INTERNATIONAL EVIDENCE

ON

PASSIVE SMOKING AND

CHILDHOOD ASTHMA INDUCTION

(PROJECT IESAST)

PART II : RESULTS OF SELECTED META-ANALYSES

Peter N Lee
Barbara A Forey and
Katharine J Young

P N Lee Statistics and Computing Ltd
17 Cedar Road
Sutton
Surrey SM2 5DA
UK

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EXECUTIVE SUMMARY

Part I of this report describes how databases were set up containing over 1200 relative risks from 190 epidemiological case-control, prospective or cross-sectional studies, of prevalent or incident asthma in children. Part I gives details of how the relevant studies and the source papers were identified, the structure of the databases, the methods used for entry and checking of data and derivation of relative risks, as well as summary information about the characteristics of the studies and relative risks themselves. Part I ends by describing techniques for conducting meta-analyses and the format of the tables presenting the results.

This part of the report, Part II, presents results of a series of meta-analyses of the database aimed at giving insight into how the relative risk of asthma varies by the source, timing and amount of the exposure to parental smoking/ETS, the definition of the unexposed group, the definition of the asthma outcome, the sex and age of the child, the location, timing, size and type of study, the source of the information on exposure and diagnosis, and the extent of adjustment for confounding variables.

The main conclusions reached from the analyses are as follows:

There is an association between in life exposure to parental smoking and either lifetime or current asthma. As illustrated in the table below, which summarizes relative risks and 95% confidence limits from random-effects meta-analyses, the association is stronger in relation to maternal than paternal smoking and is not statistically significant where the mother does not smoke (exposure = father only, or household exposure but not mother).

Exposure	Lifetime asthma n	Lifetime asthma RR (95% CI)[a]	Current asthma n	Current asthma RR (95%CI)[a]
Total[b]	93	1.23 (1.17-1.28)	73	1.18 (1.11-1.26)
Parent[c]	64	1.26 (1.20-1.33)	40	1.18 (1.08-1.29)
Both parents	9	1.44 (1.22-1.70)	6	1.68 (1.23-2.28)
Mother/mother only[d]	44	1.31 (1.23-1.39)	27	1.23 (1.10-1.38)
Mother only	4	1.16 (0.80-1.67)	4	1.35 (1.01-1.79)
Father/father only[e]	31	1.16 (1.08-1.26)	21	1.00 (0.93-1.09)
Father only	6	1.11 (0.96-1.29)	4	1.11 (0.95-1.30)
Household exposure other than parents	3	1.32 (0.92-1.89)	6	1.49 (1.30-1.71)
Household exposure but not mother[f]	10	1.14 (1.00-1.30)	4	1.11 (0.95-1.30)

[a] Based on relative risks (RR) adjusted for covariates where adjusted data are available
[b] Preferring, in order, RR estimates for biochemical, total, household and parental exposure
[c] Preferring RR estimates for mother to those for father if estimates for any parent not available
[d] Preferring RR estimates for mother regardless of father to those for mother only
[e] Preferring RR estimates for father regardless of mother to those for father only
[f] Preferring RR estimates for father only where alternatives are available

There is evidence of a dose-response relationship. For those studies which provide relative risks by extent of exposure, typically in terms of number of cigarettes per day or number of persons in the household who smoke, estimates (relative to no exposure) are higher for the highest exposure than for the lowest. For lifetime asthma, random-effects estimates based on 16 pairs of relative risks were 1.48 (1.27-1.73) for high exposure and 1.12 (0.99-1.27) for low exposure. For current asthma, estimates are 1.34 (1.23-1.46) for high exposure and 1.12 (1.04-1.21) for low exposure.

Although many of the meta-analyses conducted show statistically significant heterogeneity between the individual relative risk estimates, associations seen for total, parental and maternal exposure are generally consistently seen in subsets of the data defined by a wide range of factors. A possible exception is that studies conducted in the Far East do not show evidence of an association. There is evidence in some of the analyses, but not all, that associations may be weaker in older than younger children, in studies where the child was the respondent for questions on either smoking habits or diagnosis of asthma, in studies where steps had been taken to exclude children who

smoked, and in cross-sectional and prospective studies rather than case-control studies. However, the prevailing impression is of a highly consistent association.

Analysis of the relative risks included in the meta-analyses do not show any particular indication of publication bias. However, there are quite a large number of studies that could have provided data suitable to be included in meta-analyses, but which had not done so, and a suggestion that significant associations in these incompletely reported studies are less frequently seen than in the studies included in the meta-analyses. These findings do not, however, suggest that publication bias is a major issue.

There is no clear evidence of confounding by a variety of non-smoking lifestyle factors, although a number of different approaches were used to investigate this. There also seems no reason to believe that the association had arisen because of misclassification of exposure or diagnosis, or due to unreported smoking by the child.

There is a highly significant ($p<0.001$) association of asthma with maternal smoking in pregnancy, with a random-effects estimate of 1.30 (1.16-1.45) based on 27 individual relative risks for lifetime or current asthma. Dose-response data are limited, but quite consistently show a significant increase at high dose but little or no increase at low dose.

Eight studies presented relative risks separating the individual associations with *in utero* and in life exposure. There is a significant increase in risk associated with *in utero* only exposure (1.53, 1.05-2.23, n = 7) and with both *in utero* and in life exposure (1.32, 1.18-1.49, n = 9) but not with in life only exposure (1.08, 0.99-1.18, n = 7), based on results with a preference for lifetime over current asthma and for mother rather than father as the source of in life exposure. Alternative preferences do not affect the conclusion that in life only exposure is not associated with an increase in risk. Indeed, with the exception of one small study, all relative risk estimates are very close to 1.00.

The overall data are consistent with some effect of parental smoking on risk of asthma in the child. However, the lack of a significant association with in life only exposure and with smoking by the father only (and more generally with smoking by other household members except the mother) argues against ETS exposure being responsible. The pattern of results fits in much better with a role of smoking in pregnancy, though the possibility of some effect of ETS cannot be excluded. The increased risk of asthma seen where the mother smokes postnatally can reasonably be attributed to the fact that many of these mothers would also have smoked in pregnancy. The tendency seen in some analyses for risk to be increased where the father smokes can also reasonably be attributed to the strong correlation between smoking by parents, so that children born to fathers who smoke would be more likely to have mothers who smoked postnatally and in pregnancy. Evidence related to ex-smoking is very limited and inconclusive.

Our meta-analyses have deliberately excluded studies of asthmatic children which relate specifically to asthma exacerbation. As such, one cannot make inferences regarding asthma exacerbation from the data presented. However, it should be noted that there are difficulties in interpreting all the evidence presented here strictly in terms of asthma induction, and indeed the number of studies that relate onset of asthma to previous in-life exposure of the child to smoking by parents (or other household members) is very limited.

Our conclusion that the available evidence does not clearly demonstrate any causal effect of ETS exposure, and suggests strongly that smoking in pregnancy is responsible for most, if not all, of the association seen between asthma and smoking by parents or household members, is consistent with the view expressed by Strachan and Cook (Strachan & Cook, 1998) that ETS is not "a cause of the underlying asthmatic tendency", but not with the conclusion of the California EPA report (National Cancer Institute, 1999) that ETS induces asthma.

This report includes a brief review of both the series of papers by Strachan and Cook (Cook & Strachan, 1997; Strachan & Cook, 1997; Strachan & Cook, 1998) and the

California EPA report. The California EPA report is particularly weak, basing its findings on a meta-analysis which is extremely poorly described and presented, and is based on relative risk estimates that are not derived on any sort of consistent basis, some of which are clearly inappropriate. Furthermore, that report draws conclusions on dose-response and effects of paternal smoking without formal assessment of the available evidence, and fails properly to separate out possible effects of *in utero* and in life exposure. The papers by Strachan and Cook are much better, but pay little attention to distinguishing effects of ETS and of maternal smoking in pregnancy, and claim an increased risk of asthma in relation to smoking only by the father based on data which do not support this claim.

Claims that ETS exposure induces asthma in children cannot be regarded as conclusively demonstrated by the available data. The evidence of an effect of smoking in pregnancy is stronger. More studies are needed which distinguish effects of smoking during pregnancy from effects of ETS exposure during the child's life, which estimate the risk of asthma associated with smoking by household members in the absence of smoking by the mother, and which restrict attention to ETS exposure prior to the onset of the asthma.

Acknowledgment

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Text Tables

Tables and Appendix Tables

See §2.3 and §2.6 for explanation of the terms in this list of Tables

	Outcome (asthma)	Dose	Exposure (source)	Exposure (time)	Non-exposure	Page (Table)	Page (Appendix Table)
A1	lifetime		total	general	most	T1	A1
A2	lifetime		total	general	least		A32
A3	current		total	general	most	T9	A42
A4	current		total	general	least		A70
A5	lifetime		parent	general	most	T17	A79
A6	lifetime		parent	general	least		A106
A7	current		parent	general	most	T25	A114
A8	current		parent	general	least		A138
A9	lifetime		total	recent	most		A145
A10	lifetime		total	recent	least		A155
A11	current		total	recent	most		A165
A12	current		total	recent	least		A174
A13	lifetime		parent	recent	most		A183
A14	lifetime		parent	recent	least		A191
A15	current		parent	recent	most		A199
A16	current		parent	recent	least		A206
A17	lifetime		total	earliest	most		A213
A18	lifetime		total	earliest	least		A223
A19	current		total	earliest	most		A233
A20	current		total	earliest	least		A242
A21	lifetime		parent	earliest	most		A251
A22	lifetime		parent	earliest	least		A259
A23	current		parent	earliest	most		A267
A24	current		parent	earliest	least		A274
A25	lifetime/ current		total	general	most	T33	A281
A26	lifetime/ current		parent	general	most	T41	A318
A27	current/ lifetime		total	general	most		A349
A28	current/ lifetime		parent	general	most		A362
A29	onset		total	general	most		A372
A30	onset		parent	general	most		A378
A31	lifetime-physician		total	general	most	T49	A384
A32	lifetime-physician		parent	general	most		A411
A33	current-physician		total	general	most	T57	A418
A34	current-physician		parent	general	most		A442
A35	lifetime age<10		total	general	most		A448
A36	lifetime age inc 10		total	general	most		A455
A37	lifetime age > 10		total	general	most		A463
A38	lifetime age<10		parent	general	most		A469
A39	lifetime age inc 10		parent	general	most		A475
A40	lifetime age > 10		parent	general	most		A482
A41	lifetime		both parents	general	most	T65	A487
A42	lifetime		both parents	general	least		A508
A43	current		both parents	general	most	T73	A513
A44	current		both parents	general	least		A535
A45	lifetime		mother/mother only	general	most	T80	A541
A46	lifetime		mother/mother only	general	least		A566
A47	current		mother/mother only	general	most	T88	A573
A48	current		mother/mother only	general	least		A597
A49	lifetime		mother only	general	most		A604
A50	lifetime		mother only	general	least		A609

	Outcome (asthma)	Dose	Exposure (source)	Exposure (time)	Non-exposure	Page (Table)	Page (Appendix Table)
A51	current		mother only	general	most		A614
A52	current		mother only	general	least		A620
A53	lifetime		father/father only	general	most	T96	A626
A54	lifetime		father/father only	general	least		A651
A55	current		father/father only	general	most	T104	A658
A56	current		father/father only	general	least		A680
A57	lifetime		father only	general	most		A686
A58	lifetime		father only	general	least		A691
A59	current		father only	general	most		A696
A60	current		father only	general	least		A702
A61	lifetime		Hh other than parent	general	most		A708
A62	lifetime		Hh other than parent	general	least		A713
A63	current		Hh other than parent	general	most		A718
A64	current		Hh other than parent	general	least		A724
A65	lifetime		not mother	general	most	T112	A730
A66	lifetime		not mother	general	least		A753
A67	current		not mother	general	most	T120	A759
A68	current		not mother	general	least		A781
A69	lifetime		total	discontinued	most	T128	A787
A70	current		total	discontinued	most	T136	A810
B1	lifetime	low	total	general	most	T144	B1
B2	lifetime	high	total	general	most	T146	B9
B3	current	low	total	general	most	T148	B17
B4	current	high	total	general	most	T150	B26
B5	lifetime/current	low	total	general	most	T152	B35
B6	lifetime/current	high	total	general	most	T154	B46
C1	lifetime/current		mother	in utero	most	T156	C1
C2	current/lifetime		mother	in utero	most		C24
C3	lifetime/current		motherETS/father	in utero	most		C31
D1	lifetime/current	low	total	in utero	most	T163	D1
D2	lifetime/current	high	total	in utero	most	T165	D9
E1	lifetime/current		mother	in utero only	in life:total	T167	E1
E2	lifetime/current		total	in life only	in life:total	T169	E10
E3	lifetime/current		total	in life and in utero	in life:total	T171	E19
E4	lifetime/current		mother	in utero only	in life:total (father)		E28
E5	lifetime/current		total (father)	in life only	in life:total (father)		E34
E6	lifetime/current		total (father)	in life and in utero	in life:total (father)		E40
E7	current/lifetime		mother	in utero only	in life:total		E46
E8	current/lifetime		total	in life only	in life:total		E52
E9	current/lifetime		total	in life and in utero	in life:total		E58

Hh = household member

1. Introduction

The objective of the IESAST project is to collect and summarize published epidemiological evidence relating parental smoking and ETS exposure to childhood asthma induction, with a view to assessing how the strength of the association varies by the index of exposure to passive smoking considered and by the characteristics of the study reporting the findings. The analyses are conducted with the principal aim of determining whether or not parental smoking and ETS exposure can lead to the induction of asthma in children.

Part I of this report describes how the studies were identified, how databases were set up to allow entry of relevant study details and of relative risks relating to defined passive smoking characteristics, the structure of the databases, and how data were entered and checked. It also summarizes characteristics of the 190 studies for which data have been included, and of the over 1200 relative risks recorded. Part I also gives details of the techniques used to carry out meta-analyses, including the method of selecting the relative risks and the method of combining them, and describes the content of typical output.

This part of the report, Part II, presents and discusses results of selected meta-analyses, showing how the relative risk of asthma varies by the source of the exposure (total ETS exposure, from household members or parents smoking, or as measured biochemically), the timing of the exposure (ever, current, at a specific age, *in utero*), the amount of the exposure, the definition of the asthma outcome (lifetime or current; physician diagnosed or not), the sex and age of the child, the location of the study, the timing of the study, the type of the study (case-control, prospective or cross-sectional), the size of the study, the source of the information on exposure and diagnosis, the extent of adjustment for confounding variables and the exact definition of the numerator and denominator of the relative risk. The intent is to give the reader a good idea of the amount of data available on the various topics and insight into the magnitude and variability of the relative risks.

After §2*, which describes the methods used in this report, §3 and §4 summarize results of meta-analyses conducted in relation to ETS exposure in the child's lifetime, irrespective of *in utero* exposure. §3 concerns exposed/unexposed analyses (according to various definitions of exposure and asthma), while §4 relates to dose-response analyses by extent of exposure. §5 and §6 similarly summarize exposed/unexposed and dose-response analyses relating to *in utero* exposure, irrespective of in life exposure. §7 summarizes the results of analyses relating to the joint effects of *in utero* and in life exposure. §8 discusses the overall findings, and in particular the inferences that can be drawn from the data presented regarding the role of ETS in childhood asthma induction, before conclusions are drawn in §9.

*Note that, in this report, sections of text are indicated by the symbol §. The word 'section' is used to describe sections of output from the meta-analyses (see §2.1).

2. Methods

2.1 Introduction

As described more fully in §4.3 in Part I of this report, each meta-analysis produces a cover page followed by eight sections of output, headed -1 to -8, respectively. The cover page describes the restrictions on the data included, the order of preference for selecting relative risks to be included and a short description of the contents of the table. Sections -1 to -3 relate to 'adjusted' data (i.e. using relative risks adjusted for covariates where available and relative risks unadjusted for covariates otherwise), while sections -4 to -6 relate to 'unadjusted' data (using unadjusted relative risks where available and adjusted relative risks otherwise). Within each of these sets of three tables, the first two (-1, -2 and -4, -5) give details relating to the individual relative risks considered in the meta-analysis, while the third (-3 and -6) give the meta-analysis results. Sections -7 and -8 give additional information related to studies excluded from the meta-analysis.

The tables relate to five broad types of meta-analysis, as follows:

A. Exposure in the child's lifetime (irrespective of *in utero* exposure)
B. Amount of exposure in life
C. Exposure *in utero* (irrespective of in life exposure)
D. Amount of exposure *in utero*
E. Joint effects of *in utero* and in life exposure

Results from tables A, B, C, D and E are discussed, respectively, in §3, §4, §5, §6 and §7 of the present report.

Within each broad type, there are a variable number of meta-analyses, as discussed in §2.3 below and more fully in the section of this report summarizing their results. Thus, for example, Table A3 and Appendix Table A3 give results for the third set of meta-analyses for exposure in life, here relating to current asthma for whole-life exposure.

Note that the full output, including all of section-1 to section-8 for each set of meta-analyses, is presented in Appendix Tables A to E. Reduced output, which, for a selected subset of 'key' meta-analyses, usually only includes the cover page and shortened versions of sections –3 and –6 giving the meta-analysis results, is given in Tables A to E. Thus the reader who wishes only to see the 'key' meta-analysis estimates need refer only to the Tables, but the more interested reader who wishes to see full details of the individual relative risks contributing to the estimates should refer to the corresponding Appendix Tables. The two sets of output always correspond directly; thus for example both Table B2 and Appendix Table B2 give results for high amount of exposure for lifetime asthma. As only key analyses are included in the Tables, the numbering of the Tables is not continuous.

In the following sections of the methods section, some general restrictions to the analyses are noted first (in §2.2), followed by a description of the various ways outcome and exposure are defined (§2.3) and of the various other factors considered in the analysis (§2.4). Further sections then describe the format of the output (§2.5) and how meta-analyses by amount of exposure (§2.6) and by age (§2.7) are conducted. Finally (in §2.8), an explanation is given as to certain rules used in presenting the findings in the results sections of this report.

2.2 General restrictions to the analyses

The analyses presented all satisfy the following conditions for selecting relative risks:

Results complete enough for use in meta-analysis Adjusted relative risks which lack a confidence interval are excluded from meta-analyses. Where a 2×2 table has a zero, the relative risk and confidence interval is calculated by adding 0.5 to each cell of the table. In practice, whether or not such data are included in

meta-analyses makes little difference to the results as a relative risk calculated with a 0.5 in one cell will have a large standard error and therefore little weight.

Follow-up period for whole study or longest available This applies only to prospective studies. Where case-control studies present both interim and final results, only the final results are included on the database anyway (except if the interim reports give results relating to comparisons not considered in the final report).

Race all or nearest available Results are chosen for the whole population (or nearest available). Otherwise results are chosen by separate racial group.

Principal rather than subsidiary studies See §3.3.3 of Part I for a discussion of the problem of overlapping studies and the definition of 'principal' and 'subsidiary' studies.

Age Whole study if available, otherwise by widest available age group.

Sex Single sex results rather than combined sex results.

2.3 Defining the outcome and the exposure

For each of the main sets of tables (A, B, C, D and E), there is considerable choice as to the outcome and the exposure when selecting the relative risks to be included in the meta-analysis.

Outcome 'Lifetime asthma' is present if, at the time of interest (time of interview for case-control or cross-sectional studies, or time of follow up for prospective studies) the child has ever had asthma, while 'current asthma' is present if the child is considered to be asthmatic at the time of interest. Assuming that children are not asthmatic at birth, lifetime asthma is equivalent to induction of asthma by the time of interest. The main outcomes considered for meta-

analysis are lifetime asthma and current asthma, and some meta-analyses are restricted to those studies which provide results specifically for the definition chosen. However since some, but not all, studies give results for both definitions, some meta-analyses are also carried out for lifetime asthma if available but for current asthma for those studies where lifetime is not available, this outcome being referred to as 'lifetime/current asthma'. Some meta-analyses are also carried out for 'current/lifetime asthma' which is similarly defined but in the opposite order. All studies are eligible to contribute to such an analysis, so these outcomes may be preferred when looking at aspects of exposure for which few studies provide results. Some meta-analyses are restricted to those studies where the definition of asthma required that it had been diagnosed by a physician (whether obtained from medical records or as reported by either the child or a parent). Some meta-analyses are restricted to those studies which carried out an analysis of the onset of asthma (rather than prevalence), but there are very few such studies. In order to address the question of whether risk may vary with age, some meta-analyses are restricted to results which refer to children aged under 10, to children in an age group which includes 10, and to children aged over 10. Studies which did not provide age-specific results would be eligible to enter only one of these meta-analyses at most, whereas studies which provided results for several age groups may appear in more than one.

Source of exposure to ETS The two main sources of ETS exposure meta-analysed are total exposure (or nearest available), and parental exposure. For total exposure, biochemically-assessed exposure is chosen if available from a study, otherwise questionnaire-assessed total exposure is chosen; failing that, results for any household exposure, any parental exposure, maternal exposure, or finally paternal exposure are accepted in that order of preference. For parental exposure, the order of preference is any parental exposure (i.e. mother and/or father smokes), maternal (i.e. mother smokes irrespective of father), maternal only (i.e. mother smokes but father does not), paternal and paternal only. In addition, some meta-analyses are carried out for specific sources of exposure such as both parents

smoke, mother (or father) only smokes (and the other parent does not), household member other than the parent smokes, or household member smokes but the mother does not (referred to as 'not mother').

