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Maternal smoking alters body proportions at birth: A register-based cohort study of 1.4 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^3)
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^{th} 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 1st 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 22nd 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 1st January 1991 and 31st 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-variates (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 1st 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) quitted smoking during the 1st trimester, and (3) continued smoking after the 1st 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 10th 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 (10-90th percentile, used as the reference) and high (>90th percentile) of the study population. The lowest 10th percentile was excluded.

Equation 1.

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

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

Equation 2.

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

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 (10-90th percentile, reference) and high (>90th percentile) of the study population. The lowest 10th percentile was excluded.

Equation 3.

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

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 (famers, 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 Pubic 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 1st trimester and 12.0% continued smoking after the 1st 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
Preterm birth	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)*		
Low birth weight	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)*		
Small for gestational age						
Weight	<10th 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	
Crown heel length	<10th 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)*		
Head circumference	<10th 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)*		
Body proportions						
Ponderal index	>90th 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)*		
Brain:body ratio [a]	<10th 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)*		
Head:length ratio [a]	>90th 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)*		

[a] Available 2004-2016

quitted: Quitted smoking during 1st trimester

continued: Continued smoking after the 1st 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 (<10th 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 1st trimester than among those who quitted

smoking during the 1st trimester. Nevertheless, smoking only during early pregnancy was associated with statistically significantly increased risks for altered body proportions. Especially the risk for BBR was almost similar in those exposed only during the 1st trimester and those exposed throughout pregnancy (Fig 1).

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

We stratified the analysis by socioeconomic status (SES) in order to investigate the influence of lifestyle factors and health behaviours that correlate with SES. Stratification by SES did not show statistically significant differences in the risk estimates (Supplement, Figure S2). We stratified the data by birth year to investigate potential influence of changes in tobacco composition and social acceptability of smoking during the study period on the risk estimates. Stratification by birth year did not indicate a clear temporal pattern in any of the analysed endpoints (Supplement, Figure S3). Sensitivity analysis was performed to test the robustness of results against choice of adjustment factors in the regression model. Different adjustment models did not significantly alter the risk estimates for any of the reported endpoints (Supplement, Figure S4).

DISCUSSION

In this work we investigated the effect of smoking during early and late pregnancy on body size and proportions at birth. The most important finding of our study is that although the risk for low birth weight decreases by smoking cessation during the first trimester, brain size and crown-heel length in relation to body weight seem not to catch up. All anthropometric indices showed signs of growth restriction and body proportions were altered in newborns exposed to maternal smoking only during the 1st trimester.

This work indicated a difference in susceptibility for growth restriction between the anthropometric indices. The association with PI suggests a stronger reduction in length than in weight. Similarly, the association with low BBR suggests reduction rather in brain size than in

weight. However, the association of maternal smoking with high HLR suggests a stronger reduction in length than in head size. It is in line with previous research showing that smoking during pregnancy predominantly affect lean body mass and not fat body mass.[4] Although risks are lower in newborns whose mothers quit smoking during the 1st trimester than in those who continued smoking, suggest a direct effect of maternal smoking on cell proliferation during organogenesis in early prenatal development. Insults during this period are persistent throughout life.[5] This stresses the importance of smoking cessation before pregnancy since even smoking only during very early pregnancy has potentially a devastating effect on the long term health of the unborn child.

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

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

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

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

nicotine replace product (NCP) use during pregnancy has already been suggested.[30] Epidemiological studies on the effects of nicotine products, other than cigarettes, are needed in order to give informed recommendations to pregnant women who wish to quit smoking. We recommend the inclusion of information on the use of nicotine products in the MBR. This would allow detecting pregnancies at risk more reliably and facilitating epidemiological research on nicotine exposure during pregnancy beyond maternal smoking.

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. 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.[31] It was not possible to analyse the impact of timing of smoking cessation in more detail or possible dose response relationships due to lack of data. In addition, we lack information on paternal and household smoking. Second hand tobacco smoke exposure during pregnancy has been shown to increase the risk for low birth weight and growth restriction.[32]. We cannot exclude the possibility that some observed effects are partly attributable to second hand tobacco smoke exposure, especially in those women who ceased smoking during their 1st trimester.

Strength of this work is the register-based design with, to our knowledge, the biggest study population. Overall, the MBR data, including the smoking information, have been shown to be reliable.[33-35] SES was assigned solely on maternal occupation and no information about the father´s occupation was available. For a high proportion of mothers (18%) the occupation was not available. Previous studies applied the same SES categorization and showed that the missing information did not bias the proportions in the other SES categories.[24] Overall, occupation is well correlated with education and income in Finland and it can be used as an indicator for socioeconomic health differences.[33]

CONCLUSIONS

This study shows that growth restriction by maternal smoking during pregnancy is not proportional. Maternal smoking was associated with a stronger reduction in crown-heel length and head circumference than weight. It seems that especially brain is suffering as judged by the more extensive reduction of head circumference than weight. The effects were more

pronounced for smoking throughout pregnancy than for smoking only during early pregnancy. Although quitting smoking during early pregnancy reduced the risk for preterm birth to background level, the association with generalized reduction in all anthropometric indices and changed body proportions stresses the importance of the period of early prenatal development and the limited potential to repair damages induced in early pregnancy.

Animal studies suggest nicotine as a potential causative agent, which questions the safety of nicotine replacement therapy during pregnancy. It is highly important to study the association of growth restriction and other adverse effects with the use of nicotine therapy products. Until their safety has been proven, caution should be taken and nicotine therapy products should not be recommended for pregnant women as safer alternative to active smoking. Routine collection of information on the use of nicotine replacement products in the Medical Birth Register is needed for more careful follow-up of risk pregnancies and to facilitate scientific research on specific effects associated with nicotine replacement products.

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CONTRIBUTORS

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

COMPETING INTERESTS

Kirsi Vähäkangas is currently the chair of the scientific committee of the Savuton Suomi (Smoke-free Finland) 2030 initiative. Other authors declare no competing interests.

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DISCLAIMER

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

DATA SHARING STATEMENT

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

PATIENT CONSENT

Not required.

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).

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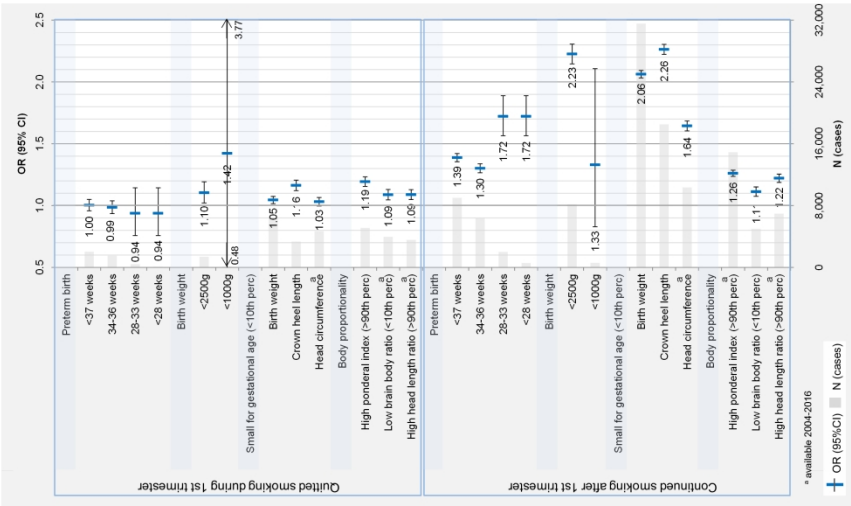
TABLE

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



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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 22nd 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 1st January 1991 and 31st December 2016. From initial 1.75 million children born in this period, 1.38 million were included in the analyses after exclusion of multiple births, congenital malformations and newborns with missing information on maternal smoking status or co-variates (Figure S1).

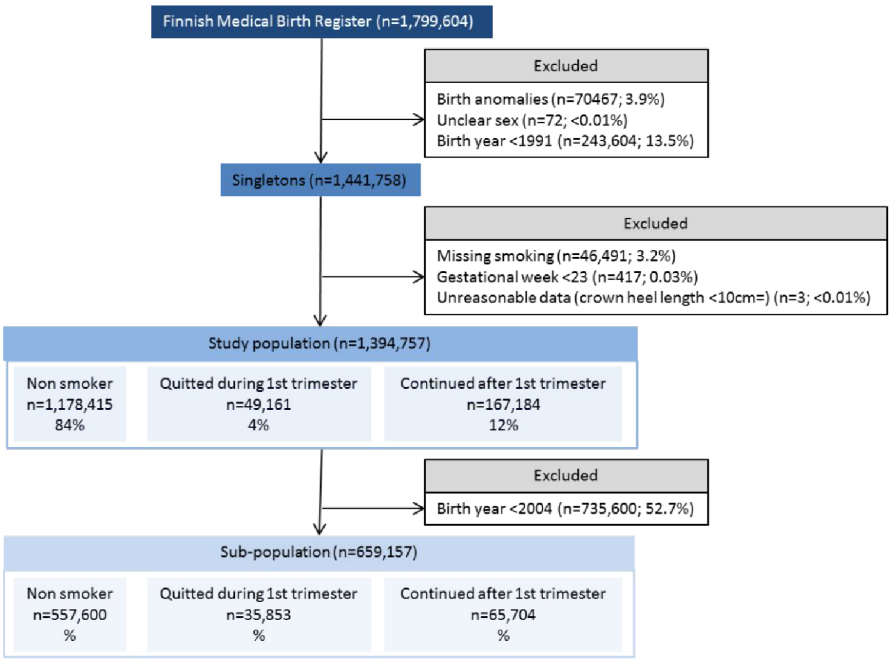

Figure S1. Data cleaning process with exclusion criteria and number of excluded children

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*

		Complete MATEX cohort		Sub-cohort*	
Incidence rate	**Endpoint(s)**	**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) quitted smoking during the 1st trimester and 12.0% (n=165,734) continued smoking after the 1st trimester. Smoking pregnant women tend to be younger and nulliparous, and prenatally exposed children tend to be born lighter (Table S2).

