ORIGINAL ARTICLE

Effect of parental smoking on cotinine levels in newborns

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Background: Smoking is a major risk factor for cot death. Many infants smoke passively as a result of parental smoking. This paper reports on infants exposed to a smoking environment and how they accumulate metabolites of cigarette smoke, such as cotinine, which may be physiologically harmful.
Aim: To assess cotinine levels in infants of smoking parents.
Method: Cotinine excretion in urine was assessed in 104 infants, of whom 71 had smoking parents and 33 had non-smoking parents. All cotinine levels were measured at approximately 12 weeks of age. The subjects were selected from a database of infants in developmental physiological studies which assessed the impact of various factors on early postnatal development.
Results: On average babies with at least one parent who was a current cigarette smoker excreted 5.58 (95% CI 3.4 to 9.5) times as much cotinine in the urine as did the babies of non-smoking parents. Maternal smoking was the largest contributing factor. Co-sleeping ($p = 0.037$) and the minimum room temperature ($p = 0.028$) were significant contributory factors.
Conclusion: Infants from smoking households accumulate cotinine, a metabolite of nicotine, which may have a detrimental effect on the cardiorespiratory system.

The impact of cigarette smoke on health is seen in all age groups. It causes heart and lung disease in adults[1] and respiratory illness in children,[2–5] and more recently, it has been linked with smallness at birth[6–8] and sudden death in infancy.[9 10] The active or passive inhalation of cigarette smoke, with its numerous chemical components, is probably the mode of contamination, but the mechanism by which pathophysiological changes occur is unknown. Specifically, antenatal smoking may affect up to 25% of pregnancies,[11] causing morphological placental changes that lead to chronic fetal hypoxic stress and abnormal lung and brain development.[5] Fetal and infant physiology are disrupted,[12–14] lung function is reduced[15] and arousal mechanisms are impaired,[16] with a tendency to central apnoea and reduced ventilatory response to hypoxia. Law *et al*[17] showed the effects of neonatal nicotine withdrawal on infant neurobehaviour. Gergen *et al*[18] have shown that nearly 40% of under-fives are exposed to environmental tobacco smoke in the home, and that as many as 6000 deaths in young children may be a direct result of this.[19]

In the present study, we investigated the extent to which the nicotine metabolite, cotinine, is transferred to newborn infants as a consequence of parental smoking.

METHODS

During studies of postnatal developmental physiology of human infants, in which deep body temperature was monitored over night, we collected information on parental smoking habits and urine samples from the babies for cotinine estimation. Details of parental reported smoking were recorded and validated by direct observation by a trained researcher.

The studies were carried out over a period of five years up to and including 1998,[20–22] and for this study, infants were recruited sequentially from the database according to whether the parents smoked (in the original studies, infants who met the inclusion criteria were selected at random from the Birth Notification Register). Infants with insufficient physiological data were excluded. For the purpose of this study, a smoking household was defined as one in which either parent (or main carer) smoked. Co-sleeping was defined as an infant who routinely bed shared with the carer(s) for the main night-time sleep over the duration of the study.

The database contained 493 infants. We sequentially selected the first 104 infants who provided a cotinine urine sample and for whom full physiological data were available. The infants were split into those from smoking and non-smoking households for analysis. All infants were monitored during the same period. Their weight, record of feeding and care practices, and evidence of illness or immunisation were obtained from the database. In the original study, at bedtime, a paediatric urine collector (Hollister U bag), which was modified to reduce the risk of detachment, was attached to the infant to collect the evening urine sample. Samples were frozen within four hours of collection. Care was taken to avoid contamination of the specimen containers with any suspected source of nicotine.

The infants were approximately 10–12 weeks of age at the time of the study. The local ethics committee approved the study, and informed consent was obtained from all parents.

We report on the infants' cotinine levels, in relation to the reported smoking habits of parents, social circumstances and the care practices applied to the infant.

