WHO Indoor Air Quality Guidelines: Household Fuel Combustion

Review 4: Health effects of household air pollution (HAP) exposure

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Convening lead author: those authors who led the planning and scope of the review, and managed the process of working with other lead authors and contributing authors, and ensuring that all external peer review comments were responded to.

Lead authors: those authors who contributed to one or more parts of the full review, and reviewed and commented on the entire review at various stages.

Contributing authors: those authors providing one section of the review, but not reviewing and commenting on the entire review at various stages.

Full details of these procedures are described in the Guidelines, available at: http://www.who.int/indoorair/guidelines/hhfc ; these include declarations by the authors that they have no actual or potential competing financial interests. The review was conducted in order to inform the development of recommendations by the Guidelines Development Group. Some of the authors are staff members of, or consultants to, the WHO. The authors alone are responsible for the views expressed in this publication, which do not necessarily represent the views, decisions, or policies of the WHO.

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General summary

Background

Household fuel combustion, particularly of solid fuels in developing countries, results in high levels of household air pollution (HAP) and exposure to health-damaging pollutants especially to women (including during pregnancy) and young children. This life-long exposure, including through critical periods of child development, can be expected to have serious consequences for health. Household solid fuel use is not restricted to developing countries, although the ventilated stoves typically used in more developed country settings mean that average exposures are lower. Gas, while much cleaner, does also emit health-damaging pollutants including particulates and nitrogen oxides, and may be linked to respiratory illness. In areas of the world where vector-borne disease including malaria is common, the question has often been asked as to whether interventions to reduce smoke levels and HAP exposure might increase disease risk of these diseases.

Aims and key questions for reviews

The aim of the review was to compile and review the evidence on the impacts household fuel combustion have on child and adult health , with an emphasis on solid fuel use in developing countries. The review examined estimates of risk and strength of causal evidence, sought exposure-response evidence and estimates of intervention impacts. It also summarized the health risks of household use of gas, and any impacts the control of HAP have on vector-borne disease. The key questions for the review are as follows, (note: further elaboration of these is provided in the relevant sections).

1. What child and adult disease outcomes are linked to solid fuel HAP exposure, and what are the estimated risks and strength of causal evidence?
2. What information is available on the relationships between exposure level and risk of important disease outcomes? What are the shapes of these relationships (exposure-response functions)?
3. What are the health risks of exposure to gas used as a household fuel?
4. What are the impacts of potential interventions to reduce HAP exposure (reduced smoke levels, increased ventilation) on the risk of vector-borne disease? What are the effects of smoke on insecticide treated nets (ITNs)?

Methods

In view of the wide range of health outcomes affected by HAP, the approach taken by this review is to summarize recent systematic reviews and other types of evidence (i.e. exposure response function models), and to synthesize this evidence where appropriate. All systematic reviews summarized here have been conducted recently, most published (or otherwise available in full) and most use comparable methods consistent with PRISMA[1] guidance. More detailed assessment of study quality, sensitivity analysis and heterogeneity has been made for those outcomes with the largest disease burden and/or strongest evidence base, as this evidence can best inform guideline recommendations. Strength of evidence in respect of causality has been assessed using the Bradford-Hill viewpoints, while 'grading of evidence for public health interventions' (GEPHI - see 'Methods used for evidence assessment'), is used to assess overall sets of evidence and confidence in intervention effect estimates. Since limited direct exposure-response evidence is available for HAP, the findings of recently published work on integrating risk from combustion-derived $PM_{2.5}$ from multiple sources across the range of exposure (ambient air pollution, second-hand smoke, HAP and active smoking) are reported.

Main findings

[1] PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses. See: http://www.prisma-statement.org/

Question 1 (Section 2)

For children, there is substantial evidence that solid-fuel HAP increases risk of acute lower respiratory infections (ALRI), a number of adverse pregnancy outcomes, and may impair cognitive development. Risk of severe and fatal ALRI may be more than doubled, with important consequences for child survival. Among adults, HAP increases risk of chronic obstructive pulmonary disease (COPD), lung cancer (both for coal and biomass) and cataracts; evidence for a number of other conditions including cardiovascular diseases (CVD), ALRI, Tuberculosis (TB), and upper aero-digestive cancers is based on more limited and/or inconsistent evidence. For CVD, the combination of a few new studies, associations with risk factor and disease markers, and evidence from other combustion sources, suggest a causal relationship is plausible, but additional empirical evidence for HAP exposure is required. GEPHI assessments were rated moderate for ALRI, low birth weight and stunting for children, and COPD and lung cancer (both coal and biomass) for adults, with intervention effect estimates of between 20-50% risk reduction, while for other outcomes these estimates were less certain.

Question 2 (Section 3)

The 'integrated exposure-response' (IER) functions, based on a combination of direct HAP evidence and other $PM_{2.5}$ sources, suggests a curve for child ALRI with a steep portion from low levels up to around 100 μg/m^3 $PM_{2.5}$, and thereafter with a much shallower slope across the rest of the range of HAP exposure. The functions for IHD and stroke do not have direct HAP data, but based on the other $PM_{2.5}$ sources have a similar shape to that for ALRI. The function for lung cancer is more or less linear in shape, reaching very high relative risk with heavy smoking, while that for COPD is less certain, but appears more linear than for ALRI and risk continues to increase with exposures above the HAP range. The main conclusions from this evidence, which is assessed to be of moderate quality, are that for ALRI (and probably IHD and stroke) low levels of exposure are required to achieve substantial health benefits. For lung cancer (and possibly COPD), risk reduction may be more proportional to exposure reduction.

Question 3 (Section 4)

Findings for health risks from the use of gas in the home have been inconsistent, although a previous systematic review and meta-analysis (SRMA) reported an increased risk of lower respiratory illness in children with higher levels of nitrogen dioxide (NO_2), one of the main pollutants from gas. The most recent and comprehensive SRMA found an increased risk of asthma with gas cooking, and of wheeze with increased NO_2, and while some uncertainty remains about the role of confounding, it is concluded that gas can pose some risk of respiratory illness particularly where ventilation is inadequate and/or equipment is poorly made or maintained..

Question 4 (Section 5)

The available evidence was found to focus on malaria. There is currently no strong evidence that reducing household smoke pollution increases the risk of malaria transmission, and no firm conclusions could be drawn about the effects of ventilation or on the effects of smoke on the effectiveness of ITNs.

Conclusions

Solid fuel HAP is linked to a wide range of child and adult disease outcomes: for several of these, there is compelling evidence of causation, and interventions have the potential to reduce risk by 20-50%. Exposure-response evidence shows that reduction of exposure to levels approaching the WHO annual IT-1 of 35 μg/m^3 $PM_{2.5}$, are required to prevent most of the child ALRI cases attributable to HAP. The IER function suggests a similar conclusion for IHD and stroke but more linear relationships for lung cancer and possibly COPD. Gas remains one of the cleanest fuels, and small risks of adverse respiratory effects from

emissions can be largely avoided by good maintenance of stoves and ventilation. While there is no strong evidence to date that interventions to reduce HAP exposure increases the risk of malaria (and by implication other vector-borne disease), further research is warranted.

1. Introduction

1.1 Aims

The foregoing reviews have described the fuels used in homes across the world, the emissions from a range of technologies used to burn these fuels (Review 2), a model for relating emission rates to household air pollution (Review 3), and a review of actual measured levels of household air pollution (HAP) and personal exposure (Review 5). This review addresses the health effects of this air pollution exposure. Given that the highest exposure levels and largest numbers of people affected by HAP are those using solid fuels in developing countries, they are the main focus, although the health effects of pollution from one of the main clean alternative fuels, gas, is also described. Evidence on the risks of emissions from another commonly used liquid fuel, kerosene (paraffin) is discussed in Review 9.

The aim of this review is to summarize the most important health risk evidence required to inform and support recommendations on controlling the health burden resulting from household fuel combustion practices globally. Given the similarities between combustion pollutants from solid fuels and tobacco smoking, it may be expected that the diseases for which risk is increased by household air pollution (HAP) would be very similar to those established for active and passive smoking – albeit with risks at a level consistent with the respective levels of exposure. The list of conditions caused by smoking covers CVD, acute and chronic respiratory disease, a wide range of types and sites of cancer (11 are listed in the United States Surgeon General's report), and adverse reproductive outcomes including fertility, low birth weight (LBW) and pre-term births (PTB) *(1)*. The need for further research on smoking-related outcomes not already linked with HAP exposure is discussed Section 6 of this review.

A fully comprehensive review of all known, suspected and emerging health risks is, however, not required for the primary purpose of this review, and would have been beyond the scope of this publication in terms of resources, time and space. Consequently, attention is focused on outcomes with the largest health burden and most substantive evidence, including those affecting more vulnerable groups – particularly pregnant women and young children. These are listed under the PICO[2] questions in Section 2. As exposure-response evidence is critical to guidance on the health benefits expected to result from the exposure levels achieved by different intervention fuels and technologies, more attention is also given to those outcomes for which this type of evidence is becoming available, in Section 3. These higher priority outcomes, for which more detailed accounts of the findings of systematic reviews are presented, are those included in the Global Burden of Disease (GBD) 2010 comparative risk assessment *(2)*, or which otherwise relate to pregnancy outcomes and child survival.

1.2 Scope and key questions for reviews

This review summarizes evidence on the health effects of exposures to household air pollution (HAP) from combustion, here being defined as emissions from solid and gaseous fuels in household settings in both developed and developing countries (as noted above, the main liquid fuel, kerosene, is described in Review 9). It thus does not cover emissions from

[2] PICO: Framework for defining questions for systematic reviews encompassing the **P**opulation, **I**ntervention, **C**omparison and **O**utcome.

non-combustion sources, such as consumer products, construction materials, and furnishings; or from non-fuel combustion, such as tobacco, incense, and mosquito coils; or from moisture, mould and other biological agents in the household. Evidence from some of these other sources of combustion pollution, in particular tobacco smoking, are referred to in drawing on what is known about the risks from these analogous exposures. Prior volumes of WHO air quality guidelines provide extensive reviews of main combustion and other pollutants in the indoor environment, *(3-4)* including damp and mould *(5)*.

The review also does not include a comprehensive assessment of toxicity of solid fuel smoke which has been discussed elsewhere *(6-8)*, although evidence on mechanisms for specific health outcomes are included in relevant sections.

The key questions for the review are as follows, noting that some further elaboration of these is provided in the relevant sections.

1. What child and adult disease outcomes are linked to solid fuel HAP exposure, and what are the estimated risks and strength of causal evidence (Section 2)?
2. What information is available on the relationships between exposure level and risk of important disease outcomes, and what are the shapes of these relationships (exposure-response functions) (Section 3)?
3. What are the health risks of exposure to gas used as a household fuel (Section 4)?
4. What are the impacts of potential interventions to reduce HAP exposure (reduced smoke levels, increased ventilation) on risk of vector-borne disease, and also the effects of smoke on insecticide treated nets (ITNs) (Section 5)?

In view of the wide range of health outcomes affected by HAP, the approach taken by this review is to summarize recent systematic reviews and other types of evidence (i.e. exposure response function models), and to synthesize this evidence where appropriate. All reviews and related evidence have recently been published, or are otherwise available in full.

1.3 Exposure measures in health risk studies

One general point regarding the nature of exposure measures available is made here as it applies across the range of evidence reported in this review.

It is important to recognize that the measures of pollution available vary between the types of health risk evidence discussed in this review. While the majority of epidemiological studies reporting the risk of specific disease outcomes have used exposure proxies which represent all combustion products, the available exposure-response evidence reports risk for specific pollutants, principally $PM_{2.5}$, but also carbon monoxide (CO) where this has been used as a proxy for combustion mixtures. The type of exposure information available for each set of evidence is described in the relevant section and taken into account where different types of evidence are synthesized.

2. Health impacts from combustion of solid fuels

2.1. Summary

Background

Household fuel combustion, particularly of solid fuels in developing countries, results in high levels of household air pollution (HAP) and exposure to health-damaging pollutants especially to women (including during pregnancy) and young children. This life-long

exposure, including through critical periods of child development, can be expected to have serious consequences for health.

Aims and key questions

The aim of this section of the review is to summarize available epidemiological evidence on the risks to children and adults from exposure to emissions from solid fuels used in the home. The reviews address the following key questions:

1. What child and adult disease outcomes are linked to solid fuel HAP exposure?
2. What are the estimated risks for these outcomes, including estimated intervention impacts?
3. What is the strength of causal evidence for these outcomes?

Methods

In view of the wide range of health outcomes affected by HAP, the approach taken by this review is to summarize recent systematic reviews, and to synthesize this evidence where appropriate. All systematic reviews summarized here have been conducted recently, most published (or otherwise available in full) and most use comparable methods consistent with PRISMA guidance. More detailed assessment of study quality, sensitivity analysis and heterogeneity has been made for those outcomes with the largest disease burden and/or strongest evidence base, as this evidence can best inform guideline recommendations. Strength of evidence in respect of causality has been assessed using the Bradford-Hill viewpoints, while 'grading of evidence for public health interventions' (GEPHI - see 'Methods used for evidence assessment'), is used to assess overall sets of evidence and confidence in intervention effect estimates.

Main findings

For children, there is substantial evidence that solid-fuel HAP increases risk of acute lower respiratory infections (ALRI), a number of adverse pregnancy outcomes, and may impair cognitive development. Risk of severe and fatal ALRI may be more than doubled, with important consequences for child survival. Among adults, HAP increases risk of COPD, lung cancer (both for coal and biomass) and cataracts; evidence for a number of other conditions including CVD, ALRI, TB, and upper aero-digestive cancers is based on more limited and/or inconsistent evidence. For CVD, the combination of a few new studies, associations with risk factor and disease markers, and evidence from other combustion sources, suggest a causal relationship is plausible, but additional empirical evidence for HAP exposure is required. GEPHI assessments were rated moderate for ALRI, low birth weight and stunting for children, and COPD and lung cancer (both coal and biomass) for adults, with intervention effect estimates of between 20-50% risk reduction, while for other outcomes these estimates were less certain.

Conclusions

Solid fuel HAP is linked to a wide range of child and adult disease outcomes: for several of these, there is compelling evidence of causation, and interventions have the potential to reduce risk by 20-50%.

2.2. Introduction

This section reports on risks for specific disease outcomes arising from household use of solid fuels. In almost all cases, these are based on recent systematic reviews (SR) carried out for the Global Burden of Disease (2010) study comparative risk assessment (CRA) *(2, 9)*, or have been published separately, and are referenced as appropriate. The few unpublished reviews conducted for the GBD-2010 study are being prepared for publication and can be made available in full.

As noted in Section 1.1, more attention has been given to (and detail reported for) outcomes linked to the highest disease burden and/or child survival, and for which the most substantive evidence (including exposure-response) is available. This does not imply other outcomes with currently less robust evidence are not important for health, or that these may not turn out to be responsible for large disease burdens. It is rather that much of that evidence is limited and/or inconsistent and not all is required at this time for making effective recommendations in these Guidelines. Exposure-response evidence (as reported in Section 3) is, however, critical for this purpose so special attention has been given to health outcomes with such evidence as well as to assessing consistency between epidemiological studies and recently developed 'integrated exposure-response' (IER) functions for these outcomes. The outcomes included in the 'higher priority' and 'other' categories are listed in Table 2.1, and those for which exposure-response evidence is discussed in more detail in section 3 are marked with an asterisk.

Table 2.1: Outcomes of higher priority for recommendations and other outcomes reviewed. GEPHI refers to 'grading of evidence for public health evidence', described in 'Methods used for evidence assessment'.

Higher priority disease outcomes for Recommendations (GEPHI applied, except CVD)	Other disease outcomes (GEPHI not applied)
• Child acute lower respiratory infections (ALRI)* • Adverse pregnancy outcomes (low birth weight, stillbirth, pre-term birth) • Stunting • All-cause child mortality (under 5-years) • Chronic obstructive pulmonary disease (COPD)* • Lung cancer* • Cardiovascular disease (CVD)* • Cataract	• Adult acute lower respiratory infections (ALRI) • Child cognitive development • Asthma • Cancer of the upper aero-digestive tract • Cancer of the uterine cervix • Tuberculosis

*Exposure-response evidence for these outcomes is presented in Section 3 of this review.

As many of the reviews have used similar methods, a generic overview is provided in Section 2.3 below. For the higher priority outcomes, reporting in the respective sections summarizes key elements of the SR conforming as closely as space allows to the PRISMA statement *(10)*, covering search methods, the total number of studies (and estimates), study types and main results with forest plot, evidence of publication bias and heterogeneity (with discussion of explanations), and main sensitivity analyses. Details including search terms and flow charts are not included for reasons of space but are available in the published reports of these reviews. Study quality assessment is described in the generic methods section, and any substantive deviation from that is reported under each review where overviews are provided of individual study assessment of risk of bias and quality. This is followed by an assessment of the quality and strength of the overall body of evidence for each outcome by reference to the Bradford Hill viewpoints and GEPHI as described in the description of 'Methods used for evidence assessment', and Section 2.3 of this review for further explanation.

For the other outcomes in Table 2.1, a less detailed summary is provided which includes the main forest plot and important information on the extent and quality of evidence, main findings (including pooled estimates if meta-analysis carried out), and confidence about the association with HAP exposure; GEPHI has not been applied to these outcomes.

The section first considers diseases and outcomes for young children up to age of 5 years of age, then adult outcomes.

2.3 Overview of methods used for SRMAs for individual disease conditions

The methods used for the various systematic reviews reported here have much in common, as many were carried out during preparation of the GBD 2010 study CRA work, a full account of which can be found in Smith et al. (2014) *(9)*. In order to avoid unnecessary repetition and excessive detail, a generic description that applies to most of the reviews is provided below. Further details and deviations from these methods are described in more detail in the reports for specific disease conditions.

2.3.1 Search methods

Search terms

Details of search terms are generally included in published versions of these reviews; for unpublished reviews, these are available on request. For a few of the reviews, very few terms were used and these are reported in the respective section; for the majority which used more extensive lists of terms, the general conditions that determined the selection of search terms were as follows:

- Exposure: these covered a broad range of terms and synonyms for (i) indoor/household air pollution including major pollutants, and (ii) types of fuel and stoves that may be associated with a reduction of exposure compared to traditional stove/fuel combinations. Commonly used terms for stoves, such as chulha (and variants) in the Indian sub-continent were included.
- Outcome: while specific to the outcome being studied for each review, the terms sought to cover the range of diagnostic methods and definitions encountered across studies, for example in the case of child pneumonia, encompassing signs used in community-based assessment of ALRI through to pneumonia diagnosis and identification of specific pathogens such as *Streptococcus pneumoniae*.

Databases and sources

Most of the review searches used a broad range of databases and sources, including the main US (PubMed) and European-based (SCOPUS) databases, and Latin American databases (SCIELO, LILACS). Some also interrogated the African Index Medicus and the Chinese language literature (CNKI), conference abstracts and grey literature. Reference lists of selected papers were also checked.

Languages

All reviews drew primarily on English language publications, some of them exclusively so. Most included non-English European languages, most commonly Spanish. A minority (mainly of cancers) also included a search of the China National Knowledge Infrastructure (CNKI) database, with screening of relevant Chinese language papers. The languages included are reported for each review.

Unpublished studies

A number of the reviews included unpublished studies, and these were subjected to the same extraction methods and quality appraisal as published studies.

2.3.2 Data extraction and analysis

Independent selection and data extraction

Most reviews included some degree of independent study selection, usually on a percentage (10-20%). Duplicate extraction of eligible studies was carried out for most reviews: where this was done, disagreements were discussed and referred to the third author if this could not be resolved.

Publication bias

This was assessed for the majority of the reviews with reasonable numbers of eligible studies (typically more than four) using visual inspection of funnel plots and analysis using either Begg's or Eggar's test, or both.

Random and fixed effects meta-analysis

The I^2 test was used to assess statistical heterogeneity. A conservative approach was taken to using fixed or random effects meta-analysis. In practice, fixed effects was used when the I^2 value was around 10-20% or less; for higher values both methods were compared and the more conservative (in terms of pooled effect and p-value) was used, and random effects always used when the I^2 value was statistically significant, with the exception of one separately published review, where fixed effect was used with a significant I^2 of 52% *(11)*, although re-analysis was conducted for this review and reported below. Unless specified otherwise, the generic inverse variance-weighted method was used for pooling in fixed effect meta-analysis *(12)*, and the method of DerSimonian and Laird for random effects meta-analysis *(12-13)*. Fixed effects analysis was also used for some outcomes to combine multiple effect estimates from individual studies relating to different exposure durations or levels (e.g. lung cancer with biomass), for which details are provided in the sections describing these reviews.

2.3.3 Assessment of individual study quality

The methods used for quality assessment vary across this set of reviews. Most of those prepared for the GBD 2010 study CRA used modified versions of the Newcastle-Ottawa scale, with bespoke tools re-designed for the different study types (cross-sectional, case control, cohort, experimental) [Pope et al., in preparation]. A number of the reviews do not specify the methods or use of a tool, beyond stating that various components of quality including risk of bias were assessed. For these, the methods used and how the assessments were recorded (e.g. in the study summary table) are reported, or if no method was described, this is also stated.

2.3.4 Assessing the strength of evidence for disease outcomes

A distinction is drawn between assessing (i) causal inference (for which the Bradford Hill viewpoints are evaluated – see Box 2.1), and (ii) the level of certainty about the precision of intervention impact estimates for which GEPHI has been used.

Box 2.1: Bradford-Hill viewpoints

1. Strength of association
2. Consistency across populations, study designs, etc.
3. Specificity
4. Temporality (exposure precedes outcome)
5. Biological gradient (dose-response)
6. Biological plausibility
7. Coherence with natural history, animal studies, etc.
8. Experiment
9. Analogy

Thus, it is quite possible to have strong evidence for causal inference in the face of considerably more uncertainty about an expected intervention effect size. This applies for a number of outcomes considered in this section of the review. A systematic assessment of the Bradford-Hill viewpoints in tabular format (with supporting text) is provided for the outcomes classified as of higher priority in Table 2.1, and for which a good case for a causal association can be made. Since HAP, as with other sources of combustion pollution (including smoking), has been linked to a

wide range of health outcomes, the perspective of specificity (viewpoint 2 in Box 2.1) is not considered useful in establishing causation and is not further discussed in this review.

An initial step in GRADE is the assessment of the importance of disease outcomes on a scale of 1-9. GEPHI has only been applied to those outcomes selected as of higher priority in making recommendations (Table 2.1, Section 2.2), with the exception of cardiovascular disease; all of these outcomes were assessed as either 'Important' (score 4-6) or 'Critical' (score 7-9).

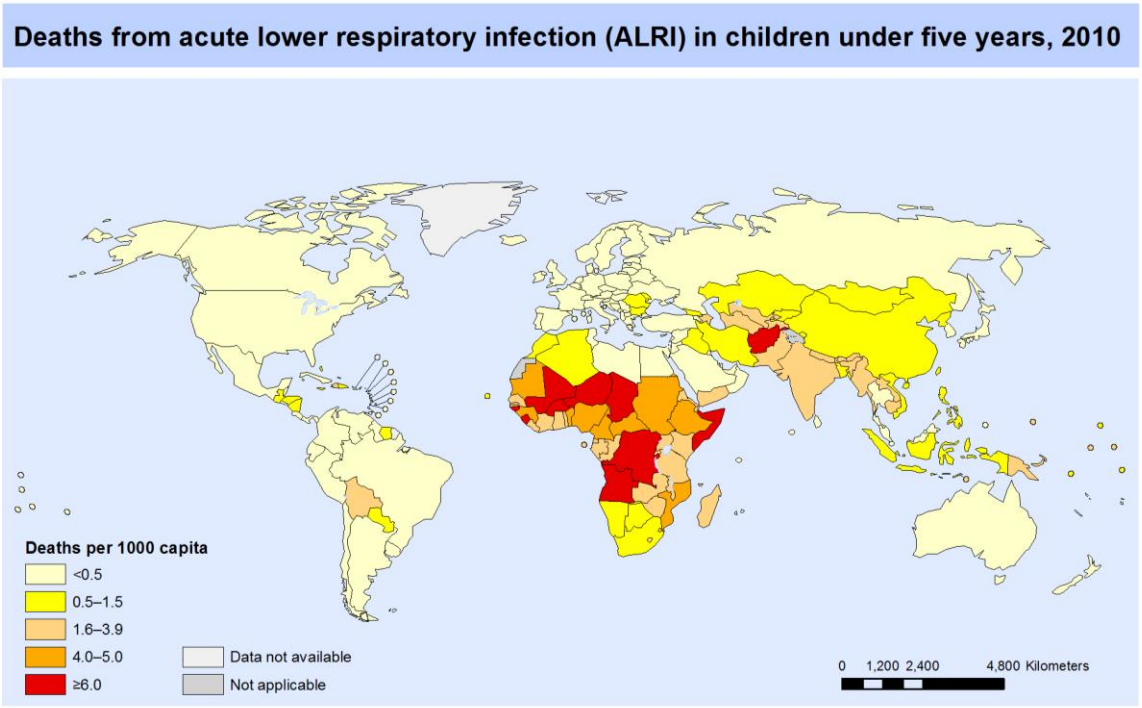
For this review of health risks, the great majority of epidemiological studies available are observational and report risks of high vs. low exposure, most of which find rate ratios (RR) or odds ratios (OR) greater than 1.0. In addition to reporting the increased risk associated with exposure, it was also important for the Guidelines to provide estimates of the preventive impact of interventions. Only one randomized controlled trial is available, which reports results as a protective RR. In order to achieve consistency across studies while avoiding potentially misleading changes to the published results of the observational studies, all forest plots are presented as increased risk associated with higher exposure (as published by the incorporated studies), and for this purpose the rate ratios from the trial are inverted. In the GEPHI tables, which summarize evidence from the perspective of intervention impacts (Annex tables A1), all RR and OR are presented as preventive effects. Issues arising from estimating intervention effects from observational studies are considered further in the conclusions of Sections 2 and 3.

