Environmental Tobacco Smoke and Respiratory Health in Children: A Critical Review and Analysis of the Literature from 1969 to 1998[1]

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Abstract
This analysis of parental/household smoking (a surro-
gate for environmental tobacco smoke, ETS) and respira-
tory symptoms and disease in children updates an ear-
lier analysis. Some 94 studies of preschool children and
152 studies of school-age or older children published
between 1969 and 1998 were examined. Both analyses
have shown an age dependency in the relationship
between parental/household smoking and respiratory
symptoms and disease in children. A statistically signifi-
cant, though moderate, relationship between parental/
household smoking and respiratory illness was ob-
served in most (86%) of the studies in preschool chil-
dren. While almost two thirds (98 of 152) of the studies of
school-age children showed a statistically significant re-
lationship between parental/household smoking and re-
spiratory symptoms and disease, there was a general
lack of consistency of statistical association for specific
respiratory endpoints (e.g., asthma, wheeze, bronchitis,

and cough). In addition to outcome, specific charac
tics of these studies were analyzed for consistency
commonest index of ETS exposure was a respons
questionnaire regarding adult smoking in the house
Clinical endpoints, usually determined from que:
naire responses, were validated with physical exan
tion and/or medical records in 56% of preschool st
and 30% of school-age studies. The way in whic
predetermined potential confounding variables
treated in both sets of studies was also examined
average number considered per study ranged bety
7.4 and 8.5 for both sets of studies. In preschool st
the most frequently considered potential confoun
variables were socioeconomic status, age, gend
subject's health, family health, and family size (60–
of the studies). In the school-age studies they were s
economic status, age, and gender (68–82% of the s
ies) and less frequently infant feeding, day care, st
season, quality of housing, and nutrition (less than
of the studies). Several variables were identified as
tential risk factors on the basis of relatively consis
associations with respiratory endpoints. In presc
children these were family health history, subje
health history, heating type/presence of air condition
young age, maternal smoking during pregnancy,
son, low birthweight, and stress. In school-age child
such potential risk factors were family health hist
subject's health history, heating type/presence of air c
ditioning, active smoking by the subject, and stress.

Introduction

We have previously conducted analytical reviews of the epidemiological literature pertaining to environmental tobacco smoke (ETS) exposure and respiratory health in children [1–3]. These reviews involved papers published between 1969 and 1991. Our analysis revealed that studies in preschool children (0–5 years of age) exhibited a consistent association between parental smoking (as a surrogate for ETS) and the incidence of respiratory symptoms (e.g., cough, wheeze) and diseases (e.g., asthma, bronchitis, pneumonia) [1]. Although the majority of studies in school-age or older children also revealed one or more statistically significant relationships between parental smoking and respiratory endpoints, there was a lack of specificity in these associations. There was considerable variation from study to study with regard to the particular symptom and/or disease that was statistically associated with parental smoking. When individual endpoints, such as asthma, cough, wheeze, and bronchitis were considered, a particular statistically significant association with ETS exposure was usually confirmed in no more than 25–50% of the studies [1].

In order to gain insight into the apparent age dependency of this association as well as the lack of statistical consistency that existed in the series of studies in older children, we undertook a systematic examination of specific characteristics of the studies in preschool children and those in school-age or older children. The studies were reviewed to obtain the following information: (1) which of 21 predetermined potential confounding variables were considered; (2) how such variables were classified, coded and adjusted for; (3) whether a statistically significant association existed between a potential confounder and a clinical endpoint, and (4) whether the clinical endpoints (i.e., the prevalence of respiratory symptoms and disease) were verified by physical examination and/or medical records [2, 3].

Our analysis indicated that the studies of both age-groups of children considered relatively few of the 21 predetermined potential confounders. For example, those considered in the majority of papers were such variables as socioeconomic status (SES), age, gender, and subject's personal health history, while those receiving little or no attention were day care, dampness and cold, nutritional status of the subject (in both age-groups), maternal smoking during pregnancy (in preschool children), and active smoking by the subject (in school-age children). In addition, there was wide variation in how individual potential confounders were classified and coded, and how they

were accounted for (e.g., matching, regression analysis, stratification). Several of the variables were found to be consistently associated with increased prevalence of respiratory symptoms and disease. Among these were family health history, subject's health history, and male gender in both age-groups and, in addition, young age, day care use, and winter season in preschool children. The other variables showed either no association or provided equivocal results. Finally, the clinical endpoints were validated by physical examination and/or medical records in about 50% of the preschool studies and about 20% of the studies in school-age or older children [2, 3].

We suggested that the lack of consistent statistically significant association between parental smoking and the prevalence of individual respiratory symptoms and disease in school-age children could reflect inadequacies in the treatment of potential confounding variables and lack of validation of clinical endpoints. Since the majority of studies of ETS exposure in children have relied on obtaining from questionnaires the smoking status of the parent or other household member, and lacked verification by a specific biomarker (such as body fluid cotinine), inconsistency of statistical association could also be due to smoker and/or exposure misclassification. While the consistent association between parental smoking and respiratory symptoms and disease in preschool children could be due to ETS, other possibilities could not be ruled out, such as residual effects of certain confounders (such as maternal smoking during pregnancy) and/or smoker or exposure misclassification [2, 3].

The current study is an update of these earlier analyses. In addition to including papers published since (or inadvertently excluded from) our initial review, we have reexamined those papers that comprised our initial analysis. Furthermore, the current analysis is more thorough than those conducted previously, since considerably more information has been extracted from the papers and compared. The current review incorporates studies published up to 1998.

Materials and Methods

In this analysis of the literature we have reexamined studies considered in our previous reports [1–3] as well as papers published since (or inadvertently excluded from) our previous analysis. As in previous analyses, the papers were analyzed separately in two groups according to the age of the subject, studies dealing with preschool children (0–5 years of age) and studies dealing with school-age children (5 years and older). In the initial analysis we identified 41 papers in preschool children and 46 papers in school-age children. A literature search from 1991 to 1998 identified an additional 53 stud-

ies dealing with preschool-age children [4–56] and an additional 106 studies dealing with school-age children [5, 9, 12, 13, 15, 22, 27, 29, 30, 32, 35, 43, 44, 54, 57–148], bringing the total number of preschool children studies to 94 and school-age children studies to 152.

