

Estimating the health-care costs of children born to pregnant smokers in England: cohort study using primary and secondary health-care data

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ABSTRACT

Background and aims Little is known about the long-term economic consequences of smoking during pregnancy. We estimated the association between smoking in pregnancy and the costs of delivering health-care to infants and children in England, and investigated which aspects of care are the key drivers of these costs. **Methods** We used Hospital Episode Statistics (HES) linked with Clinical Practice Research Datalink (CPRD) data in England from January 2003 to January 2015 in children with longitudinal data for at least 1, 5 and 10 years after birth. Poisson regression provided rate ratios (RR) and 95% confidence intervals (CIs) comparing health-care episode rates between those exposed and not exposed to smoking during pregnancy. Linear regression was used to compare estimated costs between groups (£ sterling, 2015 prices) and generalized linear multivariable (GLM) models adjusted for potentially moderating factors. **Results** A total of 93 152 singleton pregnancies with the required data were identified. Maternal smoking in pregnancy was associated with higher primary care, prescription and hospital in-patient episode rates, but lower out-patient visit and diagnostic test rates. Adjusting for year of birth, socio-economic deprivation, parity, sex of child and delivery method showed that maternal smoking in pregnancy was associated with increased child health-care costs at 1 year [average cost difference for children of smokers, $\beta = \text{£}91.18$, 95% confidence interval (CI) = $\text{£}47.52\text{--}134.83$ and 5 years of age ($\beta = \text{£}221.80$, 95% CI = $\text{£}17.78\text{--}425.83$), but not at 10 years of age ($\beta = \text{£}365.94$, 95% CI = $-\text{£}192.72$ to $\text{£}924.60$). **Conclusion** In England, maternal smoking in pregnancy is associated with increased child health-care costs over the first 5 years of life; these costs are driven primarily by greater hospital in-patient care.

Keywords Health-care costs, health-care utilisation, maternal smoking, pregnancy, smoking cessation, tobacco.

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INTRODUCTION

In Europe, the prevalence of smoking during pregnancy has been estimated to vary from 4.2% in Iceland to 18.9% in Croatia [1]. Maternal smoking during pregnancy is associated with many adverse infant and child outcomes, including an elevated risk of asthma, respiratory illness, sudden infant death syndrome (SIDS), behavioural difficulties [attention deficit hyperactivity disorder (ADHD)], preterm delivery and low birth weight, as well as poor maternal outcomes such as ectopic pregnancy and miscarriage [2–4]. These adverse sequelae are likely to increase

the costs of health care for children born to pregnant smokers.

Few studies have quantified the additional burden on health-care services for infants and children, which is attributable to smoking in pregnancy [5–9]. Godfrey *et al.* estimated the additional smoking-related costs to the UK National Health Service (NHS) incurred by infants during the first 12 months of life as between $\text{£}12$ and $\text{£}23.5$ million annually (2006 prices) [7]. However, this work used literature-based estimates for costs arising from only selected morbidities believed to be associated with smoking, rather than deriving cost estimates for all health-care use.

Petrou *et al.* used medical record linkage to investigate children's excess hospital in-patient costs attributable to smoking in pregnancy during their first 5 years of life [9], and other studies investigating this subject have similarly been restricted to estimating specific elements of overall health-care use, such as neonatal intensive care admissions or health care during very early childhood [5,6,8]. We could find no studies which investigated infants' and children's health-care costs attributable to smoking in pregnancy, which included a consideration of most health-care episodes including those in hospital out-patient and primary care.

The primary aim of this paper was to estimate the impact of maternal smoking during pregnancy on the total cost of providing health-care services for children. This was carried out using English data from the UK NHS, a public provider of care in England, Scotland, Wales and Northern Ireland. The government's annual NHS budget is more than £90 billion, and care is provided free at the point of use [10]. The structure varies in individual countries, but all provide primary [community care, general practitioners (GPs), pharmacists], secondary (hospital-based access via referral) and tertiary (specialist hospital facilities) care [10]. We used long-term, comprehensive, prospective and routinely collected data to investigate children's use and cost of GP services, including consultations, prescriptions and diagnostic tests, along with hospital care services. Our secondary aim was to determine the distribution of costs borne by primary and secondary care providers.

METHODS

Data sources

UK-wide Clinical Practice Research Datalink (CPRD) [11], Hospital Episode Statistics (HES) [12], Office for National Statistics (ONS) mortality data [13] and Index of Multiple Deprivation (IMD) data were used (linked data provided by CPRD) [14]. The study was approved by the CPRD Independent Scientific Advisory Committee (ISAC, protocol number: 15_186R). CPRD contains more than 13 million anonymized primary care medical records from 684 UK general practices; prospectively collected records are available from 1987. Linked records are available for approximately 10 million patients in 398 practices. Linked HES in-patient data are available from 1997, linked HES out-patient data from 2003 and ONS mortality data from 1998 onwards. The IMD is an indicator of deprivation socio-economic status (SES) based on census information from the patients' home postcodes grouped into lower super output areas (LSOA); each LSOA covers approximately 1500 residents/650 households.