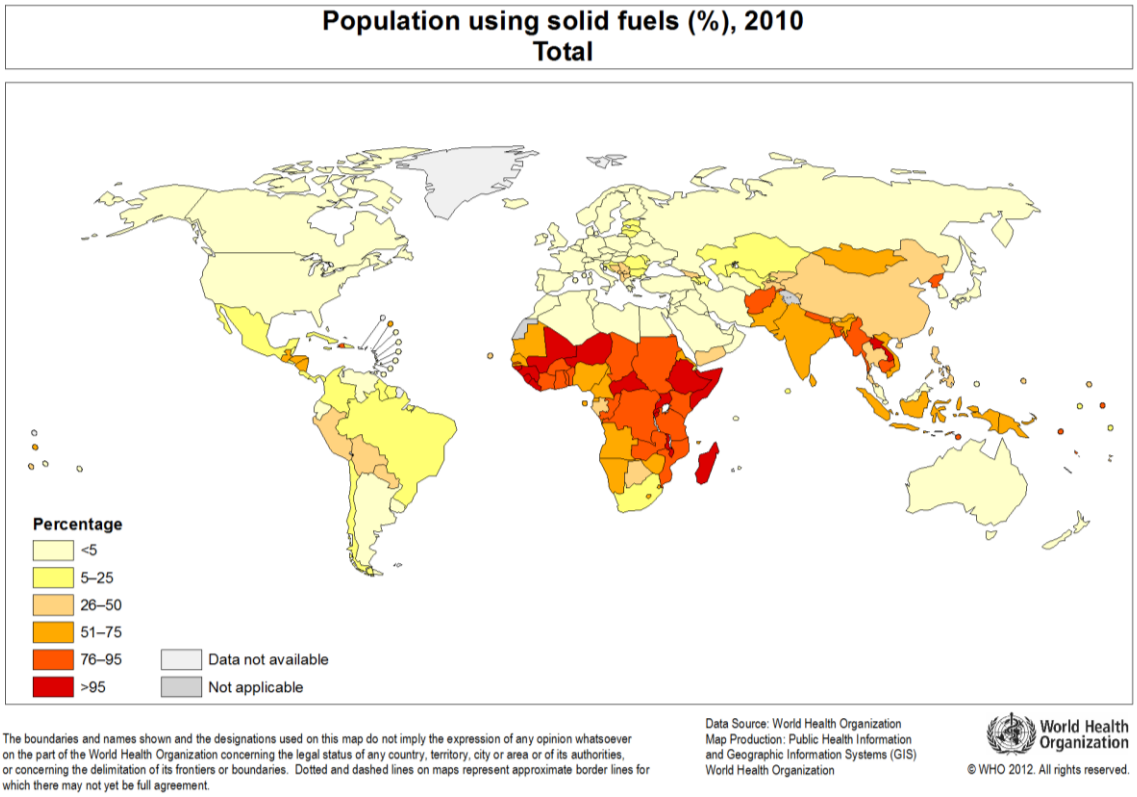
2.4 Disease outcomes for young children (up to 5 years)

2.4.1 Childhood acute lower respiratory infections (ALRI)

Child ALRI remains the single most important cause of death among children under 5 years of age, and the incidence and mortality are generally highest in those regions and countries where solid fuel use is greatest, see Figure 2.1.

Figure 2.1: Global under-5 mortality rate from ALRI (2010) and % solid fuel use for cooking, by country (Source: WHO/GHO)[3]





[3] See: http://www.who.int/gho/en/

This strong ecological association implies that, if a substantial, causal link between HAP exposure and child ALRI can be demonstrated, then removal of (or large reduction in) exposure will have a large impact on this disease.

A prior review by Dherani et al. 2008 *(14)*, reported a pooled OR of 1.78 (95% CI). This was updated and a number of new studies were identified which allowed stratification by severity of outcome, Box 2.2.

A total of 26 eligible studies (providing 28 estimates) were found for child ALRI, including all non-fatal ALRI (severity not defined), severe ALRI, and fatal ALRI outcomes. These three outcomes are reported separately below. The pooled OR for all studies was 1.73 (95% CI=1.47, 2.03), slightly lower than the original estimate. Although there was evidence of publication bias (Egger's test p=0.046), this may be partly the result of larger effects for more severe and fatal outcomes being reported in smaller studies. This heterogeneity is one reason for reporting this evidence on ALRI separately for non-fatal (severity not defined), severe, and fatal.

Box 2.2: Key search features for review of child ALRI

- Search period: 1996-July 2012
- Search hits: 6212 (original) + 1556 (new)
- Inclusion: all designs that included measures of (i) HAP and (ii) ALRI
- Exclusion: studies in which it was not possible to distinguish upper and lower ARI
- Eligible studies: 26 (28 independent estimates)
- Languages: English, French, Spanish, Chinese

All non-fatal ALRI (severity not defined)

A total of 21 studies (23 estimates) reported on non-fatal ALRI, without defining severity, including one randomized controlled trial (RCT) *(15)*, 4 cross-sectional *(16-19)*, 11 case-control *(20-30)* and 5 cohort studies *(31-35)*.

The one RCT included in this systematic review was carried out in rural highland Guatemala, involved 534 children aged less than 19 months, randomized to use a chimney wood stove or continue using the traditional 3-stone open fire *(15)*. Pneumonia was assessed through weekly homes visits by fieldworker trained to assess key signs of pneumonia (fast breathing, chest indrawing, etc.), followed by referral of possible cases to study physicians working in nearby community centres (to maintain blindness) who conducted clinical examinations with pulse oximetry for assessment of severity *(36)*. All pneumonia cases were referred for chest X-ray at the local district hospital. On all children, 48-hr carbon monoxide (CO) was measured every three months during follow-up to provide an exposure proxy for $PM_{2.5}$, the latter being measured along with CO in a sub-set of homes to describe the relationship between the two pollutants *(37)*. This allowed, in addition to the intention to treat (ITT) analysis of the impact of the stove on ALRI included here, an adjusted analysis of child exposure and ALRI incidence described in Section 3.3.

One other RCT by Hanna et al. was not eligible as the outcome measures did not allow distinction of upper and lower respiratory infections *(38)*. As has been described previously, this set of studies is characterized by considerable variation in outcome assessment (parental recall of ALRI signs, fieldworker assessed community ALRI, physician diagnosed pneumonia, and X-ray confirmed pneumonia), and almost exclusively indirect assessment of exposure through a variety of proxy measures (cooking fuel type, heating fuel type also in some, reported exposure to or presence of cooking smoke, whether mother carries child while cooking, average hours per day near fireplace). Only the trial included personal exposure measurement on all children *(15)*, one study measured $PM_{2.5}$ in all homes *(26)*, while two others included measurement in a sub-sample of homes *(34-35)*, combined with time-activity information in one *(34)*. Quality assessment identified risk of bias in many

studies and arising for a range of reasons: the potential impact of these biases was assessed in sensitivity analysis.

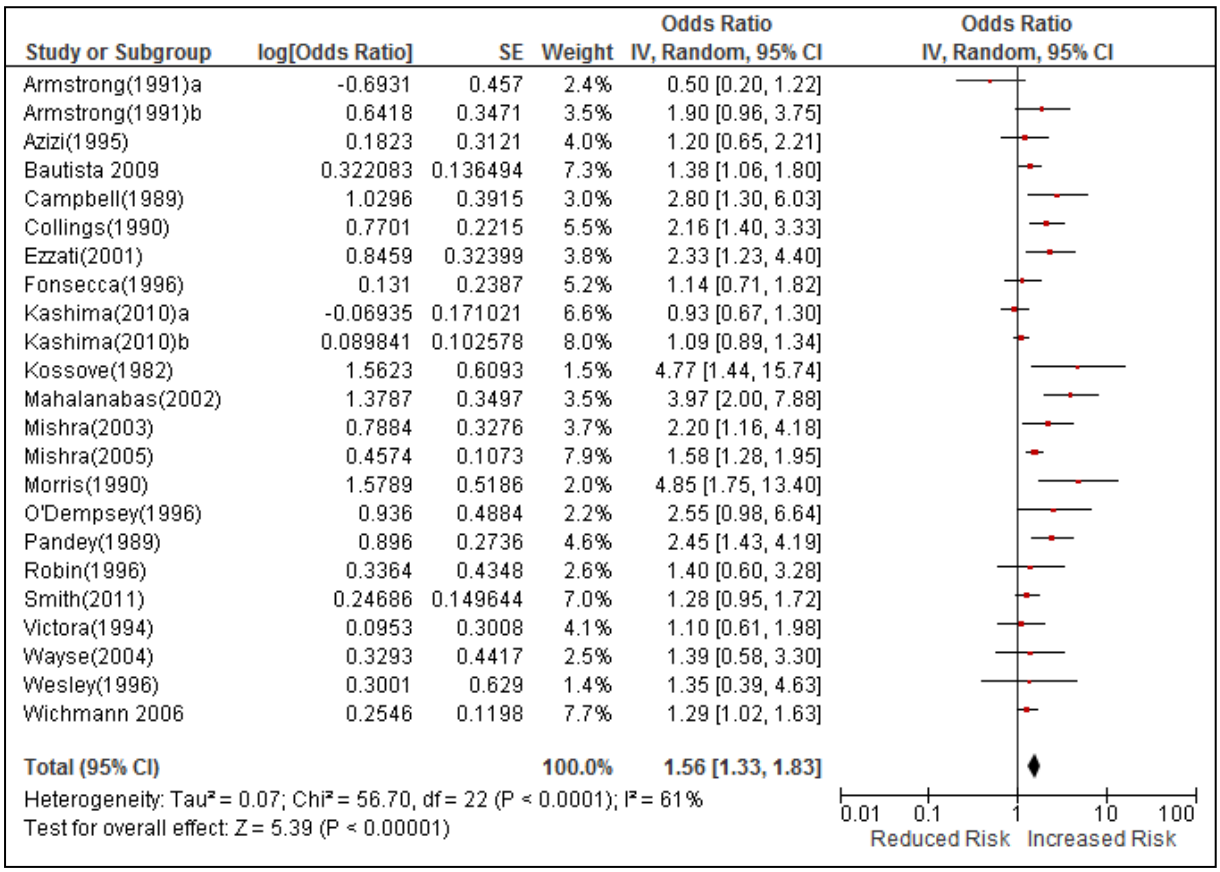
In contrast to the full set of studies, publication bias was not apparent for this set with Begg's (p=0.56) and Eggar's (p=0.091) tests non-significant. There was significant heterogeneity (I^2 = 61%, p<0.0001), and the pooled OR was 1.56 (1.33, 1.83), p<0.0001, see Figure 2.2.
Some duplication of cases in the RESPIRE trial occurs with the severe ALRI analysis below, but exclusion of this study results in a small increase in the effect estimate to 1.59 (1.34, 1.89). A concern with several studies in this review is inclusion of kerosene in the 'unexposed' group (see Review 9 on kerosene), although this occurred only in the Indonesian DHS study for this outcome *(16)*: the pooled OR following exclusion of this study was 1.66 (1.41, 1.97) with I^2 reduced to 52% (p=0.003).

Discussion

The impact of various sources of bias was extensively assessed in sensitivity analysis in the original review by Dherani et al. 2008, and similar analysis for this update has not altered the conclusion that no systematic impact of these design issues could be identified. There was substantial statistical heterogeneity, but in only two estimates was the OR below 1.0 and in neither case significantly so. Given the wide range of settings, study designs, exposure measures and outcome definitions, it is perhaps more remarkable that most studies report results in a fairly narrow range. This conclusion is strengthened by the fact that, having separated this set of non-fatal (severity not specified) outcomes from those defined as severe or fatal, there was also no strong evidence of publication bias.

In another systematic review published by Po et al. in 2011, a much larger pooled effect of 3.53 (1.94, 6.43) for child ARI was reported, but there were some important methodological differences *(39)*. Thus, Po et al. grouped studies reporting ARI and ALRI, whereas here studies not distinguishing upper and lower ARI are excluded, while some other studies not cited by Po et al. are included. Also excluded were two studies cited by Po et al. that reported surprisingly large estimates, the first as the unadjusted OR of 32.6 was stated as non-significant in adjusted analysis but not provided *(40)*, while for the second study the OR for children of 7.98 (quoted by Po et al.) used comparison with an 'unexposed' group of 'other members of the family' *(41)*.

Figure 2.2: **Forest plot for 21 studies (23 estimates) of non-fatal ALRI, where severity is not defined**



There is relatively limited specific evidence on mechanisms by which combustion-derived air pollution may cause pneumonia in children and very few studies of these mechanisms on humans *(42)*. Zhou et al. have stated noted that the mechanisms are not fully elucidated by which PM reduces resistance to infection, but the alveolar macrophage (AM) has an important role *(43)*. These authors state that AM interaction with air pollution particles results in particle phagocytosis, oxidant production, and release of inflammatory mediators such as TNF-α, and macrophage inflammatory protein (MIP)-2. Kulkarni et al. showed that higher levels of exposure to PM from use of biomass fuel in Ethiopia, compared with UK residents, resulted in higher levels of carbon loading in AMs obtained by sputum induction *(44)*.

A number of studies have been carried out in mice. Among male BALB/c mice, Zhou et al. found that exposure to concentrated ambient particles (CAP) resulted in less bacterial (*Streptococcus pneumoniae*) killing, mainly due to reduced internalization of bacteria, despite increased binding *(43)*. These effects were mediated by soluble components of CAPs, and iron played a part as the effect was reduced by iron chelation. Two other studies, using human and rat alveolar macrophages, have found that particles, both carbon black and more complex diesel exhaust particles, impair phagocytosis for both inert (silica) and micro-organisms including yeasts and *Streptococcus pneumoniae (45-46)*. Oxidative stress has been shown to increase adherence of *Staphylococcus aureus* to airway epithelial cells*(47)*, and Mudway et al. found that dung-derived PM depleted ascorbate (an antioxidant) in a human respiratory tract lining fluid model and that this effect was diminished by the metal chelator diethylene triamino penta acetic acid (DTPA) *(48)*. Several studies have examined survival of mice infected with *Streptococcus pneumoniae,* and exposed to carbonaceous PM, but results may not be consistent. Hatch et al. found that both ultrafine carbon black (UF-CB) and diesel exhaust particle exposure reduced survival,*(49)* while

Tellabati found increased survival compared to controls in mice exposed to UF-CB a finding which might have resulted from increased neutrophils in the PM-exposed group but leading to the conclusion that carbon-loading per se does not seem to be the mechanism by which vulnerability to infection is mediated *(50)*.

A number of studies have examined the effect of particles on responses to viral infection, including respiratory syncytial virus (RSV), and interactions with bacterial infection. In male BALB/c mice, Sigaud et al. studied whether and how prior viral infection modified the effect of CAP exposure on *Streptococcus pneumoniae* infection, using pre-treatment (priming) of the animals with IFN-γ aerosol (representing the gamma interferon characteristic of successful host anti-viral responses) *(51)*. They reported that priming exacerbated the effects of CAP, namely impaired bacterial clearance, increased oxidant production and reduced bacterial uptake by AMs. Lambert et al. found that mice exposed to carbon black, then infected with RSV showed no increase in replication of the virus compared to controls, but did show an increase in neutrophils and TNF-alpha; in addition, secondary bacterial infection was only seen in the mice exposed to PM *(52)*.

In summary, these studies do suggest plausible mechanisms and some evidence that combustion particles from a range of sources, and possibly CB and small particles in general, can interfere with some of the importance defense mechanisms in the lung for bacterial infection, and possibly also increase the risk of secondary bacterial infection following RSV. Studies of survival in mice following infection may be inconsistent.

Overall assessment of evidence

Reference to the Bradford-Hill viewpoints, including the trial-based evidence, exposure-response relationships, relative consistency across widely differing settings, biological plausibility and analogous evidence from other sources of pollution suggest confidence in causal inference. An overview of this evidence including that for severe and fatal outcomes (below), is presented together in Table 2.2. In the GEPHI assessment [Annex Table A1.1(a)], the single RCT has marginal power for the main outcome and is graded MODERATE; the observational studies have risk of bias and marked statistical heterogeneity, and are downgraded to VERY LOW. With only one RCT, the initial assessment was based on the observational studies and therefore VERY LOW. Consideration of additional criteria upgraded for consistency of results across studies of differing designs conducted in many different settings, and for analogous evidence from other sources of combustion pollution, resulting in a final score of MODERATE.

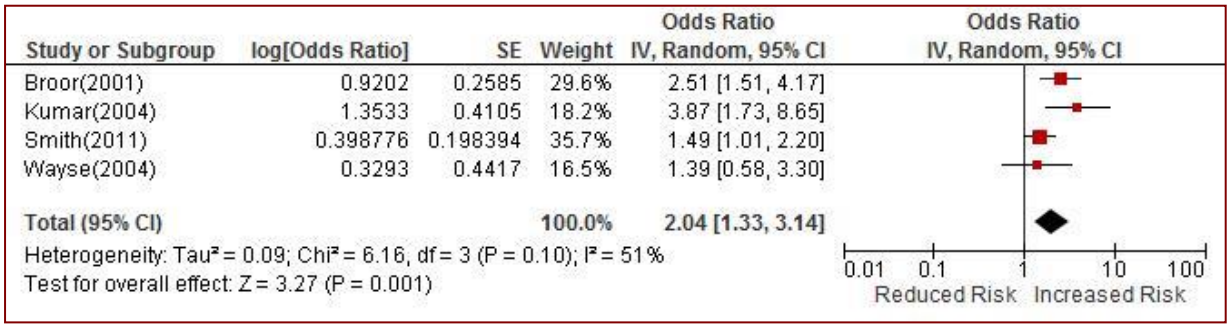
Taking this assessment together, there is a convincing case for causality so reducing HAP to the levels typical of the 'unexposed' groups in this set of studies would prevent child ALRI, while the GEPHI assessment of MODERATE indicates reasonable confidence about the effect [OR=0.63 (0.53, 0.75)], but that further research may (well) alter the size of this effect. Following GRADE rules, this estimate is taken from the largest (observational) body of evidence and is conservative, although a risk reduction of 37% (25%, 47%) is still large relative to those for most other important child pneumonia prevention interventions *(53)*. The contributions to our understanding of the likely effect size of findings for severe and fatal pneumonia are considered further at the end of this section on Child ALRI.

Severe ALRI

Four studies, including one RCT *(15)* and three case-control studies *(54-56)* reported on severe ALRI. All three case-control studies used hospital cases and outpatient/immunization clinic controls, which does raise the possibility of control selection bias. The outcome assessment was based on physician diagnosis in all studies, but the trial used low oxygen saturation to define severity *(15)*. Exposure assessment was by type of cooking fuel, except for the trial which used direct measurement. Heterogeneity was substantial although of

borderline significance (I^2=51%, p=0.10), and the pooled OR was 2.04 (1.33, 3.14) p=0.001, see Figure 2.3.

Figure 2.3: Forest plot for four studies of severe ALRI



Discussion

Although this finding of a larger effect than for non-fatal (severity not defined) ALRI is based on only four studies, these results show a good degree of consistency. All used physician diagnosis for the outcome and reported odds ratios in excess of 1.0, three significantly so. The trial also reported a larger effect on severe compared to all physician-diagnosed cases. It also found a significant exposure-response relationship for severe pneumonia; although the OR for intention to treat analysis of the trial of 1.49 (1.01, 2.20) is somewhat lower than the overall pooled result of 2.04 (1.33, 3.14) or that of the three case-control studies of 2.45 (1.50, 3.98), exposure in the trial's intervention group was relatively high (estimated to be >100 µg/m^3 $PM_{2.5}$), and likely to be well above that in the (unexposed) groups using cleaner fuels in the case-control studies (see Review 5). At lower levels, the exposure-response analysis in the trial found larger reductions in risk.

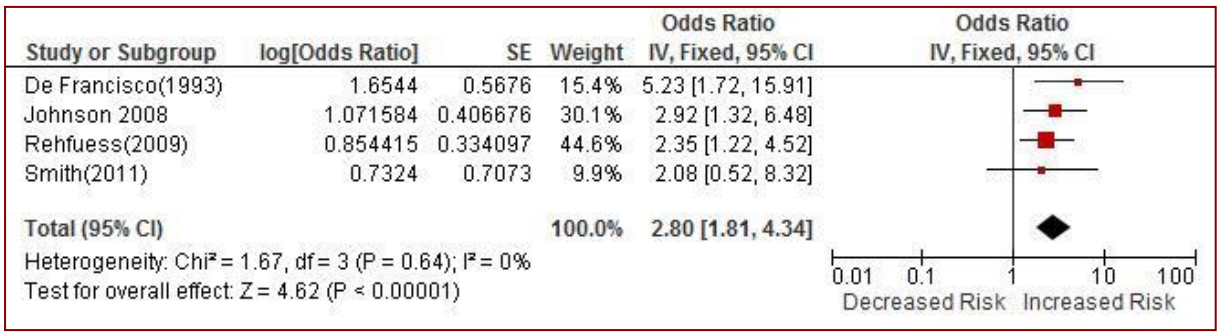
Overall assessment of evidence for severe pneumonia

With reference to the Bradford-Hill viewpoints and overall body of evidence for ALRI, there is adequate evidence to support a causal link with severe pneumonia, but so far little to support a stronger effect on the severe outcome, and this currently has to be considered a tentative conclusion. GEPHI assessment (Annex Table A1.1(b)) for the RCT was HIGH as findings were significant including for the exposure-response relationship, while the three observational studies were rated LOW with downgrading for risk of bias and upgrading for a strong effect (>2). The initial overall assessment was therefore LOW, and there was insufficient additional evidence on consistency or analogy to revise this. Overall, this evidence suggests that reducing HAP sufficiently will prevent severe pneumonia, and the risk reduction may be greater than for all pneumonia. The effect size reported here is not estimated with great confidence, and further research is required which is may well change this result.

Fatal ALRI

Four studies, including the trial (albeit with only nine eligible events)*(15)*, one case-control study using community controls *(57)*, one case-fatality study *(58)* and one cross sectional study *(59)* reported risk of fatal pneumonia. Outcome assessment varied considerably, including verbal autopsy (2 studies), survey-based parental recall of key signs over a period of up to ten years (1 study) and deaths in hospital following clinical diagnosis with radiological confirmation (1 study). Exposure assessment in the observational studies included type of fuel (2 studies), and whether the child was carried on the mother's back while cooking (1 study). There was no evidence of statistical heterogeneity (I^2=0), and the pooled OR was 2.80 (1.81, 4.34) p<0.0001, see Figure 2.4.

Figure 2.4: Forest plot for four studies of fatal ALRI



Discussion

Despite the widely differing study designs and methods, the findings are consistent with no statistical heterogeneity. In all studies, the RR or OR was >1.0, for three significantly so. The relatively large effect of 2.80 (1.81, 4.34) is consistent with the findings for severe vs. all non-fatal ALRI reported above, as case-fatality of severe pneumonia is known to be substantially higher than for non-severe *(60)*.

Overall assessment of evidence for fatal pneumonia

As for severe pneumonia, overall assessment by reference to the Bradford-Hill viewpoints supports a causal association with fatal pneumonia, but the higher risk estimate of almost 3.0 needs further confirmation. GEPHI assessment (Annex Table 1.1(c)) rated the RCT as MODERATE and the three observational studies as LOW, being downgraded for risk of bias and upgraded for a large effect (>2). The initial overall assessment was therefore LOW and there was insufficient additional evidence on consistency or analogy to revise this. The overall assessment is therefore the same as for severe pneumonia, and further studies are needed to obtain a more reliable intervention effect estimate.

Conclusion on evidence for childhood ALRI

The available studies were stratified by severity, as there is evidence of possibly higher risk for more severe outcomes and as some were smaller studies this led to detection of publication bias in the full set of studies. There is a strong case for causality for child pneumonia, based on a review of the Bradford-Hill viewpoints (Table 2.2).

The lack of exposure measurement in the great majority of studies makes quantification of intervention effects problematic, but some assessment is possible. In Review 5 (Population levels of household air pollution and exposures), it was shown that average HAP levels in those habitually using solid fuels is in the order of several hundred μg/m^3 $PM_{2.5}$, while that for clean fuel users (LPG, etc.) it is in the range 35-80 μg/m^3 $PM_{2.5}$. This is associated with a risk reduction of 35% (25% to 47%). Although the effect in the RESPIRE trial was on the low side at 22% (-6% to 41) the confidence interval is wide and also the intervention group mean exposure was higher (in excess of 100 μg/m^3 $PM_{2.5}$) than that estimated for the majority of observational studies, and the intention-to-treat findings should be interpreted with this in mind.

Table 2.2: **Evaluation of Bradford-Hill viewpoints for effect of HAP exposure on child pneumonia**

Viewpoint		Explanation
1	Strength of association	OR of 1.56 (CI) for all pneumonia (severity not defined), with findings suggesting a large effect with an OR>2 for severe/fatal pneumonia.
2	Consistency across populations, study designs	Majority of studies from many different countries and regions and widely differing designs report increased risk, although not all statistically significant
3	Specificity	HAP exposure, as with smoking, causes a wide range of disease outcomes due to varied impacts of mechanisms (e.g. oxidative stress) and the different pollutant types (carcinogens, respiratory irritants, fine PM, etc.). Epidemiological studies do not, however, find association between HAP and outcomes such as diarrhoea, also closely associated with poverty.
4	Temporality (exposure precedes outcome)	Although exposure varies within and between days for children in developing countries exposure will have occurred through pregnancy and from birth and hence preceded infection.
5	Biological gradient (dose-response)	Statistically significant biological gradients have been reported from two studies, summarized further in Section 3
6	Biological plausibility	A number of studies have shown effects of combustion-derived particles on plausible mechanisms, including impaired defense against *Streptococcus pneumoniae*.
7	Coherence with natural history, animal studies	Pneumonia incidence and mortality are closely associated with solid fuel use (see Figure 2.1); some limited animal survival evidence is available but may be inconsistent.
8	Experiment	One RCT is available (RESPIRE) reported here and further in Section 3. A cohort study of adult pneumonia mortality following introduction of improved chimney stoves in a coal-using area of China also lends some support (see Section 3.5)
9	Analogy	The two other main sources of combustion-derived pollution, second-hand smoke and ambient air pollution, increase the risk of pneumonia.

