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Journal of Developmental Origins of Health and Disease, 2015; 6(6):485-492

Originally Published at: http://dx.doi.org/10.1017/S2040174415007151

Association of early and late maternal smoking during pregnancy with offspring body mass index at 4- to 5-years of age

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Short Title: Maternal smoking and offspring body mass index

Abstract Word Count: 241

Main Text Word Count: 3,262

Conflict of Interest: The authors declare no conflict of interest

Abstract

The objective was to investigate the association between early and late maternal smoking during pregnancy on offspring body mass index (BMI). We undertook a retrospective cohort study using linked records from the Women's and Children's Health Network in South Australia. Among a cohort of women delivering a singleton, live-born infants between January 2000 and December 2005 (n=7,658), 5,961 did not report smoking during pregnancy, 297 reported quitting smoking during the first trimester of pregnancy, and 1,400 reported continued smoking throughout pregnancy. Trained nurses measured the height and weight of the children at preschool visits in a state-wide surveillance program. The main outcome measure was age- and sex-specific BMI z-score. At 4- to 5-years-old, mean (SD) BMI z-score was 0.40 (1.05), 0.60 (1.07), and 0.65 (1.18) in children of mothers who reported never smoking, quitting smoking, and continued smoking during pregnancy respectively. Compared to the group of non-smokers, both quitting smoking and continued smoking were associated with an increased in child BMI z-score of 0.15 (95% confidence interval: 0.01 to 0.29) and 0.21 (0.13 to 0.29), respectively. A significant dose-response relationship was also observed between the number of cigarettes smoked per day on average during the second half of pregnancy and the increase in offspring BMI z-score ($p<0.001$). In conclusion, any maternal smoking in pregnancy, even if mothers quit, is associated with an increase in offspring BMI at 4- to 5-years of age.

Key Words: smoking, childhood overweight, pregnancy, childhood obesity, smoking cessation

Introduction:

Across the developed world the prevalence of childhood overweight and obesity has seen dramatic increases over the last 20 years,[1, 2] bringing with it an increased risk of adult obesity and obesity-related morbidity and mortality. In Australia, the estimated prevalence of overweight and obesity among children aged 2-18 years of age rose from 10.2% to 23.7% in boys and 11.6% to 24.8% in girls from 1985 to 2008.[3] In 2008, at least 32% of children and adolescents between 2- to 19-years of age were identified as being overweight or obese in the United States.[4] While solutions to this problem will be multifactorial, understanding the mechanisms that may contribute towards increases in childhood BMI are of significant public health importance.

Cigarette smoking represents one of the most common, and yet avoidable, pregnancy insults. While estimates differ widely according to country and location, approximately 15-25% of women smoke during pregnancy,[5] with prevalence of smoking highest amongst socially disadvantaged populations[6]. Despite significant reductions in smoking as a result of immense public health campaigns, this reported prevalence is still too high given the reported associations between maternal smoking and perinatal morbidity and mortality.[5] Maternal smoking is well demonstrated to be associated with increased risk of spontaneous abortion, small-for-gestational-age, preterm birth, stillbirth, neonatal mortality and a range of behavioural and psychiatric diseases in childhood.[5] Coupled with these effects is the strong association between maternal smoking and increases in offspring BMI, including an increased risk of childhood overweight[7-23] supported by a recent meta-analysis (aOR 1.52 (1.36-1.70)).[24] This association remains strong regardless of whether the comparison group consisted of women who were never smokers or women who were former smokers (i.e. women who quit smoking prior to the index pregnancy).[24] Furthermore, within all studies that obtained information on the amount of maternal smoking, a clear dose-response relationship was

observed between the number of cigarettes smoked on average each day and increases in childhood BMI, strengthening arguments for a causal relationship.[8, 13, 20, 21, 23, 25]

What remains less clear is the relationship between timing of maternal smoking during pregnancy and childhood BMI, which has been investigated in few studies to date and with conflicting results.[7, 11, 22, 23, 25-27] Some studies have demonstrated that smoking throughout pregnancy is associated with a greater increase in childhood BMI,[11, 22, 23, 25] while others have observed similar estimates for those only exposed in the first trimester.[7, 20]

In light of these findings, we aimed to investigate the association between early and late maternal smoking during pregnancy, in addition to the quantity of cigarette smoking, on offspring body mass index (BMI) at 4- to 5-years of age.