Cohort of children born to pregnant smokers and non-smokers

We included children born in England following singleton pregnancies who had up-to-standard linked CPRD-HES data, with at least 1, 5 or 10 years of follow-up from birth and whose mothers were aged 13–49 years at delivery. Mothers and children were identified first from the CPRD mother–baby link; we included women with a CPRD record of smoking status or use of smoking cessation medications in pregnancy. As records of smoking status in pregnancy are generally valid [15], we were confident that using these attributions of exposure or non-exposure to smoking in pregnancy would be generally correct. The study ran from January 2003 to January 2015, when both in-patient and out-patient CPRD-linked HES data were available. Data on delivery method, parity, gestation and delivery dates, sex of the baby and IMD were extracted from HES. Children's duration of follow-up was measured from birth until death, transfer out of a CPRD general practice or the end of the study period, whichever was earliest, and individual children had data available for different lengths of time. To minimize any cluster effects, if a woman had more than one child during the follow-up period only one was selected randomly for inclusion.

Exposure definitions

Smoking in pregnancy. Children were considered exposed to smoking in pregnancy when born to women who, between conception and delivery, had one or more smoking Medcodes or Multilex codes for smoking cessation medication prescriptions (i.e. NRT, bupropion, varenicline) recorded in CPRD. This method has been used previously in a study using The Health Improvement Network (THIN) database [16].

Not smoking in pregnancy. Children were considered not exposed to smoking in pregnancy if their mother had a Medcode for being a non-smoker (including ex-smokers) recorded in CPRD during the gestational period. Consistent with the guidelines for attributing smoking status used by the UK Quality and Outcomes Framework (QOF) [17], women were also considered non-smokers if they were recorded as such at least three times before the age of 25 years, or before becoming pregnant, had been recorded as an ex-smoker in 3 or more consecutive years. Additionally, during pregnancy, women could not be issued with smoking pharmacotherapy prescriptions.

Primary care consultation costing

Different primary care events held with a health-care professional on the same date were classified as one consultation, and costs were attributed to consultations using the 2015 Personal Social Services Research Unit (PSSRU)

reference costs [18]; attribution was based on the type of health-care professional providing the consultation (see below) and the consultation setting (i.e. surgery, home visit, clinic, out-of-hours, telephone). Primary health-care consultations were defined as those with GP partners/senior partners, registrars, locums or sole practitioners, community/practice nurses and dispensers/pharmacists. Where the 2015 PSSRU unit cost compendium provided no unit cost for a provider and setting combination, this was taken instead from the most recent PSSRU unit cost compendia and adjusted to 2015 prices using the NHS Hospital and Community Health Services Pay and Price Index [18].

Prescription costing

We recorded children's prescription items and used the British National Formulary (BNF) to cost prescriptions at the BNF chapter subparagraph level [19]. BNF chapters relate to body systems, BNF sections to prescribing for systems, and paragraph and subparagraph levels relate to the pharmacology and therapeutic use. The Prescription Cost Analysis (PCA) database for 2015 [20] was used to attribute all prescription costs, irrespective of the year in which they were issued. Where the 2015 PCA database did not specify costs for items prescribed (32.3% of all prescriptions), the average 2015 PCA prescription cost (£30.96) was used.

Primary care diagnostic test costing

Children's diagnostic tests in the CPRD test file were identified and included. Costs for diagnostic tests were based on those listed in the National Schedule of Reference Costs (2015) for direct access pathology and diagnostic services [18]. Average costs were assigned for asthma tests (e.g. lung function/spirometry), biochemistry (e.g. hormone, thyroid function, electrolytes), diabetic retinopathy, diagnostic imaging (e.g. chest X-ray), haematology (e.g. full blood count, clotting tests), microbiology (e.g. stool culture, sputum culture), histology, other pathology services (e.g. sputum cytology, urine cytology) and serology and immunology (e.g. immunoglobulin tests, rubella/tuberculin tests). Individual costs, inflated to 2015 prices where necessary, were assigned to each diagnostic test (e.g. electrocardiogram, diagnostic bone marrow extraction, etc.).

Secondary care costing

Secondary care encounters were derived from HES in-patient and out-patient data. HES in-patient data were extracted and each hospital admission was identified by a unique spell number. HES in-patient data were then reformatted to apply appropriate reference costs to admissions using the national tariff prices, based on the national

average unit service provision costs taken from the 2015 National Schedule of Reference Costs [18]. This was achieved by using the hierarchical algorithm in the Health Resource Group (HRG) 4 2015/16 Local Payment Grouper programme [21], provided by the Health and Social Care Information Centre (HSCIC). This programme applied HRG codes to care episodes, which were linked to NHS tariff costs [18]. HRG codes were generated for each episode of in-patient care experienced by children, and the sum of NHS tariff costs for these episodes was calculated for each child.

HES out-patient data were extracted by the CPRD Knowledge Centre [11]; 3.4% of out-patient episodes were costed using the HSCIC Grouper, while the majority (90.7%) of out-patient episodes were costed using treatment speciality average costs from the relevant NHS reference cost schedules. The remaining 5.9% of episodes had an average out-patient cost applied (£147.30), as they could not be costed by Grouper or treatment speciality. Reference costs for secondary NHS care in the United Kingdom are calculated on a full absorption costing basis and encompass staff salaries, on-costs, equipment, consumables and revenue and capital overheads.

