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EXPOSURE TO ENVIRONMENTAL TOBACCO SMOKE AND CHILDREN HEALTH

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Abstract. This paper reviews the investigations of the effects of pre- and/or postnatal exposure to environmental tobacco smoke (ETS) on children health reported in the literature. The evidence from epidemiological studies demonstrate that children's exposure to ETS is a risk factor for a variety of diseases, including respiratory disorders and middle ear disease. However, the current research base on the ETS-associated risks is still inadequate to fully support strategies, programs and policy development in this area. For example, it is not definitively determined what methods should be used for assessing ETS exposure and predicting potential health risks of exposed children. Based on the available data, we tried to find out which methods seem to be most desirable for quantifying ETS exposure in children. It is our opinion that among all biomarkers, the measurements of blood, saliva or urinary cotinine and hair nicotine are, as for today, the most specific and sensitive methods for an objective assessment of ETS exposure in children. A combination of the measurement of body fluids cotinine and hair nicotine with the questionnaire and interview-derived information seems to be the optimal method for assessing ETS exposure in children.

Key words:
Environmental tobacco smoke, Nicotine, Cotinine, Asthma, Children health, Birth weight

INTRODUCTION

Environmental tobacco smoke (ETS) is a term used to refer to the mixture of sidestream smoke and exhaled mainstream smoke that pollutes air in locations where tobacco is being smoked [1]. ETS has been regarded as one of the most important and controversial public health issues. In addition, ETS exposure entails serious economic consequences for the health care system [2].

It has been estimated that approximately 38% of American children, 2 months to 5 years old, have been exposed to ETS in their homes, whereas near 24% of children have been exposed by maternal smoking during pregnancy [3]. The data from the Nordic countries has shown that in households where there is at least one parent smoker, 57% of parents report that their children are exposed to ETS at home [4]. In Poland, about 4 million children are involuntarily exposed to ETS [5]. Sixty six percent of urban and sixty two percent of Polish rural children, aged 7–11 years, have been reported to be exposed to ETS at home as a result of parental smoking [6]. In brief, ETS exposure among Polish children is unacceptably high.

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Although there is now little doubt about ETS being an important health hazard, the effects of ETS on children health are not definitively and fully determined. There is a great need to develop studies assessing and monitoring exposure to ETS and the risks of developing ETS-related diseases.

EFFECTS OF ENVIRONMENTAL TOBACCO SMOKE EXPOSURE ON CHILDREN HEALTH

Children are more likely than adults to suffer health effects from ETS exposure [7]. Compared with adults, they have higher relative ventilation rates leading to higher intend exposures to ETS, as measured by urinary cotinine, for the same level of external exposure. Furthermore, young children are often not able to remove themselves from exposure, and thus depend on other measures to protect them.

ETS exposure affects children of all ages but its exact health effects may vary between age groups [8]. A prospective birth cohort study conducted at 47 Maternal and Child Health Centers in Hong Kong has shown that in utero exposure to ETS via maternal smoking is positively associated with a higher number of consultation visits (odds ratio (OR) = 1.26; 95% confidence interval (CI): 1.14–1.29) and hospitalization (OR = 1.18; CI: 1.05–1.31) in infants [2]. High hospital admission rates were significantly more prevalent among infants exposed to ETS either before or after birth, and for respiratory and febrile illness or any illness. A clear dose-response gradient between the total number of smokers at home and increased hospitalizations in infants was demonstrated (linear test for trend, $p = 0.03$ for respiratory and febrile illness; $p < 0.001$ for any illness) [2].

BIRTH WEIGHT

The influence of ETS exposure on fetal growth has not been conclusively determined, because there are numerous studies, which have well demonstrated an association between maternal smoking and low birth weight (below 2500 g) [9–14], whereas others have not confirmed this relationship [15,16].

Babies of mothers who smoked more than 20 cigarettes a day have a birth weight about 290 g less than those born to non-smokers [10]. As estimated in the US population, 21 to 39% of low birth weight births have been attributed to maternal cigarette smoking [17], and the incidence of low birth weight have risen with increasing cigarette consumption. A study carried out in three regions of Poland has shown that the prevalence of low birth weight is higher among smoking pregnant women (Olsztyn – 12.8%, Białystok – 9.5%, Poznań – 11%) than in non-smoking pregnant women (5.8%, 3.5% and 4.3%, respectively). An analysis of sub-population data from the region of Olsztyn has shown a significant dose-response relationship between birth weight and the amount of cigarettes smoked during pregnancy [18].