The method of extracting information from each of the studies was an improved version of that used in our initial analysis. With the current approach, considerably more information was extracted than previously. Each paper was carefully read and selected items of information were systematically extracted from the article and tabulated. The following information was extracted from each of the published papers:

(1) type of study (e.g., case-control, cohort, etc.) and statistical methodology (logistic regression or otherwise);

(2) location of study (and, if available, whether rural, urban, or suburban, etc.);

(3) age of subjects;

(4) size of sample (total and, if available, number of ETS exposed);

(5) type of ETS exposure (usually a surrogate such as parental or household smoking) and, if available, verification with a specific biomarker;

(6) type of endpoint and, if available, whether such an endpoint was verified by physical examination of the subject by a physician or medical records;

(7) whether or not there was a statistically significant association between ETS exposure and a clinical endpoint (i.e., 95% confidence interval did not incorporate unity) and, if so, the magnitude of risk (e.g., odds ratio or relative risk), and

(8) whether or not a dose-response relationship existed between the magnitude of ETS exposure and the magnitude of risk.

In order for a study to be judged as showing a dose-response relationship, the magnitude of the relative risk had to vary directly with the quantitative estimate of ETS exposure (e.g., number of household smokers, number of cigarettes consumed daily by parental/household smoker, or levels of tobacco marker, such as cotinine in saliva, urine, or plasma). Some studies, but not all, reported statistical significance for trend. In other cases, a dose-response relationship was considered to have been demonstrated if a statistically significant relative risk was achieved if exposure exceeded a certain critical level (e.g., number of cigarettes exposed per day, number of smokers, level of body fluid cotinine).

Information pertaining to potential confounding variables (i.e., possible risk factors that might explain an association between ETS exposure and respiratory endpoint) was also systematically extracted from each paper. To aid this process, a set of 21 predetermined variables was developed from our previous analyses. These were derived from factors considered in the original set of studies reviewed (i.e., those derived from other epidemiological studies or from factors that intuitively seemed likely to have a potential direct or indirect effect on the respiratory system). The individual potential confounders considered in the preschool and school-age studies are listed in table 9. The only difference between the list of confounders for the preschool set and school-age set of studies is item 21. 'Maternal smoking during pregnancy' is indicated for the former set of studies and 'active smoking by the subject' is indicated for the latter set of studies. These differences reflect reasonable differences in the situation for the two age-groups under investigation. In each set, item 22 is the category listed as 'other', which reflects variables identified that could not be categorized in the original 21 items.

Table 1. Distribution of type of study

Type of study	Studies	
	pre-school[a]	school-ag
Unspecified	0	1
Retrospective cohort	28[c]	47
Prospective cohort	32	33
Case-control	29	27
Cross-sectional	7	71
Case studies	1	0
Total	97[d]	179[e]

[a] 94 studies.

[b] 152 studies.

[c] 1 study questionable.

[d] Total of 97 studies in preschool children (instead of 94) bec studies had both case-control and retrospective cohort designs study had both prospective and retrospective designs.

[e] Several of the studies in school-age children were multidesi counting for greater than expected number of papers), such as spective/prospective (3 papers), retrospective/cross-sectional (pers), retrospective/prospective/cross-sectional (3 papers), spective/case-control (2 papers), prospective/case-control (1 pa

Potential confounders were regarded as having been addre: any one of the following criteria was fulfilled: (1) The authors study considered the population homogeneous with regard potential confounder. (2) The exposed and nonexposed subject: said to be matched with regard to the potential confounder (incl those conditions in which a subset of subjects was excluded fr examination). (3) Statistical adjustment was made for the pot confounder. (4) It was regarded in the study as an independer factor.

In addition to its inclusion in the study, additional inform about potential confounders was extracted from these studies, r ly: (1) how it was addressed (as listed in 1–4 above); (2) how i classified and coded, and (3) whether a statistically significant ciation was looked for between the potential confounder and ar point and, if so, what was the direction of this association.

Results

Characteristics of Studies: Study Design, Location of Study, Age Distribution, Number of Subjects

As shown in table 1 all of the major study designs represented in epidemiology studies of parental/ho hold smoking and respiratory health in preschool school-age children. In preschool studies about one tʰ each of the studies were retrospective cohort, prospec cohort, and case-control studies. Relatively few were scribed as cross-sectional studies. In contrast, almost

Table 2. Distribution of location

Location	Studies	
	preschool[a]	school-age[h]
US/Canada	31	54
Mexico/Central/South America	2	1
Europe	39	68
Middle East	2	5
Africa	4	4
Asia	10	11
Australia/New Zealand/Pacific Islands	7	9
Total	95[c]	152

[a] 94 studies.
[b] 152 studies.
[c] 1 study involved both Europe and Canada, hence a total of 95 instead of 94 studies.

Table 3. Distribution of age of subjects

Approximate age of subjects	Studies	
	pre-school[a]	school-age[b]
Under 1 year[c]	18	
Under 2 years	22	
Under 3 years	5	
Under 4 years	11	
Under 5 years	23	
Under 6 years	16[d]	
Not specified		2
Under 6 years		5
Under 10 years		36
Under 15 years		74
15+ years		37
Total	95[e]	154[f]

[a] 94 studies.
[b] 152 studies.
[c] The relevant literature for both age-groups exhibited a wide variety of age designations (e.g., 0–5 years, 1–12 months, 1 month to 6 years, 3 years, 2–5 years, etc.). The system employed indicating the upper age for each group is an attempt to categorize these various types of age designations.
[d] Subjects were older than 6 years of age in 4 studies.
[e] One study in preschool children examined 2 age-groups, 0–2 and 3–5 years.
[f] Two studies in school children examined 2 age-groups (6–7 years and 13–14 years; 8 years, 15 years).

(or 46.7%) of the studies in school-age children were cross-sectional in design, while approximately one third of these were retrospective cohort studies. Prospective cohort and case-control each comprised about one fifth of these studies.

As shown in table 2, over 40% of the studies in preschool children were conducted in Europe whereas about one third of this group came from the US and Canada. Considerably fewer studies involved cohorts from Asia (about 10%), Australia, New Zealand, and the Pacific Islands (about 7%), Africa, Latin America, and the Middle East (8.5%). Table 2 also demonstrates a similar regional distribution of studies in school-age children with regard to the proportion of studies conducted in Europe (about 45%) and the US and Canada (about 35%), with relatively fewer studies from Asia (about 7%), Australia, New Zealand, and the Pacific Islands (about 5%), and Africa, Latin America and the Middle East (6.5%).

As summarized in table 3, various age designations between birth and 6 years were represented in studies of preschool children with no real age-group predominating. Similarly, in studies of school-age children, heterogeneity is evident in age groupings. About one fourth of the studies examined children under 10 years of age and another one fourth of the studies examined children 15 years or older. The remaining half of the studies examined children under 15 years of age (table 3).