Method:

This project was approved by the Human Research Ethics Committees of the Women's and Children's Health Network, University of South Australia, and the University of Adelaide in South Australia.

This was a retrospective cohort study relating to all births in the Women's and Children's Health Network (WCHN) in South Australia between January 2000 and December 2005 that occurred at the Women's and Children's Hospital, Adelaide (WCH). The WCH is a specialist metropolitan tertiary level teaching hospital and South Australia's largest maternity and obstetric service provider, caring for over 4,000 pregnancies each year. The study utilised linkable health administrative data within the WCHN, which included the WCH Perinatal Statistics Collection and the WCHN Child Health Record, to obtain follow-up data on child weight and height. Electronic records were first matched using each individual's unique hospital identifier number, and where this was not possible, through an exact match on the following three variables; surname, sex and date of birth.

South Australia's WCHN provides a range of health and social services and programs for parents, children, and young people across the state. As part of these services, child and family health nurses have performed health checks on 4- to 5-year-old children at all kindergartens and preschool centres since 1995. During these visits, a standard protocol is used to measure height with a fixed tape and weight of children. Data are recorded electronically and have been utilised in previous studies.[28] From 1997 through 2007, the average participation rate was 65% of South Australian children.

A total of 24,377 pregnancies occurred during the study period. Women who were eligible for the current analysis were those who gave birth to singleton, live born infants (n= 22,615). We excluded women where data on smoking status was missing (n=823), leaving a total eligible study cohort of 21,792 mother-child-dyads. We further obtained height and weight data at 4- to 5-years-old for 7,678 children, of whom 20 were considered outside of biologically plausible values based on predefined criteria. This left a final study cohort of 7,658 mother-child-dyads (**Figure 1**).

Data on smoking status were obtained from the Perinatal Statistics Collection. These data are originally collected during the first antenatal booking visit and, based on maternal self-report, women were classified as either: non-smokers, quit smoking or smokers during pregnancy. Women who were smokers were asked to estimate how many cigarettes they smoked each day, on average in second half of pregnancy. These data were used to stratify smokers into three groups (1-9; 10-19; ≥20).

The primary outcome measure was childhood BMI z-score at 4- to 5-years of age. Body Mass Index (BMI= weight (kg)/(height(m)^2) was calculated based on measured height and weight at the health check. We expressed BMI according to age- and sex- specific z-score utilising the US Centres for Disease Control (CDC) 2000 reference standards[31]. The secondary outcome measure was childhood overweight, classified as a BMI for sex and age at or above

the 85th percentile on CDC 2000 reference standards[31]. For additional comparison and robustness, we also calculated BMI age- and sex- specific z-scores according to the British 1990[30] and International Obesity Task Force[29], reference standards.

Information on maternal age, BMI, parity, race, socioeconomic status and breastfeeding at discharge from hospital was obtained from the Perinatal Statistics Collection. Data were collected on the pregnancy and outcome of every live birth and late fetal death occurring at the WCH according to the guidelines of the Pregnancy Outcome Unit of the South Australian Department of Health for the Supplementary Birth Records (SBRs) and in consultation with the senior clinicians at the hospital. Data were collected from the woman's medical records following delivery by a specially trained research midwife through use of a structured coding sheet. It is important to note that included in the medical record is the South Australian Pregnancy Record (SAPR), which is a hand-held antenatal record carried by each woman throughout her pregnancy and contains notes by all health providers consulted during the pregnancy. From the medical records, information is collected on maternal illnesses (e.g. diabetes, gestational diabetes, epilepsy, asthma and psychiatric illness), lifestyle factors (e.g. smoking), obstetric history, course of delivery, pregnancy complications, and newborn characteristics (e.g. birthweight). All SBRs were checked manually for completeness and data discrepancies by a senior research midwife and then go through a series of automated validation procedures during data entry. The information in the Perinatal Statistics Collection has been previously validated and is reliable when compared with hospital case records.[32] These data have also been utilised in previous studies.[33]

The estimated length of gestational age at delivery is based on the last menstrual period and ultrasound examination. Appropriateness of intrauterine growth was assessed using percentage of optimal birthweight (POBW).[34] POBW is the ratio of the observed to the 'optimal' birthweight, with the later calculated from a regression equation that takes account

of major non-pathological determinants of intrauterine growth including gestational age, infant sex, maternal height and parity.[34] We used a POBW score less than the 10th percentile to define small-for-gestational-age (SGA) infants and a score greater than the 90th percentile to define large-for-gestational-age (LGA) infants.