Infants born to women exposed to ETS are generally 2–4 times more likely to be small-for-their-gestational age [13]. Infants with smoking fathers weigh 11 g less than those with non-smoking fathers, and the mean birth weight of infants is reduced by 19 g among mothers exposed to ETS [14]. A population study of 1147 Czech mothers has shown that infants born to mothers heavily exposed to ETS both at home and at work, had birth weight lower by 189 g than those born to non-exposed, never smoking mothers, and by 70 g compared with babies born to mothers smoking during pregnancy [19]. A cause of the former difference has not been clear. Of note, when pre-term neonates were excluded, the difference in birth weight was lower.

In the Polish study of Hanke et al. [20], the birth weight of newborns of non-smoking mothers exposed to ETS was lower by 30 g on average, as compared to that of newborns born to non-exposed women.

The presented data on the association between exposure to ETS and low birth weight are not consistent with other reports demonstrating that exposure to ETS has no negative effect on birth weight [15,16]. As shown by Fried et al. [15], height and head circumference, other important growth measurements at birth, are not significantly related to prenatal exposure to cigarette smoke.

Because prenatal maternal smoking is almost invariably associated with postnatal smoking, it is difficult to assess,

using epidemiological studies, the influence of postnatal ETS exposure on growth parameters after birth.

SUDDEN INFANT DEATH SYNDROME

There is ample evidence that low birth weight increases infant morbidity and mortality. Sudden infant death syndrome (SIDS) is a term used to refer to the unexpected and unexplained death of an apparently well infant [21]. A number of cohort and case-control studies have well documented clear dose-related association between active maternal smoking and SIDS [22–24]. Most hypotheses regarding the associations between maternal smoking during pregnancy and SIDS address possible effects of smoking on fetal oxygenation and fetal development. Smoking can result in hypoxic tissue damage via reduced uteroplacental blood flow, increased carboxyhemoglobin, and premature placenta calcification [22,25]. Smoking can also result in direct fetal cell toxicity. Furthermore, a failure of the central nervous system over cardiorespiratory activity has been postulated as another mechanism of SIDS [26].

Some studies have discussed the possibility of exposure to ETS after birth as the risk for SIDS [21,27,28]. However, relatively little evidence exists in support of a hypothesis that SIDS can be induced by passsive smoking.

The case-control analysis using the data included in the US National Maternal Infant Health Survey (a representative sample of 10 000 births and 6000 infant deaths) have shown that among infants with normal weight whose mothers smoked during pregnancy and continued to smoke postpartum, the OR for SIDS, after adjustment for demographic risk factors, is 3 (CI: 2.27–4.24), while for infants with only postpartum tobacco smoke exposure this value is 1.75 (CI: 1.04–2.95) [21]. However, the study had several significant limitations. First, it was not possible to find out whether the mother spent a substantial amount of time with and smoked cigarettes near the infant. Second, no information was given on smoking habits of other persons being in close contact with the infant. Therefore, further research on the relationship between exposure to ETS and SIDS is needed with more detailed information on smoking.

RESPIRATORY DISEASES

The best described effect of exposure to ETS in children is an increased incidence of respiratory diseases, documented by the pulmonary function impairment, increased emergency and physician's visits, as well as hospitalization rates [29–36]. A study of Gilliland et al. [37] has demonstrated an association between in utero exposure to maternal smoking and reduced peak respiratory flow rate, mean mid expiratory flow, and forced expiratory flow. Although maternal smoking during pregnancy did not cause deficits in children's forced expiratory volume in one second (FEV_1), a decrease in the FEV_1/forced vital capacity ratio has been observed [36].

Meta-analysis of the association between ETS exposure and the prevalence of lower respiratory tract infection has provided strong evidence that ETS exposure causes serious lower respiratory tract infections in infancy and early childhood that require hospitalization. The summary OR for lower respiratory diseases from birth until 2 years of age if either parent smoked has been reported as 1.57 [35]. In the same study, OR was higher for maternal smoking than for paternal smoking. However, the effect of paternal smoking in households where the mother did not smoke was statistically significant. These results are consistent with the results published by Margolis et al. [38] and Nafstad et al. [39].

It is noteworthy that maternal smoking does not seem to be significantly associated with the prevalence of influenza or common cold in children [34].

The results of the studies conducted in Poland have also demonstrated that ETS exposure in children is associated with respiratory symptoms and lung function level. In the cross-sectional survey, investigating the susceptibility to respiratory tract infections among preadolescent children, ETS increased the predisposition to acute respiratory infections, defined as frequent spells (3 or more) of acute respiratory infections experienced by a child over 12 months preceding the interview [40,41]. In a study con-

ducted by the Institute of Occupational Medicine and Environmental Health in Sosnowiec on the relationship between parental smoking and respiratory problems among 1211 urban children, aged 7–9 years, it has been found that exposure to ETS was significantly associated with persistent cough and wheezing [6].