Timing of exposure Exposure during the child's lifetime is considered here and in §3 and §4. However studies which gave results only in terms of the smoker's lifetime (e.g. whether the mother was an ever or never smoker, irrespective of whether any smoking coincided with the child's lifetime) are also considered, as are studies of exposure at the time of birth. Exposure *in utero* will be considered separately later in §5 and §6, as will joint assessment of exposure *in utero* and/or in life in §7. Usually the exposure chosen for meta-analysis is that referring to exposure during the child's whole lifetime, or the nearest available. This is chosen from those available from each study in the following order of preference: in life (i.e. since birth); ever (i.e. in the life of the smoker); unspecified; in life and/or in utero (i.e. since conception); at a specific age (including at baseline for prospective studies); current, and is referred to as 'general' exposure[i]. Meta-analyses are also carried out using alternative orders of preference favouring the most recent exposure available, or the exposure earliest in the child's life. In addition, separate meta-analyses are carried out for exposure which has discontinued (e.g. when the mother is an ex-smoker).

Definition of the unexposed comparison group For many meta-analyses, the unexposed group chosen is that which is as near as possible to the reciprocal of the exposed group, both in terms of the source of exposure and the timing of exposure. (This is referred to as the 'most' unexposed, both because the most subjects are eligible for inclusion and because they have the most exposure.) Alternative meta-analyses are also carried out choosing the least exposed comparison group. Thus if, for instance, in a meta-analysis of maternal smoking, a study has three relative risks for current exposure, where the comparison group is

[i] Smoking "ever but not during pregnancy" was also mistakenly included here rather than in §7, but there was only one such RR which was not complete enough for meta-analysis

‘mother not current smoker’, ‘mother not smoked since child’s birth’ or ‘neither parent smoked since child’s birth’ respectively, then for the ‘most’ unexposed analysis the result comparing with ‘mother not current smoker’ would be chosen, while in the ‘least’ unexposed analysis, the result comparing with ‘neither parent smoked since child’s birth’ would be chosen.

Clearly if meta-analyses were conducted for all possible combinations of the four aspects considered in the previous paragraphs, the number of such analyses would be enormous. Consequently, most attention has been given to certain key analyses (described more fully in §3), with full output produced for them. Other analyses involve variation in the definitions from the key analyses, and produce a more limited output, which includes examination of the number of studies for which the change in the definition of the analysis actually changed the relative risks included. The number of relative risks which actually differ between a key analysis and a variant analysis is generally quite small, or even zero, because many studies do not offer relative risks for any alternative definitions of exposure/non-exposure. The number of relative risks differing will also tend to be smaller when the key analysis used a wide ranging definition of exposure than when it uses a narrow one. For instance, if a key meta-analysis refers to total exposure with ‘most’ non-exposure, then for any study which looked at various sources of exposure, the widest will be included; it follows that the ‘most’ non-exposed comparison group will almost certainly be the only one available. Therefore when a variant meta-analysis is run by choosing the ‘least unexposed’ comparison group, this is likely to choose exactly the same relative risks. On the other hand, if the key meta-analysis refers to maternal smoking and ‘most’ non-exposure, then it is much more likely that, within some studies, there will be a choice of relative risks with different comparison groups (e.g. mother does not smoke, neither parent smokes, no smoker in household); thus the variant meta-analysis with ‘least unexposed’ comparison group is likely to have a larger number of studies where a different relative risk is included when compared with the key meta-analysis.

2.4 Factors considered

The meta-analyses first give overall results for all the relative risks selected. Then results of an analysis of risk by the factor **sex** are shown with estimates shown, and compared, for combined sex results and those specifically for males and females. Depending on the particular exposure being considered, further analyses may show results for the following factors:

Continent

The levels are: NAmer (= North America); SCAmer (= South or Central America); Europe; Asia; Auslia (= Australasia); and Africa.

Country in Europe

The levels are: UK; Italy; Germany; Scand (= Scandinavia); othWest (= other West European countries: France, Ireland, Netherlands, Spain and Switzerland); and East/Bal (= East European and Balkan countries: Poland, Russia and Turkey).

Country in Asia

The levels are: Far East (= China, Japan, Hong Kong, Taiwan and Korea); Cent/SE (= Central and SE: Malaysia, India, Nepal and Sri Lanka); and MidlEast (= Middle East: Israel, Saudi Arabia and UAE).

Start year of study

The levels are: <1970; 1970-79; 1980-89;1990+; and unknown.

Publication year

The levels are: <1990; 1990-94; 1995-99; and 2000+. This refers to the principal publication for the study.

Study type

The levels are: CC (= Case-control); Pr (= Prospective); and CS (= Cross-sectional). The allocation of certain studies to these three types has been discussed in §3.3.4 of Part I.

Highest age in RR

The levels are: 0-9; 10-14; 15+; and unknown.

Population / setting

The levels are: general (= studies covering all children or randomly selected children in an area, or household surveys); school (= studies of school pupils); medical (= studies carried out in a medical setting, including school health checks, and new-borns recruited at maternity facilities); allergy (= studies of children with a family history of asthma or allergic conditions); and other (= school athletes, children living on farms, twins, travellers, children at high risk of SIDS, and unspecified).

Respondent for smoking

The levels are: child (= questionnaire completed by the child); parent (= questionnaire completed by a parent); med rec (= data extracted from medical records); and mix/oth (= a mixture of sources, or other household member).

Child smokers

This refers to how the study treated smoking by the child in its analysis. The levels are exc/none (= those studies where smokers were specifically excluded from analysis, having been identified either biochemically or by questionnaire, those studies which looked for smokers but found there were none, and those studies which explicitly assumed there were no smokers due to the young age of the subjects); included (= those studies where smokers were known to exist and were included in analysis, including studies which adjusted for, or tested for, effects of child's smoking in the analysis); and ignored (= studies which did not

mention the possibility of smoking by the children, often because they were conducted in young children, and those studies which mentioned the possibility but took no action).

Physician diagnosis

The levels are: yes (= diagnosis by physician); and no/mixed (= self-diagnosis, definition based on a list of reported symptoms, or physician-diagnosis plus self-report of symptoms).

Respondent for diagnosis

The levels are: medrec (= diagnosis extracted from medical records or made by the physician conducting the survey); parent (= from a questionnaire completed by the parent); child (= from a questionnaire completed by the child); and mixed (= a mixture of sources or unspecified).

Questionnaire for symptoms

The levels are: ISAAC (= International Study of Asthma and Allergies in Childhood); ATS (= American Thoracic Society); and other.

Analysis type

The levels are: prevlence (= prevalence); and onset.

Number of cases

This refers to the number of asthma cases (lifetime or current as relevant to the meta-analysis) in the whole study, rather than in the specific relative risk. The levels are : 1-50; 51-100; 101-200; 201+; and unknown.

Study adjustment

A number of factors refer to whether any of the relative risks on the data base were adjusted for certain potential confounders, although the specific relative risk included in a meta-analysis may not have been adjusted for that confounder. In

each case the levels are yes; and no. The confounders considered are: sex; age; race; location; SES (= socioeconomic status); family medical history; family composition (e.g. number of siblings, single parent); cooking, heating or air conditioning (including type of fuel, use of dehumidifiers or mosquito coils); housing quality, crowding, damp, mould; pets, animal contact or farming; child's medical history (including breastfeeding, nutrition and allergy skin-prick tests); ETS exposure *in utero*; and ETS exposure in lifetime. For the first five of these confounders considered, matching in the study design (for case-control studies only) was considered equivalent to adjustment for confounding.

Source of ETS exposure

Depending on the specific meta-analysis, the levels may include: Biochem (= biochemically assessed exposure); TotETS (= questionnaire-based total ETS exposure); AnyHh (= exposure from any household member); AnyPar (= exposure from mother and/or father); Mother (= exposure from mother irrespective of father); MothOnly (= exposure from the mother but not the father); Father; FathOnly; Other; OthrOnly (defined similarly to Mother and MothOnly but relating to the father or to household members other than the parents); Grandpar (= exposure from grandparents or grandfather); and Sibling (= exposure from siblings).

Timing of exposure

For exposure during the child's life, the levels are: lif/ev (= exposure in child's life, ever in smoker's life, or in life and/or *in utero*); age<7y (= at a specific age which is wholly below age 7); current; unspec (= unspecified); and other (= other specific ages or not applicable, e.g. for biochemically assessed exposure). For discontinued exposure the levels are: Ex (= ever in smoker's life but not current); and LifeNotC (= exposure in child's life but not current).

Unexposed group: who is smoker

The levels may include: NoHhMemb (= no household member smokes); NoParent (= neither parent smokes); NotSpPar (= specified parent does not smoke); and NotSpHhM (= specified household member does not smoke).

Unexposed group: time

The levels are: non (= not at the time specified by time of exposure); never (= never smoked in smoker's life); non+other (= not at the time specified by time of exposure and not at some additional time); and NA (= not applicable i.e. for biochemical exposure).

Measure of exposure

For analyses of high or low exposure, the levels are: cigs (= number of cigarettes exposed to or smoked by smoker); persn (= number of persons smoking in household); other (= minutes per day or occasional/several hours per day).

Number of adjustment variables

This refers the adjustment variables used in the specific relative risk included in the meta-analysis. The levels are: 0; 1; 2; 3-5; 6-9; and 10+.

Relative risk adjustment

This refers to the adjustment variables used in the specific relative risk included in the meta-analysis, rather than in the study as a whole, as above. The variables considered, each with levels yes or no, are: sex, age, other ETS (i.e. other than the specific exposure to which the relative risk refers); any other variables.

Derivation of RR/CI

The levels are: Original; Numbers (= calculated from the 2×2 table, adjusted calculation from a 2×2×n table, or recalculation due to a discrepancy between a 2×2 table and an original RR/CI); SumNumbs (= calculation from 2×2 table after

combining categories); and other (= other methods, as described in §3.4.3 of Part I).

2.5 Format of the meta-analysis output

§4.3 of Part I provides a detailed description of the output, including the meta-analyses shown in sections –3 (adjusted data) and –6 (unadjusted data). An example output is presented in Appendix G of Part I.

2.6 Meta-analysis of results by amount of exposure

Results by amount of exposure generally take the form of a relative risk for each of a set of categories (e.g. mother smokes 1-10, 11-20 etc cigarettes) compared with a common base group, e.g. mother non smoker. These are not independent.

The approach adopted in this report is to use only the first and last from each set of categories, then to carry out a standard meta-analysis for each level. Effectively only one relative risk is chosen from each study for each level (or from each sex × age × race stratum), thus ensuring independent results for a valid meta-analysis of 'low dose' and 'high dose' respectively. The sets of categories are included irrespective of the measure of exposure used, and for those studies which give results for more than one measure, they are chosen in the following order of preference: biochemical measures; number of cigarettes; number of persons smoking[ii]; time per day of exposure. Because the individual studies used different definitions for the categories, the range of values included in the 'low' and 'high' analyses may overlap. For instance, if one study used the categories 1-10 and 11+, while another used 1-29 and 30+, then exposure to 11-29 cigarettes would be included in the low category for one study, but in the high category for the other. However this approach ensures that the same studies are included in both of the low/high pair of analyses, and allows within-study comparisons to be

[ii] Results for the number of parents who smoke (i.e. none, one only, both) have not been analysed as dose-response – see analyses in §3.8.

made. Relatively few of the sets contained 3 or more categories (29/112 sets), so it was not practical to carry out any meta-analysis of 'medium dose'. More complex regression analyses modelling the dose response and allowing all the results to be retained are considered beyond the scope of this report.

2.7 Meta-analysis of results by age

Two approaches are adopted in this report. Firstly, as mentioned above, in the main meta-analyses, which include results for the whole study or the widest available age range for the exposure of interest, age is used as a factor.

The second approach is to define a set of age groups, and to carry out standard meta-analyses of the relative risks relevant to each age group separately. Although this is to some extent similar to the approach taken for results by amount smoked, a fundamental difference is that results for different age groups are independent, and there is therefore no constraint to choose just one result per study for each analysis. Relative risks are only accepted for age ranges that fall completely within the age range specified. These may be either age-specific results from studies with a wide age range, or whole-study results from studies with narrow age criteria. The age groups studied are <10; including 10; and >10 years.

2.8 Presentation of findings in the results sections of this report

In most of the text of this report we refer to the output as being in e.g. Table A6 even where, in the case of meta-analyses which are not selected as 'key', results can only be found in Appendix Table A6.

Relative risks and 95% confidence intervals are typically referred to simply as e.g. 1.23 (1.18-1.28), where it is obvious in the text that these are what are referred to. On occasion, the abbreviations RR and CI are used. The standard notation may be extended to e.g. 1.23 (1.18-1.28, n=32) or 1.17 (1.10-1.25, $p<0.001$) to indicate the number of relative risk estimates on which a meta-

analysis estimate is based or the level of significance. Unless otherwise stated, it should be assumed that meta-analysis relative risk estimates are fixed-effects, and that they are calculated using individual estimates that are adjusted for covariates where there is a choice of unadjusted and adjusted estimates.

3. Risk from exposure in the child's lifetime (irrespective of *in utero* exposure)

3.1 Table A (and Appendix Table A)

All analyses considered in §3, Appendix Table A (which gives the full meta-analyses results) and Table A (which gives the reduced results) have the restriction, in addition to those already defined in §2.2, that the relative risks are selected for exposure in the child's lifetime if available, otherwise for ever smoking by a parent or household member and rarely, where no other exposure period is available, for exposure in life and/or *in utero*. 'Ever smoking' by a parent or household member is irrespective of whether this coincided with the child's life. Exposure of timing unspecified in the source paper is also included. 'Exposure' may be defined as parents or household members smoking, irrespective of whether this is actually in the presence of the child.

Appendix Table A presents results for 70 meta-analyses, 18 of which are key analyses with fuller output than the other 52 variant analyses. Table A contains less detailed results for the 18 key analyses. The key analyses are as follows:

Text Table 3.1 – Key analyses for in life exposure

Table	Definition of asthma outcome	Source of ETS exposure	Time of ETS exposure	Definition of non exposure
A1	Lifetime	Total	General	Most
A3	Current	Total	General	Most
A5	Lifetime	Parent	General	Most
A7	Current	Parent	General	Most
A25	Lifetime/current	Total	General	Most
A26	Lifetime/current	Parent	General	Most
A31	Lifetime-physician	Total	General	Most
A33	Current-physician	Total	General	Most
A41	Lifetime	Both parents	General	Most
A43	Current	Both parents	General	Most
A45	Lifetime	Mother/mother only	General	Most
A47	Current	Mother/mother only	General	Most
A53	Lifetime	Father/father only	General	Most
A55	Current	Father/father only	General	Most
A65	Lifetime	Not mother	General	Most
A67	Current	Not mother	General	Most
A69	Lifetime	Total	Discontinued	Most
A70	Current	Total	Discontinued	Most

The terms ‘lifetime’, ‘current’, ‘lifetime/current’, ‘lifetime-physician’ and ‘current-physician’ are explained in §2.3 **Outcome**, as are the alternatives ‘current/lifetime’ and ‘onset’, used in the variant analyses.

The terms ‘total’, ‘parent’, ‘both parents’, ‘mother/mother only’, ‘father/father only’ and ‘not mother’ are explained in §2.3 **Source of exposure to ETS**, as are the alternatives ‘mother only’, ‘father only’, and ‘household member other than parent’ used in the variant analyses.

The terms ‘general’ and ‘discontinued’ are explained in §2.3 **Timing of exposure**, as are the alternatives ‘recent’ and ‘earliest’, used in the variant analyses.

The term ‘most’ is explained in §2.3 **Definition of the unexposed comparison group**, as is the alternative ‘least’, used in the variant analyses.

The precise numbering of the variant analyses will become apparent later in §3.

3.2 Table A1: Lifetime asthma/total exposure

Table A1 (and Appendix Table A1) present meta-analyses relating lifetime asthma to the nearest equivalent of total ETS exposure. As in all analyses in Table A, the results relate to exposure during the child’s lifetime (or nearest equivalent) and the relative risks relate to the exposed/unexposed comparison and are not concerned with the extent of the exposure.

There are a total of 93 relative risks included in the meta-analysis, of which 76 are >1.00, 30 are statistically significantly positive (i.e. lower 95% confidence limit >1.00) and one is statistically significantly negative. Overall, there is a highly significant ($p<0.001$) increased risk of lifetime asthma in relation to total exposure, with the relative risk 1.24 (95% CI 1.20-1.27) for the fixed-

effects analysis and 1.23 (1.17-1.28) for the random-effects analysis using analyses adjusted for covariates where possible and 1.25 (1.21-1.28) for the fixed-effects analysis and 1.24 (1.19-1.29) for the random-effects analysis using analysis unadjusted for covariates where possible. Egger's test showed no significant evidence of publication bias. In the following text we restrict attention to the adjusted analyses. The heterogeneity chisquared is 153.76 on 92 d.f. ($p<0.001$). The excess of the chisquared over the degrees of freedom is not obviously explained by any specific outlying study, the largest Q_s value being 10.04 in the KERSHA study which has a relative risk of 3.12 (1.76-5.54). The STANHO study with the statistically significant negative relative risk of 0.40 (0.16-0.97) has a Q_s of 6.24. The study with by far the largest weight is MCKEEV, which reports a relative risk of 1.31 (1.24-1.39) based on 3697 cases. Its weight, 1119, is more than five times larger than in any other study and is almost a quarter of the total weight of 4666.

Below variations in relative risk by various factors are considered:

Sex Remarkably, 82 of the 88 studies report results only for the sexes combined, where the relative risk is 1.24 (1.21-1.28). Although no significant increase is seen in the studies reporting results only for male children (1.14, 0.98-1.32) or female children (1.12, 0.94-1.33), these estimates do not in fact differ significantly from the estimate for sexes combined.

Location Relative risk estimates vary somewhat by continent ($p<0.05$) but are significantly above 1.00 for all continents except South/Central America where only two relatively small studies have been conducted. Within Asia there is also some variation ($p=0.01$), with relative risks significantly elevated in Central and South Eastern Asian studies and in Middle Eastern studies but not in the five Far Eastern studies (0.99, 0.87-1.14).

Timing Significantly increased relative risks, mostly between 1.2 to 1.3, are seen in all periods studied, whether classified by year of the start of the study or year of publication, with no evidence of heterogeneity.

Study type Of the 88 studies providing data, 14 are prospective, 12 case-control and 62 cross-sectional. Relative risk estimates do not vary significantly between the cross-sectional studies (1.21, 1.16-1.25), the prospective studies (1.27, 1.22-1.34) and the case-control studies (1.29, 1.10-1.51).

Age of children There is no evidence of heterogeneity when studies are classified according to the highest age considered.

Population setting There is some evidence of heterogeneity ($p<0.05$) according to the setting of the study. For the three types most commonly seen, relative risks are higher for medical setting studies (1.30, 1.24-1.37) than for school studies (1.19, 1.14-1.24), with general population studies (1.25, 1.15-1.35) intermediate, though they are significantly elevated in all of these settings.

Respondent for smoking There is highly significant evidence of heterogeneity here (χ^2_{het} = 18.71 on 3 d.f., $p<0.001$[iii]) due to the lack of association of lifetime asthma with total ETS exposure seen in the seven studies where the child was the respondent (0.99, 0.89-1.11). Where the respondent was the parent (1.24, 1.19-1.29), the data came from medical records (1.31, 1.24-1.38) or where it came from mixed or other sources (1.21, 1.13-1.30) a significant elevation of risk is clearly seen.

Child smokers There is significant evidence of heterogeneity ($p<0.01$), with the relative risk estimate lower where studies specifically did not include children who smoked (1.09, 1.01-1.19) than in those where smokers had been included

[iii] Referred to as Between Chi on the output

(1.29, 1.17-1.42) or where the question had been ignored (1.25, 1.21-1.29). A significantly increased relative risk is seen in all these categories.

Physician diagnosis There is no evidence of heterogeneity of the relative risk according to whether the diagnosis of asthma was or was not made by the physician.

Respondent for diagnosis There is highly significant evidence of heterogeneity here (χ^2_{het} = 16.59 on 3 d.f., p<0.001). As for respondent of smoking (see above) this is due to the lack of association seen where the child answered the questions concerning the diagnosis (1.02, 0.93-1.13). Where the parent answered the question (1.23, 1.19-1.28), the information was obtained from medical records (1.30, 1.23-1.37) or the information came from mixed sources (1.25, 1.14-1.37) a significant elevation in risk is seen. Note that though the parent or the child answered the question, the actual diagnosis may still have been made by a physician.

Questionnaire for symptoms There is no evidence of significant heterogeneity according to use of standard questionnaires to obtain details of symptoms.

Analysis type Relative risks are similar whether onset or prevalence analysis was used.