Parity was defined as no previous deliveries (nulliparous) or 1 or more previous deliveries. Maternal race was classified as Caucasian, Asian or Other. Socioeconomic status for each woman was determined using her residential postcode at the time of delivery. Women were then ranked according to their level of advantage or relative disadvantage, based on data from the Socio-Economic Indexes for Areas (SEIFA), calculated from the Australian Bureau of Statistics' five-yearly Census of Population and Housing. SEIFA scores were converted to quintiles, and these are widely used measures of relative socio-economic status.[12]

All data analysis was undertaken on de-identified data. We conducted univariate categorical analyses using the chi-square test or Fisher's exact test where appropriate. Unpaired t-tests were used for two-group comparisons and one-way analysis of variance for three-group comparisons of normally distributed continuous variables. Bivariate and multivariate linear regression was used to investigate the relationship between maternal smoking status and offspring BMI z-score, expressed as a continuous variable. Potential confounding maternal and child covariates were categorised as shown in **Table 1**. All categorical variables were coded as a number of dummy variables equal to the number of categories minus 1. In the first adjusted model we included confounders and covariates chosen *a priori*, including maternal age, race, socioeconomic status, parity, and pre-existing or gestational diabetes. In the second adjusted model we also included maternal BMI, data on which was available for approximately 70% of the cohort. Statistical analyses were performed using Stata IC 11.0 (Stata, College Station, TX). Statistical significance was defined as a 2-sided *P* value of < 0.05.

Inverse probability weighting was used to evaluate the potential for bias a result of loss to follow-up.[9] This involved using a logistic regression analysis (complete data vs. lost to follow-up as outcome) to determine weights for each individual using the inverse probability of response.[9] Complete follow-up data was predicted based on maternal smoking status, maternal age, parity, neonatal birthweight, maternal BMI and socioeconomic status. The individual weighting factor for these covariates (their inverse probability) was used as a sample weighting adjustment in the multivariable linear and logistic regressions.

Results:

Of the mother-child-dyads who had follow-up data on weight and height (n=7,658), 5,961 did not report smoking during pregnancy (non-smokers), 297 reported stopping smoking during pregnancy (quit smoking), and 1,400 reported continued smoking during pregnancy (smokers). Compared to mothers of children with follow-up data, mothers lost to follow-up were more likely to be younger, multiparous, smokers, non-Caucasian, and from a higher socioeconomic status (Supplemental Table 1).

Women who were non-smokers were comparable to those who quit during pregnancy in terms of socioeconomic status, asthmatic prevalence and rates of breastfeeding at discharge, but were more likely to be older, have lower BMI, were primiparous and Caucasian (**Table 1**). However, women who were non-smokers differed substantially from those who continued smoking in pregnancy. Compared to smokers, non-smokers were more likely to be older, of lower BMI, primiparous, Caucasian, of higher socioeconomic status, non-asthmatic, and to be breastfeeding their infant at discharge from hospital (**Table 1**). Compared to smokers, those who quit smoking during pregnancy were more likely to be primiparous, of higher socioeconomic status and were more likely to have been breastfeeding their infant at discharge

from hospital (**Table 1**). Underlying rates of pre-existing and gestational diabetes were the same in all three groups. The age of the children at follow-up was comparable between groups.

Birthweight was lowest in the group of women who continued smoking throughout pregnancy (3,155 ± 628g), while being similar in the group of women who never smoked during pregnancy (3410 ± 610g) and quit smoking during early pregnancy (3408 ± 608g) (**Table 2**). Despite this birthweight disparity between continued smokers and those who quit during pregnancy, compared with non-smokers, both continued smoking (0.21, 95% CI 0.13 to 0.29) and quitting smoking during early pregnancy (0.15, 95% CI 0.01 to 0.29) were associated with statistically significant increases in BMI z-score at 4- to 5-years of age (**Table 3**). Similarly, both continued smoking (aRR 1.31; 95% CI 1.18-1.46) and quitting smoking during early pregnancy (aRR 1.26; 95% CI 1.05-1.51) were associated with an increased risk of childhood overweight. These findings were consistent across each of the different growth chart reference standards compared (data not shown).

