INTERNATIONAL EVIDENCE

ON

PASSIVE SMOKING AND

CHILDHOOD ASTHMA INDUCTION

(PROJECT IESAST)

PART I: THE DATABASES; METHODS USED TO COLLECT AND ANALYSE THE DATA AND SCOPE OF THE INFORMATION OBTAINED

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

Based on papers published up to the end of 2002, 190 studies have been identified which provide information from epidemiological case-control, prospective or cross-sectional studies of prevalent or incident asthma in children. Only studies where the endpoint was 'asthma' were included, and studies of 'wheeze', 'wheezing bronchitis', 'chronic wheezing', 'asthma or wheeze' or 'asthmatic bronchitis' were excluded.

Two linked databases have been set up. One contains details of the characteristics of each study, while the other contains relative risk data relating to certain aspects of passive smoke exposure (for parental or household exposure, when exposed, and who smoked; biochemically assessed exposure). For each study, the study database contains details of the study itself, the definition of asthma used, and the potential confounding variables considered. For each of the 1220 relative risks included, the relative risk database contains not only the relative risks and 95% confidence intervals, but precise details of their definition and information on how they were derived.

This report starts by describing the methods used to identify relevant papers, which involved examining over 1000 papers, and classifying them into separate studies. It then describes in detail the structure of the databases and the methods used for entry and checking of data. The methods by which relative risks were derived from data presented in various ways are also described. Although the intention was to have non overlapping studies, this could not always be achieved without marked loss of useful data. There were 181 independent principal studies, with nine subsidiary studies where data will only be used in meta-analyses where equivalent results are not available from the principal studies.

The 181 principal studies were conducted in 41 countries, with five starting before 1970. 65% were of cross-sectional design, and all but two include both males and females. The largest study involved over 20000 asthma cases with a further five studies involving 10000 or more. 111 studies give results for lifetime or incident asthma, and 89 studies for current (active) asthma. Data on parental smoking are available for 69% of

the studies, while data on household smoking are available for 48%. Data on amount of passive smoke exposure are available for 20% of the studies. The potential non smoking confounding variables most commonly taken into account are family medical history (61 studies), socio-economic status or parental education (56), child's medical history (51), age (46) and cooking/heating methods (37). Fuller details of the studies are given in this report.

Of the 1220 relative risks, 1205 relate to the principal studies and 15 to the subsidiary studies. The number of relative risks per principal study varies widely, from only one in 53, to over 10 in 11, the largest being one with 79 relative risks entered. 93% of the relative risks are for sexes combined, and 85% relate to results for the full age range of the study. 93% relate to all races within the area studied. 45% relate to lifetime asthma prevalence, 49% to current asthma prevalence and 6% to asthma incidence. 63% of the risks relate to parental smoking (including *in utero* exposure), with 25% relating to household smoking. 52% are adjusted for at least one variable. 52 (4%) have a relative risk value with no confidence interval available, and 114 (9%) have no relative risk value but a statement of significance or non-significance. Only 50% of the relative risks and confidence intervals are as given originally or calculated directly from the numbers in the relevant 2×2 table. The rest involve more complex calculations. Fuller details of the relative risks are given in the report.

The report ends by describing techniques for conducting meta-analyses and the format of the tables presenting the results. The process of selecting which relative risks to include in an analysis is described in detail. It has to be quite complex to ensure that all the relevant data are included, while at the same time avoiding double-counting.

Results from a variety of meta-analyses will be described in Part II of this report.

Acknowledgment

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1. Introduction

The objective of the IESAST project is to collect and summarize published epidemiological evidence relating passive smoking 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 work, which started in January 2002, has involved a number of stages. These included:

i) **Identification of the studies** Attention has been restricted to epidemiological case-control, prospective or cross-sectional studies which refer either to prevalent asthma (lifetime or current), or to incident (i.e. newly occurring) asthma, and to papers published up to the end of 2002. Only studies where the endpoint was 'asthma' were included, with studies of endpoints such as 'wheeze' or 'asthmatic bronchitis' excluded. Studies with any form of passive smoke exposure, or with *in utero* exposure (maternal smoking in pregnancy), were considered relevant.

ii) **Setting up databases to allow entry of relevant data** In-house software (ROELEE) has been used. The structure involves two linked databases, one containing study details, with a record for each study, the other containing relative risk details, with a record for each relative risk (RR). The study database contains details of the study itself (e.g. location, timing, design, treatment of child smokers), the disease definition, and the potential confounding variables considered. The relative risk database contains all RRs reported relevant to the exposure indices of 'major interest' (see next paragraph), for the whole population and broken down by the more important demographic variables, with sufficient detail stored to define the RR precisely.

iii) **Entry and checking of data** It was anticipated that RRs would be available for five passive smoking exposure indices of 'major interest'.

parental smoking
parental passive smoking
household smoking
total ETS exposure (as assessed by questionnaire)
biochemically assessed exposure

In addition, it was found that a number of studies which looked at parental smoking *in utero* (i.e. smoking by the mother during pregnancy) also gave results for combinations of *in utero* and in lifetime exposures (relative to neither exposure), and it was decided to include these combined exposures also.

For these indices, data were entered, where available, for prevalence of lifetime asthma, for prevalence of current asthma and (from prospective studies only) for incidence of asthma. These were entered for the whole population, and broken down by age, sex and race. For prospective studies, data were generally entered for different lengths of follow up period because these related to different ages. Any dose-response measures for these indices were also entered. For a few studies, data were available for other exposure indices or broken down by other stratifying factors. The availability of these data have been noted in the database but the data have not been entered. Where possible, results restricted to non-smoking children were selected.

iv) **Carrying out analyses** Although a certain amount of analysis using the study database has been carried out to summarise the characteristics of the studies considered and the quantity and type of data available, the main work has involved carrying out numerous meta-analyses to meet the main objectives of the project.

This report describes the work carried out in fuller detail and presents the results of the analyses so far conducted. It also considers how the databases might be further used in the future. Part I of the report describes the method of identifying the studies, the databases and the methods used to carry out meta-analyses, while Part II presents and discusses results.

2. Identifying the studies

The objective was to identify epidemiological studies of case-control, prospective or cross-sectional design, which either reported RRs relating any aspect of passive smoking to asthma induction in children (or provided data from which such RRs could be calculated), or which commented on the significance or non-significance of the relationship. Uncontrolled case studies were not included, as RRs cannot be calculated. Studies of asthma exacerbation were not included. As expected, no studies of asthma mortality were found.

As initially specified in the protocol for this review, only studies where the endpoint was 'asthma' were to be included, and studies of 'wheeze', 'wheezing bronchitis' or 'chronic wheezing' were to be excluded. We further decided that 'asthma or wheeze' and 'asthmatic bronchitis' should be excluded. In practice this distinction was not always clear-cut, and we decided that if the endpoint was 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. This may have led to some anomalies. For instance, two studies may have used the same questionnaire-based list of symptoms to define the outcome. If one study merely described this as 'asthma', that would be included, while the other study, describing it more accurately as, say, 'asthma/wheeze syndrome' would be excluded. This strategy may have had the unfortunate effect of excluding some well-conducted studies, where the original authors deliberately avoided the use of the term 'asthma' or deliberately included the term 'wheezy bronchitis' because of local linguistic or diagnostic considerations. We made one exception, by including the study FERGUS where the outcome was "attended physician for wheeze diagnosed as asthma or wheezy bronchitis", this outcome having been selected by the original authors[1] "on the basis of Williams and McNicol's[2] conclusion that the two conditions are indistinguishable", with the results for asthma alone having been stated not to differ.

The protocol also specified that studies should be restricted to children up to age 18. We additionally included results from prospective studies which had recruited the subjects when they were children and continued to follow them into early adulthood, and from cross-sectional studies where a small proportion of the subjects were aged over 18.

A collection of potentially relevant papers was supplied by Philip Morris (PM). The extensive files on smoking and health accumulated by P N Lee Statistics and Computing Ltd (PNLSC) were examined. Papers in those files which were likely to contain material of interest for the project were examined to see if they either provided relevant information. In addition, searches were made on Medline using the strategy

("asthma"[MeSH Terms]) AND ("child"[MeSH Terms]) AND ("tobacco smoke pollution"[MeSH Terms])

Abstracts were examined and the apparently relevant papers obtained from the British Library.

Attention was restricted to papers published by the end of 2002 (with the exception of three review papers published in 2003), but no restriction was made on language. Translations were obtained of non-English-language papers (except for a few cases where dictionaries were used to identify key information from non-English papers.)

The next step was to take the papers that contained relevant data and classify them into the separate studies they described, taking account of the fact that some papers described results from more than one study[i], and that results from the same study were often described in multiple publications. Thus, for each study identified, a file was built up of papers relevant to that study, the files being sorted by continent, by country within continent, and by state within the USA.

[i] Results available separately for different countries or for different study design features have been treated as belonging to separate studies

This sorting made it easier to ensure that studies identified as separate really were so.

For any paper finally accepted into the study (see §3.2), and for review papers covering the relevant subject matter, the reference lists of cited papers were studied to identify potentially relevant papers. Where possible, the abstracts of such cited papers were examined on Medline, and then, if still relevant, the papers obtained, added to the PNLSC reference system and examined as above. Ultimately, a position was reached whereby no paper accepted for the study cited a paper of possible relevance that had not already been examined.

Overall, 1012 papers were identified, of which 1008 could be obtained and examined. Of these, 268 contained data relevant to the project, 75 were review papers (including three published in 2003), and the remaining 665 did not provide relevant data at all.

Ultimately, the project included 268 papers relating to 190 studies.

Appendix A gives certain details of the 190 studies, the 6-character reference used to identify the study, a longer study title (which includes information on the location and timing of the study), the reference key to the principal publication used to extract data and the reference keys to other relevant publications. Reference keys are those used in the PNLSC reference system. Appendix B gives all the reference keys used, in alphabetical order, together with the associated full references.

3. The databases

3.1 Structure of the two databases

There are two linked databases. The first, the study database, contains one record for each study. This record is identified by a unique six-character reference (REF), and holds information relevant to the study as a whole, described more fully in §3.3. The second, the relative risk (RR) database, holds the detailed results, and can contain multiple records for each study. Each record refers to a specific comparison, and contains the information describing that comparison (e.g. current smoking by the father vs. no smokers in the household, for a particular sex, age, race and asthma type) and the actual results. Each record also contains the study REF, which links it to the relevant record in the study database. The RR database is described more fully in §3.4.

3.2 Data entry and checking

Detailed instructions on the methods of data extraction and entry onto the databases were prepared by BAF and amplified as necessary as new problems were encountered in the course of carrying out the data entry. These are available on request.

Before data entry on computer, master copies of the papers in the study file were read through closely. Some studies were rejected at this stage because it was found on more detailed examination that they did not meet the inclusion criteria after all. The information that would need to be entered was identified and marked with highlighter pen (and notes made on the paper where necessary) to facilitate later checking. Where multiple papers were available for the same study, a principal publication was selected to provide most of the information, though details of interest not described in the principal publication but available elsewhere were also entered. The principal publication was usually that which provided information on the largest number of asthma cases, for example based on longer follow-up for a prospective study or avoiding interim results from a case-control study. On occasion, descriptions of some aspects of the study

conflicted between different papers – where necessary, the most likely version was determined by consultation between the authors of this report, with notes of the problem being recorded on the database.

Any preliminary calculations prior to data entry were done in Excel spreadsheets. The study data and the RR data, whether as given directly in the paper or as derived, were entered on the database by BAF. An automatic checking program which investigated the completeness and consistency of the data entered was run. (See Appendix C for details of the automated checks.) A full printout of the data for each study was then produced and both the calculations and the data entry were checked against the original papers by PNL.

In order to maintain consistency of data entry, the checking stage by PNL was not started until about two-thirds of the studies had been entered by BAF, so that we could be reasonably confident that no further changes would be needed to the data entry instructions. Identification of relevant papers continued throughout the period of data entry, and care was taken to ensure that if another paper was obtained relevant to a study that had already been entered, then the original data entry was rechecked in the light of any additional information.

3.3 The study database

3.3.1 Structure of the database

As described in more detail in Appendix D, the study database contains one record for each study, with each record consisting of 'fields' within 'cards'. The 'cards' separate the different main classes of information recorded, while the 'fields' contain the individual data items within each class. Each field may contain data of various types, including:

presence : the item may be present or absent,

graded or graded >0 : the item may have one or more discrete levels defined in its associated grading system

measured	:	the item may take any integer value within the specified range (measured +v is used for items which must be positive)
character	:	the item is text with up to the defined number of characters
real	:	the item may take any decimal value within the defined range (in fact only the RR database contains real data)

For all field types, data items may be entered as missing or not applicable.

The six cards used for data entry, together with a brief description of the fields included in each, are as follows:

Study description This includes the study short and full title, details of possible overlaps or links with other studies on the database, whether the study is restricted to boys or to girls or is unrestricted, the age range and the race of the population considered, the location of the study, the period of the study, the year and reference key of the principal publication and the reference keys of any other publications. A free text comment also contains additional detail where required, particularly concerning overlapping studies.

Study design This includes the study type (case-control, prospective, or cross-sectional), the type of controls used (e.g. healthy, diseased/hospital), the type of population studied (e.g. general population, schoolchildren, children with family history of allergy). It also includes details on the source of the ETS exposure data, whether this was ascertained by questionnaire (and, if so, whether from the parents or the child) or by biochemical measurement. A free text comment also contains additional detail where required.

Asthma This includes two presence fields, indicating whether results are presented for lifetime asthma and for current asthma respectively. For prospective studies, incident asthma is recorded in the 'lifetime' field. It also

includes further fields giving the source of the asthma diagnosis, the timing of the asthma and a text field giving the detailed definition of the asthma. (This is extended by use of a free text comment if more space is required.) For current asthma, it is also recorded whether the asthma was restricted to first occurrence and, in prospective studies, whether current asthma was measured on more than one occasion. This card also includes the number of asthma cases and the total number of subjects included in the study.

Matching factors For case-control studies, this includes which matching factors were used.

Confounders considered The first field gives the total number of potential confounding variables considered for all the RRs entered in the RR database. The remaining fields indicate whether adjustment has occurred for 29 separate potential confounders. On most occasions, data entry is 0 for confounder not adjusted for or 1 for confounder adjusted for. Exceptionally, a higher number than 1 indicates that the confounder was adjusted for by use of more than 1 variable (e.g. family medical history by several specific conditions). A presence field indicates that other potential confounding factors were formally considered but rejected (e.g. in a step-wise multiple logistic regression model) and these factors are listed in a free-text comment.

Other results This card records the availability of various data which have not at present been entered on the database. The first field indicates whether the study provides data on other definitions of asthma, which could have been used in this review in place of the outcome(s) chosen. The second field indicates other outcomes related to asthma which would not have qualified for this review, such as wheeze. Further fields indicate the availability of results for other ETS exposure indices (such as smoke exposure outside the home, or changes to parental smoking habits), of results for active smoking by the child, and of results stratified by other factors (or restricted to subsets of the study population.)

Further **Derived** fields cards are used to hold data derived from the other fields rather than entered directly.

The record itself is uniquely identified by a six character study reference, usually based on the principal author's name.

3.3.2 The study data

The data recorded on the study database for each of the 190 studies are presented in Appendix E. This is in the form of a computer-generated report. Note that this report is based only on fields which provide positive information. Thus, for example, the card 'matching factors' is shown only for case-control studies, and only those factors actually used are shown. Other factors for this card, for which no output is shown, are taken not to be used.

3.3.3 Problems with overlapping studies

In theory, RRs being meta-analysed should come from independent studies involving distinct asthma cases; if some asthma cases feature in more than one study, they will be 'double-counted' in any meta-analysis which includes results from both studies. In practice, avoidance of such double-counting is difficult and may not always be the most desirable solution. For example, suppose study A describes a cross-sectional study conducted in 1970 involving all primary school children (age 5-11) in a particular town, while study B describes a similar cross-sectional study in the same town conducted in 1975. Including results from both studies would involve some double-counting (i.e. of children aged 5-6 in 1970 and 10-11 in 1975), but avoiding this would require totally ignoring results from one study (or both), with a substantial loss of power, which would seem to be less desirable than allowing some double-counting. Even omitting study B if it had been conducted in 10-11 year-olds (totally within the population of study A) may not necessarily be appropriate, if the paper describing study B reports data for some exposure indices not considered in the paper

describing study A. One would not want to include results from both studies in analysis of the same exposure index (and would omit study B if both RR estimates were available), but one might want to use data from either study if only one provides the required RR. There are other possibilities too that need to be borne in mind; for example, studies of overlapping regions or studies which do not completely describe where or when they were conducted and may overlap other studies.

In entering data from individual studies, care was taken to avoid double-counting by, for example, not entering results for the same exposure index for all cases and for a study subset. Nevertheless, there were some sets of studies which were noted on the database as having overlaps or links. For the purposes of analysis, these sets of studies were grouped into two categories.

The first category are studies with a modest degree of overlap, which cannot be disentangled and which it was decided to ignore. These sets are described below briefly:

1. Results from the annual UK National Study on Health and Growth were available for 1977 (MELIA), 1982 (SOMERV) and 1987-88 (CHINN). The study included ages 5-11, so that youngest children in each reported phase of the study would also have been included in the following phase. However this overlap is small – stated to be 5% between 1982 and 1988. During the 1980s, additional study areas were added for England and these were studied in alternate years to the original areas, so that there is no overlap for the English areas between 1987 and 1988. For the Scottish areas the position is unclear and it seems likely that at least some areas were repeated between 1987 and 1988. However as the results are only available for 1987 and 1988 combined, there was no satisfactory alternative to including both years. (There is also a possibility of some overlap with the British Births Survey (TAYLOR), which included all

children born in a single week in 1970, who would thus have been in the eligible age range for MELIA in 1977.)