Among various environmental factors, passive smoking is by far the best documented risk factor of childhood asthma [42]. Over the past decade, numerous studies have evidenced that children whose parents smoke show higher rates of asthma and its increased severity, and develop allergy [3,43–46]. A large Scandinavian survey of 15 962 children, aged 6–12 years, has found that asthma attacks were inversely associated with current smoking at home, but positively associated with smoking at home during the first two years of life [47]. In meta-analysis by Di Franza and Lew [48], including thirty-three studies of ETS and asthma, the pooled risk ratio for the association between parental smoking and asthma in children of smokers has been reported as 1.43 (CI: 1.31–1.56; $p < 0.0001$) and the pooled OR was 1.46 (CI: 1.14–1.85; $p < 0.005$). The association between ETS exposure and asthma development may relate to both pre- and postnatal effects on the airway caliber or bronchial responsiveness [49]. Prenatal ETS exposure in utero has been shown to impair fetal lung development and cause airflow obstruction and airway hyperresponsiveness [45]. Most likely, a low level of lung function is associated with wheeze, and thus prenatal ETS exposure may also be a risk factor for wheeze, during infancy and early childhood [46,50–52] that is independent of postnatal ETS exposure [52]. Interestingly, light smoking during the third trimester of pregnancy appears to pose the same risk for wheeze as heavier smoking between 18 and 30 months of age [52].

Children exposed to ETS postnatally have more symptoms of cough, wheeze and increased airway responsiveness [45,53,54] although some studies have shown no increase in the prevalence of cough in exposed children [3]. Indicators of asthma severity, including symptom scores, attack frequency, medication use, hospital attendance, and life threatening bronchospasm are, in general, positively correlated with household ETS exposure [54]. Tonsillectomy or adenoidectomy increases the prevalence of cough in children living in families that smoke at home more than 20 cigarettes per day [53]. The US Third National Health and Nutrition Examination Survey has shown that ETS exposure appears to increase the prevalence of asthma, wheezing and chronic bronchitis among children 2 months through 2 years of age, but has little effect on the respiratory health of children aged between 3 and 5 years, with the exception of asthma [3]. This study has confirmed that the exact effects of ETS exposure on respiratory health in children may vary between age groups. Another study has shown that the association between asthmatic symptoms observed at the age of 2 and ETS exposure is not observed at the age of 4, and maternal smoking does not increase allergen sensitization at the latter age [55]. There is a strong association between ETS exposure and airway complications in children receiving general anesthesia. This relationship is strongest for girls and for children whose mothers have a lower level of education [56].

At present, it is unknown why some children with similar ETS exposure develop asthma and others do not. It has been suggested that of all the children exposed to ETS, those with asthma have a higher systemic exposure to nicotine, possibly due to lower clearance rate, and thus pharmacokinetic factors may be responsible for their higher rates of asthma [43].

The influence of ETS exposure on the occurrence of upper respiratory tract infection in children is less clear and debatable. Some studies have found no association between exposure to ETS and the prevalence of upper respiratory infection [3], others have shown that exposure to ETS is one of the most important risk factors for recurrent upper respiratory tract infections [57].

MIDDLE EAR DISEASE

Sidestream smoking increases the risk of otitis media with effusion and recurrent otitis media [58]. Infants with lower birth weight are especially at high risk for recurrent otitis media during the first year of life if their mothers are

heavy smokers [24]. ETS is also an important risk factor for middle ear disease in urban preschool-age children [48,58,59]. In meta-analysis, including thirty-two cohort and case-control studies of ETS and middle-ear disease, the pooled risk ratio for the association between parental smoking and otitis media prevalence in children of smokers was 1.19 (CI: 1.05–1.35; $p < 0.01$) and the pooled OR was 1.58 (CI: 1.11– 2.24; $p < 0.05$) [48].

In addition, there is growing evidence that passive smoking in children can have a significant impact on nasal and sinus functions, and be associated with acute and chronic rhinitis, snoring and a predisposition to develop allergies [60,61]. In the study of possible effects of ETS on cellular infiltrates in the nasal mucosa of children exposed to more than 15 cigarettes per day, no sign of allergic sensitization have been found in the nasal mucosa [61]. However, ETS exposure was responsible for changes in cellular infiltrates, which partly resembled those seen in the nasal mucosa of allergic children. Therefore, Vinke et al. [61] have concluded that children with a genetic predisposition to allergic disease could suffer most from the "unstable" mucosa due to ETS.