A significant dose response relationship was also observed between the average number of cigarettes smoked per day and difference in BMI z-score and risk of childhood overweight at 4- to 5-years of age (P_{trend}<0.001; **Table 3**).

Discussion:

This study has demonstrated that any maternal smoking, even in early pregnancy, is associated with an increase in offspring BMI at 4- to 5-years of age. These findings add to a growing body of literature supporting an association between active maternal smoking, degree of smoking in pregnancy and increased childhood BMI.[7-23] Notably, the observed association between maternal smoking and childhood BMI was independent of birthweight, a finding consistent with a small number of previous studies.[16-18]

A number of potential mechanisms and pathways have been proposed to explain the association between maternal smoking and childhood BMI including: postnatal catch-up growth, the thrifty phenotype theory, neurotransmitter or endocrine imbalances and behavioural differences between smoking and non-smoking mothers.[35] An initial proposed mechanism that is not supported by our findings, or those from other studies,[16-18] is that maternal smoking results in reduced fetal growth and low birthweight but more rapid postnatal weight gain (catch-up growth), which itself has been associated with increases in BMI in later life.[24] Given that we did not see differences in birthweight between smokers and those who quit smoking during pregnancy, a more substantive explanation may lie in the thrifty phenotype theory. This theory posits that in situations of undernutrition, the fetus undergoes permanent metabolic adaptations to enhance its immediate survival chances.[36] Problems emerge when these adaptions made to suit the *in utero* environment do not accurately predict the *ex utero* environment.[37] Maternal smoking in the first trimester may lead to a reduction in fetal nutrition supply due to a reduction in placental blood flow associated with the vasoconstrictive effect of nicotine.[24] Postnatally, however, where nutrition is readily available, the adaptations made *in utero* are no longer adaptive and the child develops a higher BMI. This explanation supports the current findings of increased childhood BMI where mothers smoked during first trimester of pregnancy, regardless of whether this continued past first trimester. Supporting this proposed mechanism are findings from the Dutch Famine Study, which demonstrated gestation-specific associations between exposure to famine and offspring health in later life.[38] Offspring exposed to famine only during the first trimester were more likely to have a range of metabolic complications in later life, including obesity; this was not observed in offspring exposed during late gestation.[38] Biological mechanisms underpinning these observations may involve programmed permanent alterations in hypothalamic regulation of food intake and energy expenditure.[39] It is also possible that nicotine has a direct effect on hypothalamic structures,

resulting in impaired metabolic functioning in later life.[7] The final proposed mechanism does not involve maternal smoking itself, but rather that increases in childhood BMI is a product of unfavourable living conditions or lifestyle habits (i.e. poor dietary intake and/or physical activity patterns) commonly associated with maternal and paternal smoking behaviours.[40] Supporting this mechanism is research demonstrating that maternal and paternal smoking in the postnatal period is also associated with increases in childhood BMI,[19, 20, 35, 40] suggesting either exposure to passive smoke or other unmeasured confounders associated with or that occur with smoking may play a role. Further evidence towards unmeasured confounding comes from one study which conducted sibling-based analyses, with smaller associations between maternal smoking and childhood overweight observed from within-family analyses then among the cohort as a whole, suggesting the presence of partial confounding by familial factors.[41] These findings for the presence of unmeasured confounding, however, have not been consistent, with Gilman et al. demonstrating that the increased risk of childhood overweight associated with maternal smoking that was observed among their full cohort remained following a conditional sibling fixed effects analysis that adjusted for familial factors.[42]

