weight and growth  
45 349 restriction.[32]. We cannot exclude the possibility that some observed effects are partly  
46 350 attributable to second hand tobacco smoke exposure, especially in those women who ceased  
47 351 smoking during their 1<sup>st</sup> trimester. Our definition of indicators for body proportions were  
48 352 constrained by available data in the register. Ideally, the outcomes in this work would be  
49 353 supplemented with clinical criteria collected during for example prenatal ultrasound scans,

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3 354 such as femur length, abdominal circumference, and skinfold thickness. Further, the cut-off at  
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5 355 the 10<sup>th</sup> percentile for the definition of small body size and abnormal body proportions was  
6  
7 356 arbitrary due to a lack of clear data on a threshold for increased risk for complications later in  
8  
9 357 life. Socioeconomic status was assigned here solely on maternal occupation and no  
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11 358 information about the father's occupation was available. For a high proportion of mothers  
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13 359 (18%) the occupation was not available. Previous studies applied the same SES categorization  
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15 360 and showed that the missing information did not bias the proportions in the other SES  
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17 361 categories.[24]

18 362 Study strengths include the register-based design with a large study size and practically  
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20 363 complete population representativeness. Earlier analyses on the occupation codes available in  
21  
22 364 the Medical Birth Register have shown that the socioeconomic confounding is reasonably  
23  
24 365 well taken into account. Overall, occupation is well correlated with education and income in  
25  
26 366 Finland and it can be used as an indicator for socioeconomic health differences. [33, 34] An  
27  
28 367 earlier study showed a reasonable match between serum cotinine and self-reported smoking  
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30 368 status as applied in the Medical Birth Register.[35]

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## 32 370 **CONCLUSIONS**

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35 371 This study showed that maternal smoking is associated with a stronger reduction in body  
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37 372 length and head circumference than in birth weight, leading to changed body proportions. The  
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39 373 effects on body proportions of having quit smoking during the 1<sup>st</sup> trimester or having  
40  
41 374 continued smoking after the 1<sup>st</sup> trimester were similar, stressing the importance of early  
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43 375 pregnancy as a sensitive exposure window. Furthermore, it suggests a limited potential to  
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45 376 repair fetal damage induced in early pregnancy. Lower brain-to-body ratio suggests that any  
46  
47 377 smoking during the pregnancy may lead to losses in the development of central nervous  
48  
49 378 system. The effects on body size (weight, length and head circumference) were more  
50  
51 379 pronounced in newborns of mothers who continued smoking after the 1<sup>st</sup> trimester.

52  
53 380 It seems important to study the association of growth restriction and other adverse effects with  
54  
55 381 the use of nicotine therapy products, as already demonstrated in animal studies. Until their  
56  
57 382 safety has been proven, caution should be taken when advising pregnant women. Routine  
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59 383 collection of information on the use of nicotine replacement products in the Medical Birth  
60  
384 Register is needed for more careful follow-up of risk pregnancies and to facilitate scientific  
385 research on specific effects associated with nicotine replacement products.

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9  
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13  
14 391 Cluster environment and implementing the Medical Birth Register linkage. We also thank the  
15  
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20 393 **CONTRIBUTORS**

21  
22 394 IKR, OH, KV and MV conceived the research question and designed the study. IKR  
23  
24 395 conducted statistical analysis, interpreted the results and wrote the first and subsequent drafts  
25  
26 396 of the manuscript with support of OH. KV, MV, MG and HdR contributed to data  
27  
28 397 interpretation and revisions of the manuscript. MV, OH, KV and IKR obtained funding. All  
29  
30 398 authors approved the final version of the submitted manuscript.

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35  
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39  
40 403 interests.

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47  
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5 412 institutions.

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11 414 **DISCLAIMER**

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13 415 None of the funding agencies had a role in n the study design; in the collection, analysis and  
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15 416 interpretation of the data; in the writing of the report; and in the decision to submit the paper  
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17 417 for publication.