OTHER HEALTH PROBLEMS ASSOCIATED WITH EXPOSURE TO ENVIRONMENTAL TOBACCO SMOKE

Although some evidence has shown that maternal smoking during pregnancy could be associated with deficits in intellectual ability and behavioral problems in children, the impact of pre- or postnatal ETS exposure remains less clear [62]. It has been suggested that exposure to ETS could cause neurobehavioral and neurodevelopmental deficits [63], including hyperactivity, decreased attention span, reduced general intellectual ability, skills in language and auditory tasks, and academic achievement.

One of the potential negative effects of passive smoking is exposure of fetus and child to carcinogens. ETS exposure, including postnatal, seems to be associated with childhood brain tumors and leukemia-lymphoma, with a twofold or even higher risk reported in some studies [64]. ETS could be also related to the increased incidence of nasal and sinus cancer [60]. In a few studies, risks associated with paternal smoking have been higher than those of maternal smoking. However, some other investigators have not reported strong association between exposure to ETS and childhood cancer [65]. Therefore, further studies are needed to investigate whether parental tobacco smoke is a risk factor for childhood cancer.

The results of a questionnaire-based study of Polish urban schoolgirls have indicated that active maternal smoking during pregnancy could be associated with earlier menarcheal age of their daughters. This effect has been still present when confounding factors, such as family size, the economic status of the family and parental education have been controlled [66]. These interesting results give some support to a hypothesis that earlier maturation of girls might be due to their exposure to tobacco during fetal life by actively smoking mothers. However, it is yet to be determined whether earlier maturation of girls may be associated with childhood exposure to ETS.

Finally, passive smoking has been reported as a risk factor in meningococcal disease and tuberculosis in young children [24].

The evidence from human studies described above, demonstrating numerous adverse effects of ETS exposure on the child health, strongly reinforce the need to reduce ETS exposure of fetuses and children. Home is the most important site in children exposure to ETS [7], and parents' smoking habits are its major source [67]. Therefore, pregnant women and members of their families should be strongly encouraged to and assisted in stopping cigarette smoking.

ASSESSMENT OF EXPOSURE TO ENVIRONMENTAL TOBACCO SMOKE

Current research base on risks associated with ETS is still inadequate to fully support strategies, programs and policy development in this area. For example, many studies have investigated the effects of parental smoking on children health without clearly distinguishing between maternal, paternal, and other sources. Because most mothers exposed to ETS during pregnancy are likely to be exposed

postpartum, there are major difficulties in separating the effects of ETS exposure in the pre- and postnatal period of life. Therefore, there is a great need to develop a comprehensive environmental research project in this area with an assessment of ETS exposure as its integral component.

There are a variety of methods for estimating ETS exposure. Among them, reported and biological measures are most commonly used. Indirect assessment methods include questionnaire and interview-derived information, modeled with time-activity information [68]. Self-report measures, such as ETS exposure hours per day defined by individuals, seem to be imprecise indicators of tobacco smoke intake owing to variations in the number of cigarettes smoked, proximity of non-smokers to smokers, room ventilation and other environmental characteristics, as well as individual differences in sensitivity to and/or concern about adverse effects of ETS [69]. For that reason, the alternative evaluation of ETS exposure by biological measures is commonly used. These methods involve the measurement of concentrations of smoke components in body fluids of an exposed individual, called biomarkers [70].

Empirical studies have shown general moderate concordance of reported ETS exposure measures (parent records) and biological ETS measures [71]. For instance, memory-based reports obtained from smoking mothers have shown moderately strong and consistent linear relationships with urine cotinine levels of their infants and children, a commonly used measure of tobacco smoke exposure [72]. Some investigators have suggested that the validity of biological measures in evaluating the degree of ETS exposure and ETS-related health problems seems to be greater than that of even very detailed questionnaire [70,73,74]. However, the best approach to assess ETS exposure depends on the aim of the study, the health outcomes, and the resources [68]. Methods based on self-reports are suitable when studying health outcomes with a long latency period and rare diseases requiring large study populations. Biomarkers are suitable when assessing long-term exposure to cigarette smoke over days or months [68]. A combination of both reported and objective measures has been proposed as the optimal method [68].