Overall, therefore, these findings suggest that ALRI incidence would be reduced by around one-third with interventions that bring average $PM_{2.5}$ down from several hundreds of $\mu g/m^3$ to levels experienced by 'unexposed' groups in the majority of epidemiological studies (35-80 $\mu g/m^3$ $PM_{2.5}$). The smaller risk reduction in the RESPIRE trial is consistent with the relatively high exposure in the intervention group. It may be expected that reductions to levels at or below the WHO annual average AQG of 10 $\mu g/m^3$ of $PM_{2.5}$ would result in a larger risk reduction: this is discussed further in Section 3, but remains to be demonstrated in practice. Finally, the evidence suggests that there could be even larger effects on the risk of severe and fatal pneumonia, but this is a tentative finding and a priority for future research.

2.4.2 Low birth weight (LBW)

Globally, some 15.5% of births are of low birth weight (< 2500 gm), with the highest rates in Asia (18.3%) and Africa (14.3%) *(61)*. Reduced birth weight, especially when caused by restricted fetal growth, places the child at higher risk of a range of diseases, impaired development, and lifelong sequelae *(61)*. A systematic review on the risk of low birth weight and solid fuel use was published in 2010 *(62)*; this was updated and found one new study and publication of several previously unpublished studies, Box 2.3.

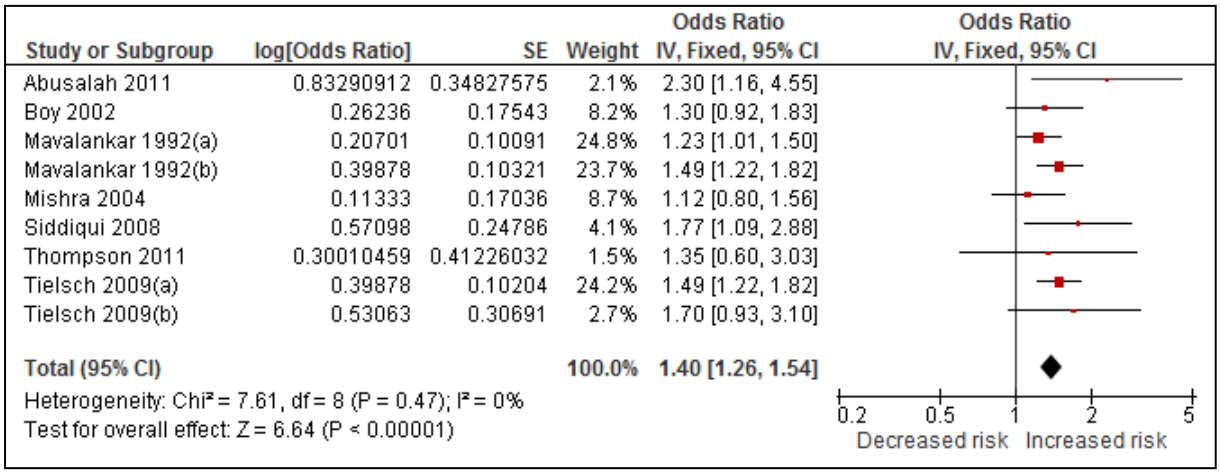
Seven studies, including one RCT (analyzed per protocol) *(63)* and six observational studies *(64-69)* reported on the risk of low birth weight (<2500 gm at term). Two of the studies provided separate, independent estimates for pre-term small for gestational age (SGA) and term low birth weight (LBW) *(65, 68)*

Box 2.3: Key search features for review of low birth weight

- Search period: to July 2012
- Search hits: 982 (original) + 442 (new)
- Inclusion: all designs that included measures of (i) HAP and (ii) term LBW (<2500 gm) or pre-term small for gestational age (SGA)
- Eligible studies: 7 (9 independent estimates)
- Languages: English, French, Spanish; not Chinese

Birth weight was measured by trained field staff using scales in five studies, and obtained from health cards (with a proportion by maternal recall) in one study, and is not described in one hospital based study. Exposure assessment was by fuel type in four studies, reported exposure to wood smoke in two, and by per protocol analysis of the single trial comparing open fires with a chimney stove. There was no evidence of statistical heterogeneity (I2=0), nor of publication bias (Begg's p=0.348, Eggar's p=0.356). The pooled OR was 1.40 (1.26, 1.54) p<0.0001 for all births, see Figure 2.5, and 1.36 [1.20, 1.54] for term births (7 estimates), while for pre-term (2 estimates) the OR was slightly higher at 1.51 [1.25, 1.83]. Sensitivity analysis restricted to four studies carrying out adequate adjustment *(63, 67-69)* had a larger effect for term LBW of 1.57 (1.33, 1.86); adjustment was made for SES characteristics, maternal age, primiparity, household characteristics and environmental (second-hand) tobacco smoke exposure, but only one study adjusted for gestational age.

Figure 2.4: Forest plot for 7 studies (9 estimates) of low birth weight. Those marked (a) are term LBW and (b) are for pre-term SGA



Five studies had adjusted estimates of mean birth weight providing a weighted mean difference (lower exposure group mean minus higher exposure group mean) of 96.6g (68.5, 124.7), although two of these studies did not adjust for gestational age. Exclusion of one estimate using maternal recall of birth weight *(66)* marginally reduced the effect to 93.1g (64.6, 121.6).

Discussion

There is supportive mechanistic evidence of the association between components of HAP (carbon monoxide (CO), particulate matter (PM) and polyaromatic hydrocarbons (PAH)) and low birth weight *(70)*. Despite differences in components of pollution mixtures, the reported estimates are consistent with those for analogous exposures, including outdoor air pollution, environmental tobacco smoke and active smoking; the mean birth weight effect lies between published estimates for SHS and active smoking as would be expected from the relative levels of exposure to $PM_{2.5}$ *(62)*.

Overall assessment of evidence

Reference to the Bradford-Hill viewpoints suggest moderately strong evidence for causation, with consistency, feasible temporal relationships, biological plausibility and analogy, although none of the studies has demonstrated an exposure-response relationship, Table 2.3.

Table 2.3: Evaluation of Bradford-Hill viewpoints for effect of HAP exposure on low birth weight

Viewpoint		Explanation
1	Strength of association	The adjusted risk estimate for LBW with exposure to HAP of 1.57 (1.33, 1.86) is of moderate strength
2	Consistency across populations, study designs	Although relatively few studies are available, these are very consistent in terms of the findings
3	Specificity	As noted for child ALRI (Table 2.2), HAP exposure is linked to a wide range of outcomes
4	Temporality (exposure precedes outcome)	Exposure typically occurs throughout pregnancy; evidence includes several longitudinal studies
5	Biological gradient (dose-response)	None reported to date
6	Biological plausibility	Studies of mechanisms for pollutants including carbon monoxide provide supportive evidence
7	Coherence with natural history, animal studies	Prevalence of LBW is consistent with patterns of solid fuel use; animal studies provide supportive evidence
8	Experiment	Only one RCT with small sample size for LBW is available to date
9	Analogy	Evidence from other combustion sources including smoking by pregnant women, second-hand smoke, and ambient air pollution, all provide consistent supportive evidence.

GEPHI assessment (Annex Table A1.2) downgraded the trial for imprecision to MODERATE, while the observational studies were not down or upgraded and rated LOW. Initial assessment was therefore LOW, but the consistency and analogous evidence could both have resulted in upgrading: on balance, given that only seven studies are available, the evidence was rated MODERATE with an intervention effect estimate of 0.71 (0.64, 0.79).

2.4.3 Stillbirth

It is estimated that of the 2.65 million stillbirths that occur annually, 98% take place in low and middle-income countries *(71)*. Around half (45%) are intrapartum, and for those occurring prenatally, smoking and HAP have been recognized as risk factors *(71)*.

The systematic review by Pope et al. also included stillbirth, *(62)*; this was updated but no new eligible studies were identified, Box 2.4. A RCT reported by Hanna et al. included stillbirth but was not eligible as this outcome was combined with infant mortality and miscarriage. *(38)* An Indonesian DHS-based study by Kashima et al. was also excluded as stillbirth was combined with miscarriage and abortion *(16)*.

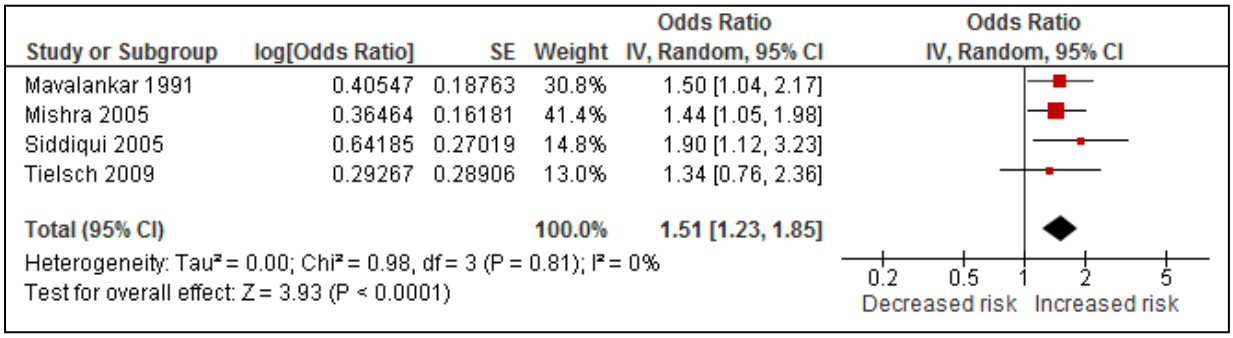
Box 2.4: Key search features for review of stillbirth

- Search period: To July 2012
- Search hits: 171 (original) + 151 (new)
- Inclusion: all designs that included measures of (i) HAP and (ii) stillbirth
- Eligible studies: 4 (4 independent estimates)
- Languages: English, French, Spanish; not Chinese

All were observational designs and included two cohort studies, one from Pakistan *(72)* and one from India *(73)*, one case-control study *(74)* and one cross-sectional study in India *(75)*.

Outcome assessment varied and included hospital cases (1 study), parental recall in a population survey (1 study), and surveillance in the two cohorts studies. Exposure assessment was based on cooking fuel type with biomass compared to clean fuels, i.e. electricity or gas, but including kerosene in one study *(73)*. All studies provided adjusted estimates. There was no evidence of statistical heterogeneity (I^2=0%), and the pooled OR was 1.51 (1.23, 1.85), see Figure 2.6.

Figure 2.5: Forest plot for 4 studies of stillbirths



Discussion

Only four studies were identified, all from India and Pakistan. Despite variations in study design, the findings are consistent, all studies reporting an OR above 1.0 and three significantly so. This consistency may in part be due to the relatively unambiguous nature of the outcome, although there is still the possibility of some early neonatal deaths being described as stillbirths. There is less epidemiologic evidence linking stillbirth with exposure to ambient air pollution *(62)*, but maternal smoking is an important risk factor *(76)*. The mechanistic evidence is also less clear, although is likely to share some common pathways with those for low birth weight and other adverse pregnancy outcomes.

Overall assessment of evidence

Reference to the Bradford-Hill viewpoints including analogous evidence suggests that a causal association is possible, but not is less convincing than for low birth weight, Table 2.4.

Table 2.3: Evaluation of Bradford-Hill viewpoints for effect of HAP exposure on stillbirth

Viewpoint		Explanation
1	Strength of association	The risk estimate for stillbirth 1.51 (1.23, 1.85) is of moderate strength, but based on only four studies
2	Consistency across populations, study designs	Although relatively few studies are available, these are very consistent in terms of the findings
3	Specificity	As noted for child ALRI (Table 2.2), HAP exposure is linked to a wide range of outcomes
4	Temporality (exposure precedes outcome)	Exposure typically occurs throughout pregnancy; evidence includes two longitudinal studies
5	Biological gradient (dose-response)	None reported to date
6	Biological plausibility	Studies of mechanisms for pollutants including carbon monoxide provide supportive evidence, but this is weaker than for LBW
7	Coherence with natural history, animal studies	Prevalence of stillbirth is consistent with patterns of solid fuel use; animal studies provide some supportive evidence
8	Experiment	None reported to date
9	Analogy	Evidence from other combustion sources including smoking by pregnant women and second-hand smoke provide supportive evidence, findings for ambient air pollution are less clear.

The GEPHI assessment (Annex Table A1.3) did not downgrade the studies, so initial assessment was LOW. There were two few to upgrade for consistency, and although there is some analogous evidence, this was not felt to be strong enough to change the grading, so the final assessment was LOW. The intervention effect estimate was 0.66 (0.54, 0.81), but this may well change with new studies. One recent study based on the Indian DLHS-II survey (not included in the meta-analysis as publication followed the search period) reported an adjusted prevalence ratio (PR) of 1.24 (1.08, 1.41) for cooking with biomass compared with LPG/electricity; although somewhat lower than with the pooled OR, this study does also report significantly increased risk and is consistent in terms of the 95% confidence interval *(77)*.

2.4.4 Pre-term birth

In the GBD 2010 study, complications of pre-term birth (PTB) were assessed as responsible to 860,000 deaths in 2010 *(78)*, and this is an important factor in subsequent poor outcomes in the neonatal and post-natal periods. The original review by Pope et al. included this outcome as a search team *(62)*, as did the update. Only one study with an estimate for pre-term birth was identified, the same cohort study from India that was included in the reviews of low birth weight and stillbirth: this reported an adjusted OR of 1.43 (1.11, 1.84) for cooking with biomass compared to liquefied petroleum gas (LPG) or kerosene *(68)*. Grading of the study was not carried out, and this should be seen as a preliminary indication of possible risk, not least as some common mechanisms may be involved as for low birth weight and stillbirth.

2.4.5 Stunting

Stunting is a key indicator of poor growth and where present puts the child at risk of multiple adverse health outcomes, as well as death. The GBD 2010 study comparative risk assessment attributed more than 850,000 deaths to childhood underweight in 2010 *(79)*. In a systematic review covering stunting and under-5 year mortality, Box 2.5, three studies (four estimates) reported on the risk of stunting, two for moderate stunting (-3 SD $\leq$ Z to -2 SD) *(68, 80)*, and two for severe stunting (Z < -3 SD) *(80-81)*.

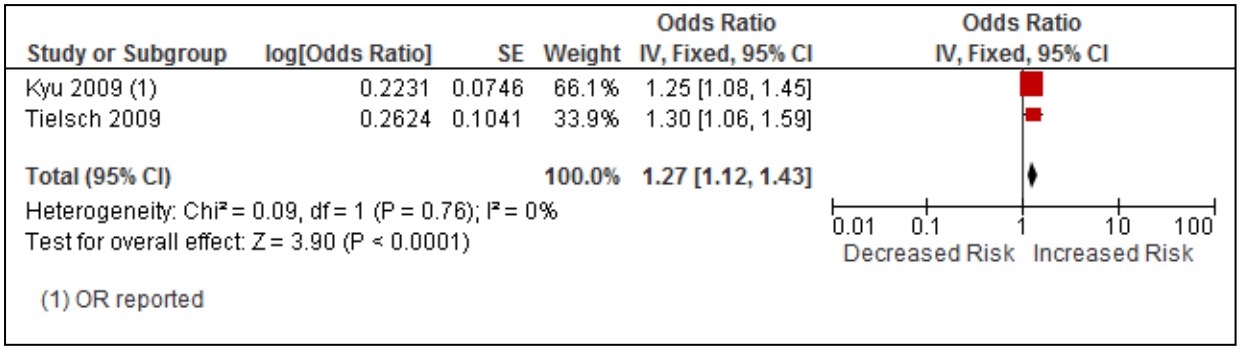
One was based on an Indian cohort study *(68)*, the others cross-sectional using DHS data for 7 countries *(80)*, and India *(81)*. Outcomes were assessed through survey-based measurement in all studies, while exposure was determined by fuel type at interview. Kerosene was included in the 'clean' group for all four studies. All studies provided adjusted estimates.

For moderate stunting, there was no evidence of statistical heterogeneity (I^2=0%), and the pooled OR was 1.27 (1.12, 1.43) p<0.0001, see Figure 2.7.

Box 2.5: Key search features for stunting and mortality outcomes

- Search period: 1996 - July 2012
- Search hits: 3676
- Inclusion: all designs that included measures of (i) HAP from solid fuel use and (ii) stunting and any definition of child mortality under 5 years
- Eligible studies for stunting: 3 (4 independent estimates)
- Languages: English, French, Spanish, not Chinese

Figure 2.6 Forest plot for 2 studies of moderate stunting

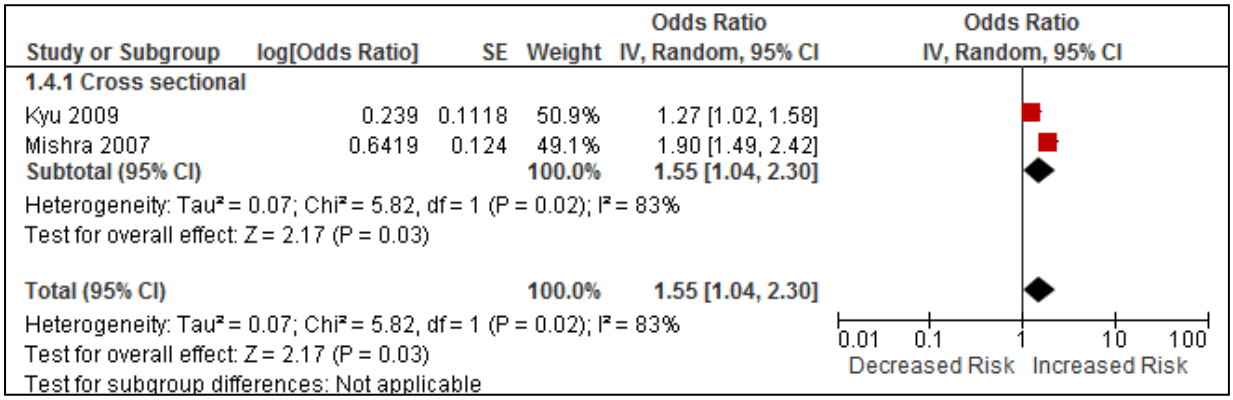


For severe stunting, there was evidence of significant heterogeneity (I^2=83%, p=0.02), and the pooled OR was 1.55 (1.04, 2.30), see Figure 2.8.

Discussion

This is a small, and for severe stunting, heterogeneous body of evidence, and although the study by Kyu et al. combined DHS data from 7 countries, these had widely differing socio-economic conditions, including percentage use of solid fuels and children's nutritional status *(80)*. There is some support from findings for second-hand smoke and maternal smoking, and plausible causal mechanisms, as discussed by Kyu et al *(80)*. The inclusion of kerosene in the clean fuel group for all studies could also contribute to bias towards the null.

Figure 2.7: Forest plot for 2 studies of severe stunting



Overall assessment of evidence
Reference to the Bradford Hill viewpoints suggests causation is plausible but tentative (see Table 2.5).

For moderate stunting, initial GEPHI assessment was LOW, Annex Table A1.4. Although analogous evidence from second-hand and maternal smoking is available, upgrading for this additional criterion was not done due to the very small number of studies. The intervention effect estimate was 0.79 (0.70, 0.89). For severe stunting, initial assessment was rated VERY LOW due to heterogeneity. Given the analogous evidence on second-hand smoking, including the independent effect of maternal smoking with an OR of 1.49 (1.29, 1.71) reported by Kyu et al., this outcome was upgraded to LOW; the intervention effect estimate was 0.64 (0.43, 0.96). Further studies are however needed to confirm this evidence and increase confidence about potential intervention impacts.

Table 2.4: Evaluation of Bradford-Hill viewpoints for effect of HAP exposure on child stunting

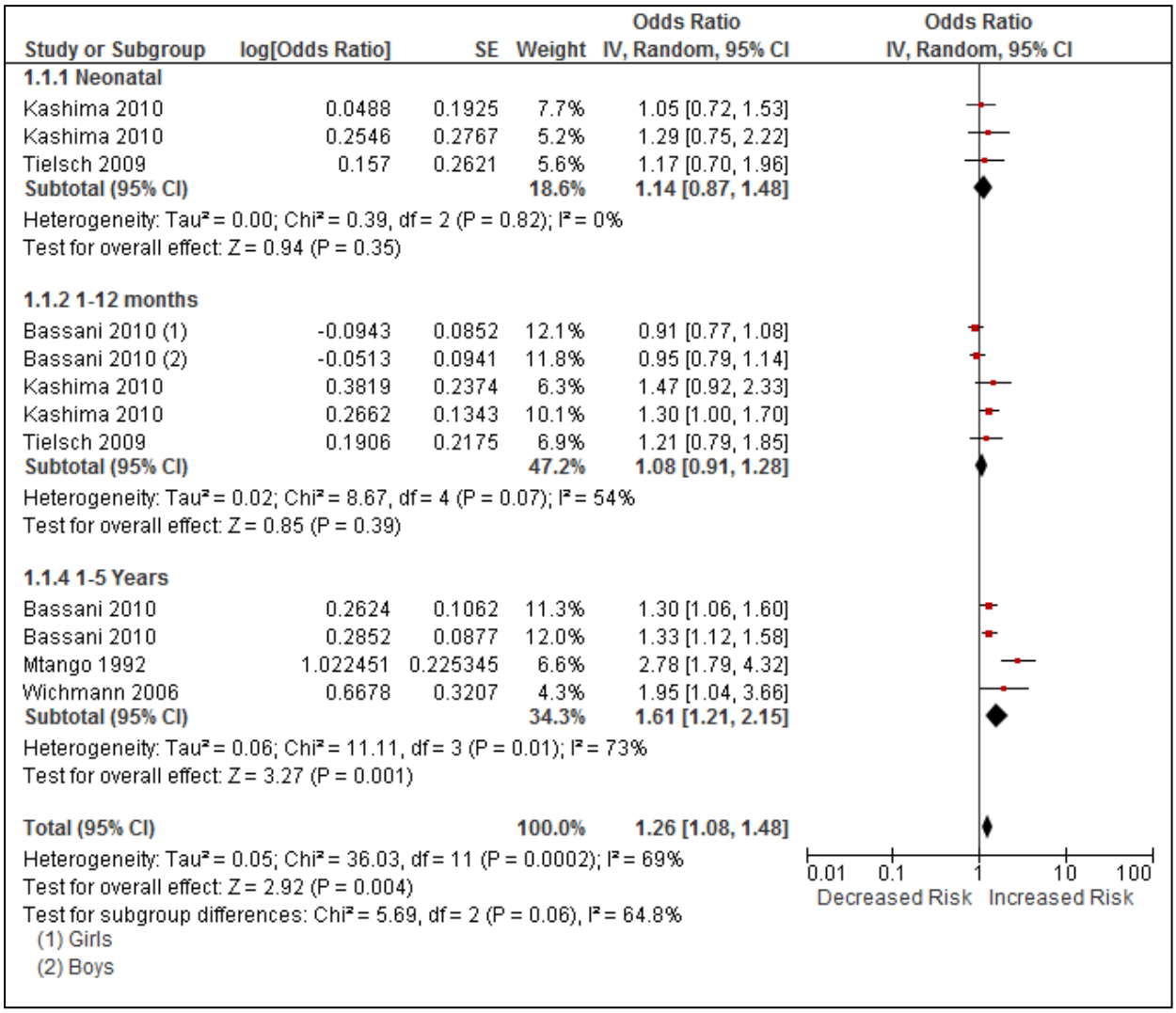
Viewpoint		Explanation
1	Strength of association	Based on few studies, the risk estimates for moderate 1.27 (1.12, 1.43) and severe stunting 1.55 (1.04, 2.30) are small to moderate.
2	Consistency across populations, study designs	Too few countries and studies are available to assess (study by Kyu et al. includes seven countries, but relationship between risk and solid fuel use not reported)
3	Specificity	As noted for child ALRI (Table 2.2), HAP exposure is linked to a wide range of outcomes
4	Temporality (exposure precedes outcome)	Exposure typically occurs throughout pregnancy and through childhood from birth; evidence limited to cross-sectional studies
5	Biological gradient (dose-response)	None reported to date
6	Biological plausibility	No studies on mechanisms for solid fuel HAP reported to date
7	Coherence with natural history, animal studies	Prevalence of stunting is consistent with patterns of solid fuel use; animal studies were not available
8	Experiment	None reported to date
9	Analogy	Evidence from other combustion sources, notably second-hand smoking, provides supportive evidence.

2.4.6 All-cause under-5 year mortality

Child mortality is influenced by the risks of all of the outcomes discussed in foregoing sections (2.3.1-2.3.5), and is an important outcome in its own right. This search was combined with that for stunting (see 3.3.5), and five studies provided 10 fully-independent estimates for all-cause mortality. Two were case control *(82-83)*, two cross-sectional based on the DHS *(16, 84)*, and one cohort study *(68)*, spanning several age groups. The DHS-based study by Kashima provides independent urban and rural estimates. The RCT by Hanna et al. assessed infant mortality, but has not been included as the intervention achieved no exposure reduction in children*(38)*. The outcome (mortality) was determined by a mix of interview and surveillance, and since this was all-cause mortality, the reasons for the deaths were not required. Exposure was assessed by fuel type at interview in all studies, and by whether the child slept in the cooking area in one *(82)*; three of the studies included kerosene in the clean fuel group, while one included kerosene with the solid fuels *(19)*. All five studies provide adjusted estimates.

There was significant heterogeneity across all studies (I^2=72%, p<0.0001). The pooled OR was 1.27 (1.07, 1.50) suggesting an overall significant impact on mortality; stratified analysis with all study estimates is shown in Figure 2.9.

Figure 2.8: Forest plot for 5 studies of all-cause mortality, stratified by age group.



Two studies provided estimates for neonatal mortality, with an I^2 =0% and a non-significant pooled OR of 1.14 (0.87, 1.48) *(16, 68)*, but both included kerosene in the 'unexposed' group. For the 1-12 month age group, three studies are included, although Tielsch et al. focused on 0-6 months, and hence also covers the neonatal period. There was evidence of statistical heterogeneity (I^2=54%, p=0.07), and the pooled OR of 1.08 (0.91, 1.28) was non-significant. All three studies included kerosene in the 'unexposed' group. Exclusion of the Tielsch et al. estimate made little difference to the pooled estimate or 95% confidence interval.

The largest effect was seen in the 1-5 year age group, where there was significant statistical heterogeneity (I^2=73%, p=0.01) with a significant pooled OR of 1.61 (1.21, 2.15). Only one of these studies included kerosene in the 'unexposed' group *(83)*, while Wichmann et al. included kerosene in the 'exposed' group *(84)*. Exclusion of Bassani et al. removed the heterogeneity (I^2=0%) and the OR (fixed) was 2.47 (1.72, 3.55).