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23 419 **DATA SHARING STATEMENT**

24  
25 420 Data may be obtained from a third party and are not publicly available. The Finnish Institute  
26  
27 421 of Health and Welfare is the controller of the Medical Birth Register. Data may be obtained  
28  
29 422 from the register controller ([https://thl.fi/en/web/thlfi-en/statistics/information-on-](https://thl.fi/en/web/thlfi-en/statistics/information-on-statistics/register-descriptions/newborns)  
30  
31 423 [statistics/register-descriptions/newborns](https://thl.fi/en/web/thlfi-en/statistics/information-on-statistics/register-descriptions/newborns) accessed 29 May 2019).

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35 425 **PATIENT CONSENT**

36  
37 426 Not required.

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42 428 **ETHICAL APPROVAL**

43  
44 429 The study was approved by the ethics committee of the Northern Ostrobothnia Hospital  
45  
46 430 District (EETTMK 44/2016; issued 18th April 2016). The right to use of register data held by  
47  
48 431 the Finnish Institute for Health and Welfare was granted under the document number  
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3 543 **TABLE**  
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5 544 **Table 1.** Summary of the definitions of endpoints and adjustments in the regression model  
6 used to study the association of maternal smoking and preterm birth, low birth weight, small  
7 for gestational age and abnormal body proportions at birth.  
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14 548 **Table 2.** Baseline characteristics by smoking status for all singleton births in the MATEX  
15 cohort (1991-2016).  
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23 552 **FIGURE LEGEND**  
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26 553 **Fig 1** Adjusted odds ratios (OR) for association of maternal smoking with (A) traditional birth  
27 outcomes (preterm birth, low birth weight and small for gestational age); and with (B)  
28 abnormal body proportions; adjusted for maternal age, sex, parity, socioeconomic status, and  
29 gestational week (for low birth weight) and weight z-score (in regressions with weight  
30 included in the dependent variable); marker + error bar: OR (95% CI).  
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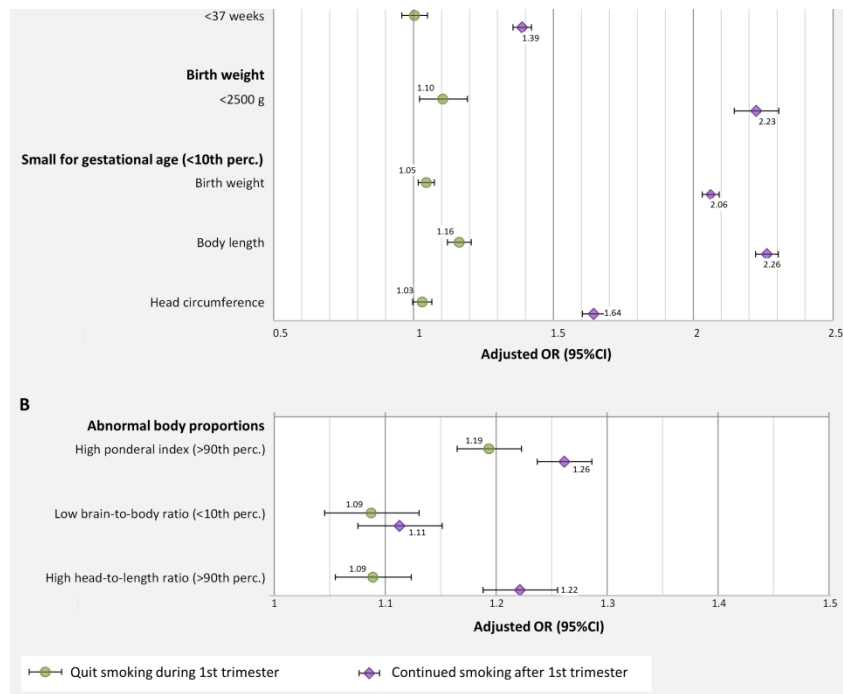


Fig 1 Adjusted odds ratios (OR) for association of maternal smoking with (A) traditional birth outcomes (preterm birth, low birth weight and small for gestational age); and with (B) abnormal body proportions; adjusted for maternal age, sex, parity, socioeconomic status, and gestational week (for low birth weight) and weight z-score (in regressions with weight included in the dependent variable); marker + error bar: OR (95% CI).