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

	All		Non smoker		Quitted smoking during 1st trimester		Continued smoking after 1st trimester	
	n		n		n		n	
Mother		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

	All		Non smoker		Quitted smoking during 1st trimester		Continued smoking after 1st trimester	
	n		n		n		n	
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)
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 1st 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)
Preterm birth				
Preterm birth (<37 weeks)	1.04 (0.99-1.08)	1.34 (1.31-1.37)	1.00 (0.95-1.04)	**1.38 (1.35-1.42)**
Late preterm birth (34-36 weeks)	1.02 (0.97-1.08)	1.26 (1.23-1.30)	0.98 (0.93-1.03)	**1.30 (1.26-1.33)**
Moderately preterm birth (28-33 weeks)	0.93 (0.75-1.14)	1.61 (1.47-1.76)	0.93 (0.75-1.14)	**1.72 (1.56-1.88)**
Extremely preterm birth (<28 weeks)	0.93 (0.75-1.14)	1.61 (1.47-1.76)	0.93 (0.75-1.14)	**1.72 (1.56-1.88)**
Low/High birth weight				
Low birth weight (<2500g)	1.10 (1.04-1.16)	1.89 (1.85-1.94)	**1.10 (1.02-1.19)**	**2.22 (2.14-2.30)**
Low birth weight (1000-2500g)	1.12 (1.05-1.18)	1.92 (1.87-1.97)	**1.10 (1.02-1.19)**	**2.22 (2.14-2.30)**
Extremely low birth weight (<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)
High birth weight (>4500g)	0.85 (0.81-0.90)	0.48 (0.47-0.50)	0.99 (0.94-1.05)	**0.50 (0.48-0.52)**
Small for gestational age (10th percentile)				
Birth weight	1.35 (1.31-1.38)	2.02 (2.00-2.05)	**1.04 (1.01-1.07)**	**2.06 (2.03-2.09)**
Crown heel length	1.38 (1.33-1.43)	2.31 (2.27-2.35)	**1.16 (1.12-1.20)**	**2.26 (2.22-2.30)**
Head circumference*	1.36 (1.32-1.40)	1.74 (1.70-1.78)	1.03 (0.99-1.06)	**1.64 (1.60-1.68)**
Body proportionality				
High ponderal index (>90th percentile)	1.06 (1.03-1.10)	0.89 (0.87-0.91)	**1.19 (1.15-1.23)**	**1.26 (1.23-1.28)**
Low brain:body ratio (<10th percentile)*	1.13 (1.09-1.17)	0.79 (0.77-0.82)	**1.08 (1.04-1.12)**	**1.11 (1.07-1.15)**
High head:length ratio (>90th percentile)*	1.11 (1.07-1.15)	1.20 (1.17-1.23)	**1.09 (1.05-1.13)**	**1.22 (1.19-1.26)**

* Available for years 2004-2016

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

Table S4. MATEX study results and previously published Finnish results

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

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

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

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

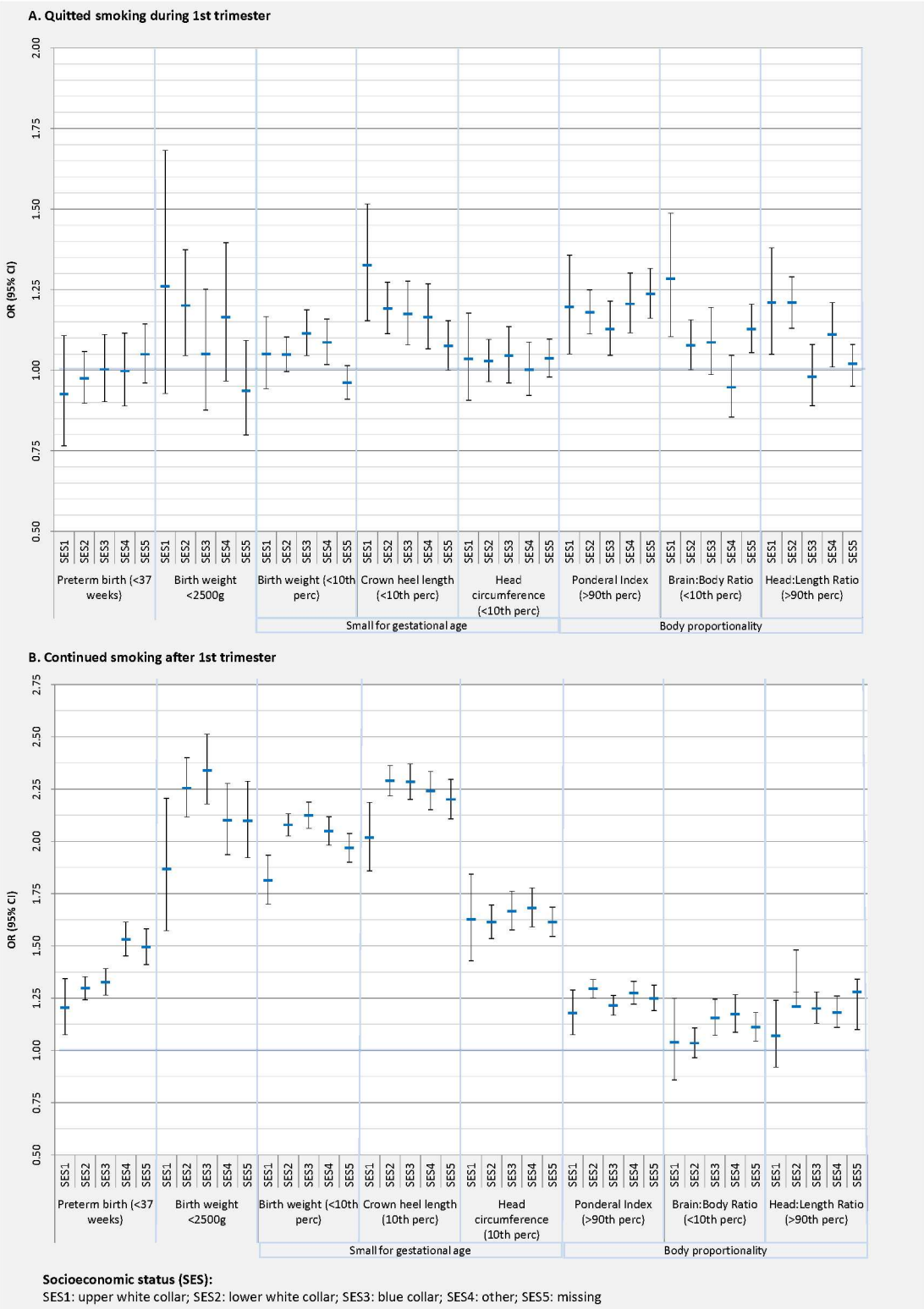

Figure S2. Association of maternal smoking and birth outcomes stratified by socioeconomic status. Pane Al: quitted smoking during 1st trimester; panel B: continued smoking after 1st trimester.

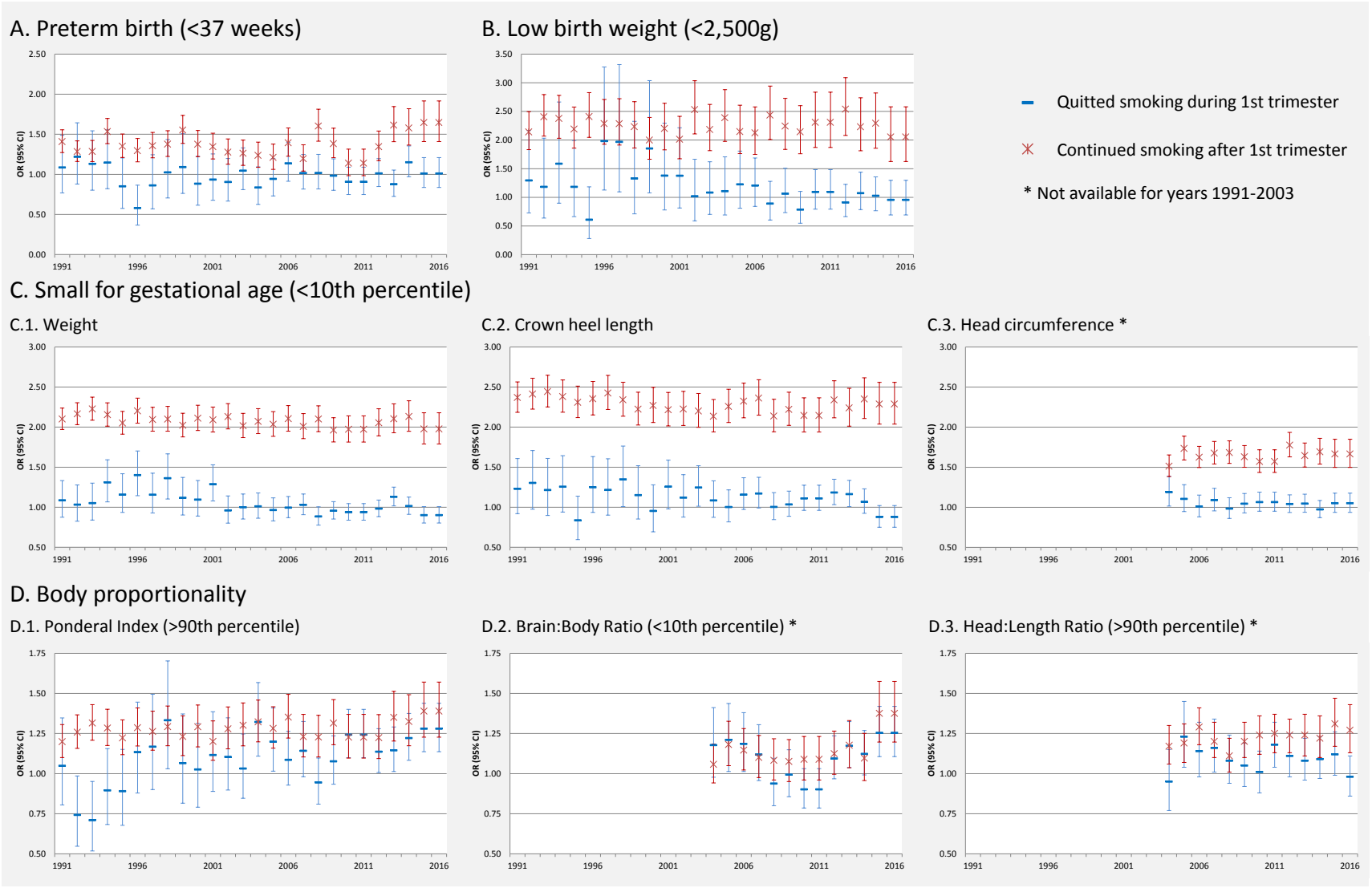

Figure S3. Association of maternal smoking with preterm birth (panel A), low birth weight (panel B), small for gestational age (panel C) and body proportionality (panel D) stratified by birth year