As shown in table 4 there was significant heterogeneity from study to study in the size of the cohort represented for both age-groups. The total number of subjects ranged in studies of preschool children from a low of 30 subjects to a maximum exceeding 12,500 subjects, while in school-age children the smallest study involved 15 subjects and the largest study involved almost 38,000 subjects. The number of ETS-exposed subjects was reported in most (70–80%), but not all of the studies. The heterogeneity from study to study reported above for total number of subjects in both age-groups was also evident with regard to ETS-exposed subjects. This number varied from a low of 17 subjects to a high of over 7,500 subjects in preschool children and a low of 11 subjects to a maximum of almost 25,000 subjects in school-age children.

Verification of ETS Exposure and Clinical Endpoints

As shown in table 5, maternal postnatal smoking was the index of ETS exposure in 35–40% of the studies in both age-groups. Household smoking served as the index of exposure in a similar proportion (39%) of preschool studies and a slightly higher proportion (47%) of school-age studies. Parental and paternal smoking served as an

Table 4. Distribution of number of subjects

Subjects	Studies			
	total preschool [a]	total school-age [b]	ETS-exposed preschool	ETS-schoo[l-age]
0–100	15[c]	9[c]	23[d]	25[d]
101–500	24	43	21	35
501–1000	15	26	11	13
1,001–5,000	30	48	16	25
5,001–10,000	6	14	4[f]	8
10,000–15,000	4[e]	6		1
15,001+		6[e]		1[f]

[a] 94 studies.
[b] 152 studies.
[c] Smallest study was n = 30 (2 studies) for preschool and n = 15 for school-age.
[d] Smallest studies was n = 17 for preschool and n = 11 for school-age.
[e] Largest study was n = 12,530 for preschool and n = 37,791 for school-age.
[f] Largest study was n = 7,527 for preschool and 24,750 for school-age.

Table 5. Distribution of exposure index and verification

Exposure index/verification	Preschool studies[a]		School-age studies[b]	
	n	%	n	%
Maternal postnatal smoking	38	40.4[c]	54	35.5[c]
Maternal prenatal smoking	9	9.6[d]	4	2.6
Maternal prenatal ETS	2	2.1		
Parental smoking	20	21.2	43	28.3
Paternal smoking	20	21.2	42	27.6
Household smoking[g]	37	39.4	71	46.7
Verified by marker	6[e]	6.4	10[f]	6.6

Some of the above studies in each age-group considered several criteria of ETS exposure, as follows: maternal/paternal smoking (15 preschool, 23 school-age); maternal/household smoking (4 preschool, 3 school-age); maternal/paternal/household smoking (6 preschool, 8 school-age); maternal/paternal/parental smoking (2 preschool, 4 school-age); parental/household smoking (5 preschool, 5 school-age); maternal/paternal/parental/other smoking (2 school-age).

[a] 94 studies.
[b] 152 studies.
[c] 2 preschool studies and 2 school-age studies included maternal prenatal and postnatal smoking as a single category.
[d] 2 preschool studies included maternal prenatal smoking and ETS exposure as a single category.
[e] Urinary cotinine (4 studies), salivary cotinine (1 study), newborn cord blood cotinine (1 study).
[f] Urinary cotinine (6 studies), urinary cotinine and hair cotinine (1 study), salivary cotinine (3 studies).

index of ETS exposure in about 20% of preschool s and almost 30% of school-age studies (table 5). Pr maternal smoking or ETS exposure (other's smok the index of exposure to a much smaller extent (2– As shown at the bottom of table 5, a significant num studies examined a variety of types of ETS exposur sifications. Table 5 shows that exposure was verifie a body fluid marker (e.g., cotinine) in 6 of 94 (6.4%) ies in preschool children and 10 of 152 (6.5%) stuc school-age children.

Verification of endpoints (e.g., respiratory illnes infection, bronchitis, pneumonia, bronchiolitis, et medical records and/or physical examination was cated in 56.4% (53 of 94) of the preschool studies ɛ 30.2% (46 of 152) of the studies in school-age childr

Outcome Variables: Statistically Significant Associations, Magnitude of RRs, Consistency of Result, Dose-Response Relationships

The vast majority of studies in preschool childre of 94 studies or 86%) reported a statistically signi association between parental/household smoking some respiratory health endpoint (e.g., respiratory il bronchitis, bronchiolitis, cough, acute respiratory infections, asthma, prick tests, serious bacterial or infections, recurrent wheezing, etc.). Since the ele risks were statistically significant in the vast major studies, this association between parental smoking respiratory illness in this age-group was judged to be sistent. Table 6 shows that most of these statisticall

Table 6. Distribution of statistically significant relative risks for parental/household smoking and respiratory health endpoints[a]

Relative risk	Preschool studies[b]		School-age studies[c]	
	n	%	n	%
<1.0	2	2.1[d]	8	5.5[d]
1.0–1.5	24[e]	25.0	68[e]	46.6
1.6–2.0	25	26.0	36	24.7
2.1–2.5	18	18.7	16	10.9
2.6–3.0	8	8.3	8	5.5
3.1–3.5	7	7.3	3	2.1
3.6+	12[f]	12.5	7[f]	4.8

[a] For some studies more than one statistically significant relative risk was reported; for preschool studies a total of 94 significant relative risks were reported in 81 studies; for school-age studies 146 significant relative risks were reported for 98 studies.
[b] 94 studies total.
[c] 152 studies total.
[c] Percent based on total number of statistically significant associations.
[e] Lowest elevated risk for preschool studies was 1.2 and for school-age studies was 1.1.
[f] Highest relative risk for preschool studies was 12.1 and for school-age studies was 23.8.

Table 7. Consistency of statistically significant association between ETS exposure and specific endpoints in studies of school-age children[a]

Endpoint	Studies with significantly increased association/studies testing for association	
	n/n	%
Asthma	23/81	28.4
Cough	27/51	52.9
Wheeze	34/62	54.8
Bronchitis	4/19	21.1
Others		
Respiratory diseases[b]	27/51	52.9
Respiratory symptoms[c]	33/62	53.2
Atopy/allergy[d]	2/24	8.3

[a] 152 studies total.
[b] Respiratory illness, adenoidectomy/tonsillectomy, collections of endpoints (e.g., phlegm, bronchial trouble, bronchiolitis, pneumonia), infection, absence from school, throat infection, tuberculosis.
[c] Breathlessness, sputum, chest congestion with phlegm, rhinitis, rhinoconjunctivitis, sore throat, eye irritation, bronchial responsiveness, wheeze, snoring, asthma exacerbation, blocked running nose, sinusitis, risk of intubation, airway complications.
[d] Hay fever/allergies, allergic disorders, skin prick tests, eczema, ectopic diseases, serum IgE, specific IgEs, allergic rhinitis.

nificant RRs were of modest magnitude. About 53% were 2.0 or less, while over 70% were 2.5 or less.