Statistical analysis

Our primary aim was to compare health-care costs among children born to women who smoked and non-smokers in pregnancy within the first, the first 5 and the first 10 years of life; hence, findings are presented in cohorts with at least 1, 5 or 10 years of follow-up data available. Descriptive statistics of baseline maternal demographic characteristics for pregnancies were calculated, including the numbers of children with 1, 5 and 10 years of cohort data available, and the proportions of each born to smoking and non-smoking mothers.

Poisson regression was used to compute annualized rate ratios (RRs) and 95% confidence intervals (CIs) for the association between smoking status and each component of primary and secondary health care. Numbers of primary and secondary care health-care episodes used were collapsed into counts which were analysed cross-sectionally in these Poisson models. The analysis was stratified by factors considered to potentially affect children's health-care use: maternal age (< 20, 20–24, 25–29, 30–34 and ≥ 35 years), parity (0 or ≥ 1 children), SES (IMD quintiles), sex of infant (male, female) and mode of delivery (spontaneous, assisted, elective caesarean, emergency caesarean). Furthermore, year of birth was adjusted for to allow for the possibility that the volume and or pattern of health care provided to infants and children might have evolved through the course of each cohort, as well as the recorded prevalence of maternal smoking. As analyses employed multiple significance

testing of strata on the same health-care outcome, a Bonferroni correction was applied to tests at the 99.7% confidence level (i.e. $\alpha = 0.05/19$, $P \leq 0.003$, 19 = number of significance tests per outcome) to determine the significance of each association. The mean and standard deviations for the number of encounters were also calculated for each stratum.

Linear regression was used to compute coefficients and 95% CIs for the association between maternal smoking during pregnancy and the estimated costs of child health-care utilization, adjusting for year of birth. The absolute difference in average annual cost between children of smoking and non-smoking mothers was calculated. A similar Bonferroni correction was applied to the costs as to the previous analysis of health-care utilization. In the Supplementary information, findings are also presented in strata for maternal age, parity, SES, sex of child and delivery method. As little is known about the costs attributable to smoking in primary and secondary care, especially beyond 5 years of follow up, this stratified analysis was carried out to present the findings in a descriptive way by these variables. Stratification of the follow-up into 1, 5 and 10-year periods was chosen based on prior knowledge; costing in the first year is important, as utilization during infancy may be associated with longer-term costs. The first 5 years is a marker that is used commonly in the United Kingdom and partially by the World Health Organization (WHO), as children start formal schooling at approximately age 5 and allows a comparison to other studies, and 10-year follow-up was the longest available with a significant number of participants to analyse.

In each cohort the variation in total health-care costs for children of women who smoked in pregnancy, versus those who did not, was assessed using a multivariable generalized linear model (GLM) to generate cost coefficients and 95% CIs. The association between smoking in pregnancy and overall health-care cost was adjusted for year of birth, maternal age, IMD, parity, sex of infant and mode of birth. A gamma distribution and fitted robust standard errors were applied. We further replicated the GLM models over 1- and 5-year time horizons, restricting the sample to those who had complete 10-year data, to investigate whether the effects of smoking during pregnancy waned or persisted in the reduced sample size with complete follow-up data.

Where data were missing for the stratification covariates for the multivariable models (maternal age, SES, parity, infant gender or mode of delivery) or for outcomes (described below), individuals were excluded from analyses. A comparative analysis investigating the distribution of the baseline covariates was performed to investigate whether removal of these cases biased the sample. Analyses were conducted using Stata version 14.0 (Stata Corporation, College Station, TX, USA).

RESULTS

Cohort selection

There were 586 017 pregnancies with 'up-to-standard' CPRD-HES data from January 2003 onwards; 244 012 of these women had sufficient data to attribute smoking status within the pregnancy; 203 159 of these pregnancies had the minimum length of child follow-up (1 year). Of these children, 137 737 had the necessary HES-linked secondary care data and 44 585 children were excluded randomly, as they were siblings and shared a mother. No participants were excluded due to there being missing data for other baseline maternal covariates. Therefore, the final cohort comprised 93 152 children, 21.8% of whom were born to women who had smoked in pregnancy.

Cohort characteristics

A total of 34 260 children had at least 5 years' and 5824 at least 10 years' data. Approximately one-fifth of children in 5- and 10-year cohorts were children of maternal smokers. The largest proportion of mothers fell into the 30–34-year age range in each cohort. The proportions of children exposed to maternal smoking during pregnancy stratified by maternal age, IMD, parity, infant sex and mode of birth are listed in Table 1. In all three cohorts, women who smoked during pregnancy were, on average, younger and resided in more deprived areas. A slightly higher proportion of first-time mothers smoked during pregnancy. A higher proportion of male children were contained in each of the follow-up cohorts and this did not differ by maternal smoking status. Finally, non-smoking mothers had a lower spontaneous vaginal delivery rate and a higher proportion had an instrumental delivery or a caesarean section; this may be attributable to the greater average age of mothers who did not smoke during pregnancy.