A strength of our present study is that it compared outcomes in offspring of not only mothers who smoked throughout pregnancy, but also those who quit during early pregnancy. Few studies have examined the effect of maternal smoking in different periods of pregnancy, with inconsistent results.[7, 11, 22, 23, 25-27] Some studies have demonstrated no increased risk from first trimester exposure[25, 27] or a greater risk associated with smoking throughout pregnancy,[11, 22, 23] while others, including our study, demonstrate an increased risk regardless of duration of exposure during pregnancy[7, 20, 26]. Supporting the argument that intrauterine exposure to maternal smoking may play an important role is evidence from studies that have failed to demonstrate associations between maternal smoking prior to and/or after, but not during, pregnancy.[8, 11, 43] Furthermore, a recent meta-analysis of 12 studies identified a higher effect

estimate of maternal smoking during pregnancy on childhood overweight and obesity than the effect estimates of paternal smoking at any time.[44] In addition, supporting evidence comes from a recent study investigating associations between prenatal exposure to maternal smoking and offspring DNA methylation.[45] In this study the major contributant towards altered offspring DNA methylation status, identified from longitudinal samples taken at birth, age 7 and 17 years, was intrauterine exposure to maternal smoking, rather than postnatal smoke exposure.[45]

There are a number of limitations associated with this study. We relied on maternal self-report to ascertain smoking status during pregnancy, rather than biochemical measurements. Given the negative perception of smoking during pregnancy, some women may be reluctant to admit their smoking habits. This is demonstrated in a recent study where 16% of women identified as being an active smoker according to a cotinine concentration >14 ng/mL had actually reported that they did not smoke during pregnancy.[40] As such, it is possible that some women who reported being non-smokers actually smoked during pregnancy, or that women who stated quitting in early pregnancy resumed smoking in later pregnancy. This is likely to underestimate any associations observed between maternal smoking in pregnancy and childhood BMI. Furthermore, we had no information on how many women smoked in the postnatal period or on paternal smoking behaviours. The lack of data on postnatal factors such as the child's diet, energy intake and physical activity represents an additional study limitation. However, studies that have adjusted for a number of important postnatal factors have also demonstrated a strong association between maternal smoking in pregnancy and childhood BMI.[7, 8, 13, 15, 25, 35, 40] Other potentially important covariates that could not be adjusted for in this study include paternal BMI, pregnancy weight gain and duration of breastfeeding. With height and weight follow-up data only available for 40% of the original cohort eligible for this study, there is also the potential for selection bias. To assess the impact of this, we attached inverse probability weighting to subjects included in

the analyses to restore the representation of those lost to follow-up. This aims to construct a pseudo-population of the same size as the original study population, but in which nobody is lost to follow-up.[9] We found no difference between the weighted and non-weighted results (data not presented), which suggests that loss to follow-up is unlikely to have substantially biased our findings. Lastly, given the cohort consisted of women who delivered at a specialist public metropolitan tertiary level teaching hospital and likely reflects a higher risk obstetric population, the findings may not be completely generalisable to all pregnancies across the state.

Notably, it is clear that maternal smoking during pregnancy represents just one of a myriad of important factors influencing childhood BMI.[46] It is extremely difficult to disentangle the complex web of associations between each of these risk factors, where factors may independently, cumulatively and interactively contribute to increases in childhood BMI.[46]

Smoking during pregnancy remains a major public health issue due to its relationship with adverse perinatal outcomes. The results of this study suggest that any maternal smoking in pregnancy, even if mothers quit in the first trimester, is associated with significant increases in childhood BMI by 4- to 5-years of age and that this association is independent of intrauterine growth and subsequent birthweight. While the mechanism underpinning this association is not yet completely understood, these results strongly support encouraging women to quit smoking during their reproductive years to minimise the number of women who enter pregnancy as a current smoker. Quit smoking campaigns should be introduced pre-pregnancy and may serve as one solution to alleviating the current health burden of childhood obesity. It is feasible that health programs introduced in adolescence may be a starting point. We acknowledge, however, that the pathways leading to childhood obesity post pregnancy are also major contributors to this outcome and will also need to be addressed. For women who enter pregnancy as a smoker, advising and supporting them to quit smoking will never

represent a lost cause. We have clearly demonstrated that smoking cessation is associated with significant improvements in gestational age, birthweight and a reduced risk of SGA compared to smoking throughout pregnancy. Further, a lower quantity of cigarettes smoked during pregnancy is associated with a smaller increase in childhood BMI. Smoking cessation or reduction is also likely to positively improve a range of other perinatal and child health outcomes not measured within this study. In the absence of getting women to quit smoking prior to pregnancy, the antenatal period still represents an important opportunity to address both maternal and paternal smoking behaviours with the aim of maximising child health outcomes.