254x190mm (300 x 300 DPI)

# 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 22<sup>nd</sup> 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 1<sup>st</sup> January 1991 and 31<sup>st</sup> 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-variates. 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).

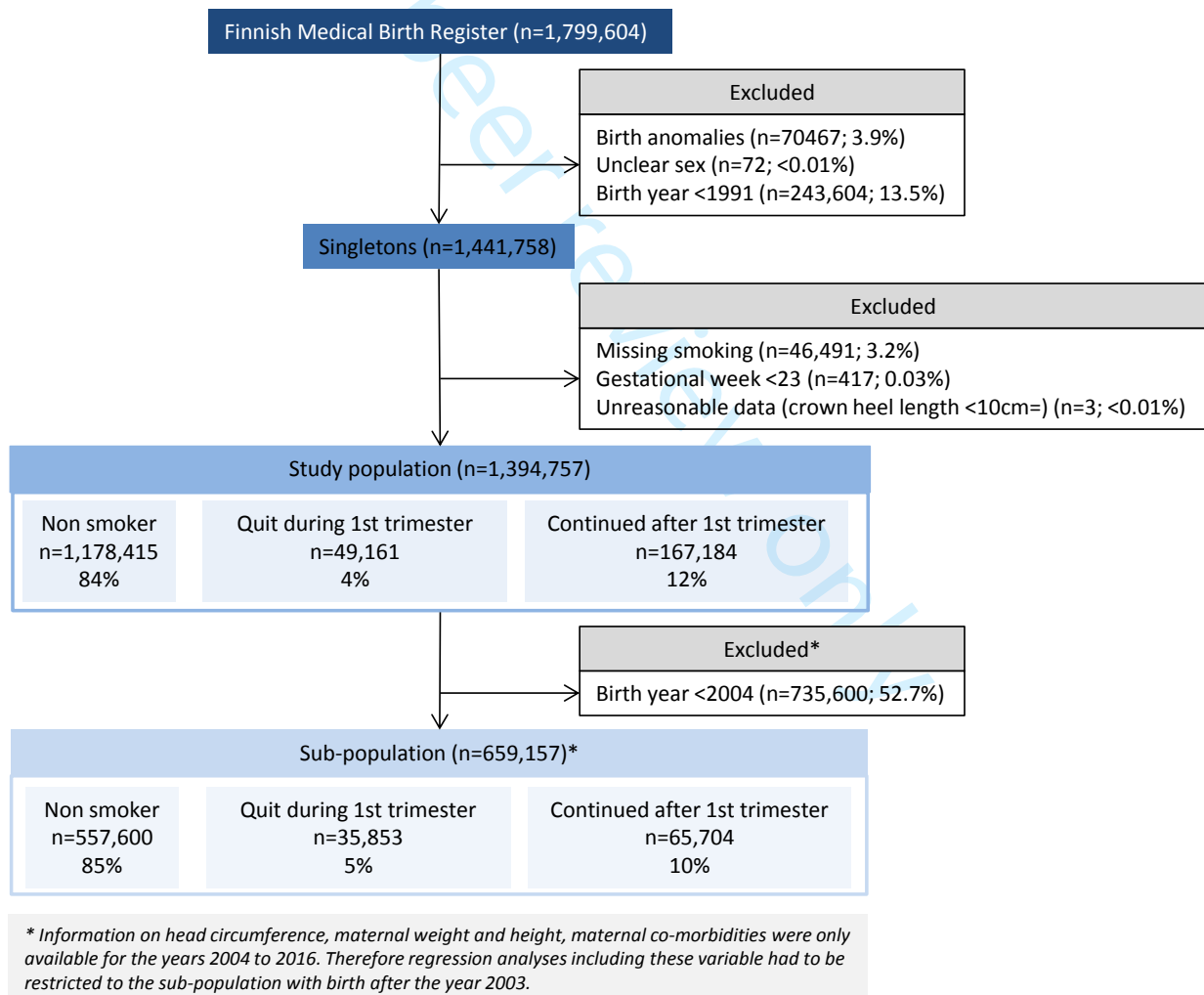


Figure S1. Data cleaning process with exclusion criteria and number of excluded children