Comparison of health-care utilization by smokers' and non-smokers' children

Table 2 presents the adjusted annual RRs for primary and secondary care health-care utilization by children of rate ratios for year of birth, maternal age, parity, SES, gender of child and delivery method. In the whole cohort, infants exposed to maternal smoking in pregnancy had higher primary care consultation (RR = 1.015, 95% CI = 1.007–1.022) and in-patient admission (RR = 1.040, 95% CI = 1.020–1.060) rates during the first year of life. In children for whom at least 5 years' data were available, those born to pregnant smokers had higher annual primary care (RR = 1.021, 95% CI = 1.005–1.038) and out-patient consultation (RR = 1.084, 95% CI = 1.036–1.134) rates, but a lower annual primary care diagnostic test rate (RR = 0.961, 95% CI = 0.924–0.999)

Table 1 Maternal and child characteristics according to mother's smoking status during pregnancy.

	<i>At least 1 year's follow-up^b</i>		<i>At least 5 years' follow-up</i>		<i>At least 10 years' follow-up</i>	
	<i>Non-smokers (%)</i>	<i>Smokers (%)</i>	<i>Non-smokers (%)</i>	<i>Smokers (%)</i>	<i>Non-smokers (%)</i>	<i>Smokers (%)</i>
Overall	72 863 (78.2) ^a	20 289 (21.8) ^a	26 958 (78.7) ^a	7302 (21.3) ^a	4666 (80.1) ^a	1158 (19.9) ^a
Maternal age (years)						
< 20	2475 (3.4)	2188 (10.8)	797 (3.0)	790 (10.8)	121 (2.6)	105 (9.1)
20–24	9298 (12.8)	5548 (27.3)	3178 (11.8)	1879 (25.7)	538 (11.5)	273 (23.6)
25–29	19 352 (26.6)	5516 (27.2)	6693 (24.8)	1871 (25.6)	1128 (24.2)	304 (26.3)
30–34	24 690 (33.9)	4368 (21.5)	9224 (34.2)	1655 (22.7)	1668 (35.8)	305 (26.3)
≥ 35	17 048 (23.4)	2669 (13.2)	7066 (26.2)	1107 (15.2)	1211 (26.0)	171 (14.8)
Socio-economic status: Index of Multiple Deprivation						
1 (least deprived)	18 142 (24.9)	2585 (12.7)	7550 (28.0)	1019 (14.0)	1442 (30.9)	174 (15.0)
2	15 735 (21.6)	3195 (15.8)	6053 (22.5)	1203 (16.5)	1110 (23.8)	197 (17.0)
3	13 872 (19.0)	3855 (19.0)	5028 (18.7)	1376 (18.8)	864 (18.5)	232 (20.0)
4	13 789 (18.9)	4968 (24.5)	4668 (17.3)	1788 (24.5)	735 (15.8)	278 (24.0)
5 (most deprived)	11 325 (15.5)	5686 (28.0)	3659 (13.6)	1916 (26.2)	515 (11.0)	277 (23.9)
Parity						
0	42 358 (58.1)	12 370 (61.0)	11 774 (43.7)	3370 (46.2)	1842 (39.5)	461 (39.8)
≥ 1	30 505 (41.9)	7919 (39.0)	15 184 (56.3)	3932 (53.9)	2824 (60.5)	697 (60.2)
Sex of child						
Female	34 585 (47.5)	9620 (47.4)	12 533 (46.5)	3411 (46.7)	2107 (45.2)	543 (46.9)
Male	38 278 (52.5)	10 669 (52.6)	14 425 (53.5)	3891 (53.3)	2559 (54.8)	615 (53.1)
Delivery method						
Spontaneous vaginal delivery	42 756 (58.7)	13 068 (64.4)	15 999 (59.4)	4736 (64.9)	2729 (58.5)	756 (65.3)
Assisted delivery	10 693 (14.7)	2513 (12.4)	3491 (13.0)	848 (11.6)	618 (13.2)	126 (10.9)
Elective caesarean	7769 (10.7)	1724 (8.5)	3178 (11.8)	658 (9.0)	575 (12.3)	108 (9.3)
Emergency caesarean	11 645 (16.0)	2984 (14.7)	4290 (15.9)	1060 (14.5)	744 (16.0)	168 (14.5)

^aRow percentage, otherwise column percentage; ^bfollow-up at 1 year constitutes entire study cohort.

during the first 5 years of life. Finally, in those with at least 10 years' follow-up data, children born to pregnant smokers had higher annual primary care (RR = 1.062, 95% CI = 1.012–1.114) and out-patient consultation (RR = 1.126, 95% CI = 1.001–1.267) rates during the first 10 years of life. The risk ratios presented in Table 2 stratified by confounding factors, and Bonferroni-corrected, are presented in Supporting information, Table S1a–c.

Comparison of health-care costs incurred by smokers' and non-smokers' children

Table 3 compares overall estimated health-care costs incurred by children of women who smoked and did not smoke in pregnancy, disaggregating costs for different health-care components. All associations were adjusted by year or birth, maternal age, parity, SES, gender of child and delivery method.

