Revisiting the applicability of adult early post-operative nausea and vomiting risk factors for the paediatric patient: A prospective study using cotinine levels in children undergoing adenotonsillectomies

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ABSTRACT

Background and Aims: Post-operative vomiting (POV) in children remains a significant clinical problem. This prospective study aims to investigate the applicability of well-established adult early post-operative nausea and vomiting (PONV) risk factors on paediatric POV after adenotonsillectomies under regulated anaesthetic conditions. **Methods:** After Institutional Review Board approval, 213 children aged 3–10-year-old were enrolled. The participants had pre-operative questionnaires completed, followed protocolised anaesthetic plans and had saliva analysed for cotinine. The primary outcomes were POV as correlated with age, gender, family or personal history of PONV, motion sickness history, opioid use, surgical time, anaesthetic time and environmental tobacco smoke (ETS) exposure, as assessed by cotinine levels and questionnaire reports. Data on analgesics, antiemetics and POV incidence before post-anaesthesia care unit discharge were collected. Statistical analysis was done through multiple logistic regression. **Results:** A total of 200 patients finalised the study. Early POV occurred in 32%. Family history of PONV (odds ratio [OR] = 5.3, $P < 0.01$) and motion sickness history (OR = 4.4, $P = 0.02$) were highly significant risk factors. Age reached borderline statistical significance (OR = 1.4, $P = 0.05$). None of the other factors reached statistical significance. **Conclusion:** Early POV occurs frequently in paediatric patients undergoing adenotonsillectomies. In this paediatric-aged group, the incidence of POV was affected by the family history of PONV, and history of motion sickness. Age, female gender, opioid use, surgical and anaesthetic times did not affect the incidence of POV. ETS exposure, as assessed by cotinine levels and questionnaire reports, had no protective effect on early paediatric POV.

Key words: Adult, paediatric, post-operative nausea and vomiting, risk factors

INTRODUCTION

Post-operative vomiting (POV) in children continues to be a significant clinical problem despite advances in pharmacological therapy with rates doubling that of the adult population. In children undergoing adenotonsillectomies, POV without prophylaxis is reported in up to 80%.[1]

Paediatric research into risk factors of post-operative nausea and vomiting (PONV) lags behind the

adult research. Only two published studies, the Postoperative Vomiting in Children (POVOC) score and the Vomiting in the Post-operative Period (VPOP) score, have identified independent risk factors of POV in children.[2,3] Although overlap is present, these paediatric risk factors seem to differ from the commonly used predictors published by several adult PONV risk scores.[4] In children, only vomiting is studied because of young children's inability to communicate feelings of nausea. Eberhart *et al.* studied the applicability of 5 adult risk scores on children and found low predictive power for patients 0–12-year-old undergoing different procedures under non-standardised anaesthetic techniques.[5] There is little understanding for these differences. Our hypothesis is that adult PONV risk factors, including non-smoking status and gender are applicable to children when confounding variables are minimised. In adults, smoking clearly confers protection against PONV. In children, the relationship of environmental tobacco smoke (ETS) exposure with POV has not been researched. For long-term ETS exposure quantification, cotinine is a nicotine metabolite that is the biomarker of choice to quantify long-term ETS exposure due to its long half-life (about 20 h), and salivary cotinine is a well-accepted and established method of cotinine quantification.[6]

This study aims to investigate the relationship of well-established adult risk factors on POV incidence in children aged 3–10-year-old undergoing adenotonsillectomies under protocolised anaesthetic conditions.

METHODS

After Institutional Review Board approval for this prospective study, from 2009 to 2012, all children aged 3–10-year-old, American Society of Anesthesiologists (ASA) grade I or II, scheduled for adenotonsillectomies with or without ear tubes were offered enrolment into the study unless having an exclusion factor. This study was conducted at a single outpatient facility physically connected to a tertiary hospital which permitted the care of higher risk patients due to its immediate accessibility to the major hospital. Exclusion factors were: Difficult airway, history of malignant hyperthermia, total intravenous (IV) anaesthesia, history of menarche, smokers and pre-operative opioid use. After written informed consent, caregivers answered a questionnaire on the child's exposure to ETS and POV risk factors, such as history of PONV, motion sickness and family

history of PONV [Figure 1]. Vomiting was defined as evidence of stomach contents being regurgitated through the mouth. Early POV is defined as POV occurring before discharge from the post-anaesthesia care unit (PACU).