## 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 1<sup>st</sup> trimester and 12.0 % (n=165,734) continued smoking after the 1<sup>st</sup> 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 <sup>^</sup>		n <sup>^</sup>		n <sup>^</sup>		n <sup>^</sup>	
<b>Mother</b>		1,376,778		84 % (1,163,225)		3 % (47,819)		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)
<b>Child</b>		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 1<sup>st</sup> 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)
<b>Preterm birth</b>				
Preterm birth (<37 weeks)	1.04 (0.99-1.08)	1.34 (1.31-1.37)	1.00 (0.95-1.04)	<b>1.38 (1.35-1.42)</b>
Late preterm birth (34-36 weeks)	1.02 (0.97-1.08)	1.26 (1.23-1.30)	0.98 (0.93-1.03)	<b>1.30 (1.26-1.33)</b>
Moderately preterm birth (28-33 weeks)	0.93 (0.75-1.14)	1.61 (1.47-1.76)	0.93 (0.75-1.14)	<b>1.72 (1.56-1.88)</b>
Extremely preterm birth (<28 weeks)	0.93 (0.75-1.14)	1.61 (1.47-1.76)	0.93 (0.75-1.14)	<b>1.72 (1.56-1.88)</b>
<b>Low birth weight</b>				
Low birth weight (<2500 g)	1.10 (1.04-1.16)	1.89 (1.85-1.94)	<b>1.10 (1.02-1.19)</b>	<b>2.22 (2.14-2.30)</b>
Low birth weight (1000-2499 g)	1.12 (1.05-1.18)	1.92 (1.87-1.97)	<b>1.10 (1.02-1.19)</b>	<b>2.22 (2.14-2.30)</b>
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)
<b>Small for gestational age (&lt;10th percentile)</b>				
Birth weight	1.35 (1.31-1.38)	2.02 (2.00-2.05)	<b>1.04 (1.01-1.07)</b>	<b>2.06 (2.03-2.09)</b>
Crown heel length	1.38 (1.33-1.43)	2.31 (2.27-2.35)	<b>1.16 (1.12-1.20)</b>	<b>2.26 (2.22-2.30)</b>
Head circumference*	1.36 (1.32-1.40)	1.74 (1.70-1.78)	1.03 (0.99-1.06)	<b>1.64 (1.60-1.68)</b>
<b>Abnormal body proportions</b>				
High ponderal index (>90th percentile)	1.06 (1.03-1.10)	0.89 (0.87-0.91)	<b>1.19 (1.15-1.23)</b>	<b>1.26 (1.23-1.28)</b>
Low brain-to-body ratio (<10th percentile)*	1.13 (1.09-1.17)	0.79 (0.77-0.82)	<b>1.08 (1.04-1.12)</b>	<b>1.11 (1.07-1.15)</b>
High head-to-length ratio (>90th percentile)*	1.11 (1.07-1.15)	1.20 (1.17-1.23)	<b>1.09 (1.05-1.13)</b>	<b>1.22 (1.19-1.26)</b>