Smoking during pregnancy had the greatest influence on hospital in-patient costs, which were significantly greater for children whose mothers smoked during pregnancy ($\beta = \pounds 93.95$, 95% CI = $\pounds 39.44$ – 148.45) during the first year of life. For all other aspects of

health-care utilization (primary care, diagnostic tests, prescriptions and out-patient care), including for the 5- and 10-year cohorts, there were no significant differences in costs between the children whose mothers either smoked or did not smoke during pregnancy. The coefficients presented in Table 3, stratified by confounding factors and Bonferroni-corrected, are presented in Supporting information, Table S2a–c.

Investigation of factors influencing costs: multivariable GLM model

Table 4 presents multivariable GLM models for children with at least 1, 5 and 10 years of follow-up data, with total health-care costs as the dependent variable. Following adjustment for year of birth, IMD, parity, sex of child and delivery method, maternal smoking in pregnancy was associated with significantly higher total health-care costs during the first ($\beta = \pounds 91.18$, 95% CI = $\pounds 47.52$ – 134.83) and also the first 5 ($\beta = \pounds 221.80$, 95% CI = $\pounds 17.78$ – 425.83) years of life, but not during the first 10 years ($\beta = 365.94$, 95% CI = -192.72 to 924.60). During the first year of life, boys had greater total health-care costs compared to girls

Table 2 Adjusted annual rate ratios for primary and secondary health-care utilization for children whose mothers were smokers compared to non-smokers during pregnancy.

	Number of primary care consultations, mean (median)		RR ^a	95% CI	
	Non-smoking	Smoking		Lower	Upper
(0–1 year's follow-up for those with at least 1-year follow-up data) (n = 93 152)	12.17 (10)	12.36 (11)	1.015	1.007	1.022
(0–5 years' follow-up for those with at least 5 years' follow-up data) (n = 34 260)	31.59 (27)	32.17 (27)	1.021	1.005	1.038
(0–10 years' follow-up for those with at least 10 years' follow-up data) (n = 5824)	42.73 (35)	45.57 (37)	1.062	1.012	1.114
	Number of prescriptions, mean (median)		RR ^a	95% CI	
	Non-smoking	Smoking		Lower	Upper
(0–1 year's follow-up for those with at least 1-year follow-up data) (n = 93 152)	5.04 (3)	5.15 (3)	1.005	0.994	1.016
(0–5 years' follow-up for those with at least 5 years' follow-up data) (n = 34 260)	15.62 (10)	15.45 (11)	0.980	0.959	1.003
(0–10 years' follow-up for those with at least 10 years' follow-up data) (n = 5824)	23.71 (15)	24.64 (17)	1.016	0.953	1.084
	Number of diagnostic tests, mean (median)		RR ^a	95% CI	
	Non-smoking	Smoking		Lower	Upper
(0–1 years' follow-up for those with at least 1-year follow-up data) (n = 93 152)	2.26 (1)	2.19 (1)	0.990	0.974	1.006
(0–5 years' follow-up for those with at least 5 years' follow-up data) (n = 34 260)	5.56 (1)	5.32 (1)	0.961	0.924	0.999
(0–10 years' follow-up for those with at least 10 years' follow-up data) (n = 5824)	9.33 (2)	9.98 (3)	1.078	0.974	1.193
	In-patient, mean (median) ^b		RR ^a	95% CI	
	Non-smoking	Smoking		Lower	Upper
(0–1 years' follow-up for those with at least 1-year follow-up data) (n = 93 152)	1.54 (1)	1.63 (1)	1.040	1.020	1.060
(0–5 years' follow-up for those with at least 5 years' follow-up data) (n = 34 260)	2.09 (1)	2.27 (1)	1.048	0.986	1.114
(0–10 years' follow-up for those with at least 10 years' follow-up data) (n = 5824)	2.38 (1)	2.60 (2)	1.062	0.869	1.298
	Out-patient, mean (median) ^b		RR ^a	95% CI	
	Non-smoking	Smoking		Lower	Upper
(0–1 years' follow-up for those with at least 1-year follow-up data) (n = 93 152)	1.11 (0)	1.07 (0)	1.004	0.981	1.028
(0–5 years' follow-up for those with at least 5 years' follow-up data) (n = 34 260)	3.84 (1)	4.13 (1)	1.084	1.036	1.134
(0–10 years' follow-up for those with at least 10 years' follow-up data) (n = 5824)	6.65 (2)	7.63 (3)	1.126	1.001	1.267

Risk ratios in bold type are significant at $P \leq 0.003$. ^aPoisson regression rate ratios (RR) [95% confidence interval (CI)] for number of consultations per year of follow-up, adjusted for year of birth, maternal age, parity, socio-economic status (SES), gender of child and delivery method; ^bsecondary care consultations.

Table 3 Primary care, secondary care and overall costs of health-care utilization accrued for children whose mothers were smokers compared to non-smokers during pregnancy.