Size of study There is no overall heterogeneity by study size, with a significant elevation being seen in studies of 1-50, 51-100, 101-200 or 201+ cases of asthma, although there is some evidence of a decreasing trend (p<0.05)[iv] with RRs of 1.50, 1.41, 1.23 and 1.22 respectively.

[iv] Based on additional analysis (full details not shown) using trend coefficients of 1, 2, 3, 4

Adjustment for confounding variables There is little evidence of heterogeneity according to whether the study took into account specific factors as potential confounders, to whether the relative risk itself was adjusted for specific factors, or to the number of factors the relative risk was adjusted for. In general, relative risk estimates are in the range 1.2 to 1.3. The sole exception is that in those studies that adjusted for *in utero* exposure there is no evidence of an increase in risk (1.03, 0.88-1.19). The question of the relative importance of *in utero* and in life exposure is considered in more detail in §7.

Source of exposure Our definition of total exposure involves the following order of preference: 1. biochemical, 2. total, 3. any household member, 4. any/unspecified parent, 5. mother regardless of father, 6. mother only, 7. father regardless of mother and 8. father only. For the analysis treating source of exposure as a factor level, preferences 5 and 6 (mother) and preferences 7 and 8 (father) are combined. There is highly significant heterogeneity by source of exposure (χ^2_{het} = 20.86 on 5 d.f., $p<0.001$). For most of the 88 studies, the preferencing led to choice of any household member (38 studies), any parent (18 studies) or mother (25 studies) as the source of exposure, with biochemical data selected for only two studies, total ETS exposure selected for only four studies, and smoking by the father selected for only one study. Given the small number of studies where total exposure is defined based on these last three sources, the heterogeneity mainly arises because relative risk estimates are higher when the mother is the source (1.31, 1.25-1.36) than when any parent is (1.22, 1.12-1.33) or any household member is (1.15, 1.10-1.21). The relative risk estimate is also high when total ETS exposure is the source (1.71, 1.24-2.37) though this estimate has wider variability due to being based on only four relative risk estimates.

Time of exposure There is no evidence that risk varies according to time of exposure, risks being significantly elevated regardless of the category chosen by the preferencing. The most common categories are current exposure (1.27, 1.19-

1.35, n=29 relative risks), during child's lifetime or ever (1.24, 1.19-1.30, n=23) or unspecified time (1.19, 1.13-1.26, n=31).

Unexposed group – source of exposure There is significant heterogeneity (χ^2_{het} = 14.22 on 2 d.f., p<0.001) by the definition of the unexposed group, but this largely reflects the findings for 'source of exposure' given above. Thus the largest relative risk is for 'not the specified parent' (1.31, 1.25-1.36), based on exactly the same individual relative risks for mother reported above. For studies which reported results for mother smoking, the order of preferencing chosen for source of exposure and unexposed group in Table A1 always selected relative risks for mother vs 'not mother' smoking. For the study with data only on father smoking the only denominator available is for 'no parent'.

Unexposed group – time of exposure There is no evidence of significant heterogeneity by the definition of the unexposed time.

Note that additional analysis in §3 will investigate further and more completely the role of the definition of source of exposure, time of exposure, and the unexposed group. The results presented in Table A1 are incomplete in the sense that additional data are available for many of the levels considered there. For example, only two relative risks from one study are included for father smoking in Table A1 as in nearly all cases where data for father smoking are available, data for mother smoking, and possibly other indices of exposure higher up the preference list for total exposure, are chosen instead.

Derivation of RR (CI) There is no clear heterogeneity (χ^2_{het} = 6.19 on 3 d.f., p>0.1) according to whether the relative risk was available directly in the source publication (1.27, 1.21-1.34, n=29), had been calculated directly from numbers in the 2 × 2 table (1.22, 1.15-1.29, n=32), had been calculated by summing numbers over strata (1.10, 0.99-1.22, n=13) or more complex methods had been used (1.25, 1.19-1.30, n=19).

Overall, the main sources of heterogeneity appear to be the lack of association seen in Far Eastern studies (China, Japan, Hong Kong, Taiwan and Korea), the lack of association seen in studies where the child reported the data on smoking or asthma diagnosis, the lower relative risks seen in studies which specifically did not include children who smoked in the analysis, the lack of association seen in studies that adjusted for *in utero* exposure and the higher relative risks where the data related to smoking by the mother.

Alternative relative risks which would have been selected as higher preference except that they had incomplete results are available for nine studies. In three of these, the incomplete relative risk is non-significant, whereas the included relative risk is significant (ALFRA1, adjusted, RR = 1.01 with no CI; LISTER, any household exposure, not significant; RASANE, any parental exposure, not significant).

A further 18 studies provide only incomplete data (20 relative risks) – three >1.00 and significant; two >1.00 with significance not stated; one <1.00 with significance not stated; and the remaining 14 not significant. This is a slightly but non-significantly higher proportion of non-significant relative risks than in the included studies (at least 14/17 = 82% compared with 62/93 = 66%).

3.3. Table A3 : Current asthma/total exposure

Whereas Table A1 considers meta-analysis results for lifetime asthma, Table A3 considers results for current asthma, other preferences being identical. Here there are 73 relative risks included in the meta-analyses. These come from 14 studies which contributed to the meta-analyses in §3.2, together with 57 studies which did not provide data for lifetime asthma. Of the 73 relative risks, 48 are >1.00. 18 are statistically significantly positive (at $p<0.05$) and none are significantly negative. Overall there is a highly significant ($p<0.001$) increased risk of current asthma in relation to total exposure, with the relative risk 1.13 (1.10-1.16) for the fixed-effects analysis and 1.18 (1.11-1.26) for the random-

effects analysis using analyses adjusted for covariates where possible, and 1.10 (1.07-1.12) for the fixed-effects analysis and 1.20 (1.13-1.28) for the random-effects analysis using analyses unadjusted for covariates where possible. All estimates above are rather lower than the corresponding estimates for lifetime asthma (see §3.2). Again we restrict attention below to the adjusted analyses. There is no evidence of publication bias from Egger's test. The heterogeneity chisquared is 177.00 on 72 d.f. ($p<0.001$), a somewhat greater chisquared per d.f., 2.5, than seen in Table A1. The studies contributing most to the heterogeneity are LEE1 which has a Q_s of 14.90 based on a relative risk of 1.37 (1.24-1.51) and DOTTER which has a Q_s for the sexes combined of 10.53 based on relative risk estimates of 0.50 (0.30-1.00) for males and 0.50 (0.20-1.10) for females. The study with by far the largest weight is WANG which reports a relative risk of 1.08 (1.05-1.12). Its weight is 3689 of a total of 6396, or 58% of the total.

Interpretation of the analyses studying variation in risk by level of the various factors is complicated by the large weight given to the WANG study, so that risk estimates always tend to be low for any factor level that includes this study. However, bearing in mind these reservations, there seems to be evidence that the relative risk:

(a) varies markedly between region of Asia, being highest in those in the Central/South East region and lowest in the Far Eastern studies;

(b) is not elevated in studies starting early (1970-79) or published early (<1990);

(c) is higher in case-control studies than in prospective or cross-sectional studies;

(d) is higher the younger the child;

(e) is higher in those studies which had ignored the question of the child smoking;

(f) is lower if the child reported the asthma diagnosis than if the parent did or the diagnosis came directly from medical records;

(g) is higher if the study adjusted for aspects of the child's medical history;

(h) is higher if exposure was current than if the exposure was 'life/ever'; and

(i) is higher if relative risk was adjusted for other sources of ETS exposure.

These comparisons are all evident whether fixed- or random-effects relative risk estimates are compared. There are a number of other statistically significant sources of heterogeneity indicated in Table A3 but these are not seen in the random-effects analysis and are considered less reliable.

Incomplete relative risks of higher preference are available for 7 studies. In one study (ADDOYO, adjusted) the incomplete relative risk is non-significant, whereas that included is significant. In two studies (PALMIE, adjusted; STRACH, exposure as newborn), the opposite is true.

A further 11 studies provide only incomplete data – one significant but relative risk not stated; one >1.00 and one <1.00, both not significant; and the remaining eight not significant. This is a higher proportion of non-significant relative risks than in the included studies (10/11 = 91% compared with 55/73 = 75%).

3.4 Table A5 : Lifetime asthma/parent exposure

Table A5 is similar to Table A1 except that the definition of exposure changes from 'total' to 'parent'. Thus studies which have results available only for biochemical exposure, total ETS exposure or overall household ETS exposure are excluded, while for studies which have both those exposures and parental exposure, the parental exposure is now selected for the meta-analysis. Overall, there are 64 relative risks available, 48 of which are identical to those in Table A1. Among the studies for which a different relative risk is now selected, there is a change in the significance of the relative risk in only two (where the parental relative risk is significantly >1.00 while the total relative risk is not), and no consistent direction of change among the others. The overall relative risk adjusted for covariates is 1.28 (1.23-1.32) for the fixed-effects analysis and 1.26

(1.20-1.33) for the random-effects analysis (both p<0.001). Relative risks unadjusted for covariates are virtually identical. There is no significant evidence of publication bias. The fixed- and random-effects estimates are quite similar, because there is much less evidence of heterogeneity, the heterogeneity chisquared of 92.02 on 63 d.f. being significant only at p<0.01. Only three factors show significance on a heterogeneity analysis.

(i) Relative risks vary by country in Asia, being lower in Far East studies (1.04, 0.86-1.26, n=4) than for Middle East studies (1.36, 1.18-1.57, n=6), there being only one Central/South East study with relevant data.

(ii) Relative risks vary by the exposed group, being highest for the mother (1.30, 1.25-1.35, n=39), intermediate for any parent (1.22, 1.12-1.31, n=21) and lowest for father (1.00, 0.83-1.20, n=4).

(iii) Relative risks also vary quite similarly for the unexposed group, being highest for not specified parent (1.30, 1.25-1.35, n=39), intermediate for no parent (1.21, 1.12-1.30, n=22) and lowest for no household member (0.97, 0.76-1.24, n=3). This analysis is strongly correlated with the previous one.

As discussed previously, results presented here by source of exposure are limited as exposure by the mother or father is only chosen when exposures higher on the preference list are not available.

13 studies provide only incomplete relative risks – four significant and 9 not significant.

3.5 Table A7: Current asthma/parent exposure

This analysis varies from Table A1 in both definition of asthma and of exposure. Here there are 40 relative risks available. Overall the increase in risk of current asthma in relation to parent exposure is highly significant (p<0.001), being estimated as 1.19 (1.12-1.26) for the fixed-effects analysis and 1.18 (1.08-1.29) for the random-effects analysis using relative risk estimates adjusted for

covariates where possible, and somewhat higher, at 1.25 (1.19-1.32), for the fixed-effects analysis and 1.23 (1.13-1.34) for the random-effects analysis using relative risk estimates unadjusted for covariates where possible. There is no significant evidence of publication bias. There is some evidence of heterogeneity ($p<0.01$) with the chisquared 71.20 on 39 d.f. Looking at specific factors one can observe:

(i) a lack of association in studies starting or publishing early;

(ii) a stronger association in younger children;

(iii) a lack of association if the child reported the diagnosis;

(iv) a stronger association in studies adjusting for in life ETS exposure; and

(v) a stronger association if exposure was current (or unspecified) than if exposure was 'life/ever'.

Generally, these factors seem quite similar to those noted in Table A3 (Current asthma/total exposure).

A further nine studies provide only incomplete data – one <1.00 with significance not stated, and the remainder all not significant.

3.6 Variants on Tables A1, A3, A5 and A7 by definition of exposure time and of non-exposure: Tables A1 to A24

Below we summarize some relevant results (for covariate adjusted analyses) from Appendix Tables A1 to A24. These look at how variations in the definitions of exposure time and of non-exposure affect the findings.

Text Table 3.2 – Variant analyses by exposure time

Table	Exposure time	Non-exposure	Number of estimates	Fixed-effects RR (95% CI)	Heterogeneity Chisq. per df
Outcome: lifetime; exposure: total					
A1[k]	General	Most	93	1.24 (1.20-1.27)	1.67***
A2	General	Least	93	1.24 (1.20-1.27)	1.67***
A9	Recent	Most	93	1.24 (1.20-1.27)	1.56***
A10	Recent	Least	93	1.25 (1.21-1.28)	1.61***
A17	Earliest	Most	93	1.23 (1.20-1.27)	1.63***
A18	Earliest	Least	93	1.23 (1.20-1.27)	1.63***
Outcome: lifetime; exposure: parent					
A5[k]	General	Most	64	1.27 (1.23-1.32)	1.46**
A6	General	Least	64	1.27 (1.23-1.32)	1.42*
A13	Recent	Most	64	1.27 (1.22-1.31)	1.41*
A14	Recent	Least	64	1.28 (1.24-1.33)	1.42*
A21	Earliest	Most	64	1.27 (1.23-1.31)	1.40*
A22	Earliest	Least	64	1.27 (1.23-1.32)	1.36*
Outcome: current; exposure: total					
A3[k]	General	Most	73	1.13 (1.10-1.16)	2.46***
A4	General	Least	73	1.13 (1.10-1.16)	2.46***
A11	Recent	Most	73	1.13 (1.10-1.15)	2.62***
A12	Recent	Least	73	1.12 (1.10-1.15)	2.65***
A19	Earliest	Most	73	1.13 (1.10-1.16)	2.46***
A20	Earliest	Least	73	1.13 (1.10-1.16)	2.46***
Outcome: current; exposure: parent					
A7[k]	General	Most	40	1.19 (1.12-1.26)	1.83**
A8	General	Least	40	1.19 (1.12-1.26)	1.83**
A15	Recent	Most	40	1.22 (1.15-1.29)	1.53*
A16	Recent	Least	40	1.22 (1.14-1.29)	1.59*
A23	Earliest	Most	40	1.19 (1.12-1.26)	1.83**
A24	Earliest	Least	40	1.19 (1.12-1.26)	1.83**

Notes : Fixed effects relative risks (RR) are adjusted for covariates where adjusted data are available.
Significance of heterogeneity: *** $p<0.001$, ** $p<0.01$, * $p<0.05$, (*) $p<0.1$, NS $p\geq0.1$.
Table: Except for tables marked with a k (key), further results are only shown in the Appendix Tables.

Given the outcome, the exposure and the exposure time, it can be seen (by comparison of successive pairs of results) that whether or not non-exposure is based on a preference for the most exposed group (both in terms of the source and of the timing of exposure – see §2.3) or for the least exposed group, makes little or no difference to the findings. This is unsurprising because for many studies there is actually no available choice of a different most and least exposed relative risk.

Given the outcome, the exposure and the definition of non-exposure, it also makes not a great deal of difference whether one uses the 'general' definition of exposure, or chooses the available relative risk which relates to the most recent or the earliest exposure in the child's life. The only noticeable difference is for recent vs general (or earliest) for current asthma and parental exposure. Here, of the 40 relative risks in analyses A7 and A15, only five differ between the two analyses. These are as follows:

Text Table 3.3 – Variant RRs for recent exposure

Study	A7 general		A15 most recent	
CHEN2	ever/never	1.11 (0.67-1.83)	current/non	1.02 (0.55-1.90)
GOLD	ever/never	0.99 (0.83-1.18)	current/non	1.10 (0.92-1.31)
HJERN1	ever/never	0.72 (0.52-1.01)	current/non	0.87 (0.58-1.30)
HJERN2	ever/never	0.94 (0.62-1.43)	current/non	0.81 (0.45-1.47)
TARIQ	in life/non	0.89 (0.57-1.40)	current/non	1.20 (0.30-2.70)

The main contributor to the slightly higher estimate of 1.22 (1.15-1.29) in Table A15 compared to 1.19 (1.12-1.26) is the GOLD study, which has by far the largest weight.

Generally, however, the data do not provide any reliable indication that the exact definition of time of exposure makes any difference to the relative risk obtained.

3.7 Other definitions of asthma outcome: Tables A25 to A40

Tables A1, A3, A5 and A7 present results of analyses with asthma outcome = lifetime or current and ETS exposure source = total or parent. In all these analyses, the exposure time was defined as 'general' and the non-exposure as 'most' exposed. Tables A25 to A40 are variants of these analyses, involving alternative definitions of the asthma outcome. Below results of these analyses are summarized, with results of the earlier analyses repeated for convenience.

Text Table 3.4 – Variant analyses by outcome

Table	Asthma outcome	No. of estimates	Fixed-effects RR (95% CI)	Random-effects RR (95% CI)	Heterogeneity chisq per df
Exposure : total					
A1[k]	Lifetime	93	1.24 (1.20-1.27)	1.23 (1.17-1.28)	1.67***
A3[k]	Current	73	1.13 (1.10-1.16)	1.18 (1.11-1.26)	2.46***
A25[k]	Lifetime/current	152	1.18 (1.15-1.20)	1.22 (1.17-1.27)	2.18***
A27	Current/lifetime	152	1.17 (1.15-1.19)	1.22 (1.17-1.27)	2.16***
A29	Onset	15	1.27 (1.20-1.33)	1.21 (1.11-1.32)	1.26NS
A31[k]	Lifetime-physician	53	1.22 (1.18-1.27)	1.20 (1.14-1.27)	1.69**
A33[k]	Current-physician	29	1.17 (1.07-1.27)	1.19 (1.05-1.35)	1.77**
A35	Lifetime, age <10	22	1.29 (1.23-1.36)	1.30 (1.18-1.44)	2.02**
A36	Lifetime, age inc 10	62	1.25 (1.21-1.29)	1.23 (1.17-1.29)	1.34*
A37	Lifetime, age >10	12	1.12 (1.03-1.23)	1.19 (1.00-1.42)	2.79**
Exposure : parent					
A5[k]	Lifetime	64	1.27 (1.23-1.32)	1.26 (1.20-1.33)	1.46**
A7[k]	Current	40	1.19 (1.12-1.26)	1.18 (1.08-1.29)	1.83**
A26[k]	Lifetime/current	95	1.26 (1.22-1.30)	1.25 (1.19-1.31)	1.54***
A28	Current/lifetime	95	1.25 (1.22-1.29)	1.24 (1.19-1.30)	1.58***
A30	Onset	13	1.26 (1.20-1.33)	1.20 (1.07-1.33)	1.47NS
A32	Lifetime-physician	34	1.28 (1.22-1.34)	1.26 (1.16-1.36)	1.58*
A34	Current-physician	16	1.19 (1.04-1.35)	1.23 (0.98-1.53)	2.33**
A38	Lifetime, age <10	15	1.32 (1.25-1.40)	1.34 (1.19-1.51)	2.22**
A39	Lifetime, age inc 10	43	1.27 (1.22-1.32)	1.25 (1.18-1.32)	1.24NS
A40	Lifetime, age >10	7	1.34 (1.16-1.54)	1.30 (1.05-1.60)	2.00(*)

Notes : Fixed effects relative risks (RR) are adjusted for covariates where adjusted data are available.
Significance of heterogeneity: *** p<0.001, ** p<0.01, * p<0.05, (*) p<0.1, NS p≥0.1.
Table: Except for tables marked with a k (key), further results are only shown in the Appendix Tables.

In Tables A1 to A24 studies for which data are only available for current asthma are not included in analyses of lifetime asthma, and *vice versa*. Tables A25 to A28 are based on more studies by introducing a preferencing on asthma outcome. In 'lifetime/current' analyses, data for lifetime asthma are chosen if available and for current asthma if not, whereas in 'current/lifetime' analyses data for current asthma are preferred. As seen from the above table, given the studies with data for either current or lifetime asthma, it makes little difference which order of preference was used. Particularly in the random-effects analyses, meta-analysis relative risks tend to be intermediate between that of the lifetime and current analyses, and closer to that for the lifetime analysis, both in the exposure: total and exposure: parent analyses.

For Tables A25 and A26, analyses of heterogeneity are available. For Table A25, where there is a large excess of the heterogeneity chisquared, 329.1, over the degrees of freedom, 151, with two studies having very large weight (WANG 3689, MCKEEV 1119 of a total of 10688), there are a very large number of factors that showed significant ($p<0.05$) variation by level. These can be seen from Table A25 itself, but are not discussed further here. It should be noted that the WANG study, which has a relative risk of 1.08 (1.05-1.12), compared to an overall fixed-effects relative risk of 1.18 (1.15-1.20), has a Q_s of 26.26, so that factor levels including this estimate tend to have significantly lower relative risk estimates than factor levels that did not.

For Table A26, the excess of heterogeneity, 144.79, over the degrees of freedom, 94, is much smaller and there are no 'outlying' results (large Q_s) with very large weight. Here the most notable variations are in relation to:

(a) higher relative risks in Asia in Middle Eastern than in Far Eastern studies,

(b) low relative risks if the child reported the asthma diagnosis, and

(c) higher relative risks if exposure is from the mother rather than the father.

Tables A29 and A30 are based on those prospective studies which conducted analyses of onset of asthma and case-control studies of first occurrence of asthma. Here the number of relative risk estimates included is much lower (15 for total exposure and 13 for parent exposure), but highly significant ($p<0.001$) increases are seen in both Tables, with no significant evidence of heterogeneity. Of the 15 estimates for total exposure, 13 are >1.00, the highest being 1.98, with two significantly positive, the only estimates <1.00 being 0.99 and 0.96, leading to an overall estimate of 1.27 (1.20-1.33). Note that the total weight of 1545 is dominated by the results from the MCKEEV study (1.31, 1.24-1.39 with weight 1119).