Laboratory techniques

We used the cotinine:creatinine ratio as the measure of exposure to smoke. It was estimated by the enzyme-linked immunosorbent assay (ELISA) method (Cosazt Bioscience Ltd, UK), a competitive enzyme immunoassay. The logarithm transformation was used to attain normal distribution. All analyses on the ELISA kit were carried out in duplicate and we used cotinine standards from 0 µg/l to 880 µg/l for calibration. All samples with cotinine levels greater than 880 µg/l were reanalysed after diluting in deionised water. Creatinine levels were determined by the Jaffe reaction on a Cobas Fara analyser (Roche Diagnostics, UK). The results were expressed as µg/l of cotinine per mmol/l creatinine. All analyses were performed blind (standards and reagents, Sigma Chemical Co, UK).

Statistical methods

We used Student's t test to compare birth weight, gestational age and other approximately normally distributed variables,

Table 1 Demographic data on infants from non-smoking and smoking households

	Non-smoking (n = 33)	Smoking (n = 71)	p Value	95% CI*
Sex, n (%)				
Male	14 (42)	43 (61)		
Female	19 (58)	28 (39)	0.080	−0.02 to 0.37
Birth weight (g), mean (SD)	3607 (600)	3205 (544)	0.002	152 to 652
Gestation (weeks), mean (SD)	39.9 (1.47)	39.6 (1.66)	0.424	−0.42 to 0.98
Feeding, n (%)				
Breast fed	24 (73)	17 (24)		
Bottle fed	9 (27)	54 (76)	<0.001	−0.64 to −0.29
Social class, n (%)†				
I or II	15 (50)	6 (11)		
III or IV	5 (17)	10 (18)		−0.61 to −0.05
V or VI	7 (23)	17 (30)		−0.63 to −0.13
VII or VIII	3 (10)	24 (42)	0.002	−0.78 to −0.35
Not known	3	14		
Birth order, mean (SD)	1.79 (0.86)	2.66 (1.50)	0.003	−1.43 to −0.31
Age (weeks), mean (SD)‡	10 (2.97)	12 (3.59)	0.090	−2.90 to 0.25
Weight (g), mean (SD)‡	5796 (1053)	5444 (1206)	0.278	−290 to 995

*95% CI for differences in mean values (for continuous variables) or differences in % (categorical variables)
†Social class was based the reported occupation of the highest earner in the household.
‡Measurement taken at time of cotinine estimation.

according to the smoking status of parents. Cotinine and creatinine levels were found to be largely positively skewed; they were therefore logarithm transformed for analysis. The geometric means are presented here. Homogeneity of variance was formally tested. The residual plots were examined visually and found to be satisfactory. The χ^2 test was used to examine the association between parental smoking status and sex, feeding methods, social class of the family and other characteristics.

We used general linear models to examine the association between combinations of characteristics, primarily smoking status and the cotinine:creatinine ratio (on a logarithmic scale). Effects of potential confounders were examined by building models using forwards and backwards selection procedures. The pool of variables used for this consisted of: feeding method; father's employment status; social class; whether the baby co-slept; inadequate heating in the home; the time of maturation of the adult core body temperature pattern and whether this was delayed; the minimum room temperature where baby slept; and the season.

All analyses were undertaken using SPSS for Windows (version 14.0). The level for statistically significant results was set at 5% ($p<0.05$), and 95% confidence intervals are presented for the main results.

RESULTS

Characteristics of the study population

We identified 104 infants, 33 (32%) from non-smoking and 71 (68%) from smoking homes. Both parents of 44 (62%) infants smoked, of 13 (18%) infants only the mother smoked and of 14 (20%) infants only the father smoked. On average each parent smoked 16 cigarettes a day (mean (SD) number of cigarettes smoked: maternal 16 (10.28); paternal 16.6 (10.48)).

Table 1 shows the demographic data on these infants. The most striking feature was a difference of 400 g in birth weight for the same gestational age, with passively smoking babies being lighter. These infants were also from poorer families and were more likely to be bottle fed. The percentage of stillbirths or miscarriage/termination of pregnancy was similar in both groups (20% in non-smoking group and 37% in smoking group; $p = 0.188$). Also one mother who smoked had a history of premature labour.

The sex distribution was similar in the two groups. Infants from smoking homes were more likely to be bottle fed and were of higher birth order (range in non-smoking families was 1–4 children and in smoking families was 1–7 children; $p = 0.003$). Families who smoked were of lower social class: 72% of smoking families were in social class V or lower compared with 33% of the non-smoking families ($p = 0.001$). A third of fathers were unemployed in smoking households compared with only 8% in the non-smoking group ($p = 0.032$). There was no difference in the age or weight of the infants between the two groups, at the time of cotinine estimation.