Conflict of Interest:

The authors declare no conflict of interest

Acknowledgments

The authors wish to acknowledge salary support through a Heart Foundation South Australian Cardiovascular Research Network Fellowship (ID CR10A4988 to JLM), National Health and Medical Research Council Australia Biomedical (Training) Fellowship (ID 1016379 to NAH) and a National Health and Medical Research Council Senior Fellowship (ID 510703 to VLC).

Authorship

LEG and JLM conceived the study, obtained the data and conducted initial data analyses. MJS, NAH and VLC were involved in reviewing study design and data interpretation. All authors were involved in writing the paper and had final approval of the submitted and published versions.

Figure 1: Selection of study population

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Table 1. Demographic and Clinical Measures for Women who were Non-Smokers, Quit Smoking During Pregnancy, or Continued Smoked During Pregnancy

Maternal Measure	Non-Smoker (n=5,961)	Quit Smoking During Pregnancy (n=297)	*P* for Quit Smoking vs. Non-Smoker	Continued Smoking During Pregnancy (n=1,400)	*P* for Continued Smoking vs. Non-Smoker
Age (years), mean (SD)	29.6 (5.4)	27.8 (5.7)	<0.001	27.9 (5.8)	<0.001
BMI (kg/m^2), n (%)			0.002		0.006
<25	2,307 (57.4)	113 (49.6)		511 (52.4)	
≥25 to <30	992 (24.7)	80 (35.1)		252 (25.8)	
≥30	721 (17.9)	35 (15.4)		213 (21.8)	
Parity, n (%)			<0.001		<0.001
≥1	3,211 (54.3)	99 (33.7)		825 (59.2)	
Race, n (%)			<0.001		<0.001
Caucasian	5,125 (86.0)	274 (92.3)		1,284 (91.7)	
Socioeconomic Status (SEIFA) , n (%)			0.854		<0.001
5 (Highest)	1,095 (18.5)	50 (16.9)		142 (10.2)	
4	1,312 (22.1)	68 (23.0)		218 (15.6)	
3	1,164 (19.6)	62 (21.0)		280 (20.1)	
2	1,188 (20.0)	54 (18.2)		345 (24.7)	
1 (Lowest)	1,177 (19.8)	62 (21.0)		411 (29.4)	
Asthma, n (%)	505 (8.5)	33 (11.1)	0.113	195 (13.9)	<0.001
Pre-existing & Gestational Diabetes, n (%)	300 (5.0)	8 (2.7)	0.073	82 (5.9)	0.228
Breastfeeding at Discharge from Hospital, n (%)	5,399 (90.6)	271 (91.3)	0.698	112 (79.4)	<0.001

Abbreviations: BMI, body mass index

Percentages are calculated from non-missing data

Table 2. Demographic and Clinical Measures for Infants of Women who were Non-Smokers, Quit Smoking During Pregnancy, or Continued Smoked During Pregnancy

Infant Measure	Non-Smoker (n=5,961)	Quit Smoking During Pregnancy (n=297)	*P* for Quit Smoking vs. Non-Smoker	Continued Smoking During Pregnancy (n=1,400)	*P* for Continued Smoking vs. Non-Smoker
Birthweight (grams), mean (SD)	3,410 (610)	3,408 (608)	0.968	3,155 (628)	<0.001
Gestational Age (weeks), mean (SD)	38.9 (2.1)	39.0 (2.3)	0.845	38.5 (2.4)	<0.001
Sex, n (%)			0.623		0.473
Male	3,044 (51.1)	156 (52.5)		700 (50)	
Birthweight for Gestational Age, n (%)			0.813		<0.001
< 10th Percentile (SGA)	290 (7.1)	17 (8.1)		155 (15.3)	
> 90th Percentile (LGA)	474 (11.6)	28 (12.0)		52 (5.1)	
Age of Child at Measurement (years), mean (SD)	4.7 (0.3)	4.8 (0.3)	0.246	4.8 (0.3)	0.301
BMI z-score[a], mean (SD)	0.40 (1.05)	0.60 (1.07)	0.002	0.65 (1.18)	<0.001
Overweight or obese[b], n (%)	1612 (27.0)	104 (35.0)	0.003	488 (34.9)	<0.001