Tables A31 to A34 are based on physician diagnosed asthma. Meta-analysis estimates are generally quite similar to those for the corresponding analysis with no restriction on physician diagnosis (e.g. Table A1 vs A31 or Table A7 vs A34). However, being based on less relative risk estimates, particularly for current asthma, the confidence limits are rather wider and are not clearly significant for Table A34 (exposure: parent, current asthma). Analyses of heterogeneity are presented in the Tables and are not discussed further here.

Tables A35 to A40 are based on lifetime asthma, with relative risks selected by the age of the child. In all the analyses significant associations of exposure with outcome are seen with some evidence of heterogeneity (though not always significant), as shown in the summary table above. For total exposure there is a tendency for relative risk estimates to be highest where the children studied are aged <10, intermediate where the age range spans 10, and lowest for age >10. This is true both for fixed-effects and random-effect estimates. For parent exposure, this pattern is not so clear, though it should be noted that there are only seven relative risk estimates available for children aged >10.

3.8 Other definitions of exposure source: Tables A41 to A69

In these analyses, the exposure source, previously total or parent in all previous analyses is varied. Results are presented for each combination of lifetime or current asthma times most or least non-exposure. There are thus four tables for each exposure source. Below the results are summarized for most non-exposure. Results for least non-exposure tended to be very similar and are not discussed further here.

Text Table 3.5 – Variant analyses by exposure source

Table	Exposure Source	No. of estimates	Fixed-effects RR (95% CI)	Random-effects RR (95% CI)	Heterogeneity chisq per df
Outcome: Lifetime asthma					
A1[k]	Total	93	1.24 (1.20-1.27)	1.23 (1.17-1.28)	1.67***
A5[k]	Parent	64	1.27 (1.23-1.32)	1.26 (1.20-1.33)	1.46**
A41[k]	Both parents	9	1.40 (1.24-1.58)	1.44 (1.22-1.70)	1.62NS
A45[k]	Mother/mother only	44	1.30 (1.25-1.35)	1.31 (1.23-1.39)	1.73**
A49	Mother only	4	1.24 (1.02-1.51)	1.16 (0.80-1.67)	2.93*
A53[k]	Father/father only	31	1.18 (1.13-1.23)	1.16 (1.08-1.26)	2.22***
A57	Father only	6	1.11 (0.96-1.29)	1.11 (0.96-1.29)	0.80NS
A61	Household exposure other than parents	3	1.31 (0.96-1.89)	1.32 (0.92-1.89)	1.12NS
A65[k]	Household exposure but not mother	10	1.14 (1.01-1.29)	1.14 (1.00-1.30)	1.10NS
Outcome: Current asthma					
A3[k]	Total	73	1.13 (1.10-1.16)	1.18 (1.11-1.26)	2.46***
A7[k]	Parent	40	1.19 (1.12-1.26)	1.18 (1.08-1.29)	1.83**
A43[k]	Both parents	6	1.41 (1.23-1.61)	1.68 (1.23-2.28)	3.02**
A47[k]	Mother/mother only	27	1.21 (1.14-1.28)	1.23 (1.10-1.38)	2.26***
A51	Mother only	4	1.32 (1.13-1.55)	1.35 (1.01-1.79)	2.31(*)
A55[k]	Father/father only	21	1.03 (0.96-1.10)	1.00 (0.93-1.09)	1.26NS
A59	Father only	4	1.11 (0.97-1.28)	1.11 (0.95-1.30)	1.11NS
A63	Household exposure other than parents	6	1.49 (1.30-1.71)	1.49 (1.30-1.71)	0.89NS
A67[k]	Household exposure but not mother	4	1.11 (0.97-1.28)	1.11 (0.95-1.30)	1.11NS

Notes : Fixed effects relative risks (RR) are adjusted for covariates where adjusted data are available.
Significance of heterogeneity: *** $p<0.001$, ** $p<0.01$, * $p<0.05$, (*) $p<0.1$, NS $p\geq0.1$.
Table: Except for tables marked with a k (key), further results are only shown in the Appendix Tables.

Where both parents smoke, relative risk estimates for both lifetime and current asthma, tend to be larger and more consistently positive than for the more general parent exposure. For lifetime asthma there are nine relative risk estimates, all greater than 1.00, in the range 1.10 to 2.90 with six significantly positive, and no statistically significant heterogeneity. Although the fixed-effects estimate for current asthma (1.41, 1.23-1.61) is similar to that for lifetime asthma (1.40, 1.24-1.58), it is based on far more variable estimates, of 1.29, 1.35, 1.40, 1.94, 3.30 and 11.00, with the lower confidence limit of the two high estimates, 1.70 for the 3.30 and 2.50 for the 11.00, exceeding the overall estimate. As a

result, the random-effects estimate is somewhat higher, at 1.68 (1.23-2.28) for current asthma than the 1.44 (1.22-1.70) for lifetime asthma. Although heterogeneity analyses by factor level are included in Table A43, they are of little value.

Tables A45 to A48 relate to whether the mother smokes. While the analysis is run using a preference for mother regardless of father, then mother only, in all cases the relative risk selected was for mother regardless of father. These can be contrasted with the much sparser data for Tables A49 to A52 relating to whether, specifically, the mother only smokes. Similarly Tables A53 to A56 relate to whether the father smoked and Tables A57 to A60 to whether the father only smoked. Here the data for father smoked does include the occasional estimate for father only smoked (GILLIL – findings for father regardless of mother were not available and VENNER – all mothers were never smokers).

With asthma outcome (lifetime or current), use of preference (e.g. mother/mother only or mother only specifically) and type of meta-analysis estimate (fixed-effects or random-effects) held constant, it is clear that estimates based on mother as the exposure source are always greater than the corresponding estimate based on father as the exposure source. While the eight mother-based estimates, with one minor exception, are all statistically significant, only two of the eight father-based estimates are.

For father smoking, there is no real evidence at all of an increase in risk in relation to father smoking in the results for current asthma. Thus, in Table A55, one has 21 relative risk estimates, eight >1.00, 13 <1.0, none statistically significant (as judged by a relative risk with lower confidence interval >1.00), and with no evidence of heterogeneity. Furthermore, there are an additional five studies with incomplete data, four of which reported no significant association of father smoking with current asthma, the other reporting a relative risk of 1.13 likely also to be non-significant.

In Table A53, for lifetime asthma, there is a significant increase in relation to father/father only exposure, with the fixed-effects relative risk 1.18 (1.13-1.23, p<0.001). However, there is considerable heterogeneity in the data (χ^2_{het} = 66.46 on 30 d.f., p<0.001), with estimates varying from a significant decrease of 0.77 (0.60-0.98) for LISTER to a significant increase of 2.73 (1.92-3.88) for ALDAWO. Both these studies are major contributors to the heterogeneity, as is the MCKEEV study with an estimate of 1.28 (1.19-1.38) with a weight of 694, 34% of the total weight. Nevertheless the random-effects relative risk estimate is still significant (1.16, 1.08-1.26, p<0.001), with 22 individual estimates >1.00 and eight <1.00. However it should be noted that there are an additional four studies with incomplete data, three of which reported no significant association of father smoking with lifetime asthma, the other reporting relative risks of 0.84 and 0.65 for boys and girls respectively, also consistent with no association.

For mother smoking, the data seem far more consistently positive. For mother/mother only and lifetime asthma (Table A45), 38 of the 44 relative risk estimates are >1.00, 21 significantly so (at p<0.05), with only six <1.00, one significant, and no very obvious outliers. Though there is statistically significant heterogeneity (χ^2_{het} = 74.60 on 43 d.f.; p<0.01), no single factor shows marked (p<0.01) heterogeneity. Of eight studies with incomplete data which reported statistical significance, four (50.0%) reported a significant association, in line with the 47.7% (21/44) in the studies considered in Table A45.

For mother/mother only and current asthma (Table A47), the data are rather more heterogeneous, with six of the 27 estimates >2.00 and seven <1.00 (χ^2_{het} = 58.67 on 26 d.f., p<0.001), but the tendency to a positive association seems clear enough. However, this tendency seems less evident in the six studies with incomplete data, none of which reported a significant association.

Tables A61 to A64 relate to household exposure other than the parents. For lifetime asthma there are only three estimates, giving an overall estimate of 1.31 (0.96-1.79) which is borderline significant ($p<0.1$) but with no heterogeneity. All three relate to other household exposure irrespective of smoking by the parents (ALDAWO – any other household member, LAM2 – grandparents, RATAGE – grandfather), all non-significantly >1.00. For study LAM2, an estimate of 0.71 (0.28-1.78) for siblings smoking is also available.

For current asthma there are six estimates, which give an overall estimate of 1.49 (1.30-1.71) which is significant at $p<0.001$, without heterogeneity. Only one of these estimates is for other household only exposure (i.e. without exposure from parents) and that shows no association – GILLIL, 1.00 (0.60-1.90).

Tables A65 to A68 relate to household exposure other than from the mother, and are specifically restricted to where there is no exposure from the mother. For current asthma, the only available results are for father only, so that Tables A67 to A68 are identical to Tables A59 to A60. However for lifetime asthma, four studies provide estimates for household member other than mother, in addition to the six already considered for father only in Tables A57 to A58. The 10 estimates give an overall estimate of 1.14 (1.01-1.29) which is marginally significant at $p<0.05$, without heterogeneity.

3.9 Discontinued exposure: Tables A69 and A70

Table A69 (lifetime asthma) and Table A70 (current asthma) both relate to household or parental ETS exposure, but specifically concern exposure that has been discontinued. This includes having a parent who is an ex-smoker, but not specific *in utero* exposure.

Table A69 is based on seven relative risk estimates, which together give a fixed-effects estimate of 1.20 (1.11-1.30). As there is no evidence of heterogeneity, with the chisquared per degree of freedom less than 1 (0.60), the

random-effects estimate is the same. The significant finding leans heavily upon the estimate of 1.22 (1.12-1.33) from the MCKEEV study which has a weight of 513, 85% of the total weight. Of the other six estimates, four are >1.00, two are <1.00, and none statistically significant.

For current asthma, Table A70 is based on eight relative risk estimates, one significantly >1.00, which together give a fixed-effects estimate of 1.02 (0.94-1.12). There is some heterogeneity (χ^2_{het} = 12.76 on 7 d.f., p<0.1), but the random-effects estimate is similar, at 1.01 (0.88-1.15).

4. Risk by amount of exposure in life

4.1 Table B (and Appendix Table B)

All analyses considered in §4, Appendix Table B (which gives the full meta-analysis results) and Table B (which gives the reduced results), have the restriction, in addition to those already defined in §2.2, that the relative risks are selected for exposure in the child's lifetime if available, otherwise for alternatives as already defined in §3.1, and that the exposure is subdivided into categories by amount of exposure, with each category compared with a base group of no exposure if available, otherwise of 'no + low' exposure. Number of cigarettes is the most common measure of exposure, followed by number of persons in the household who smoke. Two studies (CHEN2 and CUNNI1) used both these measures, while ZHENG used persons and minutes per day. MAIER categorized exposure as "occasionally" or "several hours/day".

Table B and Appendix Table B both present results for six meta-analyses:

Text Table 4.1 – Dose-response analyses for in life exposure

Table	Definition of asthma outcome	Amount of exposure
B1	Lifetime	Low
B2	Lifetime	High
B3	Current	Low
B4	Current	High
B5	Lifetime/current	Low
B6	Lifetime/current	High

The terms 'lifetime', 'current' and 'lifetime/current' are explained in §2.3 **Outcome**. The terms 'high' and 'low' refer to the first and last RRs from the sets of categorical data, as explained in §2.6.

In all tables, the source of exposure is 'total' exposure as explained in §2.3 **Source of exposure to ETS**, the time of exposure is 'general' as explained in §2.3 **Timing of exposure**, and the unexposed group is 'most' as explained in §2.3 **Definition of the unexposed comparison group**. Additional tables where the unexposed group is 'least' as explained in §2.3 are discussed in §4.5 but are not

presented. Apart from five studies which presented results both for exposure from mother and from father, no study presented results for more than one definition of exposure, so use of the alternative sources of exposure described in §2.3 would not have made any difference to the relative risks included in the Tables. Additional tables choosing exposure from the father rather than for the mother for those studies which had both were also run and are discussed in §4.5, but are not presented.

Only the factors **sex** and **measure of exposure** are included in sections –3 and –6 of these Tables.

4.2 Tables B1-B2: Lifetime asthma

There are a total of 16 pairs of relative risks included in the meta-analyses. For all but three of the pairs, the high dose relative risk is greater than the low dose relative risk. In the low dose analysis (Table B1) one relative risk is significantly < 1.00 and one significantly >1.00, compared with eight significantly > 1.00 in the high dose analysis (Table B2). Overall, there is a significant increased risk of lifetime asthma in relation both to low dose exposure, with a relative risk of 1.11 (1.01-1.22), and to high dose exposure with a relative risk of 1.47 (1.29-1.67) for the fixed-effects model using relative risks adjusted for covariates where possible. Results are similar with the random-effects model although the low dose estimate loses its significance (low dose: 1.12 (0.99-1.27); high dose: 1.48 (1.27-1.73)). Results are also similar when unadjusted relative risks are chosen in preference, and in the following text, attention is restricted to the adjusted analyses. There is no significant evidence of publication bias. There is no evidence of heterogeneity in either analysis (low dose: $\chi^2_{het} = 22.48$ on 15 d.f., $0.1<p<0.05$; high dose: $\chi^2_{het} = 19.78$ on 15 d.f., $p>0.1$).

Three studies provide dose-response data in forms other than categorical, as described in §3.4.4 and Table 11 of Part I of this report. For biochemically assessed exposure, EHRLI2 reports a significant increase in risk of 1.009 per

ng/ml of urinary cotinine, but a non-significant increase of 1.004 for cotinine/creatinine ratio. PONSON reports a non-significant increase of 1.04 per 20 cigarettes smoked in the household at time of birth, while ALFRA1 reports a significant association with number of cigarettes smoked by both parents but without any further detail[v]. A further three studies[vi] provide only incomplete categorical data. In all three, both the low and high dose relative risks were <1.0 with significance not stated, and the high dose relative risk was lower than the low dose relative risk.

4.3 Tables B3-B4: Current asthma

Whereas Tables B1-B2 consider meta-analysis of lifetime asthma, Tables B3-B4 consider results for current asthma, other preferences being identical.

Here there are 18 pairs of relative risks, all for sexes combined. In all but three of the pairs, the high dose relative risk is greater than the low dose relative risk. In the low dose analysis (Table B3), there are three relative risks significantly >1.00, and two significantly <1.00 (only one when unadjusted relative risks are preferred), while in the high dose analysis (Table B4) there are nine relative risks significantly >1.00. Overall estimates were very similar to those for lifetime asthma, with a significant increased risk of current asthma in relation both to low dose exposure, 1.12 (1.04-1.21), and to high dose exposure 1.34 (95% CI 1.23-1.46) (this being slightly lower than for lifetime asthma) for the fixed-effects model using relative risks adjusted for covariates where possible. Again with the random-effects model the overall estimate for low dose is non-significant: 1.05 (0.93-1.20), but the overall estimate for high dose is little changed: 1.40 (1.22-1.62). However for current asthma, in the both high and low dose analyses, there is significant heterogeneity (low dose: χ^2_{het} = 36.30 on 17 d.f., p<0.01; high dose χ^2_{het} = 33.76 on 17 d.f., p<0.01). Within the high dose

[v] There were some concerns about the quality of statistical analysis in this study, see Part I §3.3.3, §3.4.4 and Table 12

[vi] Including the partially overlapping studies WOLFO1 and WOLFO2, see Part I §3.3.3

analysis, there is some evidence that estimates from studies categorizing by numbers of cigarettes were lower than for studies using other measures of dose. However given the widely differing definitions of 'high dose' within each type of measure, this finding probably has little real meaning. There is no significant evidence of publication bias. Results are similar when unadjusted relative risks are chosen in preference.

Seven studies provide dose-response data in forms other than categorical, as described in §3.4.4 and Table 11 of Part I of this report. Four (CHINN, EHRLI1, TARIQ and SCHMIDT) report a non-significant association, and one (DIJKST) a negative association but with significance not stated (risk per 10 cigarettes 0.93). SOMERV reported a marginally significant positive association for boys but not for girls. KNIGHT studied four measures of exposure and reports a significant positive association for hair cotinine, but a non-significant negative association for the other three measures (number of cigarettes smoked by household members, urinary cotinine and urinary cotinine/creatinine).

A further four studies provide only incomplete categorical results. One (STRACH) merely gives results as non-significant for both low and high dose, while the other three studies give RRs without CIs or significance: for CUNNI1 both RRs are >1.00, with the low dose RR greater than the high dose RR; for LAM2 both RRs are <1.00, with the low dose RR less than the high dose RR; and for WOLFO2 the low dose RR is <1.00 and the high dose RR is >1.00.

4.4 Tables B5-B6: Lifetime/current asthma

The meta-analyses discussed above chose either lifetime asthma only, or current asthma only. In Tables B5-B6 more studies are included by introducing a preferencing on asthma outcome, with data for lifetime asthma chosen if available or for current asthma if not, giving 31 pairs of relative risks. Results are very similar to the previous analyses for low dose, except that the overall estimate from

the random model now retains significance. For the high dose analysis, the overall estimate is intermediate between the previous estimates.

4.5 Variants on Tables B1-B4 by definition of source of exposure/non-exposure

Additional tables (not presented) vary the preferencing by choosing the 'least' unexposed comparison group rather than the 'most' as in Tables B1-B4. For lifetime asthma, there is no change in the relative risks selected for the analysis, while for current asthma there are some changes (relative risks with exposure: 'current' and non-exposure: 'non' replaced by exposure: 'current' and non-exposure: 'never') but this has virtually no effect on the overall estimates or the heterogeneity.

These additional tables also vary the preference by choosing paternal rather than maternal exposure if available. For lifetime asthma, only one alternative pair of relative risks is selected, giving little change to the results. For current asthma, alternative relative risks are selected from four studies. The overall estimates are lower than when maternal exposure is preferred (and non-significant in the low dose analysis) – low dose: 1.01 (0.94-1.10), high dose: 1.29 (1.17-1.42). Heterogeneity is also somewhat higher than in the analysis with maternal exposure.

5. Risk from *in utero* exposure (irrespective of in life exposure)

5.1 Table C (and Appendix Table C)

All analyses considered in §5, Appendix Table C (which gives the full meta-analysis results) and Table C (which gives the reduced results), have the restriction, in addition to those already defined in §2.2, that the relative risks are selected for exposure during pregnancy, i.e. *in utero* exposure of the fetus. Appendix Table C presents results for three meta-analyses, Tables C1 and C2 relating to exposure from the mother being a smoker, with Table C3 relating to exposure from the father being a smoker or the mother being ETS exposed. Tables C1 and C3 relate to lifetime asthma, or current asthma if lifetime asthma is not available, while Table C2 relates to current asthma, or lifetime asthma if current asthma is not available. Only Table C1 includes detailed heterogeneity analyses.

5.2 Tables C1 and C2: maternal smoking in pregnancy

26 studies provide 27 estimates of risk in relation to maternal exposure. In all but one study the relative risks relate to mother smoked vs mother did not smoke. In the CUNNI1 study, the relative risk relates to mother smoked vs no household member smoked. Below relevant meta-analysis results are summarized.

Text Table 5.1 – Summary of in utero analyses

Table	Definition of asthma	Adjusted for covariates	Fixed-effects RR (95% CI)	Random-effects RR (95% CI)	Heterogeneity chisq per df
C1	Lifetime/current	Adjusted	1.25 (1.17-1.33)	1.30 (1.16-1.45)	2.31***
	Lifetime/current	Unadjusted	1.34 (1.26-1.42)	1.37 (1.23-1.52)	2.54***
C2	Current/lifetime	Adjusted	1.26 (1.18-1.35)	1.31 (1.17-1.47)	2.25***

Key : Significance of heterogeneity: *** p<0.001, ** p<0.01, * p<0.05, (*) p<0.1, NS p≥0.1.

All the analyses show a highly significant (p<0.001) elevated risk of childhood asthma associated with maternal smoking in pregnancy.

The analyses using the lifetime/current preference are based on 16 estimates using lifetime asthma and 11 using current asthma. Those based using the current/lifetime preference are based on 14 estimates using lifetime asthma and 13 using current asthma. This is because only two studies (HU1, WEITZ1) had relative risks available for both alternatives. One produced a higher relative risk estimate using lifetime/current, and one produced a lower relative risk. The overall results are so similar that the results for C2 will not be considered further.

The analyses using data adjusted for covariates where available include 19 adjusted and eight unadjusted estimates. Those using the data unadjusted for covariates where available include four adjusted and 23 unadjusted estimates. Here 16 studies have both adjusted and unadjusted estimates. We will consider first the results using adjusted estimates where available.