Smoking mothers were on average three years younger than their non-smoking counterparts (mean maternal age 27.6 years and 30.2 years, respectively; $p = 0.011$, mean difference 95% CI 0.63 to 4.8 years), as were the smoking fathers (30 years and 32 years, respectively, $p = 0.065$). Family history of respiratory illness and exposure to pets were similar in the two groups, and the babies experienced similar types and episodes of minor illness.

Infants' sleeping arrangements

The proportion of infants who slept in the same room as their parents was not different between the groups (smoking group, $n = 43$ (86%) and non-smoking group, $n = 15$ (67%), $p = 0.067$, $\chi^2 = 5.4$); similarly the number of babies who slept in the bed with their parents (co-sleeping) was similar in both groups ($n = 3$ (13%) of babies from non-smoking house holds and $n = 8$ (16%) from smoking households were co-sleepers; $p>0.05$, $\chi^2 = 0.13$).

Most babies slept supine or in the lateral position. There was 1 (3%) prone sleeper in the non-smoking household group and 2 (2% of total) prone sleepers in the smoking household group ($p>0.05$, $\chi^2 = 0.004$).

Infants' thermal environment

Most families had central heating and/or gas fires although a large percentage of the central heating in the deprived estates was centrally controlled. The individual tenants could not adjust the temperature in their own flats/homes. All non-smoking families had full gas central heating. Twenty per cent of smoking households had no or inadequate heating arrangements ($p = 0.017$, $\chi^2 = 5.65$).

The minimum and maximum temperatures in the room in which the baby slept, were on average, higher in the households where a parent smoked (mean minimum room temperature 18.7℃ and 17.2℃ for smoking and non-smoking households respectively; $p = 0.014$; mean maximum room

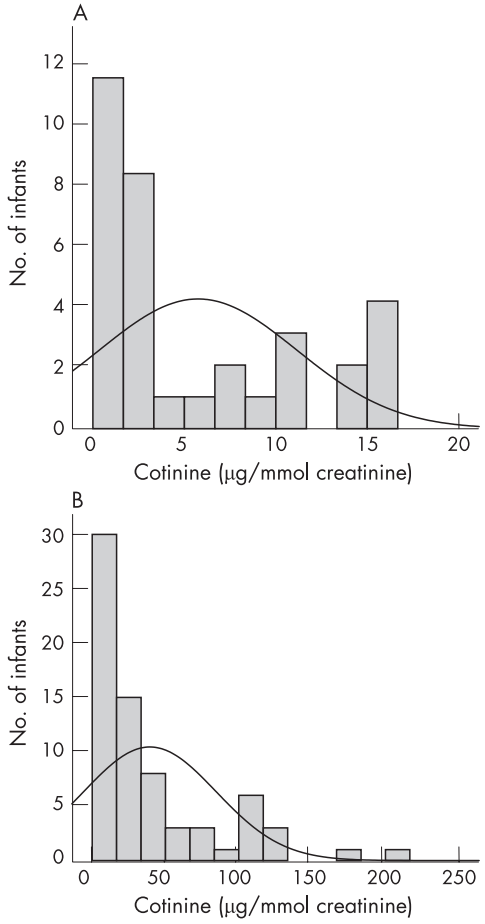

Figure 1 Distribution of urinary cotinine levels in infants from (A) non-smoking households and (B) smoking households. The arithmetic mean level for infants from non-smoking households was 5 μg/mmol and for those from smoking households was 39 μg/mmol.