Discussion

Although ten estimates are available, these are based on a very heterogeneous set of five studies, and span stages over the first five years of life where differing factors act to put young children at risk of dying, especially when comparing the neonatal and post-neonatal periods, and then with ages 1-4 years. The relative simplicity of the outcome definition adds some strength to the findings. On the other hand, the inclusion of kerosene in the clean fuel group of three studies (all those in the post-neonatal period), but in the 'exposed' group of one other increases uncertainty; the findings of a recently published study (outside the search period of this review) that household use of kerosene may be associated with neonatal mortality with an OR of 2.30 (0.95, 5.55) add to the evidence on the probable adverse health impacts of this fuel (see also Section 4.1) *(85)*.

Overall assessment of evidence

The evidence provided here, together with that for a set of child outcomes known to be linked to increased risk of death (especially severe ALRI), support a causal relationship between HAP exposure and under 5-year child mortality, Table 2.6. The evidence on mortality as an outcome is however very heterogeneous, and does not yet provide exposure-response or any convincing experimental-based evidence.

Table 2.5: Evaluation of Bradford-Hill viewpoints for effect of HAP exposure on child mortality (all cause)

Viewpoint		Explanation
1	Strength of association	Based on few studies, the risk estimate 1.26 (1.08, 1.48) is small; larger effects for important causes (e.g. severe and fatal child pneumonia) do however provide supportive evidence.
2	Consistency across populations, study designs	The few available studies provide very heterogeneous results
3	Specificity	As noted for child ALRI (Table 2.2), HAP exposure is linked to a wide range of outcomes
4	Temporality (exposure precedes outcome)	Exposure typically occurs throughout pregnancy and through childhood from birth; evidence limited to cross-sectional studies
5	Biological gradient (dose-response)	None reported to date
6	Biological plausibility	Mechanisms relating to specific disease outcomes which increase risk of death (e.g. child pneumonia and LBW) would apply.
7	Coherence with natural history, animal studies	Prevalence of child mortality is consistent with patterns of solid fuel use; animal evidence relating to specific causes would apply.
8	Experiment	None reported to date
9	Analogy	Evidence from other combustion sources, notably smoking by pregnant women, second-hand smoking and ambient air pollution, provide supportive evidence.

Initial GEPHI assessment rated the evidence as VERY LOW, due to inconsistency and possible publication bias, Annex Table A1.5. No upgrading for additional criteria was done; the intervention estimate was 0.79 (0.67, 0.93) and very likely to be modified by future studies. While assessment within age groups would be possible, this is unlikely to change the overall rating as significant heterogeneity was seen in the one age group with a significantly elevated risk (1-5 years). New studies of mortality associated with HAP exposure, and the impacts of interventions, are required to strengthen this evidence and should investigate risk within key age sub-groups.

2.4.7 Asthma

Because exposure to secondhand tobacco smoke has been associated with the development of asthma in children *(86)*, it is reasonable to suspect that exposure to HAP might also increase risk for this disease. On the other hand, asthma is much more prevalent in urban settings than in the largely rural settings where exposure to solid fuel smoke more commonly occurs *(87)*. Furthermore, living on farms, especially with livestock, has been associated with protection from the development of asthma *(88)*.

Although a disease that typically begins in childhood, asthma is also an important condition for adults. Since most of the evidence available is for children (particularly since publication of analysis of the impact of biomass fuels from the ISAAC study in 2013 – see below), asthma is discussed in this section on child health outcomes; the more limited evidence for adults is also included here.

A systematic review and meta-analysis of the risks of asthma in children and women as a consequence of exposure to biomass fuel combustion, as part of a larger review of respiratory disease, was published in 2011 *(89)*, Box 2.6. A separate review has not been conducted.

The methods used by Po et al. are consistent with those described generically for the reviews reported here. Due to statistical heterogeneity random-effects models were used, and sources of heterogeneity were systematically examined by multivariable meta-regression.

Box 2.6: Key search features for asthma and solid fuel HAP (Po et al. 2011)

- Search period: 1974 - 2010
- Search hits: 2717
- Inclusion: (i) exposure to biomass fuel in home (ii) respiratory-related disease, symptoms and functioning; and (iii) non-industrialized or domestic settings
- Exclusion: lack of separate male and female estimates
- Eligible studies: 9 (4 child; 5 women)
- Languages: English

The review identified nine studies that were used in the meta-analysis of the risk of asthma from exposure to HAP, four in children and five in women. Given the small numbers of studies, it was not possible formally evaluate publication bias for these two age groups. The meta-analysis of four studies in children found a non-significant protective effect with a summary OR (95% CI) of 0.50 (0.12 to 1.98), with very substantial heterogeneity (I^2=89%, p <0.001) *(90-93)*. The meta-analysis of five studies in women found a non-significant increase in the risk of asthma with a summary OR (95% CI) of 1.34 (0.93 to 1.93), with rather less heterogeneity than for the children (I^2=59%, p<0.046) *(94-98)*.

Although published after the period during which evidence was compiled for the CRA 2010, a recently published report from the multi-country ISAAC study adds substantially to the body of evidence available on household solid fuel exposure from use of open fires *(99)*. Data relating to over 500,000 primary and secondary school children from 108 centers in 47 countries were analyzed. Exposure was defined as use of solid fuels in an open fire for cooking, in comparison with electricity as a cooking fuel. Solid fuel use with exclusive use of an open fire was associated with an increased risk of asthma, with adjusted ORs for wheeze in the past year of 2·17 (1·64–2·87) for children aged 6–7 years and 1·35 (1·11–1·64) for children aged 13–14 years. No evidence of an association between the use of gas as a cooking fuel and either asthma symptoms or asthma diagnosis was reported in either age group.

The results from the ISAAC study for children are inconsistent with those from the review by Po et al., and this adds to the heterogeneity already noted. The non-significant increase in risk among women may be consistent with the ISAAC findings, especially those for the older age group of 13-14 years. In reviewing the Bradford-Hill viewpoints, substantial heterogeneity is noted, but also the large and relatively precise adjusted OR for wheeze in the past year among 6-7 years old children in the ISAAC study. The published report for the

ISAAC study does not allow an assessment of consistency in asthma prevalence and percentage solid fuel use by country, but such an analysis would be possible. Exposure can be expected to have preceded onset of disease, but no exposure-response or experimental findings have been reported. Analogous evidence on impacts of second-hand smoke and outdoor air pollution on asthma provides support. In conclusion, while there is a suggestive case for a causal effect of HAP exposure (particularly in respect of exacerbations of asthma), this requires strengthening through studies using consistent methodology, exposure assessment, and including some intervention-based studies.

2.4.8 Cognitive development

Neurological development has very important consequences for the growing child, as well as for his or her prospects as an adult. This is an emerging area of research in respect of HAP exposure, and a systematic review has not thus far been conducted. Very few studies investigating impacts of HAP on child development appear to have been carried out to date. The most direct evidence comes from a small study in rural Guatemala, in which 39 children age 6–7 years were assessed using non-verbal, culturally adapted neuro-developmental tests *(100)*. Results were compared to their mothers' personal CO exposure during pregnancy. The authors found inverse associations between CO exposure and child neuropsychological performance. Despite the small sample, scores on 4 out of 11 tests were significantly inversely associated with mothers' 3rd trimester CO exposures, including visual-spatial integration ($p < 0.05$), short-term memory recall ($p < 0.05$), long-term memory recall ($p < 0.05$), and fine motor performance ($p < 0.01$). These findings persisted with adjustment for child sex, age, visual acuity, and household assets (socio-economic status). Summary performance scores were also significantly associated with maternal 3rd trimester CO when adjusted for these covariates.

In a second study, open fire cooking using solid fuels – mainly wood – was inversely correlated with block forming, memory, and embedded figures in a retrospective study compiling data on children aged 3 to 9 years from four countries *(101)*. The design of this study was mainly ecological (comparing four communities with different fuel types) although single adjustment was made of correlation coefficients for schooling and socio-economic status. Mixed fuel use in one study community (Garifuna, Belize) allowed within-country analysis that reported similar findings, with significant results for two of the outcome measures (embedded figures, structured play) after similar adjustment. The main comparison fuel was kerosene, however, and no measurements were made of HAP or exposure.

Evidence from studies of outdoor air pollution provide some support, finding that chronic, early life exposures to pollutant mixtures including polycyclic aromatic hydrocarbons (PAHs), nitrogen oxide (NO_2), or black carbon (pollutants also found in biomass smoke), are associated with IQ and learning deficits among urban children under 11 years of age *(102)*. Prenatal exposure to outdoor ambient PAHs were associated with slower language and cognitive development up to age 2 years in China *(103)* and intelligence at age 5 years in Poland*(104)*. Maternal smoking has also been linked to a range of developmental and behavioral disorders *(105)*.

Mechanistic evidence is also consistent. Pollutants in HAP have been reported to impair cognitive development: for example, PAHs are known carcinogens and endocrine disruptors that interfere with the growth and development of neurons *(106)*. Inhaled ultrafine PM reaches other organs of the body including the brain through the circulation *(107-108)* and can cause inflammation of neurons *(106)*. The exact mechanism of these effects are still to be established, but direct inflammatory responses and oxidative stress appear implicated *(109)*. More neuro-inflammation and prefrontal vascular lesions on MRI scans were

observed in children exposed to a higher level of pollution in children in Mexico resulting in cognitive dysfunction *(101)*.

Firm conclusions cannot be reached based on so few studies, and there is relatively little evidence to assess against the Bradford-Hill viewpoints beyond the very preliminary epidemiological evidence, and supporting analogous evidence from outdoor air pollution, maternal smoking and biological plausibility. If a causal association between HAP exposure – especially during pregnancy – and cognitive development is confirmed this would have important implications for child health and development, and further research should be carried out to confirm and quantify this effect.

2.5 Disease outcomes for adults

2.5.1 Chronic obstructive pulmonary disease (COPD)

Chronic obstructive pulmonary disease (COPD) was the sixth leading cause of chronic morbidity and mortality worldwide in 1990 and is projected to rank third in 2020 *(110)*. The GBD 2010 study estimated COPD to be responsible for 2.9 million deaths in 2010, ranked 3rd globally in terms of numbers of deaths *(78)*. While cigarette smoking is the leading preventable cause of COPD in the developed world, household air pollution (HAP) from inefficient burning of solid fuels may be the leading preventable cause among women in developing countries *(111)*. This assessment of risk of adult COPD from exposure to HAP is based on several sources of evidence, (i) a systematic review and meta-analysis conducted by Stern-Nezer for the CRA expert group in 2010 *(112)*, summarized in Box 2.7 and (ii) three additional and independent systematic reviews and meta-analyses, published in 2010. The former review is used as the primary source here, as the methods are more comparable with those used for other health outcomes.

CRA Expert group systematic review

The overall disease category of COPD included either COPD – physician diagnosis or fixed obstruction by spirometric criteria, FEV1/FVC<70% or FEV1<70% predicted – or chronic bronchitis (CB), defined as cough productive of phlegm for ≥3 months per year for two consecutive years. Studies including asthma in their outcome definition were excluded. As COPD is a chronic disease, only studies presenting separate data on adult populations (defined as ≥15 years of age) were included. From 4027 search results published to January 2009, 24 studies (26 estimates) were included in the final analysis. All but seven included in the meta-analysis were cross-sectional in design.

Box 2.7: Key search features for review of solid fuel and COPD (Stern-Nezer 2010)

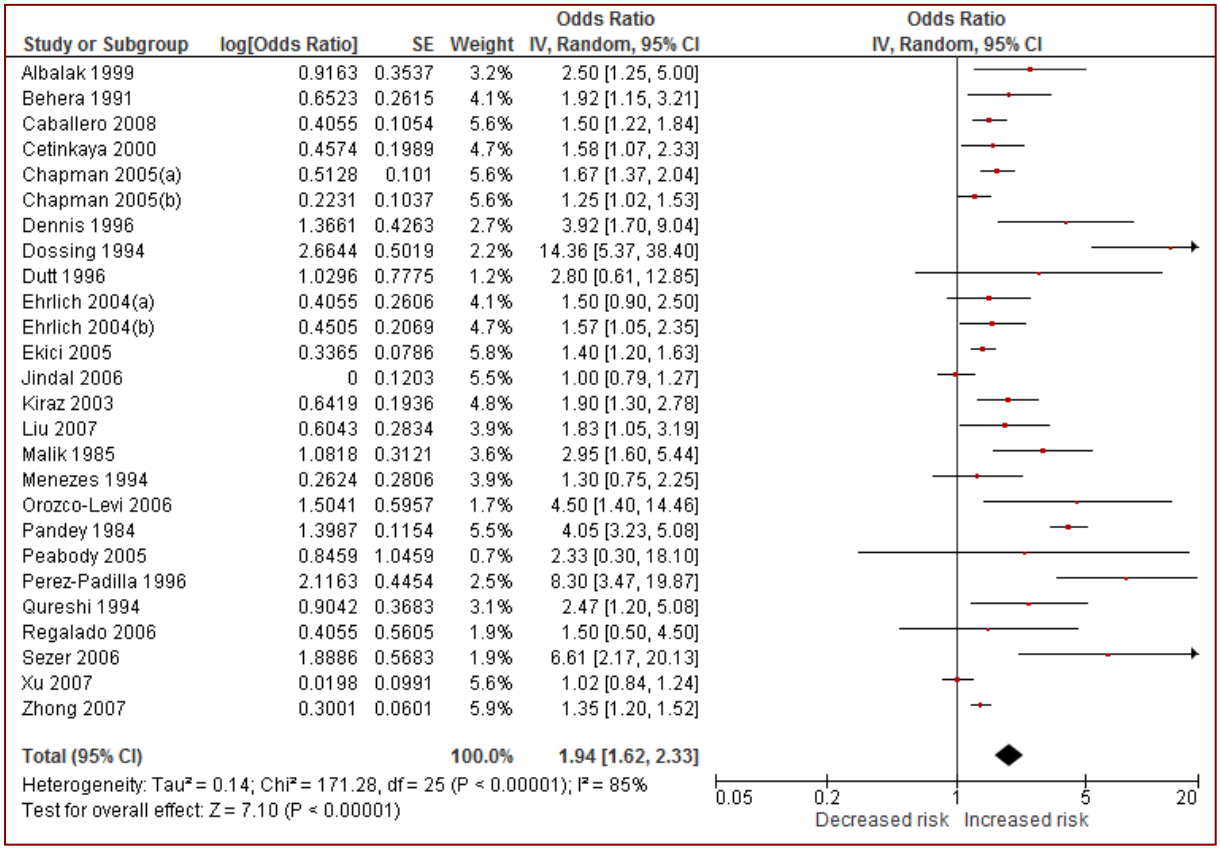
- Search period: to 2010
- Search hits: 4027
- Inclusion: all designs of adults (≥ 15 years) that included measures of (i) HAP and (ii) COPD defined by physician diagnosis and/or spirometry, or chronic bronchitis based on symptoms (productive cough ≥3 months per year for 2 consecutive years.
- Exclusion: asthma in outcome definition
- Eligible studies: 24 (26 independent estimates)
- Languages: English only

One study was a retrospective cohort *(113)* and six were case-control *(114-119)*. Two RCTs have been conducted on the impact of an improved (chimney) wood stove on adult respiratory symptoms and lung function, one carried out in Mexico *(76)*, the other in Guatemala as part of the RESPIRE trial *(120)*. Neither was not eligible as the outcomes studied did not meet the criteria for definitions of CB or COPD. These studies are described further below.

Case-control studies recruited controls from various sources, including visitors to the hospital, patients from other hospital services without presence of pulmonary disease, and population-based selection. Widely differing measures of exposure were used in these studies, including: rural-urban comparisons (where data supported the use of place of residence as a proxy for fuel use); outdoor versus indoor cooking; fuel type for cooking and/or heating; stove type, and; duration of exposure to biomass fuel combustion.

There was significant heterogeneity (I^2 = 85%, p<0.001), and in random effects meta-analysis the pooled OR was 1.94 (1.62, 2.33), see Figure 2.10. There was quite strong evidence of publication bias, with both Egger's (p=0.007) and Begg's (p=0.002) tests being significant.

Figure 2.9: Forest plot for 24 studies (26 estimates) of solid fuel use for cooking and COPD



(a) = Male; (b) = Female

Source: Stern-Nezer, 2010 *(112)* Reproduced with permission

Sensitivity analysis that stratified risk by study design showed that the summary OR (95% CI) was stronger for the six case-control studies, 4.74 (1.60-14.00), than for the 18 cross-sectional studies, 1.98 (1.57-2.50). Analysis of only studies adjusting for smoking yielded a smaller association between exposure and outcome, OR (95% CI), 1.90 (1.56-2.32). The summary OR (95% CI) decreased further when only studies adjusting for both age and smoking were included, but remained statistically significant, 1.54 (1.33, 1,78). Of those studies including men and women, the majority adjusted for gender in the final analysis or presented data for men and women separately.

Sub-analysis by gender revealed a stronger association between HAP and COPD in women, OR (95% CI), 2.30 (1.73, 3.06). The association remained significant in women even after

excluding studies that did not adjusting for both age and smoking, OR=1.79 (1.36, 2.37), probably reflecting the fact that in many studies, women had a negligible or zero prevalence of smoking. In male populations, the association was significant when all studies were included [1.90 (1.15-3.13)], but became non-significant when studies not adjusting for age and smoking were excluded from the analysis, with an OR of 1.26 (0.76, 2.06).

Coal combustion produces a somewhat different profile of emissions than other biomass fuels, and it has been suggested that wood is more strongly associated with COPD than other biomass fuels. Peabody et al. *(121)* found a statistically significant difference in the risk for COPD between coal and wood users, with coal being "protective" relative to wood use. Studies of COPD risk that compared biomass fuel to a cleaner fuel had a summary OR (95% CI) of 2.10 (1.66-2.67). Analysis stratified by fuel type did show that wood [2.39 (1.18-4.85)] was more strongly associated with COPD than coal [1.45 (1.25-1.69)], but there was more heterogeneity between studies in the wood group. Pathogenesis of COPD is likely related to personal exposure to HAP over a lifetime. Nine studies included analysis of length of time exposed, and numerous studies showed a significant trend of exposure duration and increased disease risk, although not all adjusted for age and/or smoking. Specific measures of time varied considerably among studies, and data were not reported in a manner permitting calculation of a standardized exposure length. Given the importance of duration of exposure in disease pathogenesis, a sub-analysis of these studies was performed, comparing highest time exposure categories to lowest. This analysis yielded a stronger summary OR (95% CI), 6.91 (3.64-13.12), than when all studies were included. The association was largely unchanged in magnitude when only studies adjusting for smoking status were included, 6.48, (3.30-12.74). When the studies were stratified by type of outcome, COPD and CB, there was little difference in the strength of the association. For the seven studies that used COPD as the outcome (three used physician diagnosis and four used spirometric criteria), the OR was 2.34 (1.57-3.49). For the 12 studies that used CB, the summary OR (95% CI) was 2.40 (1.59-3.64).

The RCT conducted in rural Mexico involved 668 households randomized to use an improved stove (Patsari) or continue with the traditional open fire *(76)*. A total of 552 women (mean age approximately 26 years) were followed up monthly for 10 months, with data on symptoms and stove use collected by questionnaire. Spirometry was conducted at baseline and during follow-up visits, with an average of 3.6 observations per woman. Results showed that around 30% of the women in the intervention group mainly used the Patsari for one of the major cooking tasks (preparing tortillas), with 50% using mainly the open fire and the remainder a more even mix. This categorization of actual use for tortilla making was used as the basis for the main results reported. Adjusted analysis of respiratory symptoms among mainly Patsari users compared to mainly open fire users found ORs of 0.29 (95% CI: 0.11, 0.77) for wheezing and 0.77 (0.62, 0.95) for cough. A similar analysis of lung function, excluding women under 20 years (age at which lung function began to decline), found among the remaining 426 subjects that there was an adjusted 31 (7, 55) ml lesser decline in FEV_1 in Patsari users compared to open fire users over 1 year of follow-up. No effect of the Patsari stove on lung function was seen in intention-to-treat analysis.

The second RCT involved 504 women in rural Guatemala aged 15–50 years, randomized to use an improved chimney stove (plancha) or continue using the traditional open fire *(120)*. Follow-up assessment were made every 6 monthly up to 18 months and included recall of respiratory symptoms and measurement of lung function. Adherence to allocated stoves was good and analysis conducted by intention-to-treat. In the intervention group, CO exposure was significantly reduced by 61.6%; this was associated with reductions in risk of all symptoms, but statistically significant only for wheeze, with an RR of 0.42 (95% CI: 0.25, 0.70). The number of respiratory symptoms was also significantly reduced in the intervention group, OR = 0.7 (0.50, 0.97). No significant effects on lung function were found after 12–18

months, and it was concluded that a longer period of follow-up would be required to detect any impact of the intervention on lung function.

Three other recently published systematic reviews and meta-analyses reported similar summary estimates for the effect of HAP on risk of COPD. Kurmi et al. *(122)* reported a summary OR (95% CI) for the use of solid fuels and COPD from 23 studies of 2.80 (1.85-4.0) and for HAP and CB of 2.32 (1.92-2.80). Pooled estimates for different types of fuel showed that exposure to wood smoke carried a greater risk than coal. Hu et al. *(123)* reported a summary OR (95% CI) from 15 studies of 2.44 (1.9-3.33) for the risk of developing COPD with HAP exposure. Po et al. *(89)* included data from 12 studies of female populations and reported a summary OR (95% CI) for CB of 2.52 (1.88-3.38) and for COPD of 2.40 (1.47-3.93).

These three reviews also provide some further analysis of several important aspects of the CRA review reported above, namely adjustment for confounding, explaining heterogeneity and publication bias. None of the reviews explicitly report how well studies were adjusted, although one eligibility criterion for Kurmi et al. *(122)* was that adjustment for confounding by smoking was addressed. Hu et al. *(123)* reported meta-analysis stratified by smoking status, with ORs of 4.39 (3.38, 5.70) for three studies of smokers, and 2.55 (2.06, 3.25) for seven studies of non-smokers; this latter value was somewhat higher than that reported by Stern-Nezer for non-smokers of 1.45 (1.12, 1.88), although these two non-smoker estimates were obtained by fixed and random effects, respectively. Using meta-regression, Po et al. *(89)* found no effect of smoking for studies of COPD, but a higher OR of 2.89 (2.07, 4.04) among smokers than the estimate of 1.50 (0.89, 2.54) among non-smokers. Adjustment for, and any effect of, age, appeared to receive no comment in the three reviews.

There were somewhat inconsistent findings regarding publication bias. Hu et al. found a significant Egger's test value (p=0.025) overall, this was non-significant for the eleven studies of women *(123)*. Kurmi reported a non-significant Egger's test for all studies, but a value of p=0.021 for studies of COPD diagnosed by spirometry, and furthermore this effect became non-significant on removing three studies conducted prior to 2000 *(122)*. Finally, Po et al. present an Egger's test value for all studies of p=0.014, but this includes ARI in children and asthma in children and women, and no sub-analysis is provided; visual inspection of the funnel plot does suggest the presence of publication bias for CB and COPD *(89)*. Among other factors which should also be taken into consideration in the interpretation of these review results, Kurmi et al. *(122)* note the lack of direct exposure assessment and consequent risk of exposure misclassification), and the issue of possible earlier lifetime exposure to biomass in 'clean fuel' users where current use only has been assessed; both of these effects could result in bias of risk estimates towards the null.

Overall Assessment of evidence

The set of observational studies suffer various limitations, and sensitivity analysis found that exclusion of studies not adjusting for smoking and age reduced the odds ratios, especially for men. There was also strong evidence of publication bias. Countering this, indirect (proxy) exposure assessment will have led to exposure misclassification. The three other reviews express concern about publication bias, although findings are mixed and interpretation somewhat inconclusive; higher risks are reported among smokers and one review *(122)* claims to have only included studies with adequate adjustment for smoking; age adjustment does not appear to be addressed by any of the reviews. Despite these uncertainties, reference to the Bradford-Hill viewpoints supports a good case for the relationship between HAP and COPD being causal, with evidence clearest for women, Table 2.7.

Table 2.7: Evaluation of Bradford-Hill viewpoints for effect of HAP exposure on COPD

Viewpoint		Explanation
1	Strength of association	Meta-analysis of a moderately substantial number of studies finds ORs of almost 2.0 overall, and more than 2.0 for women. When restricted to studies with more complete adjustment, however, the OR was around 1.5
2	Consistency across populations, study designs	Although heterogeneity was substantial, the great majority of studies reported increased risk estimates, not all of which were significant. There was strong evidence of publication bias, however.
3	Specificity	As noted for child ALRI (Table 2.2), HAP exposure is linked to a wide range of outcomes
4	Temporality (exposure precedes outcome)	Although most studies were cross-sectional, subject exposed at the time of data collection would almost certainly have been exposed in the past for many years.
5	Biological gradient (dose-response)	Numerous studies report significant relationships between duration of exposure and risk, although not all were adjusted.
6	Biological plausibility	[Brief summary of main findings from mechanistic studies in preparation]
7	Coherence with natural history, animal studies	Prevalence of child mortality is consistent with patterns of solid fuel use; animal evidence relating to specific causes would apply.
8	Experiment	Two RCTs have been conducted, both of which found an impact on respiratory symptoms (but not including chronic CB symptoms), and one on the rate of decline in FEV1 (but not in intention-to-treat analysis). A cohort study in China found large effects of an improved chimney stove after 10 years use (exposure not measured) on COPD in men and women.
9	Analogy	Evidence from other combustion sources, including active and second-hand smoking, and ambient air pollution, is supportive.

The GEPHI assessment (Annex Table A1.6) downgraded these observational studies for risk of bias, inconsistency and publication bias, upgraded for large effect (for women), so the initial assessment was VERY LOW. The additional criteria of strong analogous evidence and the findings of increased risk in most studies with widely differing settings, methods and designs resulted in a final assessment of LOW. The intervention effect estimate for women is 0.43 (0.33, 0.58) and for men 0.53 (0.32, 0.87), but given the uncertainties concerning confounding, publication bias and exposure assessment, further research may well alter these effect sizes.