\* 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)
<b>Preterm birth</b>				
<b>Preterm birth (&lt;37 weeks)</b>	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]
<b>Late preterm birth (34-36 weeks)</b>	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]
<b>Moderately preterm birth (28-33 weeks)</b>	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]
<b>Extremely preterm birth (&lt;28 weeks)</b>	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]
<b>Low birth weight</b>				
<b>Low birth weight (&lt;2500 g)</b>	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]
<b>Low birth weight (1000-2499 g)</b>	1.10 (1.02-1.19)	2.22 (2.14-2.30)		
<b>Extremely low birth weight (&lt;1000 g)</b>	1.42 (0.48-3.77)	1.32 (0.82-2.10)		
<b>Small for gestational age (10th percentile)</b>				
<b>Birth weight</b>	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]
<b>Crown heel length</b>	1.16 (1.12-1.20)	2.26 (2.22-2.30)		
<b>Head circumference</b>	1.03 (0.99-1.06)	1.64 (1.60-1.68)		
<b>Abnormal body proportions</b>				
<b>High ponderal index (&gt;90th percentile)</b>	1.19 (1.15-1.23)	1.26 (1.23-1.28)		
<b>Low brain-to-body ratio (&lt;10th percentile)</b>	1.08 (1.04-1.12)	1.11 (1.07-1.15)		
<b>High head-to-length ratio (&gt;90<sup>th</sup> percentile)</b>	1.09 (1.05-1.13)	1.22 (1.19-1.26)		

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### 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:**
  - o *Preterm birth*: maternal age (continuous), sex, parity (nulli/multi), SES
  - o *Birth weight (<2500g)*: maternal age (continuous), sex, parity (nulli/multi), gestational weeks (continuous), SES
  - o *Small for gestational age (weight/length/head <10th percentile)*: maternal age (continuous), sex, parity (nulli/multi), SES
  - o *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