All enrolled subjects followed an anaesthetic management regulated for most factors affecting POV. Factors that are widely accepted as having equivalent impact on POV, such as potent inhalation agents and opioids, were allowed variation to accommodate the anaesthesia provider's preference. Oral midazolam pre-medication 0.5 mg/kg with a maximum of 15 mg for anxiolysis was given at the discretion of the anaesthetic provider. All subjects were induced with general anaesthesia using sevoflurane ± nitrous oxide, peripheral IV cannulation was performed and propofol 1 mg/kg was added as needed to optimise conditions for successful endotracheal intubation. No neuromuscular blocking agents were used to facilitate endotracheal intubation. Anaesthesia was maintained with either sevoflurane or desflurane without nitrous oxide, delivered in a mixture of oxygen in air. One-time fentanyl 1–2 μg/kg IV or morphine 0.1 mg/kg IV was administered for pain relief and dexamethasone 0.1 mg/kg IV was given for antiemetic prophylaxis. This analgesic protocol was determined after reviewing the most commonly used intraoperative analgesic regimens used by the anaesthesiology personnel for adenotonsillectomies at this centre. No further antiemetics were used intraoperatively. The stomach was suctioned through an orogastric tube before tracheal extubation. The same surgical and anaesthesiology personnel were involved in the study.

Salivary swabbing was performed when the child was under general anaesthesia. The sample kits and

Figure 1: Questionnaire for caregivers of enrolled patients

processing were per an outside laboratory with adherence to standardised instructions for cotinine analysis (Salimetrics LLC, Carlsbad, CA). The post-operative care was managed per routine post-anaesthetic recovery orders which included rescue analgesics and antiemetics as needed per the anaesthesiology team's preferences. In the PACU, antiemetic rescue was given for emetic events. Data on POV before discharge from the PACU and rescue pain and antiemetic medications given in PACU were collected. All opioids used were converted to IV morphine equivalents - 'opioid equivalents' - using a well-established opioid conversion chart.[7] Post-discharge POV (after PACU discharge) information was collected during the 24 h after ending anaesthesia - if discharged to home, the caregivers were contacted after 24 h, or chart-reviewed for POV if admitted overnight after PACU stay.

The primary outcomes are the correlations of the adult risk factors on paediatric POV: age, gender, family or personal history of PONV, history of motion sickness, opioid use, surgical time, anaesthetic time and the substitution of smoking with ETS exposure by quantification of salivary cotinine and pre-operative questionnaire report.

A power analysis indicated that a total sample of 197 participants would be needed to detect a small to medium effect size with 80% power and $\alpha = 0.05$. The required sample size was calculated by Hsieh *et al.*'s method, as a function of overall event proportion, odds ratio (OR) of the covariate, multiple correlation coefficient between covariates as well as the type one error, and power.[8] A medium size proportion, medium size OR of 2 and small size multiple correlation coefficient of 0.1 were used. In this study, the effect size for OR and multiple correlation coefficient were estimated based on a review of the existing literature.

For early POV, univariate analysis were performed for the following factors: age, gender, family history of PONV, personal history of POV, history of motion sickness, procedural time, anaesthesia time, intraoperative morphine versus fentanyl use, total number of opioid doses, intraoperative opioid equivalents/kg, PACU opioid equivalents/kg, overall total opioid equivalents/kg, cotinine levels, reported-ETS exposure, midazolam use, propofol use, nitrous oxide at induction, total IV fluids/kg and inpatient admission. Past POV patient history was excluded because of the very few patients with prior surgical exposure. For those patients with inadequate

salivary quantities for analysis, the missing cotinine levels were imputed using a regression tree based on the ETS exposure questionnaires.[9] Logistic regression was used to model the effect of potential risk factors on the probability of POV; reported 95% confidence intervals were based on the profile likelihood method. R was used for all data analysis.[10]