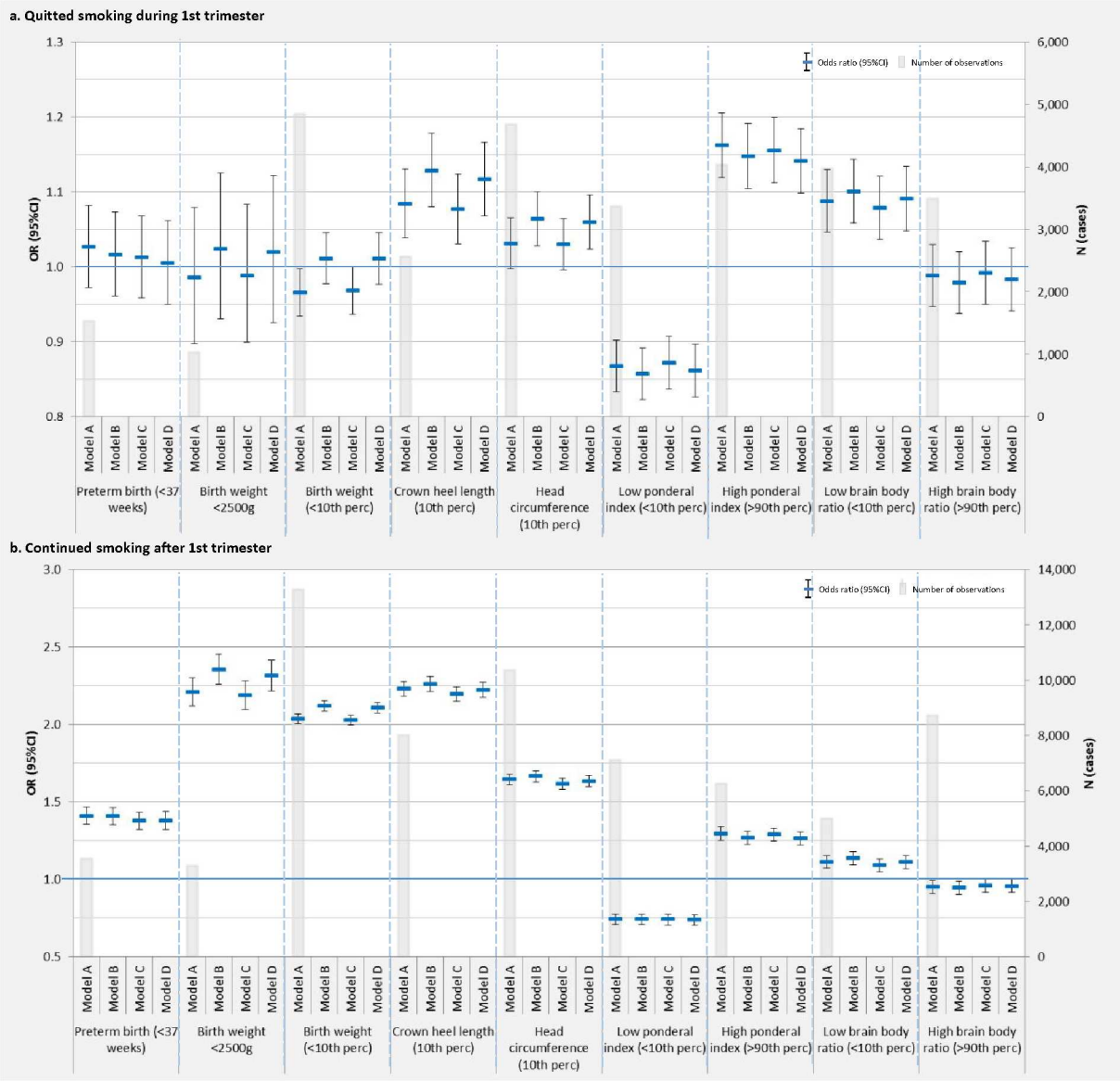

Figure S4. Results for a sensitivity analyses for additional adjustment models for regression on singletons births 2004-2016. Upper panel (a): quitted smoking during 1st trimester, lower pane (b)l: continued smoking after 1st trimester:

3.3 Discussion

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

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

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

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

	Item No	Recommendation	Page No
Title and abstract	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
Introduction			
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
Methods			
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
Results			
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
Discussion			
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
Other information			
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.

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

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Maternal smoking alters body proportions at birth: A register-based cohort study of 1.4 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 1st trimester or continued after the 1st 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 1st 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 1st trimester or continued after the 1st 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 (10th 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 1st 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 1st trimester on body size and body proportions at birth, and preterm birth. 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 and proportions 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 described in more detail elsewhere.[10] This register contains perinatal outcomes, pregnancy characteristics and sociodemographic information for all live births and stillbirths after the 22nd gestational week or with a birth weight of at least 500g. The Medical Birth Register 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 1st January 1991 and 31st 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-variates (Supplementary Material, Figure S1). 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 (Supplementary Material. Figure S1).

We analysed the effect of smoking quitted during the 1st trimester and smoking continued after the 1st trimester separately with no smoking during pregnancy as a reference on four groups of outcomes: (i) preterm birth (PTB); (ii) low birth weight (LBW) (as a crude measure of small body size); (iii) small body size for gestational age, and (iv) body proportions (Table 1).

Exposure

Maternal smoking data is recorded in the Medical Birth Register 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) quitted smoking during the 1st trimester, and (3)

continued smoking after the 1st 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), further divided into late preterm (34-36 weeks), moderately preterm (28-33 weeks), and extremely preterm (<28 weeks).

Low birth weight (LBW) was categorized in accordance with ICD10 diagnosis criteria as generally low (<2,500g), further divided into 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 10th 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 three anthropometric indices in relation with each other: ponderal index, brain: body ratio and head: length ratio.

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

Equation 1.

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

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

Equation 2.

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

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 (10-90th percentile of the study population, reference) and high (>90th percentile). The lowest 10th percentile was excluded.

Equation 3.

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

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 (famers, 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[a]	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	

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

[a] quitted: Quitted smoking during 1st trimester; continued: Continued smoking after the 1st trimester
[b] 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 Pubic 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 1st trimester and 12.0% continued smoking after the 1st 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
	1,376,778	**84% (1,163,225)**	**3.5% (47,819)**	**12% (165,734)**
Mother				
	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)
Child				
	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 (<2500g)	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 (<1000g)	0.3 (3,360)	0.2 (2,660)	0.2 (103)	0.4 (597)
High birth weight (>4500g)	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)
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 1st trimester (Fig. 1; Supplementary Material, Table S3).

[Figure 1]

Maternal smoking increased the risk for low birth weight (LBW, <2,500g). Smoking continued after the 1st trimester doubled the risk for LBW (OR 2.22, 95% CI 2.14-2.30). Smoking quitted during the 1st 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 (<10th percentile) in the weight and crown-heel dimension. Mothers who quitted smoking during the 1st 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 1st 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 1st trimester than among those who quitted smoking during the 1st trimester. Nevertheless, smoking quitted during the 1st trimester was associated with statistically significantly

increased risks for altered body proportions. Especially the risk for brain-to-body ratio was almost similar in those exposed only during the 1st trimester and those exposed throughout pregnancy (Fig 1B).

We stratified the analysis by socioeconomic status (SES) in order to investigate the influence of lifestyle factors and health behaviours that correlate with SES. Stratification by SES did not show statistically significant differences in the risk estimates (Supplementary Material, Figure S2). We stratified the data by birth year to investigate potential influence of changes in tobacco composition and social acceptability of smoking during the study period on the risk estimates. Stratification by birth year did not indicate a clear temporal pattern in any of the analysed endpoints (Supplementary Material, Figure S3). Sensitivity analysis was performed to test the robustness of results against choice of adjustment factors in the regression model. Different adjustment models did not significantly alter the risk estimates for any of the reported endpoints (Supplementary Material, Figure S4).

DISCUSSION

In this work we investigated the effect of smoking quitted during the 1st trimester and continued after the 1st trimester on preterm birth, body size and body proportions at birth. The most important finding of our study is that although the risk for low birth weight decreases by smoking cessation during the first trimester, brain size and body length in relation to body weight seem not to catch up. Among the newborns exposed to maternal smoking only during the 1st trimester all three measurements of body size (birth weight, body length and head circumference) showed signs of growth restriction. In addition, body proportions were altered.

Our work indicates a difference in susceptibility for growth restriction between weight, body length and head circumference. The association with ponderal index suggests a stronger reduction in length than in weight. Similarly, the association with low brain-to-body ratio suggests reduction rather in brain size than in weight. However, the association of maternal smoking with high head-to-length ratio suggests a stronger reduction in length than in head size. It is in line with previous research showing that smoking during pregnancy predominantly affect lean body mass and not fat body mass.[4] Although risks are lower in newborns whose mothers quitted smoking during the 1st trimester than in those who continued smoking, the results suggest a direct effect of maternal smoking on cell proliferation during organogenesis in early prenatal development. Insults during this period are persistent

throughout life.[5] This stresses the importance of smoking cessation before pregnancy since even smoking only during very early pregnancy has potentially devastating effects on long term health of the unborn child.

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

Additionally, smaller head circumference has been shown to directly translate into a smaller brain.[16, 17] I Insults, such as maternal smoking, during early development of the brain have been shown to result in differences in DNA methylation, altered expression of genes regulating brain structure and function [18] and reduce neuronal content of the brain,[19]. Also, neurophysiological functions and overall brain functions are altered due to prenatal smoking.[20] The smaller brain volume observed in newborns has been shown to persist into young adulthood.[21]

Overall, our results are in line with previously reported studies by other groups (Supplementary Material, Table S4).[22-25] Smoking quitted during the 1st trimester had a weaker effect on reduction in weight or length measures, whereas smoking especially at the end of pregnancy reduced femur length, abdominal circumference and biparietal diameter.[26] A clear dose response of smoking (number of cigarettes per day) on reduction of birth weight and increase in ponderal index has been demonstrated.[17, 27] Previous studies examining the effect of smoking cessation during pregnancy consistently reported a reduction in harm compared with continued smoking.[4]

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 nicotine replacement products use during pregnancy has already been suggested.[30] Epidemiological studies on the effects of nicotine products, other than cigarettes, are still needed.. We recommend the inclusion of information on the use of nicotine products in the MBR. This would allow detecting pregnancies at risk more reliably and facilitating epidemiological research on nicotine exposure during pregnancy beyond maternal smoking.

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. 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.[31] It was not possible to analyse the impact of timing of smoking cessation in more detail or possible dose response relationships due to lack of data. In addition, we lack information on paternal and household smoking. Second hand tobacco smoke exposure during pregnancy has been shown to increase the risk for low birth weight and growth restriction.[32]. We cannot exclude the possibility that some observed effects are partly attributable to second hand tobacco smoke exposure, especially in those women who ceased smoking during their 1st trimester.