About two thirds (i.e., 98 of 152) of the studies in school-age children reported a statistically significant positive association between parental/household smoking and respiratory illness. Whereas there appeared to be some consistency between this surrogate of ETS exposure and respiratory illness overall, a general lack of consistency for statistically significant associations was evident when specific respiratory endpoints were considered. As shown in table 7, a statistically significant association was evident for asthma in about 28% of the cases, for cough in about 53% of the cases, for wheeze in about 55% of the cases and for bronchitis in about 21% of the cases. In addition to the four endpoints that could be readily classified as asthma, cough, wheeze, and bronchitis, there were a large number of 'other' endpoints that were more difficult to categorize. Nevertheless, we attempted to categorize them into three groups on the basis of specificity and/or intensity of classification. The categories were: respiratory disease (a specific or generally more severe condition), respiratory symptoms (those more difficult to classify or which were less severe), and allergy/atopy (condi-

Table 8. Frequency of observing a dose-response relationship between ETS exposure and respiratory illness

Dose response?	Studies	
	preschool[a]	school-age[b]
Yes	34	41
No	10	19
Not reported/determined	45	59

[a] 94 studies.
[b] 152 studies.

tions that appeared to demonstrate an allergic response). As shown in table 7 these arbitrarily classified 'other' endpoints also exhibited lack of statistical consistency. Respiratory diseases and respiratory symptoms exhibited statistically significant elevated risks in slightly over 50% of the tests for association, whereas the frequency of those classified as allergy and atopy were statistically significant in under 10% of the comparisons. As in the studies of preschool children, the statistically significant RRs in school-

Table 9. Frequency of consideration of potential confounding variables

Potential confounder	Preschool studies[a]		School-age[b]	
	n	%	n	
1 SES	72	76.6	104	6
2 Gas fuel usage (cook/heat)	20	21.3	44	2
3 Family health history	56	59.6	78	5
4 Subject's health history	63	67.0	86	5
5 Infant feeding (breast vs. bottle)	43	45.7	22	1
6 Outdoor pollution	24	25.5	42	2
7 Indoor pollution[c]	25	26.6	38	2
8 Day care use	25	26.6	9	
9 Family size	58	61.7	68	4
10 Animal exposures	16	17.0	43	2
11 Stress	2	2.1	5	
12 Dampness and cold	10	10.6	40	2
13 Heating type/presence of air conditioning	20	21.3	38	2
14 Season	38	40.4	25	1
15 Occupational exposure (from parents)		0		
16 Quality of housing	22	23.4	25	1
17 Nutritional status	9	9.6	4	
18 Residence location	43	45.7	72	4
19 Age of subject	89	94.7	124	8
20 Gender of subject	69	73.4	115	7
21 Maternal smoking in pregnancy[d]	13	13.8		
21 Active smoking by subject	–		47	3
22 Others	61[e]	64.9	90[f]	5
Ethnicity	31	33.0	52	3
Birthweight	27	28.7	18	1

[a] 94 studies total.

[b] 152 studies total.

[c] Other than that attributed to gas stove.

[d] As distinguished from postnatal smoking.

[e] In addition to those listed in the table, parental age was considered in 9 studies wh variables considered (1 or 2 times) were gestational age, active smoking by subject, cl istics of care, type of caretaker, birth order, gravidity, parity, maternal exposures, with parents, mother's management of illness, and duration of gestation.

[f] In addition to those listed in the table, maternal smoking during pregnancy was ered in 16 studies, while other variables considered (1–3 times) were additional bias, age, characteristics of car, maternal age, English speaking, birth order, year of survey, ty of family, type of survey, type of respondent, body weight or mass, parental age, gender, month of birth, time interval of study, height, gender of respondent, year of oldest/youngest child, gestational age, and premature birth.

age children were usually modest in magnitude. Table 6 shows that over half of these associations had a relative risk of 1.5 or less and about 77% of them were under 2.0.

The existence of a dose-response relationship was tested for in only a portion of studies in preschool and school-age children. Table 8 shows that such a relationship was demonstrable about three fourths of the time (34 of 44 studies) in preschool children and about two thirds of the time (41 of 60 studies) in school-age children.

Potential Confounding Variables

Statistical adjustment for potential confoundin ables (by such methods as multivariate logistic regre log-linear models, stratification, and the proportion ards model) was performed in 55 of 94 (58.5%) of tl school studies and 107 of 152 (70.4%) of the sch studies. The frequency with which individual po confounding variables were considered in studie both age-groups is presented in table 9. In preschoo

Table 10. Distribution of potential confounders/paper

Potential confounders/paper	Preschool studies[a]		School-age studies[b]	
	n	%	n	%
0–5	19[c]	20.2	51[c]	33.6
6–10	53	56.4	80	52.6
11+	22[d]	23.4	21[d]	13.8
Mean number per paper	8.5		7.4	

[a] 94 studies.

[b] 152 studies.

[c] Lowest number of potential confounders considered was 1/paper for both preschool and school-age studies.

[d] Highest number of potential confounders considered was 15/paper for both preschool and school-age studies.

ies the most frequently considered variables among the original 21 were age (94.7% of the studies), socioeconomic status (SES, 76.6.% of the studies), gender (73.4% of the studies), subject's health history (67.0% of the studies), family size (61.7% of the studies) and family health history (59.6%). Among the more infrequently considered variables (0–20% of the studies) were exposure to animals, stress, dampness/cold, nutritional status and maternal smoking during pregnancy. Studies in school-age children exhibited the same three most prevalently considered variables: age (81.6%), gender (75.7%) and SES (68.4%). The variables considered infrequently (0–20%) in this age-group were stress and nutritional status, as in the younger age-group, as well as infant feeding, day care, season, and quality of housing.

It was noted that for several of the potential confounding variables (e.g., SES in preschool studies, age of subjects and gender of subjects in studies of both age-groups), the frequency of consideration exceeded that stated above for statistical adjustment of potential confounders (58.5% for preschool and 70.4% for school-age studies). This apparent discrepancy is explained by the fact that consideration of a potential confounder included three other possible criteria in addition to statistical adjustment (e.g., homogeneity, matching, or consideration as independent risk factor) as noted in 'Materials and Methods'.