2.5.2 Lung cancer with exposure to coal

The two main solid fuels used for cooking, biomass and coal, may have different cancer risks due to the specific chemicals found in their combustion emissions. Separate reviews have therefore been conducted for coal and biomass.

Household use of coal for cooking and heating has previously been reported by IARC to be carcinogenic to humans (Group 1) *(124)*. Two reviews have been conducted since, one by Hosgood et al. used as the basis for the GBD 2010 CRA update, Box 2.8 *(125)*, and one by Kurmi et al. *(126)*. The former review is used as the primary source here, as the methods are more comparable with those used for other

Box 2.8: Key search features for lung cancer with exposure to coal (Hosgood 2011)

- Search period: To 2009
- Search hits: 10,369
- Inclusion: (i) case-control designs (ii) primary use of coal as household fuel for cooking and/or heating (iii) provided adjusted OR and 95% CI (iv) differentiated coal and biomass use.
- Eligible studies: 25 (providing 25 independent estimates)
- Languages: English and Chinese

health outcomes. Searches of the English and Chinese databases yielded 25 case-control studies (16 in English and 9 in Chinese) met the inclusion criteria for meta-analysis.

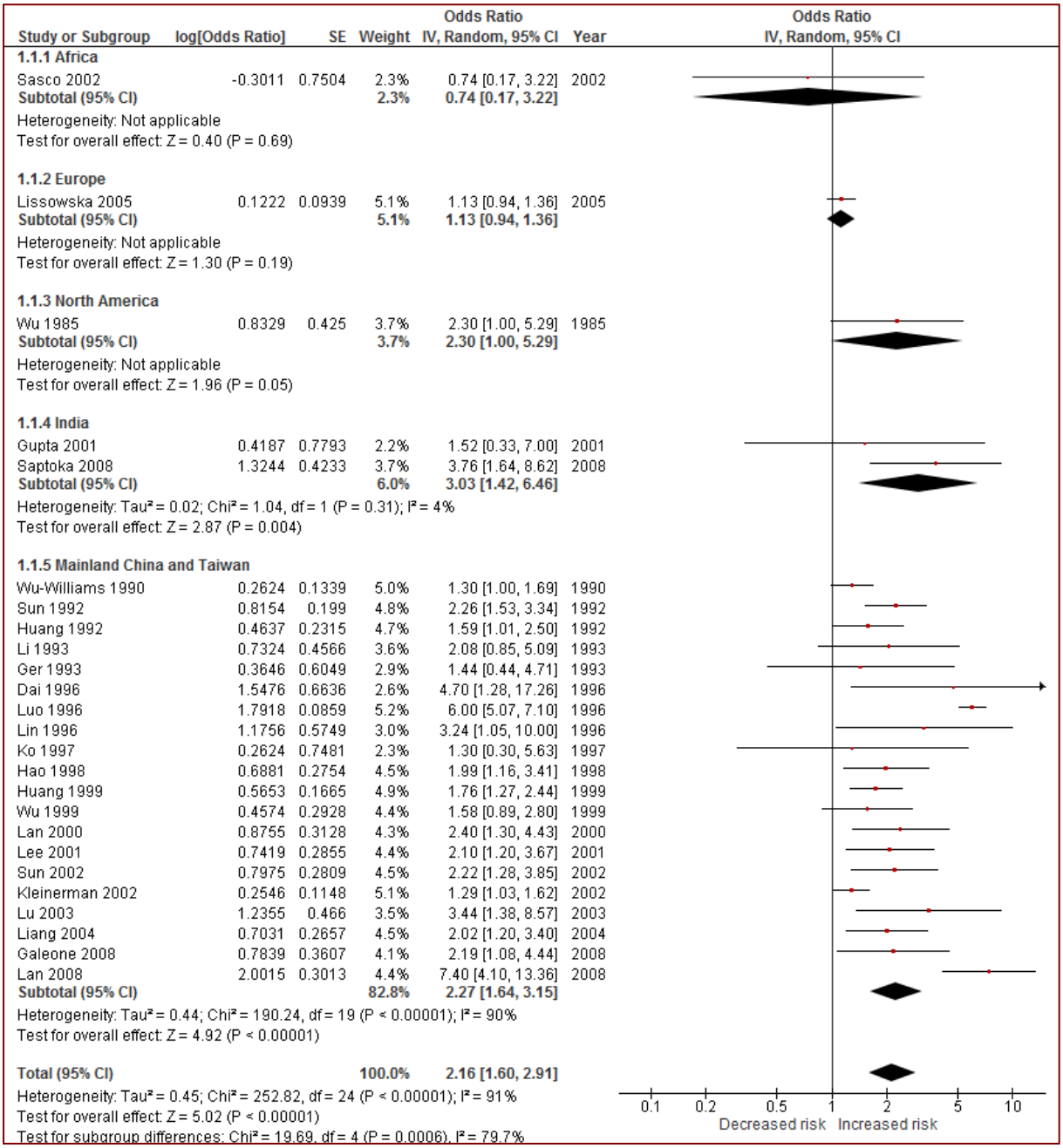
Exposure was assessed by questionnaire, and based on type of fuel used in the home (coal vs. alternatives, and this was not always a clean fuel), or reported amount or duration of coal use. For the latter studies, multiple risk estimates were extracted according to higher and lower exposure. For each study, the point estimate of the coal use effect for the highest exposure category was selected for use in the main pooled analysis, but sensitivity analysis was also performed using the lowest exposure category point estimates. The lung cancer outcome was defined by histology for the majority of cases, otherwise by physician diagnosis with X-ray. Only studies with adjusted ORs were included; adjustment was carried out for smoking, age, and socioeconomic status, among others.

The 25 studies contributed a total of 23,558 cases and controls. Only five studies evaluated the association between lung cancer and household coal use outside of mainland China and Taiwan. Household coal use for cooking and heating was associated with an increased risk of lung cancer when evaluating all studies, OR=2.15 (1.61, 2.89), see Figure 2.11. Sensitivity analysis using the lowest exposure category point estimates for studies when results for multiple exposure categories were available, found similar results with an OR = 2.14 (1.59 – 2.87), N = 25 studies. No significant publication bias was found among all studies (Begg's p= 0.15). Seven studies provided cooking-specific estimates, with the remaining studies provided only heating-specific estimates or did not differentiate between coal use for heating or cooking. Household coal use for cooking was associated with an increased risk, OR=1.81 (1.19, 2.76), and when restricted to four studies conducted in mainland China and Taiwan, OR 2.07 (1.40-3.05). For two studies where the unexposed group used clean fuels, the OR for cooking-specific coal use was 1.98 (1.16-3.36).

Three studies reported estimates for men, with a pooled OR of 2.76 (1.44, 5.27), and 8 studies reported estimates for women with a pooled OR of 2.50 (1.56, 4.00). Since both of these estimates are higher than the overall pooled value, and that for men higher than for women, they may not be reliable. For cooking only, analysis focused on studies carried out in mainland China and Taiwan since homes in these countries typically use (or have used) coal for cooking more consistently throughout their lifetimes than other parts of the world. Only two studies in this subgroup compared coal to clean fuel and were restricted to women; the pooled OR was 1.98 (1.16, 3.36). No studies provided estimates for men in mainland China.

Further sensitivity analysis found higher effects in rural vs. urban areas, and in south and south-west China. No important difference was seen in comparing English and Chinese language papers. Population-based studies (n=13) had an OR of 2.57 (1.64, 4.03) while hospital based studies (n=6) had a lower OR of 1.75 (1.47, 2.09); the remaining studies had mixed designs.

Figure 2.10: Summary risk estimates for lung cancer risk associated with household coal use for heating and cooking, overall and by geographic region.



Based on Hosgood 2011*(125)* Reproduced with permission

Not included in this review was a cohort study carried out in Xuanwei by Lan et al. *(127)*. This reported ORs for long-term users of improved coal stokes (with chimneys) compared to those using traditional stoves of 0.59 (0.49 to 0.71) for men and 0.54 (0.44 to 0.65) for women, equivalent (when inverted for higher vs. lower exposure) to 1.69 and 1.85, respectively. Although users of both improved and traditional stoves used coal, these findings are consistent with the pooled results for case-control studies.

The second review, by Kurmi et al., had some aspects in common and some differences. Eligible studies included coal use for cooking and/or heating, provided adjusted ORs, and were in English and Chinese. In contrast to the review by Hosgood, all study designs were included, and both coal and biomass use were studied (separately and combined). The

review pooled a total of 22 studies, with 28 independent estimates reflecting separate findings by sex, and by histological type. Publication bias was detected (Egger's test p=0.016), but this became non-significant when two high outliers were excluded; the estimates reported by Kurmi for these two 'outlier' studies appear to be considerably higher than those reported by Hosgood for the same studies. The pooled OR for all studies (including the two high outliers) was 1.82 (1.60, 2.06), with results of 1.54 (1.25, 1.88) and 1.70 (1.40, 2.06) for men (3 studies) and women (10 studies) respectively. Other sensitivity analyses examined histological type (but for the majority of studies this was not specified), and a number of design and analytic features, but these did not yield any very striking findings.

Discussion

The studies of household coal use and lung cancer are also characterized by variations in the method and quality of exposure assessment, and none were quantified in terms of pollutant levels. The long latent period and need to capture lifelong exposure, however, does present challenges for exposure assessment. Furthermore, few explicitly compared coal use to clean fuel. Exposure misclassification can be expected to have occurred commonly throughout this body of evidence, and would tend to bias effect estimates towards the null. One strength of the review is that all estimates were adjusted, and sensitivity analysis did not find strong evidence of bias related to study design issues, although population-based studies somewhat unusually had higher estimates than hospital-based. The second review incorporated all study designs, and reported a similar overall estimate.

Overall assessment of evidence for lung cancer with coal exposure

The designation by the International Agency for Research on Cancer (IARC) of household coal use as a Group 1 carcinogen allows causality to be assumed, but does not provide an estimate of the expected risk reduction with interventions. GEPHI downgraded the studies for inconsistency (which is apparent even within the Mainland China and Taiwan group), but upgraded for large effect, resulting in an initial assessment of LOW, Annex Table A1.7. For the additional criteria, consistency across studies of differing designs and settings is not used as there is evidence that risk levels do vary by geography (which may be due to coal type, as well as how it is used and ultimately exposure levels), but there is strong analogous evidence from other uses of coal; the final assessment was MODERATE, with an intervention effect of 0.46 (0.35, 0.62). Reliable, separate estimates for men and women are not available at this time, but it is expected that risk for men will generally be lower than for women as a consequence of lower long-term exposure.

2.5.3 Lung cancer with exposure to biomass

While household use of coal for cooking and heating is recognized by IARC as a Group 1 carcinogen, use of biomass was reported to be probably carcinogenic (Group 2A), primarily due to weaker human epidemiology evidence *(124, 128)*. The question of whether biomass fuel use is causing lung cancer is an important one to revisit, since the great majority of the 2.8 billion solid fuel users globally are exposed to biomass rather than coal smoke. A systematic review to update the epidemiological evidence was carried out for the GBD 2010 CRA, Box 2.9, and serves as the main source for this section as methods are most comparable to other outcomes, but reference is also made to a second systematic review published by Kurmi

Box 2.9: Key search features for lung cancer with exposure to biomass

- Search period: to 2012
- Search hits: 19,833
- Inclusion: (i) all designs (ii) primary use of biomass (see main text) as household fuel for cooking and/or heating (iii) differentiated coal and biomass use (iv) case definition by histology or diagnosis with X-ray.
- Eligible studies: 14 (providing 25 independent estimates)
- Languages: English, Spanish and Chinese

et al. in 2012 *(126)*.

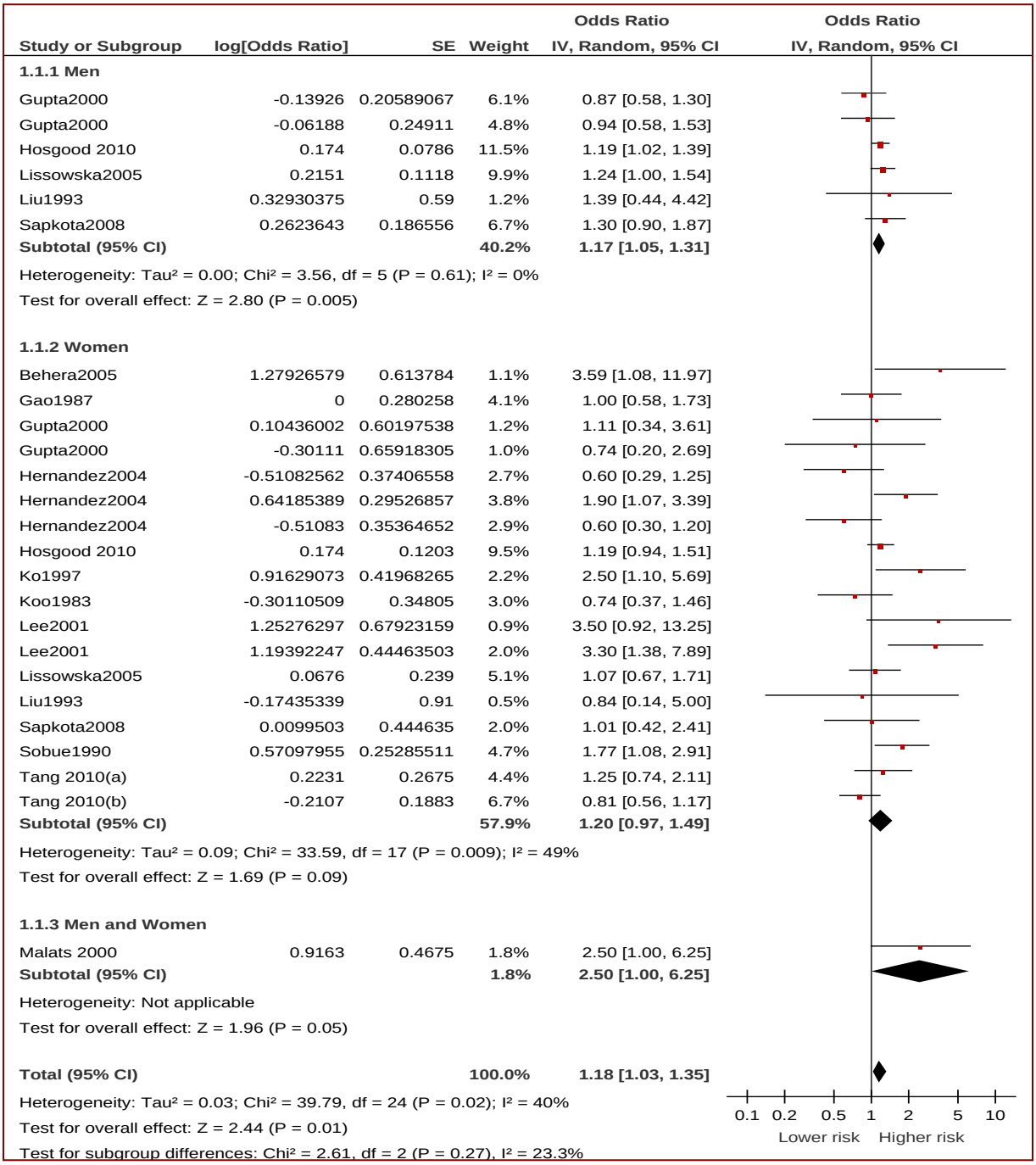
A search of English and Spanish language databases returned 19,833 results; a parallel search of the Chinese database did not identify additional studies. A total of 14 studies provided 25 independent estimates, most of the latter being for varying durations of biomass fuel use.

All studies were case-control designs, and the majority were conducted in Asia; three in India, *(129-131)* five in China, Hong Kong or Taiwan *(132-136)* one among Chinese women but conducted in Singapore *(137)*, and one in Japan *(138)*. Elsewhere, one study combined results from seven European countries *(139)*; one pooled seven studies carried out in Europe (1), USA (2), Canada (1), Singapore (1) and China (2), *(140)*; one other combined data from six European countries and Brazil *(141)*, and finally one was conducted in Mexico *(142)*. The published report of the European study *(139)* did not provide separate male and female estimates for use of biomass for cooking, so further analysis was undertaken by IARC for the purposes of this review (IARC, personal communication).

Biomass fuel was defined as including; wood, straw, grass, crop waste or residue, animal dung and charcoal, and only household use of biomass fuel was considered, whether for cooking or heating. Exposure assessment used questionnaire-based information on fuel type, along with duration and period of life for which it was used in some. No direct measurement of pollutants was made in any of the studies, and in seven of the studies there was either no clear description of the fuel used in the 'unexposed' groups, or the comparison was not with a clean fuel *(132-133)*, *(130, 135, 137-138, 142)*. At least one of the studies with a non-solid fuel comparison group included kerosene, which may increase risk of lung cancer [see Section 4.1 on kerosene] *(131)*. Confirmation of lung cancer was determined by histology in the majority of studies, while in some a proportion was based on clinical diagnosis. All but two studies *(133, 135)* carried out adjustment for major confounders and five provided analysis for non-smokers.

There was moderate heterogeneity for all 14 studies (I^2 = 40%, p=0.02), and the pooled odds ratio (random effects), treating multiple exposure duration estimates separately for those studies which reported these, was 1.18 (1.03, 1.35), see Figure 2.12. For men (5 studies, 6 estimates) however, heterogeneity was absent, and the pooled OR (fixed effects) was 1.17 (1.05, 1.31), while for women the 13 studies (18 estimates) showed more heterogeneity (49%) and the OR (random effects) was 1.20 (0.97, 1.49). One study only provided a combined estimate for men and women of 2.50 (1.0, 6.25). There was no evidence of publication bias, either overall (Begg's p=0.48; Egger's p=0.61), or for men or women separately.

Figure 2.11: Forest plots of 14 studies (25 estimates) of biomass and lung cancer, stratified by sex.



Given the very different levels of heterogeneity between studies for men and women, and the expectation that exposures will differ by sex, further analysis considered men and women separately, although this resulted in exclusion of the study by Malats et al. *(141)*. For this further analysis, multiple estimates from studies were combined using fixed effect analysis, although the effect of using only the longest duration exposure estimate was also studied (see below).

The OR for the five studies of men with the two estimates from Gupta et al. combined was unchanged at 1.17 (1.05, 1.31) p=0.005, and since there were few studies and no statistical heterogeneity, sensitivity analysis was only carried out to assess the effect of excluding

studies with weak adjustment and/or comparison with a group not using clean fuel. This left three studies, with a fixed effect OR of 1.22 (1.08, 1.37) p=0.001, I^2=0%. For women, the overall pooled OR remained marginally non-significant (using the combined intra-study estimates) at 1.21 (0.99, 1.49) p=0.06. Given the larger number of studies and importance of exposure among women, detailed sensitivity analysis was conducted, Table 2.7.

Table 2.6: **Summary of female (only) sensitivity analyses: pooling carried out with random effects unless specified (FE)**

Group	Sub-group	Number of studies	Heterogeneity (I^2; p-value)	OR (95% CI) FE=Fixed Effects	p-value
All		13	46% (p=0.03)	1.21 (0.99, 1.49)	0.06
Clean fuel comparison	All	6	60% (p=0.03)	**1.58 (1.08, 2.32)**	**0.02**
Design	Hospital	9	59% (p=0.01)	1.37 (1.00, 1.86)	0.05
	Population	2	0 %	0.89 (0.58, 1.37) (FE)	0.59
	Mixed	2	0%	1.16 (0.94, 1.44) (FE)	0.16
Strong or moderate adjustment	All	11	51% (p=0.02)	**1.26 (1.02, 1.56)**	**0.03**
	Clean fuel comparison	6	60% (p=0.03)	**1.58 (1.08, 2.32)**	**0.02**
	Excluding kerosene[2]	5	67% (p=0.02)	**1.71 (1.11, 2.64)**	**0.02**
Asia + Mexico	All	10	57% (p=0.01)	1.31 (0.96, 1.78)	0.09
	Clean fuel comparison	4	40% (p=0.17)	**2.19 (1.28, 3.76)**	**0.004**
Europe & North America	All (all clean fuel)	2	0%	1.16 (0.94, 1.44) (FE)	0.16
Highest exposure category	All	7	39% (p=0.13)	**1.67 (1.20, 2.31)**	**0.002**
	Clean fuel comparison[3]	4	66% (p=0.03)	**1.70 (0.92, 3.12)**	0.09
Non-smokers only[1]	All	4	70% (p=0.02)	1.24 (0.82, 1.88)	0.32
	Clean fuel	1	N/A	**2.08 (1.06, 4.07)**	**0.03**

[1]All results in this sensitivity analysis are women only, who can be expected to smoke less than men
[2]Exclusion of one study with kerosene in the clean fuel group
[3]All four studies in this group also had strong (1) or moderate (3) adjustment.

Sensitivity analysis for studies of women

Clean fuel comparison: a major limitation of this set of studies is that more than half do not compare biomass with a clean fuel, or do not describe the comparison clearly enough to confirm this. Exclusion of these studies resulted in a set of six with a higher OR of 1.58 (1.08, 2.32).

Study design: Nine out of 13 studies were hospital based, and these had a slightly larger OR of 1.37 (1.00, 1.86) compared to the two groups of population and mixed designs, although these had only two studies per group.

Adjustment for confounding: Eleven of the 13 studies had strong (5) or moderate (8) adjustment, and this set of studies had a significant OR of 1.26 (1.02, 1.56), although still with substantial heterogeneity of 51% (p=0.02). This effect was increased when also restricted to clean fuel comparisons, the remaining six studies having an OR of 1.58 (1.08, 2.32). This may represent the single best estimate of risk for women, although heterogeneity is still marked at 60% (p=0.03). Exclusion of the study with kerosene in the clean fuel group increased the estimate still further to 1.71 (1.11, 2.64), a finding which would be consistent with kerosene use increasing the risk of lung cancer.

Geographical analysis: This is important as exposure in developing countries is mostly related to open fire/stove use, whereas in Europe and North America exposure is more likely to be from enclosed stoves with chimneys and at lower levels. For Asia and Mexico (the latter included here as wood use more similar to developing country settings), the OR was 1.31 (0.96, 1.78) but when only clean fuel comparison studies were included this increased further to 2.19 (1.28, 3.76). As expected, the two studies from Europe and North America (albeit pooling a total of 11 country studies) had a lower OR of 1.16 (0.94, 1.44) and both used clean fuel comparisons.

Duration of use: Eight out of 13 assessed duration of exposure and these studies had an OR of 1.34 (1.04, 1.74), increased to 1.51 (1.10, 2.07) when restricted to those with a clean fuel comparison.

Smoking: A number of studies have reported a smaller or even no effect for non-smokers, and one has suggested that smoking interacts with wood smoke to increase risk of lung cancer *(137)*. Among this set of studies, four provided estimates for non-smoking women with a non-significant OR of 1.24 (0.82, 1.88); two of the studies however had significantly elevated risks. Only one had a clean fuel comparison and an OR of 2.08 (1.06, 4.07). The study by Hosgood et al. also report a separate estimate for non-smoking western women using biomass of 1.15 (0.81, 1.64)*(140)* (not included in pooled results as the equivalent result for smoking women not provided separately). One other case-control study using data from seven countries (6 in Europe, plus Brazil), involved both sexes but mainly women, reported an adjusted OR of 2.50 (1.0, 6.2) for cooking or heating with wood among non-smokers *(141)*. Together these results suggest wood smoke does increase risk of lung cancer independent of smoking, but an interaction is also possible.

Exposure-response

Five of the 13 studies which examined the effect of cooking with biomass on lung cancer risk included information on duration of exposure, but only one demonstrated a statistically significant dose-response effect for men, *(140)* and none has done so for women. Re-analysis by IARC of data from the European study by Lissowska et al. for duration of biomass use for heating or cooking found a significant trend for men (trend p = < 0.01), with ORs of 1.06 (<25% lifetime exposed); OR 1.13 (25 -50% lifetime exposed); and OR 1.37 (1.03-1.81) for >50% lifetime exposed; this analysis for non-significant for women.

Discussion

This review, building on the IARC monograph review, has found a significantly elevated risk for lung cancer with exposure to biomass in men, based mainly on studies from Europe and North America showing little heterogeneity (including in Lissowska et al. *(139)* when analysed by duration of fuel use across seven European countries, p=0.25), and with a significant exposure-response relationship in re-analysis of one study (IARC, personal communication). The most reliable estimate is expected to be the OR of 1.22 (1.08, 1.37), p=0.001 from well-adjusted studies with clean fuel comparisons, although exposures in the studies are expected to be lower than would be experienced by men in developing countries where open fires are used.

The studies of women are characterized by a great deal of heterogeneity, even among sub-analyses of better quality studies, and no significant exposure-response relationship has been reported to date. The most reliable estimate is expected to be the OR of 1.58 (1.08, 2.32), p=0.001 from the six well-adjusted studies with clean fuel comparisons, but with this group there was still a high level of heterogeneity (I^2=60%). The reason for this heterogeneity compared to men is unexplained, but may arise from the greater focus on non-western settings, and more variability in the extent to which women with lung cancer seek and obtain a diagnosis and care. Future studies should pay particular attention to this issue.

The second systematic review by Kurmi et al. reported seven studies (9 estimates), included all designs, biomass use of cooking and/or heating, and only used adjusted estimates *(126)*. The overall pooled OR was somewhat higher than for the CRA review at 1.50 (1.17, 1.94), with I^2 of 41.2% (p=0.092); Eggar's test for publication bias was non-significant. The results for men were 1.78 (0.46, 6.93) and for women 1.98 (1.44, 2.71). Extensive sensitivity analyses were conducted including for histological type (on two studies provided data), studies that adjusted for smoking for which the OR was 1.36 (0.99, 1.86), and those with a higher quality score for which the OR was 1.42 (1.04, 1.94). The findings for studies with better adjustment and quality are consistent with similar restricted (sensitivity) analysis in the CRA review.

Overall assessment of evidence for Lung cancer with biomass fuel

The main reason for IARC concluding that household use of biomass was a probable rather than definite carcinogen was limitations of the epidemiological evidence. Since that review was undertaken, some new evidence has become available, strengthening the consistency of findings, and providing exposure-response evidence at least for men. If this evidence supports causality for men, it would be expected that exposure would also be causal for women, and generally this review has found that women do have a higher risk estimate consistent with what is known about sex differences in exposure to wood smoke. No intervention-based evidence is available. Formal confirmation of carcinogenicity will need to await a further assessment by IARC, but drawing on the Bradford-Hill viewpoints as summarized in Table 2.8, there does appear to be a stronger case for causality.