Strength of this work is the register-based design with, to our knowledge, the biggest study population so far. Overall, the Medical Birth Register data, including the smoking information, have been shown to be reliable.[33-35] SES was assigned solely on maternal occupation and no information about the father´s occupation was available. For a high proportion of mothers (18%) the occupation was not available. Previous studies applied the same SES categorization and showed that the missing information did not bias the proportions in the other SES categories.[24] Overall, occupation is well correlated with education and income in Finland and it can be used as an indicator for socioeconomic health differences.[33]

CONCLUSIONS

This study shows that growth restriction by maternal smoking during pregnancy is not proportional. Maternal smoking was associated with a stronger reduction in crown-heel length and head circumference than weight. It seems that especially brain is suffering as judged by the more extensive reduction of head circumference than weight. The effects were more pronounced for smoking continued after 1st trimester than for smoking quitted during 1st trimester. Although quitting smoking during 1st trimester reduced the risk for preterm birth to background level, the association with generalized reduction in all anthropometric indices and changed body proportions stresses the importance of the period of early prenatal development and the limited potential to repair damages induced in early pregnancy.

Animal studies suggest nicotine as a potential causative agent, which questions the safety of nicotine replacement therapy during pregnancy. It is highly important to study the association of growth restriction and other adverse effects with the use of nicotine therapy products. Until their safety has been proven, caution should be taken when advising pregnant women. Routine collection of information on the use of nicotine replacement products in the Medical Birth Register is needed for more careful follow-up of risk pregnancies and to facilitate scientific research on specific effects associated with nicotine replacement products.

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CONTRIBUTORS

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

COMPETING INTERESTS

Kirsi Vähäkangas is currently the chair of the scientific committee of the Savuton Suomi (Smoke-free Finland) 2030 initiative. Other authors declare no competing interests.

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DISCLAIMER

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

DATA SHARING STATEMENT

Data may be obtained from a third party and are not publicly available. The Finnish Institute of Health and Welfare is controller of the Medical Birth Register. Data may be obtained from the register controller (https://thl.fi/en/web/thlfi-en/statistics/information-on-statistics/register-descriptions/newborns accessed 29 May 2019).

PATIENT CONSENT

Not required.

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 Finnish 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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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).

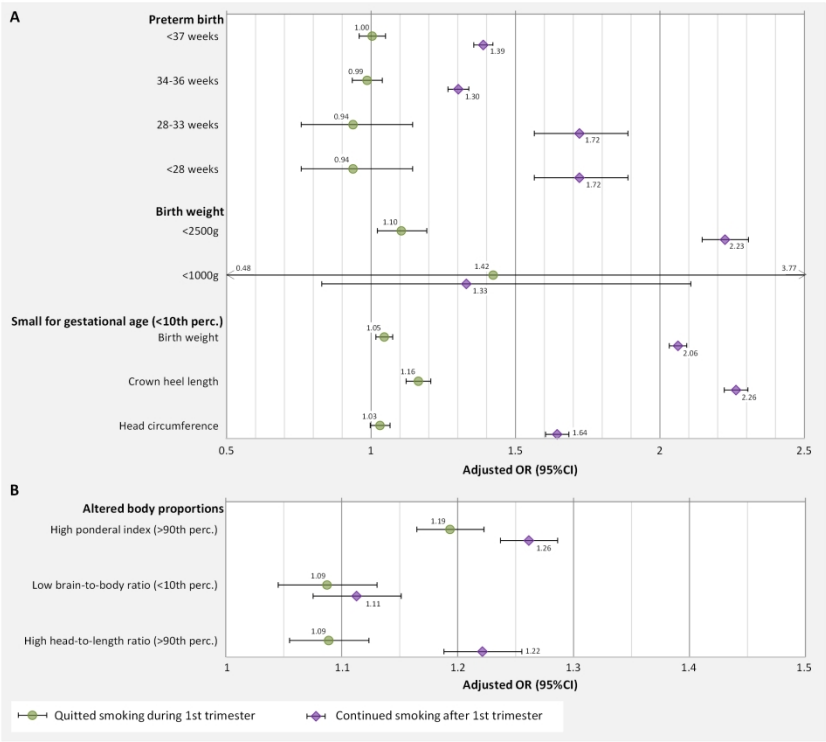

Fig 1 Adjusted odds ratios (OR) for association of maternal smoking with (A) traditional birth outcomes (preterm birth, low birth weight and small for gestational age); and with (B) altered body proportions; adjusted for maternal age, sex, parity, socioeconomic status, and gestational week (for low birth 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 22nd 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 1st January 1991 and 31st December 2016. From initial 1.75 million children born in this period, 1.38 million were included in the analyses after exclusion of multiple births, congenital malformations and newborns with missing information on maternal smoking status or co-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).

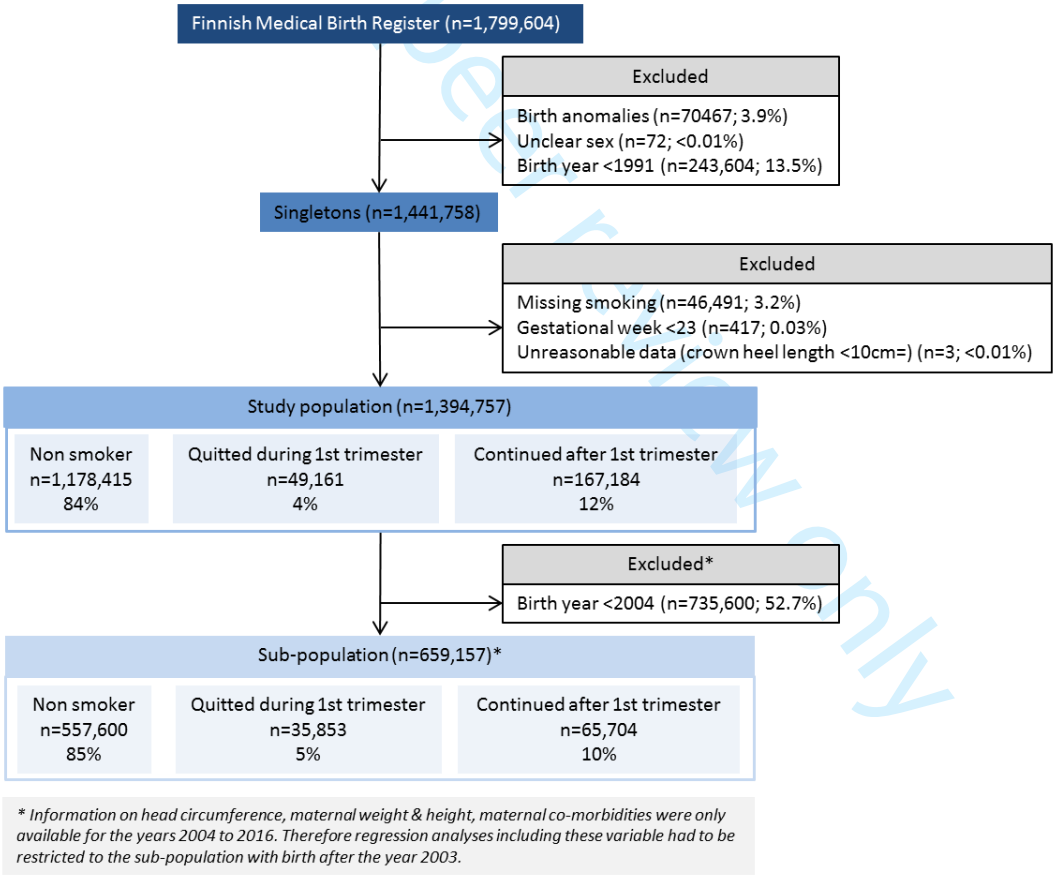

Figure S1. Data cleaning process with exclusion criteria and number of excluded children

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*

		Complete MATEX cohort		Sub-cohort*	
Incidence rate	**Endpoint(s)**	**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) quitted smoking during the 1st trimester and 12.0% (n=165,734) continued smoking after the 1st trimester. Smoking pregnant women tend to be younger and nulliparous, and prenatally exposed children tend to be born lighter (Table S2).

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

	All		Non smoker		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)

Cont. Table S2

	All		Non smoker		Quitted smoking during 1st trimester		Continued smoking after 1st trimester	
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)
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^ number of mother-child pairs with available information

* Available 2004-2016

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

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

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

* Available for years 2004-2016

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

Table S4. MATEX study results and previously published Finnish results

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

1. Raisanen, S., U. Sankilampi, M. Gissler, M. R. Kramer, T. Hakulinen-Viitanen, J. Saari, and S. Heinonen. 2014. "Smoking Cessation in the First Trimester Reduces most Obstetric Risks, but Not the Risks of Major Congenital Anomalies and Admission to Neonatal Care: A Population-Based Cohort Study of 1,164,953 Singleton Pregnancies in Finland." *Journal of Epidemiology and Community Health* 68 (2): 159-164. doi:10.1136/jech-2013-202991 [doi].

2. Raisanen, S., M. R. Kramer, M. Gissler, J. Saari, and S. Heinonen. 2014. "Unemployment at Municipality Level is Associated with an Increased Risk of Small for Gestational Age Births--a Multilevel Analysis of all Singleton Births during 2005-2010 in Finland." *International Journal for Equity in Health* 13 (1): 1. doi:10.1186/s12939-014-0095-1 [doi].