2. In the Swedish Survey of Living Conditions, a random sample of adults was drawn and the results presented here refer to their children. These have been entered on the database as separate studies according to whether the adult respondent was the mother (HJERN1) or father (HJERN2), because they are effectively independent subsets. However an apparent discrepancy in the numbers suggests that 10 children (0.2%) may have been in both parts.
3. Two Canadian studies of 7-12 year olds may have overlapped. Tillonsburg is one of 2 towns included in STERN1 in 1983, and one of 10 towns in STERN2. The timing of STERN2 is not stated, but it was probably only a few years later, so that the youngest children from STERN1 would have been included again.
4. Three identically designed cross-sectional studies were carried out in SW Germany, including the same cohort of children on each occasion, when they were in 2nd grade in 1977 (WOLFO1), 4th grade in 1979 (WOLFO2) and 10th grade in 1985 (WOLFO3). However, relatively few children were included more than once (17% included in all three phases, and a further 24% included twice).

The second category contains sets of studies which clearly do overlap, where one member of the set ('principal study') contains the most appropriate data and where, for other members ('subsidiary studies'), RRs should only be included in meta-analyses if equivalent results are not available from the principal study. In addition, some prospective studies where results are available from both baseline and follow-up phases but with some differences in analysis or inclusion criteria, have been more conveniently entered as two separate studies. These sets are described below:

1. The California Children's Health Study gave results as a baseline prevalence study (GILLIL – principal study), and a follow-up study of those who were asthma-free at baseline (MCCON1 – subsidiary study). This was entered as two separate studies because of some methodological differences (asthma status based on parent report in GILLIL but child report in MCCON1; exclusion of some subjects with other medical conditions from MCCON1; different treatment of child smokers).
2. KUEHR is a baseline prevalence study, and has been designated as a principal study. SPIEKE is a follow-up study of less than half the original subjects, and has been designated as the subsidiary study.
3. The Bogalusa Heart Study gave results from three surveys within a 10 year period, including all children aged 5-17 (or 7-17). This clearly involved substantial overlap. The middle phase (FARBE2 – 1987-8) was designated as the principal study and the first (FARBE1 – 1984-5) and last (FARBE3 – 1992-4) as subsidiaries.
4. Results are available from two studies of 5-11 year olds conducted in two schools two years apart. The first (BRABIN – 1991) used a 50% random sample while the second (KELLY – 1993) included all children. A substantial proportion of children participated in both surveys (58% of BRABIN subjects also participated in KELLY). Although it had the smaller sample, BRABIN (1991) has been designated as the principal study because it gave actual RR results, whereas KELLY (1993) merely stated that the results were non-significant.
5. FORSB3 is a cross-sectional study conducted in two areas. All the asthmatic children from one area only (Malmo) were also included in a second study WILLE2, together with a small number of the symptom-free children as controls. This second study was marked as subsidiary.
6. Similar studies were conducted in three regions of Saudi Arabia – Jeddah, Damman and Riyadh. Although results for all three areas combined were available[3], these were not entered because of apparent inconsistencies. (The only results were from a multiple logistic regression (MLR) and the

standard errors given were completely inconsistent with the total number of subjects in the study). Less unsatisfactory[ii] unadjusted results were available and were entered, as study ALFRA1 (principal) for Jeddah and Damman, and as ALFRA2 (subsidiary) for Damman and Riyadh. Adjusted results for ALFRA1 which appeared to suffer from the same problem as the combined results were entered without their suspect CIs, and one rather vague result relevant to all three regions was also entered under study ALFRA1.

7. A series of cross-sectional school studies were carried out at three year intervals in the vicinity of a power plant in Israel. Results from the first study (1980) were for children in school grades 2, 5, and 8, and for convenience, this was split and entered as GOREN1 for grades 2 and 5, and as GOREN3 for grade 8. Results from the later studies were for grade 8 only. Thus the children in the 1983 study (GOREN4) were largely those who had been included as grade 5 in 1980, and similarly those in the 1986 study (GOREN5) had been included as grade 2 in 1980, and so these were designated as subsidiary studies. The final study in 1989 (GOREN6) did not overlap. (Note that GOREN2 is an unrelated study.)

3.3.4 Study characteristics

Table 1 gives the distribution of various selected study characteristics by study type and overall. Except where specified otherwise, the discussion in the rest of this section refers to the principal studies only.

Design Of the 181 principal studies, 39 (22%) are of case-control design, 25 (14%) are of prospective design, and 117 (65%) are of cross-sectional design. The nine subsidiary studies comprise one of case-control design, two of prospective design and six of cross-sectional design. The case-control studies include eight principal and one subsidiary studies where an initial cross-sectional phase was carried out to identify cases (EHRLI1, LEEN, MELSOM, MOHAME,

[ii] See also Table 12B

POKHAR, SQUILL, STRACH, WILLE2, ZHENG), and three studies conducted as cross-sectional but analysed as case-control (AGABI1/AGABI2, DEKKER). Note that cross-sectional is taken to include studies where only the baseline phase of a prospective study, or only one phase of a longitudinal study, provided relevant results; it also includes each phase of a longitudinal study where children from specific schools were repeatedly recruited but no effort was made to link results for individual children between phases. Three studies designed as intervention trials (on allergen avoidance – ARSHAD, ZEIGER and on ultrasonography – ODDY) and one designed as a case-control study of bronchiolitis (SIGURS) were analysed ignoring their original status and have been entered as prospective studies. One retrospective study, MCKEEV, which used primary care records from birth including date of diagnosis of asthma, was also entered as prospective.

Sexes considered All studies included both sexes, except two which considered males only (KEARNE in Ireland and ALDAWO in Saudi Arabia).

Age of subjects The lower age limit was below 5 for 64 studies, in the range 5-9 for 95, and 10 or more for 21. For the case-control and cross-sectional studies, the upper age limit was below 10 for 30 studies, in the range 10-14 for 67, 15-18 for 53 and 19-21 for four. For the prospective studies, the age at final follow-up was under 10 for 13 studies, 10-18 for nine and 22-23 for three.

Race of subjects In 168 studies, there was no selection on race though clearly variation in the location of the study would cause major variation in the racial distribution. In five studies (2 in USA, 1 in UK, 1 in Italy and 1 in Russia), subjects were specifically restricted to whites. In four other studies, subjects were specifically restricted to a race other than white (blacks in 3 US studies, Chinese in 1 Hong Kong study), and in four further studies to two races (whites and blacks in 3 US studies, and Fijians and Indians in a Fijian study).

Location Studies were most commonly conducted in West Europe or Scandinavia (40%), North America (23%), and Asia or Middle East (18%), and less commonly conducted in East Europe or the Balkans (7%), Australasia (7%), South or Central America (3%), and Africa (2%). Apart from the fact that all four African studies were of case-control design, while none in Australasia were, the distribution of study types was similar within each region.

Of the 73 studies conducted in West Europe or Scandinavia, 22 were conducted in the UK, 10 in Italy, nine in Sweden and seven in Germany with studies also conducted less commonly in a further 10 countries.

Of the 41 studies conducted in North America, 33 were conducted in the USA and nine in Canada, with one involving both these countries.

Of the 33 studies conducted in Asia, seven were conducted in Israel (of which five were the linked GOREN series discussed in §3.3.3 above), and the remainder in 11 further countries[iii].

Of the 34 studies conducted in other areas, seven were conducted in Turkey, six in Australia and no more than four in any other country.

Overall, studies were conducted in 41 countries.

Timing The earliest period considered by any study was KAPLAN, a prospective study of all UK children born in a specific week in 1958. Four studies started in the 1960s (another birth cohort study in the UK, an American and an Australian cross-sectional study, and an American case-control study). The number of studies starting accelerated, with 16 studies starting in the 1970s, 50 in the 1980s and 85 in the 1990s. All but three of the case-control studies

[iii] Hong Kong is counted here separately from China

started in 1988 or later. The timing of the study was not stated for 24 studies. For 158 (87%) of the studies, the principal publication year was 1990 or later.

Population studied Most studies were of the general population with no major restrictions – 97 conducted in school settings, 43 in hospital, clinic or routine health check settings and 31 in household or other general settings. Some of these studies imposed further restrictions which are listed in Table 2 and although these were generally of a minor nature, some may have materially affected the representativeness of the population studied. For instance a requirement that the respondent was the biological mother would have reduced the proportion of children in step-families below that for the general population, as well as excluding adopted children.

One study gave no information about the population considered. The remaining studies involved a variety of special populations – four were restricted to children with a family history of allergy, one to school athletes, one to twins, one to children living on farms and one to infants at high risk of SIDS; one study included a high proportion of travellers' children.

Although no information has been entered on the database regarding response or retention rates, it can be noted that many of the prospective studies based their analysis on children who were alive and could be traced through to the final follow-up. Thus they excluded any children who died during the course of the study, and, depending on the individual study design, may have under-represented children from more mobile families.

Type of controls Of the 39 case-control studies, 28 used healthy (population) controls. The other 11 studies used other patients as controls, usually from the same hospital or primary care unit as the cases. Thus for two studies (SARRAZ and ROSASV) controls were attending an allergy clinic, while conversely another study (OCONNE) excluded patients with a personal or family history of allergic

conditions. A further five studies excluded patients with a history of respiratory disorders.

Matching factors The commonest matching factors used in the 39 case-control studies were sex (13 studies) and age (18 studies), while a further eight studies matched for factors such as hospital or location within study area. The only other matching factors used were socio-economic status and race (two studies each). 20 studies were unmatched.

Respondent Most commonly (133 studies, 73%) information about the passive smoke exposure was provide by a parent. In 12 studies it was provided by the child, in two studies children above a given age responded in person, while in 21 studies information was provided by both parent and child (including some studies which asked children privately about their own smoking). Of the remaining studies, four obtained information from medical records and nine obtained it from unspecified household members.

Questionnaire About one third of the studies used either the ISAAC[4], ATS[5] or WHO[6] questionnaires for respiratory symptoms.

Definition of disease outcome – lifetime and incident asthma Results for lifetime or incident asthma (including prevalent asthma of unspecified timing) were available from 111 principal studies, about two-thirds of the prospective and cross-sectional studies but only about one third of the case-control studies. In two studies (BECKET, VONMAF), the unit of study was the family and the outcome was "at least one child in the family has asthma".

The diagnosis was taken from medical records (or was made by a physician in the course of the study design) in 12 studies (11%), and the details of the diagnostic criteria used are shown in Table 3A. In a further 51 studies (46%) a diagnosis made by a physician but reported by the parent and/or child was used. As shown

in Table 3A most of these were simply described as ‘asthma’ or ‘bronchial asthma’, while for a few, the definition of asthma included asthmatic bronchitis, spastic bronchitis, recurrent wheezy bronchitis, or bronchial obstruction verified by a physician. In the 48 remaining studies, asthma was at least partly based on the parent’s or child’s own assessment rather than physician diagnosis. This was simply described as ‘asthma’ or ‘bronchial asthma’ in most of these studies (31), ‘asthma attack’ or ‘asthmatic’ in a further 4 studies, while in the remaining 13 studies the outcome was defined in terms of a set of symptoms. For some studies, the threshold at which symptoms were accepted as defining asthma was quite low, for instance in POKHAR and ULRIK, ‘wheeze ever’ would have qualified. In one study (ANDRAE), ‘allergic asthma’ was defined in terms of symptoms occurring on contact with plants or animals.

11 prospective studies recruited mothers of potential subjects in the prenatal period, or infants under 1 year of age. For these studies, analysis of lifetime asthma has been entered on the database as incident asthma, although it could equally well have been described as lifetime prevalence. Four other prospective studies recruited at a later age and presented incidence analysis excluding subjects with baseline history of asthma. Only two of these also reported results for baseline prevalence (RONMAR, GILLIL/MCCON1[iv]). In study SHERMA, age at onset was used to combine pre-existing asthma at baseline with subsequent incident asthma in a single analysis.

Results entered as lifetime prevalence are in fact restricted to onset after age 2 or age 3 in two studies (FAROOQ and NYSTAD respectively), and are for asthma of unspecified timing in 13 studies.

Definition of disease outcome – current asthma Results for current (i.e. active) asthma were available from 89 principal studies, including about two-thirds of case-control studies, half of cross-sectional and a third of prospective. In

[iv] MCCON1 designated as a subsidiary study. See §3.3.3.

three of the case-control studies, this was restricted to being the first episode of asthma. The diagnosis was taken from medical records (or was made by a physician in the course of the study design) in 21 studies (24%), and the details of the diagnostic criteria used are shown in Table 3B. In a further 14 studies (16%) a diagnosis made by a physician but reported by the parent and/or child was used, while in the 54 (61%) remaining studies, asthma was at least partly based on the parent's or child's own assessment rather than physician diagnosis. Many of these latter studies combined 'ever diagnosed asthma' with a report of attacks, symptoms or medication use in the last year. In four studies (LOPEZC, HJERN1/HJERN2 and DOTTER) the definition refers to allergic asthma. Comparing with the definitions for lifetime asthma, although some studies had quite a low threshold of symptoms to qualify as asthma (e.g. for MELSOM wheeze in last 12 months would qualify), generally the criteria were stricter, and several studies were restricted to severer asthma (e.g. CALL – subjects presenting at ER with acute wheezing; DAIGLE – asthma requiring hospitalization or two primary care visits; HU2 – episode lasting 3+ days; STRACH – 12+ episodes or a severe episode; WEITZ1/WEITZ2 – asthma lasting 3+ months)

In six of the nine prospective studies which gave results for current asthma, the current asthma status was repeatedly measured in successive phases of the study. Studies GOLD and BALL (and probably also BERGMA at ages 3-6) combined the repeat measures in a single analysis which dealt appropriately with the non-independent nature of the measures, and thus the results are suitable to include in a meta-analysis. ARSHAD, PETERS, TARIQ (and BERGMA at age 7) presented separate analyses each relevant to a single phase. These have been entered on the database as they are potentially of interest in age-specific analyses, but they are not independent. In order to prevent more than one estimate entering a meta-analysis simultaneously, the results from the final follow-up have been marked as principal and others as subsidiary.

In about half the studies (46 studies, 52%), current asthma was defined as asthma that had been active in the last year (or in the last two years for another study). A few studies (seven) specified a shorter period, while for the remaining studies, the diagnosis was made in the course of the study design (14 studies) or the timing was unspecified (21 studies).

Availability of alternative disease outcome Table 4 gives details of the 35 studies from which results are available for alternative asthma definitions. In some cases, these refer to past asthma, or to exacerbation of asthma which would not have been eligible for the current review. In other cases, comparison between Table 4 and Table 3 shows the decisions made when choosing which results to enter and they are summarized here:

Study	Preferred	Alternative(s)
ANDRAE	triggered by tree, grass, flowers or furred animals	triggered by birch pollen
BRABIN	asthma	well controlled asthma
CUNNI1	experienced symptoms	taken medication
EHRLI2	acute or non-acute	acute
FERGUS	physician diagnosed asthma or wheezy bronchitis (see §2)	asthmatic attack (irrespective of medical treatment)
FORSB1/2/3	treatment by physician	experienced attacks
GILLIL	asthma	taken medication
GORTM1/2	asthma	functionally impairing asthma
HU1	taken medication	emergency hospital treatment
JAAKO	asthma	early onset asthma
KEARNE	asthma	exercise-induced asthma
KUEHR	asthma	allergic asthma
LISTER	asthma	use of health services for asthma
MONTEF	asthma	very severe attack of asthma
NHANE3	asthma	moderate or severe asthma; any hospital visit or recent physician visit for asthma; taken medication
RATAGE	asthma	severe asthma
RONMAR (incidence)	asthma	physician diagnosed asthma[v]
RONMAR (prevalence)	physician diagnosed and either symptoms or medication	symptoms or medication; medication
SENNHA	bronchial asthma	asthma symptom (frequent night-time irritable cough)

[v] An exception to the usual order of preference was made because results for the usually preferred outcome were much sparser.

STANHO	episodes labelled as asthma	sub-clinical asthma (wheeze not labelled as asthma)
TARIQ	3+ episodes each lasting 3+ days	medication; nocturnal asthmatic symptoms; atopic and nonatopic asthma
WEITZ1	asthma not cured	taken medication
WOLFO1/2/3	asthma	score based on symptoms

The availability of results for wheeze, wheezy bronchitis, 'asthma or wheeze' or similar conditions was noted for 78 of the principal studies.

Study size The distribution of the number of asthma cases was very skew. Where the number of cases was known, for lifetime or incident asthma, it ranged from 6 to 5842, with the median being 140, and 15 studies (14%) having over 500 cases. Similarly for current asthma, the range was 8 to 20637, with median 134 and 10 studies (12%) having over 500 cases. By far the largest study was WANG, conducted in Taiwan with 20637 current asthma cases, followed by MCKEEV in UK with 5842 incident cases and VOLKME in Australia with 3178 lifetime prevalent cases. Other studies with over 1000 cases were conducted in Australia (JENKIN, 1349), Italy (AGABI2, 1306) and USA (NHANE3, 1025). In addition, there were seven other large studies (>1000 subjects) for which the number of asthma cases was unknown.

Exposures For each exposure type, information about the studies for which RRs have been recorded in the relative risk database is presented in §3.4.4. Table 5 provides details on which studies provided information on other aspects of ETS exposure, for which data have not so far been recorded on the relative risk database. Three studies (ALBA, CHEN2 and PONSON) provided results for alternative aspects of household smoking related to whether smoking was anywhere, in the home, or in the presence of the child (see also §3.4.2.1). AZIZI also gave results for sharing a bedroom with an adult smoker, VARELA for whether the mother was the main active smoker, and GOLD considered respirable particulate matter as equivalent to household smoking. Four studies (BALL, BUTZ, KUEHR and LEEDER) looked at changes in parental smoking habits,

while SOYSET looked at duration of parental smoking. Only two studies looked at exposure outside the home (PONSON – exposure outside the home at age 1 month, and BUTZ – exposure in daycare).