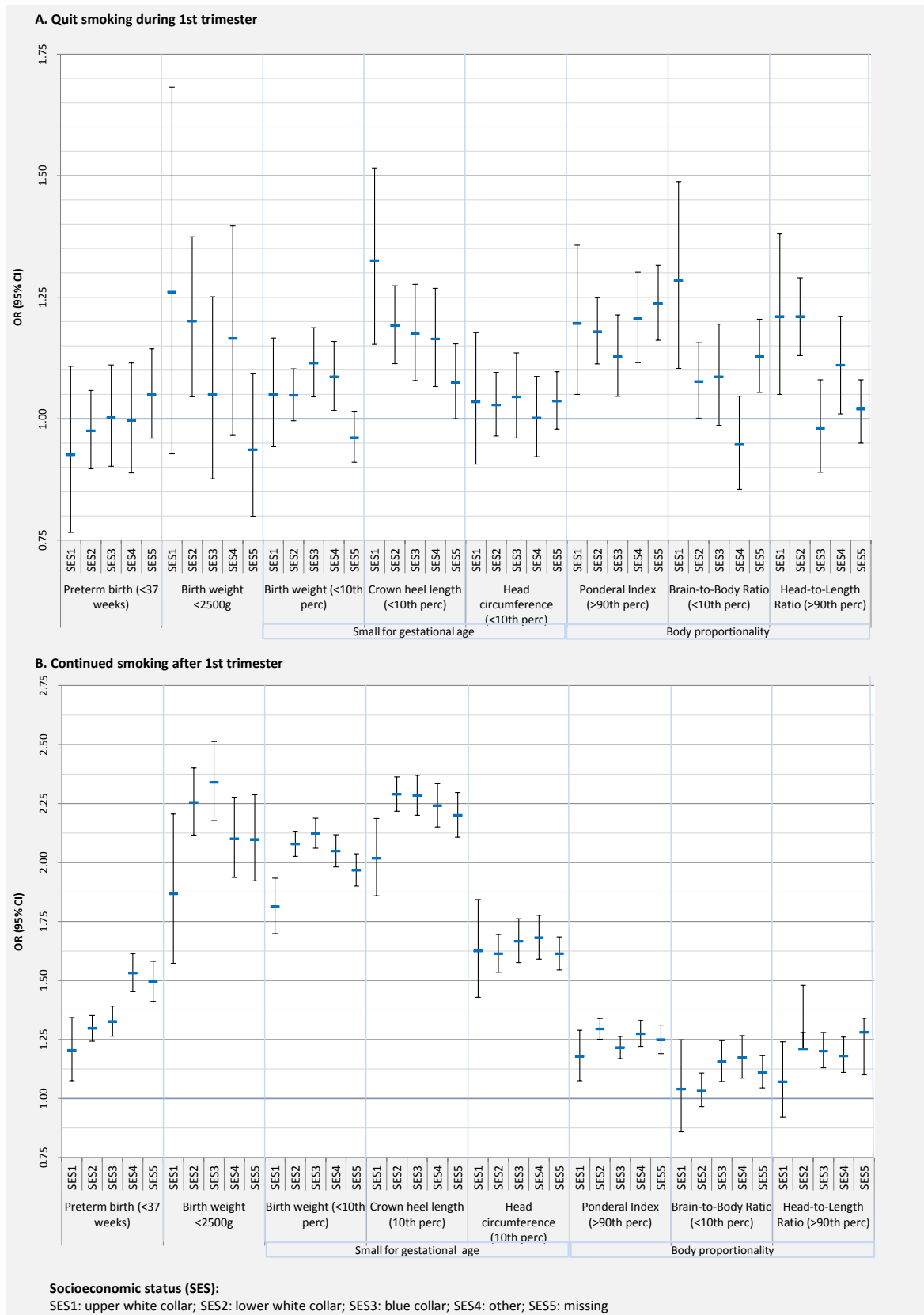


Figure S2. Association of maternal smoking and birth outcomes stratified by socioeconomic status. Pane A: quit smoking during 1<sup>st</sup> trimester; panel B: continued smoking after 1<sup>st</sup> trimester.