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

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

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

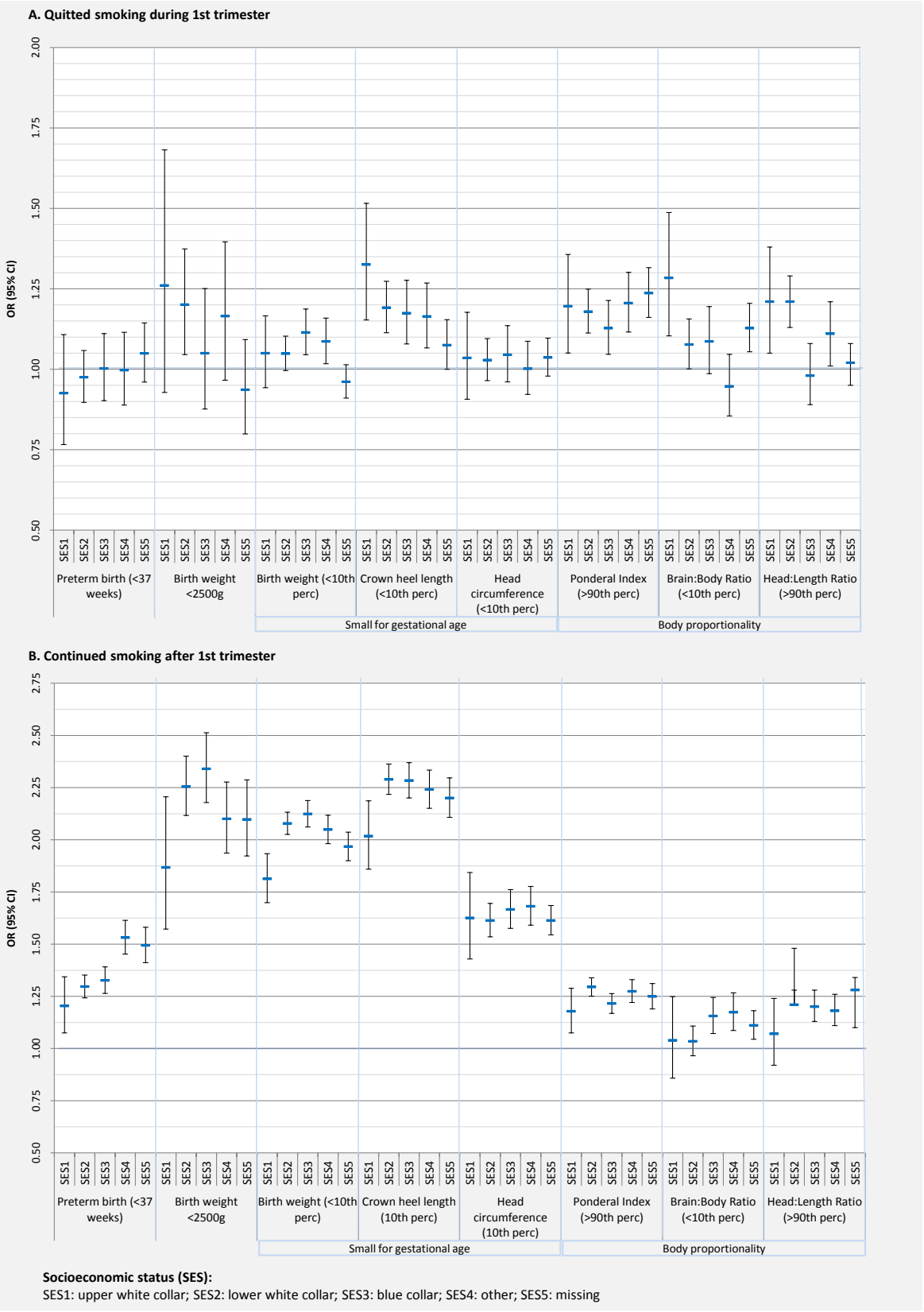

Figure S2. Association of maternal smoking and birth outcomes stratified by socioeconomic status. Pane Al: quitted smoking during 1st trimester; panel B: continued smoking after 1st trimester.

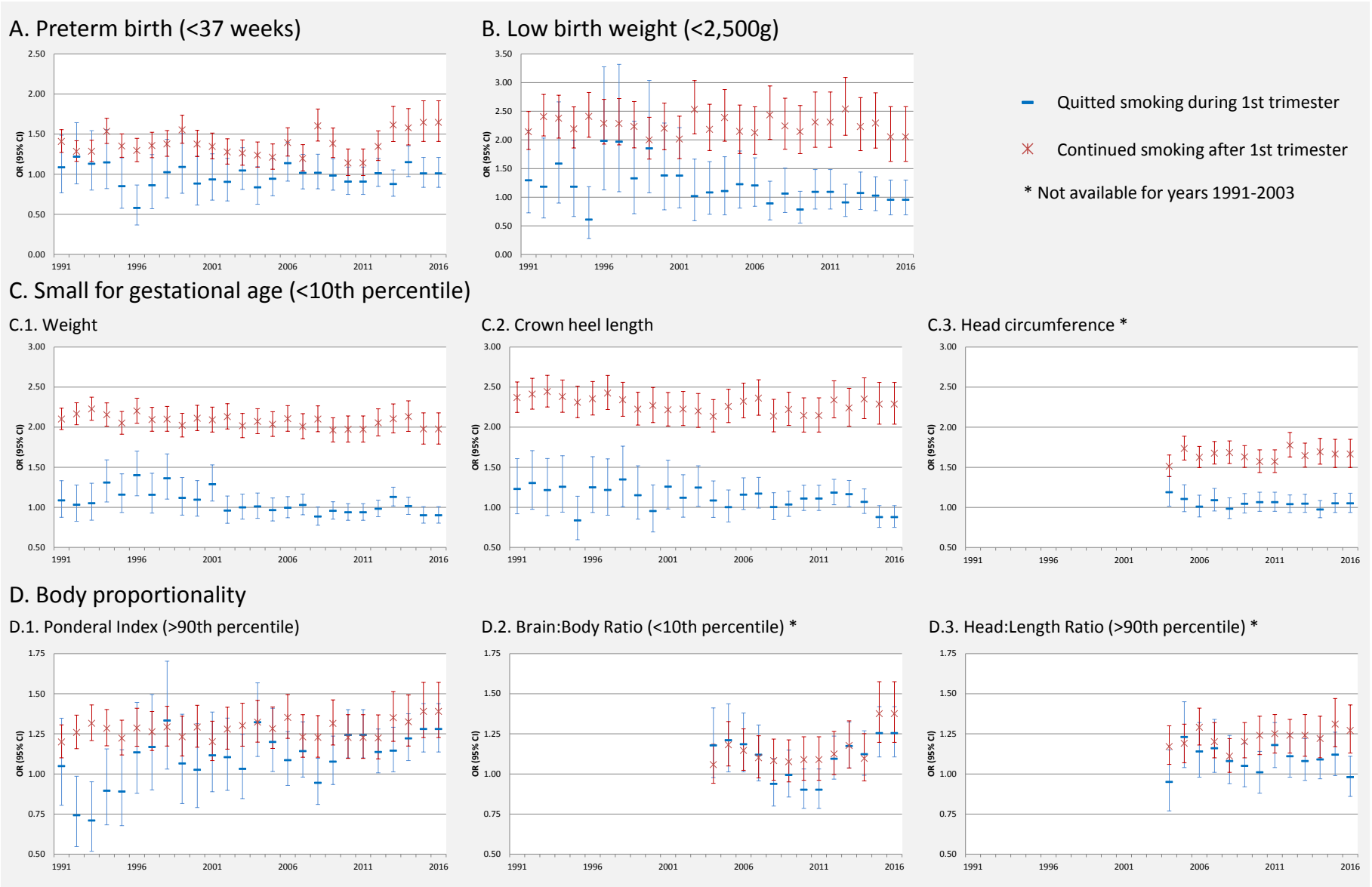

Figure S3. Association of maternal smoking with preterm birth (panel A), low birth weight (panel B), small for gestational age (panel C) and body proportionality (panel D) stratified by birth year

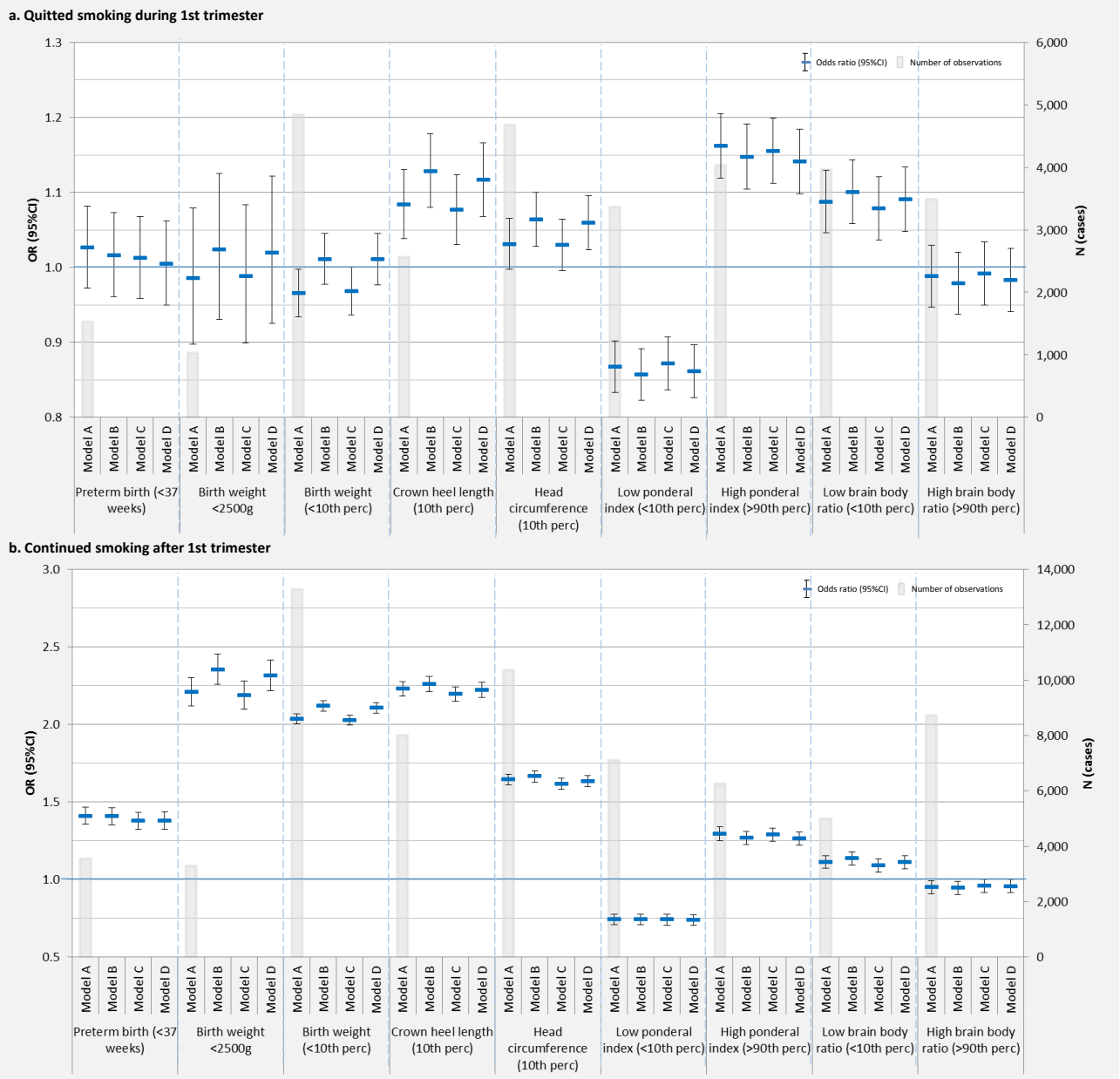

Figure S4. Results for a sensitivity analyses for additional adjustment models for regression on singletons births 2004-2016. Upper panel (a): quitted smoking during 1st trimester, lower pane (b)l: continued smoking after 1st trimester:

3.3 Discussion

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

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

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

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.
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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
Title and abstract	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
Introduction			
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
Methods			
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
Results			
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
Discussion			
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
Other information			
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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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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ABSTRACT

Objectives: The aim of our work was to analyse the effect of maternal smoking on body size and body proportions of newborns when the mother had smoked only during the 1st trimester, in comparison with continued smoking after the 1st trimester. Furthermore, we have evaluated how growth restriction associated with maternal smoking contributes to changes in body proportions.

Design: Register-based cohort study

Setting: MATEX cohort identified from the Finnish Medical Birth Register

Participants: Singleton births without congenital anomalies and missing data (1.38 million) from 1st of January 1991 to 31st of December 2016.