Active smoking (smoking by the child) Many studies (134, 74%) made no mention of smoking by the child. Although this would be expected in studies of young children, the situation was similar in the 136 studies which included children age 10 and above, with no mention of smoking by the child in 94 (69%). Smokers were excluded from analysis in 15 studies (by means of questionnaire or biochemically), two studies investigated smoking but found that there were no smokers, another included only non-smokers without specifying whether some smokers had been omitted, while another three studies assumed that there were no smokers because of the age of the subjects (even though in two, MARTIN and AGABI1, subjects were up to age 12). The remaining 26 studies included smokers in the analysis, with six studies discussing the need to take active smoking into account but having no data available, and with seven either testing formally for its significance or using it as an adjusting factor. In addition, 11 studies gave results for active smoking (Table 6). These results have not been entered on the database.

Confounders Of the 181 principal studies, 73 (38%) did not adjust for any variable at all in analysis. This percentage was higher for the case-control studies (49%) though some of these will have matched for sex and/or age at the design stage. About half of the studies adjusted for four or more potential confounders, with 27 (15%) adjusting for 10 or more.

Table 1 also shows all those variables taken account of. Sex is the commonest, with 74 studies adjusting for it. Other commonly used variables were aspects of family medical history (61 studies), socio-economic status (SES) or parental education (56), child's medical history (including diet) (51), age (46), cooking, heating or air conditioning methods (37), household composition (e.g. number of

siblings, single parent) (31), animal contact (28), housing quality or crowding (23), damp or mould in the home (22), and race (20).

Results adjusted for other aspects of passive smoking were available, for *in utero* exposure in 13 studies, for parental smoking (in lifetime) in 28 studies and for household smoking in seven studies. Active smoking by the child was used as an adjusting factor in four studies.

Additional confounders were formally considered by the study authors but rejected from analysis (usually in a step-wise multiple logistic regression) in 33 studies.

Other stratifying variables So far only sex, age and race have been considered as stratifying variables in the relative risk database. However, some studies give details on how the association of passive smoking with asthma varies by level of other stratifying variables. Table 7 presents details of which studies considered other stratifying variables, or presented results for particular subsets of the subjects. By far the commonest are aspects of medical history (14 studies using the child's medical history and a further 6 using family medical history). Other are location (particularly as related to urban/rural or air pollution), social class, parental education, and housing conditions.

Derived fields Fields have been derived holding the total number of RRs, and the number of RRs for each exposure type, that are present for each study in the relative risk database. These are discussed in §3.4.4.

3.4 The relative risk database

3.4.1 Structure of the database

As described in more detail in Appendix F, the relative risk database contains one record for each relative risk. Again, each record consists of 'fields'

within ‘cards.’ The four cards used for data entry, together with a brief description of the fields included in each, are as follows:

RR description This includes an RR identification number which is unique within the study, together with details defining the RR. These include the sex, age range, race, asthma type (lifetime or current) and, for prospective studies, whether the analysis was of prevalence or incidence. The passive smoking exposure is defined by type (parental (including *in utero*), household, total, biochemically assessed, or a combination with *in utero*), specific source within the family and time of exposure, together with similar information about the unexposed base, or details of the biochemical assessment. See Appendix F for fuller details of the possible levels of the grading systems used. The source of the RR (including reference key, table and page numbers) is also given.

RR adjustment This includes whether or not the RR is adjusted for sex, age, race, other aspect of passive smoking or other confounders, and in the case of other confounders, the number of variables adjusted for. The actual other confounders adjusted for are given in a text comment if they are less than the full set already defined in the study database.

RR data This includes the numbers of exposed and unexposed cases. For unadjusted results only, it also includes the numbers of exposed and unexposed controls or disease-free subjects for prevalence analyses, or the at-risk population or person-years at risk for incidence analyses. For all results, it includes the RR estimate itself and its upper and lower 95% confidence limits. For unadjusted data the RR and 95% confidence limits are calculated from the 2×2 table (if available). For adjusted data, they may be as given in the source papers or as derived by other means, a further variable indicating the method of derivation. The possible methods of derivation are described in §3.4.5.

Discrepancy Any alternative discrepant results are noted here, or results adjusted for alternative variables.

The record includes the six character study reference linking it to the corresponding record on the study database.

3.4.2 Identifying which relative risks to enter

In identifying what RRs to enter, four aspects – passive smoking index, asthma type, confounders adjusted for, and strata – were considered and these are discussed in the following sections. RRs relating to all combinations of these aspects were entered.

RRs based on non-smoking children were entered if available, otherwise RRs based on all children (including smokers, if any) were entered. RRs restricted to smoking children were not entered.

As discussed above (§3.3.3), it is important in meta-analyses to avoid 'double counting', and this applies equally within studies. Although in some circumstances it is quite legitimate for more than one RR from a study to be included in a meta-analysis (for instance by strata such as sex and contiguous age groups), in other circumstances it is not (for instance if maternally exposed and paternally exposed subjects were each compared to those with no smokers in the family, including both in a meta-analysis of parental smoking would double count the unexposed group; also if current asthma is measured repeatedly in a cohort and analysed at successive attained ages, then the estimated RRs will not be independent). For a simple stratifying variable, it is readily apparent at the analysis stage whether or not inclusion of multiple RRs is valid. However for the other aspects it is not. It was therefore decided that, with the exception of the straightforward strata of sex, all valid combinations would be constructed at the outset. This resulted in a considerably larger numbers of RRs being entered for some studies than had been presented in the original papers.

3.4.2.1 Passive smoking indices

Passive smoking exposure was either based on questionnaire responses or on biochemical assessment.

For questionnaire based exposures, it was necessary to define the smoking exposure of the numerator and of the denominator separately for each RR, exposure being defined according to whether the exposure was from parents or other household members smoking (and, in both cases, who specifically smoked and any measures of the amount of exposure such as number of smokers, amount smoked or duration of smoking), or from total exposure, and the timing of the exposure.

When identifying the numerator, exposure type is defined as one of 4 levels:

1 parental, i.e. active smoking by the parents (regardless of whether or not this in the presence of the child)
2 parental ETS, i.e. passive smoking by non-smoking parents (in practice this refers only to exposure of the mother during pregnancy)
3 household, i.e. smoking by household members (except as already covered by parental smoking – level 1), or smoking in the home (i.e. including by visitors) and regardless of whether or not this in the presence of the child,
4 total exposure, i.e. involving exposure outside the home, or unspecified exposure

For parental (and parental ETS) exposures, one of the following levels is additionally selected to indicate who smoked (or was exposed):

1 mother and not father
2 mother (irrespective of father's smoking)
3 father and not mother
4 father (irrespective of mother's smoking)
5 both parents
6 any parent (i.e. mother and/or father)
7 one parent but not both

and similarly for household smoking:

1 any household member
2 siblings

3 grandparents
4 grandfather
5 any household member other than parents, and neither parent smokes
6 any household member other than parents, (irrespective of parents' smoking)
7 any household member other than mother, and mother does not smoke
8 any household member other than mother, (irrespective of mother's smoking)

For total exposure, the exposure is further defined as:

1 total (not otherwise specified)
2 home and peers
3 home and daycare

The timing of the exposure is defined according to the following levels:

1 before conception
2 during pregnancy (i.e. *in utero*)
3 since birth (i.e. in the child's lifetime)
4 during pregnancy and/or since birth
5 ever (i.e. the parent/household smoker has ever smoked, irrespective of the child's lifetime)
6 past (i.e. the smoker is an ex-smoker, irrespective of whether any smoking was during the child's lifetime)
7 current, or in the past year
8 unspecified
9 at time of birth or at age 1 month
10 at age 18 months
11 age < 6months
12 age < 1 year
13 age < 2 years
14 age < 3 years
15 age < 5 years
16 age < 6 years
17 age < 7 years
18 age 13-15
19 age 9-16
20 since birth (as level 3) but not current
21 during pregnancy and/or since birth (as level 4) but not current
22 ever (as level 5) but not during pregnancy
23 ever (as level 5) up to 1 year ago

The RR is further described as relating to the whole exposed group so far defined (e.g. current maternal smoking) or to a level of exposure within that

group, whether by number of cigarettes exposed to (or smoked by the smoker in question) (e.g. 1-10, 11-20, etc. per day), minutes per day of exposure, number of persons smoking in the household[vi], or a semi-quantitative level (e.g. occasionally). The categories used vary considerably from study to study, and have been entered as given in the original paper. An open-ended group is coded as 999.

When identifying the denominator, attention is restricted to five groups:

1 no exposure at all
2 no household exposure
3 no exposure from the specified household member
4 no parental exposure
5 no exposure from the specified parent

If 'no' exposure is not available as a denominator, then 'no or low' exposure may be used. The denominator is further defined as:

1 not at the time defined for the numerator
2 never smoked (only relevant when the numerator refers to current/former/ever smoking and relates to the smoker's lifetime, not the child's)
3 not at the time defined for the numerator and not at some additional time

Generally, all valid combinations of the above definitions of numerators and denominators are used. Thus if parental smoking data were available for the following exposure groups:

A none
B mother (not father) smokes
C father (not mother) smokes
D both parents smoke

then RRs would be entered for:

[vi] Number of parents smoking was not specifically entered as a dose response, but the levels 'one only' and 'both' can be interpreted as such.

B vs A	mother only	vs	neither parent	
C vs A	father only	vs	neither parent	
D vs A	both	vs	neither parent	
B+C vs A	one (not both)	vs	neither parent	
B+D vs A	mother (+/-father)	vs	neither parent	
C+D vs A	father (+/-mother)	vs	neither parent	
B+C+D vs A	any parent	vs	neither parent	
B vs A+C	mother only	vs	not specified parent	
C vs A+B	father only	vs	not specified parent	
B+D vs A+C	mother (+/- father)	vs	not specified parent	
C+D vs A+B	father (+/-mother)	vs	not specified parent	
BvsA & DvsC	mother (+/- father)	vs	not specified parent	adjusted for father
CvsA & DvsB	father (+/-mother)	vs	not specified parent	adjusted for mother

However 'both parents' vs 'one or no parent' would not be entered. For household smoking, the comparison of 'any household member' vs 'no household exposure' would be constructed if possible, but no other combining would be done.

Also, if smoking data (for any specified source person) were available as never, current and former, then RRs would be entered for:

current vs non
current vs never
ex vs never
and ever vs never.

Note that ever smoker versus non smoker would not be valid, as ex-smokers would be counted in both the numerator and denominator.

All results for biochemically assessed exposure are entered, with the source (saliva, blood etc), the biomarker measured (cotinine, cotinine/creatinine ratio etc), and the value used to distinguish between unexposed and exposed all noted in the database.

3.4.2.2 Asthma type

Results are entered for lifetime, incident and current asthma, as defined in the study database.

3.4.2.3 Confounders adjusted for

Results are entered unadjusted, and adjusted for the most confounders for which results were available. If the confounders included other aspects of passive smoke exposure as well as other confounders, then results adjusted for the other confounders but not for the other passive smoke exposure are also entered.

3.4.2.4 Strata

Three strata were considered – sex, age and race. Results are entered for males and females separately when available. Combined sex results are only entered when the equivalent results (i.e. for the same passive smoking indices, confounders, age and race) were not available. Results are entered both for all ages combined[vii], and for individual age groups. The age groups used vary considerably from study to study, and have been entered as found. Results are entered for all races and for individual racial groups

3.4.3 Derivation of the relative risks

Adjusted RRs and their 95% CIs are entered as given when available. For an incidence analysis, the odds ratio is entered only if the relative risk is not available (typically when estimated from a multiple logistic regression), and this is noted in the database. Unadjusted RRs are calculated from their 2 × 2 table, if available, otherwise entered as given. If the numbers of cases are denoted by a_i and the numbers of controls (or the disease-free population in a cross-sectional study) by b_i, where the subscript $i = 0$ refers to the unexposed group and $i = 1$ refers to the exposed group, then the RR and its confidence limits estimated by the odds ratio are calculated by:

$$RR = (a_1\, b_0) / (a_0\, b_1)$$
$$LCL = RR / \phi$$
$$UCL = RR\ \phi$$

where ϕ, a factor based on the variance of the RR, is given by

$$\ln(\ \phi\ ) = 1.96 \sqrt{((1/a_0) + (1/a_1) + (1/b_0) + (1/b_1))}$$

[vii] This does not apply to repeat measures of current asthma in prospective studies

For an incidence analysis, b_i denotes the at-risk population, and the formulae to calculate the relative risk and its confidence interval are the same, except that

$$\ln(\phi) = 1.96\sqrt{((1/a_0)+(1/a_1)-(1/b_0)-(1/b_1))}$$

If both a 2 × 2 table and an unadjusted RR/CI were presented originally, then the RR/CI calculated as above is used, and any discrepancy from that originally given is noted in the database.

The 2 × 2 table may be constructed by summing groups (e.g. adding current and ex smokers to obtain ever smokers, or adding over other stratifying factors), or from a percentage distribution.

A variety of other methods are used to provide estimates of the RR and CI in other circumstances. The main methods are described briefly here, and fuller details are given in an earlier report[7(Appendix G)]. Calculations were mainly carried out using Excel spreadsheets.

Correction for zero cell If the 2 × 2 table has one cell with value zero, the RR and CI cannot be calculated by the usual formula. The method used is to add a correction of 0.5 to each of the four cells, and then to apply the formula.

Combining independent RRs Combining RRs over strata uses the method of Fleiss and Gross,[8] the same method as for meta-analysis. The resulting estimate is adjusted for the stratifying variable. When this combined RR is subsequently used in a meta-analysis, the end result will be exactly the same as if all the original RRs had been included. This method is also appropriate for combining RRs for individual disease groups, provided they are independent estimates (i.e. each disease group has a separate control group).

Combining non-independent RRs When non-independent RRs are to be combined, for instance if adjusted RRs are available for parent current and ex smokers, each versus never smokers, then the method of Fry and Lee[9] is used to provide a combined estimate for ever smokers. This method starts from a source table giving adjusted RRs and CIs for *n* exposed groups relative to a single non-exposed base group. The hypothetical underlying $2 \times (n + 1)$ table of numbers of 'adjusted cases and controls' is estimated, these then being summed to give the required groups for the numerator and denominator, and the resulting 2×2 table used with the usual formula to estimate the adjusted RR and CI. A variation of the method allows non-independent disease groups to be combined. Thus when RRs for several disease groups are given, each relative to a single shared control group, the disease groups can be combined, or one disease group (e.g. asthma) can be compared with a combination of another disease group (e.g. wheeze without asthma) and the control group.

CI estimated from p-value When an adjusted RR was presented originally without a CI but with a p-value, then the original RR is used and its confidence interval is calculated using the formula

$$\ln(\phi) = 1.96 \ \ln(\mathrm{RR}) \ / \ \mathrm{ND}$$

where ND is the standard normal deviate corresponding to the p value.

CI estimated from crude numbers When an adjusted RR was presented originally without a CI or p-value, but the corresponding 2×2 table is available, then the original RR is used and its confidence interval is estimated by assuming its width is the same as the width of the interval for the equivalent unadjusted RR. In fact, the estimated interval will be narrower than the true one (since adjustment widens the interval[10]), and thus this method will increase the weight that the estimate is given when entered into a meta-analysis. However this will usually be a small effect and the only alternative is to omit the RR altogether from all meta-analyses.

3.4.4 Characteristics of the relative risks

A total of 1220 relative risks are entered on the database, of which 1205 relate to the principal studies and 15 to the subsidiary studies. Among the 181 principal studies, 53 (29%) have only one RR, and a further 100 (55%) have between two and 10 RRs, while 11 (6%) have over 20 RRs, the highest number being 79. The median number of RRs per principal study is 6 (Table 8). The subsidiary studies had either one or two RRs. [See Addendum p97.]

Table 9 gives the distribution of various selected RR characteristics by study type and overall, based on all the 190 studies. Table 10 shows how many of the principal studies or their subsidiaries had RRs with selected characteristics, and except where specified otherwise, in the discussion in the rest of this section 'study' refers to 'a principal study or its subsidiary/ies.'

Sex Only 10 studies give any results for males and females separately, in addition to the two studies which included males only. The great majority of RRs (1132, 93%) are for sexes combined

Age 1033 (85%) RRs refer to the full age range of the study, and 163 studies give such results only. The RRs which refer to specific age groups are from 18 studies. 16 RRs from four of these studies are marked as subsidiary RRs because they refer to interim follow-up phases of a prospective study.

Race 1141 (93%) RRs refer to all races (within the scope of the study). The 80 RRs where a restriction applied come from three studies where the results were stratified on race (non-hispanic and hispanic white in BECKET and DODGE, and as Jewish and Arab in KIVITY) and two studies which gave results restricted to a subset (whites only in GOLD, and whites and blacks in NHANE3).

Asthma type The RRs refer about equally to lifetime (552) or to current (595) asthma prevalence. The remaining 73 refer to incidence, with 10 of these being

odds ratios rather than relative risks. The majority of RRs from case-control studies (85%) refer to current asthma, while the majority from cross-sectional studies (65%) refer to lifetime asthma.

Passive smoking exposure (questionnaire assessed) Over half the RRs (771, 63%) refer to parental smoking (i.e. active smoking by the parent(s), at any time including during pregnancy), and these come from 125 (69%) studies. Five of these studies have an additional 32 RRs referring to combinations of parental smoking (since birth) × *in utero* exposure. The most common are for maternal smoking (404 RRs from 90 studies irrespective of father's smoking, and 21 RRs from nine studies for mother only), followed by paternal smoking (217 RRs from 49 studies irrespective of mother's smoking and 27 from 10 studies for father only). 95 RRs from 48 studies refer to any parental smoking. Only 13 RRs from two studies refer to parental ETS exposure (i.e. passive smoking by a parent).