Table 10 summarizes the data on the distribution of potential confounders per paper and the average number considered per paper in studies from both age-groups. For both preschool and school-age studies more than half considered 6–10 per paper, with a minimum of 1 and a maxi-

mum of 15 per paper for both age-groups. The mean number considered was similar for both age-groups, ranging between 7.4 per paper and 8.5 per paper.

For both age-groups, a considerable variation from study to study was evident in how individual potential confounders were classified and coded. For example, SES was scored based on several criteria (e.g., occupation, salary, education, type of dwelling of breadwinner), automatic dishwasher in the home, median yearly income, social class, civilian and armed service, work status of mother, number of rooms occupied in house, and marital status of mother. Variation was also observed in how the confounder was dealt with (e.g., matching, adjustment, or stratification). Similar variations were evident for most other potential confounding variables (data not shown).

Table 11 summarizes the frequency with which individual potential confounders are statistically associated with a respiratory illness or disease. Several of these appeared to be consistently associated with the endpoint (i.e., when an association between the variable and endpoint was statistically tested for, a statistically significant association was demonstrated). Among those that showed a consistent statistical association with adverse respiratory health in preschool children were maternal smoking in pregnancy (85.7%), season (usually winter, 84.6%), subject's health history (i.e., episode of illness in the family, 82.3%), younger age of subjects (80.9%), residence location (71.4%), family health history (i.e., subject had history of illness, 68.1%), and low birthweight (62.5%). Also suggestive of an association was stress, significant in 2 of 2 studies. Three of the above variables show consistent statistical association with respiratory illness in school-age children, namely family health history (90.7%), subject's health history (72.8%), and stress (2 of 3 studies). Two other variables that appear to have some statistical consistency with respiratory illness in school-age children are heating type/presence of air conditioning (66% of the studies) and active smoking by the subject (61.1% of the studies).

Whereas such consistency of statistical association was less evident for the remaining variables, there appeared to be in some, evidence of consistency in the *direction of association*. In other words, when statistically significant associations were evident in these remaining variables, they usually tended to influence risk in the same direction. Among those that appeared to increase risk of respiratory illness were *low* SES, *male* gender, *minority* ethnicity (in both age-groups), *large* family size (preschool), gas fuel usage (preschool), bottle vs. breast-feeding (preschool), outdoor pollution (preschool and school-age), in-

Table 11. Statistically significant associations between potential confounders and endpoints

Potential confounder	Significant associations/total ass		
	preschool[a]		schoo
	n/n	%	n/n
1 SES	25/56	44.6	35/91
2 Gas fuel usage (cook/heat)	6/12	50.0	10/37
3 Family health history	32/47	68.1	80/88
4 Subject's health history	28/34	82.3	75/10.
5 Infant feeding (breast vs. bottle)	16/30	53.3	6/17
6 Outdoor pollution	3/6	50.0	28/47
7 Indoor pollution[c]	10/20	50.0	14/41
8 Day care use	8/14	57.1	2/6
9 Family size	16/39	41.0	16/43
10 Animal exposures	4/11	36.3	21/46
11 Stress	2/2	100	2/3
12 Dampness and cold	2/9	22.2	33/67
13 Heating type/presence of air conditioning	8/14	57.1	33/50
14 Season	11/13	84.6	3/6
15 Occupational exposure (from parents)	0/0	0	0/0
16 Quality of housing	3/7	42.8	3/19
17 Nutritional status	1/8	12.5	2/4
18 Residence location	5/7	71.4	17/31
19 Age of subject[d]	17/21	80.9	28/62
20 Gender of subject (male)	24/45	53.3	49/93
21 Maternal smoking in pregnancy[e]	6/7	85.7	
22 Active smoking by subject			22/36
23 Others			
Ethnicity	8/15	53.3	11/20
Birthweight	10/16	62.5	6/12
Maternal smoking in pregnancy			8/15

[a] 94 studies.
[b] 152 studies.
[c] Other than that attributed to gas stove.
[d] Younger age.
[e] As distinguished from postnatal smoking.

door pollution (preschool), dampness/cold (school age), low birthweight (school age), and maternal smoking during pregnancy (school age).

Discussion

Within the last few years, several research groups have published analytical reviews of the literature pertaining to the relationship between parental smoking and respiratory illness in children [149–153]. As listed in table 12, the objective of all of these reviews was to conduct a meta-analysis of the published studies with the ultimate goal of estimating a composite elevated risk. For reasons to be discussed later, our analysis, which is an extension vious analyses [1–3], has avoided generating a con risk estimate. Our updated analysis includes 223² vational epidemiological papers spanning a 30-ye. od (1969–1998) in which parental and/or hot smoking served as a surrogate for ETS exposure respiratory symptoms and diseases served as end Each of these papers was examined thoroughly an mation of particular interest was extracted in a syst fashion. To our knowledge, ours is the most comp sive analysis of its kind in this area.

² Although the survey totals 246 individual studies (94 pre-schoc and 152 school-age studies), 23 of these studies included data pertainii age-groups.

Table 12. Summary of published meta-analytical studies of parental smoking and respiratory symptoms and disease in children

Meta-analytical study	Age-group of children	Exposure (smoker)	Endpoint	OR or RR 95% CI[a]	Studies	Type of study considered
DiFranza and Lew [149]	preschool and school age	parental	asthma, wheeze, wheezy bronchitis	1.46, 1.14–1.85	3[b]	C-C
				1.43, 1.31–1.52	14	C
	school age	parental	cough	1.36, 1.26–1.46	6[c]	C-C
	0–5 years	parental	LRI	2.50, 1.86–3.36	5	C-C
				1.46, 1.44–1.60	9	C
	0–5 years	parental	hospitalization for respiratory illness	2.41, 1.75–3.30	4	C-C
				1.55, 1.41–1.71	6	C
Strachan and Cook [150]	infancy, early childhood	either	upper, lower respiratory illness	1.57, 1.42–1.75	27	C-C, C
		mother	upper, lower respiratory illness	1.72, 1.55–1.91	27	C-C, C
		father	upper, lower respiratory illness	1.29, 1.16–1.44	16[d]	C-C, C
Cook and Strachan [151]	school age	either	asthma	1.21, 1.10–1.34	21[e]	C-C, C
			wheeze	1.24, 1.17–1.31	30[f]	C-C, C
			chronic cough	1.40, 1.27–1.53	30[g]	C-C, C
			phlegm	1.31, 1.13–1.52	6[h]	C-C, C
			breathlessness	1.31, 1.08–1.59	6[i]	C-C, C
Strachan and Cook [152]	0–5 to 7 years	maternal	asthma, wheeze, illness	1.31, 1.22–1.41	4	L
	school age	maternal	asthma, wheeze, illness	1.13, 1.04–1.22	4[j]	L
	preschool and school age	parental	wheezing	1.35, 0.87–2.08	8[k]	L (natural history)
		either	asthma, wheeze	1.37, 1.15–1.64	14[l]	C-C
		mother	asthma, wheeze	1.59, 1.27–1.99	8[m]	C-C
		father	asthma, wheeze	0.94, 0.78–1.12	8[n]	C-C
Li et al., [153]	Infancy and early childhood	parental	hospitalization for LRI	1.93, 1.66–2.24	9	C-C, C
	0–2 years	parental	serious LRI	1.71, 1.33–2.20	7	C-C, C
	0–6 years	parental	serious LRI	1.57, 1.28–1.71	10[o]	C-C, C
	3–6 years	parental	serious LRI	1.25, 0.81–1.78	3	C-C, C