RESULTS

In total, 213 patients were enrolled. The collected data for enrolled patients were reviewed in small batches. After including all the patients in the last group enrolled to reach the 197 subjects needed, a total of 200 patients were found to qualify for the study. Thirteen patients were excluded from the study: Eight did not follow the research protocol, and five did not meet inclusion criteria (four were just short of becoming 3-year-old; one patient had an adenoidectomy only and did not undergo the planned tonsillectomy). Table 1 summarises relevant patient and perioperative characteristics of the analysed subjects. Sixty-four patients out of 200 (32%) experienced POV. Midazolam pre-medication was administered to 32 patients (16%), propofol to 122 patients (61%), nitrous oxide during induction to 185 patients (92.5%), intraoperative morphine versus fentanyl to 155 and 45 patients, respectively (77.5% vs. 22.5%). A total of 60 patients required antiemetics (30%) in the PACU; all of them received ondansetron (0.1 mg/kg up to 4 mg IV). Seven out of those 60 patients (11.6%) received a dose of promethazine (0.1 mg/kg up to 6.25 mg IV) after the ondansetron. In the PACU, 193 patients (96.5%) received additional opioids, six patients (3%) received paracetamol only and one patient (0.5%) received no additional analgesics. The mean PACU stay was 121 min, with a median of 118 min and range 58 min–215 min. Inpatient admission occurred in

Table 1: Patient and perioperative characteristics of enrolled subjects	
Variable	**Mean±SD**
Age (years old)	5.5±1.9
Weight (kg)	25.4±10.8
Gender (male/female)	100/100
Total surgical time (minutes)	25.8±9.8
Total anaesthesia time (minutes)	45.3±12.3
Total OR IV fluids (ml/kg)	10.3±5.0
Total opioid equivalents* (mg/kg)	0.12±0.04
Opioid equivalents*-PACU only (mg/kg)	0.036±0.027

*Opioid equivalents-all opioids used were converted to morphine equivalents by using a well-established opioid conversion table. OR – Operating room; IV – Intravenous; PACU – Post-anaesthesia care unit; SD – Standard deviation

31 patients (15.5%); one patient was admitted because of recurrent emesis while the other patients were admitted for planned overnight observation due to the obstructive sleep apnoea severity. Thirty-three patients (16.5%) did not have adequate quantity in their salivary samples for analysis although each subject had a corresponding completed questionnaire. Data collection on post-discharge POV was completed in 123 patients (61.5%). Inability to reach the caregivers by phone after multiple attempts was the reason for the unavailable patient information for post-discharge POV. Of those reached, 98 patients (79.7%) were reported to have no post-discharge POV and 25 (20.3%) reported one or more episodes of post-discharge POV within 24 h after the procedure. Due to the large percentage of unavailable post-discharge data (38.5%), it was decided to only analyse early POV data and not pursue analysis of post-discharge POV.

No relationship was found between cotinine levels and emesis, either as a linear association or a threshold value. The range of cotinine was 0–25 ng/ml. There was a clear relationship between reported-ETS and cotinine levels ($P = 4 \times 10^{-9}$), but no relationship was found between either one with POV. No difference was found when comparing the effect of morphine versus fentanyl on POV ($P = 0.72$). Also, no relationships were found between POV and each of the following opioid-related factors: total number of opioid doses ($P = 0.90$), intraoperative opioid equivalents/kg ($P = 0.90$), PACU opioid equivalents/kg ($P = 0.67$) and total opioid equivalents/kg ($P = 0.90$). History of motion sickness ($P < 0.001$) and family history of PONV ($P < 0.001$) were the only factors achieving statistical significance in the univariate analysis [Table 2].

A subgroup analysis was performed to investigate the interaction between gender and age on POV [Figure 2]. It was found that in children >6-year-old (52 of 200), 45% girls versus 29% of boys experienced POV, as compared to 32% girls versus 28% boys in children <6-year-old (148 of 200), although the correlation was not significant ($P = 0.41$).

For multivariate analysis, two models were used for the logistic regression [Figure 3]. The models are the same except for how smoke exposure was included: one model used reported-ETS while the other used cotinine. The results of both models were very similar. The analysis found family history of PONV (OR = 5.3, $P < 0.01$ by reported-ETS model and OR = 5.4,

| Table 2: Univariate analysis results for selected categorical variables					
Factor	**POV**		**OR**	**CI**	***P***
	Yes (%)	**No (%)**			
Family history PONV					
Yes	66.7	33.3	5.3	2.0-15.2	<0.001
No	27.3	72.3			
History motion sickness					
Yes	70.6	29.4	6.0	1.9-22.8	<0.001
No	28.4	71.6			
Gender					
Female	36.0	64.0	1.4	0.76-2.8	0.29
Male	28.0	72.0			
Reported ETS exposure					
Yes	25.3	74.7	0.60	0.30-1.2	0.16
No	36.0	64.0			
Morphine (*n*=155)	32.9	67.1	0.83	0.37-1.8	0.72
Fentanyl (*n*=45)	28.9	71.1			
Nitrous oxide					
Yes	31.4	68.6	0.69	0.21-2.5	0.57
No	40	60			