A further 309 RRs from 87 studies refer to household exposure, and 27 RRs from three of these studies to combinations of household exposure × *in utero* exposure. Overwhelmingly these refer to all household members, with just 25 RRs referring to specific family members. Only 10 RRs from five studies refer to total passive smoking exposure. [See Addendum p97.]

The most frequent timing of the passive smoke exposure is current, with 464 (38%) RRs from 74 (41%) studies, followed by unspecified timing with 282 (23%) RRs from 75 studies. There are 115 RRs from 34 studies which refer to *in utero* exposure (regardless of in life exposure). Results for exposure during the child's lifetime generally are given in 119 RRs from 15 studies, with a further 10 RRs (four studies) referring to lifetime and/or *in utero*, 81 RRs (21 studies) referring to a specific time in the child's life[viii] and 13 RRs (three studies) to lifetime but not current exposure. 17 studies give results referring to whether the parent was an ever or ex-smoker (irrespective of how this related to the child's

[viii] Including exposure at baseline in some prospective studies

lifetime), with 49 and 25 RRs respectively, and there is one RR for maternal ever smoking but not smoking during pregnancy. Three RRs from two studies refer to smoking before the child's conception.

For most RRs (961, 83%), the denominator group comprises all those not exposed at the defined exposure time for the numerator. In 23 RRs from three cross-sectional studies (CUNNI1, GILLIL, KUHR) some longer period is unexposed (e.g. if the numerator exposure group is 'currently exposed' then the denominator group may be 'no exposure in lifetime'). In 178 RRs from 20 studies, the denominator group is those whose parents (or rarely, other household members) have never smoked (not even before the child's lifetime).

Passive smoking exposure (biochemically assessed) Most of the results for biochemically assessed exposure come from study NHANE3 (42 RRs, of which 12 are for combinations of biochemically assessed exposure × *in utero* exposure), and refer to serum cotinine. The remaining 16 results refer either to cotinine or cotinine/creatinine ratio, in saliva (CLARK), urine (EHRLI2, KNIGHT, SPIEKE, WILLE1), or hair (also KNIGHT).

Dose response 255 RRs (21%) from 36 studies refer to categories by amount of passive smoke exposures, comprising 83 sets of 2 categories, 27 sets of 3 categories and 2 sets of 4 categories. Of these sets, 51 are for parental smoking (all based on cigarettes per day), four sets are for parental ETS, 44 sets for household smoking (roughly equally divided between cigarettes per day and number of persons smoking and just two sets for time per day), one set for total smoking and 12 sets for biochemical exposure. In addition one RR refers to heavy vs light maternal smoking (i.e. among smokers only – study XU). [See Addendum p97.]

14 RRs hold results regarding the dose response relationship which could not be expressed in the usual categorical format (Table 11). These comprise seven

results from four studies expressed as risk per unit dose (CHINN – parental cigarettes/day; DIJKST and PONSON – household cigarettes/day; EHRLI2 – urinary cotinine), four results from study KNIGHT where the mean exposure (household cigarettes/day or cotinine) is given for cases and controls, together with a p-value, and three results where the dose-response (household or parental cigarettes/day) is simply stated to be significant (ALFRA1, TARIQ) or non-significant (SCHMIT).

Adjustment 634 (52%) RRs have some adjustment. Of sexes combined RRs, 37% are adjusted for sex. Among the adjusted RRs, 55% are adjusted for age, 30% for race, 31% for other passive smoking exposure and 89% for other factors. The adjusted RRs come from 113 studies (76% of prospective studies, 63% of cross-sectional studies and 51% of case-control studies). 27 studies only have adjusted RRs.

2 × 2 table Among the unadjusted RRs, the full 2 × 2 table is available for 529 (76%) RRs and the numbers of cases for another one. Among the adjusted RRs, the numbers of cases is available for 363 (70%). There are 63 studies which do not have the numbers of cases for any RR.

RR and CI 114 (9%) RRs have no values for the RR or CI, having only a statement of significance[ix] (15) or non-significance (99). A further 52 lack a CI, and of these six are stated to be significant and seven non-significant. There are 29 studies which have no complete RR/CIs.

The RR values range from 0.04 to 11.32.

The centrality of the RR in the CI was checked using the statistic

$$C = (RR^2) / (UCL * LCL)$$

[ix] These probably all refer to a significant increase, although this was not always explicitly stated in the original paper

which should have the value 1.0. The value of C was outside the range 0.95 - 1.05 for 48 RRs. For all but four of these, C was in the range 0.80 - 1.25 and the CI was either given originally to only one decimal place or was read from a graph, so the difference is probably due to rounding error. The remaining four RRs are shown in Table 12A.

For case-control and cross-sectional studies, the minimum number of cases and the total number of subjects implied by the CI[10] are compared with the actual numbers, as entered in the study database. The RRs where this showed a problem are listed in Tables 12B and 12C. In many, the difference is associated with a problem in establishing the number of cases which was noted on data entry, or may be due to rounding error. However in some RRs, the CI implies about twice the number of cases than actually reported, without any apparent explanation (ALFRA1, STAZI).

For analyses of prospective studies, the equivalent check on the number of cases is only approximate (see formula 16 of Lee[10]) and there were no RRs where a gross difference was seen, the largest ratio of implied to actual cases being 1.7 (data not shown).

Derivation method 606 (50%) RRs are either as given originally, are calculated directly from the numbers in the 2×2 table, or are calculated adjusting for strata from the numbers in the $2 \times 2 \times n$ table. For a further 21 RRs where both the 2×2 table and the RR and CI were originally available, the RR and CI are recalculated because of a discrepancy and 244 are calculated after summing categories to obtain a 2×2 table. Just 2 RRs are calculated using a zero cell correction (both from case-control studies, one having no exposed cases and the other no exposed controls). 15 RRs are read from graphs or charts and 20 RRs are calculated by other straightforward methods (CI from p-value, combining from independent estimates). The method of Fry and Lee[9] for combining non-independent estimates is used for 102 RRs. Other methods, or combinations of

methods (but not estimation of adjusted CIs from crude numbers) are used for 78 RRs. The remaining five RRs involve estimation of the CI from crude numbers (from studies BURCHF, ANDRAE and KUHR, all of which also have RRs with other types of estimation).

Discrepancy Discrepancies, or the availability of alternative adjusted results, are noted on 147 RRs from 35 studies.

4. Carrying out meta-analyses

4.1 Selecting the relative risks for the meta-analyses

The process of selecting which RRs to include in an analysis can be quite complex as it has to address two main objectives – to include all the relevant data but at the same time to avoid double counting. The rules used when entering data will ensure that double counting is avoided if (1) within each study, values of the stratifying fields (sex, age, race) are non-overlapping; (2) within each strata only one value is chosen for each of: the passive smoke exposure index, the asthma type, the follow-up period and the number of confounders adjusted for; and (3) either a principal study or its subsidiary but not both are included.

When defining the relevant data for a particular analysis, it may be possible to choose a single specific value of a passive smoke exposure index (e.g. for an analysis of mother only smoked). Only RRs with that value will be included, and studies without any such RRs will be excluded altogether. However more commonly, a number of values may be acceptable in the analysis (e.g. in an analysis of parental smoking, RRs for either parent smoked, mother smoked and father smoked may all be acceptable). An order of priority is defined, so that one value only will be chosen from those studies which had RRs entered for more than one acceptable value. In a similar way, preferred values of asthma type can be chosen, and the number of adjusting variables can be chosen to be the minimum or maximum available.

The choice between principal and subsidiary studies can be specified in a similar way, except that the preference is now implemented over the group of linked studies. RRs from the subsidiary study will only be allowed if there are no eligible RRs from the principal study.

For the stratifying variables of age and race, RRs may have been entered on the database for the whole study, or for individual strata, or both. For many analyses, results for the whole study will be preferred if available. However

where only strata-specific RRs are available then the widest available strata will be preferred. For example, if a study included children of ages 5-14, but reported parental smoking results only for ages 9-14, and moreover additionally presented these results split into age groups 9-10, 11-12 and 13-14, then an analysis of parental smoking irrespective of age would choose the RR for age 9-14, whereas an analysis restricted to children aged up to 13 would include the two RRs for ages 9-10 and 11-12.

When specifying 'preferences' on a number of fields, the order in which they are implemented may affect the outcome. For instance, suppose an analysis of maternal smoking for lifetime asthma is required. The exposures 'maternal smoking (regardless of paternal smoking)' and 'maternal smoking only' are defined as 1st and 2nd preferences respectively, as are asthma types 'lifetime' and 'current'. Further supposing that a study has two RRs, (1) for 'maternal smoking (regardless of paternal smoking)' and 'current' asthma, and (2) for 'maternal smoking only' and 'lifetime' asthma. If the preference on maternal smoking is implemented first, then RR 1 will be chosen, whereas if the preference on asthma type is implemented first, then RR 2 will be chosen. Therefore, attention is first restricted to those RRs which have acceptable values for all the preferencing fields. Preferences for the most important aspects of the analysis, usually the passive smoking exposures, are implemented next, while the less important aspects, usually the demographic strata and the principal/subsidiary study status, are implemented later.

It was decided at the outset that single-sex results would be preferred to combined-sex results, and the latter have only been entered on the database when the former are not available. For single-sex results, the passive smoking results that are available are sometimes different for the two sexes (e.g. a principal study may present only male results while a subsidiary has results for both sexes). For these reasons, all setting of preferences is done within sex, and then the choice between sex-specific or sexes-combined is implemented afterwards. A further

possible complication is that some studies may present unadjusted results for the separate sexes but adjusted results only for sexes combined, or other combinations. To handle this situation, the final stage is to choose in the following order of preference:

for an analysis of 'most adjusted' – both MA and FA; CA; both MA and FU; both MU and FA; MA; FA; both MU and FU; CU; MU; FU.

for an analysis of 'least adjusted' – both MU and FU; CU; both MA and FU; both MU and FA; MU; FU; both MA and FA; CA; MA; FA.

(where U and A refer to least and most adjusted results respectively, and M, F and C refer to males, females and sexes combined).

4.2 Combining the relative risks

The method used to carry out the meta-analysis of the selected relative risks is as described by Fleiss and Gross[8]. Both fixed-effects and random-effects meta-analysis have been carried out to form combined estimates of the individual independent risks. Fixed-effects meta-analysis assumes a common underlying relative risk estimate and only takes into account within-study variability in calculating the combined relative risk estimate and its 95% confidence limit. Random-effects meta-analysis also takes into account between-study variability. Where there is no evidence of heterogeneity between the sets of estimates, the two analyses give the same results.

The notation used in some of the output is the same, where relevant, as that used by Fleiss and Gross[8]. Thus, we have:

N	the number of relative risks being combined
NS	the number of studies from which the relative risks are taken (except when the analysis is subdivided into factor levels (see "Section 3" in §4.3) NS in the Total column is the sum of the values in the individual columns, i.e. the number of study × factor levels from which the relative risks are taken)

s	the individual relative risk estimate being combined (s = 1, …N)
Y_s	the logarithm of relative risk estimate s
W_s	the associated weight, calculated as the inverse of the variance of the logarithm of the relative risk
Wt	the total weight for all the relative risks being combined
Fixed RR	the fixed effects relative risk estimate, calculated by exp $((\sum W_s Y_s)/(\sum W_s)) = \exp(\overline{Y})$ summation being over s = 1, … N
Fixed RRl	the lower 95% confidence limit of the fixed effects relative risk estimate, calculated by $\exp(\overline{Y} - 1.96/\sqrt{\sum W_s})$
Fixed RRu	the upper 95% confidence limit of the fixed effects relative risk estimate, calculated by $\exp(\overline{Y} + 1.96/\sqrt{\sum W_s})$
Fixed P	the probability value associated with the fixed effects relative risk estimate, given in coded form as +++, --- p<0.001; ++, -- p<0.01; +, - p<0.05; (+), (-) p<0.1; N.S. (not significant) p≥0.1. Plus signs indicate the relative risk is significantly greater than 1.0, minus signs that it is significantly less
Q_s	the study's contribution to the heterogeneity estimate, calculated by $W_s(Y_s - \overline{Y})^2$. Where N is large, this can be regarded approximately as a chisquared on 1 d.f.
P_s	the associated probability value, used to indicate outliers, coded as for Fixed P
Het Chi	(or Q in Fleiss and Gross notation) the heterogeneity chisquared on N-1 d.f., calculated by $\sum Q_s$. If Q ≤ N-1, the random effects and fixed effects estimates are the same, but if Q > N-1 they differ.
Het df	the degrees of freedom corresponding to Het Chi (= N-1)
Het P	the probability value associated with Het Chi, and Het df, coded as for Fixed P

Random RR,
Random RRl,
Random RRu The random effects relative risk estimate and its lower and upper 95% confidence limits. The method for deriving this, originally described by DerSimonian and Laird[11], is most conveniently given by Fleiss and Gross[8]

Random P the probability value associated with the random effects relative risk estimate, coded as for Fixed P

Asymm P the probability value associated with Egger's test of publication bias,[12] coded as for Fixed P. Only presented for analyses not subdivided by factor levels

Between Chi where the meta-analysis is subdivided by levels of a factor, this is the chisquared value for the difference between the fixed effects relative risk estimates for the factor levels

Between df the degrees of freedom corresponding to Between Chi, equal to the number of factor levels minus 1

Between P the probability value associated with between Chi and between df, coded as for Fixed P

4.3 Detailed output

For each meta-analysis, the full detailed output comes in eight sections preceded by a cover page. All the pages for the meta-analysis are given the same main table number and main heading (describing the analysis), with the section number blank for the cover page and 1 to 8 for the specific section (e.g. Table A3-5 is section 5 within Table A3). The content of each section is as follows:

Cover page : This shows

(i) restrictions on the data included,

(ii) the order of preference for selecting relative risks to be included, and

(iii) a short description of the contents of the table

Note that Sections 1 to 3 concern adjusted data, with relative

risks adjusted for the most potential confounders chosen from a study, while Sections 4 to 6 concern unadjusted data, with relative risks adjusted for the least potential confounders chosen from a study.

Section 1 : For each adjusted relative risk selected, a listing of the relevant characteristics of those relative risks. This includes the values of certain variables used to select the relative risk and used as 'factors' in Section 3, as well as the two key identifiers of the relative risk: the study 6-character reference (REF) and the number of the relative risk within that study (NRR). It also may indicate where relative risks differ from those in another table – for example, if table A1 presented lifetime asthma analyses not restricted by age and table A35 presented lifetime asthma analyses restricted to age below 10 years, a character "x" in a column headed "Comp A1" in the output for table A35-1 would indicate those studies where the relative risk estimates in tables A1 and A35 actually differ.

Section 2 : For each adjusted relative risk selected, the output shows in the first part of the section the sex, the number of potential confounding variables adjusted for, the 2×2 table of results (where available), the relative risk with its 95% CI, and in the second part of the section Y_s, W_s, Q_s and P_s (as defined in §4.2). Where multiple independent estimates are available for a study (typically different sexes or age groups), combined results are also shown for the study. Note that the 2×2 table is headed "exposed/non-exposed" × "case/control". Exposed and non-exposed are as defined in the cover page and include any comparison (e.g. mother smoked vs mother did not smoke). Control will be numbers at risk or person-years for prospective studies, indicated by an asterisk (*) in the left-hand margin. Relative risks calculated by adding 0.5 to each

cell (where a zero is present) are indicated by a tilde (~). Section 2 ends with the results of a meta-analysis of the overall data, identical to that shown at the start of section 3 and described below.

Section 3 : This gives the results of fixed effects and random effects meta-analyses of the adjusted data. For the overall data and for data subdivided by sex, and for data subdivided by various other factors, the output indicates, for each factor level, the number of estimates combined (N), the number of studies from which these estimates come (NS), the combined weight for the studies combined (Wt) as well as the relative risks and confidence limits themselves (RR, RRl, RRu) and coded P values testing for heterogeneity and for variation between factor level: P values are coded as +++, --- or *** $p<0.001$; ++, -- or ** $p<0.01$; +, - or * $p<0.05$; (+), (-) or (*) $p<0.1$ and N.S. $p>0.1$, with plus signs indicating significant positive differences or relative risks greater than 1, minus signs indicating significant negative differences or relative risks less than 1, and asterisks indicating significant non-directional heterogeneity. For the first analysis, of the overall data not subdivided by levels of any factor, coded P values for Egger's test of publication bias (Asymm P)[12] are also given.

Sections 4 to 6 : As for Sections 1 to 3 but for unadjusted data. A column headed X indicates, in the section 4 output, by entries of X against specific relative risks, those that differ from the corresponding adjusted relative risks. Typically, an X will not be entered where a study only has one relevant relative risk available, adjusted or unadjusted but not both.

Section 7 : This lists the studies excluded from consideration, together with information on the stage at which they were excluded. The stage refers back to the various restriction and selection stages described in the cover page. A study is excluded when no relative risk can be found to satisfy the criteria required.

Section 8 : This lists potentially overlapping studies for which data have been included, and also any results which would have been included in preference except that they had incomplete data (typically a relative risk without confidence interval).

Note that the main results are given in Sections 3 and 6 while Sections 1, 2, 4, 5, 7 and 8 mainly provide detailed information only required when one wants to see the individual estimates or to check the program is correctly selecting the data. Accordingly, when results are presented, the full output is shown in Appendices with only selected parts of the Section 3 and 6 results given in the main tables.

An example full output is shown in Appendix G.

Results of the analyses are described separately in Part II of this report.