C-C = Case-control study; C = cohort study; L = longitudinal study; LRI = lower respiratory infections.

[a] Most of the risks listed are OR except for those listed for cohort studies of DiFranza and Lew [149] which are RR.

[b] In order to deal with publication bias, DiFranza and Lew [149] estimated the number of extra neutral studies (ENS) required to render the pooled risk not significant ($p > 0.05$). The ENS contained an OR or RR = 1.0 and the average number of subjects for the studies involved in the composite risk. This OR had an ENS = 2, suggesting that it was of marginal statistical significance.

[c] This OR had an ENS = 1, suggesting that it was of marginal statistical significance.

[d] Statistically significant in 6 or 16 studies.

[e] Statistically significant in 4 of 21 studies.

[f] Statistically significant in 9 of 30 studies.

[g] Statistically significant in 19 of 30 studies.

[h] Statistically significant in 3 of 6 studies.

[i] Statistically significant in 2 of 6 studies.

[j] Statistically significant in 2 of 4 studies.

[k] Statistically significant in 2 of 8 studies.

[l] Statistically significant in 5 of 14 studies.

[m] Statistically significant in 5 of 8 studies.

[n] Statistically significant in 0 of 8 studies.

[o] Statistically significant in 5 of 10 studies.

Although composite risk was not estimated in our analyses, the endpoints of interest from individual studies were considered from the perspective of consistency of effect (i.e., statistical significance of RR) and magnitude of this significant RR. In addition, other important aspects of individual papers that might bear on outcome were also considered, namely design aspects (e.g., type of study, location, age of subjects, sample size), verification of endpoints with medical records, verification of exposure with biological marker, and a very thorough analysis of the treatment of potential confounders. Our approach was an outgrowth of earlier studies where inconsistency in endpoint was evident in studies of school-age and older children as opposed to consistency in preschool children

[1] and it was hoped that such an in-depth analysis of the literature would provide insights about the cause of such inconsistency [2, 3].

The current updated analysis of the literature confirmed our earlier observation as well as that of individual studies of an apparent age dependency of an association between parental/household smoking and respiratory illness in children [1]. While a statistically significant association between parental smoking and respiratory symptoms and disease was consistently observed in children under 5 years of age, such a consistency could not be found in school-age and older children when specific respiratory endpoints (such as asthma, wheeze, and bronchitis) were taken into consideration, including those that were arbitrarily classified as respiratory disease, respiratory symptoms, and allergy/atopy. In both sets of studies, however, the magnitude of RR was usually modest, under 2.0 in the majority of studies. A majority of studies which tested for dose-response revealed such a relationship between the prevalence of respiratory illness in children and the number of household smokers or cigarettes smoked in the home. Endpoints were verified by medical examination or records as opposed to a questionnaire response in about half of the preschool and one third of the school-age studies. Exposure to ETS was verified by body fluid marker (e.g., cotinine) as opposed to questionnaire responses in very few (about 6.5%) of the studies from both sets. With regard to other aspects of the relevant studies, such as study design, location of studies, age of subjects, sample sizes, a significant heterogeneity was observed among the various studies. In addition, our analysis revealed a diverse and complex treatment of potential confounders in both sets of studies. Some were commonly considered while others were rarely considered, or not at all. Considerable variation was also evident from study to study in the specific variables considered, and how they were coded, classified and taken into account. Finally, we observed that some potential confounders consistently exhibited a statistically significant association with adverse respiratory effects.

Meta-Analyses of Others vs. Our Analytical Approach

As shown in table 12, most of the composite relative risks presented in the above-mentioned meta-analyses of others are statistically significant (i.e., the lower level of the 95% confidence interval excluded unity). On the other hand, in many respects, the data reported by these studies are consistent with our observations. Although, usually statistically significant, elevated composite RRs or ORs are small, well below 2.0. Several of the composite risk estimates suggest an age dependency as noted i₁ rent and previous analyses, as well as in individi miological studies of others [1]. For example, and Cook [150] and Cook and Strachan [151] sh₁ when ETS is based upon 'either' parent smoking posite OR for respiratory illness in infancy ₐ childhood (1.57) is greater than those estimate₁ cific illnesses in school-age children (1.21–1.40). and Cook [152] also reported that in children ₁ and younger, the OR for asthma and wheeze illn₁ was higher than that of school-age children (ble 12). While the elevated RRs of respiratory i younger children exposed to parental smoking statistically significant, those with older children in several instances, where the lower level of the ₍ fidence intervals incorporated unity [152, 153]. also shows that the composite RRs from gro included older children revealed considerable ₁ tency with regard to statistical significance of in RRs, though, in most cases, the composite RR w tically significant. As seen in footnotes d–o of these composite relative risks were comprised n individual relative risks that failed to achieve s₁ significance. In addition, two of the composite R of marginal significance since very few extra neut ies (ENS) were required to render the pooled risk ₁ not significant (footnotes b and c, table 12).

The use of meta-analysis leading to the estimat composite RR has been and continues to be an major controversy in the field of epidemiology. ₁ approach requires that data used to estimate co RR come from studies that have minimal heter₁ with regard to endpoints examined, study type, co₁ ing, indices of exposure, and decreased possibility lication bias [154–158].