PONV – Post-operative nausea and vomiting; POV – Post-operative vomiting; ETS – Environmental tobacco smoke; *n* – Number of patients; OR – Odds ratio; CI – Confidence interval
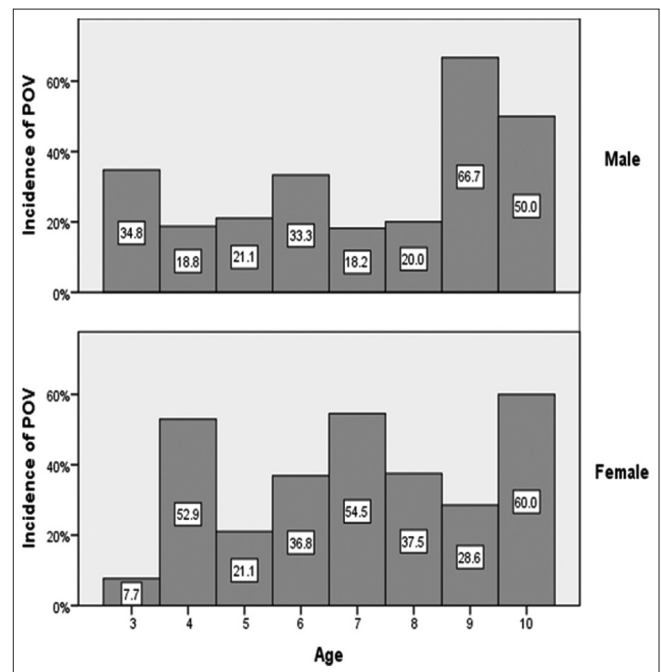
Figure 2: Incidence of post-operative vomiting by gender and age. POV - Post-operative vomiting

$P < 0.01$ by cotinine model) and history of motion sickness (OR = 4.4, $P = 0.02$ by reported-ETS model and OR = 4.3, $P = 0.02$ by cotinine model) to be highly significant risk factors for POV. Age reached borderline statistical significance (OR = 1.4, $P = 0.05$ by reported-ETS model and OR = 1.4, $P = 0.06$ by cotinine model). None of the other factors analysed reached statistical significance in either model; all of
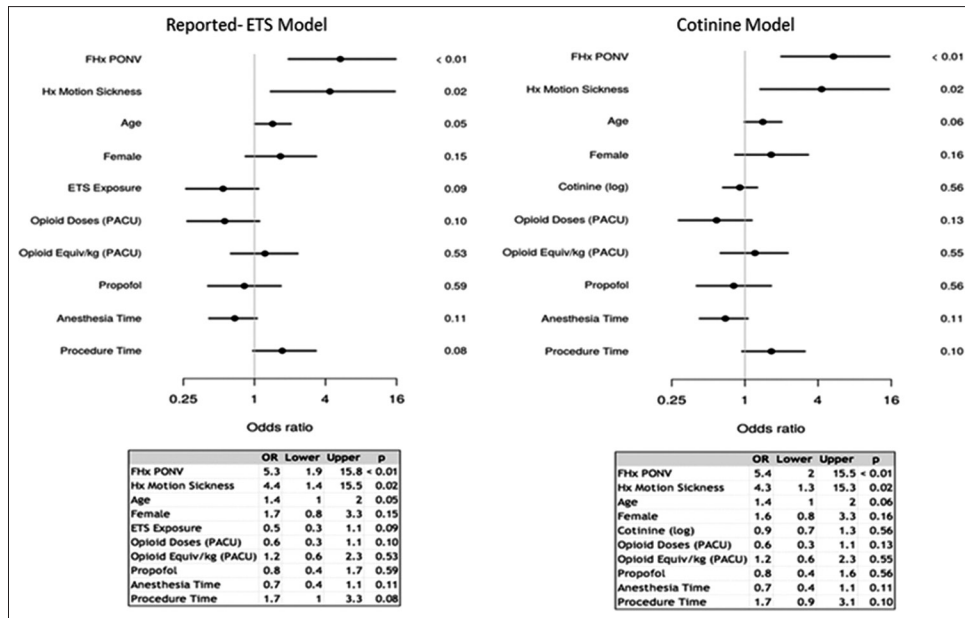
Figure 3: Multivariate analysis of factors affecting post-operative vomiting. POV - Post-operative vomiting; ETS - Environmental tobacco exposure; FHx - Family history; PONV - Post-operative nausea and vomiting; Hx - History; PACU - Post-anaesthetic care unit; Equiv - Equivalents; kg - Kilograms