Methods: Logistic regression was used to quantify the effect of maternal smoking, stratified by the maternal smoking status.

Outcome measures: Body proportions indicated by low brain-to-body ratio (defined as <10th percentile); high ponderal index and high head-to-length ratio (defined as >90th percentile); small body size for gestational age at birth (defined as weight, length, or head circumference <10th percentile); and preterm birth (<37weeks) and low birth weight (2,500 g).

Results: Continued smoking after the 1st trimester was associated with 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), corresponding with absolute risks of 22%, 10% and 19% respectively). The effects were slightly lower when smoking had been quit during the 1st trimester. Similar effects were seen for the body size variables and low birth weight. Preterm birth was not associated with smoking only during 1st trimester.

Conclusions: Maternal smoking, independent of smoking duration during pregnancy, was associated with abnormal body proportions resulting from larger reduction of length and head circumference in comparison to weight. The effects of having quit smoking during the 1st trimester and having continued smoking after the 1st trimester were 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 (10th smallest percentile)
PTB	Preterm birth
LBW	Low birth weight
SES	Socioeconomic status
CI	Confidence interval

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The register-based design of this study provided a big study size to detect small risks and minimises risks for recall bias.
- The register-based design of this study allowed for sensitivity analyses including stratification by socioeconomic status and birth year, as well as testing of additional adjustment models for sociodemographic factors and co-morbidities.
- The data content of the Finnish Medical Birth Register has been validated for accuracy and completeness.
- Smoking status was self-reported during antenatal visits, leading to possible reporting bias.
- The register-based design restricted availability of information on confounders. Thus lifestyle related confounders, such as alcohol consumption and exposure to second hand tobacco smoke, could not be adjusted for.

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 much later, potentially in late adulthood.[1] Tobacco smoke contains thousands of chemicals, which can cross the placenta and enter fetal circulation. Among them nicotine has a multitude of adverse effects on the development of organs including brain.[2] Other well-known toxic chemicals in tobacco smoke include carbon monoxide, which can interfere with oxygen supply of the unborn child, as well as 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 2,500 g, is well established. In addition, data on 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 anthropometric index alone fails to identify abnormal body proportions. Symmetrical growth restriction in utero 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, is not an optimal proxy.[6] This clearly demonstrates the importance of body proportions for future health of the newborn.

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

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

interpretations of differences in body proportions in newborns of smoking mothers compared to non-exposed newborns.

MATERIALS & METHODS

Study design

To study the effects of maternal smoking on body size and proportions 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. It is described in more detail elsewhere.[10] The Finnish Medical Birth register contains perinatal outcomes, pregnancy characteristics and sociodemographic information for all live births and stillbirths after the 22nd gestational week or with a birth weight of at least 500 g. The Medical Birth Register receives information from standardised forms filled out by nurses and midwives during antenatal care visits and after the delivery of the baby.

This work focused on the effects of maternal smoking on singleton pregnancies delivered between the 1st of January 1991 and the 31st of December 2016. From initial 1.75 million mother-child 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 the co-variates (Supplementary Material, Figure S1). Within the MATEX birth cohort, information on head circumference and maternal weight and height, as well as maternal co-morbidities was available only for the sub-population born between 2004 and 2016. The sub-population included 659,157 mother-child pairs (Supplementary Material. Figure S1). Thus, the analyses of endpoints related to head size (small head circumference, brain-to-body ratio and head-to-length ratio), as well as sensitivity analyses, were limited to the smaller sub-population.

Exposure

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

Outcomes

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

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

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

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

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

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

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

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

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

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 and body length (Equation 3). It was categorized normal (10-90th percentile of the study population, reference) and high (>90th percentile). Newborns below the 10th percentile were excluded.

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

Covariates

Maternal age and gestational age in weeks were used as continuous variables in the regression models. Parity was defined as nulli- 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 (famers, self-employed, students, pensioners), 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 abnormal body proportions at birth.

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

[a] available for the years 2004-2016

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

[c] Comparison Quit smoking during the 1st trimester with no smoking during pregnancy

[d] Comparison Continued smoking after the 1st trimester with no smoking during pregnancy

SES: socioeconomic status

Statistical analyses

Multiple logistic regressions were performed to estimate odds ratios (ORs) with 95% confidence intervals (CI). The regressions were stratified by exposure status with no smoking as reference, i.e. smoking after the 1st trimester was compared to no smoking, and separately smoking only during the 1st trimester was compared to no smoking. The regression models were adjusted for potential confounders (Table 1; Supplementary Material, Chapter 3.2). The potential confounding factors were selected based on a combination of available data and previously published factors that could affect both maternal smoking and the outcome measures. The data were analysed using R Statistical software (version 3.4.3). The study power was estimated as the smallest detectable risk ratio. The calculations were done using R Statistical Software epiR package with assumed 95% CI and a study power of 90%. (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 of April, 2016). The right to use 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 of June, 2016). Due to the full register-based design of the study, no informed consent was required from the study participants according to the Finnish Personal Data Act 1050/2018.

Patient and Pubic Involvement

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

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 1st trimester and 12.0 % continued smoking after the 1st trimester. Smoking pregnant women were younger and more likely to be nulliparous (Table 2, Supplementary Material, Table S2).

Table 2. Baseline characteristics by smoking status for singleton births in the MATEX cohort (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)**
Mother				
	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)
Child				
	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 1st 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 1st 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 1st 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).

Any smoking during pregnancy was associated with an increased risk for weight or body length at birth being below the 10th percentile. Mothers who quit smoking during the 1st trimester were at elevated, but not statistically significant risk for giving birth to a child with a small head circumference. Among the newborns of the mothers who continued smoking after the 1st 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 abnormal body proportions of newborns was significantly increased by any 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 if smoking was continued after the 1st trimester than when the mothers quit smoking during the 1st trimester. Nevertheless, smoking only during the 1st trimester was associated with statistically significantly increased risks for abnormal body proportions in newborns. Especially the risk for brain-to-body ratio was almost similar in those exposed only during the 1st trimester and those exposed also after the 1st trimester (Fig 1B).

We stratified the analysis by socioeconomic status (SES) in order to investigate the influence of lifestyle factors and health behaviours that correlate with SES. Stratification by SES did not result in statistically significant differences in the risk estimates between the SES groups (Supplementary Material, Figure S2). We stratified the data by birth year to investigate potential influence of changes in the composition of tobacco (e.g. use of additives and changes in tar and nicotine content) and decreased social acceptability of smoking during the study period on the risk estimates. Stratification by birth year did not indicate a clear temporal pattern in risk estimates for any of the analysed endpoints (Supplementary Material, Figure S3). Sensitivity analysis was performed to test the sensitivity of risk estimates to choice of adjustment factors in the regression model. Alternative multivariate adjustment models, including co-morbidities or additional socio-economic factors, did not significantly alter the risk estimates for any of the reported endpoints (Supplementary Material, Figure S4).

DISCUSSION

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

and body length in relation to body weight seem not to catch up. Among the newborns exposed to maternal smoking only during the 1st trimester all three measurements of body size (birth weight, body length and head circumference) showed signs of growth restriction. In addition, body proportions were abnormal.

Our work indicates a difference in susceptibility for growth restriction between weight, body length and head circumference. The observed positive association of maternal smoking with ponderal index suggests a stronger reduction in length than in weight. Similarly, the association with low brain-to-body ratio suggests reduction rather in brain size than in weight. However, the association of maternal smoking with high head-to-length ratio suggests a stronger reduction in length than in head size. It is in line with previous research showing that smoking during pregnancy predominantly affects lean body mass and not fat tissue.[4] While the associations with reduced body size and abnormal body proportion were stronger in newborns of mothers who continued smoking after the 1st trimester, there was a clear association also in newborns exposed only during the 1st trimester. This can be interpreted as an effect of maternal smoking on cell proliferation during organogenesis in early prenatal development. Insults during this period have been shown to persist throughout life.[5] This stresses the importance of smoking cessation before pregnancy since even smoking only during early pregnancy has potentially devastating effects on long term health of the unborn child.

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

Additionally, smaller head circumference has been shown to directly translate into a smaller brain.[16, 17] Insults during early development of the brain, such as maternal smoking, have been shown to result in differences in DNA methylation, altered expression of genes regulating brain structure and function [18] and reduction in neuronal content of the brain,[19]. Also, neurophysiological functions and overall brain functions are altered due to prenatal smoking.[20] The smaller brain volume observed in newborns has been shown to persist into young adulthood.[21]

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

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 nicotine replacement products used during pregnancy has already been suggested.[30] Epidemiological studies on the effects of nicotine products, other than cigarettes, are still needed. We recommend the inclusion of information on the use of nicotine products in the Medical Birth Register. This would allow detecting pregnancies at risk more reliably and facilitating epidemiological research on nicotine exposure during pregnancy beyond maternal smoking.

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. Our results were robust against inclusion of maternal co-morbidities, maternal anthropometric indices, social background and reproductive history as confounders in the statistical model. Smoking and socioeconomic status have been shown to correlate well with other lifestyle related factors and they are reliable markers for the unaccounted factors.[31] The smoking information was self-reported by the mother during antenatal care visits. Thus, reporting bias cannot be excluded. It was not possible to analyse the impact of timing of smoking cessation in more detail or possible dose response relationships due to lack of data. In addition, we lack information on paternal and household smoking. Second hand tobacco smoke exposure during pregnancy has been shown to increase the risk for low birth weight and growth restriction.[32]. We cannot exclude the possibility that some observed effects are partly attributable to second hand tobacco smoke exposure, especially in those women who ceased smoking during their 1st trimester. Our definition of indicators for body proportions were constrained by available data in the register. Ideally, the outcomes in this work would be supplemented with clinical criteria collected during for example prenatal ultrasound scans,

such as femur length, abdominal circumference, and skinfold thickness. Further, the cut-off at the 10th percentile for the definition of small body size and abnormal body proportions was arbitrary due to a lack of clear data on a threshold for increased risk for complications later in life. Socioeconomic status was assigned here solely on maternal occupation and no information about the father´s occupation was available. For a high proportion of mothers (18%) the occupation was not available. Previous studies applied the same SES categorization and showed that the missing information did not bias the proportions in the other SES categories.[24]

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

CONCLUSIONS

This study showed that maternal smoking is associated with a stronger reduction in body length and head circumference than in birth weight, leading to changed body proportions. The effects on body proportions of having quit smoking during the 1st trimester or having continued smoking after the 1st trimester were similar, stressing the importance of early pregnancy as a sensitive exposure window. Furthermore, it suggests a limited potential to repair fetal damage induced in early pregnancy. Lower brain-to-body ratio suggests that any smoking during the pregnancy may lead to losses in the development of central nervous system. The effects on body size (weight, length and head circumference) were more pronounced in newborns of mothers who continued smoking after the 1st trimester.