Publication bias, where studies with significant are more likely to be published than those without cant results, also referred to as the 'file drawer p₁ [159], and a very well-recognized concern of met₁ sis, can derive from several sources. As noted by Eg Smith [160], significant results from individual stu₁ more likely to be published in English language j₁ (English language bias), tend to be cited more fre₁ (citation bias), tend to be published repeatedly (mul tion bias) and, when published in undeveloped co₁ will more likely be published in journals indexed in ature database (database bias). These authors indic₁ sources of funding may also be a component of publ bias, since published studies supported by the gover₁ tend to be more prevalent than those supported by

try [160]. Egger and Smith [160] also suggest that the criteria for inclusion of a study in a meta-analysis may be influenced by whether it is consistent with the general trend (i.e., favoring an increased risk) of other studies in the set (inclusion bias). Along these lines, Bailar [157, 158] has expressed concern with this methodology regarding the bias on the part of the meta-analyst.

It has also been noted that confounding variables, potential errors in exposure measurement, and publication bias, are particularly problematic in the analysis of weak associations (e.g., RR estimates of less than 2.0) [159, 161]. Egger et al. [162] note that whereas meta-analysis appears to be commonly used for both randomized controlled trials and observational studies, the outcome of the latter would tend to be more subject to distortion by confounding and/or biases. Therefore, these authors suggest that the statistical estimation of combined RRs should not be a major component in the review of observational studies. Egger et al. [162] also note that other authors have been even more strongly opposed to the use of meta-analysis. Although a variety of measures exist for consideration of confounders, errors in exposure, and publication bias, Weed and Kramer [163] commented that 'meta-analyses may increase statistical precision and narrow confidence intervals around estimates of effect, but cannot correct for confounders or for biases'. Egger et al. [162] note that even with an adjustment, residual confounding is still a problem in meta-analyses because of imprecision in the methodology.

Several published examples where meta-analysis has provided misleading or erroneous information are worth noting. A comparison of 12 individual large randomized controlled trials (involving 1,000 or more subjects), considered the 'gold standard' for evaluation of treatment efficacy, exhibited 'only fair' agreement with 19 meta-analyses on the same issues. For example, 35% of the time there was lack of statistical agreement between randomized controlled trials and meta-analyses [164]. Egger et al. [162] note several additional examples of misleading meta-analytical results:

(1) A close dose-dependent association between smoking and suicide, suggestive of causality but considered implausible, is more likely due to such confounders as social and mental state.

(2) Meta-analysis of observational studies suggesting that dietary β-carotene protected against cardiovascular mortality was at odds with that of randomized controlled trials showing a moderate but statistically significant increased risk of cardiovascular mortality with β-carotene supplements.

(3) Meta-analysis of case-control studies suggest a positive association between dietary fat and breast cancer not evident from meta-analysis of cohort studies.

(4) Meta-analysis revealed a significant association between melanoma and intermittent sunlight exposure when the studies were not blinded whereas no significant association was observed when studies were blinded.

While a concern has been raised regarding the tallying of studies that show an association versus those that do not [154], tallying as performed by us can be of some value. We complied with the criterion of statistical significance (i.e., a $p < 0.05$ or exclusion of unity by the lower level of the 95% confidence interval) rather than merely direction (positive or negative) of an association without regard to statistical significance. Statistical significance or rejection of the null hypothesis, the minimal standard for the evaluation of scientific data, suggests (but does not prove) that a real difference between two or more populations exists as opposed to one resulting from chance alone. Although failure to reject the null hypothesis could be due to reasons other than absence of an effect (i.e., type II errors) and rejection of the null hypothesis could reflect a systematic flaw in the design of studies (e.g., confounders and/or bias) [165–167], 'tallying' based on statistical significance among a series of studies does provide a crude estimate of whether an observation (e.g., association between parental smoking and a respiratory disease) is reproducible. Reproducibility, a benchmark of scientific inquiry, is a principal determinant of the validity of an observation. Furthermore, consistency of association is well recognized as one of the nine criteria noted by Hill [168] for causation.

Studies in Preschool Children

The consistent association between parental and household smoking and respiratory illness in young children observed by us and the aforementioned meta-analyses suggests that ETS adversely affects the respiratory system of young children. On the other hand, alternative explanations cannot be ruled out at this time. Our analysis reveals that potential confounders were addressed inadequately in the studies. While some were considered in most or the majority of preschool studies (e.g., SES, age of subject, gender of subject, subject's health history, family health history, family size), more were considered in relatively few of the studies (e.g., gas fuel usage, outdoor pollution, day care use, animal exposures, dampness and cold, heating type/presence of air conditioning, quality of housing, nutritional status, maternal smoking during pregnancy) or virtually ignored (e.g., stress, occupational

exposure from parents, table 9). Furthermore, the specific criterion used to define a potential confounder (e.g., financial status and/or education for SES) varied considerably from study to study. Thus, little or no standardization existed in the consideration of potential confounders. Similarly, little consistency exists in their consideration for the generation of composite relative risks in the meta-analyses alluded to above (table 12). As noted previously, even in the case of thorough treatment of potential confounding variables, the possibility of residual confounding due to imprecision could have an impact on moderately sized RRs. Our analysis of preschool studies also revealed certain variables that, in the face of considerable heterogeneity of study design, location, and endpoint examined, consistently showed a statistically significant association with respiratory illness. As shown in table 11, these are family health history, subject's health history, season, residence location, age of subject, maternal smoking during pregnancy, and possibly stress (2 of 2 cases). In addition, other variables have been recognized as adversely affecting respiratory illness in children (such as SES, outdoor pollution, family size) [1, 3, 169], even though they did not emerge in our analysis as being consistent. These variables, individually or in combination, could have an impact on outcome either by their omission from consideration or by residual effects.

Maternal Smoking during Pregnancy vs. Postnatal Smoking Effects

Among the alternative explanations for ETS (or postnatal parental smoking) effects in preschool children worthy of further consideration are the possible effects of smoking during pregnancy. It is noteworthy that, in our analysis, maternal smoking during pregnancy (adjusted for postnatal smoking) is rarely considered as a confounder (13.8% of the studies, table 9) and when this variable is considered, it is associated with a statistically significant relative risk of respiratory illness almost 86% of the time (table 11). Few, if any, studies that examine postnatal smoking adjust for smoking during pregnancy. Maternal smoking during pregnancy is consistently associated with respiratory illness, pulmonary dysfunction and anatomical changes in infant offspring [170–180]. In fact, some data suggest that in utero effects of maternal smoking in pregnancy on the respiratory system are carried by offspring into school age [91, 110, 181].