Table 1 Characteristics of the 190 studies

Characteristic	Level	Study type				
		CC	Prosp	CrSec	Subsid	Total
Total		39	25	117	9	190
Study type	case/control	39	0	0	1	40
	prospective	0	25	0	2	27
	cross-sectional	0	0	117	6	123
Study sex	both	39	25	115	9	188
	male	0	0	2	0	2
Lowest age in study	0	5	17	12	0	34
	1	4	0	5	0	9
	2	1	0	1	0	2
	3	6	0	7	0	13
	4	3	0	3	0	6
	5	3	1	11	2	17
	6	6	1	32	1	40
	7	2	2	16	2	22
	8	2	3	8	1	14
	9	2	0	6	1	9
	10	0	0	2	0	2
	11	2	0	1	0	3
	12	0	0	5	0	5
	13	2	1	5	2	10
	14	0	0	1	0	1
	16	0	0	2	0	2
	missing	1	0	0	0	1
Highest age in study (at baseline for prospective studies)	0	0	15	0	0	15
	1	0	1	2	0	3
	3	1	0	1	0	2
	4	2	0	1	0	3
	5	2	1	4	0	7
	7	2	0	4	0	6
	8	1	1	3	1	6
	9	3	1	4	0	8
	10	4	1	5	0	10
	11	2	0	16	1	19
	12	2	1	17	1	21
	13	1	0	5	1	7
	14	2	0	13	2	17
	15	7	1	11	0	19
	16	3	0	9	1	13
	17	2	1	15	2	20
	18	3	0	3	0	6
	19	0	0	2	0	2
	20	0	0	1	0	1
	21	0	0	1	0	1
	missing	2	2	0	0	4

Table 1 (continued)

Characteristic	Level	Study type				
		CC	Prosp	CrSec	Subsid	Total
Highest age in study at final followup (prospective studies)	3	-	1	-	0	1
	4	-	3	-	0	3
	5	-	1	-	0	1
	6	-	2	-	0	2
	7	-	6	-	0	6
	10	-	0	-	1	1
	11	-	2	-	0	2
	12	-	2	-	0	2
	13	-	1	-	0	1
	14	-	1	-	0	1
	16	-	2	-	0	2
	18	-	1	-	1	2
	22	-	1	-	0	1
	23	-	2	-	0	2
Study race	all (in country)	35	23	110	7	175
	whites (including Hispanics)	2	0	2	0	4
	blacks	2	0	1	0	3
	whites and blacks	0	1	2	2	5
	whites (excluding Hispanics)	0	1	0	0	1
	Chinese	0	0	1	0	1
	Fijians and Indians	0	0	1	0	1
Continent	N America	9	7	25	3	44
	S/C America	3	0	3	0	6
	W Europe/Scandinavia	13	13	47	3	76
	E Europe/Balkans	2	1	9	0	12
	Asia	8	1	24	3	36
	Australasia	0	3	9	0	12
	Africa	4	0	0	0	4
Country in N America	USA	7	7	17	3	34
	Canada	2	0	7	0	9
	USA and Canada	0	0	1	0	1
US state	all	0	0	4	0	4
	Cal,Wash,Oreg	0	2	2	1	5
	Nev,Ut,Ariz	0	3	0	0	3
	Minn,Ia,Wis,Ill,Mo	1	0	1	0	2
	Ark,Miss,La,Al	0	0	1	2	3
	Mich,Ind,Oh,Tenn	1	0	2	0	3
	Fla,Ga,SC,NC	1	0	0	0	1
	Pa,NJ,Md,WVa,Va, Del,WasDC	2	0	2	0	4
	Vt,Me,NY,NH,Mass, RI,Conn	2	1	4	0	7
	multi (but not all)	0	1	2	0	3
Country in S/C America	Costa Rica	0	0	1	0	1
	Brazil	0	0	1	0	1
	Mexico	3	0	1	0	4

Table 1 (continued /2)

Characteristic	Level	Study type				
		CC	Prosp	CrSec	Subsid	Total
Country in W Europe	UK	5	7	10	1	23
	Ireland	1	0	1	0	2
	Denmark	0	1	1	0	2
	Norway	0	1	4	0	5
	Sweden	2	2	5	1	10
	Finland	0	1	4	0	5
	Spain	1	0	1	0	2
	France	0	0	2	0	2
	Netherlands	1	0	2	0	3
	Switzerland	0	0	2	0	2
	Germany	0	1	6	1	8
	Austria	0	0	1	0	1
	Italy	3	0	7	0	10
	Malta	0	0	1	0	1
Country in E Europe/ Balkans	Poland	0	1	2	0	3
	Turkey	1	0	6	0	7
	Russia	1	0	1	0	2
Country in Asia	Japan	0	0	4	0	4
	China	1	0	2	0	3
	Hong Kong	0	1	3	0	4
	Malaysia	1	0	0	0	1
	India	2	0	2	0	4
	Nepal	1	0	0	0	1
	Saudi Arabia	0	0	2	1	3
	UAE	1	0	1	0	2
	Taiwan	0	0	2	0	2
	Israel	1	0	6	2	9
	Sri Lanka	1	0	0	0	1
	Korea	0	0	2	0	2
Country in Australasia	Australia	0	2	4	0	6
	New Zealand	0	1	3	0	4
	Fiji	0	0	2	0	2
Country in Africa	Ghana	1	0	0	0	1
	Kenya	1	0	0	0	1
	Nigeria	1	0	0	0	1
	South Africa	1	0	0	0	1
Start year of study	before 1960	0	1	0	0	1
	1960-1969	1	1	2	0	4
	1970-1979	0	7	9	0	16
	1980-1989	9	11	30	4	54
	1990-1999	20	4	61	5	90
	2000-2001	0	0	1	0	1
	missing	9	1	14	0	24

Table 1 (continued /3)

Characteristic	Level	Study type				
		CC	Prosp	CrSec	Subsid	Total
End year of study (of baseline for prospective studies)	before 1960	0	1	0	0	1
	1960-1969	0	1	2	0	3
	1970-1979	1	6	8	0	15
	1980-1989	7	9	25	4	45
	1990-1999	21	7	64	5	97
	2000-2001	1	0	4	0	5
	missing	9	1	14	0	24
Final follow up year (prospective studies)	1960-1969	-	1	-	0	1
	1970-1979	-	1	-	0	1
	1980-1989	-	8	-	0	8
	1990-1999	-	14	-	2	16
	missing	-	1	-	0	1
Principal publication year	1970-1979	1	1	1	0	3
	1980-1989	1	5	14	0	20
	1990-1999	27	12	70	7	116
	2000-2002	10	7	32	2	51
Type of population[1] (for CC studies refers to cases)	all children	0	5	7	1	13
	random children	0	2	11	1	14
	all schoolchildren	4	2	16	2	24
	random schoolchildren	6	2	33	2	43
	all in given school(s)	2	1	17	0	20
	random in given school(s)	0	0	2	1	3
	schoolchildren NOS	1	2	9	2	14
	all hospital/clinic patients	1	0	1	0	2
	all patients in given hospital/clinic(s)	10	0	1	0	11
	random patients in given hospital/ clinic(s)	3	0	0	0	3
	hospital NOS	3	0	0	0	3
	all primary care patients	0	0	1	0	1
	random primary care patients	1	0	0	0	1
	all patients at given primary care(s)	4	1	2	0	7
	random patients at given prim care(s)	0	0	1	0	1
	primary care NOS	2	0	1	0	3
	all children attending pre-school routine health check	0	0	1	0	1
	all children receiving primary care at hospital clinic who had been born same hospital /continued	1	0	0	0	1

Table 1 (continued /4)

Characteristic	Level	Study type				
		CC	Prosp	CrSec	Subsid	Total
	all children from random households	0	0	5	0	5
	all newborns at given hospital(s)	0	4	1	0	5
	families of all newborns delivered at given hospital(s)	0	0	2	0	2
	random newborns at given hosp(s)	0	1	0	0	1
	all children of random parent who had participated in NCDS	0	0	1	0	1
	all children hospitalized with bronchiolitis at given hospital + population controls	0	1	0	0	1
	all children from all asthmatic families	0	0	1	0	1
	all patients at given hospital with high allergy risk	0	2	0	0	2
	all patients at given primary care with high allergy risk	0	1	0	0	1
	random athletes in given school(s)	0	0	1	0	1
	all twins still resident in country of birth	0	0	1	0	1
	all schoolchildren living on farms	0	0	1	0	1
	random newborns with high SIDS risk	0	1	0	0	1
	all travellers' children + all at given school	0	0	1	0	1
	unspecified	1	0	0	0	1
Type of controls (for CC studies)	healthy	28	-	-	1	29
	diseased/hospital	11	-	-	0	11
Type of control population (Case-control studies)	same as cases	17	-	-	1	18
	same as cases but excluding children with chest/respiratory symptoms, allergy or history of asthma	14	-	-	0	14
	all at given school(s)	1	-	-	0	1
	random at given schools excluding children with respiratory symptoms or history of asthma	2	-	-	0	2

/continued

Table 1 (continued /5)

Characteristic	Level	Study type				
		CC	Prosp	CrSec	Subsid	Total
	random schoolchildren excluding children using asthma medication	1	-	-	0	1
	random children from hospital catchment area	1	-	-	0	1
	random children from hospital catchment area with no history of asthma	1	-	-	0	1
	no siblings with allergic disorders	1	-	-	0	1
	all newborns	1	-	-	0	1
Matching factors (Case- control studies)	sex	13	-	-	1	14
	age	18	-	-	1	19
	race	2	-	-	0	2
	location (within study area)	7	-	-	1	8
	socioeconomic status	2	-	-	0	2
	hospital admission (ward, date)	1	-	-	0	1
Respondent (for passive smoking information)	Child	2	0	10	0	12
	Parent	27	19	87	8	141
	Medical records	2	1	1	0	4
	Parent and child	2	5	14	1	22
	Unspecified (parent/child)	5	0	1	0	6
	Household member or accompanying adult	1	0	2	0	3
	Parent or child (depending on age)	0	0	2	0	2
Standard questionnaire	No	28	19	68	7	122
	ISAAC	7	2	20	0	29
	ATS/NHLI/ESP	2	3	18	2	25
	MRC	1	0	1	0	2
	IUATLD	1	0	2	0	3
	WHO	0	1	7	0	8
	ICHPPC	0	0	1	0	1
Lifetime[2]/incidence asthma available	No	27	6	37	1	71
	Yes	12	19	80	8	119

Table 1 (continued /6)

Characteristic	Level	Study type				
		CC	Prosp	CrSec	Subsid	Total
Source of lifetime[2]/ incidence asthma diagnosis	Medical records	6	4	2	0	12
	Parent report (physician diagnosis)	0	5	35	3	43
	Parent report (other/ unspecified/mixed)	0	5	31	4	40
	Child report (physician diagnosis)	0	1	6	1	8
	Child report (other/ unspecified/mixed)	1	1	2	0	4
	Medical records or parent report (physician diagnosis)	1	1	0	0	2
	Medical records or parent report (other/ unspecified/mixed)	1	0	0	0	1
	Parent or child report (physician diagnosis)	0	1	1	0	2
	Parent or child report (other/ unspecified/mixed)	1	1	2	0	4
	Unspecified	2	0	1	0	3
Timing of lifetime[2] asthma	lifetime	5	3	55	6	69
	unspecified	7	2	23	0	32
	from age 2	0	0	1	0	1
	from age 3	0	0	1	0	1
	up to baseline	0	0	0	1	1
	NA (incidence only)	0	14	0	1	15
Timing of incidence asthma	since baseline (earlier excl)	0	3	0	1	4
	lifetime (recruit at birth)	0	11	0	0	11
	lifetime (retrospective)	0	1	0	0	1
	NA (prevalence analysis only)	12	4	80	7	103
Number of lifetime[2]/ incidence asthma cases	1-100	4	8	24	3	39
	101-200	7	1	21	2	31
	201-500	1	6	20	2	29
	501-1000	0	2	9	1	12
	>1000	0	1	3	0	4
	N	12	18	77	8	115[3]
	Median	104.5	188.0	163.0	161.0	140.0
	Min	40	12	6	50	6
	Max	400	5842	3178	748	5842
	Miss	0	1	3	0	4

Table 1 (continued /7)

Characteristic	Level	Study type				
		CC	Prosp	CrSec	Subsid	Total
Current asthma available	No	12	16	64	8	100
	Yes	27	9	53	1	90
Current asthma is first occurrence		3	0	0	0	3
Repeat measures for current asthma (prospective studies)		-	6	-	0	6
Source of current asthma diagnosis	Medical records	18	1	2	1	22
	Parent report (physician diagnosis)	0	0	9	0	9
	Parent report (other/ unspecified/mixed)	7	5	30	0	42
	Child report (physician diagnosis)	0	0	2	0	2
	Child report (other/ unspecified/mixed)	1	1	8	0	10
	Medical records or parent report (physician diagnosis)	1	1	0	0	2
	Parent or child report (physician diagnosis)	0	1	0	0	1
	Parent or child report (other/ unspecified/mixed)	0	0	2	0	2
Timing of current asthma	current diagnosis	12	0	2	1	15
	last n months (n<6)	0	0	5	0	5
	last n months (6<=n<12)	1	0	1	0	2
	last n months (12<=n<24)	10	6	30	0	46
	last n years (2<=n<5)	0	0	1	0	1
	current NOS	4	3	14	0	21
Number of current asthma cases	1-100	9	1	25	1	36
	101-200	8	5	9	0	22
	201-500	7	2	8	0	17
	501-1000	2	0	6	0	8
	>1000	1	0	1	0	2
	N	27	8	49	1	85[4]
	Median	140.0	181.5	86.0	85.0	131.0
	Min	14	36	8	85	8
	Max	1306	470	20637	85	20637
	Miss	0	1	4	0	5

Table 1 (continued /8)

Characteristic	Level	Study type				
		CC	Prosp	CrSec	Subsid	Total
Total number of subjects	1-100	5	0	1	0	6
	101-200	7	2	5	1	15
	201-500	15	3	6	0	24
	501-1000	7	4	17	3	31
	>1000	5	16	87	5	113
	N	39	25	116	9	189[5]
	Median	262.0	1314.0	2139.5	1942.0	1447.0
	Min	35	140	57	111	35
	Max	16445	29238	155284	3746	155284
	Miss	0	0	1	0	1
Other definitions of asthma available		7	4	24	0	35
Wheezing/wheezing bronchitis available		5	16	57	4	82
Other exposures available		3	4	4	1	12
Child smokes	No mention	31	17	86	8	142
	Smokers excluded biochemically	0	0	1	0	1
	Smokers excluded questionnaire	0	0	11	0	11
	Smokers excluded unspecified	0	0	1	0	1
	Smokers above given age excluded (below assumed to be non-smokers)	0	0	2	0	2
	No smokers found above given age (below assumed to be non-smokers)	1	1	0	0	2
	Assumed no smokers	1	1	1	0	3
	No smokers NOS	0	0	1	0	1
	Smokers included but stated to be few	0	1	2	1	4
	Smokers included	2	2	3	0	7
	Smokers included and adjusted for in analysis	1	1	2	0	4
	Smokers included because active smoking was tested in univariate analysis and found not significant	0	0	1	0	1
	Smokers included because active smoking rejected from MLR due to lack of significance	0	1	1	0	2
	Discussed, but no data available	1	0	5	0	6
	Biochemical exclusion discussed but not used	1	0	0	0	1
	No mention in analysis but was in questionnaire	1	1	0	0	2

Table 1 (continued /9)

Characteristic	Level	Study type				
		CC	Prosp	CrSec	Subsid	Total
Other results for child smokers available		2	4	6	1	13
Total number of adjustment factors used	none	19	6	44	4	73
	1	4	2	1	0	7
	2	1	2	2	0	5
	3	1	1	11	2	15
	4	3	3	6	0	12
	5	3	0	6	3	12
	6	1	2	9	0	12
	7	0	1	7	0	8
	8	1	2	10	0	13
	9	2	1	3	0	6
	10	1	2	6	0	9
	11	0	2	3	0	5
	12	0	0	1	0	1
	13	0	0	3	0	3
	15	1	1	2	0	4
	16	1	0	1	0	2
	17	0	0	1	0	1
	19	0	0	1	0	1
	29	1	0	0	0	1
Confounders considered[6]:	sex	8	15	51	3	77
	age	8	3	35	3	49
	race	3	4	13	3	23
	location within study area (including urban/rural, air pollution)	6	5	32	3	46
	type of respondent	3	0	4	0	7
	interview setting	0	0	1	0	1
	year of diagnosis	0	1	0	0	1
	family medical history (parent/sibling) (by 1-3 variables)	8	10	40	2	60
	family medical history (parent/sibling) (by 4-6 variables)	1	2	0	0	3
	Parent's age	0	1	6	0	7
	SES or parental education (by 1-4 variables)	8	13	35	2	58
	household composition (number of children, single parent, position in sibship etc)	2	6	23	0	31
	day care	0	2	5	0	7

/continued

Table 1 (continued /10)

Characteristic	Level	Study type				
		CC	Prosp	CrSec	Subsid	Total
	air conditioning, humidifier (by 1-4 variables)	2	1	3	0	6
	cooking & heating methods, incense, mosquito coils (by 1-3 variables)	7	1	24	2	34
	cooking & heating methods, incense, mosquito coils (by 4-5 variables)	1	0	2	0	3
	damp or mould in home	6	1	15	0	22
	housing quality, age, size, crowding, shared bedroom, owned/rented	7	1	15	2	25
	pets or close animal contact	4	4	20	0	28
	exposure to food or housedust allergens, carpets, type of bedding, houseplants	3	1	8	0	12
	farming	0	0	2	0	2
	religion	0	0	1	0	1
	mobility (e.g. parent or child born abroad, moved house, time of residence, language spoken at home)	0	0	6	0	6
	child's medical history/symptoms (including breastfeeding and SPT results) (by 1-3 variables)	9	9	25	1	44
	child's medical history/symptoms (including breastfeeding and SPT results) (by 4-6 variables)	1	3	3	0	7
	obesity/BMI	0	1	8	0	9
	exercise	0	0	1	0	1
	diet (excluding breastfeeding)	0	0	1	0	1
	child active smoking	1	1	2	0	4
	maternal smoking in pregnancy	2	1	10	0	13
	parental smoking current/since birth	6	3	19	0	28
	household ETS exposure	4	0	3	0	7
Other confounders considered but rejected		7	5	21	0	33
Results by other stratifying factors available		11	9	21	1	42

Table 1 (continued /11)

CC = case-control; Prosp = prospective; CrSec = Cross-sectional; Subsid = Subsidiary

[1] Refers to children within the study area, age group etc as defined by other variables. 'Random schoolchildren' includes all children from randomly selected schools and randomly selected children from all schools, and similarly for hospital and primary care.