For the adjusted analysis, 23 of the 27 relative risk estimates are >1.00, with 10 statistically significant at $p<0.05$. None of the four relative risks <1.00 are statistically significant. The fixed-effects relative risk estimate is 1.25 (1.17-1.33), with significant evidence of heterogeneity (χ^2_{het} = 60.12 on 26 d.f., $p<0.001$) and a random-effects estimate of 1.30 (1.16-1.45). No single study is responsible for the heterogeneity, the largest Q_s being 7.49 for KUEHR with an estimate of 0.61 (0.37-1.03). Of the total weight of 873, five studies each have a weight of about 100 (varying between 89 and 114) and no single study has a result that dominates the findings.

Looking at how the relative risk estimates vary by factor level, one notes the following main findings:

Sex 25 of the 26 studies report results only for the sexes combined so one cannot usefully see how estimates vary by the sex of the child.

Continent All but four of the studies were conducted in Europe or the USA. In the nine US studies estimates are somewhat higher (1.41, 1.24-1.59) than in the 13 European studies (1.20, 1.10-1.31). There is no variation by country within Europe.

Study type Of the 26 studies, 15 are cross-sectional, seven case-control and four prospective. Estimates do not vary by study type.

Age of child Estimates do not vary by the age of the child.

Population setting Estimates are larger in studies conducted in a medical setting (1.83, 1.34-2.50, n=4) than in studies conducted in a general setting (1.22, 1.08-1.38, n=9) or in a school setting (1.26, 1.15-1.39, n=13).

Respondent for smoking Estimates where the parent had supplied the data on smoking (1.20, 1.12-1.29, n=21) are lower than where the data came from other sources ($\chi^2_{het} = 11.08$ on 2 d.f., $p<0.01$).

Child smokes Estimates where children who smoked were not included (1.47, 1.30-1.66, n=6) are higher than if they were included (1.04, 0.87-1.25, n=2) or ignored (1.20, 1.10-1.31, n=19).

Physician diagnosis Estimates are higher where the asthma had been diagnosed by a physician (1.38, 1.23-1.55, n=13) than where it may not have been (1.19, 1.10-1.29, n=14) ($\chi^2_{het} = 4.26$ on 1 d.f., $p<0.05$).

Size of study Estimates do not vary by the number of asthma cases studied.

Adjustment factors Estimates are higher in studies that adjusted for race (1.43, 1.26-1.64, n=9) than in studies that did not (1.19, 1.10-1.28, n=18), reflecting the fact that US studies are much more likely than other studies to

adjust for race. Otherwise there is no evidence that estimates varied significantly according to which factors studies had adjusted for. There was no evidence of significant variation according to which factors the relative risks themselves had been adjusted for.

Asthma definition Estimates do not vary significantly by whether they were for lifetime asthma (1.20, 1.11-1.31, n=16) or current asthma (1.32, 1.18-1.46, n=11).

These conclusions are generally evident whether one considers the fixed-effects analyses (cited above) or random-effects analyses. It is clear that no factor, on its own, explains a major part of the overall heterogeneity.

As can be seen in the previous text-table, meta-analysis estimates based on unadjusted relative risks tend to be higher than those based on adjusted relative risks. Comparing the individual estimates shown in sections –2 and –5 of Table C1, one sees that there are three studies in which the two estimates are substantially (>0.2) different.

Text Table 5.2 – Selected adjusted and unadjusted RRs for in utero exposure

Study	Adjusted RR (95% CI)	Unadjusted RR (95% CI)
DELL	1.39 (0.83-2.34)	1.96 (1.21-3.17)
HABY	0.77 (0.40-1.48)	1.19 (0.81-1.74)
SOYSET	0.60 (0.30-1.30)	1.26 (0.71-2.25)

All of these show a larger unadjusted estimate. Of the other estimates which vary between the adjusted and unadjusted analyses, nine show slightly larger unadjusted relative risks and four slightly larger adjusted relative risks.

It should be noted that the unadjusted estimates have a very large heterogeneity (χ^2_{het} = 66.07 on 26 d.f., p<0.001). This is particularly due to a high Q_s value for NHANE3 (1.91, 1.56-2.33, Q_s = 11.91). However, despite the

heterogeneity, the random-effects estimate (1.37, 1.23-1.52) is only slightly larger than the fixed-effects estimate (1.34, 1.26-1.42).

A further nine studies provide only incomplete results. Study STERN2 gives RR = 1.38, significant for lifetime asthma but 0.98, not significant, for current asthma. Otherwise, there are two significant results and 6 non-significant.

5.3 Table C3 : other exposure in pregnancy

Two studies (AGABI1 and AGABI2) provide estimates for paternal smoking during the mother's pregnancy, both adjusting for other household smokers and for current paternal smoking. Study ZHENG, which was conducted in China and found very few smoking mothers, provides estimates for maternal ETS exposure during pregnancy. All three estimates are >1.00, with one significant, one non-significant and one borderline (lower CI=1.0).

The overall meta-analysis shows a significant relative risk of 1.19 (1.07-1.31), with no evidence of heterogeneity.

6. Risk by amount of exposure *in utero*

6.1 Table D and (Appendix D)

The analyses considered in §6, Appendix Table D (which gives the full meta-analysis results) and Table D (which gives the reduced results), have the restriction, in addition to those already defined in 2.2, that the relative risks are selected for exposure during pregnancy, i.e. *in utero* exposure of the fetus, and that the exposure is subdivided into categories by amount of exposure as already defined in §4.1.

One pair of tables is presented, Table D1 for low exposure and Table D2 for high exposure, where 'low' and 'high' are as already described in §4.1. For both tables, the outcome is 'lifetime/current' and the source of exposure is 'total', as explained in §2.3, and as none of the studies with relevant data present results for more than one outcome or for more than one source of exposure, use of the alternative preferences described in §2.3 would not have made any difference to the RRs included in the Tables.

Five studies presented results by amount of exposure *in utero*. In four of these, the measure of exposure was number of cigarettes, but only two of these studies (OLIVET and WEITZ1) could be included in the meta-analysis as the others had only incomplete data (TAYLOR) or compared high vs low exposure omitting non-exposed subjects (XU). Study ZHENG presented results for number of persons smoking in the presence of the mother during pregnancy, and minutes per day of exposure, and the results for number of persons are selected for the meta-analyses.

6.2 Results

There are three pairs of relative risks included in the meta-analyses. Only one study (ZHENG) had both adjusted and unadjusted relative risks available, and they are very similar, so attention is restricted in this text to the adjusted meta-analyses. For each study, the low dose relative risk is lower than the high dose

relative risk. The low dose relative risks are all non-significant and close to 1 (OLIVET 0.96, WEITZ1 0.85, ZHENG 1.10), while the high dose relative risks are all significantly >1.00 (OLIVET 11.32, WEITZ 2.60, ZHENG 3.30).

Overall, no effect is seen at low dose, with the fixed-effects relative risk estimate 0.98 (0.78-1.24), but there is a significantly increased risk at high dose of 3.30 (2.27-4.80). In neither analysis is there any evidence of heterogeneity.

Results from study TAYLOR (relative risks 1.29 and 1.71 without CI for the low and high doses respectively), and the alternative 'minutes per day' results from ZHENG are consistent with this pattern. Study XU found no significant difference between high and low dose exposure, but did not report any further details.

7. Separating effects of in life and *in utero* exposure

7.1 Table E (and Appendix Table E)

Six studies (AGABI1, AGABI2, CUNNI1, GILLIL, NHANE3, TARIQ) have presented separate relative risks for in life exposure only, *in utero* exposure only and both in life and *in utero* exposure. Two additional studies (HAJNAL, STERN2) have also presented results for exposure both in life and *in utero*. In each case, the unexposed comparison group has no exposure either in life or *in utero*. As there are sex-specific results for one of the studies (GILLIL) this leaves us seven estimates for meta-analysis of results for in life exposure only and *in utero* exposure only and nine estimates of results for both exposures.

In all the studies, *in utero* exposure refers to smoking by the mother during pregnancy. However the definitions of in life exposure vary, and are shown in sections –1 and –4 of the Tables. These are relevant even where the comparison is between *in utero* only exposure and neither exposure (Tables E1, E4, E7), in that only subjects unexposed according to the specified definitions are included in the comparison. Thus for studies AGABI1 and AGABI2, where in life exposure was defined as parental smoking currently, and for study NHANE3 where in life exposure was biochemically assessed (and is thus intrinsically current), the '*in utero* only' group and the 'neither exposure' group may contain children with past in life exposure. Conversely, for study CUNNI1, the analysis excludes children with current exposure and refers only to past in life exposure. Further, for study NHANE3, the exposure is defined as highest vs lowest tertile serum cotinine (there being no results available for the middle tertile), and children with levels above 113.6 nmol/L were excluded as being likely smokers.

Tables E1, E2 and E3 present the results of meta-analyses for the three types of exposure (*in utero* only, in life only, both) for the following preferences: asthma outcome = lifetime/current, and in life element of exposure/non-exposure = Biochemical/Household (overall)/Parent (mother). Tables E4, E5, E6 repeat the

sequence but with exposure/non-exposure = Biochemical/Household (overall)/ Parent (father).

Tables E7, E7 and E9 correspond to Tables E1, E2 and E3, but with the asthma outcome preference chosen as current/lifetime.

7.2 Results

The table below summarizes the results of the meta-analyses.

Text Table 7.1 – Summary of analyses of in utero and/or in life exposure

Table	Exposure	Asthma preference	In life exposure preference	N	Fixed-effects RR (95% CI)	Random-effects RR (95% CI)	Heterogeneity chisq per df
E1	*In utero* only	L/C	Mother	7	1.41 (1.14-1.75)	1.53 (1.05-2.23)	2.66*
E2	In life only	L/C	Mother	7	1.08 (0.99-1.18)	1.08 (0.99-1.18)	0.77NS
E3	Both	L/C	Mother	9	1.33 (1.21-1.46)	1.32 (1.18-1.49)	1.46NS
E4	*In utero* only	L/C	Father	7	1.30 (1.15-1.47)	1.36 (1.15-1.61)	1.23NS
E5	In life only	L/C	Father	7	1.05 (0.94-1.17)	1.05 (0.94-1.17)	0.84NS
E6	Both	L/C	Father	9	1.23 (1.12-1.35)	1.24 (1.11-1.39)	1.27NS
E7	*In utero* only	C/L	Mother	7	1.41 (1.14-1.74)	1.52 (1.05-2.20)	2.61*
E8	In life only	C/L	Mother	7	1.08 (0.99-1.18)	1.07 (0.97-1.20)	1.28NS
E9	Both	C/L	Mother	9	1.30 (1.18-1.43)	1.29 (1.09-1.53)	2.63**

Key : Asthma preference: L/C = lifetime/current, C/L = current/lifetime
In life exposure preference : Mother implies data for mother selected in preference to data for father, with father implying the reverse
N = number of relative risk estimates combined
Heterogeneity Chisq per df: *** p<0.001, ** p<0.01, * p<0.05, (*) p<0.1, NS p≥0.1

It can be seen that, in all the analyses, there is a significant ($p<0.05$) increase in risk of asthma associated with *in utero* only exposure, or with exposure both in life and *in utero* but not with in life exposure only.

The estimates for Tables E7, E8 and E9 based on current/lifetime asthma are very similar to those for Tables E1, E2 and E3 based on lifetime/current asthma. For seven of the nine studies, the data included are in fact identical, estimates for current asthma being only selected for the NHANE3 and the STERN2 studies.[vii]

[vii] Current asthma estimates for study GILLIL were for sexes combined, so that the single sex lifetime asthma estimates were selected as higher preference

The estimates for Tables E4, E5 and E6 based on preference for father are somewhat lower than for those in Tables E1, E2 and E3, based on preference for mother. Again the differences are only based on two studies, AGABI1 and AGABI2, which allow separate estimates to be made.

In order to allow better comparison of *in utero* exposure only, in life exposure only and both exposures, it is useful to look at the individual estimates, so that one can look at between study differences. These data are reproduced below, together with other relevant data which were not included in any of the meta-analyses.

Text Table 7.2 – Individual RRs for in utero and/or in life exposure

Study(sex)	Used in Tables[b]	Asthma outcome	Source of in life exposure[c]	Time of in life exposure	Relative risk (95% CI) [a]		
					Exposure *in utero* only	Exposure in life only	Both exposures
AGABI1	E1-E3,E7-E9	current	Mother	current	**1.72 (1.13-2.63)**	**1.05 (0.88-1.26)**	**1.52 (1.27-1.83)**
AGABI1	E4-E6	current	Father	current	1.23 (0.96-1.58)	1.18 (0.92-1.52)	1.19 (1.02-1.39)
ABABI1	none	current	Mother	since birth[d]	-	1.18 (1.01-1.37)	-
ABAGI1	none	current	Father	since birth[d]	-	1.02 (0.84-1.24)	-
AGABI2	E1-E3,E7-E9	current	Mother	current	**0.69 (0.45-1.05)**	**1.14 (0.99-1.33)**	**1.21 (1.02-1.45)**
AGABI2	E4-E6	current	Father	current	1.20 (1.02-1.41)	0.97 (0.76-1.24)	1.10 (0.86-1.40)
ABABI2	none	current	Mother	since birth[d]	-	1.09 (0.96-1.25)	-
AGABI2	none	current	Father	since birth[d]	-	1.06 (0.89-1.28)	-
CUNNI1	E1-E9	current	Any Hh member	past[e]	**2.70 (1.13-6.45)**	**0.99 (0.78-1.25)**	**0.96 (0.63-1.48)**
CUNNI1	none	current[f]	Any Hh member	past[e]	2.03 (0.75-5.47)	1.04 (0.81-1.34)	1.02 (0.65-1.60)
GILLIL(m)	E1-E9	lifetime	Any Hh member	since birth	**1.70 (1.10-2.90)**	**1.00 (0.80-1.30)**	**1.10 (0.80-1.40)**
GILLIL(f)	E1-E9	lifetime	Any Hh member	since birth	**1.90 (1.10-3.50)**	**1.10 (0.80-1.40)**	**1.60 (1.20-2.20)**
GILLIL(c)[g]	none	lifetime	Any Hh member	since birth	1.80 (1.10-2.90)	1.10 (0.90-1.40)	1.30 (1.00-1.70)
GILLIL(c)	none	current	Any Hh member	since birth	2.30 (1.30-4.00)	1.10 (0.80-1.40)	1.30 (0.90-1.80)
GILLIL(c)	none	current[f]	Any Hh member	since birth	2.10 (1.20-3.60)	1.10 (0.80-1.40)	1.20 (0.90-1.70)
LOPEZC	none[h]	current	Mother	ever	-	1.06 (NS)	-
NHANE3[i]	E1-E6	lifetime	Biochemical		**2.63 (0.30-25.12)**	**2.29 (0.91-5.01)**	**3.16 (1.10-9.12)**
NHANE3[i]	E7-E9	current	Biochemical		1.74 (0.30-11.48)	4.57 (1.38-13.80)	7.24 (2.51-20.89)
NHANE3[j]	none	lifetime	Biochemical		NS	NS	NS
NHANE3[j]	none	current	Biochemical		NS	NS	NS
NHANE3[k]	none	lifetime	Any Hh member	since birth	1.30 (0.60-3.00)	0.90 (0.60-1.30)	1.70 (1.20-2.50)
TARIQ	E1-E9	current	Mother	since birth	**1.58 (0.81-3.07)**	**0.98 (0.56-1.72)**	**1.21 (0.79-1.85)**
HAJNAL	E3,E6,E9	lifetime	Mother	current	**-**	**-**	**1.31 (0.92-1.85)**
STERN2	E3,E6	lifetime	Mother	first 2 years	**-**	**-**	**1.43 (1.09-1.88)**
STERN2	E9	current	Mother	first 2 years	-	-	0.98 (0.68-1.41)

See footnotes on next page

Footnotes to Text Table 7.2

[a] Estimates in bold are from Tables E1, E2 and E3. All estimates are adjusted for covariates where available. NS = not significant. - = not available

[b] Estimates marked 'none' are not used in any meta-analyses, either due to incomplete data, not selected by the preferences, or alternative disease outcome not included in database

[c] Hh = household. Biochemical = highest vs lowest serum cotinine tertile

[d] Using the defintion of 'parental smoking since birth', estimates for '*in utero* only' and 'both exposures' are not available because ex-smokers who smoked in pregnancy, irrespective of whether they also smoked in the child's life, were considered together by the original authors

[e] Excluding current exposure

[f] Alternative definition of current asthma (ever diagnosed and taken medication in last year)

[g] Adjusted for sex and 5 additional confounders

[h] Mistakenly included in Table A, but not contributing to any meta-analysis there due to lack of CI

[i] Age 4-6

[j] Age 7-11

[k] Age 0-5

For the estimates included in Tables E1, E2 and E3, based on the preference lifetime/current and mother/father, it should be noted that the estimates for exposure *in utero* only have larger variance (weight = 85) than those for exposure in life only (496) or exposure at both times (459). The studies AGABI1 and AGABI2 together have about half the total weight for each exposure (totalling 43, 296 and 239 respectively) while the weights for the cotinine based NHANE3 study are particularly small (0.8, 5.3 and 3.4 respectively).

For exposure *in utero* only, the meta-analysis shows evidence of heterogeneity (χ^2_{het} = 15.93 on 6 d.f., $p<0.05$) due to the unusually low estimate in the ABAGI2 study (0.69, 0.45-1.05, Q_s = 11.01). However, all the other six estimates are >1.00 (indeed all are in the range 1.58 to 2.70) with four being statistically significant (at $p<0.05$), and both the fixed-effects estimate (1.41, 1.14-1.75, $p<0.01$) and the random-effects estimate (1.53, 1.05-2.23, $p<0.05$) are statistically significant.

For the data for exposure in life only, the results are generally consistent with a lack of association with asthma. None of the seven estimates are statistically significant (at $p<0.05$), there is no significant heterogeneity (χ^2_{het} = 4.64 on 6 d.f., $p\geq0.1$) of the relative risk (1.08, 0.99-1.18), and most of the estimates are close to 1.0. The apparently higher estimate of 2.29 from the NHANE3 study is highly variable, and the only real suggestion of a possible

increase is in the largest, AGABI2, study where the relative risk of 1.14 (0.99-1.33) is close to significant.

For both exposures, on the other hand, all but one of the nine estimates are greater than 1.0, and five are statistically significantly increased at $p<0.05$. The fixed-effects relative risk (1.33, 1.21-1.46) shows no significant heterogeneity ($\chi^2_{het} = 11.64$ on 8 d.f., $p \geq 0.1$). Comparing the results for both exposures with those for exposure *in utero* only there is no tendency for both exposures to show higher risks. Indeed for five of the seven studies the relative risk for both exposures is lower.

Generally, the pattern of no increase in risk for exposure in life only and an increase for exposure *in utero* only and for both exposures seems reasonably clear, given the variability of the data. The principal exception is the AGABI2 study.

The data considered from Tables E1, E2 and E3 are for relative risks adjusted for covariates where possible, with seven of the nine studies having adjusted data. Results based on relative risks unadjusted for covariates where possible are very similar and confirm the general pattern of a lack of association of asthma with in life exposure, whether considered on its own, or as a part of both exposures (compared to *in utero* exposure on its own).

For the estimates included in Tables E4, E5 and E6, based on the preference lifetime/current and father/mother, the overall pattern seen is similar, but the meta-analysis relative risk estimates are somewhat lower. As noted above, the differences relate to the AGABI1 and AGABI2 studies. Interestingly, as seen in the text-table above, the three estimates for the AGABI1 study, previously (in Tables E1 to E3) showing a pattern consistent with an effect of *in utero* but not in life exposure, now no longer do so, with all three relative risk estimates similar, at about 1.2. For the AGABI2 study, the unusually low estimate seen in Table E1

for *in utero* only exposure, is now significantly above 1.00 (1.20, 1.02-1.41) and the results do now show an association with *in utero* but not with in life exposure.

For the estimates included in Tables E7, E8 and E9, based on the preference current/lifetime and mother/father, differences, compared to the corresponding Tables E1, E2 and E3, come from the NHANE3 and STERN2 studies. The very high relative risks seen in the NHANE3 study for exposure in life only (4.57, 1.38-13.80) and for both exposures (7.24, 2.51-20.89) stand out as different. For exposure in life only, the overall heterogeneity statistic is not significant (χ^2_{het} = 7.69 on 6 d.f.), due mainly to the remarkable similarity of the other six estimates (0.98, 0.99, 1.00, 1.05, 1.10, 1.14) and the low weight of the NHANE3 estimate (3 out of a total of 494 for all the studies). However the NHANE3 result certainly seems unusual, having a lower 95% confidence limit of 1.38 and a Q_s of 6.05. For both exposures, there is more evidence of heterogeneity (χ^2_{het} = 21.07 on 8 d.f., $p<0.01$), with the NHANE3 estimate having a Q_s of 10.10 and a lower 95% confidence limit of 2.51, higher than the largest upper 95% confidence limit seen for any of the other eight estimates. The NHANE3 study results are very different from the other studies, suggesting an important role of in life exposure, not suggested by the other studies. Note that, though the Table E7, E8 and E9 NHANE3 results relate to current asthma, so do the results for five of the seven other studies.