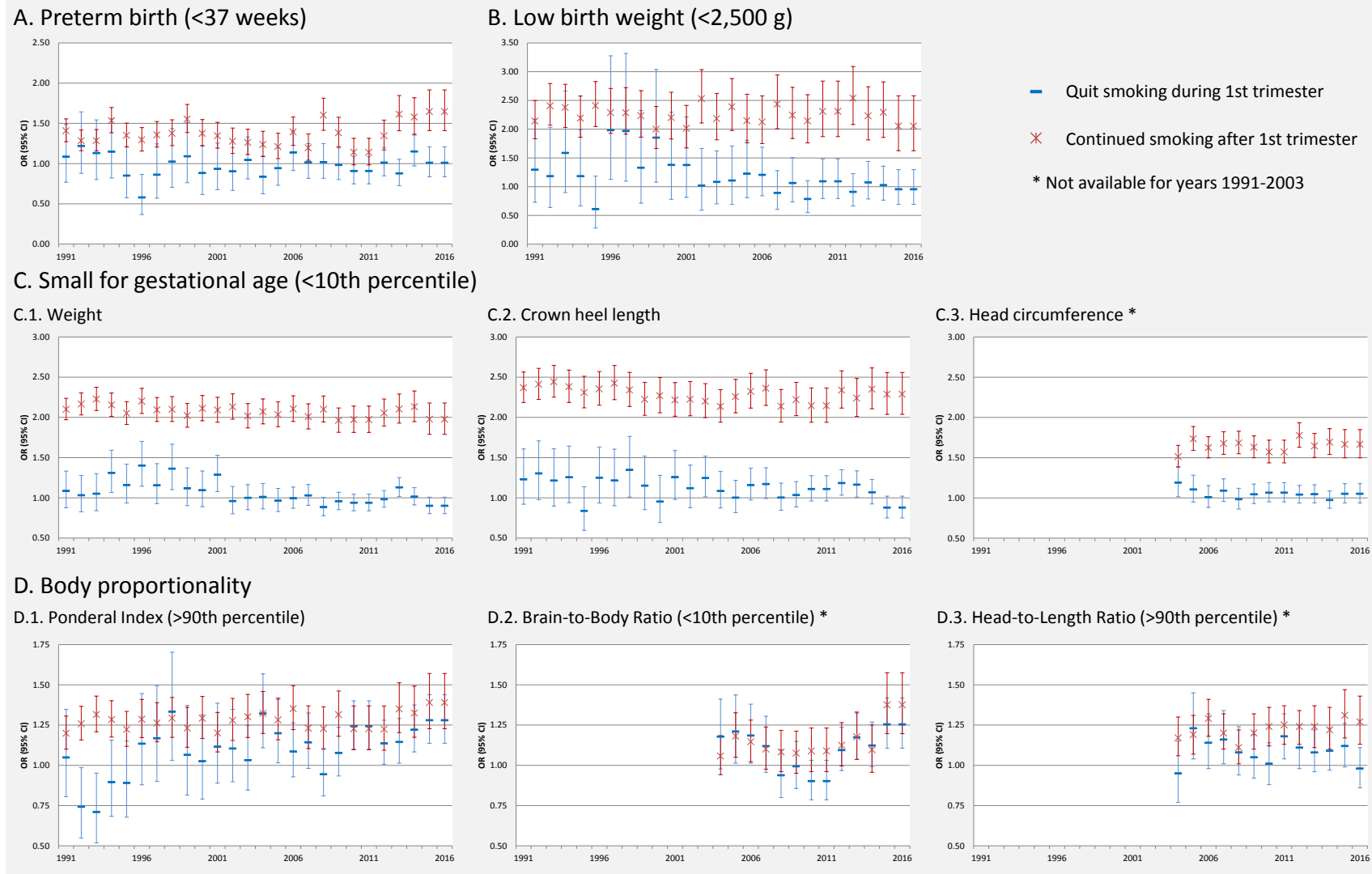


Figure S3. Association of maternal smoking with preterm birth (panel A), low birth weight (panel B), small for gestational age (panel C) and body proportionality (panel D) stratified by birth year