[2] Includes asthma of unspecified timing.

[3] Median, min and max are the same when based on the 107 principal studies only.

[4] Median is 134.0 when based on the 84 principal studies only, min and max are the same.

[5] Median is 1428.5 when based on the 180 principal studies only, min and max are the same.

[6] By up to 3 variables, unless stated otherwise.

Table 2A Exclusion from study population - Medical exclusions

Study Ref	Medical exclusions
ARSHAD	restricted to subjects with high allergy risk
AZIZI	acute bronchiolitis, pneumonia, stridor, chronic and surgical respiratory conditions, heart disease, acute and chronic renal failure, oncological disorders, tuberculosis, immunological disorders, gross malnutrition
BALL	oxygen >6hrs, major congenital abnormalities, congenital chest or lung problems (e.g. cystic fibrosis), symptomatic congenital heart problems, severe systemic disease
BECKET	birth complications/neonatal deaths, low birthweight
BUTZ	cystic fibrosis, rheumatoid arthritis
CUNNI2	history of cystic fibrosis, heart disease, chest injury/operation, neonatal oxygen/ventilation; unable to perform spirometry
DEKKER	cystic fibrosis
FAGBUL	family history asthma
FAROOQ	atopic disorder before completion of immunisations
HOST	previous asthmatic bronchitis
JAAKKO	birthweight <2000gm, serious neonatal respiratory, cardiovascular, neuromuscular or metabolic disease, assisted ventilation >6hrs
KERSHA	cystic fibrosis, tracheal-oesophageal fistula, congenital collapsing bronchus, immotile cilia syndrome
KNIGHT	history of chronic cough or wheeze, exercise-induced cough or wheeze, or SOB without current diagnosis of asthma
KUHR	acute infection
LEEDER	died within 7 days of birth
LILLJE	symptoms or diagnosis of allergies but not asthma
MCCON1	cystic fibrosis, severe chest injury, chest surgery
MCCON2	premature birth, cardiac/neuromuscular disorder, esophageal atresia, bronchiolitis
MURRAY	cystic fibrosis, marked gastroesophageal reflux
ODDY	died before age 6
OLIVET	bronchopulmonary dysplasia, cystic fibrosis, anatomic lung abnormality, neonatal oxygen/ ventilation >14 days
PALMIE	history of atopic disease
PONSON	restricted to high risk of SIDS
RATAGE	bronchiectasis, acute exacerbation of asthma
ROSASV	neurologic, cardiac or neoplastic disease; adverse systemic reaction during SPT
SARRAZ	immunodeficiency, congenital heart disease, cystic fibrosis, autoimmune disease, mental impairment
SCHMIT	respiratory tract infection in last 3w
TARIQ	perinatal deaths

Table 2A (continued)

Study Ref	Medical exclusions
VENNER	both parents have asthma
VONMAF	birth complications/neonatal deaths, low birthweight
WANG	past (but not current) asthmatic symptoms
WILLE2	acute illness
XU	died before age 7

Table 2B Exclusion from study population - Other exclusions

Study Ref	Other exclusions
ALBA	no home telephone
ALDAWO	non-nationals, not local residents
ALFRA1	non-Saudis
ALFRA2	non-Saudis
ANNESI	restricted to children with a parent born 1958 who participated in the National Child Development Study (NCDS)
BECKET	non-English speakers, newborns given for adoption
BURCHF	not living with both parents
CUNNI1	questionnaire not completed by biologic mother
CUNNI2	questionnaire not by biologic mother, height or weight outside limits
DEKKER	temporary dwelling (mobile home, boat etc)
DELL	primary caregiver not the biological mother
DIJKST	non-NW European origin
DODGE	single parent families
DOLD	non-Germans
FARBE1	female guardian not mother
FARBE2	female guardian not mother
FARBE3	female guardian not mother
FAROOQ	ever changed GP, or died during study period
FERGUS	died or left New Zealand before age 6
FLYNN2	urban schools
HJERN1	mother age 50+
HJERN2	father age 50+
INFANT	not local resident
JAAKKO	not permanent Oslo resident, plans to move away, non-Norwegian speaking, not living with any biologic parent, history of drug abuse in family
JONES	sibling also in study
KEARNE	away at time of study
LAM1	English-speaking and International schools
LEEDER	not full 5-year followup
LEROUX	parent did not attend school medical examination
LILLJE	not traceable at original address
MCCON2	adopted
MOYES1	very small rural village schools
MOYES2	very small rural village schools

Table 2B (continued)

Study Ref	Other exclusions
NILSSO	residence in first year not in same region
NYSTAD	non-Norwegians (immigrants)
PONSON	died/moved away by age 7
RASANE	co-twin died or not living in Finland
RATAGE	not local resident
RENNIE	restricted to those living on farms or acreages
RONCH3	participated in earlier study (RONCH2)
RONMAR	children who moved away were excluded from onset analyses
SARRAZ	lived <2 years at current address
SCHENK	single parent families
SCHMIT	lived in region <3y
SENNHA	non-Swiss nationals
STERN1	outlying school near military base
STRACH	changed address in last 3 years
TARIQ	adoptions, moved away from Isle of Wight
TSIMOY	restricted to athletes
VOLKME	heating by kerosene, multiple types or none
VONMAF	non-English speakers, newborns given for adoption

Table 3A Diagnostic criteria for lifetime or incident asthma

Basis of diagnosis	Study Ref	Description of lifetime asthma
Medical records	ALBA	asthma (= 3+ episodes of bronchospasm, but excluding aspiration of foreign body and bronchiolitis)
	BURR	asthma
	BUTZ	asthma
	FAROOQ	asthma (= recurrent episodes of wheeze)
	FERGUS	attended phys for wheeze diagnosed as asthma or wheezy bronchitis. (Based on conclusion by Williams & McNicol that the two conditions are indistinguishable)
	KERSHA	asthmatic (= presenting any respiratory illness, had had 3+ bouts of bronchitis or bronchiolitis in any 6m period, and also had either definite intermittent wheeze or chronic night cough)
	MCKEEV	asthma (including asthma and wheezing)
	OCONNE	asthmatic
	RATAGE	asthma (= 3+ episodes cough/wheeze with reversible airway obstruction with aerosolized salbutamol inhalation)
	ROSASV	asthma according to international guidelines
	VENNER	asthma diagnosed on basis of history of repeated onset of wheeze with dyspnea, but without symptoms between events and symptoms improved by bronchodilator
	ZEIGER	asthma (= 2+ episodes lower respiratory disorder with reversible bronchospasm unassociated with other anatomic congenital or immunologic causes)
Physician diagnosis	AKCAKA	asthma
	ALFRA1	asthma
	BECKET	at least one child in family with physician diagnosed asthma
	BRABIN	asthma
	CHEN1	asthma
	CHEN2	asthma
	CUNNI2	asthma

Table 3A (continued)

Basis of diagnosis	Study Ref	Description of lifetime asthma
Physician diagnosis (continued)	DELL	asthma
	DODGE	asthma
	DOLD	asthmatic (= at least one episode of bronchial asthma, or several episodes of asthmatic bronchitis or spastic bronchitis)
	EHRLI2	acute (current diagnosis at ER and at least one previous physician diagnosis acute asthma) or non-acute (history episodic or chronic airflow obstruction requiring medication, no acute attack in last 2 weeks)
	FIELDE	asthma
	FLYNN1	asthma
	FLYNN2	asthma
	GILLIL	asthma
	HU1	asthma
	HU2	asthma
	KALYO1	asthma
	KEARNE	asthma
	KENDIR	asthma
	KUEHR	asthma (= asthma or recurrent wheezy bronchitis)
	KUHR	answered Yes or Dont know to ever physician diagnosed asthma
	LAM1	asthma
	LAM2	asthma
	LIS	bronchial asthma
	MAIER	asthma
	MARTIN	asthma
	MCCON2	asthma
	MONTEF	asthma
	MOYES1	asthma

Table 3A (continued /2)

Basis of diagnosis	Study Ref	Description of lifetime asthma
Physician diagnosis (continued)	MOYES2	asthma
	NHANE3	asthma
	ODDY	asthma
	RASANE	asthma
	RENNIE	asthma
	SCHENK	asthma
	SELCUK	bronchial asthma
	SENNHA	bronchial asthma
	SHERMA	asthma
	SIGURS	asthma (= 3 episodes of bronchial obstruction) verified by physician
	STAZI	asthma
	STERN2	asthma
	TAYLOR	any episodes of wheezing on the chest, diagnosed as asthma (question did not prompt with asthma, this was only if mentioned as diagnosis by the parent)
	TSIMOY	asthma
	VONMAF	at least one child in family with physician diagnosed asthma
	WITHER	asthma
	WOLFO1	asthma
	WOLFO2	asthma
	WOLFO3	asthma
	XU	parent report of "child has long-term illness" specifying asthma (probably physician diagnosed), or National Hospital Discharge Record linkage indicates ever hospitalized due to asthma
	ZEJDA	asthma

Table 3A (continued /3)

Basis of diagnosis	Study Ref	Description of lifetime asthma
Other/mixed	ALDAWO	asthma (= attacks of wheezing with SOB and breathing normal between attacks)
	ANDRAE	allergic asthma (= ever had a "breathing problem" with heavy breathing and wheezing, and this occurs when in contact with deciduous trees, grass, flowers or furred animals)
	ANNESI	ever had attacks of asthma
	BARRET	asthma
	BENER	asthma attack
	BURCHF	asthma (=asthma or wheeze with at least 2 of: SOB; allergen exposure; physician diagnosis of asthma or wheezy bronchitis)
	DEBENE	bronchial asthma
	ECE	asthma
	FARBE2	asthma
	FORAST	asthma (= physician diagnosed asthma, or 3+ symptoms from: wheeze with colds, wheeze apart from colds, dyspnoea with wheeze, wheeze after exercise)
	GOLD	asthma
	GOREN1	asthma
	GOREN2	asthma
	GOREN3	asthma
	GOREN6	asthma
	GORTM1	asthma
	GORTM2	asthma
	GURKAN	ever physician diagnosed asthma or asthmatic symptoms such as SOB with wheezing
	HAJNAL	asthma
	JENKIN	asthma (= attacks of asthma or wheezy breathing)
	KAPLAN	ever had attacks of asthma

Table 3A (continued /4)

Basis of diagnosis	Study Ref	Description of lifetime asthma
Other/mixed (continued)	KAY	asthma
	KIVITY	bronchial asthma
	LEEDER	asthma
	LEROUX	asthma (= acute recurring attacks of SOB with wheeze which end spontaneously or respond to treatment)
	LISTER	asthma
	MURRAY	asthma
	NILSSO	asthma
	NYSTAD	ever had asthma and it began after age 3
	POKHAR	bronchial asthma (= 1+ of: ever wheeze; wheeze in last 12m; ever diagnosed asthma; wheeze after exercise in last 12m; persistent night cough without cold/infection in last 12m)
	PONSON	asthma
	RONCH1	ever physician diagnosed asthma, or ever had asthmatic attack (SOB with audible wheezing) and when playing becomes more breathless than other children
	RONCH2	ever physician diagnosed asthma, or ever had asthmatic attack (SOB with audible wheezing) and when playing becomes more breathless than other children
	RONCH3	ever physician diagnosed asthma, or ever had asthmatic attack (SOB with audible wheezing) and when playing becomes more breathless than other children
	RONMAR	asthma
	RUDNIK	asthma
	SANZOR	asthma
	SHAMSS	asthma
	SOYSET	asthma
	SQUILL	3+ symptoms suggestive of asthma
	STANHO	one or more episodes labelled asthma

Table 3A (continued /5)

Basis of diagnosis	Study Ref	Description of lifetime asthma
Other/mixed (continued)	ULRIK	asthma (= at least one of a) breath ever wheezy or whistling, b) attacks of SOB with wheezing, c) wheezing, chest tightness, cough, breathlessness with any of: at rest, with exertion, with emotional stress, with exposure to cold air, with chest infections or head cold, d) wheezing after exposure to: dust, fumes, moulds, pollen, food, pets, drugs)
	VARELA	asthmatic
	VAVILI	bronchial asthma
	VERHOE	asthma (subset of chronic respiratory symptoms)
	VOLKME	asthma
	WEITZ1	asthma

Table 3B Diagnostic criteria for current asthma

Basis of diagnosis	Study Ref	Timing of current asthma[1]	Description of current asthma
Medical records	ADDOYO	4	attending asthma clinic with physician diagnosed asthma, use of anti-asthma medication and symptoms (cough and/or wheeze) in last 12m
	ARSHAD	6	asthma (= 3+ separate episodes of cough & wheeze)
	AZIZI	1	asthma (diagnosed if there was previous history of wheezing, and clinical findings and subsequent progress did not suggest other diagnosis)
	CALL	1	presenting at ER with acute wheezing and diagnosed as asthma
	CLARK	1	asthmatic attending asthma or medical clinic
	DAIGLE	3	asthma requiring hospitalization or 2 primary care visits
	FAGBUL	1	asthma (= presenting with severe SOB +/- cough & wheeze, and had wheezy attack in last 6m)
	HUGHES	4	receiving treatment for asthma in last year
	INFANT	1	asthma compatible with ICD(9) code 493
	JONES	4	on practice asthma register (clinical diagnosis supported by response to treatment and/or peak flow measurement)
	KARUNA	1	inpatient admission, 2+ episodes of asthma, more severe than cough and wheeze
	KNIGHT	1	asthma (= clinic diagnosis of repeated reversible episodes of bronchoconstriction manifested as cough or wheeze, verified by pulmonary function tests)
	LINDFO	1	referral to specialist allergy clinic for evaluation of bronchial asthma, and 3+ episodes of airway obstruction with asthmatic symptoms such as wheezing, cough etc
	LOPEZC	1	allergic asthma
	MOUSSA	6	known asthmatics regularly receiving medication
	MUMCUO	1	asthma (= history of cough, SOB and wheeze, as well as low PF with at least 10% improvement after bronchodilator)
	OLIVET	4	physician diagnosed asthma and wheeze or cough requiring asthma medication in last 12m

Table 3B (continued)

Basis of diagnosis	Study Ref	Timing of current asthma[1]	Description of current asthma
Medical records (continued)	PALMIE	4	3+ asthma attacks in last 12m
	SARRAZ	1	asthma (clinical history and lung function tests)
	TOMINA	1	bronchial asthma
	WILLE1	1	asthma based on clinical history (recurrent episode of cough & wheeze) and examination
Physician diagnosis	BERGMA	6	asthma
	CHEN2	4	doctor said child has asthma in last 12m
	FORSB1	4	asthma treatment by physician
	FORSB2	4	asthma treatment by physician
	FORSB3	4	asthma treatment by physician
	HJERN1	6	allergic asthma (=gets asthma when in contact with pollen or furred animals)
	HJERN2	6	allergic asthma (=gets asthma when in contact with pollen or furred animals)
	HOST	6	current/active physician diagnosed asthma
	MOHAME	1	asthma (= either questionnaire reported history of physician diagnosed asthma or symptoms of persistent or frequent wheeze; or 10% decline in FEV after exercise test)
	PETERS	6	asthmatic diagnosis
	SCHMIT	4	physician diagnosed asthma with medication and attack rates in last 12m evaluated (although criteria used not stated)
	SELCUK	4	physician diagnosed bronchial asthma with symptoms in last 12m
	STERN2	4	asthma in previous year
	YANG	6	asthma currently present and confirmed by doctor

Table 3B (continued /2)

Basis of diagnosis	Study Ref	Timing of current asthma[1]	Description of current asthma
Other/mixed	AGABI1	4	history of asthma with wheezing in last 12m
	AGABI2	4	history of asthma with wheezing in last 12m
	BALL	4	physician diagnosed asthma with exacerbation in last 12m
	CHHABR	4	current or probable asthmatic (= recurrent wheeze in last 12m or wheezing with exercise or wheezing with a cold)
	CHINN	4	at least one asthma attack in last 12m
	CSONKA	4	asthma (= at least one of: wheezy breathing; ER or hospital treatment for acute asthma; regular anti-inflammatory therapy for chronic asthma)
	CUNNI1	4	active diagnosed asthma (= ever diagnosed and experienced symptoms in last 12m)
	DEKKER	6	ever physician diagnosed asthma and still has asthma
	DEKOK	4	asthma (= 2+ key symptoms (wheeze or SOB) in last 12m)
	DIJKST	4	asthma (= SOB with wheezing in last 12m)
	DOTTER	6	has suffered from asthma, and wheezes, coughs or has attacks of breathlessness (asthma) after exposure to extrinsic factors (pollen, animals, food, infections)
	EHRLI1	4	asthma with at least one in last 12m of: wheezing or whistling in chest; woken up by wheezing or whistling chest; wheezing or whistling chest prevented normal speech; wheezing or whistling chest after exercise; dry cough at night not from cold or chest infection; tight chest
	FIELDE	2	asthma treated in last 4w
	FUJI	5	asthma (= ever had 2+ episodes of wheeze with dyspnoea, and asthma attack or need for medical treatment for asthma in last 2 years)
	GILLIL	3	ever physician diagnosed asthma and symptoms/illness last yr
	GOLD	4	asthma