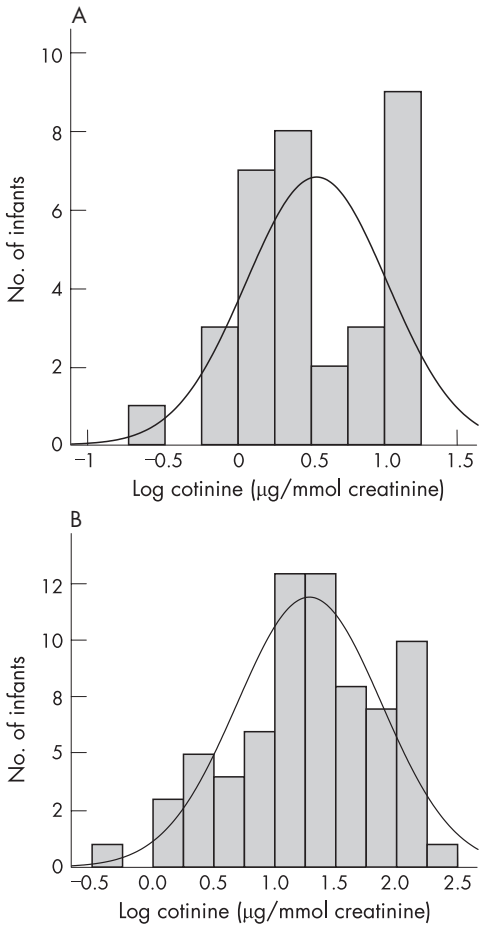

Figure 2 Distribution of logged cotinine data of infants from (A) non-smoking households and (B) smoking households. The mean for infants from non-smoking households was 0.5 μg/mmol and for those from smoking households was 1.28 μg/mmol.

temperature 22.1℃ and 21.0℃ respectively; p>0.05). There was no difference in how well the babies were wrapped (mean tog value 8.6 *v* 9.28 for babies from smoking and non-smoking households, respectively; p>0.05).

Cotinine data

All cotinine data were logarithm transformed to obtain an approximately normal distribution. For comparison with previously published work, we show the ''raw'' mean cotinine levels calculated without log transformation. The raw data (fig 1) showed that mean cotinine level in infants from the smoking households was markedly higher than that of infants from non-smoking households (mean (SD) cotinine level 39 (45) μg/mmol creatinine, range 0.35–211.67 μg/mmol creatinine; and 5 (5.39) μg/mmol creatinine, range 0.24–16.66 μg/mmol creatinine, respectively).

When the data were log transformed (fig 2) the infants from the smoking households still excreted more cotinine than infants from non-smoking households (1.28 (0.59) μg/mmol creatinine *v* 0.54 (0.48) μg/mmol creatinine, respectively). The geometric mean value of cotinine levels in infants from households in which at least one parent smoked was 5.58 times higher than that from infants from households in which the parents were non-smokers (p<0.001).

The smoking status of mothers and fathers was treated as separate predictor variables in a multivariable linear model in which each coefficient was adjusted for all other variables. Maternal smoking was the single largest contributing factor, increasing cotinine levels by a factor of four, followed by paternal smoking (table 2).

We found no significant interaction between maternal and paternal smoking and infants' cotinine level (p = 0.331). Overall, where the mother smoked, the geometric mean value for cotinine increased by a factor of four, and where the father smoked, it increased by a factor of nearly two. The results indicate that maternal smoking was the single greatest influence on the cotinine levels of a baby.

Other variables

Using a multivariable linear model, the impact of the following variables was assessed:

- smoking status of household;
- low social class;

Table 2 Multivariable linear model comparing smoking status of mothers and fathers

Covariate	Ratio of geometric means	95% CI	p Value
Maternal smoking in household	3.97	2.28 to 6.92	<0.001
Paternal smoking in household	1.83	1.05 to 3.18	0.034

Dependent variable: log cotinine:creatinine ratio.

Table 3 Results from the multivariable linear model with co-sleeping and minimum room temperature as predictor values

Covariate	Ratio of geometric means	95% CI	p Value
Baby co-slept	4.13	1.090 to 15.621	0.037
Minimum room temperature where baby slept (°C)	0.83	0.694 to 0.979	0.028
Baby with at least one parent smoker	7.39	2.535 to 21.527	<0.001
Low social class of household	0.83	0.460 to 3.097	0.703
Inadequate heating in family home	0.74	0.219 to 2.513	0.624
Paternal unemployment	1.23	0.368 to 4.111	0.730
Breast feeding	1.31	0.491 to 3.493	0.581
Delay in age baby achieved mature temperature biorhythm	1.01	0.893 to 1.160	0.784
Season	0.58	0.31 to 1.07	0.080

Dependent variable: log cotinine:creatinine ratio.