Text Table 7.2 also shows various other relative risk estimates not included in the meta-analyses. Generally, these show an increase in risk associated with exposure *in utero* only (only significant for the GILLIL study), and an estimate close to 1.00 and not significant associated with exposure in life only. Exceptionally, for study AGABI1 with exposure from the mother since birth, there is a marginally significant increase (1.18, 1.01-1.37) associated with exposure in life only.

7.3 Effect of adjusting in life exposure estimates for *in utero* exposure

To further investigate the joint effects of in life and *in utero* exposures, studies other than those included in Table E which presented equivalent results for in life exposure both unadjusted and adjusted for *in utero* exposure were examined. The available data are summarized here:

Text Table 7.3 – Selected RRs for in life exposure

			Unadjusted for *in utero* exposure		Adjusted for *in utero* exposure	
Study (sex)	Asthma	Definition of in life exposure	Other adj	RR/CI	Other adj	RR/CI
DIJKST	c	household – current	(0	1.95 (0.91-4.19)	0	NS
			(12	1.77 (no CI)		
HABY	c	any parent – age <6m	0	1.34 (0.97-1.85)	8	1.62 (0.95-2.75)
HU1	l	mother – current	0	1.22 (0.78-1.89)	6	0.80 (0.50-1.50)
SOMERV(m)	c	any parent – current – per cigarette	1	0.99 (0.97-1.01)	10	1.00 (0.97-1.02)
SOMERV(f)	c	any parent – current – per cigarette	1	1.02 (1.00-1.04)	10	1.03 (1.00-1.05)
SOYSET	l	mother – since birth	0	1.99 (1.08-3.67)	4	2.80 (1.30-6.10)
SOYSET	l	father – since birth	0	1.52 (0.84-2.75)	5[a]	NS
STAZI	l	mother – since birth	2	NS	6	NS
		mother – current	2	NS	6	NS
		father – since birth	2	NS	6	NS
		father – current	2	NS	6	NS

Asthma : c = current l = lifetime
'Other adj' gives the number of other factors for which adjustment was made
[a] Includes adjustment for maternal smoking since birth

Only in one study (DIJKST) are the definitions of the relative risks identical apart from the *in utero* adjustment. However, the adjusted result is incomplete, described in the original paper as "somewhat attenuated".

In most cases, the comparison is between an unadjusted RR and a multiply-adjusted RR, where *in utero* exposure is just one of a number of factors. Full data are available only for five cases, in none of which the significance altered, with two (HABY and SOYSET-mother) showing an increased RR, one (HU1) showing a decreased RR, and two (SOMERV-males and SOMERV-females) showing little apparent effect of adjustment. The partial data available for the other comparisons are not suggestive of any change.

The above analyses are based on within-study comparison of the effects of adjustment for *in utero* exposure. In principle, such comparisons are more reliable than those based on between-study comparisons, as for instance described in §3.2 **Adjustment for confounding variables**.

7.4 Effect of adjusting *in utero* exposure estimates for in life exposure

The available data for studies which presented equivalent results for *in utero* exposure, both unadjusted and adjusted for in life exposure, apart from those included in Table E, are summarized here:

Text Table 7.4 – Selected RRs for in utero exposure

Study	Asthma	Unadjusted for in life exposure		Adjusted for in life exposure		
		Other adj	RR/CI	Definition of in life exposure	Other adj	RR/CI
HABY	c	0	1.19 (0.81-1.74)	Either parent smoked in first 6 months	8	0.77 (0.40-1.48)
HU1	l	0	1.76 (1.11-2.79)	Current maternal smoking	6	1.90 (1.10-3.50)
NILSSO	l	0	1.40 (1.00-2.00)	Current parental smoking	6	1.30 (0.80-1.90)
SOYSET	l	0	1.26 (0.71-2.25)	Maternal smoking since birth	7	0.60 (0.30-1.30)

Asthma : c = current l = lifetime
'Other adj' gives the number of other factors for which adjustment was made

Again, the comparisons are between an unadjusted relative risk and a multiply-adjusted relative risk. For three of the studies adjustment decreased the relative risk, losing its borderline significance in one (NILSSO), and dropping well below 1.00 in two (HABY, SOYSET) although they remain non-significant. In the remaining study (HU1) adjustment increased an already significant relative risk.

8. Discussion

8.1 Evidence of an association

As can be seen from Text Table 3.5 for in life exposure and from Text Table 5.1 for *in utero* exposure, there is a highly significant association between current or lifetime asthma and various indices of exposure to smoking by parents or other household members. However, though statistically significant, the associations are not strong. For example, random-effects estimates based on covariate adjusted relative risks are 1.23 (1.17-1.28) for total in life exposure for lifetime asthma, 1.18 (1.11-1.26) for total in life exposure for current asthma, and are 1.30 (1.16-1.45) for *in utero* exposure for lifetime/current asthma. Associations for in life exposure tend to be strongest where both parents smoke and stronger in relation to maternal than paternal smoking. Indeed, when the father only smokes no significant elevation in risk is seen, with an estimate of 1.11 (0.96-1.29) for lifetime asthma based on only five studies.

8.2 Evidence of a dose-response relationship

Evidence of a dose-response relationship has been investigated in various ways in the studies considered, most commonly by number of cigarettes per day and by number of persons in the household who smoke. For in life exposure, the results summarized in Table B and section 4 show clearly that relative risks associated with high dose total exposure are substantially greater than those associated with low dose total exposure – for example for lifetime asthma random-effects estimates are 1.48 (1.27-1.73) for high exposures and 1.12 (0.99-1.27) for low exposures based on the 16 pairs of relative risks included in the meta-analyses in Tables B1 and B2. These findings seem generally to be supported by the results of other studies that provided results in terms of risk per unit dose, and could not be simply included in the categorical low dose/high dose analyses. For *in utero* exposure only three studies could be identified which provided pairs of low dose and high dose estimates. However, as discussed in section 6, the limited data strongly support a dose response relationship, with no

evidence of an increase at low dose in any of the studies, but significant evidence of an increase at high dose in all of them.

Clearly the data available show an association and a dose-response relationship that, at least for a number of the exposure indices, cannot be explained by chance. In order to interpret these findings it is necessary to consider various aspects of the data further.

8.3 Consistency of findings

As seen, for example, in Text Table 3.5 (in life exposure) and 5.1 (*in utero* exposure), there is statistically significant heterogeneity for a number of the exposure indices studied. Identifying the sources of the heterogeneity is not straightforward, partly because in some meta-analyses (e.g. Table A3) a particular study (here WANG) may have a very large weight and a risk estimate somewhat different from the remaining studies, for reasons that are not clear. Also, for some exposure indices, the number of estimates available is too small to allow detailed study of sources of heterogeneity.

We have only investigated variation in risk by one factor at a time rather than on a multivariate basis. However, looking at some of the key analyses (Table A1 – total exposure/lifetime asthma, Table A3 – total exposure/current, Table A5 – parent/lifetime, Table A7 – parent/current, Table A45 – mother/lifetime, Table A47 – mother/current, Table C1 – *in utero*/lifetime/ current) various overall impressions can be gained from these univariate analyses. Firstly, it is clear that for many of the factors considered there is little or no evidence of heterogeneity, with relative risk estimates generally >1.0 for each factor level. These factors include the continent the study was conducted in, the time the study started (or was published), the population setting, whether the asthma was physician-diagnosed or not, which questionnaire was used to identify symptoms, and the study size. There is also no evidence of variation in risk by the sex of the child, though it should be noted that the great majority of the studies

only reported results for the sexes combined, precluding any sensitive test of heterogeneity. However, there are a number of factors where there is some evidence of heterogeneity by level ($p<0.01$) for which some comment is merited.

Country in Asia Although significant heterogeneity was not found in all the analyses, it is in general true that studies conducted in the Far East (China, Japan, Hong Kong, Taiwan and Korea) showed little or no association of asthma with exposure.

Study type Risk estimates are in general elevated for all the three study types. However in some of the analyses (A5 and to some extent A7 and A45) but not others, risk estimates are higher for case-control studies than for prospective or cross-sectional studies.

Age Risk estimates are in general elevated for children in all age groups. For the in life analyses for current asthma (A3 and A7) and for the *in utero* analyses (C1), estimates are rather higher in younger children, but this is not evident in the in life analyses for lifetime asthma (A1 and A5).

Child the respondent In the in life analyses there is a tendency for relative risk estimates to be lower (though still above 1.0) when the child was the respondent for questions on either smoking habits or diagnosis of asthma. This is most clearly evident in the analyses for lifetime asthma for total exposure (A1) though the pattern is consistently seen in A3, A5 and A7. The child was rarely the respondent in studies of the effects of *in utero* exposure.

Child smoking In the in life analyses (A1, A3, A5, A7) there is a consistent tendency for risk estimates to be relatively low (though still above 1.0) in studies where steps had been taken to exclude children who smoked. Interestingly, the reverse is true for *in utero* exposure (C1), with risk estimates relatively high in such studies.

Given the variability in study methodology, it would be expected that associations observed would show some evidence of heterogeneity. However, the prevailing impression of the analyses is that where a positive association is present in the overall data, it is also seen in subsets of the data divided by levels of virtually every factor that has been investigated, with Far East studies being the only subset not exhibiting evidence of an association. Though there is some evidence, as noted above, that the magnitude of the association may vary by some factors (such as the age of the child, the study type, whether the child is the respondent and whether children who smoke are excluded), the prevailing impression is of a highly consistent association.

8.4 Publication bias

Though there is a consistent association with a dose-response relationship, this does not of itself imply a cause and effect relationship. Sources of bias and confounding have to be considered. One such source of bias is publication bias. The traditional main sources of publication bias are authors being less willing to submit for publication, and journal editors being less willing to accept for publication, papers which report no association between exposure and disease than papers which report such an association. Publication bias can be investigated by various possible techniques, all of which involve assumptions which are difficult to justify formally. Here publication bias was tested for by Egger's method (Egger et al., 1997) but was generally found not to be significant. Thus, of the 90 meta-analyses of covariate adjusted data in tables A to E, 83 show no evidence of publication bias significant at least at $p<0.05$, with only three of the remaining seven significant at $p<0.01$. This is not markedly different from the number of significant findings expected by chance based on 90 analyses (4.5 at $p<0.05$ and 0.9 at $p<0.01$), and does not provide any strong evidence of publication bias. While such analyses do not exclude the possibility of some publication bias of this type existing, it seems unlikely to explain more than a minor part of the association. This is in any case evident from the large

proportion of statistically significant positive associations seen in some analyses. For example, the analyses of lifetime parental exposure (Table A5) include 64 estimates of which 22 are significantly >1.0 and one significantly <1.0. One would expect 22 significant associations positive at $p<0.05$ using a two sided test in about 880 studies, and one would hardly expect that these unpublished studies, if they existed, would produce the compensating number of significant negative associations required to make the total data (published and unpublished) consistent with no overall relationship.

However, there is another form of publication bias that needs to be considered in studies of this type. Authors may publish a paper, and then carry out a large number of analyses relating to a variety of exposures and endpoints, only reporting fully the more 'interesting' findings. One cannot fully assess the extent of this sort of bias in the absence of access to the source data. However, some insight into the problem can be gained by comparing the frequency of statistically significant results in the findings included in the meta-analyses with the corresponding frequency in findings that were not reported in enough detail to be included. For in-life exposure, the meta-analyses in Tables A1 and A3 together provide 166 relative risks, of which 49 (29.5%) are statistically significant. This can be compared with only 4 out of 30 incompletely published relative risks (13.3%), a difference which is close to statistical significance ($0.05<p<0.1$). For *in utero* exposure, Table C1 provides 27 relative risks of which 10 (37.0%) are significant. Here the frequency of significant results amongst those which are incompletely published (3/9 = 33.3% or 2/9 = 22.2% depending on which result is selected for the STERN study – see §5.2) is also non-significantly lower.

These findings demonstrate that there are certainly quite a number of studies that could provide data suitable to be included in meta-analyses, but which have not done so. They also suggest that, were these additional results available

for inclusion, relative risk estimates might have decreased slightly. However, they still do not suggest that publication bias is a major issue in interpretation.

8.5 Diagnostic bias

Ideally, an epidemiological study of the relationship of an exposure to a disease should involve a disease which has a clearly defined and generally accepted definition, with subjects defined as cases based on accurate diagnostic criteria. Inclusion of cases with other diseases may lead to over- or under-estimation of the relationship of interest, depending on the magnitude and direction of the relationship of the exposure to these other diseases.

While asthma is recognized as a chronic respiratory condition characterized by airway inflammation and episodic airflow limitation, clinical definitions of the disease vary, as is evident by the substantial variations observed in the frequency of the disease among children (National Cancer Institute, 1999). The protocol for the present review specified that only studies where the endpoint was 'asthma' were to be included, with studies of 'wheeze', 'wheezing bronchitis' or 'chronic wheezing' to be excluded. It was further decided, in order to attempt to achieve consistency of definition, to exclude 'asthma or wheeze' and 'asthmatic bronchitis'. In practice, this distinction was not always clear-cut, and it was also decided that if the endpoint was actually called 'asthma' by the original authors, then it would be included, even if on the basis of their more detailed description of the outcome it would have been excluded. Although, as discussed further in §2 of Part I of this report, this may have led to some anomalies, it seems likely to us that the great majority of the results we consider relate to conditions which are at least quite similar and which might be expected to have a similar relationship to ETS exposure and smoking in pregnancy.

In the 111 studies which provided results for lifetime asthma, the diagnosis was taken from medical records, or was made by a physician in the course of the study design, in 12 (11%), with the diagnosis made by a physician

but reported by the parent and/or the child in 51 (46%). In the remaining 48 (43%), asthma was at least partly based on the parent's or child's own assessment rather than physician diagnosis. In the 89 studies which provided results for current asthma, the corresponding frequencies were 21 (24%) for medical records/physician diagnosis, 14 (16%) for diagnosis made by physician but reported by child or parent and 54 (61%) for diagnosis involving parent's or child's assessment.

When testing for heterogeneity according to physician diagnosis, comparison was made between those studies that only involved physician diagnosis (regardless of who reported it) and those studies that were based wholly or partly on child or parent diagnosis. In the main analyses of in life exposure (Tables A1, A3, A5, A7), there is no evidence of any difference between the risk estimates for these two groups of studies. In the analysis of *in utero* exposure (Table C1) there is, however, some evidence of a higher risk estimate in the physician diagnosed group of studies; 1.38 (1.23-1.55) based on 13 estimates vs 1.19 (1.10-1.29) based on 14 estimates ($p<0.05$).

Tests were also made for heterogeneity according to the source of diagnosis. In the main analyses of in life exposure, there is quite consistent evidence of heterogeneity, with risk estimates lower when the child was the respondent than where the asthma diagnosis was based on medical records. Thus, in Tables A1, A3, A5 and A7, the relative risk associated with the child as the source was in the range 1.01 to 1.08, while that associated with medical records as the source varied between 1.30 and 1.36, with the heterogeneity significant or near significant in all the analyses. Where the parent was the source, the risk estimates also tend to be lower than where the medical records were, but only to a much smaller extent. For *in utero* analyses, the parent was nearly always the source of the diagnosis and tests of heterogeneity are not very sensitive.

Generally, these analyses suggest that relative risk estimates are higher where the asthma diagnosis was based on physician diagnosis and derived from medical records than when the diagnosis was made or reported by the child or parent. If one can assume that physicians can diagnose asthma more accurately, these observations are consistent with the presence of some diagnostic bias.

8.6 Representativeness

It is clear that the children included in a study may not necessarily be completely representative of all the children in the population of interest. This may arise because the study is deliberately conducted in a particular subgroup (e.g. a specific school), because of unwillingness of certain children (or their parents or doctors) to participate in the study, or because of study design requirements (e.g. that the child lives with both parents). In some studies, representativeness might also arise in the selection of cases with asthma, perhaps because some children (or their parents) do not report past or present symptoms to a doctor, so that a diagnosis of asthma is never made. Unrepresentativeness may lead to errors in estimation of the frequency of exposure or of the frequency of disease in the population, but this will not necessarily cause any bias in the estimated relative risk associated with exposure. However, if there is marked variation in the relative risk in different subsets of the population, lack of representativeness can cause selection bias. The results discussed under "consistency of findings" in §8.3 above suggest, however, that such marked variation in the relative risk across subsets of the population does not occur. As such, it seems unlikely that simple unrepresentativeness is a major issue.

However, unrepresentativeness may be an issue if one or more causes of unrepresentativeness are linked to both exposure and asthma. For example, if, in a cross-sectional study, non-responders tend to be more (or less) likely to be asthmatics with smoking parents, the observed relationship between asthma and parental smoking would clearly be weaker (or stronger) than that which actually existed. Similarly, if parents who smoke are more (or less) likely to draw

attention to their child's asthma to a doctor, a case-control study based on doctor diagnosed cases may over- (or under-) estimate the true association of asthma with parental smoking. Accurate estimation of the extent of possible bias from such sources is not possible. Data on the extent of non-response are often not reported in the source papers and for this reason have not at this stage been collected in the database. Information on the extent of undiagnosed asthma and its relationship to smoking would be difficult to assess.

All one can do is note that studies conducted in various settings and by various epidemiological techniques have consistently shown an association of asthma with exposure to ETS or smoking in pregnancy, and that the specific sources of bias noted above do not seem likely to these authors to be major.

8.7 Misclassification of exposure

In the analyses of total in life exposure in Table A1 (lifetime asthma) and Table A3 (current asthma), only four of the 166 relative risk estimates (2.4%) are based on biochemical measurement. In the analyses of *in utero* exposure in Table C1, none of the 27 relative risk estimates are based on biochemical measurement. It is clear that virtually all the estimates depend on data reported, typically by the parent, on smoking by the mother, father or other household members. Though reported data are generally highly reliable, there is ample documentation that a small proportion of smokers deny smoking on interview (Lee & Forey, 1995) and also that reporting of a child's smoking by a parent is not completely accurate. Random misclassification of exposed children as unexposed (or of unexposed children as exposed) will tend to lead to some underestimation of the true association of exposure with asthma. However, misclassification may not necessarily be random. If having a child with asthma makes it more likely that ETS exposure will be reported (perhaps because the respondent is trying to explain the child's condition), then the relative risk will be overestimated. If, on the other hand, parents with asthma tend to be less likely to report their smoking (perhaps out of guilt), then the relative risk will be underestimated.

The magnitude and direction of any bias is difficult to determine with certainty, but it seems likely that any effect of misclassification of exposure will be to somewhat underestimate the true association.

8.8 Smoking by the child

Given the concordance of smoking habits between family members (Lee, 1992), a child who smokes is more likely than a nonsmoking child to be ETS exposed at home and to have a mother who smoked in pregnancy. If smoking increases the risk of asthma, as has been claimed by some (e.g. Larsson, 1994; Beeh et al., 2001), it would then be expected that some of the observed association between asthma and exposure to ETS or smoking in pregnancy would arise as a result of confounding by smoking by the child. This would not explain the association between ETS and asthma seen in children less than 10 years of age, since virtually no children of that age smoke. It is also unlikely to be a major source of bias for somewhat older children where the proportion who smoke will be relatively small. Also, some of the researchers took pains to exclude smokers from their study.

Although these considerations would suggest little bias to the overall association due to smoking by the child, it is interesting that, as noted in §8.3, the main in life analyses show a consistent tendency for risk estimates to be relatively low in studies where smokers had been excluded. For example, in Table A1, relative risk estimates are 1.29 (1.17-1.42, n = 7) where child smokers had been included, 1.25 (1.21-1.29, n = 66) where the problem of child smoking had been ignored, and 1.09 (1.01-1.19, n = 20) where child smokers had been excluded, with the heterogeneity chisquared 9.79 on 2 d.f. ($p<0.01$). A similar pattern is also evident in a further similar analysis (data not shown) limited to studies of older children, with a highest age of at least 15 years. Here the relative risk estimates are 1.31 (1.19-1.45, n = 6) where child smokers had been included, 1.30 (1.21-1.40, n = 18) where the problem had been ignored, and 1.06 (0.96-1.17,

n = 14) where child smokers had been excluded, with the heterogeneity chisquared 12.97 on 2 d.f. ($p<0.01$).

8.9 Confounding

Although the causes of childhood asthma are not fully understood, there is a wide range of potential confounding variables that have been taken into account in at least some of the studies considered. Leaving aside other sources of exposure to tobacco smoke or its constituents, factors quite commonly considered (in at least 20 studies) include the sex, age and race of the child, location within the study area (including urban/rural residence and indices of air pollution), the medical history of the child (including breastfeeding and skin prick test results), the medical history of the family (including history of asthma, allergy or other respiratory symptoms), socioeconomic status (or parental education), household composition (number of children, single parent, position in sibship, etc), cooking and heating methods (including use of incense and mosquito coils), damp or mould in the home, aspects of housing quality (including age, size, crowding, use of shared bedroom, owned/rented) and close contact with animals (including pets in the home). However, some other factors that might be considered important, such as diet, exercise, use of day care and use of air conditioning and humidifiers, have only rarely been considered. Thus only one study took diet into account.