Table 2.7: Evaluation of Bradford-Hill viewpoints for effect of biomass exposure on lung cancer

Viewpoint		Explanation
1	Strength of association	The strength of association overall with clean fuel comparisons is moderate at 1.58 (1.08, 2.32), but in studies from countries where solid fuel exposure is greater (Asia, Mexico), the pooled OR was 2.19 (1.28, 3.76) in comparison with clean fuels.
2	Consistency across populations, study designs	Findings for studies overall are not consistent, with several reporting reduced risk (albeit none statistically significant), but when restricted to clean fuel comparisons with regions of the world where levels of exposure are more comparable, heterogeneity is much reduced.
3	Specificity	As noted for child ALRI (Table 2.2), HAP exposure is linked to a wide range of outcomes
4	Temporality (exposure precedes outcome)	Although studies were retrospective case-control designs, subject exposed at the time of data collection would almost certainly have been exposed in the past for many years, and duration of exposure was assessed in some. Bias is also possible in 'unexposed' groups currently using clean fuel, as they may well have been exposed to biomass fuel in the past.
5	Biological gradient (dose-response)	Reported only from the re-analysis of European data in the Lissowka et al. study, and only statistically significant for men.
6	Biological plausibility	Established by the IARC monograph review
7	Coherence with natural history, animal studies	Geographical variation in lung cancer driven by smoking, and patterns seen for lung cancer with coal use in different regions of China (see Section 2.4.2) are not apparent to date for biomass. Animal evidence established by the IARC monograph review
8	Experiment	None
9	Analogy	Evidence from other combustion sources, including active and second-hand smoking, and ambient air pollution, is supportive.

The GEPHI assessment of potential intervention impacts has been carried out separately for men and women due to the marked differences in sources (geographical) and nature (level of heterogeneity) of the evidence, Annex Table A1.8. Furthermore, to overcome some of the major limitations of the evidence, only the sub-sets of studies with both adequate adjustment and clean fuel comparisons have been used.

For men, three observational studies were included, which were downgraded for risk of bias (due to most of the evidence being from Europe and North America) but could be upgraded for exposure-response relationship, providing an initial grading of LOW. For additional criteria, too few studies were available for consistency across settings, but analogous evidence from smoking was used to further upgrade, resulting in a final assessment of MODERATE. The intervention effect estimate was 0.82 (0.73, 0.93). This may well be reliable for the levels of exposure historically found in Europe and North America, but perhaps not for higher exposures with open wood fires and stoves, and future studies may well result in this estimate needing substantial revision and acknowledgment of geographical variations.

For women, six observational studies were included, downgraded for heterogeneity and not upgraded providing an initial grading of VERY LOW. For additional criteria, although there is consistency across Europe and the rest of North America, the largest group of studies (Asia and Mexico) are not consistent, and for this reason not upgraded. Analogous evidence from smoking did allow upgrading, resulting in a final assessment of low. The intervention effect estimate of 0.63 (0.43, 0.93) was larger than that for men, but given this grading it can be expected that future studies may well revise this.

2.5.4 Cancer of the upper aero-digestive tract (UADT)

A total of 335,000 deaths were reported for cancer of the mouth and oropharynx for 2004; while this cancer is far less common than lung cancer, 180,000 (53.7%) of these deaths occurred in low-income countries *(143)*. Although there is a well-established link between active smoking and UADT tumours, it is not as strong as for lung cancer.

A systematic review of this outcome was carried out for the GBD 2010 CRA, Box 2.10. The search found 13 case-control studies that met inclusion criteria. For the purpose of analysis, tumours of the oropharynx, larynx and hypopharynx (mainly squamous cell carcinomas) were considered separately from nasopharyngeal carcinomas (NPC), which have distinct risk factor profiles.

Box 2.10: Key search features for HAP and cancer of the upper aero-digestive tract (UADT)

- Search period: to March 2010
- Search hits: 11,627
- Inclusion: (i) all study designs, (ii) measure of HAP, (iii) cancer of the nasopharynx, larynx, oropharynx and hypopharynx.
- Eligible studies: 13 studies (9 used in meta-analysis)
- Languages: English, Spanish, Chinese

Nasopharyngeal carcinomas

Nine case-control studies reported examining the relationship between NPC and the use of household solid fuel *(144-152)*. All of the studies were from Asia: 5 from China and one each from India, Hong Kong, Singapore and Malaysia. A total of four studies had insufficient data to include an estimate in a meta-analysis.

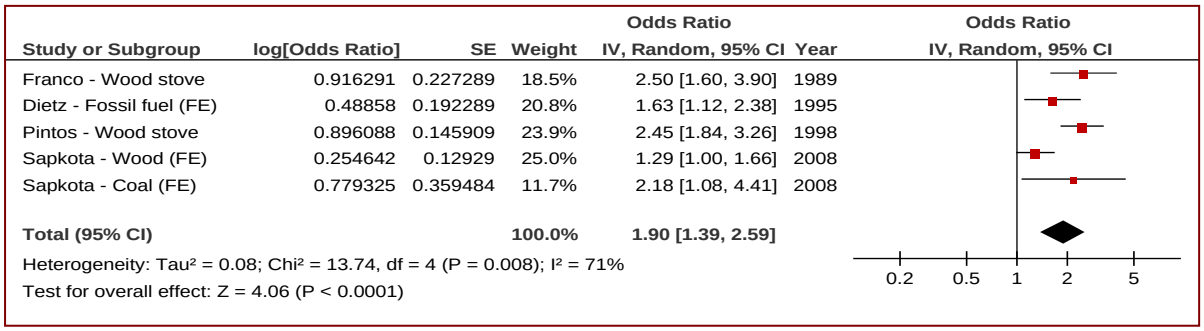
Although the remaining five studies did provide sufficient data for meta-analysis, there was a high level of heterogeneity in the methods of exposure assessment and also statistically (I^2=89%). The pooled effect of these five studies using random effects was non-significant 1.10 [0.98, 1.24]; In addition, study quality was generally weak, with only one study comparing the use of a solid fuel against a clean modern fuel OR 1.60 [0.39, 6.50] *(152)*. However this study did not adjust for basic confounders such as tobacco consumption.

Given the scarcity of studies and the poor design quality of the available studies, it was concluded that there was inadequate evidence at this time of an association between solid fuel use and the risk of nasopharyngeal carcinoma.

Tumours of the larynx, oropharynx and hypopharynx

There were four case-control studies which provided estimates of effect associated with the use of solid fuels with this outcome *(131, 153-155)*. Two of the studies were from Brazil, one from India and one from Germany. All of the studies demonstrated a positive effect associated with use of solid fuels. However there were differences in the method of exposure assessment. Franco (1998) and Pintos (1998) both studied the use of wood stoves in Brazilian populations, while Dietz (1995) studied use of a 'fossil fuel' stove in Heidelberg. However, in this study 'fossil fuel' included; wood, peat, coal, oil and gas which is mixture of both solid and clean fuels, and of fossil and biomass. Sapkota (2008) examined the risk of laryngeal and hypopharyngeal cancer associated with the use of wood or coal as cooking fuel. A random effects model estimated a pooled effect for these four studies of OR 1.90 (1.39 -2.59); I^2 = 78%, see Figure 2.13.

Figure 2.12: **Forest plot of four studies reporting on risk of tumours of the larynx, oropharynx and hypopharynx with exposure to solid fuel in the home.**



However from amongst these four, only Sapkota compared the use of solid fuel with a clean fuel: use of wood for cooking OR 1.29 (1.00 – 1.66) and use of coal for cooking OR 2.18 (1.08 – 4.41). Although the great majority of cases were male, both Pintos and Sapkota provided estimates restricted to females, and the pooled odds ratio for females only was 2.01 (0.8, 5.05). With reference to the Bradford-Hill viewpoints, there are relatively few studies but a moderate strength of effect [OR=1.90 (1.39, 2.59)], biological plausibility *(124)* and analogous evidence from smoking, but no dose-response or experimental evidence. Based on this evidence, it is concluded that HAP from solid fuels may increase the risk of cancer of the oral cavity, pharynx and larynx, but further studies are needed before a more definitive conclusion can be reached.

2.5.5 Cancer of the uterine cervix

The well-established link between smoking and cervical cancer raised the possibility that HAP is also a risk factor, as noted in the IARC Monograph volume 95 *(124)*. The disease burden from cervical cancer in developing countries is high, being the most important cause of death from cancer among women in some developing countries, especially in rural areas. From a total of 268,000 deaths from this cause in 2004, a majority (53%) occurred in low income countries *(143)*. Risk factors include multiple sexual partners and younger age at first intercourse. Human papilloma virus (HPV) is seen as 'necessary' cause, although not all women with chronic HPV-infection develop cervical cancer. In addition to smoking, other causes of cervical cancer include estrogen-progestogen contraceptives and human immunodeficiency virus type 1. A systematic review was carried out for the GBD 2010 CRA, Box 2.11.

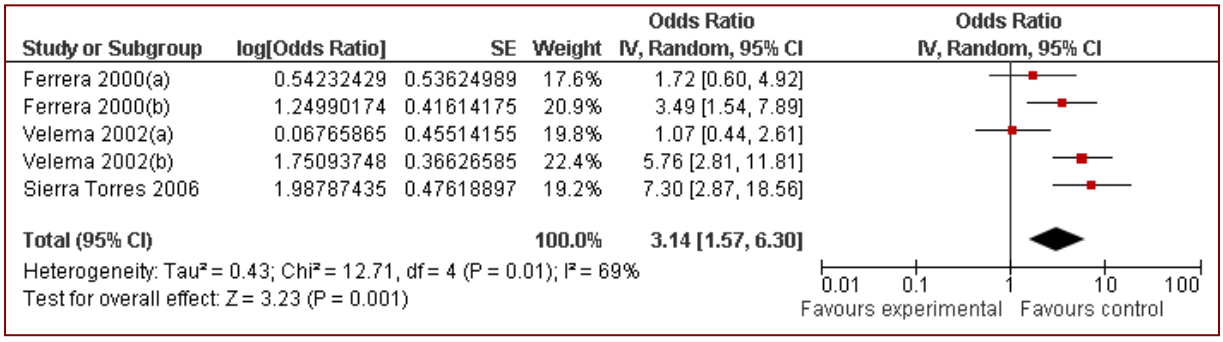
The outcome included cancer of the uterine cervix (CIN I to III; carcinoma in situ; invasive carcinoma), with case definition by histopathology. Three studies met inclusion criteria and provided effect estimates for cervical cancer, but provided a total of 14 estimates through stratification by HPV status and years of exposure *(156-158)*. Two of the studies were carried out in the same centre in Honduras, one of invasive cancer, the other of cervical dysplasia or carcinoma-in-situ (CIS) identified through screening although the case groups for these two studies did not overlap *(156-157)*.

Box 2.11: Key search features for HAP and cancer of the uterine cervix

- Search period: to March 2010
- Search hits: 11,627
- Inclusion: (i) all study designs, (ii) measure of HAP from solid fuels, (iii) outcomes including CIN I-III; carcinoma in situ, invasive cervical cancer.
- Eligible studies: 3 studies; 14 estimates
- Languages: English, Spanish, Chinese

HPV status was assessed in all three studies. Assessment of exposure was weak and poorly described, and was based on reported use of wood in the kitchen or exposure to wood smoke. All three studies showed significantly increased risk of cervical cancer with exposure to wood use or smoke. Following fixed effects pooling of multiple estimates within studies, the overall OR using random effects as I^2 = 69% was 3.14 (1.57, 6.30), see Figure 2.14.

Figure 2.13: **Forest plot of four studies reporting on risk of cervical cancer with exposure to biomass fuel in the home; studies marked (a) are for HPV negative women, those marked (b) are for HPV positive women**.



Two studies provided risk estimates stratified by HPV status, the combined effects being 1.31 (0.66, 2.58) for HPV negative and 4.63 (2.70, 7.93) for HPV positive *(156-157)*.

Significant exposure-response relationships were reported in some analyses in two of these studies, using duration of exposure. The studies have some limitations; all have poor quality exposure assessment (although this would likely have resulted in exposure misclassification with bias towards the null) and the Honduran studies were not adjusted for tobacco smoking. There may also be bias from control selection in two of the studies and the selection method is not well described in one.

With reference to the Bradford-Hill viewpoints, there are relatively few studies but a strong effect [OR=3.14 (1.57, 6.30)] particularly in HPV-positive women, biological plausibility *(124)* dose-response evidence, and analogous evidence from smoking, but no experimental evidence. Given this evidence of strong effect and bearing in mind HAP exposure starts much younger than does active smoking, there is a reasonable case for these findings for solid fuel HAP representing a real effect.

Given the high prevalence of both cancer of the cervix and solid fuel use (HAP exposure) in developing countries, further research should be conducted on the risks to women – many of whom are exposed to solid fuel pollution from a very young age.

2.5.6 Cardiovascular disease (CVD)

Introduction

Cardiovascular disease (CVD) was the highest ranked cause of death globally in 2004 with 17 million deaths *(143)*, and remains the leading cause in 2010 *(78)*. CVD is not restricted to more developed countries: age-standardized mortality rates (ages 30-70) for CVD and diabetes in 2008 were highest in SE Asia (322.4), Eastern Mediterranean (344.5) and Africa (382.3), against a global average rate of 244.7 per 100,000 *(159)*.

Given that smoking (both active and second-hand) is both a form of biomass combustion and strongly linked to CVD, it is surprising that the links between HAP and this disease outcome have not been studied more extensively. Indeed, only two epidemiological studies to date have reported on the risk of CVD outcome events and solid fuel use *(160-161)*, although there is a more extensive literature on risk factors (especially blood pressure) and other markers of disease progression and mechanisms.

This lack of recognition is beginning to change. An issue of Global Heart was devoted to the topic in 2012 *(162)*, bringing together evidence reviewed at a NIH-sponsored workshop in 2011 on health risks of HAP *(163)*. No fully systematic review of this issue is yet available, although it is unlikely that any important studies have been missed in the narrative reviews included in Global Heart. Accordingly, that publication – together with key primary publications – was used as a basis for this overview. Further evidence comes from recent work on understanding the relationship between level of exposure to combustion-derived small particulate ($PM_{2.5}$) pollution from multiple sources and risk of CVD. This made an important contribution to the rationale for including IHD and stroke in the GBD 2010 project CRA for HAP *(79)*, and is discussed in more detail in Section 3.5.

Studies of CVD event outcomes

Only two epidemiological studies appear to have studied HAP (as solid fuel use) and CVD event risk, one in China and one in Bangladesh.

The Chinese study, cross-sectional in design, was carried out in Shanghai, and involved 14,068 men and women aged 18 and over *(164)*. Solid fuel use (biomass and coal) for heating and/or cooking was assessed by questionnaire, and categorized according to ever use, duration, total amount and lifetime use. Outcomes, including CHD, Stroke and Diabetes Mellitus, were assessed by self-report of physician diagnosed conditions, while blood pressure was measured during the study. Loss of data on all confounders was small for duration of solid fuel use, but involved more than 2000 subjects for lifetime average and total amount. Although there were major imbalances in smoking and SES between solid fuel and non-solid fuel users, adjustment was thorough, and some stratified analyses are presented. The results showed elevated adjusted odds ratios for CHD, high BP and DM for ever vs. never use of solid fuels, and significant trends across duration of use for stroke, high BP and DM (Table 2.9).

Analysis stratified by sex found a significant effect only in women, OR=3.15 (1.53, 6.51) which is consistent with their having higher exposure, and among non-smokers, OR=3.65 (1.85, 7.22). The authors recognize the potential limitations of the cross-sectional design and questionnaire based assessment of exposure, and that prospective studies are needed to confirm these findings. The strong association with diabetes in interesting and as far as we are aware has not been previously reported; the authors of this study do not discuss possible mechanisms for this link.

Table 2.8: **Adjusted estimates showing odds ratios (95% CI) for exposure to solid fuel (biomass and/or coal) for heating and cooking, and trends with longer vs. shorter duration of exposure.**

Disease outcome: [1]Self report of physician diagnosis [2]Measured	**Use of solid fuel**	**Longer duration vs. shorter duration**	
	Ever use vs. never use	**Highest tertile vs. lowest tertile**	**p-value for trend**
Coronary heart disease (CHD)[1]	2.58 (1.53, 4.32)	1.46 (0.99, 2.15)	0.727
Stroke[1]	1.60 (0.80, 3.21)	1.87 (1.03, 3.38)	0.017
High blood pressure (BP)[2]	1.70 (1.40, 2.07)	1.73 (1.45, 2.06)	<0.001
Diabetes Mellitus (DM)[1]	2.48 (1.59, 3.86)	3.18 (2.11, 4.78)	<0.001

Source: adapted from Lee at al 2012 *(164)*

The second study is a retrospective cohort design, comparing rates of CVD and respiratory disease in adults aged 18 years and over living in 11 Bangladeshi village homes using either solid fuels (n=7565) or natural gas (n=508) *(161)*. Outcomes were ascertained through bimonthly home visit surveillance of all deaths, followed by diagnosis using verbal autopsy within 6 weeks of the death being notified. CVD included all circulatory causes (ICD: I00-I99). ICD Rates for CVD events were 5.1/1000 and 4.8/1000 in solid fuel and gas-using subjects respectively, giving an unadjusted rate ratio (RR) of 1.07 (0.82, 1.41). Although there were significant differences in SES and educational level between cases in the solid fuel and gas groups (and non-significant differences in smoking rates, with 47.1% and 37.5% smoking in the solid fuel and gas groups, respectively), no adjustment was reported. The unadjusted RR for respiratory disease was 2.26 (1.02, 4.99).

Impacts of HAP exposure on blood pressure

A review of studies of HAP from solid fuel use and blood pressure is provided in Global Heart (2012), by McCracken et al. *(165)*. To date, five studies have reported on this risk factor for CHD and stroke, four observational and one intervention (the latter with both RCT and before and after components). All have found that increased exposure was associated with higher systolic and/or diastolic blood pressure, with most findings being statistically significant. In the RESPIRE trial, McCracken et al. found the intervention (chimney stove) group to have 3.7 mmHg (-8.1, 0.6) lower systolic and 3.0 mmHg (-5.7, -0.4) lower diastolic blood pressure in intention to treat analysis, and similar sized effects when control group subjects received the chimney stove at the end of follow-up *(166)*.

In a rural biomass –using area of China, Baumgartner et al. reported a 1.5 mmHg (0.6, 2.6) higher systolic and 0.3 (-0.3, 0.9) mmHg higher diastolic blood pressure associated with a doubling of $PM_{2.5}$ during the previous 24 hours *(167)*. In a cross-sectional study in India, Dutta et al. found a prevalence of hypertension of 30% in solid fuel users compared to 11% in LPG users (unadjusted), and an adjusted prevalence odds ratio of 1.41 (1.22, 2.08) for those with a kitchen $PM_{2.5}$ greater than the median compared to those below the median.

Intermediate stage markers and mechanisms

The review by McCracken et al. in Global Heart (2012) also provides an account of the evidence linking HAP, second-hand smoke (SHS) and outdoor air pollution (OAP), with six markers of cardiovascular disease mechanisms and development (Table 2.10).

Table 2.9: **Summary of evidence on effects of HAP on markers of CVD**

Marker	Summary of evidence
Endothelial function and alterations in vascular tone	In India, users of biomass (animal dung) were found to have impaired flow mediated blood vessel dilation, compared to clean fuel users, but confounding was possible. In an experimental study in Canada, reduction of wood smoke exposure improved endothelial and micro-vascular function.
Markers of sub-clinical atherosclerosis	Few studies have examined the effects of HAP on atherosclerosis; one study of dung smoke found no association with intimal thickness. Studies of both OAP and SHS have found evidence of early atherosclerosis.
Markers of coagulation	In India, a study comparing biomass and LPG users found increased activation of platelets and leukocytes, and in a follow-on study reported evidence of platelet activation; confounding may be an issue however. Experimental studies have found evidence of activation of the coagulation cascade, but findings are not consistent. There is evidence that OAP leads to prothrombotic changes.
Oxidative stress and inflammation	Controlled experiments of exposure to wood smoke have found evidence of increases in markers of oxidative stress, suggesting HAP would lead to systemic inflammation which is an important mechanism in the development of CVD. There is also some supportive evidence for this from studies of SHS and OAP.
Electrocardiographic (ECG) markers	In the RESPIRE sub-study, the intervention (chimney) stove was associated with a significantly reduced risk of ST-segment depression, although no effect was seen on heart rate variability (HRV). Results of other studies of biomass smoke exposure and ECG markers are, however, not consistent. There is some evidence of effects of SHS and OAP on heart rhythm, re-polarisation abnormalities, and HRV.
Right-sided heart function	One study has found HAP exposure to be associated with impaired right-sided heart function, but as this was cross-sectional, causation is unclear. Acute exposure to woodsmoke has been found to (transiently) increase pulmonary vascular resistance. Studies of OAP have found exacerbations of heart failure, and elevated right-sided cardiac pressures.

Adapted from McCracken et al. 2012*(165)*

Conclusions

With reference to the Bradford-Hill viewpoints, the epidemiological evidence base for the effects of solid fuel HAP on cardiovascular disease remains limited, with only two epidemiological studies of completed outcomes, one of which is unadjusted for potentially important confounding. Dose-response and experimental evidence is lacking. There is, however, support in terms of biological plausibility and mechanisms, and analogous evidence from smoking (active and second-hand) and outdoor air pollution. Overall, there is a reasonable case for believing that HAP exposure would increase the risk of CVD. As has been pointed out by Smith and Peel in commenting on analysis of CVD risk with combustion-derived $PM_{2.5}$ exposure arising from OAP, SHS and active smoking (AS), it is to be expected that HAP – with exposure levels between SHS and AS and similar constituent pollutants – would also cause this disease outcome *(168)*. This evidence and the implications for the likely level of CVD risk from HAP exposure are discussed further in Section 6.4. Given what is known about the developmental origins of heart disease including the effects of low birth weight which has been linked to HAP, the high levels of exposure in pregnancy could further strengthen this case *(169)*. In view of the very limited empirical evidence and differing outcome measures, however, no attempt has been made to pool results, or to apply GEPHI.

2.5.7 Cataract

Severe lens opacification, also known as cataract, is one of the leading causes of blindness in the developing world. The WHO's Global Burden of Disease for 2004 *(170)* estimates that cataracts accounted for 1.2% of the total disease burden, 55% of which is seen in the developing regions of sub-Saharan Africa and Southeast Asia alone where cooking with solid fuels is most common.

The toxicological evidence from animal studies and epidemiological studies looking at other combustion risk factors for cataract (i.e. active smoking and second hand smoking) suggest biological plausibility for a causal association between HAP exposure and cataracts.

The systematic review carried out for the GBD 2010 CRA, (Box 2.12) identified eight studies for potential inclusion in the meta-analysis; six were case-control designs and the remaining two cross-sectional.

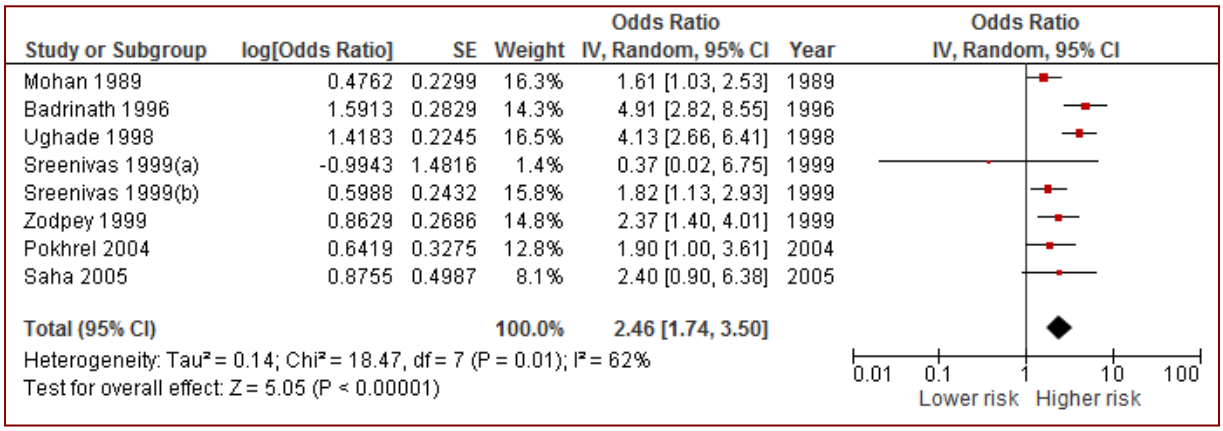
Box 2.12: Key search features for cataract

- Search period: to 2012
- Search hits: 10,235
- Inclusion: (i) all studies designs, (ii) measures of HAP from solid fuel, (iii) cataract, (iv) age and sex-adjusted effect estimate
- Eligible studies: 7 studies (8 independent estimates)
- Languages: English only

One study was excluded from the meta-analysis, as an age and sex-adjusted estimate was not provided. There was no evidence of publication bias, with Begg's (p=0.917) and Egger's test (p=0.827). The pooled relative risk for the seven studies (one of which provided two independent estimates) using a random effects model was 2.46 (1.74, 3.50), see Figure 2.15.

Although there was a high level of heterogeneity (I^2 = 0.62), all of the effect estimates were in the same direction (increased risk) with one exception, but this had a very wide 95% CI, and six studies had significantly elevated odds ratios.

Figure 2.14: Forest plot of seven studies (8 estimates) reporting on risk of cataract with exposure to solid biomass fuel in the home.



For Sreenivas 1999: (a) = Angomaly; (b) = Delhi

Several factors could confound the relationship between exposure to HAP and cataracts, including active smoking, age, sex, ultra-violet light (UV) exposure and diabetes. With respect to sex, two of the studies provided estimates for women only [RR = 2.17 (1.44, 3.27)], and one provided separate estimates for men and women (RR = 1.8 for men and 2.2 for women; no 95% CI provided). From this it was concluded that women are likely at higher risk than men, but a reliable estimate for men could not be derived from this set of studies. In

respect of smoking, analysis of the one cross-sectional study and six case-control studies that either enrolled non-smoking subjects (5) or adjusted for smoking (2) resulted in a relative risk of 2.47 (1.63 to 3.73), still with a high level of heterogeneity (I^2 = 68%).