- paternal unemployment;
- inadequate heating in household;
- breast feeding;
- minimum room temperature;
- delay in age baby achieved mature temperature biorhythm;
- co-sleeping;
- season in which measurement was taken.

One smoking parent, co-sleeping and low minimum room temperature were the only three factors found to have a significant effect on the infant's smoke exposure. Other factors such as social class and feeding method had no effect (table 3). The lower the minimum temperature of the room where the baby slept, the higher was the log cotinine:creatinine ratio. Co-sleeping seemed to have a deleterious effect—that is, babies who bed shared with their parent/main carer had higher cotinine levels. Social class, father's employment status, heating as a proxy for social class, a delay in the age of maturation of temperature rhythm, the season in which cotinine was measured and feeding method did not have independent effects. Both forwards and backwards selection methods, using the 5% level of significance, resulted in a model containing only co-sleeping, room temperature and household smoking, with p values and parameter estimates similar to those shown in table 3.

There was no interaction between household smoking and minimum room temperature ($p = 0.197$). Nor was there an interaction between the season in which the measurement was done and smoking status of the parent ($p = 0.740$).

Seasonality

There was no seasonal variation in recruitment of babies ($p = 0.093$). Log cotinine:creatinine ratios and mean minimum room temperature varied as shown in table 4, with the highest cotinine estimation values in winter.

Table 4 Seasonal variation in log cotinine creatinine ratios and mean minimum room temperature

	Log cotinine/ creatinine ratio	Minimum room temperature
Spring	0.96	18.2°C
Summer	0.67	18.9°C
Autumn	1.01	17.5°C
Winter	1.22	18.0°C

DISCUSSION

Our findings clearly show that by accumulating cotinine, babies become heavy passive smokers secondary to the active smoking of parents. Nicotine, of which cotinine is a byproduct, has recognisable cardiovascular stimulant effects.[23] However, it is merely one of the several thousand constituents of tobacco smoke and may not be the most lethal. How it affects infants is largely unknown.

As expected, maternal smoking is the single largest contributor to cotinine levels in infants, quadrupling the level in non-passively smoking babies. When the father smokes, the level is doubled. This implies that a complex relationship exists between the biomarker and the type of exposure, and varies as a function of environmental and physiological factors. The proximity of the smoker, ventilation, precise location and length of exposure compound the effect of passive smoking in infants.[24]

''Smoking'' babies tend to come from poorer homes,[25–27] which may have smaller rooms and inadequate heating. The present study has shown an independent effect of low room temperature. There was also a suggestion of summer–winter seasonality of cotinine levels, as shown in previous studies.[28 29] This is in keeping with the strong seasonal patterns in sudden infant death syndrome (SIDS). Higher cotinine levels in colder times of the year may be a reflection of the other key factors which influence exposure to passive smoking, such as poorer ventilation or a greater tendency for parents to smoke indoors in winter.

Further, we found that co-sleeping increased cotinine levels when other factors were corrected for. One simple possible biological mechanism for this may be the direct inhalation or closeness to clothing or other objects contaminated with smoke particles, which in turn are passed to the baby during periods of close contact, such as during sleep. Babies co-sleeping with ''smoking'' parents are at increased risk of cot death,[30–33] but the

What is already known on this topic

- Smoking is related to cot death.
- Babies are able to metabolise nicotine secondary to exposure to environmental tobacco smoke.

What this study adds

- If parents smoke, the baby smokes.
- Mother smoking is the most important contributing factor.
- Co-sleeping and the temperature of the room the baby sleeps in are also contributory factors.

mechanism by which this occurs may not be straightforward. An infant's chronic exposure to smoking whether before and after birth will have an accumulated biological effect, including delayed postnatal physiological maturation,[14 34 35] perhaps the basis of vulnerability. How genetic[36 37] and other factors such as infection,[38 39] impinge on this vulnerability is critical in explaining the causes and the mode of sudden infant death.

Babies and children are routinely exposed to cigarette smoke by their carers in their homes, without the legislative protection available to adults in public places. There are practical difficulties in preventing smoking in family residences, which relies heavily on the goodwill of the parent/carer and accompanying education about strategies to reduce harm related to passive smoking. The well recognised maternal desire to protect the child is the great hope for the future.

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