There are considerable problems in assessing the extent of confounding, particularly by individual variables. Many studies present only unadjusted or only adjusted relative risks, while those that do present adjusted and unadjusted risks typically only provide estimates adjusted for a number of potential confounding variables, so that the effect of adjustment for specific variables cannot readily be assessed. Furthermore, in some studies, the relative risks presented deliberately do not adjust for certain variables found in preliminary analyses not to have any material confounding effect.

The statistical analyses that we have conducted look at the issue of confounding using various methods:

A) alternative analyses are conducted using adjusted risks where possible and unadjusted risks otherwise, or using unadjusted risks where possible and adjusted risks otherwise;

B) within a given analysis, relative risk estimates are compared according to the number of adjustment variables taken account of (0, 1, 2, 3-5, 6-9 or 10 or more);

C) within a given analysis, relative risk estimates are compared according to whether or not the **study** took into account each of a specified list of potential confounding variables (sex; age; race; location; SES; family medical history; family composition; cooking, heating or air conditioning; housing quality, crowding, damp or mould; pets, animal contact or farming; or child's medical history); and

D) within a given analysis, relative risk estimates are compared according to whether the **relative risk** took into account a shorter specified list (sex; age; other ETS).

Text Table 8.1 summarizes the results from method A, for a number of the more important analyses. As can be seen, there is no consistent tendency for risk estimates to differ between the adjusted and unadjusted analyses. In six of the 11 selected Tables, the adjusted estimates are slightly lower, the difference being largest for Tables C1 (0.09), A7 (0.06) and A47 (0.06). In four of them, however, the adjusted estimates are slightly higher, the difference being largest for Table B2 (0.09). Note, however, that the adjusted and unadjusted estimates are based on relative risks which are often common to both – either because only unadjusted or only adjusted relative risks are available.

Text Table 8.1 – Comparison of adjusted and unadjusted RRs

Table	Asthma Outcome	Exposure Source	No of estimates	Adjusted[a] RR (95% CI)	Unadjusted[b] RR (95% CI)	Estimates differing[c]
A1	Lifetime	Total	93	1.24 (1.20-1.27)	1.25 (1.21-1.28)	38
A3	Current	Total	73	1.13 (1.10-1.16)	1.10 (1.07-1.12)	26
A5	Lifetime	Parent	64	1.27 (1.23-1.32)	1.28 (1.24-1.32)	27
A7	Current	Parent	40	1.19 (1.12-1.26)	1.25 (1.19-1.32)	15
A45	Lifetime	Mother	44	1.30 (1.25-1.35)	1.30 (1.26-1.35)	24
A47	Current	Mother	27	1.21 (1.14-1.28)	1.27 (1.20-1.34)	11
A53	Lifetime	Father	31	1.18 (1.13-1.23)	1.19 (1.14-1.24)	8
A55	Current	Father	21	1.03 (0.96-1.10)	1.06 (0.99-1.12)	7
B1	Lifetime	Total: low	16	1.11 (1.01-1.22)	1.08 (0.99-1.17)	6
B2	Lifetime	Total: high	16	1.47 (1.29-1.67)	1.38 (1.24-1.54)	6
C1	Lifetime/Current	*In utero*	27	1.25 (1.17-1.33)	1.34 (1.26-1.42)	16

[a] Fixed-effects estimate using relative risks adjusted for covariates where possible, and unadjusted relative risks otherwise

[b] Fixed-effects estimate using relative risks unadjusted for covariates where possible, and adjusted relative risks otherwise

[c] Number of estimates for which separate adjusted and unadjusted relative risks are available. For Tables A1, A5 and A45 the number of unadjusted estimates is slightly higher as some studies provided sex-specific unadjusted results

Perhaps a more useful test of adjustment is the method B analysis where the 'adjusted' relative risks are separated according to the number of variables actually taken into account. Thus, for example, in Table A1 (Lifetime asthma, total exposure), of the 93 relative risks considered, 47 are adjusted for no variables at all, while 14, 3, 11, 15 and 3 are adjusted, respectively, for 1, 2, 3-5, 6-9 or 10+ variables. Text Table 8.2 summarizes the results of the method B analyses for those analyses in Text Table 8.1 involving at least 20 estimates.

Text Table 8.2 – Comparison of RRs according to number of adjustment variables

	Numbers of adjustment variables						Numbers of adjustment variables						Heterogeneity		Trend
	0	1	2	3-5	6-9	10+	0	1	2	3-5	6-9	10+			
Table[a]	Number of estimates						Relative risks[b]						Chisq[c]	p	p[d]
A1	47	14	3	11	15	3	1.24	1.19	1.27	1.14	1.29	1.31	5.23	NS	NS
A3	29	3	1	9	21	10	1.15	1.08	1.78	1.21	1.11	1.19	13.79	<0.05	NS
A5	31	11	2	9	9	2	1.28	1.32	1.23	1.27	1.25	1.28	0.55	NS	NS
A7	18	3	-	7	7	5	1.18	1.09	-	1.26	1.20	1.17	0.97	NS	NS
A45	18	8	3	6	7	2	1.30	1.20	1.25	1.45	1.25	1.34	4.14	NS	NS
A47	11	3	-	4	4	5	1.32	1.16	-	1.54	1.20	1.16	6.45	NS	(-)
A53	19	4	2	2	3	1	1.23	1.16	1.33	0.90	0.97	0.95	17.33	<0.01	---
A55	9	2	-	3	4	3	1.03	0.81	-	0.81	0.88	1.12	10.69	<0.05	NS
C1	8	2	1	5	6	5	1.29	0.96	3.30	1.40	1.17	1.23	7.76	NS	NS

[a] See Text Table 8.1 for asthma outcome and exposure source corresponding to the Table number

[b] Relative risks shown are fixed-effects estimates

[c] Chisquared on five degrees of freedom (or four in the case of Tables A7, A47 and A55)

[d] Based on additional analysis (full details not shown) using trend coefficients of 0, 1, 2, 4, 8 and 12

The analyses for total lifetime exposure (Tables A1 and A3), parent smoking (A5 and A7) and smoking by the mother (A45 and A47) generally show no evidence of trend or heterogeneity of risks by number of adjustment variables. As discussed in §3, the significant heterogeneity for Table A3 may reflect, to an extent, a single study with very large weight having a quite low relative risk (WANG, which adjusted for eight variables). Nor is there any evidence of trend or heterogeneity in the analysis of *in utero* exposure (Table C1).

There is more evidence of an effect of adjustment in the analyses of smoking by the father (A53 and A55). In Table A53 (lifetime asthma), the heterogeneity is quite significant ($p<0.01$) and there is a significant ($p<0.001$) negative trend, with the relative risk estimate <1.00 in studies that had adjusted for three or more variables. In Table A55 (current asthma), the heterogeneity is also significant ($p<0.05$), with evidence of an increase only seen in those studies that had adjusted for 10 or more variables, studies which all had a relatively large weight (AGABI1, AGABI2, SHOHAT).

The general impression that there is no clear effect of adjustment for confounding variables is emphasized by the results of analyses using methods C and D as described above. For the analyses considered in Text Table 8.2, there is no consistent tendency for adjustment for any specific confounding variable to have a significant effect on the relative risk. Occasional significant findings are seen, mainly in Table A3 and Table A53 where one study (WANG in A3 and MCKEEV in A53) has a large weight and an unusual result, but there is no pattern. In any case, such comparisons are difficult to interpret as relative risks which adjust for a specific variable tend also to adjust for more other variables than do relative risks which do not adjust for the specific variable.

So far we have demonstrated an association of asthma with exposure that is consistent, dose-related and cannot readily be explained by any of the sources of bias and confounding commonly present in epidemiological studies. Though

limitations of the studies preclude a definitive judgement, especially in view of the weakness of the association, the findings seem consistent with some aspect of exposure to tobacco smoke constituents causing an increased risk of asthma. However there are still two key questions that need to be answered. Firstly, is the effect due to postnatal ETS exposure or to smoking in pregnancy, or both? Second, does the effect relate to induction or exacerbation of asthma?

8.10 Smoking by the father

The evidence for an association between smoking by the father and risk of asthma is relatively weak. For analyses based on relative risks for smoking by the father regardless of the mother (selecting relative risks for smoking by the father only when the former relative risks are not available), a significant increase of 1.18 (1.13-1.23, n=31) is seen for lifetime asthma from Table A53, but a non-significant increase of 1.03 (0.96-1.10, n=21) is seen for current asthma from Table A55. As noted in §3.8, the estimate for lifetime asthma is based on heterogeneous ($p<0.001$) data, though the random-effect estimate of 1.16 (1.08-1.26) is still significant.

A problem with the analyses based on smoking by the father regardless of the mother is that any association seen may partly reflect smoking by the mother, since the smoking habits of husbands and wives are highly correlated (Lee, 1992). In this context it should be noted that the detailed analyses showed that the association is only evident in relative risks which were adjusted for no or very few potential confounding variables, and that no real evidence of an association is seen for those relative risks that are adjusted for sex, age, other sources of ETS exposure or other factors.

For the analyses based on smoking by the father only, no significant increase in risk is seen, with meta-analysis estimates of 1.11 (0.96-1.29) for lifetime asthma from Table A57 and 1.11 (0.97-1.28) for current asthma from Table A59. These meta-analyses are based on relatively few individual relative

risk estimates, six for lifetime asthma, none of which are statistically significant, and four for current asthma, one of which is significant – the estimate of 1.26 (1.01-1.58) for AGABI1.

Note that there is only one estimate relating risk of asthma to smoking only by household members other than the parents – the estimate of 1.00 (0.60-1.99) for current asthma for GILLIL which is not significant.

Whereas Tables A57-A60 relate to smoking by the father only, Tables A65-A68 relate to smoking by any household member in the absence of smoking by the mother. For current asthma, the meta-analysis estimates in Tables A67 and A68 are in fact identical to those in Tables A59 and A60, as there are no relevant additional relative risk estimates. For lifetime asthma, there are four additional estimates, one significant – that of 2.41 (1.20-4.87) for KERSHA – and the meta-analysis estimate becomes marginally significant, at 1.14 (1.01-1.29).

It should also be noted that, in many of the analyses relating to exposure from sources other than the mother (Tables A57-A68), there are additional studies with incomplete data that could not be included in the meta-analyses, and that none of them reported a significant association with lifetime or current asthma.

Overall, these data provide no clear evidence that smoking by the father, or indeed by household members other than the mother, is associated with an increased risk of asthma. However, though an effect of paternal smoking cannot be inferred with any confidence, the possibility that one exists cannot be excluded. In this context, it is important to note the relatively small number of studies with relevant data, and the rather lower ETS exposure of the child (as judged by cotinine levels) associated with paternal than maternal smoking (Lee, 1999b).

8.11 Discontinued exposure

As discussed in §3.9, some studies have related asthma to discontinued exposure, investigating whether previous but not current exposure is linked to an increased risk. For lifetime asthma, seven relative risks give a combined estimate of 1.20 (1.11-1.30). However, the significance is heavily dependent upon the relative risk (1.22, 1.12-1.33) for a single large study (MCKEEV) and three of the relative risk estimates are <1.00. For current asthma, though one study (AGABI1) shows a significant increase (1.27, 1.06-1.52), the eight relative risks taken together show no association, with the combined estimate 1.02 (0.94-1.12). The relative risks for discontinued exposure tend to be somewhat lower than those seen for current exposure in the same studies. For lifetime asthma, one can compare meta-analysis estimates of 1.34 (1.26-1.42) for current exposure and 1.20 (1.11-1.30) for discontinued exposure, while for current asthma one can compare estimates of 1.17 (1.08-1.27) for current exposure and 1.04 (0.95-1.15) based on those studies providing estimates for both exposures.

If ETS causes asthma, one might expect to see an increased risk of lifetime asthma and no increased risk of current asthma in the children of smokers who quit smoking. If, on the other hand, the association of asthma with parental smoking is due only to an effect of maternal smoking in pregnancy, quitting smoking should not eliminate the risk. Although, superficially, the results for discontinued exposure might seem consistent with the former hypothesis, there are a number of reasons why an effect of ETS cannot reliably be inferred. These include the relatively small number of studies, and the dominance of individual studies, as well as the fact that the exposure which was discontinued comes from a variety of sources – for lifetime asthma, two of the relative risks relate to the mother, three to any parent and two to any household member, while for current asthma, five relate to the mother, one to the father and two to any household member. Another problem is that all but one of the estimates for mother, father or any parent relate to being an ex-smoker, so that smoking may have been discontinued before the child was born (or conceived). Also, smokers who quit

may tend to have smoked less when they were smoking than did smokers who continued to smoke. More data are clearly needed on discontinued exposure.

8.12 Smoking in pregnancy

The data on smoking by the father and on discontinued exposure summarized in the previous two sections offer somewhat indirect evidence relating to the role of ETS in the causation of asthma. Of more direct relevance are the data from studies that have presented separate relative risks for in life exposure only, *in utero* exposure only, and for both in life and *in utero* exposure. The relevant data are discussed in some detail in §7. These data, though somewhat limited, show no significant association of in life only exposure with risk of asthma, but a significant increase associated with *in utero* only exposure or with both exposures. The relative risks for lifetime/current asthma associated with maternal smoking are 1.08 (0.99-1.18) for in life only exposure, 1.41 (1.14-1.75) for *in utero* only exposure and 1.33 (1.21-1.46) for both exposures. These results are consistent with smoking in pregnancy, but not ETS, causing asthma, though they do not exclude the possibility of a weaker effect of ETS exposure.

§7 also includes presentation of rather limited data relating to the effect that adjustment for *in utero* exposure had on relative risks for in life exposure and the effect that adjustment for in life exposure had on relative risks for *in utero* exposure. These comparisons tend not to be very informative, partly because they are based on few studies, partly because quite a number of the results are reported simply as not significant, and partly because comparison is typically between unadjusted risks and risks adjusted for a whole range of potential confounding variables in addition to the exposure of interest.

8.13 Exacerbation or induction?

In one model of asthma, children remain asthma free until some exposure first induces symptoms of the disease and leads to the child being diagnosed as asthmatic. Subsequently other exposures (not necessarily to the same agent) may

lead to exacerbation of the asthmatic symptoms. As the main interest of this project is in induction rather than exacerbation, we have not considered studies that clearly related to exacerbation, in which the frequency of symptoms in asthmatic children is related to ETS exposure (either in everyday life, or controlled in chamber studies). Instead we have limited attention to studies that relate to the whole population and compare the frequency of asthma in exposed and unexposed children, whether using a prospective, case-control or cross-sectional design.

It is important to realize that there are difficulties in interpreting all the results from these studies strictly in terms of induction. In theory induction relates to the probability of a previously asthma free child getting the condition for the first time. Ideally one would conduct a prospective study in which information is collected on onset of asthma in children asthma free at the start of the study, and on regularly updated exposure information. Then one would base the analysis (using life-table methods) on data for each of a number of relatively short periods of time, which classified asthma free children by exposure at the start of the period and compared the probability of onset of asthma in the different exposure groups. In principle one could also conduct a similar analysis using retrospective data on time of asthma onset and on history of exposure obtained in a case-control or cross-sectional study.

In practice the data collected rarely conform to this ideal situation. Many of the studies are cross-sectional and only collect information on whether the child is currently asthmatic. The lack of data on time of onset of asthma means that one cannot interpret an association of, say, maternal smoking with asthma as indicating a specific effect on either induction or exacerbation. More insight can be gained from studies of whether the child has ever had asthma. Assuming that the child did not have asthma diagnosed at birth, which seems unlikely, the endpoint can be interpreted as induction between birth and age C, the current age of the child.

Even then there is a problem in that many studies collect data relating to ETS exposure at age C rather than between birth and onset of asthma. For induction to be inferred, exposure has to occur before onset. However, if one is willing to accept that the smoking habits of parents (and household members) are likely to remain relatively constant, current smoking habits may be taken to approximate smoking habits before the time of onset of asthma. However, this may not be the case if presence of asthma in a child affects the smoking habits of the parents – parents may cut down or give up smoking if they believe that their smoking may exacerbate their child's asthma. However, the data provide little evidence of this. As discussed in §3.6, relative risk estimates for lifetime asthma for both total and parental exposure are virtually unaffected by whether the most recent or the earliest estimate of in life exposure is used. For example, for parental exposure, Table A13 (recent exposure) gives a meta-analysis estimate of 1.27 (1.22-1.31), while Table A21 (earliest exposure) gives an estimate of 1.27 (1.23-1.31). Although, of the 64 estimates included in each of these meta-analyses, 55 are the same (as the study only provides one relevant estimate), the eight pairs that are based on different exposure timing show no consistent or marked difference, as shown in Text Table 8.3.

Text Table 8.3 – Effect of timing of parental smoking on RR for lifetime asthma

	Study	Recent smoking (Table A13)		Earliest smoking (Table A21)	
Study	type[a]	When	RR (95% CI)	When	RR (95% CI)
BUTZ	CC	Current	1.12 (0.51-2.46)	Ever	1.24 (0.72-2.14)
CHEN2	CS	Current	1.72 (0.95-3.10)	Ever	1.67 (1.01-2.77)
EHRLI2	CC	Current	1.90 (1.10-3.60)	Ever	2.00 (1.10-3.80)
KUEHR	CS	Current	0.77 (0.53-1.12)	<1 year	0.68 (0.44-1.06)
KUHR	CS	Current	1.90 (1.01-3.59)	In life	2.01 (0.88-4.61)
SHERMA	Pr	Ever	1.18 (0.76-1.83)	Ever 1 year ago	1.09 (0.68-1.74)
SOYSET	CS	Current	1.17 (0.66-2.07)	<1 year	1.24 (0.70-2.20)
VERHOE	CC	Current	0.74 (0.48-1.14)	Ever	0.78 (0.49-1.25)

[a] CC = Case-control CS = Cross-sectional Pr = Prospective

Inspection of this table reveals a further difficulty in that in four of the eight studies, the index of earliest smoking used was 'ever,' so that, as they were all of case-control or cross-sectional design, the smoking by the parent may have

occurred before the birth of the child. For only three studies (KUEHR, SHERMA and SOYSET) did earliest smoking relate to a period in the child's life that was very likely to be before asthma onset.

Of the 190 studies considered in this review, few actually reported results which appeared to relate onset of asthma to smoking by parents (or other household members) occurring in the preceding lifetime of the child. Only six studies, four prospective and two case-control studies, clearly qualify in this respect. The two case-control studies limited attention to cases with first occurrence of asthma, INFANT considering exposure since birth and WILLE1 current exposure. Of the prospective studies, PONSON followed up children from shortly after birth and related postnatal exposure at baseline to subsequent onset of asthma. MARTIN and MCCON1 followed up older children, but restricted attention to those asthma free at baseline, linking exposure at baseline to subsequent onset of asthma. SHERMA had a baseline interview in 1975, when the children were aged 5-9, and then subsequent interviews from 1978-1988, covering both exposure and presence of asthma. Formal onset analysis methods were used, so that only exposure of asthma-free children was considered at any point.

There are also two other prospective studies, which might also be considered to qualify, but not so clearly. These studies, JAAKKO and STRACH, both followed up children from shortly after birth, but the exposure indices, respectively "at birth" and "around time of child's birth", do not clearly distinguish *in utero* and in-life exposure. There are also a number of cross-sectional studies which related smoking when the child was very young to the presence of asthma some years later. Thus HABY considered smoking before age six months, KUEHR and SOYSET childhood smoking before age one year, and FORSB1, FORSB2, FORSB3, STERN2, TIMONE and WILLE2 considered smoking before age two years, but here one cannot strictly rule out that the asthma occurred before the smoking.

It is interesting to note that there were some other prospective studies where data seemed to have been collected that would have allowed relevant analysis, but where either the appropriate analysis was clearly not done (LEEDER, TAYLOR) or where the description of the exposure variable was too unclear to be confident that the smoking preceded the asthma (FERGUS, MCKEEV, ODDY, SIGURS, ZEIGER).

8.14 Reviews of childhood asthma by Cook and Strachan

Strachan and Cook have published a number of review papers concerning parental smoking and health effects in children. The first of these (Strachan & Cook, 1997) is entitled "Parental smoking and lower respiratory illness in infancy and early childhood." Although this did not specifically look at asthma, part of the review considered 10 community studies of wheezing illness. Five provided data on risk relating to either parent smoking, for which a relative risk of 1.54 (1.30-1.81) was reported. For mother smoking the estimate was 1.98 (1.71-2.30), based on seven studies, and for father only smoking it was 1.19 (0.92-1.53), based on three studies. The main conclusion of the paper was:

> "The relationship between parental smoking and acute lower respiratory illness in infancy is very likely to be causal. Although it is impossible to distinguish the independent contributions of prenatal and postnatal maternal smoking, the increased risk associated with smoking by other household members suggests that exposure to environmental tobacco smoke after birth is a cause of acute chest illness in young children."

However, it should be noted that this was based to a considerable extent on analyses for endpoints alternative to wheezing illness. Elsewhere in the paper the authors state that "maternal smoking appears to be relatively more important, and paternal smoking perhaps less important in studies which have ascertained wheezing illness specifically."