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

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CONTRIBUTORS

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

COMPETING INTERESTS

Kirsi Vähäkangas was the chair in 2018-2019 of the scientific advisory committee of the Savuton Suomi (Smoke-free Finland) 2030 initiative. Other authors declare no competing interests.

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DISCLAIMER

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

DATA SHARING STATEMENT

Data may be obtained from a third party and are not publicly available. The Finnish Institute of Health and Welfare is the controller of the Medical Birth Register. Data may be obtained from the register controller (https://thl.fi/en/web/thlfi-en/statistics/information-on-statistics/register-descriptions/newborns accessed 29 May 2019).

PATIENT CONSENT

Not required.

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 Finnish Institute for Health and Welfare was granted under the document number THL/838/6.02.00/2016 (issued 22nd June 2016).

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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 abnormal 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) 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).

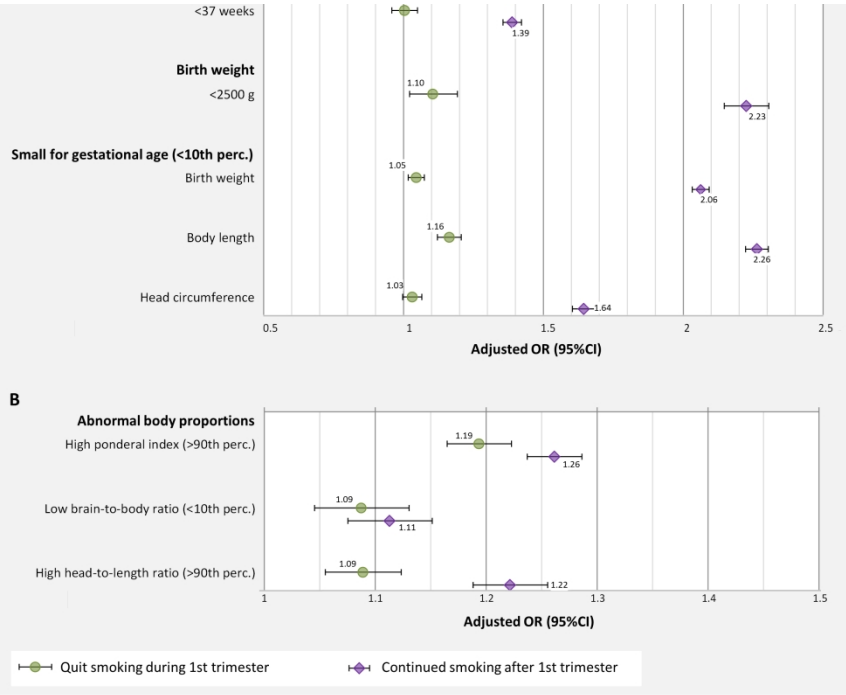

Fig 1 Adjusted odds ratios (OR) for association of maternal smoking with (A) traditional birth outcomes (preterm birth, low birth weight and small for gestational age); and with (B) abnormal body proportions; adjusted for maternal age, sex, parity, socioeconomic status, and gestational week (for low 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 22nd gestational week or with a birth weight of at least 500 g.

This work focuses on the effects of maternal smoking on singleton pregnancies born between 1st January 1991 and 31st December 2016. From initial 1.75 million children born in this period, 1.38 million were included in the analyses after exclusion of multiple births, congenital malformations and newborns with missing information on maternal smoking status or co-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).

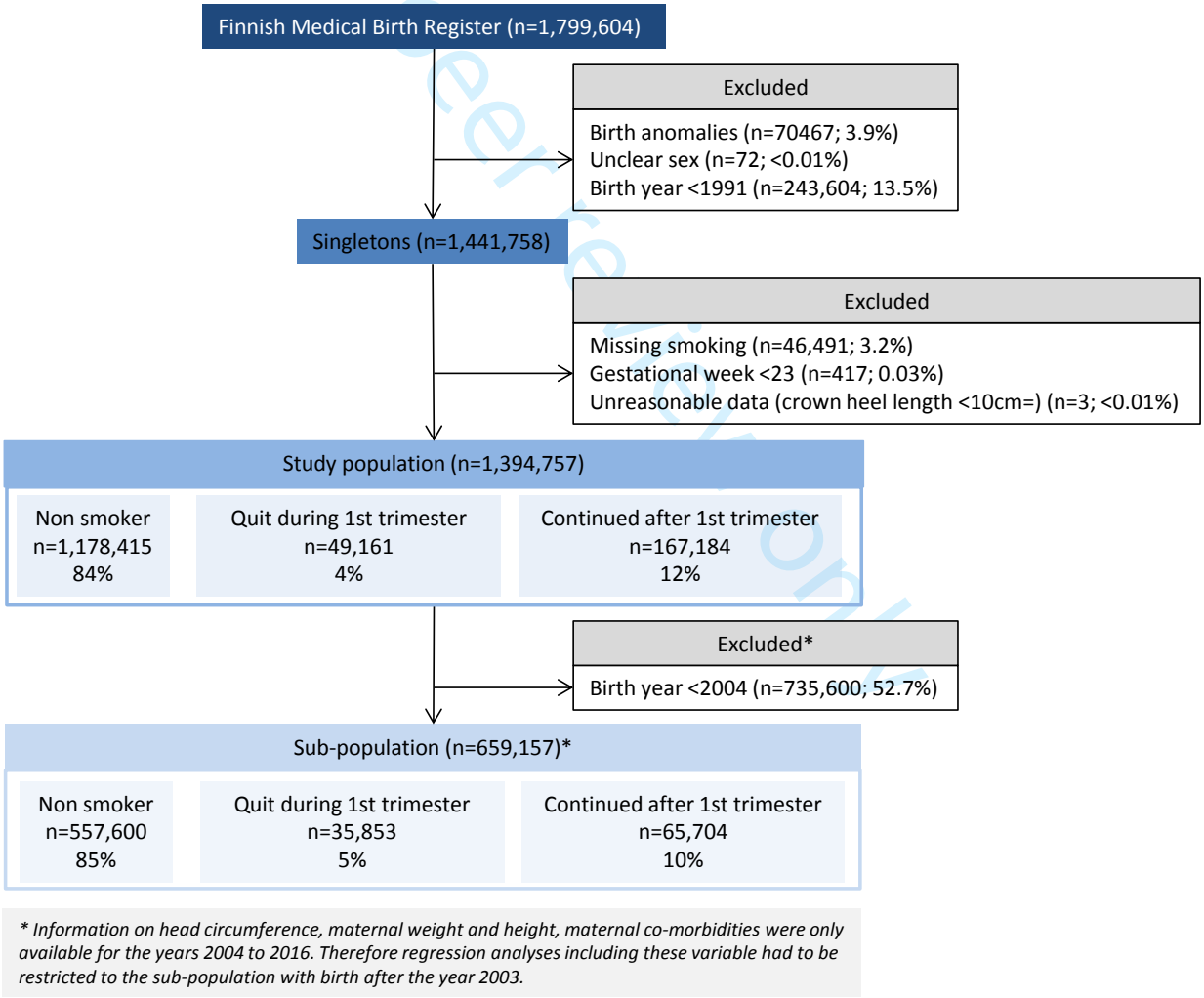

Figure S1. Data cleaning process with exclusion criteria and number of excluded children

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*

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

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

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

2.2 Main Analyses

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

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

	All		Non smoker		Quit smoking during 1st trimester		Continued smoking after 1st trimester	
	n^		n^		n^		n^	
Mother		1,376,778		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)

Cont. Table S2

	All		Non smoker		Quit smoking during 1st trimester		Continued smoking after 1st trimester	
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)
Abnormal body proportions		% (count)		% (count)		% (count)		% (count)
High ponderal index	1,239,427	11.0 (136,918)	1,048,672	11.1 (116,902)	43,235	11.8 (5,111)	147,520	10.1 (14,905)
Low brain-to-body ratio*	573,360	11.1 (63,520)	487,052	11.2 (54,554)	31,731	12.5 (3,968)	54,577	9.2 (4,998)
High head-to-length ratio*	573,655	9.6 (60,358)	483,613	9.8 (49,830)	31,979	8.9 (3,560)	58,063	8.3 (6,960)

n^ number of mother-child pairs with available information

* Available 2004-2016

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

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

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

* Available for years 2004-2016

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

Table S4. MATEX study results and previously published Finnish results

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

1. Raisanen, S., U. Sankilampi, M. Gissler, M. R. Kramer, T. Hakulinen-Viitanen, J. Saari, and S. Heinonen. 2014. "Smoking Cessation in the First Trimester Reduces most Obstetric Risks, but Not the Risks of Major Congenital Anomalies and Admission to Neonatal Care: A Population-Based Cohort Study of 1,164,953 Singleton Pregnancies in Finland." *Journal of Epidemiology and Community Health* 68 (2): 159-164. doi:10.1136/jech-2013-202991 [doi].

2. Raisanen, S., M. R. Kramer, M. Gissler, J. Saari, and S. Heinonen. 2014. "Unemployment at Municipality Level is Associated with an Increased Risk of Small for Gestational Age Births--a Multilevel Analysis of all Singleton Births during 2005-2010 in Finland." *International Journal for Equity in Health* 13 (1): 1. doi:10.1186/s12939-014-0095-1 [doi].