Table 3B (continued /3)

Basis of diagnosis	Study Ref	Timing of current asthma[1]	Description of current asthma
Other/mixed (continued)	GUPTA	4	either wheezing or tightness in chest, and at least one of: previous diagnosis of asthma, asthma attack in last 12m, use of medication for asthma
	HABY	4	ever physician diagnosed asthma and medication in last 12m and symptoms of cough or wheeze in last 12m
	HU1	2	asthma medication (taken in last 2 weeks for asthma, wheezing or whistling in chest)
	HU2	4	ever physician diagnosed asthma and, in last 12m, either taking asthma medication or episode of cough/ wheeze/SOB lasting 3+ days
	JAAKKO	4	physician diagnosed asthma, and symptoms in last 12m
	KALYO1	4	ever physician diagnosed asthma and symptoms in last 12m
	KALYO2	4	ever physician diagnosed asthma and symptoms in last 12m
	LAM1	2	use of asthma medication in last 2 days
	LAM2	2	use of asthma medication in last 2 days
	LAU	6	asthma
	LEE1	4	ever diagnosed asthma and symptoms in last 12m
	LEE2	4	ever diagnosed asthma and symptoms in last 12m
	LEEN	6	asthma (= current wheeze)
	LILLJE	6	asthma symptoms
	MCCON2	6	ever physician diagnosed and currently taking medication
	MELIA	4	at least one asthma attack in last 12m
	MELSOM	4	asthma (= at least one symptom in last year from both written and video questionnaires- Written: wheeze; dry cough at night apart from with cold. Video: moderate wheeze at rest; woken by nocturnal wheeze; woken by nocturnal cough; severe wheeze at rest)
	NHANE3	6	ever physician diagnosed asthma and still has asthma

Table 3B (continued /4)

Basis of diagnosis	Study Ref	Timing of current asthma[1]	Description of current asthma
Other/mixed (continued)	NITTA	6	current asthma not clearly defined, but based on attacks of SOB with cough, phlegm and/or wheeze, and physician diagnosed asthma
	OHARA	4	diagnosed asthma and wheezing in last 12m
	PIC	4	asthma attacks in last 12m
	RIBEIR	2	asthma attack
	RONMAR	4	physician diagnosed asthma with either symptoms or use of asthma medication in last 12m
	SHOHAT	6	asthma (= asthma or spastic bronchitis. The term "spastic bronchitis" was described as "more commonly used by the public for asthma")
	SOMERV	4	at least one asthma attack in last 12m
	SOTOQU	6	asthma (= symptom score 3, based on symptoms after URTI, symptoms after exercise, frequent cough), or symptom score 2 + physician diagnosis of asthma)
	STANHO	4	one or more episodes labelled asthma in last 12m
	STERN1	4	asthma attack in past year
	STODDA	4	asthma (= asthma or wheezing in last 12m)
	STRACH	4	severe asthma (= in last 12m, 12+ episodes of wheezing or wheezing that limited speech to only 1 or 2 words between breaths)
	TARIQ	4	asthma (= 3+ episodes of cough & wheeze per year, each 3+ days)
	WANG	4	asthma (= any one of 5 symptoms in last year: moderate wheeze at rest; wheeze and SOB after exercise; nocturnal waking with wheeze; nocturnal waking with cough; severe wheeze and SOB at rest)
	WEITZ1	6	ever had asthma lasting 3m+, not been cured
	WEITZ2	6	asthma onset > age 5 lasting 3m+, not been cured
	WOLFO1	4	asthma in last year
	WOLFO2	4	asthma in last year

Table 3B (continued /5)

Basis of diagnosis	Study Ref	Timing of current asthma[1]	Description of current asthma
Other/mixed (continued)	WOLFO3	4	asthma in last year
	ZHENG	6	ever physician diagnosed asthma and parents consider child has asthma

[1] 1=current diagnosis; 2=in last n months, n<6; 3=in last n months, 6<=n<12; 4=in last n months, 12<=n<24; 5=in last 2 years; 6=current NOS.

Table 4 Other asthma outcomes for which results are available but which have not been entered on the relative risk database

Study Ref	Other asthma outcomes
AGABI1	Results available for past asthma (i.e. history of asthma but no symptoms in last 12m)
AGABI2	Results available for past asthma (i.e. history of asthma but no symptoms in last 12m)
ALFRA1	Results available for frequent asthma attack (>1/m) vs infrequent (<4/y)
ANDRAE	Results available for birch pollen induced asthma
BRABIN	Results available for well controlled asthma
CUNNI1	Results available for ever diagnosed asthma and taken medication in last 12m
DEKOK	Multiple logistic regression was carried out for a number of symptoms and potential risk factors, with the results reported as "positive but not significant". However it is not clear exactly which other symptoms (possibly various definitions of wheeze, SOB with wheeze (ever and current), ever physician diagnosed asthma, current asthma medication as well as "current asthma defined" which has been entered here), or which other risk factors (possibly family smoking in the house as well as "maternal smoking" entered here) were used
EHRLI2	Results available separately for acute asthma
FERGUS	Results available for maternal report of asthmatic attack (irrespective of medical treatment); for at least 2 medical consultations diagnosed as asthma or wheezy bronchitis; results for at least 2 medical consultations for asthma (excl wheezy bronchitis) are stated not to differ from the combination of asthma and wheezy bronchitis
FORSB1	Results available for recent asthma attacks (attacks of SOB with wheezing in last 12m)
FORSB2	Results available for recent asthma attacks (attacks of SOB with wheezing in last 12m)
FORSB3	Results available for recent asthma attacks (attacks of SOB with wheezing in last 12m)
GILLIL	Results available for medication for asthma
GORTM1	Results available for functionally impairing asthma (Does it affect his/her ability to attend school or do any of the things a child his/her age usually does?)
GORTM2	Results available for functionally impairing asthma (Does it affect his/her ability to attend school or do any of the things a child his/her age usually does?)
HU1	Results available for emergency hospital treatment for asthma in last 12 months
INFANT	Results available for persistent and transient asthma (assessed at 7-year followup of cases)

Table 4 (continued)

Study Ref	Other asthma outcomes
JAAKKO	Results available for early onset asthma (bronchial obstruction before age 2, physician diagnosed asthma, symptoms of asthma in 12m to age 4) (Bronchial obstruction is defined as physician diagnosed, at least 3 of: wheezing, chest recession, rhonchi during ausculation, forced expiration, rapid breathing; at least 2 episodes or 1 episode lasting more than 1 month)
KEARNE	Result available for exercise induced asthma
KUEHR	Results available for allergic asthma (= as sensitization in SPT to 1+ aeroallergen, and either physician diagnosed bronchial asthma or at least one symptom: frequent cough after exercise/when exposed to cold; ever wheezing; cough or SOB at night; ever had attacks of SOB or breathlessness)
LISTER	Results available for use of health services for asthma (doctor, outpatient or emergency consultation in last 2 weeks, or hospital admission in last year)
MONTEF	Results available for very severe attacks of asthma
NHANE3	Results available for moderate or severe asthma; any hospital visit or any physician visit in last year; medication in past month
OCONNE	Results available for exacerbation of asthma
RATAGE	Results available for severe asthma (as asthma but with troublesome wheeze most days/nights, affecting activity and growth and requiring frequent medication), and for severe vs mild asthma
RONMAR	Results available for prevalence for: asthma profile (current asthma or wheezing or use of asthma medicines in last 12m); for asthma medication in last 12m; for a small subset, for physician validated asthma; and for onset for: physician diagnosed asthma (not entered as less detail available than for 'ever asthma')
SENNHA	Results available for asthma symptom (= frequent night-time irritable cough)
SHAMSS	Text refers to "severe asthma attack", but results are only presented for various wheezing symptoms and it is not clear which of these is referred to
SQUILL	Results available (from a subset of the study) for 3+ symptoms suggestive of asthma and responded to histamine bronchoprovocation
STANHO	Results available for subclinical asthma (= 1+ episodes of wheeze not labelled as asthma and not associated with respiratory infection)
TARIQ	Results available for medication for asthma; for nocturnal asthmatic symptoms; for atopic and nonatopic asthma (i.e. with or without +ve SPT)
WEITZ1	Results available for physician-prescribed medication in last 2 weeks
WOLFO1	Results available for asthma score (sum of SOB with wheeze, physician diagnosed asthma and asthma in last year)

Table 4 (continued /2)

Study Ref	Other asthma outcomes
WOLFO2	Results available for asthma score (sum of SOB with wheeze, physician diagnosed asthma and asthma in last year)
WOLFO3	Results available for asthma score (sum of SOB with wheeze, physician diagnosed asthma and asthma in last year)

Table 5 Other aspects of passive smoke exposure for which results are available but which have not been entered on the relative risk database

Study Ref	Other aspects of passive smoking
ALBA	Results available for family members smoke (as well as smoke in home which has been entered)
AZIZI	Results available for sharing bedroom with an adult smoker
BALL	Results available for parents likelihood of quitting
BUTZ	Results available for exposure in daycare; for change in smoking behaviour since diagnosis
CHEN2	Results available for total daily cigarette consumption by household members (as well as number smoked in home which has been entered)
GOLD	Results available for respirable particulate matter (shown to correspond to household smoking)
KUEHR	Results available for mother started/quit smoking between child's age 1 and age 7
LEEDER	Results available for change in parental smoking habit
PONSON	Results included here are for presence of smokers in the household, but results also available broken down by whether smoking was sometimes, or usually, in the same room as child, at age 1m. Results also available for ETS exposure outside the home at age 1m
SOYSET	Results available for mother smoked for >7 yrs; for father smoked for >7yrs
VARELA	Results available according to whether mother was main active smoker
WILLE2	Graphs showing case/control status by parental smoking (maternal or household) X cotinine (salivary or urinary) are available but are not distinct enough to extract data reliably

See also Addendum, p97

Table 6 Aspects of active smoking for which results are available but which have not been entered on the relative risk database

Study Ref	Aspects of active smoking
CHEN2	Results available for child (active) smoking (age 12+?)
GOLD	Results available for child (active) smoking
HU2	Results available for child (active) smoking
LAM1	Results available for child (active) smoking
LAM2	Results available separately for ever smoking children, and with ever smoking children included (as well as never smoking)
MCCON1	Results available for child (active) smoking
MELSOM	Results available for child (active) smoking
MOUSSA	Results available for child (active) smoking
RASANE	Child (active) smoking not significant (OR close to one)
SHERMA	Results available for child (active) smoking
STANHO	Results for maternal smoking also available for active smokers; for paternal smoking and smoking by elder siblings, results are only available for child smokers and non-smokers combined, and are not significant
ULRIK	Child (active) smoking rejected from MLR due to lack of significance
WITHER	Child (active) smoking is stated to be non-significant

Table 7 Stratifying variables (other than sex, age and race) for which results are available but which have not been entered on the relative risk database

Study Ref	Stratifying variables
AGABI1	Results for maternal smoking available stratified by parental asthma
AGABI2	Results for maternal smoking available stratified by parental asthma
ALFRA1	Results available for wheeze stratified by location
ANDRAE	Results available stratified for dampness in house
BRABIN	Results available stratified by location
BURR	Results for wheeze available stratified by atopy
BUTZ	Results available stratified by SES
CHEN2	Results available stratified by presence of allergy
CHINN	Results for asthma available stratified by sex and location (England inner city, England representative, Scotland)
DOLD	Results available stratified by cough for more than 14 days; by cough on exertion; by night cough; by repeated wheezing
EHRLI1	Results available stratified by maternal education
FERGUS	Results for at least two medical consultations for asthma or wheezy bronchitis are available for sexes separately
FORAST	Results available stratified by location (air pollution)
FORSB3	Results also available stratified by region
GILLIL	Results for lifetime asthma stratified by age at diagnosis; by family history asthma; by family history atopy
GOLD	Results available stratified by sex (for exposure respirable particulate matter only)
JAAKKO	Results available stratified by parental atopy
KAPLAN	Results for asthma or bronchitis with wheezing are available by various strata
KAY	Results available stratified by child's eczema; and by social class
KERSHA	Results available stratified by father's occupation (services/civilian)
KUEHR	Results available stratified by atopy; by bronchial hyper-reactivity
LEEDER	Results available stratified by parental cough-phlegm

Table 7 (continued)

Study Ref	Stratifying variables
LINDFO	Results are available for cases subdivided on +ve skin prick test to cat and/or dog, versus combined controls. Results are also available for the age group <30m, and for those with damp housing, but only for the separate SPT groups (and with insufficient information to be able to combine)
MAIER	Results available restricted to those with history of chronic sore throat
MARTIN	Results available stratified for parental respiratory symptoms; maternal education
MCCON1	Results available stratified by wheeze at baseline
MELSOM	Results available stratified by urban/rural; by use of smoky fuels
MURRAY	Results available stratified by atopic dermatitis
NILSSO	Some results are available for the interaction with urban/rural residence
OLIVET	Results available stratified by maternal history asthma; premature birth; bronchiolitis before age 2
PALMIE	Results available for cases subdivided on SPT, against combined control group
PONSON	Results available for babies with shared bedrooms by whether the bedroom door was closed or not
RONMAR	Results available for a small subset stratified by +ve skin prick test
SCHMIT	Results available stratified by location (air pollution zones)
SHOHAT	Results for current wheeze available stratified by sex and race (Jewish/Arab)
SQUILL	Results also available for subset of study undergoing further tests
STAZI	Results also available restricted to subjects with frequent infantile colic
VAVILI	Results available by genotype strata (but no CIs)
VOLKME	Results available restricted to greater Adelaide (urban)
WOLFO1	Results available stratified by region (urban/rural)
WOLFO2	Results available stratified by region (urban/rural)
WOLFO3	Results available stratified by region (urban/rural)

Table 8 Number of relative risks per study

		Study Type			
	Number	CC	Prosp	CrSec	Total
Principal studies	1	11	5	37	53
	2	7	4	23	34
	3	2	3	10	15
	4	3	2	10	15
	5	2	1	4	7
	6	3	2	9	14
	7	2	1	2	5
	8	1	0	4	5
	9	0	0	2	2
	10	1	1	1	3
	11	0	2	1	3
	12	0	1	1	2
	14	2	0	2	4
	15	2	0	1	3
	16	0	0	2	2
	17	0	1	0	1
	20	0	0	2	2
	21	0	0	1	1
	23	0	1	0	1
	24	0	1	0	1
	26	1	0	2	3
	52	0	0	1	1
	69	0	0	1	1
	79	2	0	1	3
Subsidiary studies	1	0	1	2	3
	2	1	1	4	6

CC = case-control; Prosp = prospective; CrSec = Cross-sectional

Table 9 Characteristics of the 1220 relative risks

Characteristic	Level	Study Type				
		CC	Prosp	CrSec	Subsid	Total
Total		337	162	706	15	1220
Sex	both	335	156	626	15	1132
	male	1	3	42	0	46
	female	1	3	38	0	42
Lowest age in RR	0 - 1	3	10	35	0	48
	2 - 3	0	8	14	0	22
	4 - 5	0	14	24	0	38
	6 - 7	3	16	16	1	36
	8 - 9	0	9	0	0	9
	10 - 11	0	1	0	0	1
	12 - 13	0	0	8	0	8
	14 - 15	0	1	0	0	1
	20 - 21	0	24	0	0	24
	whole study	331	79	609	14	1033
Highest age in RR	0 - 1	0	6	4	0	10
	2 - 3	0	7	10	0	17
	4 - 5	3	17	35	0	55
	6 - 7	0	2	12	0	14
	8 - 9	0	3	0	1	4
	10 - 11	0	4	12	0	16
	12 - 13	3	6	4	0	13
	14 - 15	0	13	0	0	13
	16 - 17	0	1	20	0	21
	22 - 23	0	24	0	0	24
	whole study	331	79	609	14	1033
Race	whole study	337	155	633	15	1140
	white	0	1	0	0	1
	white excluding hispanic	0	3	2	0	5
	hispanic white	0	3	2	0	5
	white + black	0	0	66	0	66
	jewish	0	0	2	0	2
	arab	0	0	1	0	1
Time of asthma	lifetime	49	103	460	13	625
	current	288	59	246	2	595
Onset	No	337	89	706	13	1145
	yes	0	73	0	2	75
Odds ratio (onset analysis)	No	-	63	-	2	65
	yes	-	10	-	0	10

Table 9 (continued)

Characteristic	Level	Study Type				
		CC	Prosp	CrSec	Subsid	Total
Exposure type	Parents (active smoking)	226	137	397	11	771
	Parents (passive smoking)	12	0	0	1	13
	Household	58	22	227	2	309
	Total	5	0	5	0	10
	Biochemical	12	0	33	1	46
	in utero × parent	24	3	5	0	32
	in utero × household	0	0	27	0	27
	in utero × biochem	0	0	12	0	12
Parents - who smoked	not applicable	75	22	304	3	404
	Mother (and not father)	6	2	13	0	21
	Mother (irrespective of father)	119	72	202	11	404
	Father (and not mother)	6	2	19	0	27
	Father (irrespective of mother)	92	27	97	1	217
	Parents (both)	5	10	14	0	29
	Parents (any)	29	18	48	0	95
	Mother or Father (not both)	5	9	9	0	23
Household - who smoked	not applicable	279	140	452	13	884
	all	47	19	243	2	311
	siblings	0	0	2	0	2
	grandparents	0	0	2	0	2
	grandfather	2	0	0	0	2
	other than parent (and not parents)	0	0	1	0	1
	other than parents (irrespective of parents)	6	0	3	0	9
	other than mother (and not mother)	2	0	2	0	4
	other than mother (irrespective of mother)	1	3	1	0	5
Total - who smoked	not applicable	332	162	701	15	1210
	total NOS	3	0	4	0	7
	home and peers	0	0	1	0	1
	home and day care	2	0	0	0	2
Exposure - when smoked	not applicable	12	0	45	1	58
	Before conception	0	0	3	0	3
	During pregnancy	42	12	60	1	115
	Since birth	28	31	60	0	119
	Since conception	0	4	6	0	10
	Ever	11	5	33	0	49
	Ex	10	3	12	0	25
	Current	156	23	278	7	464
	Unspecified	65	39	175	3	282
	At time of birth/ up to 1m	3	11	0	0	14
	At age 18 months	0	1	0	0	1
	Age <6 months	0	0	2	0	2
	Age <1	0	0	6	0	6