A synthesis of the two studies controlling for diabetes resulted in a summary RR of 3.77 (95% CI 2.53 to 5.63, p < 0.0005) *(171-172)*, substantially higher than the RR of 2.10 (95% CI 1.69 to 2.59, p <0.0005) from those studies which do not consider diabetes (N=3) *(173-175)*, and even higher than the RR of 1.67 (95% CI 1.23 to 2.72) from the two studies which excluded diabetics from their study populations *(176-177)*. These somewhat counter-intuitive findings are difficult to explain, but may be the result of other sources of heterogeneity across this small group of studies. Additional complexity could arise from diabetes acting as both a confounding factor and component of the causal pathway between HAP and cataract. Thus, while diabetes is a known risk factor for cataract, a recent study has shown a two-fold increase in risk for self-reported diabetes among solid fuel using homes *(178)*. If these findings are confirmed, however, it would be expect that adjustment and exclusion of diabetes would tend to reduce the effect estimate; exclusion did reduce the odds ratio, but adjustment led to a higher estimate. The role of diabetes in this relationship should be further examined in future studies.

A recent study of lens opacity in the Pokhara region of Nepal among 143 women aged 20 to 65 years was not available at the time this review was completed, but is important in that it reports a statistically significant adjusted trend of higher risk with increasing duration of biomass fuel use (p=0.01) *(179)*. This was found for nuclear, but not cortical cataract.

Discussion

Reference to the Bradford hill viewpoints, including the size of effect, evidence of dose-response (albeit one study) biological plausibility and analogous evidence from smoking, suggest a reasonable case for causality, although experimental evidence is lacking. That the estimate for risk of cataract with HAP may be only a little lower than that for active smoking [smoking risk and reference to be added] could be interpreted as being – at least in part – due to women having life-long exposures to these combustion pollutants. Thus, although pollutant exposure levels may be lower on a daily basis than for active smokers, the longer duration (in terms of years of exposure), including in *utero* and possibly through critical periods in development, may explain this relatively large effect. Despite adjustment for smoking in most studies, residual confounding may also play a part. These observations are however speculative, and the impacts of HAP on cataract formation at different stages of the life cycle should be a subject for future research.

Overall assessment of evidence

The GEPHI assessment included all seven studies, and was downgraded for inconsistency, but upgraded for large effect, resulting in an initial grading of LOW. For additional criteria, the evidence was upgraded for analogous evidence, but not for consistency across designs and settings since all of the studies were conducted in the same region. This resulted in a final grading of MODERATE, with an estimated intervention effect of 0.41 (0.29, 0.57), which applies only to women. Future studies may well result in revision to this effect estimate, and are needed to provide stronger data for men.

2.5.8 Adult ALRI

Globally, Lower Respiratory Infections, accounted for 4.18 million deaths in 2004 *(143)*, the majority of which are acute (ALRI). Slightly over half of these deaths occurred among adults (15 years and above), and most in those aged 60 years and over. In low-income countries, where the majority (70.4%) of LRI deaths occur and the use of solid fuels for cooking is greatest, the picture is somewhat different, with a higher proportion of the deaths occurring among children, 59% for boys and 60% for girls. Nevertheless, a substantial number of LRI

deaths occur among adults in low-income countries, most in those over 60 years of age. Given the strong evidence that HAP causes ALRI in children most probably through reducing defences and immune resistance, an association with ALRI in adults is plausible, both in terms of pneumonias in (generally) otherwise healthy individuals, as well as those with pre-existing chronic disease. This is supported also by the established association between tobacco smoking and ALRI in adults.

A systematic review of adult ALRI was carried out for the GBD 2010 CRA, Box 2.13.

Respiratory infections can be divided into upper and lower according to whether the infection involved the respiratory tract above or below the epiglottis. Although acute exacerbations of COPD could also be included, the presence of COPD is potentially problematic as it is now well-established that HAP increases the risk of COPD. The approach taken was to assess for each study whether or not subjects with COPD and other chronic illnesses had been excluded. The term ALRI is also sometimes used only for 'infections', and sometimes for 'illness', a broader terms that may include asthma, etc., and accordingly the use of this term for the outcome definition was also carefully assessed in each paper.

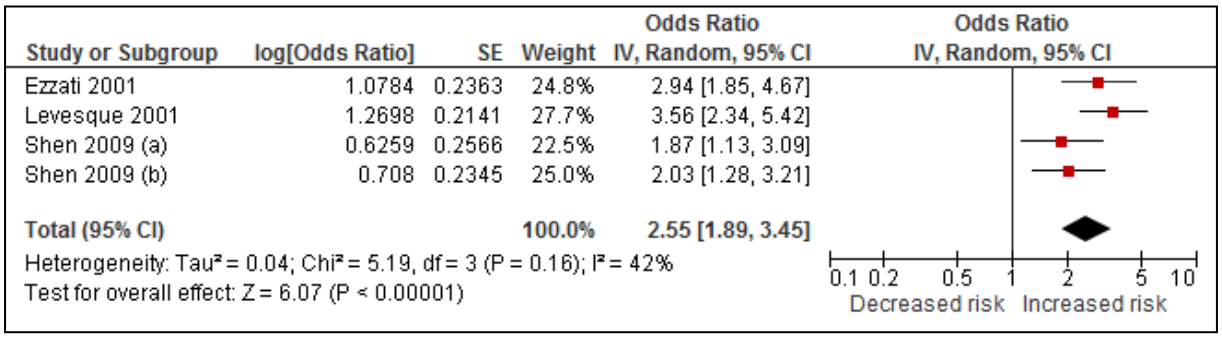
Box 2.13: Key search features for adult ALRI

- Search period: to March 2010
- Search hits: 14,624
- Inclusion: (i) All study designs (ii) primary use of solid fuel for heating and/or cooking; (iii) able to distinguish upper and lower respiratory infection
- Eligible studies: 3 studies (9 independent estimates)
- Languages: English, Spanish, Chinese

From the very large number of initial titles identified, only three suitable studies were selected *(34, 180-181)*, and were all very different. The study by Shen is a retrospective cohort study of pneumonia deaths in the coal-using area of Xianwei, China. That by Ezzati is a small prospective cohort study in rural Kenya where various forms of biomass are used (wood, charcoal) and home visits were made by trained field staff for assessment of community pneumonia. The small study by Levesque is from Canada, where biomass is used for household heating: exposure is at much lower levels, and the ALRI outcomes included were heterogeneous, self-reported (based on health care service assessment), and although may include non-pneumonia illness does report a large and relatively precisely-estimated effect.

All three studies reported significant ORs for exposed groups of between 2 and 3. The results for the three studies are illustrated in Figure 2.16.

Figure 2.15: Forest plot of 3 studies of solid fuel exposure and adult ALRI



Pooling of studies was not carried out on account of the marked differences between studies, particularly in outcome definitions and assessment. For the study by Ezzati and Kammen, the six estimates provided by level of exposure were first pooled using fixed

effects meta-analysis, to obtain an OR of 2.94 (1.85, 4.67). Importantly these data also demonstrated a significant exposure-response relationship. Despite the limited and heterogeneous nature of this small set of studies, the exposure-response relationship from the study by Ezzati, evidence from HAP exposure in children and the known effects of other sources of exposure including smoking, all suggest that solid fuel HAP increases the risk of adult ALRI. Further research is required to confirm and quantify this risk.

2.5.9 Tuberculosis

Tuberculosis (TB) was responsible for nearly 1.5 million deaths in 2004, more than 900,000 of which (62%) occurred in developing countries. There is a close association of this disease with poverty, and with the use of solid fuel in the home. Three systematic reviews of the links between HAP and TB are now available *(11, 182-183)*. In their review of five studies, Lin et al. found three case-control and two cross-sectional studies examining the relationship with solid fuels, and this report was part of a larger review also examining the risk with active and second-hand smoking *(182)*.

In sub-group analysis, the case-control studies had substantial heterogeneity (I^2=74.1%) and no overall effect with an OR of 1.06 (0.50, 2.24), while the cross-sectional studies were more consistent (I^2=0%) with an OR of 2.58 (2.00, 3.32). These authors did not present an overall pooled estimate due to concerns about heterogeneity, but noted the strong association with active smoking, and a weaker set of evidence (also five studies) for second-hand smoking. The review by Slama et al., published three years later, included one additional, unpublished cross-sectional study (from 2001) for which the OR was 1.21 with no 95% CI available *(183)*. These authors also concluded that despite the plausibility of the association, the available studies did not provide sufficient evidence of increased risk from household solid fuel use.

The most recent systematic review, with meta-analysis, was published by Sumpter and Chandramohan in 2013 *(11)* (see Box 2.14).

Box 2.14: Key search features for TB (Sumpter 2013)

- Search period: To 2012
- Search hits: 452
- Inclusion: (i) all designs (ii) primary use of solid fuels in the home, and (iii) TB as outcome.
- Eligible studies: 13 (10 case-control; 3 cross sectional)
- Languages: English

The review followed the PRISMA guidance. All main aspects of study quality were assessed, although no formal scoring tool was described. Ten case-control and three cross-sectional studies were included. The outcome was sputum positive TB in all of the case-control studies, and two of the cross-sectional studies. Exposure assessment was by fuel type recall with no direct measurement, hence open to misclassification and lacking quantification.

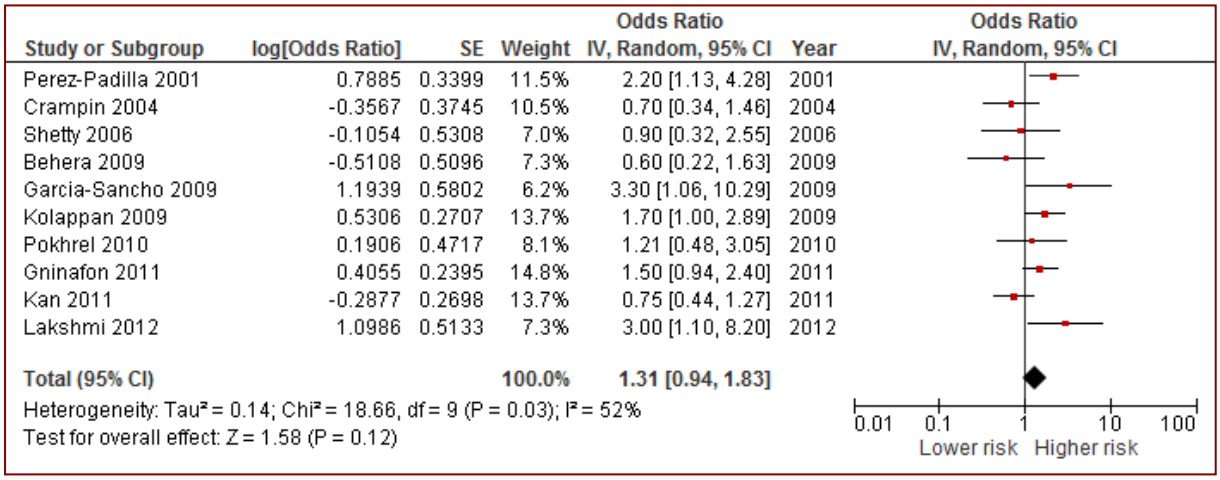
All but one case-control study carried out adjustment for smoking and crowding was adjusted for in most, but two of the cross-sectional studies adjusted only for age. Five of the case-control studies were hospital based and seven in all used hospital cases. Men were over-represented in the four studies with both male and female subjects. Possible bias arising from these design issues are discussed by Sumpter and Chandramohan, but as these may result in a mix of bias towards and away from the null, no firm conclusion could be drawn.

The pooled odds ratio (OR) for the ten case-control studies was 1.30 (1.04, 1.62), p=0.019, reported by the authors to have been calculated using fixed effects, despite substantial heterogeneity (I^2 = 52%, p=0.03). The equivalent random effects analysis gives a similar but non-significant OR of 1.31 (0.94, 1.83), p=0.12, (Figure 2.17). The six studies of female-only subjects had a (FE) pooled OR of 1.70 (1.00, 2.89), p=0.05, with an I^2 of 60% (p=0.029), but reanalysis using random effects found a non-significant OR of 1.45 (0.82, 2.57). Despite the new studies, there remains very substantial heterogeneity across this set of studies,

including for the women-only analysis, and the pooled risk estimates are not statistically significant. Future studies should be designed to carefully address the methodological limitations of previous studies.

The study by Pokhrel et al.*(184)* also examined the risk associated with the use of kerosene and found this was also positively and significantly associated with TB risk; for cooking, the OR was 3.36 (1.01, 11.22) and for lighting the OR was 9.43 (1.45, 61.32) *(184)*. This study is discussed further in the context of available evidence on health risks from kerosene emissions in Review 9.

Figure 2.16: Forest plot for ten studies (case control) reported in systematic review by Sumpter (2013) investigating risk of TB with solid fuel use, re-analyzed using random effects.



In conclusion, the most up-to-date review of this topic reported a significant OR of 1.30 from all thirteen currently available studies (p=0.019) and a marginally significant and higher OR of 1.70 for six studies of women (p=0.05), most of which have carried out reasonably adequate adjustment for confounding, but not all. Reanalysis using random effects due to heterogeneity found these both to be similar in magnitude by non-significant. Both intervention-based and exposure-response evidence are lacking. The well-established evidence that smoking increases risk of TB and biological plausibility *(85)* provide some support for this association being causal. Given the high prevalence of both HAP exposure and TB across the developing world and close geographical and socio-economic relationship between the two, reduction in HAP could make and important contribution to control of TB. This potential warrants further well-conducted studies to confirm that the link is causal and not due to confounding or other sources of bias, and to better quantify the risk estimate.

2.6 Summary of intervention-based evidence

This review has shown that the great majority of epidemiological studies providing evidence on the health risks of HAP exposure are observational. There is however a small but growing body of intervention based evidence, and a number of new RCTs are in progress. A brief overview of published[4] studies is provided in Table 2.11. Current trials are also briefly described, and some discussion on the strengths and limitations of this body of intervention-based evidence provided.

[4] All of the published studies are described in greater detail in foregoing sections of this review

Evidence from these completed studies has shown that where the intervention stoves have been well-accepted and used by households, and are inherently capable of delivering substantial reductions in exposure, some important impacts of health outcomes have been reported. Conversely, poor acceptance has resulted in minimal or no impact of HAP exposure and health outcomes. Insufficient power and/or duration of follow-up may also have contributed to negative or non-significant findings. Not all of the studies have included HAP or exposure measurement, for example the Xianwei cohorts studies, so while it is reasonable to conclude that the reductions in disease outcomes were indeed the result of improved stove use over many years, the actual level of exposure reduction achieved in practice is not known.

Table 2.10: **Overview of intervention-based evidence on the impacts of household energy interventions on health outcomes. [Findings reported were statistically significant except where stated as NS: not statistically significant]**

Disease outcome	Study and design	Main features and findings	Reference
Acute respiratory infections	RESPIRE study, Guatemala, RCT	534 homes randomized to use a plancha chimney stove compared to open fire. Kitchen HAP levels were reduced by 90%, and exposure in women and children by around 60% and 50% respectively. In children <19 months, plancha group had 22% (NS) and 33% ($p<0.05$) reductions in all and severe pneumonia, respectively.	*(15)*
	Chinese NISP retrospective cohort study	In a large cohort of over 42,000 farmers, compared to traditional open fires, long term use of improved stoves in a coal-using region of Xianwei was associated with reductions of around 50% in risk of adult ALRI mortality.	*(180)*
	MIT study, India, RCT	Comparison of an improved mud-stove design with chimney among 2651 homes in 44 villages in Orissa. Reduced emissions in laboratory tests were not translated into exposure reductions in practice, and no health benefits reported. Households had low valuation of the stove and did not use them regularly.	*(38)*
Adult respiratory health/COPD	Patsari stove trial, Mexico, RCT	668 homes were randomised to use a Patsari chimney stove compared to an open fire. Due to poor adherence to allocated stove use, authors presented most results for users vs. non-users. Improved stove users reported reduced respiratory symptoms, and a lower rate of decline in lung function, over 1 year.	*(76)*
	RESPIRE study, Guatemala, RCT	Among 504 women, those randomized to use the plancha stove reported reduced respiratory symptoms, but there was no impact on lung function up to 18 months.	*(120)*
	Chinese NISP retrospective cohort study	In a cohort of over 20,000 subjects in the coal-using region of Xianwei, those with long-term use of improved chimney stoves showed substantial reductions in COPD, with 42% and 25% reductions in men and women respectively. Results became unequivocal after 10 years of stove use.	*(113)*
Birth weight	RESPIRE study, Guatemala,	Among 174 mothers and newborns for whom birthweight was measured within 24 hours, use of the plancha chimney stove (not per randomization)	*(15)*

Disease outcome	Study and design	Main features and findings	Reference
	RCT	was associated with an adjusted 89 gm (NS) increase in birth weight, and a 26% reduction (NS) in risk of LBW.	
Lung cancer	Chinese NISP cohort study	In a cohort of over 20,000 subjects in the coal-using region of Xianwei, subjects with long term use of improved chimney stoves showed substantial reductions in lung cancer, 41% and 46% for men and women respectively. As with COPD, results became unequivocal after 10 years of stove use.	*(127)*

Several randomized controlled trials are currently underway, all of which are studying the impacts of improved stoves (both standard natural draught rocket-type as well as fan-assisted) on birth outcomes (pre-term birth, birth weight) and ALRI. Several also plan to include and LPG arm in the trial. These studies are being conducted in Nepal, Ghana and Malawi:

Table 2.11 Studies of improved stoves currently underway

Trial location	Main investigating institution (PI)	Trial registration number
Ghana	Columbia University (Kinney P.)	NCT01335490
Nepal	Johns Hopkins (Tielsch J.)	NCT00786877
Malawi	Liverpool School of Tropical Medicine (Mortimer K.)	ISRCTN59448623

A small number of studies, including randomized trials and quasi-experimental designs, have reported on the impacts of improved stoves, clean fuel and related interventions on burns and poisoning prevention; these studies are described in Review 10 (Safety). Additional discussion of issues for future intervention studies is provided in Section 6 of this review.

2.7 Conclusions

The systematic reviews reported in this section find that solid fuel use in the home for cooking and/or heating, the proxy used for HAP exposure, is associated with a wide range of child and adult health outcomes. Causal evidence for some is strong, including ALRI and low birth weight in children, and COPD, lung cancer and cataract in adults (and especially among women). Risk estimates for these outcomes are in the range from 1.5 to more than 2, including probably for severe and fatal pneumonia for which these strong effects – if confirmed – clearly demonstrate the potential contribution control of HAP exposure can make to child survival. The lack of consistent evidence and a robust case for causality for other outcomes such as pre-term birth, child cognitive development, stunting, IHD/stoke, TB and others makes the case for additional studies using consistent methods and including exposure assessment to allow firmer conclusions about the strength of causal evidence, and associated effect sizes. .

The GEPHI assessments have been carried out to assess the level of confidence in estimates of putative intervention effects. Almost all of this evidence is based on observational studies, and the GRADE approach downgrades this type of evidence, although consideration of the additional criteria as described in 'Methods used for evidence assessment' results in moderate scores for Child ALRI, low birth weight, stunting and lung cancer (for both coal and biomass). While there is a growing body of intervention-based evidence (see Section 2.5, above), this is currently too limited to serve as a basis for

GRADE assessment. It should also be kept in mind that these effect estimates, which are in the range of a 20-50% reduction in risk across those outcomes with a moderate score, are based on observational epidemiology which compares exposed (traditional stoves and fuels) with some (variable) definition of unexposed, and which in practice will not have experienced levels close to the WHO air quality guideline (AQG) levels, particularly for $PM_{2.5}$. Thus, the true effects of interventions which are able to deliver air quality at or close to the AQG may well be larger. This is further considered in Section 3 on exposure-response evidence.

3. Exposure-response evidence from combustion-related particulate pollution

3.1 Summary

Background

Information on the relationships between level of exposure to household fuel combustionpollution mixtures and disease risk are important for policy, as this evidence can help determine the levels of exposure required to deliver substantial health benefits. In low and middle income countries, this is especially important due the very high levels of exposure currently experienced in homes using solid fuels, and the technical and programmatic challenges in achieving sustained adoption of very clean (low pollution) technologies and fuels.

Aims and key questions

The aim of this section was to summarize and discuss information available on the relationships between exposure level and risk of important disease outcomes, and the shapes of these relationships (exposure-response functions).

Methods

Findings on exposure-response relationships from two individual studies of HAP exposure and ALRI risk are reported. Integrated exposure-response (IER) functions for child ALRI and four adult outcomes (IHD, stroke, lung cancer, COPD) are also reported and discussed. These IER functions were developed recently by modelling the risk estimates from systematically reviewed studies of combustion- derived $PM_{2.5}$ from four emission sources (outdoor air pollution, second-hand smoking, HASP and active smoking). The overall quality of this evidence was assesed using GRADE domains as a guide.

Main findings

Only two studies report exposure-response data for HAP, both for ALRI, and show evidence of a non-linear relationship, steepest at low levels of exposure. The 'integrated exposure-response' (IER) function, based on a combination of direct HAP evidence and other $PM_{2.5}$ sources, suggests a curve for child ALRI with a steep portion from low levels up to around 100 µg/m^3 $PM_{2.5}$, and thereafter with a much shallower slope across the rest of the range of HAP exposure. The functions for IHD and stroke do not have direct HAP data, but based on the other $PM_{2.5}$ sources, have a similar shape to that for ALRI. The function for lung cancer is more or less linear in shape, reaching very high relative risk with heavy smoking, while that for COPD is less certain, but appears more linear than for ALRI and risk continues to increase with exposures above the HAP range.

Conclusions

The main conclusions from this evidence, which is assessed to be of moderate quality, are that for ALRI (and probably IHD and stroke) low levels of exposure are required to achieve substantial health benefits. For lung cancer (and possibly COPD), risk reduction may be more proportional to exposure reduction.

3.2 Introduction

Evidence on the relationships between levels of exposure to HAP and risk of key disease outcomes has important implications for policy because this provides an indication of the health benefit that can be expected from the various intervention options available, and their respective performance in terms of emissions and resulting home, personal exposure and local environmental levels. More specifically, it is not just a question of the increased risk

associated with exposure that is important for policy. In order to make informed decisions between various interventions options with differing impacts on exposure levels, it is necessary to know the shape of the relationship between exposure and risk of the most important diseases linked to HAP. Compliance with air quality guideline levels of pollutants, and in particular $PM_{2.5}$, must be the goal for all populations. This will require more or less universal use of clean fuels, possibly with some contribution from cleaner burning solid fuel stoves and probably including ventilation with a chimney if the laboratory-based performance of these technologies can be achieved in everyday use. The reality is that for many poor solid-fuel dependent populations this transition will take some years at least and consequently, improved solid fuel stoves will continue to be in the mix of technology options under consideration. The question then arises as to whether these various stove technologies can provide useful, and indeed any, improvements in health, or whether low levels of exposure at (or close to) the WHO IT-1 for $PM_{2.5}$ (or even the actual annual air quality guideline value itself) are required for this to be the case.

Unfortunately, due to the general lack of exposure measurement in the epidemiological studies to date (see Section 3.1), very little direct exposure-response evidence is available for HAP. Two studies have reported such evidence for child ALRI *(15, 34)*, but none is available for other major health outcomes linked to HAP exposure. An additional and potentially very important source of evidence derives from recent work modeling the shape of relationships between combustion-derived $PM_{2.5}$ exposure from ambient air pollution (AAP), second-hand-smoke (SHS) and active smoking (AS) and several disease outcomes, namely ischaemic heart disease (IHD), stroke, chronic obstructive pulmonary disease (COPD) and lung cancer. This was first reported by Pope et al. for IHD, stroke, cardiopulmonary disease and lung cancer, and since then developed for use in the GBD 2010 comparative risk assessment for air pollution, for which purpose risk data on HAP exposure was also incorporated *(79)*.

3.3 HAP Exposure-response evidence for child ALRI

The most detailed analysis of child ALRI risk at different levels of HAP exposure comes from the RESPIRE trial *(15)*, described in Section 2.4.1. As noted for this study, 48-hr carbon monoxide (CO) was measured on all children every three months during follow-up to provide an exposure proxy for $PM_{2.5,}$ the latter being measured along with CO in a sub-set of homes to describe the relationship between the two pollutants *(37)*. This allowed, in addition to the intention to treat (ITT) analysis of the impact of the stove on ALRI included here, an adjusted analysis of child exposure and ALRI incidence. The relationships between exposure (as CO) and incidence rate of (A) all pneumonia and (B) severe (hypoxemic) pneumonia are shown in Figure 3.1.

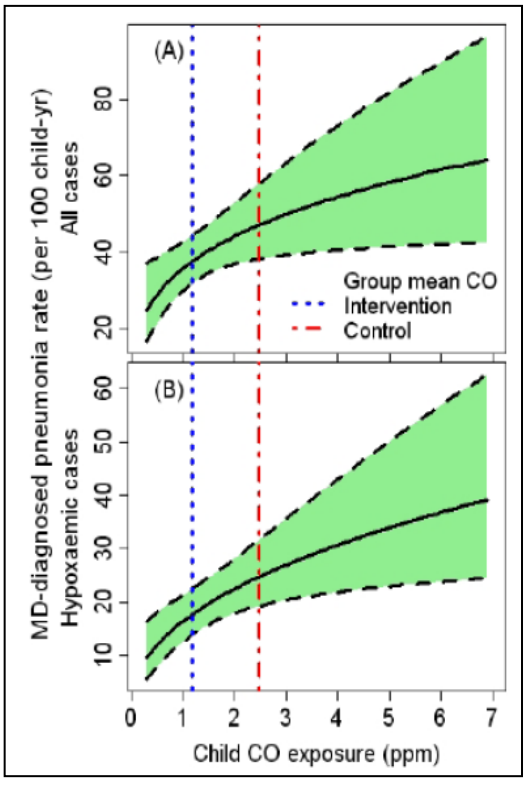


Figure 3.1: Relationships between long-term CO exposure in children and pneuonia incidence (upper curve) and severe pneumonia (lower curve), RESPIRE study. The dashed (red) and dotted (blue) lines represent the mean exposure levels in the control and intervention groups, respectively.
Reproduced with permission

The mean levels of CO for the intervention and control groups, shown by the blue and red dashed lines in the figure, were approximately equivalent to 125 and 250 $PM_{2.5}$ $\mu g/m^3$, respectively, based on the regression equation derived from the CO and $PM_{2.5}$ sub-study *(185)*. A proportion of the children had long-term exposures below the mean for the intervention group, and the lowest decile (of the whole sample) had a mean of around 45 $\mu g/m^3$. Figure 3.1 shows that risk declined further at exposure levels below the mean for the intervention, and indeed the steepest section of the curve is see at the lowest exposures.