	Cost of primary care consultations, mean (median) ^a		β	95% CI	
	Non-smoking	Smoking		Lower	Upper
Costs for children at 1 year with at least 1 year of follow-up (n = 93 152)	192 (166)	193 (167)	1.11	-1.86	4.07
Costs for children at 5 years with at least 5 years of follow-up (n = 34 260)	508 (435)	513 (440)	6.97	-6.60	20.56
Costs for children at 10 years with at least 10 years of follow-up (n = 5824)	705 (592)	742.12 (634)	31.62	-16.59	79.84
	Cost of prescriptions, mean (median) ^a		β	95% CI	
	Non-smoking	Smoking		Lower	Upper
Costs for children at 1 year with at least 1 year of follow-up (n = 93 152)	324 (177)	330 (187)	0.30	-11.81	12.40
Costs for children at 5 years with at least 5 years of follow-up (n = 34 260)	1063 (588)	1060 (617)	-6.51	-85.10	72.08
Costs for children at 10 years with at least 10 years of follow-up (n = 5824)	1781 (868)	1847 (1028)	29.84	-362.67	422.36
	Cost of diagnostic tests, mean (median) ^a		β	95% CI	
	Non-smoking	Smoking		Lower	Upper
Costs for children at 1 year with at least 1 year of follow-up (n = 93 152)	21 (0)	22 (0)	1.72	-0.27	3.71
Costs for children at 5 years with at least 5 years of follow-up (n = 34 260)	56 (4)	56 (1)	0.24	-6.88	7.36
Costs for children at 10 years with at least 10 years of follow-up (n = 5824)	124 (14)	126 (14)	0.18	-40.77	41.14
	In-patient, mean (median) ^a		β	95% CI	
	Non-smoking	Smoking		Lower	Upper
Costs for children at 1 year with at least 1 year of follow-up (n = 93 152)	755 (0)	862 (0)	93.95	39.44	148.45
Costs for children at 5 years with at least 5 years of follow-up (n = 34 260)	1299 (0)	1526 (604)	173.41	-44.83	391.65
Costs for children at 10 years with at least 10 years of follow-up (n = 5824)	1620 (595)	1841 (731)	152.69	-489.51	794.90
	Out-patient, mean (median) ^a		β	95% CI	
	Non-smoking	Smoking		Lower	Upper
Costs for children at 1 year with at least 1 year of follow-up (n = 93 152)	189 (0)	183 (0)	3.06	-8.62	14.73
Costs for children at 5 years with at least 5 years of follow-up (n = 34 260)	605 (193)	659 (193)	52.58	-5.47	110.62
Costs for children at 10 years with at least 10 years of follow-up (n = 5824)	1014 (382)	1181 (500)	135.10	-81.34	351.54

Coefficients in bold type are significant at $P \leq 0.003$. ^aRegression coefficients for cost (£) adjusted for year of birth, maternal age, socio-economic status (SES), parity, gender of child and delivery method. CI = confidence interval.

Table 4 Multivariable GLM models for total costs incurred by 1, 5 and 10 years' follow-up.

Variables	Total costs, 0-1 years (n = 93 152)			Total costs, 0-5 years (n = 34 260)			Total costs, 0-10 years (n = 58 24)				
	β	95% CI		β	95% CI		β	95% CI			
		Lower	Upper		Lower	Upper		Lower	Upper		
Maternal smoking during pregnancy	91.18	47.52	134.83	221.80	17.78	425.83	0.033	365.94	-192.72	924.60	0.199
Year of birth	25.43	20.03	30.84	10.96	-25.49	47.41	0.556	-221.99	-613.69	169.71	0.267
Maternal age (years)											
< 20	72.12	-52.03	196.26	268.01	-204.67	740.68	0.266	929.13	-515.37	2373.63	0.207
20-24	0.00	-	-	0.00	-	-	-	0.00	-	-	-
25-29	-86.11	-137.64	-34.59	-176.53	-462.52	109.46	0.226	275.07	-413.62	963.77	0.434
30-34	-117.16	-167.58	-66.74	-273.43	-542.96	-3.91	0.047	-46.98	-638.91	544.95	0.876
≥ 35	-54.26	-112.71	4.19	-75.41	-365.00	214.19	0.610	-50.04	-773.58	673.50	0.892
Socio-economic status: Index of Multiple Deprivation											
1 (least deprived)	0.00	-	-	0.00	-	-	-	0.00	-	-	-
2	67.83	17.18	118.48	-114.12	-305.36	77.12	0.242	111.25	-562.81	785.30	0.746
3	18.74	-28.97	66.45	87.01	-151.44	325.46	0.474	0.02	-732.92	732.97	1.000
4	18.07	-32.78	68.92	96.77	-131.51	325.05	0.406	289.73	-394.88	974.35	0.407
5 (most deprived)	79.03	26.46	131.61	295.80	56.61	534.98	0.015	996.54	205.62	1787.46	0.014
Parity											
0	0.00	-	-	0.00	-	-	-	0.00	-	-	-
≥ 1	25.63	-9.54	60.80	95.50	-49.02	240.02	0.195	-645.09	-1195.04	-95.14	0.022
Sex of child											
Female	0.00	-	-	0.00	-	-	-	0.00	-	-	-
Male	229.05	196.00	262.10	465.22	320.74	609.70	< 0.001	1140.25	650.11	1630.40	< 0.001
Delivery method											
Spontaneous vaginal delivery	0.00	-	-	0.00	-	-	-	0.00	-	-	-
Assisted delivery	299.98	247.48	352.47	619.49	364.87	874.11	< 0.001	588.17	-116.89	1293.23	0.102
Elective caesarean	371.81	304.12	439.49	886.30	583.07	1189.53	< 0.001	704.27	-21.35	1429.88	0.057
Emergency caesarean	655.39	599.96	710.81	1275.37	1022.32	1528.42	< 0.001	1483.91	679.90	2287.91	< 0.001

Coefficients in bold type are significant at $P < 0.05$. CI = confidence interval.