these factors had small estimated effects on POV, with odds ratio estimated to be no larger than 2.

DISCUSSION

Research into paediatric POV continues to be relevant. The assessment of POV risk factors using validated risk scores can customise antiemetic strategies tailored to the patient's risk. Improved safety profiles of modern antiemetics have prompted opinions that everyone should receive antiemetic prophylaxis unless contraindicated. The ASA endorsed consensus guidelines for the management of PONV states 'this strategy puts the low-risk patients at unnecessary risk for rare but well-described side effects.'[11] Chilkoti *et al.* illustrate this point.[12] In addition, no antiemetic has demonstrated universal efficacy and the ongoing drug shortages and financial climate beseech clinicians to judiciously administer medications.

Table 3 provides a comparison among the currently well-established adult PONV risk factors with the available published paediatric POV risk factors.[4] The adult and paediatric PONV/POV risk scores came from analysis of prospective large populations undergoing heterogeneous surgeries under non-standardised anaesthetic conditions. As shown in Table 3, although all adult and paediatric scoring systems include patient, surgical and anaesthetic factors, those factors seem to differ. The paediatric risk scores POVOC and VPOP do not include the adult factors of

gender, smoking effect and anaesthetic technique.[2,3] Therefore, (1) Are the adult and paediatric risk factors indeed different? if so (2) Why? and (3) When does the transition occur? This study aims to address that first question by prospectively investigating POV in one highly emetogenic and commonly performed paediatric procedure. Confounding variables were minimised by regulating the anaesthetic technique for most factors impacting POV.

The analysis by the reported-ETS and cotinine models showed very similar results that are in agreement. Since self-report is most practical in the clinical setting, the results from the reported-ETS model will be used to simplify the discussion. The findings show that PONV/POV pre-disposition, PONV family history and history of motion sickness, is indeed highly significant, in agreement with published adult and paediatric studies. This seems the strongest predictor and only factor appearing in every adult and paediatric PONV/POV risk-scoring system.

Regarding age, only patients 3–10-year-old were enrolled to minimise confounding variables. In this study, age reached borderline statistical significance ($P = 0.05$), with the patients having a 40% increase in the odds of POV for every 2-year increase in age. From the POVOC score study, Eberhart *et al.* found that age >3 years is significant with the risk increasing 0.2%–0.8%/year.[2] Bourdaud *et al.* found a significant age effect after 3-years old with highest risk between

Table 3. Summary of published adult and paediatric risk scoring systems for post-operative nausea and vomiting or post-operative vomiting. Adapted from Gan with permission.[4]								
Risk factors	**Adult risk scores**						**Paediatric risk scores**	
	Apfel *et al.*[13]	Koivuranta *et al.*[14]	Apfel *et al.*[15]	Van den Bosch *et al.*[16]	Palazzo and Evans[17]	Sinclair *et al.*[18]	POVOC Eberhart *et al.*[2]	VPOP Bourdaud *et al.*[3]
Patient factors								
Gender female	X	X	X	X	X	X		
Age		X		X			X	X
Prior PONV/family history PONV or history of motion sickness	X	X	X	X	X	X	X	X
Non-smoking status	X	X	X	X		X		
Surgical factors								
Duration of Procedure		X					X	
Type of surgery				X			X	X
Anaesthetic factors								
Duration of Anaesthesia			X					X
Anaesthesia Technique				X				
Opioid use	X				X			X

POVOC – Post-operative Vomiting in Children; VPOP – Vomiting in the Post-operative Period; PONV – Post-operative nausea and vomiting; X – Marks the relevant factor