/continued

Table 9 (continued /2)

Characteristic	Level	Study Type				
		CC	Prosp	CrSec	Subsid	Total
	Age <2	1	0	10	1	12
	Age <3	8	0	2	0	10
	Age <5	0	6	0	0	6
	Age <6	0	1	0	0	1
	Age <7	0	0	1	0	1
	Age 13-15 yrs	0	24	0	0	24
	Age 9-16 yrs	0	0	0	2	2
	Ever, up to 1 yr ago	0	2	0	0	2
	Since birth but not current	0	0	12	0	12
	Since conception but not current	0	0	1	0	1
	Ever but not during pregnancy	1	0	0	0	1
Biochemical measure - where taken from	not applicable	325	162	661	14	1162
	saliva	1	0	0	0	1
	blood	0	0	42	0	42
	urine	11	0	2	1	14
	hair	0	0	1	0	1
Biochemical marker	not applicable	325	162	661	14	1162
	cotinine	5	0	44	0	49
	cotinine/ creatinine ratio	7	0	1	1	9
Dose-response	all (not dose response)	230	139	566	15	950
	level 1	44	10	59	0	113
	level 2	44	9	59	0	112
	level 3	14	2	13	0	29
	level 4	1	0	1	0	2
	per unit dose regression	4	1	2	0	7
	other	0	1	6	0	7
Measure of exposure	yes/no	218	113	531	14	876
	cigarettes/day	79	44	95	0	218
	minutes/day	8	0	0	0	8
	level (semi-quantitative)	0	0	4	0	4
	persons	20	4	31	0	55
	ng/ml	12	0	1	0	13
	mmol/l	0	0	42	0	42
	cigarettes/day +ve(among smokers only)	0	1	0	0	1
	ng/mg	0	0	1	1	2
	ng/ml/mg	0	0	1	0	1
Unexposed - time	not applicable	12	0	45	1	58
	non	244	144	559	14	961
	never	81	18	79	0	178
	non+other	0	0	23	0	23

Table 9 (continued /3)

Characteristic	Level	Study Type				
		CC	Prosp	CrSec	Subsid	Total
Unexposed - source	none (or low)	18	1	65	1	85
	none in household	54	20	253	2	329
	not specified household member	7	2	5	0	14
	neither parent	56	41	100	0	197
	not specified parent	202	98	283	12	595
Combination exposure (*in utero* × in life exposure vs neither exposure)	not applicable	313	159	662	15	149
	combination 0-1	8	1	13	0	22
	combination 1-0	8	1	13	0	22
	combination 1-1	8	1	18	0	27
N adjusted for	none	204	89	331	10	634
	1	18	14	63	0	95
	2	0	5	10	0	15
	3	1	10	26	2	39
	4	8	5	49	0	62
	5	3	1	32	3	39
	6	12	11	38	0	61
	7	1	6	26	0	33
	8	2	6	42	0	50
	9	4	4	58	0	66
	10	2	0	12	0	14
	11	34	11	4	0	49
	12	37	0	4	0	41
	13	4	0	4	0	8
	14	0	0	4	0	4
	15	0	0	2	0	2
	17	0	0	1	0	1
	19	7	0	0	0	7
Adjusted for:	sex	107	57	250	3	417
	age	107	20	194	3	324
	race	17	24	134	3	178
Adjusted for other sources of ETS	None	243	148	633	15	1039
	1	78	14	72	0	164
	2	16	0	1	0	17
Adjusted for other confounders	None	216	104	364	12	696
	1	6	13	53	0	72
	2	6	1	46	1	54
	3	14	4	47	0	65
	4	2	8	33	0	43
	5	4	5	53	2	64
	6	3	10	29	0	42
	7	2	4	52	0	58
	8	38	12	11	0	61

/continued

Table 9 (continued /4)

Characteristic	Level	Study Type				
		CC	Prosp	CrSec	Subsid	Total
	9	38	1	2	0	41
	10	1	0	5	0	6
	11	0	0	8	0	8
	12	0	0	2	0	2
	13	0	0	1	0	1
	19+	7	0	0	0	7
Numbers of cases available (Unadjusted RRs)	no	2	22	56	4	104
	yes	182	67	275	6	530
Numbers of controls/at risk available (Unadjusted RRs)	no	20	22	57	4	103
	yes	184	67	274	6	531
Full 2 × 2 table available (Unadjusted RRs)	no	22	22	57	4	105
	yes	182	67	274	6	529
Numbers of cases available (Adjusted RRs)	no	7	37	177	2	223
	yes	126	36	198	3	363
Relative risk	0.01-1.00	65	26	188	3	282
	1.01-2.00	214	100	407	8	729
	2.01-3.00	20	10	35	0	65
	3.01-4.00	11	2	4	0	17
	4.01-5.00	2	2	1	0	5
	5.01-6.00	2	0	1	0	3
	6.01-7.00	1	0	0	0	1
	7.01-8.00	0	1	1	0	2
	10.01-11.00	0	1	0	0	1
	11.01-12.00	1	0	0	0	1
	N	316	142	637	11	1106
	Median	1.21	1.29	1.20	1.24	1.22
	Min	0.04	0.57	0.35	0.16	0.04
	Max	11.32	11.00	7.24	1.46	11.32
	Miss	21	20	69	4	114
CI available	no	25	25	112	4	166
	yes	312	137	594	11	1054
Derivation of RR/CI	original	63	46	197	4	310
	RR/CI from numbers	103	45	145	3	296
	RR/CI recalculated from numbers	1	1	19	0	21
	combined smoking levels/sum	69	27	67	0	163
	combined disease levels/sum	11	0	5	0	16
	other combined/sum	3	1	60	1	65
	RR/CI calculated using 0.5 for zero /continued	2	0	0	0	2

Table 9 (continued/5)

Characteristic	Level	Study Type				
		CC	Prosp	CrSec	Subsid	Total
	non-significant	18	20	63	4	105
	significant	7	0	15	0	22
	read from graph/chart	0	0	15	0	15
	RR original, CI from P-value	0	1	6	0	7
	combined smoking levels/ F&L	44	11	45	0	100
	combined disease levels/ F&L	0	0	2	0	2
	adjusted from original RR/CIs by meta	0	0	12	1	13
	combined F&L then adjusted by meta	0	0	4	0	4
	other	16	10	46	2	74
	RR original CI est from crude numbers	0	0	4	0	4
	other (with CI est from crude numbers)	0	0	1	0	1
discrepancy or alternative adjustment available	no	248	152	661	12	1073
	yes	89	10	45	3	147

CC = case-control; Prosp = prospective; CrSec = Cross-sectional; Subsid = Subsidiary

Table 10 Relative risks characteristics available from the 181 principal studies (or their subsidiaries)

Characteristic	Level	Study type			
		CC	Prosp	CrSec	Total
Total		39	25	117	181
Single sex		1	1	10	12
Specific Age		1	12	5	18
Specific Race		0	2	3	5
Lifetime/incidence asthma		12	19	80	111
Current asthma		27	9	53	89
Onset analysis		0	15	1	16
Odds ratio for onset analysis		0	7	0	7
Exposure	Parent	28	21	76	125
	Parent ETS	1	0	1	2
	Household	21	8	58	87
	Total	3	0	2	5
	Biochemical	3	0	3	6
	in utero × Parent	2	1	2	5
	in utero × Household	0	0	3	3
	in utero × Biochemical	0	0	1	1
Parent – who smoked	Mother Only	3	1	5	9
	Mother (irrespective of father)	18	16	56	90
	Father Only	3	1	6	10
	Father (irrespective of mother)	12	8	29	49
	Both parents	3	4	7	14
	Any parent	11	9	28	48
	One parent only	3	3	6	12
Biochemical measure – where taken from	saliva	1	0	0	1
	blood	0	0	1	1
	urine	2	0	2	4
	hair	0	0	1	1
Biochemical marker	cotinine	3	0	2	5
	cotinine/creatinine ratio	1	0	2	3
Exposure – when smoked	before conception	0	0	2	2
	during pregnancy	8	7	19	34
	since birth	3	3	9	15
	since conception	0	3	1	4

/continued

Table 10 (continued)

Characteristic	Level	Study type			
		CC	Prosp	CrSec	Total
	ex or ever	5	3	9	17
	current	10	4	60	74
	unspecified	23	10	42	75
	at specific age	3	7	11	21
	not current	0	0	3	3
Dose response data		13	5	19	37
Measure of exposure	yes/no	38	24	110	172
	cigarettes/day	9	7	22	38
	minutes/day	1	0	0	1
	semi-quantitative	0	0	2	2
	persons	4	1	5	10
	ng/ml	3	0	1	4
	mmol/l	0	0	1	1
	number of cigarettes/day +ve (among smokers only)	0	1	0	1
	ng/mg	0	0	2	2
	ng/ml/mg	0	0	1	1
Unexposed - time	Non	39	24	111	174
	Never	6	3	11	20
	Non + Other	0	0	3	3
Unexposed - source	None (or low)	6	1	9	16
	None in household	17	7	53	77
	Not specific household member	6	1	5	12
	No parent	11	9	31	51
	Not specific parent	19	16	55	90
Combination exposures (*in utero* × in life exposure vs neither exposure)		2	1	3	6
Adjustment for :	sex	8	15	51	74
	age	8	3	35	46
	race	3	4	12	19
	other ETS exposure	6	3	26	35
	other non-ETS variables	18	17	72	107
	any adjustment	20	19	74	113
	no adjustment	39	21	94	154
Number of cases available		34	13	71	118
RR available		36	21	100	157
CI available		35	19	98	152

Table 10 (continued /2)

Characteristic	Level	Study type			
		CC	Prosp	CrSec	Total
Derivation of RR/CI	original	13	12	53	78
	from numbers	30	11	44	85
	recalculated	1	1	11	13
	summed levels	14	6	22	42
	adjustment for zero cell	2	0	0	2
	significant/non-significant	13	12	42	67
	chart	0	0	3	3
	from p-value or combined (F&L or meta)	5	5	15	25
	other calculation	2	4	15	21
	CI from crude numbers	0	0	3	3
Discrepancy or alternative adjustment available		6	6	23	35

CC = case-control; Prosp = prospective; CrSec = Cross-sectional

Table 11 Other dose response results

Study	Asthma	Exposure	Adjusted	Results
ALFRA1	lifetime	any parent	no	number of cigarettes, significant p<0.001
CHINN	current	any parent, current	yes	RR per cigarette is 1.001 (0.991-1.011)
DIJKST	current	household, current	yes	RR per 10 cigarettes is 0.93 (CI not given)
EHRLI2	lifetime	urinary cotinine	no	RR per ng/ml is 1.009 (1.003-1.015)
EHRLI2	lifetime	urinary cotinine/creatinine ratio	no	RR per ng/ml is 1.004 (0.999-1.008)
EHRLI2	lifetime	urinary cotinine	yes	RR per ng/ml is 1.009 (1.003-1.016)
EHRLI2	lifetime	urinary cotinine/creatinine ratio	yes	RR per ng/ml is 1.004 (0.999-1.009)
KNIGHT	current	household	no	mean cigarettes 7.4 (asthmatic) vs 11.2 (non-asthmatic), p=0.144
KNIGHT	current	urinary cotinine	no	mean (ng/ml) 29.9 (asthmatic) vs 39.4 (non-asthmatic), p=0.23
KNIGHT	current	urinary cotinine/creatinine ratio	no	mean (ng/ml/mg) 47.1 (asthmatic) vs 62.6 (non-asthmatic), p=0.2
KNIGHT	current	hair cotinine	no	mean (ng/ml) 0.696 (asthmatic) vs 0.386 (non-asthmatic), p=0.0001
PONSON	incidence	household, at birth	yes	RR per 20 cigarettes is 1.04 (0.99-1.10)
TARIQ	current	household	no	non-significant. Prevalence of asthma is 18.3% for smoking ≤ 5 cigs per day, and 17.1% for smoking >20.
SCHMIDT	current	any parent	no	number of cigarettes, non-significant

See also Addendum, p97

Table 12 Relative risks with apparent errors

A – Confidence interval is non-symmetrical[1]

Study	RR number	Asthma	Exposure	RR/CI[2] RR	LCL	UCL	C[3]	Centre of CI (calculated from CI[4])
ALFRA1	2	lifetime	parent	1.51	1.04	2.37	0.925	1.57
NHANE3	57	current	biochemical	1.7	0.7	7.3	0.566	2.26
POKHAR	2	lifetime	household	3.33	1.85	7.65	0.784	3.76
TARIQ	16	current	parent	1.2	0.3	2.7	1.778	0.90

B – Number of cases implied by confidence interval is greater than actual number of cases (Case-control and cross-sectional studies)

Study	RR number	Asthma	Exposure	Number of cases	RR/CI[2] RR	LCL	UCL	Minimum cases[5]	Ratio[6]
ALFRA1	1	lifetime	parent	106	1.32	1.01	1.72	216.9	2.05
ALFRA2	1	lifetime	parent	134	1.08	0.83	1.41	218.9	1.63
FARBE2	2	lifetime	parent	225 [7]	1.51	1.17	1.96	230.9	1.03
FLYNN1	1	lifetime	household	136	1.26	0.95	1.68	189.1	1.39
HJERN1	13	current	parent	119	0.72	0.52	1.01	139.5	1.17
HJERN2	13	current	parent	78	0.94	0.62	1.43	88.0	1.13
KENDIR	1	lifetime	household	304	1.41	1.16	1.72	396.2	1.30
LEE1	1	current	household	774 [7]	1.37	1.24	1.51	1583.9	2.05
LEE2	1	current	household	148 [7]	0.99	0.87	1.13	899.1	6.07
RIBEIR	1	current	parent	25 [7]	1.20	0.59	2.41	31.0	1.24
RONCH1	7	lifetime	household	123	1.40	1.02	1.91	156.2	1.27
STAZI	1	lifetime	parent	6	3.30	1.00	10.60	11.0	1.84

C – Number of subjects implied by confidence interval is greater than actual number of subjects (Case-control and cross-sectional studies)

Study	RR number	Asthma	Exposure	Number of subjects	RR/CI[2] RR	LCL	UCL	Minimum subjects[10]	Ratio[11]
POKHAR	2	lifetime	household	120	3.33	1.85	7.65	122.0	1.02

[1] Only those which cannot be explained by rounding error are shown, see §3.4.4
[2] As given originally, except where indicated otherwise
[3] Calculated as (RR^2/(UCL*LCL)
[4] Calculated as √(LCL*UCL)
[5] Calculated from formula 9 of reference 10
[6] Ratio of minimum cases to number of cases
[7] There is a known problem with the value for the number of cases – see Appendix E
[8] Estimated by the method of Fry and Lee[9] based on RR/CIs originally given to 1 decimal place
[9] Estimated from regression coefficient and standard error
[10] Calculated from formula 7 of reference 10

[11] Ratio of minimum subjects to number of subjects

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Addendum

1. The following information was mistakenly omitted from the database, and should have been included in Table 5:

   Study INFANT, results available for smoking by the babysitter in the child's home.
   Source INFANT1991 Infante-Rivard C. Passive smoking and incidence of childhood asthma [Abstract]. *Am J Epidemiol* 1991;**134**:783.

2. Where results are available only for high exposure versus no exposure, or only for highest tertile vs lowest tertile of biochemically assessed exposure, these data were originally entered on the Relative Risk database as non-dose response (field DOSER=1), and the details given in a text comment. As this caused some problems in setting up meta-analyses, these RRs were recoded with a new level of DOSER=13, and the appropriate values entered in fields EXPLO and EXPHI. Studies affected were NHANE3 and WEITZ1.

3. The data entered on the RR database for study EHRLI1 were completely revised, deleting 4 RRs, and adding 2 RRs. The deleted RRs were for exposure maternal smoking in pregnancy, and were all significant but lacked RR/CI. The added RRs are: one for maternal smoking in pregnancy (adjusted for household exposure and other factors) with RR/CI as given; and one for number of current household smokers (adjusted for maternal smoking in pregnancy and other factors) which should have been included in Table 11 as increment per smoker of 1.07 (0.91-1.25).

4. All four RRs for SOMERV had been entered as non-dose response. This was corrected to 'per unit dose regression', for number of cigarettes. These should have appeared in Table 11.

5. Studies AZIZI and CHEN1 found no smoking mothers. RRs had been entered as father (irrespective of mother) and as all household members, respectively. As this caused problems in setting up analyses for exposure from sources other than mother, the RRs were duplicated, except that the second copy was defined as father only, and as household members other than mother, respectively.

6. An additional RR, which had mistakenly been omitted originally, was added to study TAYLOR, for maternal smoking in life and/or *in utero*.

7. For studies GORTM1 and GORTM2, the timing of lifetime/incident asthma was corrected to 'lifetime' (previously 'unspecified'). (Appendix E, pE45)

The tables in this report were compiled before these changes were implemented. The total number of RRs entered is thus 1221.