($\beta = \pounds 229.05$, 95% CI = $\pounds 196.00$ – 262.10), while the increasing intensity of the intervention delivery method was also associated with greater costs (e.g. emergency caesarean $\beta = \pounds 655.39$, 95% CI = $\pounds 599.96$ – 710.81). Greater socio-economic deprivation was associated with higher costs (5th IMD quintile: $\beta = \pounds 79.03$, 95% CI = $\pounds 26.46$ – 131.61), but increasing maternal age was associated with lower total health-care costs (e.g. for 30–34-year-olds: $\beta = -\pounds 117.16$, 95% CI = $-\pounds 167.58$ to -66.74). Compared to complete cohort findings, total health-care costs during the first 5 and first 10 years of life showed similar associations with delivery mode, sex of child and IMD distribution. However, while maternal age showed little or no effect on total costs of child health-care during extended follow-up periods, multiparity was associated with significantly reduced total health-care costs during the first 10 years of life ($-\pounds 645.09$, 95% CI = $-\pounds 1195.04$ to -95.14).

Following restriction of the GLM models to children with complete 10 years' follow-up data, the associations were similar to those for the unrestricted analysis at 1 year ($\beta = 41.18$, 95% CI = $-\pounds 98.02$ to 180.38) and 5 years ($\beta = \pounds 195.22$, 95% CI = $-\pounds 165.19$ to 555.63); however, the cost coefficients did not reach statistical significance.

DISCUSSION

Infants and children of pregnant smokers had higher health-care costs during the first 5 years of life, predominantly attributable to greater hospital in-patient care. Although rates of primary care consultations, hospital in-patient and hospital out-patient episodes were higher in smokers' children, our results indicate an inverse association between smoking during pregnancy and the number of diagnostic tests in primary care during the first 5 years of children's lives. This apparent underutilization in the use of some primary health care services may reflect differences in health-seeking behaviour between mothers characterized by different socio-demographic profiles, but this remains to be elucidated by future research studies in this clinical context.

Strengths and limitations

Among studies evaluating health-care costs of children born to pregnant smokers, this has the longest follow-up and is the first to investigate costs after 5 years of life. Additionally, it is more comprehensive; we attempted to measure use of all health care rather than, as in previous studies, only assessing impacts generated by selected conditions thought to be associated with smoking in pregnancy [7] or taking only a secondary care perspective [9]. We believe this work is the first to use multivariable methods to identify key influences on children's smoking-attributable health-care costs.

A limitation is that we defined the smoking status in pregnancy from records of tobacco use and of smoking cessation medication prescriptions in medical records, and this involved some assumptions. Some women stop smoking later in pregnancy, but our simplified classification of women as either 'smoking' or 'not smoking' for the whole of pregnancy could not reflect this, and some women may have been categorized as smoking throughout pregnancy when they may only have smoked briefly. However, patients usually provide accurate information to GPs and we have demonstrated previously that assumptions used in this study lead to valid attribution of smoking status [15], so any misclassification of smoking will be small and study findings are likely to be valid. Additionally, as misclassification would tend to reduce apparent differences between groups' health-care cost estimates, findings are conservative and actual cost differences may be larger. A further limitation was the absence of comprehensive data on the number of cigarettes smoked during pregnancy. As data on this variable were only available in the records of 22% of women, we did not account for this factor as this would have reduced the sample size and precision of estimates, especially for the analyses over an extended time horizon for which we had fewer complete cases.

As women who smoke in pregnancy are likely to smoke after childbirth, some of infants' and children's health-care use in the smoking-exposed group may be attributable to second-hand smoking (SHS). We decided not to attempt to factor this into our analyses, as smoking data were recorded inconsistently at varied time-points, and even where these data were available it was not possible to ascertain whether infants' exposure to parental smoking had occurred. Although the extent of children's SHS exposure in this cohort is not known, we do not anticipate that this will have a marked effect as, in the United Kingdom since 2007, the percentage of children exposed to SHS for 'at least one hour a week' has remained static at approximately 11% [22]. SHS exposure may have been more prevalent at the start of the cohort, but it seems unlikely that this will have had a substantial impact on findings; nevertheless, our cost estimates are probably best viewed as those which could be avoided if smoking in pregnancy was eliminated permanently and women remained abstinent after childbirth.