6–13-year-old.[3] Since the hormonal changes of puberty have been speculated to be a contributing factor, our study excluded patients above 10-year-old and excluded females who underwent menarche. As evidence indicates that current generations of children may be starting puberty earlier, future studies in this subject may show a stronger age effect if the hormonal theory effect of puberty on POV holds true.[19]

In agreement with other paediatric studies, POV was more common in girls (36%) than boys (28%), although gender did not reach statistical significance ($P = 0.15$). The small gender effect in children has also been speculated to the hormonal pubertal changes and its interaction with unknown female factors. Eberhart *et al.* proposed interaction between age and female gender.[2] Support for this idea can be seen in our data, although similarly to Eberhart *et al.*, this interaction was not statistically significant.[2] One reason may relate to the reduced sample size available for this comparison in this study as the frequency of adenotonsillectomies is decreased in children >6-year-old.

Multiple opioid doses were found as a risk factor (intra- and post-operative) by the VPOP study while the POVOC study found a trend with post-operative opioid use.[2,3] In the current study, opioid analysis showed no significant impact on POV and neither anaesthesia nor procedure duration. Possible contributing factors maybe the similar opioid dosages used and the relatively short procedural/ anaesthetic times did not allow detection of these effects.

Non-smoking status has been established as independent risk factor for adult PONV, with smoking being protective. Czarnetzki *et al.* studied the short-term effect of a transcutaneous nicotine patch and found it ineffective for PONV reduction in non-smokers.[20] Furthermore, transdermal and intranasal nicotine has been studied in adults for its opioid-sparing effects. Several studies show it worsens nausea and vomiting in the treated groups.[21,22] A 2016 Cochrane Review states that 'nicotine does not appear to reduce post-operative use of opioids or opioid-related adverse events but probably increases the risk of nausea'.[23] Its potential on inducing nicotine-dependency would outweigh any potential PONV benefits, making it questionable for clinical practice.

Most children do not smoke, but many are exposed to ETS. It is unknown if ETS exposure could provide the same protective effect as smoking. The reported health impact of ETS exposure on children seems similar to smoking, including asthma exacerbations, increased respiratory adverse events and middle ear disease and increased respiratory problems during anaesthesia emergence and recovery.[24-27] The effect of ETS exposure on paediatric POV was non-significant as assessed by both questionnaire and salivary cotinine methods.

Assessing independent risk factors for PONV/POV is a recommended strategy in the management of PONV/POV.[11] Since its incidence is still high despite all strategies, some researchers are developing risk models incorporating more physician-modifiable factors,

targeting specific settings or patient/surgical groups i.e., ambulatory surgery or adenotonsillectomies, as opposed to the broad patient populations of the older models.[13-18,28,29] These targeted models might; however, lose applicability when extrapolated to other settings. In this study, both models returned essentially the same results: That family history of PONV and history of motion sickness are the most important information to obtain for POV risk stratification of paediatric patients undergoing adenotonsillectomies.

Limitations of this study include using dexamethasone which affects PONV; however, withdrawing its administration was deemed inappropriate as it is against recommendations by the American Academy of Otolaryngology-Head and Neck Surgery Foundation guidelines for tonsillectomy in children.[30] Also, by focusing on adenotonsillectomies and protocolising anaesthetic techniques, we were unable to study varied anaesthetic techniques and differing surgical procedures on POV. Although the use of opioid-equivalents could be a potential confounding variable given the pharmacokinetic and pharmacodynamic differences between morphine and fentanyl, this variable seems unclear with regards to POV. The univariate analysis found no difference on POV by those given morphine versus fentanyl. This finding also corroborates the statement by Gan *et al*. that 'the administration of a long-acting rather than a short-acting opioid is, at best, a possible PONV risk factor', and also that none of the published risk scoring systems include this factor.[4] Finally, since only early POV was analysed, these results may not apply to post-discharge POV.

CONCLUSION

Early POV occurs frequently in paediatric patients undergoing adenotonsillectomies. Of the adult risk factors which were analysed, family history of PONV and history of motion sickness were found to affect the incidence of POV in the paediatric population. Age, female gender, opioid use, surgical time and anaesthetic time did not affect the incidence of POV. Exposure to ETS, as assessed by cotinine levels and questionnaire reports, had no protective effect on early paediatric POV.

Acknowledgement

Conflicts of interest

There are no conflicts of interest.

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