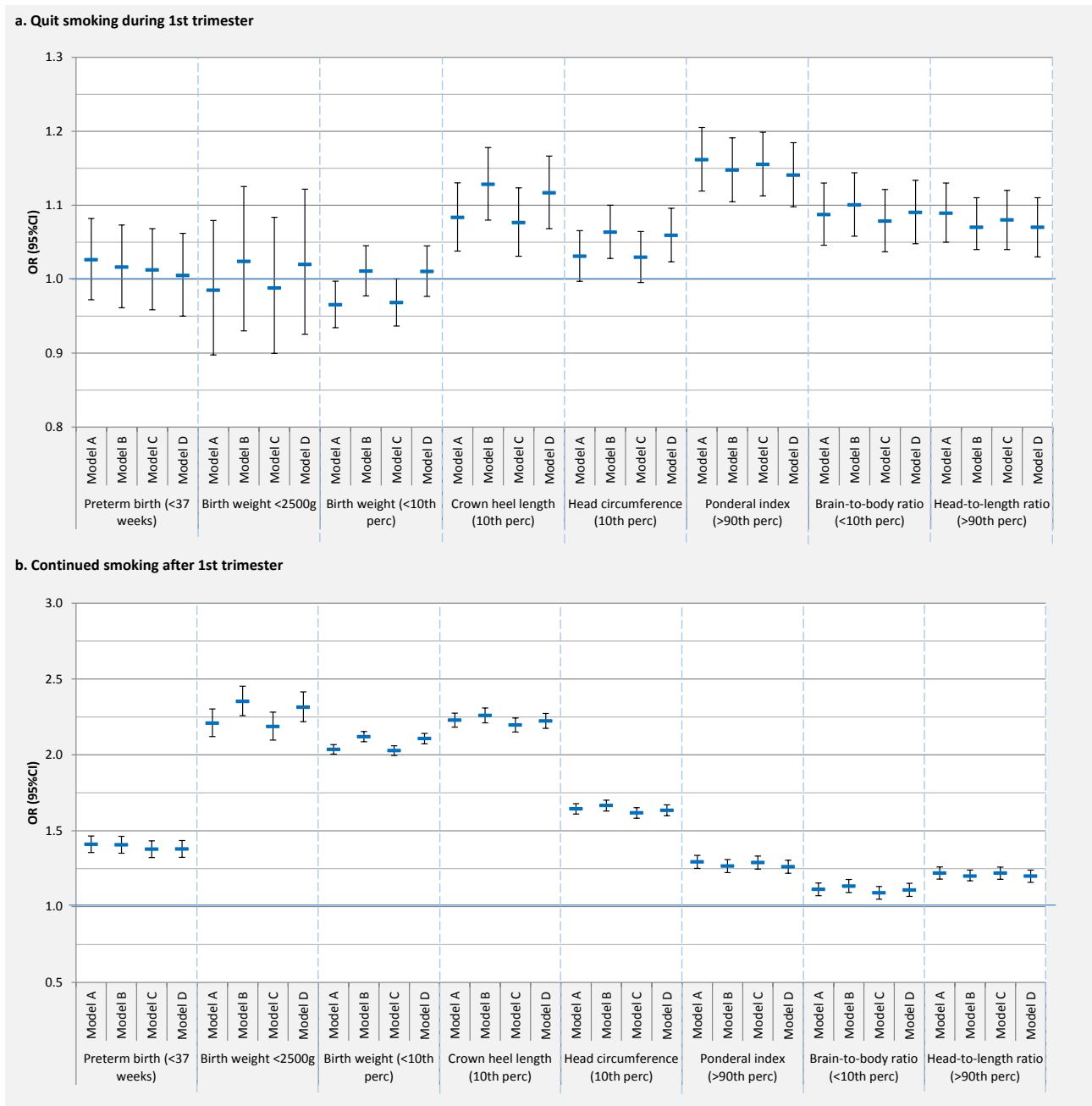


Figure S4. Results for a sensitivity analyses for additional adjustment models for regression on singletons births 2004-2016. Upper panel (a): quit smoking during 1<sup>st</sup> trimester, lower pane (b): continued smoking after 1<sup>st</sup> trimester:

### 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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2. Gissler, M., J. Merilainen, E. Vuori, and E. Hemminki. 2003. "Register Based Monitoring shows Decreasing Socioeconomic Differences in Finnish Perinatal Health." *Journal of Epidemiology and Community Health* 57 (6): 433-439.
3. Gissler, M., O. Rahkonen, A. Arntzen, S. Cnattingius, A. M. Andersen, and E. Hemminki. 2009. "Trends in Socioeconomic Differences in Finnish Perinatal Health 1991-2006." *Journal of Epidemiology and Community Health* 63 (6): 420-425. doi:10.1136/jech.2008.079921 [doi].
4. Erickson, A. C. and L. T. Arbour. 2012. "Heavy Smoking during Pregnancy as a Marker for Other Risk Factors of Adverse Birth Outcomes: A Population-Based Study in British Columbia, Canada." *BMC Public Health* 12: 102. doi:10.1186/1471-2458-12-102 [doi].

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4ff
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5f
		(b) For matched studies, give matching criteria and number of exposed and unexposed	na
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5ff
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5ff
Bias	9	Describe any efforts to address potential sources of bias	11
Study size	10	Explain how the study size was arrived at	5f
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6f
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9; 11
		(b) Describe any methods used to examine subgroups and interactions	11
		(c) Explain how missing data were addressed	5f
		(d) If applicable, explain how loss to follow-up was addressed	na
		(e) Describe any sensitivity analyses	11
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5, supplement Figure S1
		(b) Give reasons for non-participation at each stage	5, supplement Figure S1
		(c) Consider use of a flow diagram	Supplement Figure S1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10, supplement Table S3
		(b) Indicate number of participants with missing data for each variable of interest	Supplement Table S3, Figure S1
		(c) Summarise follow-up time (eg, average and total amount)	na

Outcome data	15*	Report numbers of outcome events or summary measures over time	10, supplement Table S3
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10 (Figure 1), supplement Table S3 6f; Table 1 abstract
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11, supplement p 9ff, Figures S2, S3, S4
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13f, supplement p 13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12; 14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15f

\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.