NICOTINE AND ITS METABOLITES AS BIOMARKERS OF ENVIRONMENTAL TOBACCO SMOKE EXPOSURE IN CHILDREN

An assessment of ETS exposure in children requires the adaptation of techniques that are currently applied in adult studies, as well as the development of tools and validation of strategies that are unique for children [75]. Biomarker measurements have incomparable advantages in children. These include assessment of potentially increased absorption because of behaviors that differ from adults (i.e. hand-to-mouth activity), metabolite measurement, which can help identify age-related susceptibility differences, and improved assessment of dermal exposure, an important exposure route in children [75].

A number of biomarkers of exposure to ETS have been proposed. Among them, nicotine and/or cotinine, a major metabolite of nicotine, has been used most widely as surrogate measure of consumed nicotine dose [69,70,76]. However, nicotine assessed in biological fluids has a short half-life of 2–3 h, and thus does not seem to be suitable as a marker for cigarette smoking. At present, cotinine appears to be the best available biomarker of ETS exposure [69,70,77–79]. Cotinine levels in the body, derived primarily from tobacco smoke, can be measured with extremely high sensitivity. They also reflect exposure to a variety of cigarette types over days [80]. Importantly, cotinine levels highly correlate with nicotine intake [81].

In children significantly exposed to ETS, cotinine levels are positively correlated with the risk of some adverse effects of ETS [70]. For instance, it has been found that cotinine is a better predictor of birth weight than the number of cigarettes smoked during pregnancy [82]. Cotinine levels are strongly associated with the age of the child, i.e. cotinine levels in infants are higher than in older children or adults exposed to the same quantity of ETS, most likely due to greater exposure [79,83]. Breast-feeding appears to affect cotinine levels in infants of smoking mothers [84]. Smoking parents, one or both, contact with other smokers, the frequency of smoking in the same room as the child, and crowding around household, as well as parental cotinine levels significantly influence cotinine

levels in children [85]. This supports evidence that parents can reduce their children's exposure to ETS by modifying their smoking habits at home.

Cotinine can be measured in a variety of biological fluids, including blood, urine, and saliva. In adults, plasma concentrations of cotinine are highly correlated with cotinine concentrations in urine [86]. Thus, urinary and plasma cotinine concentrations can be used interchangeably [70,87,88]. Recently, more attention has been focused on the validity of cotinine measurements in saliva. Non-invasive sampling of saliva, and the recent developments and application of a highly sensitive assay for the determination of cotinine in saliva has provided evidence to suggest that concentrations determined at sub-nanogram levels may be used as a marker for monitoring the prevalence and intensity of ETS exposure, particularly in children [73,78,79,85].

Cotinine is metabolized to 3'-hydroxycotinine, which is the most abundant metabolite of nicotine, accounting for 38% of all urinary metabolites in humans [81,89,90]. Renal excretion is the main route of 3'-hydroxycotinine elimination, and the analysis of 3'-hydroxycotinine in urine has been developed to assess exposure of individuals to ETS [91]. Virtually nothing is known about the utility of 3'-hydroxycotinine as a quantitative biomarker of exposure to cigarette smoke in children. Therefore, new studies aimed at determining conclusively the role of 3'-hydroxycotinine as a marker of ETS exposure in children should be recommended.

Notably, the quantification of cotinine in body fluids reflects ETS exposure only during the preceding few days and does not indicate exposure in persons who might deliberately abstain for several days before analysis. That is why, a method able to detect duration of ETS exposure is very desirable for biomedical screening.

It has been documented that many drugs and compounds are incorporated into hair during growth [92]. For example, gestational exposure to cocaine and haloperidol have been revealed by hair analysis of neonates [93,94]. Nicotine can also incorporate into hair and some recent studies have used hair nicotine as a biomarker of ETS in children [95,96]. In contrast to nicotine in body fluids, hair nicotine content can be used to assess cumulative exposure over months [68,97,98]. There is a linear relation between the hair uptake rates of nicotine and the duration of exposure to airborne nicotine [99]. Nicotine concentration in hair has been shown to discriminate smokers from ETS-exposed non-smokers and even between different levels of self-reported ETS exposure [100].

Hair nicotine measurement seems to be a practical and appropriate method for estimating exposure to tobacco smoke, but the validity of this method in children exposed to ETS during pre- and/or postnatal life remains unclear. It is not known whether the hair nicotine levels correlate with the risks of ETS-related health complications in children. Also, it has not been established whether the hair nicotine levels correlate with other biomarkers, especially cotinine. Recently, it has been found that the hair nicotine concentrations in children exposed to ETS are linearly related to the daily number of cigarettes smoked by the mother, and make approximately 25% of the concentrations measured in mothers themselves [39]. However, a detailed correlation between the nicotine levels in hair of children and in hair of their mothers has not as yet been conclusively determined and this issue requires more studies.

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