Abbreviations: BMI, body mass index; SGA, small-for-gestational age ; LGA, large-for-gestational age

[a] According to Centres for Disease Control (CDC) BMI for sex and age reference standards[31]

[b] Defined as BMI for sex and age at or above the 85th percentile according to Centres for Disease Control (CDC) 2000 reference standards[31]

Percentages are calculated from non-missing data

Table 3. Effect of quitting smoking and continued smoking during pregnancy on childhood BMI and risk of childhood overweight at age 4- to 5-Years

	BMI z-score[a]			Overweight[b]		
	Beta coefficient (95% CI)			RR (95% CI)		
	Unadjusted	**Model 1**[c]	**Model 2**[d]	**Unadjusted**	**Model 1**[c]	**Model 2**[d]
Non-Smoker (n=5,961)	Reference			Reference		
Quit Smoking (n=297)	0.19 (0.05, 0.34)	0.17 (0.04, 0.30)	0.15 (0.01, 0.29)	1.29 (1.10-1.52)	1.25 (1.04-1.51)	1.26 (1.05-1.51)
Continued Smoking (n=1,400)	0.24 (0.16, 0.32)	0.19 (0.12, 0.26)	0.21 (0.13, 0.29)	1.29 (1.19-1.40)	1.24 (1.12-1.37)	1.31 (1.18-1.46)
Number of Cigarettes Smoked Each Day[e]						
1-9 cigarettes/day (n=522)	0.18 (0.06, 0.30)	0.17 (0.05, 0.28)	0.12 (0.01, 0.22)	1.23 (1.08-1.39)	1.19 (1.02-1.39)	1.24 (1.07-1.45)
10-19 cigarettes/day (n=574)	0.24 (0.12, 0.35)	0.22 (0.10, 0.33)	0.21 (0.12, 0.31)	1.33 (1.19-1.50)	1.26 (1.09-1.45)	1.37 (1.18-1.58)
≥20 cigarettes/day (n=202)	0.47 (0.27, 0.68)	0.38 (0.17, 0.58)	0.33 (0.16, 0.50)	1.43 (1.19-1.71)	1.39 (1.13-1.71)	1.52 (1.24-1.86)

Abbreviations: BMI, body mass index; CI, confidence interval;

[a] According to Centres for Disease Control (CDC) BMI for sex and age reference standards[31]

[b] Defined as BMI for sex and age at or above the 85th percentile according to Centres for Disease Control (CDC) 2000 reference standards[31]

[c] Adjusted for maternal age, socioeconomic status, race, parity, and diabetes (pre-existing and gestational)

[d] Adjusted for covariates in Model 1 and maternal BMI

[e] Test for trend statistically significant (P<0.001)