We cannot discount the possibility that there are unobserved clinical and behavioural characteristics that are correlated positively with both smoking in pregnancy and economic outcomes, and not accounting for them in the models may have biased upwards the apparent effect of smoking. A number of clinical conditions that increase the risk of poor birth outcomes with long-term sequelae, such as gestational hypertension [23,24], are likely to have been present with the sample. Similarly, we did not adjust for other risky behaviours associated with smoking in

pregnancy, such as illicit drug or alcohol use. Illicit drug use is not recorded reliably in routinely collected electronic medical records and may be treated in specialist facilities not covered by primary and secondary care records, while the GP-enhanced services contract provides an opt-out clause to not be involved in the treatment of drug dependence [25]. As a result, drug dependence could have been recorded differentially during the study period, and thus we could not adjust for it reliably. Similarly, alcohol use during pregnancy is poorly recorded and has low prevalence (6.8%) [26], and there is some evidence of systematic misclassification in routinely recorded data by doctors [27]. Therefore, the effects of illicit drug and alcohol use were not accounted for explicitly. However, drug- and alcohol-related problems are associated very strongly with socio-economic deprivation, and we adjusted for this in the form of IMD scores in all our analyses which, as a proxy for these factors, may have reduced this bias.

Another limitation derives from linked HES data only having been available for 12 years, resulting in relatively few children having 10 years' follow-up data, a comparatively small 10-year cohort and analyses at this time-point having limited power. Restricting the analyses for total costs at 1 and 5 years to a group with 10-year follow-up data found that, although the associations were similar to those for the unrestricted analysis, the cost coefficients did not reach statistical significance. This may have been due to an insufficient sample size, rather than a proven waning of the effect of smoking during pregnancy. Future, larger studies might be necessary for a more definitive investigation of findings at 10-year follow-up. Nevertheless, this cohort has a substantially longer follow-up period than the previous longest study, and as such is a substantial contribution to the literature [9].

Results in context

Petrou *et al.* estimated mean hospital in-patient cost differences between children born to smokers and non-smokers as £138, 307 and 462 during the first 5 years of life in women who reported smoking 1–9, 10–19 or ≥ 20 cigarettes, respectively [9]. Although these cost estimates were derived from hospital in-patient data extracted from a limited geographical area of England (Oxford Record Linkage Study), they are broadly similar in magnitude to the mean total health-care cost differences we generated [multivariable model at 5 years: £221.80 (£17.78–425.83)]. This may reflect our finding that overall health-care costs were influenced most strongly by hospital admissions. Godfrey *et al.* investigated average costs for maternal outcomes and infant outcomes attributable to smoking and non-smoking in pregnancy [7]. Using literature-based unit costs, infant outcomes during the first year of life related to smoking in pregnancy were estimated

to cost the NHS £12–23.5 million per year. Our multivariable model generated a mean incremental child health-care cost attributable to maternal smoking during pregnancy of £91.18 (£47.52–134.83) during the first year of life. Assuming approximately 700 000 pregnancies per year and a UK prevalence of smoking during pregnancy of 15% [28,29], this translates to an additional annual health-care cost of £9.6 (£4.9–14.1) million when the health sequelae of smoking during pregnancy are restricted to those experienced during the first year of life. This represents a more conservative estimate of costs attributable to smoking during pregnancy compared to those derived from the published literature. When the health sequelae of smoking during pregnancy are extended to the first 5 years of life, additional annual health-care costs increase to £23.3 (£1.9–44.7) million. Overall findings from this direct analysis of health-care use suggest that excess infant health-care costs attributable to maternal smoking in pregnancy are smaller than estimated previously. Actual costs could be higher or lower than our point estimates although because, as noted previously, biases within the analyses might inflate or reduce derived point estimates.

Although health benefit remains the principal reason for encouraging smoking cessation in pregnancy, our findings suggest that smoking cessation in pregnancy is also likely to reduce the costs of providing health-care to children. When assessing the potential economic benefits of providing stop smoking services for pregnant women, any reduction in maternal health-care costs associated with smoking during pregnancy should be considered in addition to the infant and childhood ones we have quantified. For example, recent estimates suggest that English NHS Stop Smoking Services cost £235 per quitter [29], so most of the investment made providing such services could be recouped in the medium term by the reduced spending on infant's and children's health care generated by the smoking cessation which these services promote. Indeed, adding in any reductions in the costs of providing health care to pregnant women who stop smoking permanently, the provision of cessation support in pregnancy could even be cost-saving to a health system.

CONCLUSIONS

Maternal smoking in pregnancy is a leading preventable cause of harm to mothers and babies, and we found that it is associated with increased children's health-care costs during the first 5 years of life, with elevated costs driven primarily by more costly hospital admissions. Findings imply that funding cessation support for pregnant smokers could have economic benefits in addition to those health benefits which accrue from permanent smoking cessation in pregnancy.

Declaration of interests

None.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

Table S1a Adjusted annual rate ratios for primary and secondary health-care utilization for children of smokers compared to non-smokers (\leq 1-year follow-up) ($n = 93\,152$).

Table S1b Adjusted annual rate ratios for primary and secondary health-care utilization for children of smokers compared to non-smokers (0–5 years' follow-up) ($n = 34\,260$).

Table S1c Adjusted annual rate ratios for primary and secondary health-care utilization for children of smokers compared to non-smokers (0–10 years' follow-up) ($n = 58\,24$).