While the mechanism by which maternal smoking during pregnancy may adversely affect the respiratory system of offspring has yet to be elucidated, a likely candidate pertains to maternal smoking effects on fetal growth and development. Maternal smoking during pregna sistently associated with low birthweight, or ir growth retardation of term offspring and prem [182–186]. In addition, maternal smoking du nancy can be associated with pregnancy con adversely affecting birth outcome, such as place and preterm premature rupture of membranes [thermore, low birthweight and prematurity, th are risk factors for respiratory illness and pulme function [25, 178, 188–191]. In fact, our data a tent with low birthweight as a risk for respirator preschool children. We observed a statistically s association between low birthweight and respi ness in 62.5% of the cases (table 11). Interestin; weight is one of the underrepresented potential ders (28.7% of the studies) in preschool studies Contradictory to the concept that in utero effect for the association between parental smoking an tory illness in young children are the reports fro where paternal smoking is associated with respi ness and few, if any, mothers are said to smoke [1 On the other hand, the association between smoking and respiratory illness does not appea consistent observation in individual studies. As in the meta-analytical data of Strachan and Co 10 of 16 studies failed to achieve statistical sign even though a statistically significant composite upper and lower respiratory illness and paternal is reported (table 12, footnote d). Strachan ar [152] also report an OR and 95% confidence between paternal smoking and asthma and wl 0.95, 0.78–1.12, where none of the 8 studies were cally significant (table 12, footnote n).

Studies in School-Age Children

If ETS does adversely affect the respiratory sy young children, the lack of a consistent statistical tion between parental/household smoking and respiratory illnesses in school-age children coul sent a diminished sensitivity to the adverse effects or to a reduced exposure to ETS due to a diminish macy between the child and mother, as discuss viously [1]. If ETS is, in fact, a persistent risk fa respiratory illness in older children, a lack of cor statistical association between ETS exposure and i tory illness in this age group could also be due to β (II) errors [165] related to the fact that the magnitu putative risk would be modest coupled with inade in study design (such as diminished sample size).

Our analysis revealed several areas of deficiency in the studies pertaining to parental smoking and respiratory illness in older children that can account for the inconsistency of the association. In this set, as in younger children, verification of ETS exposure of subjects with a biochemical marker is virtually nonexistent. Almost 95% of the studies rely solely on questionnaire responses pertaining to smoking status of parents and household members. As discussed previously, misclassification of smoking status can distort the outcome of a study either positively or negatively. Erroneous reporting of parental or household smoking or change of parental smoking status would tend to diminish risk estimates, whereas active smoking by the subject, which can be substantial in children and is more prevalent in smoking households, would tend to amplify relative risk [1, 169]. In our analysis, active smoking by the school-age subject is significantly associated with an increased risk of respiratory illness in 61% of the cases (table 11). In this regard, it is noteworthy that active smoking by the child was *not* considered as a potential confounder in 69% of the studies in school-age children (table 9). Furthermore, more than two thirds (72 of 105) of those studies that have not considered active smoking in children contain subjects older than age 10 where active smoking would be more likely.

The clinical endpoints examined in school-age children relied solely on questionnaire responses and lacked verification by medical examination or medical records in 70% of the studies. This too can account for the inconsistency of association observed in this age-group. As discussed previously, lack of clinical verification of endpoints renders the data subject to recall bias, inaccuracy, and influence by such socioeconomic-related factors as education and access to medical care [169]. Another source of statistical inconsistency relates to the general inadequacy of these studies with regard to the treatment of potential confounding variables, such as their omission, significant variation in the array of variables considered from paper to paper, and lack of standardization in their definition (e.g., criterion used to define SES). If, for example, ETS is not an actual risk factor for increased respiratory illness in school-age children, any number of variables alone or in combination could be responsible for statistically significant associations. These spurious results could be due to neglect of particular confounders or to residual effects of those undergoing consideration. Our analysis revealed several confounders in this set that were consistently associated with statistically significant RRs of respiratory illness, namely family health history (91% of the cases), subject's health history (73% of the cases),

heating and air conditioning (66% of the cases), as well as active smoking by the subject. Other potential confounders were of marginal significance (i.e., increased RRs in more than 50% of the cases), namely outdoor pollution (55%), residence location (55%), ethnicity (55%), and maternal smoking during pregnancy (53%). Even those variables that did *not* emerge as potential risk factors for respiratory illness in our analysis could have affected the outcome of these epidemiology studies, since the methodology used for the consideration of confounding variables is imprecise.

With the large amount of information now available on important attributes of the relevant studies, namely study size, exposure type and verification, endpoint verification, and number and categorization of potential confounding variables, it may be possible to determine the role played by selected characteristics, alone or in combination, on the outcome of a study. Finally, with the available information, it may be possible to grade the papers on the basis of combinations of characteristics and, thus, determine whether outcome and/or consistency of association is a function of study quality[3].

Conclusion

The meta-analytical studies listed in table 12 report statistically significant composite relative risks and, most of these [149–151, 153], conclude that ETS is causally related to respiratory illness in children, regardless of age. On the basis of our independent analysis, as well as examination of the meta-analytical studies of others, we conclude that there is insufficient evidence at this time to support such a claim of causation and that two of the Hill criteria [168], namely strength of association and consistency, are not satisfied. Most of the elevated RRs in both preschool children and school-age children are small and thus subject to distortion by confounders and other biases [195]. In fact, it has been suggested that in order for an elevated relative risk to be persuasive, the lower level of the 95% confidence interval should be either 2 or 3 [159, 196] and, in most cases, even the point estimate fails to achieve this level.

As demonstrated in our analysis and evident in the meta-analyses of others (table 12), the association between parental smoking and respiratory illness in school-

[3] The data upon which this study is based can be obtained for further analysis upon request from the sponsor of this study, Brown & Williamson Tobacco Corporation, Louisville, KY 40202 (USA).

age children fails the test of consistency when the usual accepted standard of statistical significance of individual relative risks is considered. As discussed previously, the estimated composite RR derived from meta-analyses is suspect, especially when it is weak. Whereas ETS exposure postpartum could explain the consistent elevated relative risk of respiratory illness in preschool children, there are other explanations for this association that are of equivalent plausibility, such as in utero effects of mater-

nal smoking, subject's health history, and fam history. Our analysis, as well as an examinat published meta-analytical studies, reveals a : deficiency in the treatment of confounders . biases that can explain the consistency of the d: school children and the not so consistent dat: children. As discussed previously, inadequate of confounding variables may also explain appa related associations attributed to ETS [1].

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