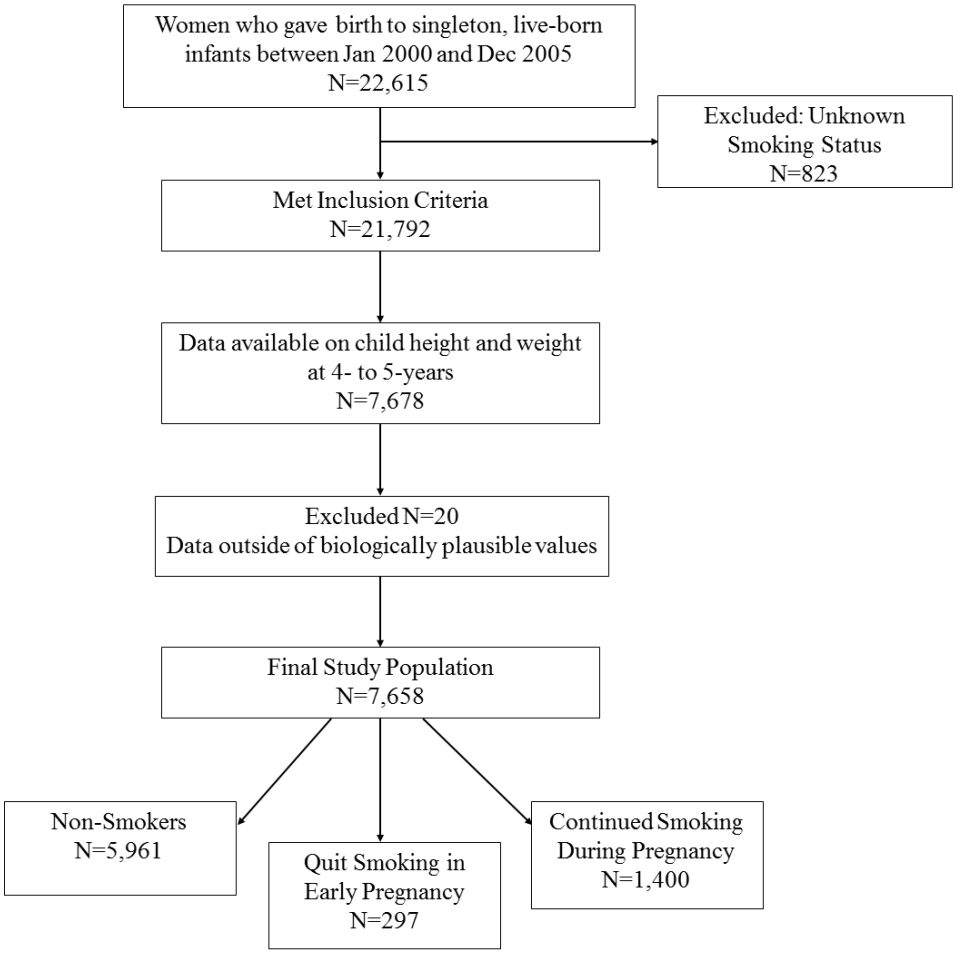

Figure 1: Selection of study population

Supplementary Table 1. Demographic and Clinical Measures According to Loss to Follow-Up

Maternal Measure	**Not lost to follow-up (N=7,658)**	**Lost to follow-up (N=14,134)**	***P* for Quit Smoking vs. Non-Smoker**
	Mean (SD)	**Mean (SD)**	
Age (years)	29.2 (5.5)	28.9 (5.8)	<0.001
	N (%)[a]	**N (%)[a]**	
BMI (kg/m^2)			0.234
<25	2931 (56.1)	5165 (57.0)	
≥25 to <30	1324 (25.3)	2321 (25.6)	
≥30	969 (18.6)	1579 (17.4)	
Parity			0.005
≥1	4135 (54.4)	7911 (56.4)	
Race			<0.001
Caucasian, n (%)	6683 (87.3)	11487 (81.3)	
Socioeconomic Status (SEIFA)			<0.001
5 (Highest)	1287 (16.9)	3022 (21.4)	
4	1598 (21.0)	2776 (19.7)	
3	1506 (19.7)	2733 (19.4)	
2	1587 (20.8)	2696 (19.1)	
1 (Lowest)	1650 (21.6)	2869 (20.4)	
Asthma	733 (9.6)	1348 (9.5)	0.934
Pre-existing & Gestational Diabetes	390 (5.1)	687 (4.9)	0.452
Breastfeeding at Discharge from Hospital	6782 (88.6)	12402 (87.8)	0.077
Smoking Status			<0.001
Non-Smoker	5961 (77.8)	10433 (73.8)	
Quit Smoking	297 (3.9)	691 (4.9)	
Smoker	1400 (18.3)	3010 (21.3)	
Neonatal Measure			
	Mean (SD)	**Mean (SD)**	
Birthweight (grams)	3363 (621)	3317 (660)	<0.001
Gestational Age (weeks)	38.9 (2.2)	38.7 (2.5)	<0.001
	N (%)[a]	**N (%)[a]**	
Sex			0.273
Male	3900 (50.9)	7308 (51.7)	
Birthweight for Gestational Age			0.245
< 10th Percentile (SGA)	464 (8.7)	896 (9.5)	
> 90th Percentile (LGA)	554 (10.4)	990 (10.5)	

Abbreviations: BMI, body mass index [a] Percentages are calculated from non-missing data