The same year these two authors published a further paper (Cook & Strachan, 1997) entitled "Parental smoking and prevalence of respiratory symptoms and asthma in school age children." This review considered asthma, wheeze, cough, phlegm and breathlessness and was restricted to population surveys (i.e. cross-sectional studies). They identified 25 studies of asthma, with results reported for five indices of parental smoking. Meta-analysis results were as follows: either parent smokes 1.21 (1.10-1.34, n=21), one parent smokes 1.04 (0.78-1.38, n=6), both parents smoke 1.50 (1.29-1.73, n=8), mother only smokes 1.36 (1.20-1.55, n=11) and father only smokes 1.07 (0.92-1.24, n=9).

They concluded that:

> "The relationship between parental smoking and respiratory symptoms seems very likely to be causal given statistical significance, robustness to adjustment for confounding factors, consistency of the findings in different countries, and the evidence of dose response. The raised risk in households where the father, but not the mother, smoked argues for a postnatal effect."

There are a number of similarities about their analyses and ours. Thus, they reported a similar magnitude of association, statistical significance but some heterogeneity, consistency across countries, a dose-response relationship and lack of effect of confounder adjustment. They found that "those studies reporting the highest odds ratio were more likely to be early publications, to be small and not to adjust for confounders," suggesting some publication bias. We did not find evidence of publication bias in our analyses based on studies of all designs, but we agree that publication bias is not likely to be an important biasing factor. They also noted that the evidence relating to parental smoking in the past is unclear because "so few data have been published and ex-smokers are likely to have been lighter smokers."

It is important to note, however, that their final conclusion that "the raised risk in households where the father, but not the mother, smoked argues for a postnatal effect" appears to be largely due to their analyses of data for wheeze and cough, where the relative risks for father only smoking were higher and statistically significant – 1.14 (1.06-1.23, n=10 for wheeze) and 1.21 (1.09-1.34, n=9 for cough).

It is interesting that, whereas Cook and Strachan reported nine relative risk estimates for father only smoking based on cross-sectional studies alone, our analyses based on all study designs include only six such estimates for lifetime asthma and four for current asthma. An investigation to see whether we might have missed relevant data revealed that, of the nine estimates for father only smoking reported by Cook and Strachan, five (for studies CHEN2, GOREN2, SOTOQU, SOYSET and STERN1) have a footnote in their Table 2 indicating that the data are actually for "father currently smokes versus not" and are thus not actually for father only smoking at all. Furthermore, for study GOREN1, the estimate cited is actually for household member other than mother smokes and not for father only smokes, and for study KAY, though we both include estimates, they cited an estimate unadjusted for covariates (1.3, 0.86-1.97), whereas we use a somewhat lower adjusted estimate (1.25, 0.81-1.92). They included an estimate from study BURCHF of 0.76 (0.56-1.04) for which the source is unclear – we only have nonsignificant estimates of 0.84 for boys and 0.65 for girls without any CI and cannot see how Cook and Strachan derived their CI estimates so as to allow inclusion of the study in the meta-analyses. Indeed, our estimates only agree for one study (FORAST), and we also have data from three further cross-sectional studies (DOLD, GILLIL and VENNER).

Our conclusion from this investigation is that Cook and Strachan's estimate of 1.07 (0.92-1.24) for father only smoking is not actually a true estimate for father only smoking at all, and emphasizes the importance of deriving meta-analysis estimates for consistently defined indices of exposure (and disease). The

same conclusions can be drawn from a similar investigation of their data for mother only smoking, for which six of the eleven estimates included in their meta-analyses have footnotes indicating that they actually relate to "mother currently smokes versus not" and one to "mother smoked in pregnancy and infancy versus not".

In 1998 the same authors published a paper entitled "Parental smoking and childhood asthma: longitudinal and case-control studies." (Strachan & Cook, 1998) Four main groups of studies were considered: incidence studies, natural history studies, case-control studies and case series. The natural history studies and the case series relate to asthma exacerbation (or prognosis) and are not considered in detail here. Their definition of asthma included some studies which we would have excluded as being based on wheezing. There were two relevant relative risks reported for the incidence (prospective) studies, maternal smoking for occurrence in the first 5-7 years of life 1.31 (1.22-1.41, n=4) and maternal smoking for occurrence later in childhood 1.13 (1.04-1.22, n=4). Based on the case-control studies they reported meta-analysis estimates of 1.37 (1.15-1.64, n=14) for parental smoking, 1.59 (1.27-1.99, n=8) for maternal smoking and 0.94 (0.78-1.12, n=8) for paternal smoking. However, they do not report results for mother only or father only smoking. The authors concluded that:

> "The excess incidence of wheezing in smoking households appears to be largely non-atopic "wheezy bronchitis" with a relatively benign prognosis, but among children with established asthma, parental smoking is associated with more severe disease. This apparent paradox may be reconciled if environmental tobacco smoke is considered a co-factor provoking wheezing attacks, rather than a cause of the underlying asthmatic tendency."

It is interesting that this conclusion, based on the results of all the studies, including those on asthma exacerbation, supports the view that ETS does not

induce asthma. However, it is clear from the paper that the mechanism they propose, considering ETS as "a co-factor operating with intercurrent infections as a trigger of wheezing attacks, rather than as a factor initiating or inducing the asthmatic state" is more a proposal than a definitive conclusion. It is interesting that they note in the paper that "in case-control studies maternal smoking appears to be the dominant influence, with little effect from smoking by the father" and that the "weak association between the incidence of asthma and paternal smoking" seen in "most longitudinal studies" "could be partially due to confounding by maternal smoking."

Comparison of our findings with those of Strachan and Cook is complicated by their splitting their analyses into three papers, their not using consistent exposure indices in each paper, their consideration of endpoints other than asthma and tending to generalize from these results to asthma, and their including wheezing in asthma in some analyses. Nevertheless their results show considerable similarity to ours. In this context it is interesting particularly to note that none of their meta-analyses for father smoking show a significant increase in risk. Even when combined, the estimates from the three papers, (Cook & Strachan, 1997; Strachan & Cook, 1997; Strachan & Cook, 1998) of 1.19 (0.92-1.53) and 1.07 (0.92-1.24) for father only smoking, and 0.94 (0.78-1.12) for father smoking give an overall estimate of 1.04 (0.94-1.16), which is not significant. This agrees with our conclusions.

Their papers pay little attention to distinguishing effects of ETS and of maternal smoking in pregnancy, tending to assume associations seen with maternal smoking are due to ETS. Even then, however, they are much more certain there is an exacerbating rather than an inducing effect.

8.15 The Report of the California EPA

In their review of the "Health Effects of Exposure to Environmental Tobacco Smoke" the California EPA (National Cancer Institute, 1999) devoted

separate sections to asthma exacerbation and to asthma induction. They concluded that "there is consistent and compelling evidence that ETS is a risk factor for induction of new cases of asthma."

They identified 37 studies that satisfied four criteria:

(a) The endpoint must represent the development of asthma in persons up to 18 years of age. Studies that examined outcomes of 'wheezy bronchitis' or 'constant wheeze/whistling in the chest' were also included and analysed separately and jointly with those studies which examined only physician diagnosed asthma.
(b) Postnatal household exposure must be studied.
(c) Relative risks or odds ratios (and their standard errors) must be reported or be calculable from data available.
(d) Studies must be independent.

Relative risks and 95% CIs were presented graphically for 27 studies that used clinically recognized asthma as the outcome and for 17 studies that used 'wheezing bronchitis' or 'chronic wheezing/whistling in the chest' as an outcome. No indication was given in the figures or text as to which exposure index is selected.

They reported a combined estimate of 1.44 (1.27-1.64) for clinically recognized asthma and 1.47 (1.34-1.61) for the alternative outcome. They noted some heterogeneity but elevated RRs in all subgroups investigated. The pooled RR was noted to be 1.60 (1.29-1.99) for maternal smoking and 1.34 (1.11-1.61) for household smoking only. The analyses reported include no formal assessment of dose-response or any estimation of the association with paternal smoking.

They appear to have based their conclusion of a causal effect of ETS exposure on asthma induction on a number of factors:

(a) A "strong and consistent association between exposure to ETS and development of childhood asthma" – though they do not define strong and relative risks of about 1.5 are not generally considered to be strong;

(b) A dose-response – noting that "there appears to be a simple biological gradient of effect (or dose-response) in studies that collected data on levels of smoking, where effects were detectable only when the mother smoked 10 or more cigarettes per day (e.g. Martinez et al. 1992)";

(c) Higher relative risk estimates in studies using "more precise measures of exposure" – basing this conclusion on a very limited number of studies that used cotinine, some of which related to their alternative outcome rather than to asthma;

(d) Higher relative risk estimates in studies involving pre-school children;

(e) The association with ETS being generally independent of confounder adjustment, with those studies which "controlled for three or more potential confounders and effect modifiers" tending "to have greater estimates of relative risk of asthma than those studies that adjusted for fewer than three covariates", a conclusion that we certainly did not find;

(f) Effects seen in relation to paternal smoking – citing results from various studies in China by Chen (Chen & Li, 1986; Chen et al., 1986; Chen et al., 1988; Chen, 1989), only one of which actually concerns asthma at all; and

(g) Biological plausibility – claiming that:

"1) ETS exposure predisposes young children to an increased risk of repeated respiratory infection, a recognized risk factor for the development of asthma; 2) ETS causes airway hyperresponsiveness; 3) ETS may increase the risk of childhood atopy and of increased circulating allergy-related antibodies (IgE), enhancing the probability of allergic asthma; and 4) cigarette smoke causes airway inflammation in active smokers (Niewohner, 1974) and may have similar (but lower-level) effects in people exposed to sidestream smoke."

Study of this report reveals a number of severe limitations. These include drawing conclusions on dose-response and effects of paternal smoking without carrying out any proper overall assessment of the evidence, failure to look at effects of confounder adjustment within-study, failure properly to separate possible effects of *in utero* and in life exposure, and failure adequately to address the difficulties in distinguishing effects on asthma induction and asthma exacerbation from the data that they have considered.

The meta-analysis estimate of 1.44 (1.27-1.64) that they reported for clinically recognized asthma is markedly higher than those that we found for total exposure; 1.24 (1.20-1.27) for lifetime asthma and 1.13 (1.10-1.16) for current asthma, and it is therefore important to try to see why this difference arose. An investigation of the issue led to the following observations:

(a) The data included in the meta-analysis are only presented graphically in Figure 6.1 of their report (National Cancer Institute, 1999), which makes it difficult to assess the actual data used.
(b) Neither the text of the report, nor Figure 6.1, makes it clear what exposure index has been used. The second criterion noted above demands that it must be "postnatal household exposure" but within that definition there is considerable scope for selection of estimates in some studies.
(c) Nor does the report or the figure define whether the relative risk concerns lifetime or current asthma.
(d) Nor is any information given concerning whether results cited are adjusted or unadjusted for covariates.
(e) We have included estimates for all 27 studies considered in Figure 6.1, though for some studies we used alternative estimates from other papers.
(f) Figure 6.1 includes an estimate from one study (Bener et al., 1991) which has a 95% CI that is so narrow that it cannot be seen. We had rejected this paper because of various discrepancies and because, from comparison with two

other papers (al Frayh et al., 1989; al Frayh, 1990), which we did use for our estimates, it appeared to relate to wheeze, not asthma. The paper EPA used (Bener et al., 1991) reported results from a logistic regression which, when converted into odds ratios, gave estimates of 1.15 (1.09-1.22) for father smoking and 1.04 (0.99-1.10) for mother smoking, which both implied (see Lee, 1999a) numbers of subjects far in excess of those studied. Clearly, the estimate used by California EPA from this study had a CI that was far too narrow, so that its weighting in the meta-analysis would be totally wrong.

(g) In two studies (PALMIE and MURRAY), the source data give separate relative risks for atopic and non-atopic children. While these estimates can readily be combined, and we have done so for our estimates, Figure 6.1 selects, for no apparent reason, results for atopic children for MURRAY and results for non-atopic children for PALMIE.

(h) Where the source data give results by level of exposure, we have calculated estimates for combined exposure, but the California EPA have not, apparently using only the relative risk for high exposure in studies PALMIE, INFANT and DODGE.

(i) In study BURCHF, where equivalent results for both sexes are available, Figure 6.1 (asthma) appears to present data for boys, while Figure 6.2 (wheeze) appears to present data for girls.

(j) For study MCCON2, we had included an estimate of 0.56 (0.12-2.56) for lifetime asthma based on results reported in (McConnochie & Roghmann, 1986), having rejected the paper cited in Figure 6.1 (McConnochie & Roghmann, 1989) as lacking detail. Although the later paper presents some data suggesting an association of maternal smoking with wheezing, it presents no relative risk for asthma consistent with the value of about 2.8 shown in the Figure, and indeed includes a statement "None of the passive smoking variables predicted asthma at either of the interviews."

(k) Study WEITZ1 was included although exposure was *in utero*, so did not meet the second criterion noted above.

From this investigation, it can be concluded that the meta-analysis is extremely poorly described and presented, and is based on estimates that are not derived on any sort of consistent basis, some of which are clearly inappropriate. Taking into account also the limitations noted above, it is abundantly clear that this rather poor piece of work provides no valid scientific justification for the conclusion of the California EPA that ETS induces asthma in children.

9. Summary and conclusions

Part I of this report describes how databases were set up containing over 1200 relative risks from 190 epidemiological case-control, prospective or cross-sectional studies, of prevalent or incident asthma in children. Part I gives details of how the relevant studies and the source papers were identified, the structure of the databases, the methods used for entry and checking of data and derivation of relative risks, as well as summary information about the characteristics of the studies and relative risks themselves. Part I ends by describing techniques for conducting meta-analyses and the format of the tables presenting the results.

This part of the report, Part II, presents results of a series of meta-analyses of the database aimed at giving insight into how the relative risk of asthma varies by the source, timing and amount of the exposure to parental smoking/ETS, the definition of the unexposed group, the definition of the asthma outcome, the sex and age of the child, the location, timing, size and type of study, the source of the information on exposure and diagnosis, and the extent of adjustment for confounding variables.

The main conclusions reached from the analyses are as follows:

There is an association between in life exposure to parental smoking and either lifetime or current asthma. As illustrated in the table below, which summarizes relative risks and 95% confidence limits from random-effects meta-analyses, the association is stronger in relation to maternal than paternal smoking and is not statistically significant where the mother does not smoke (exposure = father only, or household exposure but not mother).

Text Table 9.1 – Summary of meta-analyses for in life exposure

	Lifetime asthma		Current asthma	
Exposure	n	RR (95% CI)[a]	n	RR (95%CI)[a]
Total[b]	93	1.23 (1.17-1.28)	73	1.18 (1.11-1.26)
Parent[c]	64	1.26 (1.20-1.33)	40	1.18 (1.08-1.29)
Both parents	9	1.44 (1.22-1.70)	6	1.68 (1.23-2.28)
Mother/mother only[d]	44	1.31 (1.23-1.39)	27	1.23 (1.10-1.38)
Mother only	4	1.16 (0.80-1.67)	4	1.35 (1.01-1.79)
Father/father only[e]	31	1.16 (1.08-1.26)	21	1.00 (0.93-1.09)
Father only	6	1.11 (0.96-1.29)	4	1.11 (0.95-1.30)
Household exposure other than parents	3	1.32 (0.92-1.89)	6	1.49 (1.30-1.71)
Household exposure but not mother[f]	10	1.14 (1.00-1.30)	4	1.11 (0.95-1.30)

[a] Based on relative risks (RR) adjusted for covariates where adjusted data are available
[b] Preferring, in order, RR estimates for biochemical, total, household and parental exposure
[c] Preferring RR estimates for mother to those for father if estimates for any parent not available
[d] Preferring RR estimates for mother regardless of father to those for mother only
[e] Preferring RR estimates for father regardless of mother to those for father only
[f] Preferring RR estimates for father only where alternatives are available

There is evidence of a dose-response relationship. For those studies which provide relative risks by extent of exposure, typically in terms of number of cigarettes per day or number of persons in the household who smoke, estimates (relative to no exposure) are higher for the highest exposure than for the lowest. For lifetime asthma, random-effects estimates based on 16 pairs of relative risks were 1.48 (1.27-1.73) for high exposure and 1.12 (0.99-1.27) for low exposure. For current asthma, estimates are 1.34 (1.23-1.46) for high exposure and 1.12 (1.04-1.21) for low exposure.

Although many of the meta-analyses conducted show statistically significant heterogeneity between the individual relative risk estimates, associations seen for total, parental and maternal exposure are generally consistently seen in subsets of the data defined by a wide range of factors. A possible exception is that studies conducted in the Far East do not show evidence of an association. There is evidence in some of the analyses, but not all, that associations may be weaker in older than younger children, in studies where the child was the respondent for questions on either smoking habits or diagnosis of

asthma, in studies where steps had been taken to exclude children who smoked, and in cross-sectional and prospective studies rather than case-control studies. However, the prevailing impression is of a highly consistent association.

Analysis of the relative risks included in the meta-analyses do not show any particular indication of publication bias. However, there are quite a large number of studies that could have provided data suitable to be included in meta-analyses, but which had not done so, and a suggestion that significant associations in these incompletely reported studies are less frequently seen than in the studies included in the meta-analyses. These findings do not, however, suggest that publication bias is a major issue.

There is no clear evidence of confounding by a variety of non-smoking lifestyle factors, although a number of different approaches were used to investigate this. There also seems no reason to believe that the association had arisen because of misclassification of exposure or diagnosis, or due to unreported smoking by the child.

There is a highly significant ($p<0.001$) association of asthma with maternal smoking in pregnancy, with a random-effects estimate of 1.30 (1.16-1.45) based on 27 individual relative risks for lifetime or current asthma. Dose-response data are limited, but quite consistently show a significant increase at high dose but little or no increase at low dose.

Eight studies presented relative risks separating the individual associations with *in utero* and in life exposure. There is a significant increase in risk associated with *in utero* only exposure (1.53, 1.05-2.23, n = 7) and with both *in utero* and in life exposure (1.32, 1.18-1.49, n = 9) but not with in life only exposure (1.08, 0.99-1.18, n = 7), based on results with a preference for lifetime over current asthma and for mother rather than father as the source of in life exposure. Alternative preferences do not affect the conclusion that in life only

exposure is not associated with an increase in risk. Indeed, with the exception of one small study, all relative risk estimates are very close to 1.00.

The overall data are consistent with some effect of parental smoking on risk of asthma in the child. However, the lack of a significant association with in life only exposure and with smoking by the father only (and more generally with smoking by other household members except the mother) argues against ETS exposure being responsible. The pattern of results fits in much better with a role of smoking in pregnancy, though the possibility of some effect of ETS cannot be excluded. The increased risk of asthma seen where the mother smokes postnatally can reasonably be attributed to the fact that many of these mothers would also have smoked in pregnancy. The tendency seen in some analyses for risk to be increased where the father smokes can also reasonably be attributed to the strong correlation between smoking by parents, so that children born to fathers who smoke would be more likely to have mothers who smoked postnatally and in pregnancy. Evidence related to ex-smoking is very limited and inconclusive.

Our meta-analyses have deliberately excluded studies of asthmatic children which relate specifically to asthma exacerbation. As such, one cannot make inferences regarding asthma exacerbation from the data presented. However, it should be noted that there are difficulties in interpreting all the evidence presented here strictly in terms of asthma induction, and indeed the number of studies that relate onset of asthma to previous in-life exposure of the child to smoking by parents (or other household members) is very limited.

Our conclusion that the available evidence does not clearly demonstrate any causal effect of ETS exposure, and suggests strongly that smoking in pregnancy is responsible for most, if not all, of the association seen between asthma and smoking by parents or household members, is consistent with the view expressed by Strachan and Cook (Strachan & Cook, 1998) that ETS is not "a

cause of the underlying asthmatic tendency", but not with the conclusion of the California EPA report (National Cancer Institute, 1999) that ETS induces asthma.

This report includes a brief review of both the series of papers by Strachan and Cook (Cook & Strachan, 1997; Strachan & Cook, 1997; Strachan & Cook, 1998) and the California EPA report. The California EPA report is particularly weak, basing its findings on a meta-analysis which is extremely poorly described and presented, and is based on relative risk estimates that are not derived on any sort of consistent basis, some of which are clearly inappropriate. Furthermore, that report draws conclusions on dose-response and effects of paternal smoking without formal assessment of the available evidence, and fails properly to separate out possible effects of *in utero* and in life exposure. The papers by Strachan and Cook are much better, but pay little attention to distinguishing effects of ETS and of maternal smoking in pregnancy, and claim an increased risk of asthma in relation to smoking only by the father based on data which do not support this claim.

Claims that ETS exposure induces asthma in children cannot be regarded as conclusively demonstrated by the available data. The evidence of an effect of smoking in pregnancy is stronger. More studies are needed which distinguish effects of smoking during pregnancy from effects of ETS exposure during the child's life, which estimate the risk of asthma associated with smoking by household members in the absence of smoking by the mother, and which restrict attention to ETS exposure prior to the onset of the asthma.

10. References

References to the source papers for the individual studies are given in Appendices A and B to Part I of this report.

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