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

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

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

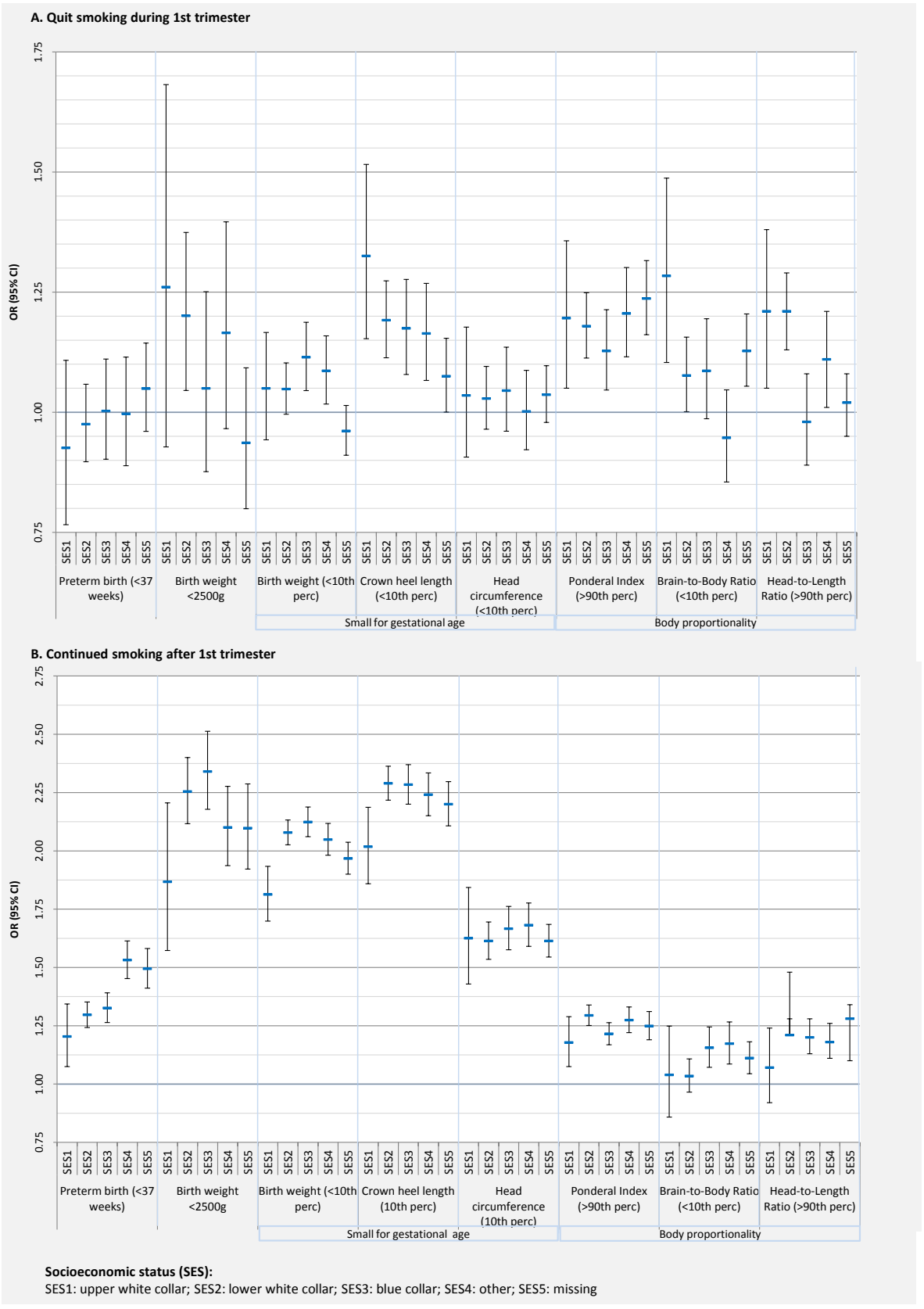

Figure S2. Association of maternal smoking and birth outcomes stratified by socioeconomic status. Pane Al: quit smoking during 1st trimester; panel B: continued smoking after 1st trimester.

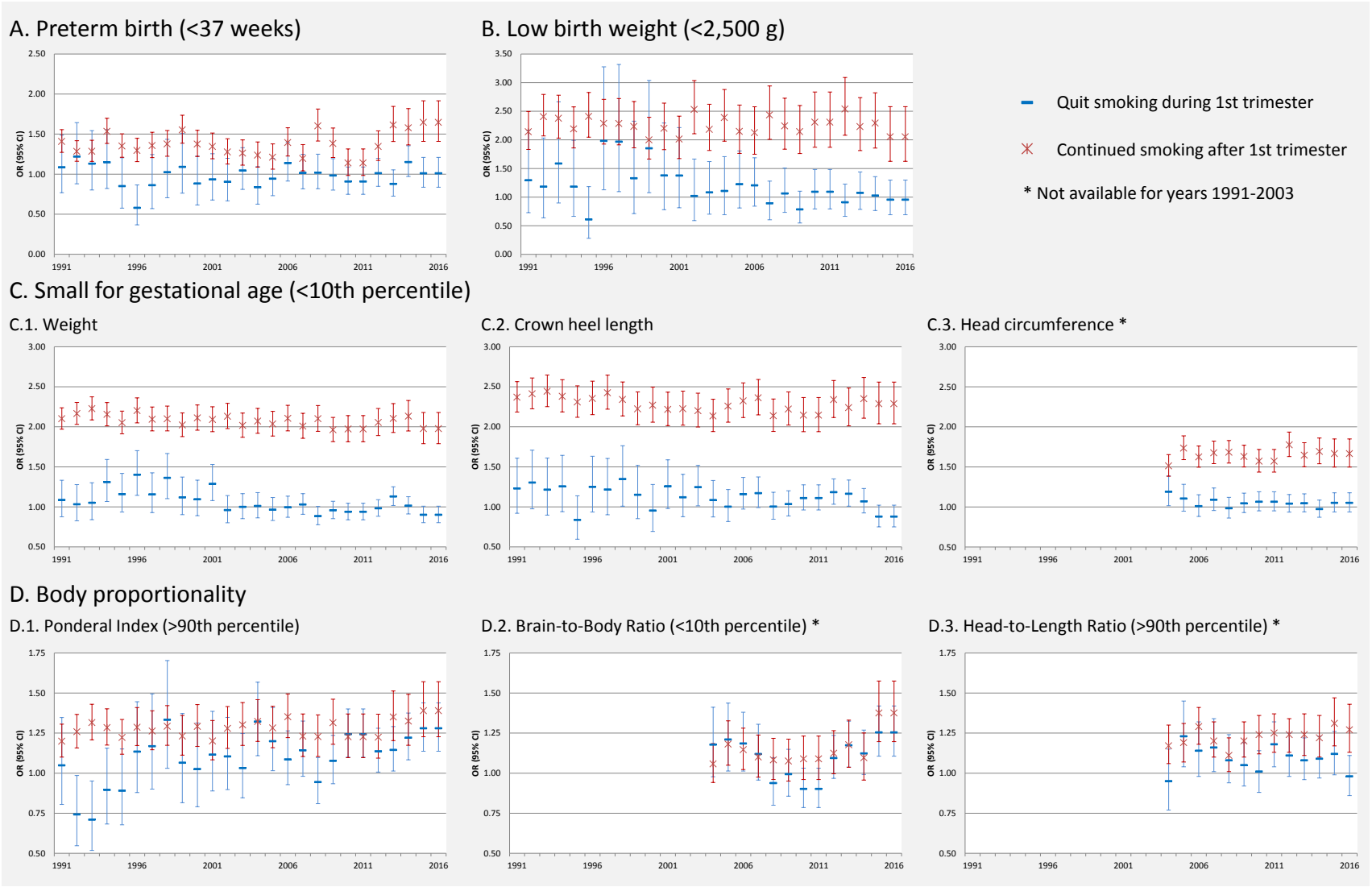

Figure S3. Association of maternal smoking with preterm birth (panel A), low birth weight (panel B), small for gestational age (panel C) and body proportionality (panel D) stratified by birth year

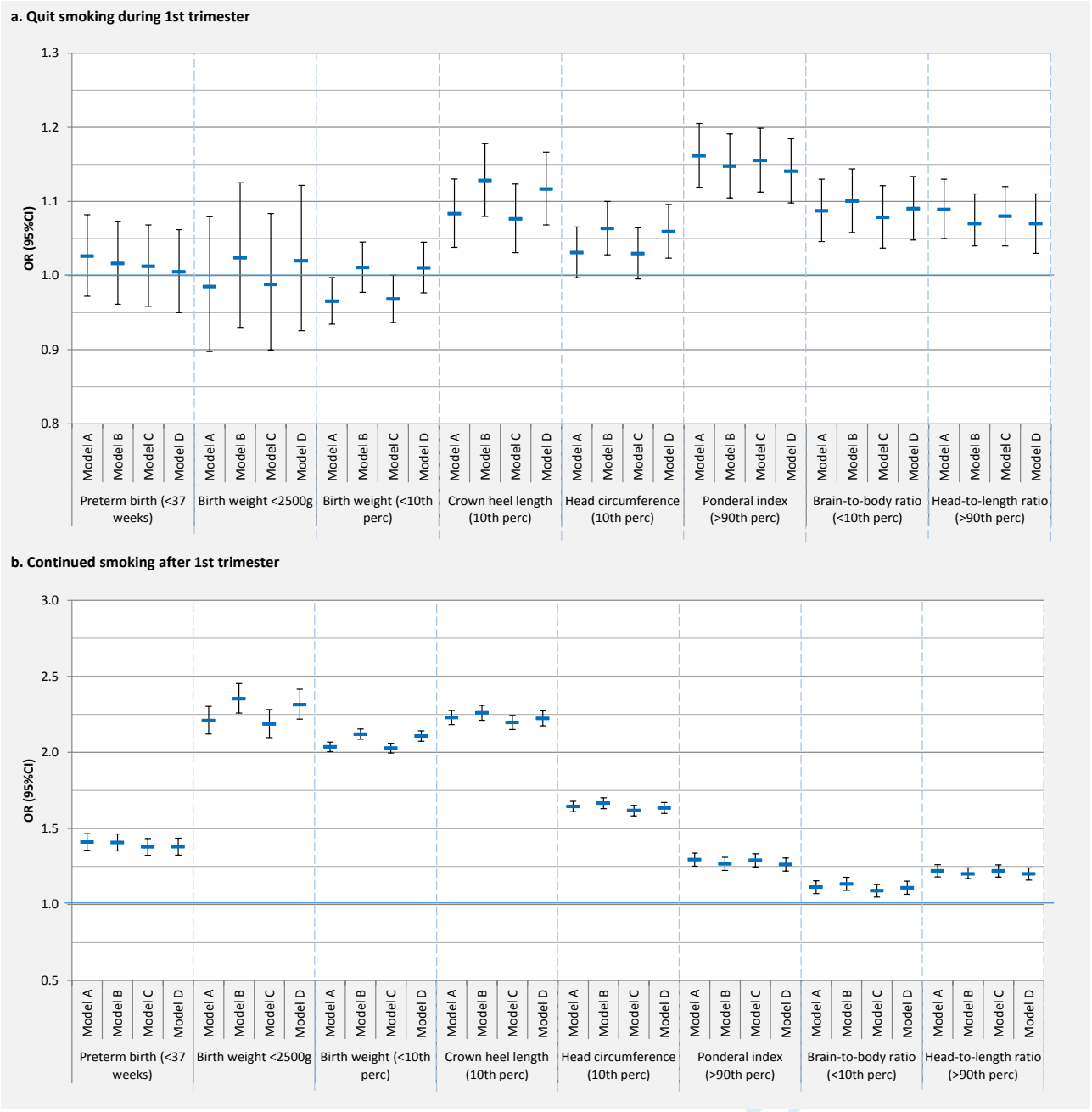

Figure S4. Results for a sensitivity analyses for additional adjustment models for regression on singletons births 2004-2016. Upper panel (a): quit smoking during 1st trimester, lower pane (b)l: continued smoking after 1st trimester:

3.3 Discussion

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

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

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

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
Title and abstract	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
Introduction			
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
Methods			
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
Results			
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
Discussion				
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
Other information				
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.