These findings imply that, while the reduction from high levels (in the control group) by some 50% to the still moderately elevated levels in the intervention group were associated with some risk reduction (ITT analysis: 0.78 95%CI 0.59, 1.06 for all pneumonia; 0.67 95%CI 0.45, 0.98 for severe pneumonia), the greatest risk reduction appears to occur at levels around or below that seen for the least exposed group of children with levels approaching the WHO IT-1 of 35 $\mu g/m^3$ in annual mean $PM_{2.5}$. These data from the RESPIRE study also contributed to the integrated exposure-response function for child ALRI used in the GBD 2010 CRA, as described in Section 3.4, below.

The second study that has reported an exposure-response function for ALRI (both adult and child) was carried out by Ezzati and Kammen among 55 homes in rural Kenya *(34)*. Exposure was assessed using a combination of area measurements of PM_{10} and time-activity information. For children aged 0-4 years, risk was found to increase up to exposures of 1,000-2,000 $\mu g/m^3$ PM_{10}, thereafter leveling off with the OR reaching a value of almost 3.0, Table 3.1. Similar findings were reported for the older age group, with the exception of a much higher OR of 7.10 (2.26, 22.32) for the >7,000 $\mu g/m^3$ PM_{10} exposure category, but this estimate does have a very wide confidence interval.

Table 3.1: **Exposure-response relationships for ALRI at ages 0-4 years and 5-49 years in a study from rural Kenya.**

Age 0-4 years		Age 5-49 years	
Exposure category (PM10 $\mu g/m^3$)	**Odds ratio (95% CI)**	**Exposure category (PM10 $\mu g/m^3$)**	**Odds ratio (95% CI)**
<200	Reference	<200	Reference
200-500	1.48 (0.83, 2.63)	200-500	1.65 (0.50, 5.45)
500-1,000	1.40 (0.74, 2.67)	500-1,000	1.87 (0.61, 5.71)
1,000-2,000	2.33 (1.23, 4.38)	1,000-2,000	2.74 (0.93, 8.12)
2,000-3,500	1.93 (0.99, 3.78)	2,000-4,000	3.28 (1.09, 9.85)
>3,500	2.93 (1.34, 6.39)	4,000-7,000	3.21 (1.01, 10.24)
-	-	>7,000	7.10 (2.26, 22.32)

Adapted from Ezzati and Kammen 2001 *(34)*

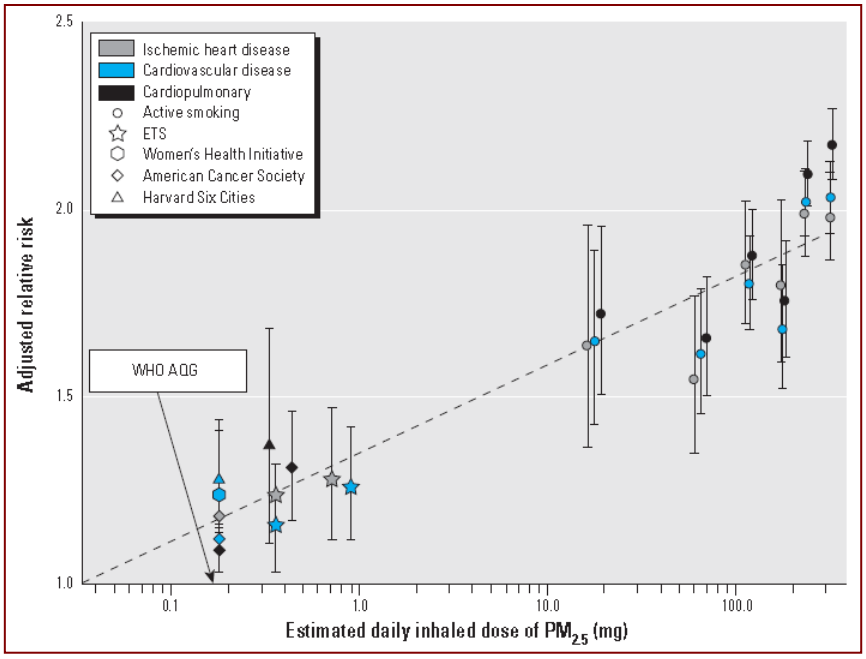
The authors concluded that the shape of the curves were 'concave increasing functions', with the rate of increase declining after 1-2,000 $\mu g/m^3$ PM_{10} in daily average exposure.

In this analysis, the lowest category was <200 $\mu g/m^3$ PM_{10}. Even though this is PM_{10} rather than $PM_{2.5}$ (the equivalent $PM_{2.5}$ would still be expected to be greater than 100 $\mu g/m^3$), this relatively high reference category means that there are no data available from this study on risk at levels approaching WHO IT-1 and the air quality guidelines. No attempt has been made to combine these findings with those of RESPIRE as there are substantial differences in the methods for exposure assessment (estimated from area measurement and time-activity in Kenya vs. direct measurement of CO in all children and $PM_{2.5}$ in a sub-sample in Guatemala) and in outcome definition (community ALRI in Kenya vs. physician diagnosis in Guatemala). The findings are however consistent with RESPIRE in terms of the shape, but levels of exposure and risk may or may not be consistent.

3.4 Exposure-response evidence from other combustion sources

The first attempt to study disease risk across the exposure range to $PM_{2.5}$ from sources other than HAP (that is AAP, SHS and AS) was carried out for IHD, CVD and cardiopulmonary disease by Pope et al. in 2009 *(186)*. This showed a relationship that was relatively steep at lower exposures, flattening off at an adjusted RR of around 2 at high exposures: this is shown in Figure 3.2, but appears linear as the exposure scale is logarithmic.

Figure 3.2: **Relationship between estimated daily inhaled dose of $PM_{2.5}$ from ambient air pollution, second-hand and active smoking, and IHD, CVD and cardiopulmonary mortality. Reproduced from Pope et al. 2009 *(186)* Reproduced with permission**

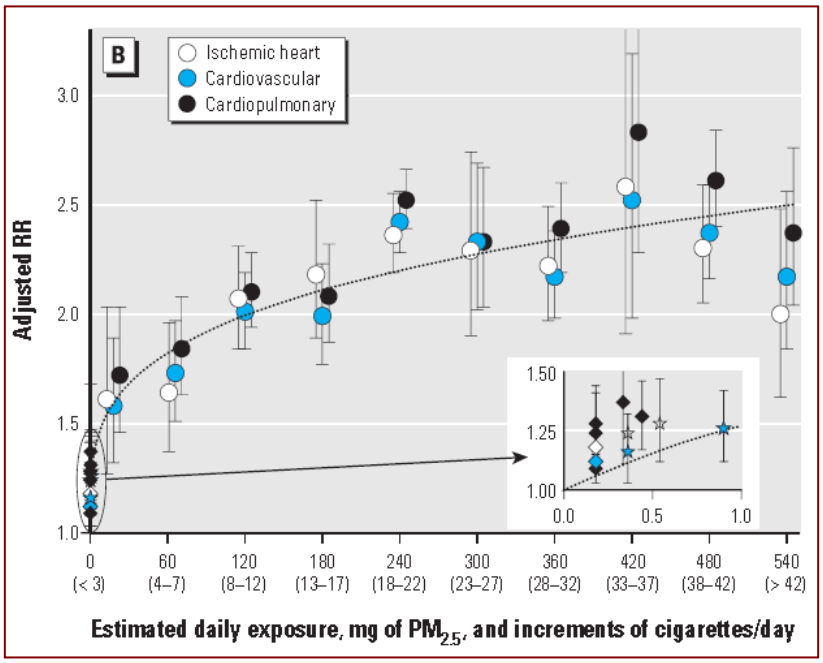


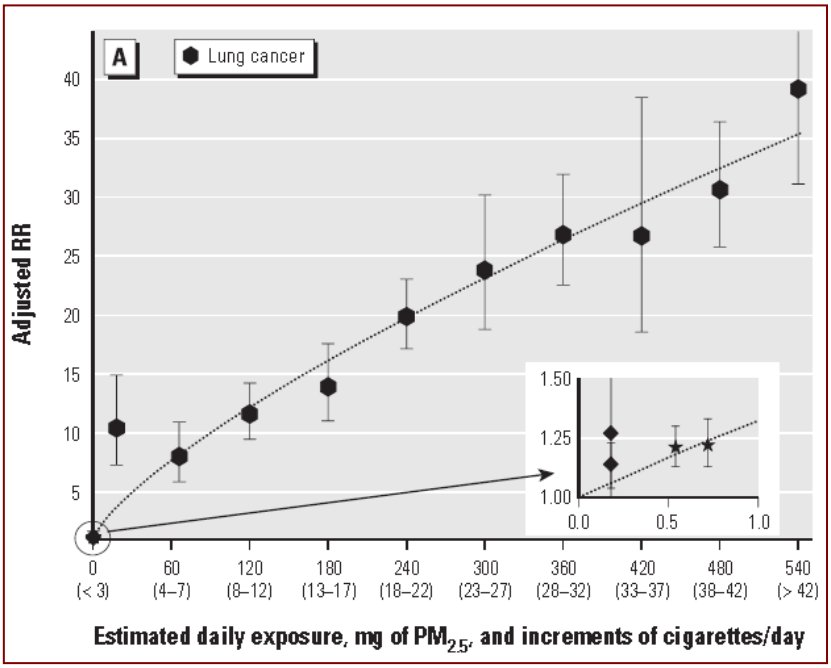
As noted, HAP exposures are not included in this analysis, but would generally lie somewhere between SHS and light AS. The implications of this for risk of CVD from HAP exposure was identified by Smith and Peel in 2010 in their paper 'Mind the Gap' *(173)*. They pointed out that HAP exposure, with daily inhaled dose values of about 4-8 mg/m^3 (equivalent to average ambient concentrations in the home of 250-500 µg/m^3) lying in the gap between AS and SHS studies in Figure 3.3, would imply significant risks from HAP exposure for these health outcomes.

In a further development, Pope et al. conducted a more detailed analysis in 2011 of disease risk across the exposure range to $PM_{2.5}$ from AAP, SHS and AS for IHD, stroke, cardiopulmonary disease and lung cancer *(187)*. This included a larger number of primary studies and benefitted from formal but still relatively simple modeling, the results of which are shown in Figure 3.3 (a) for IHD, CVD and cardiopulmonary, and in (b) for lung cancer.

For the cardiovascular and cardiopulmonary outcomes, the 'supralinear' curve is clearly apparent, very steep at low levels of exposure, then flattening off to reach an (adjusted) relative risk (RR) at the highest levels of (smoking-derived) $PM_{2.5}$ exposure of around 2.5. For lung cancer, by contrast, the shape of the line is almost linear, reaching an adjusted RR of around 35 at the highest exposure level shown.

Figure 3.3: **Adjusted RR across range of $PM_{2.5}$ dose derived from AAP, SHS and AS for (a) above: IHD, CVD and Cardiopulmonary, and (b) below: Lung cancer. Reproduced from Pope et al. 2011: *(187)***





3.5 Integrated exposure response (IER) functions developed for GBD 2010

In developing risk estimates for outdoor air pollution that could be applied in the GBD 2010 CRA, the expert group was faced with the problem that, while long-term average $PM_{2.5}$ exposures in some cities in low and middle income countries (LMICs) reached levels of around 100 µg/m^3, the epidemiology from which existing estimates had been derived was carried out in developed country urban settings where concentrations did not exceed 30 µg/m^3. For the previous (2000) GBD exercise, up to this level, a linear association was

adopted, and at higher levels this linear relationship had been assumed to continue to 50 μg/m^3, thereafter being flat with no further increase in risk *(188)*.
In order to allow prediction of risk at levels of AAP $PM_{2.5}$ above 30 μg/m^3, the expert group developed models that built on the prior work of Pope et al., drawing on risk estimates from AAP, AS, HAP (where available) and AS to describe the shape of the relationship at the higher level of exposure experienced in more polluted cities *(188)*.

This work also provided an opportunity to propose IHD and Stroke risk values for typical HAP exposure by interpolation, following on the argument put forward by Smith and Peel *(168)*. Deriving a risk estimate in this way, however, relies on the assumption of equitoxicity of combustion-derived $PM_{2.5}$ from the different sources contributing to the IER functions. This and other important assumptions used in the derivation of the IER functions are discussed further below.

Models were developed for mortality for four diseases (IHD, Stroke, COPD and lung cancer), and for child ALRI incidence, as most of the epidemiology relating to the last of these reports incidence not mortality. For HAP exposure with COPD and lung cancer, available epidemiological studies reported on living cases rather than deaths, although for lung cancer this is more or less equivalent as the majority of patients with this disease would be expected to have a very low 5-year survival, and to die from this cause. For COPD the situation is different since the timeframe between diagnosis, detection or treatment of prevalent cases (the point at which subjects are recruited into studies) and death attributed to this disease has a variable and potentially quite long time scale, and is amenable to some slowing of the process by preventive and therapeutic measures (albeit these may not be available to, or accessed by, populations in especially rural areas of developing countries). Over this period of time during which the patient has COPD, death may well occur from another cause. The implications of this are discussed further below.

Full details of the modeling are provided in Burnett et al. (2014) *(188)*. In brief, eight alternative models were assessed, including the form used by Cohen et al., linear, exponential, and the final version (ultimately adopted) that used an arbitrary power of concentration (hereafter referred to as the IER model). Goodness of fit was assessed by the Akaike (AIC) and Bayesian (BIC) information criteria, and the IER model returned the lowest values for both criteria. As risk of IHD and stroke declines with the logarithm of age, a linear regression model was used to adjust the relative risk from each source study, based on the mean age at death and with the intercept set at a risk of 1.0 for age 110 years.

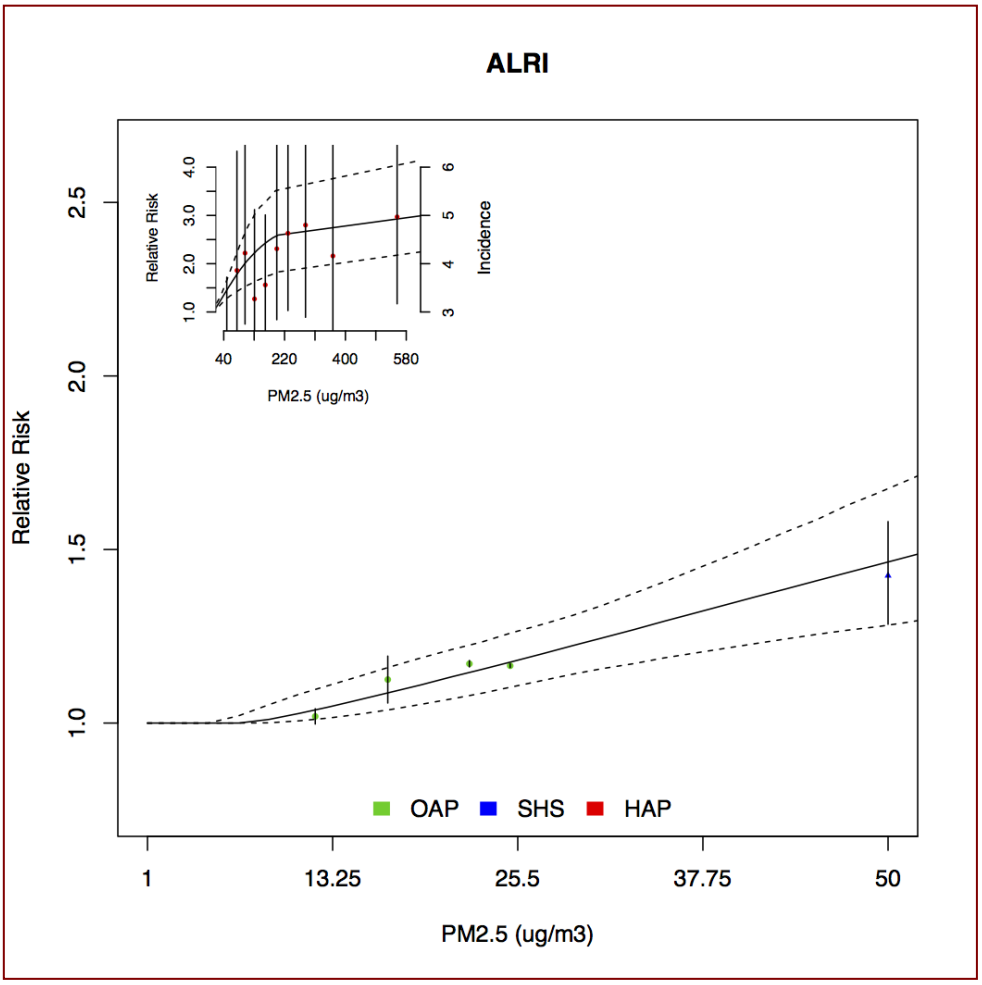
3.5.1 Child ALRI

For child ALRI, the model was built from risk estimates for AAP, SHS and HAP as follows (as young children do not smoke, no AS estimates are available):

- For AAP, a systematic review by Mehta et al. *(189)* identified four cohort studies as being suitable for inclusion.
- For SHS, 23 studies of parental smoking and ALRI reported by the Surgeon General (2006) *(190)* were included, each with an OR (95% CI) and an assumed exposure concentration of 50 μg/m^3 $PM_{2.5}$.
- For HAP, the incidence rates for ALRI at each decile of exposure in the RESPIRE study exposure-response analysis were used to provide rate ratios for all possible pairs (n=45), along with their corresponding estimated $PM_{2.5}$ exposure values. As noted in Section 3.2, the regression equation reported by Northcross et al. was used for the conversion of CO values to $PM_{2.5}$ *(185)*.
- The counterfactual used, that is the $PM_{2.5}$ concentration for which the RR is assumed to be 1.0, is the TMRED, centered on (approximately) 7 μg/m^3.

Given the importance of child ALRI as a health outcome, and the fact that direct HAP-related exposure-response data were available for this but no other outcome, particular attention is given to ALRI for the guideline recommendations, although the implications of IER findings for the other outcomes reported in this section are also important in terms of intervention impacts. The model for child ALRI is shown in Figure 3.4 where the predicted values of the model are indicated by the solid line and 95% confidence interval by the dashed line. Relative risks (RR) by exposure-type (i.e. AAP, SHS, and HAP) and 95% confidence intervals (error bars) drawn from the studies contributing to the model are presented (colour-coded by exposure type). The lower part of the graph includes data points for studies of AAP and SHS. The upper left hand insert graph represents household air pollution (HAP) concentration range, and shows the RR estimates based on each decile of CO exposure derived from the RESPIRE as described above.

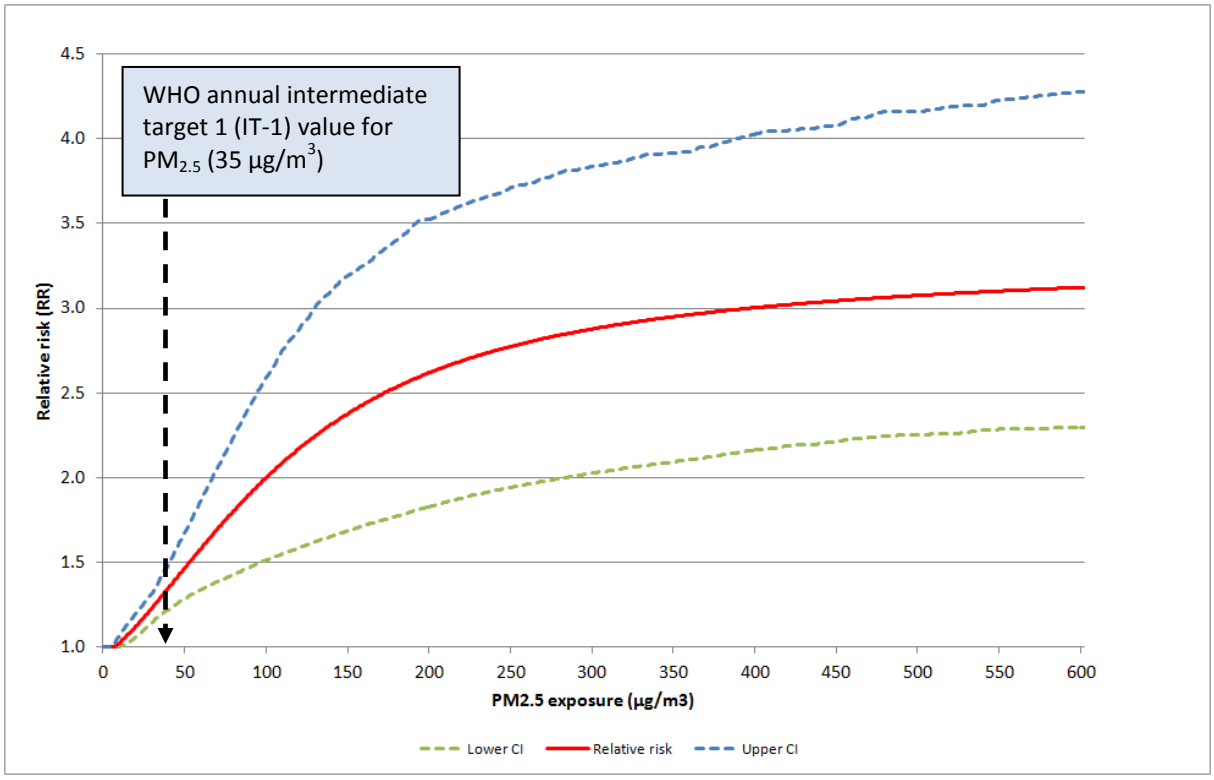
Figure 3.4: **IER model risk predictions for child ALRI incidence. Source: Burnett et al. 2014 *(188)*.**

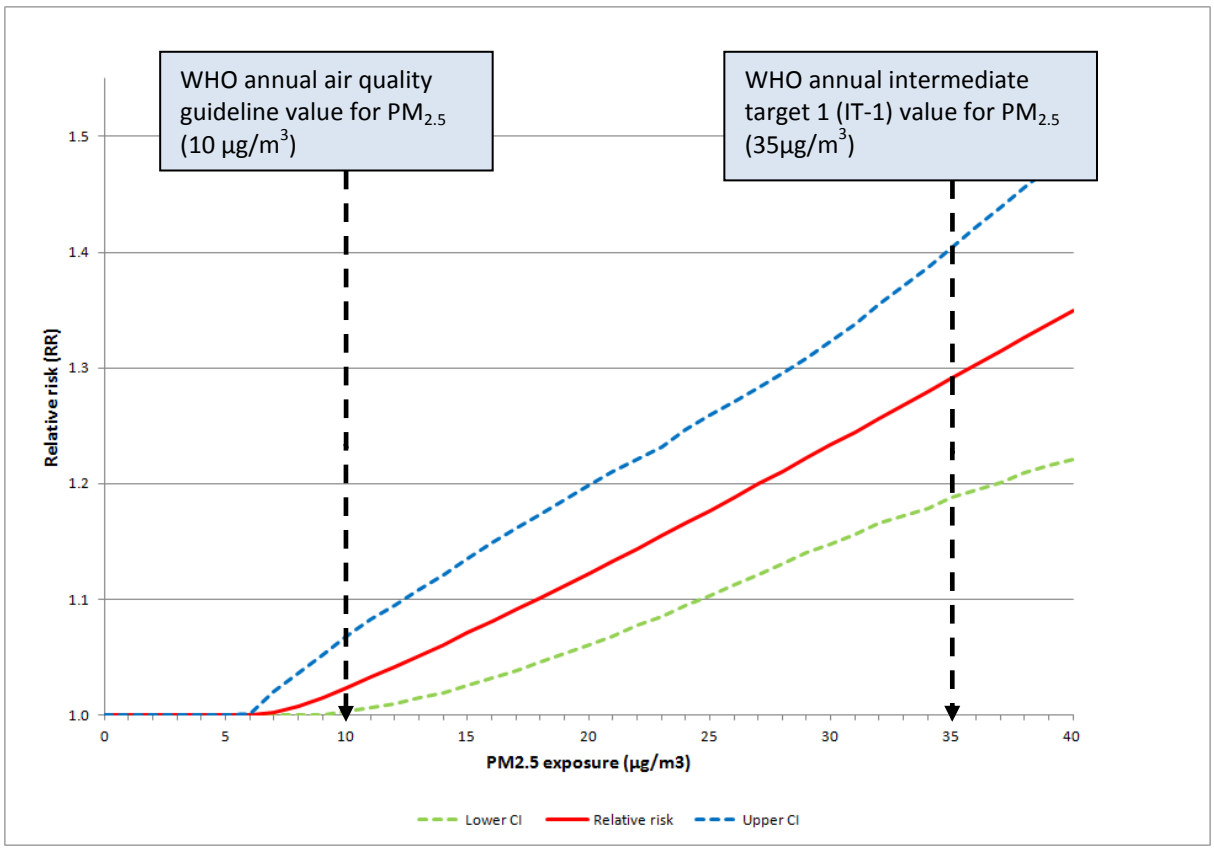


For ease of interpretation, the predicted values for ALRI risk are shown in Figure 3.5(a)

Figure 3.5 for the range 0-500 μg/m^3 with the WHO IT-1 annual average value of 35 μg/m^3 indicated, and in (b) for the range 0-40 μg/m^3 with the WHO air quality guideline annual average value of 10 μg/m^3 and the IT-1 indicated.

Figure 3.5: **The relationships between level of $PM_{2.5}$ exposure (µg/m^3) and relative risk (95% CI) of child ALRI predicted from the IER model for (a – upper graph) 0-600 µg/m^3 and (b – lower graph) 0-40 µg/m^3, with WHO AQG and IT-1 values indicated.**





The exposure-response findings for ALRI show a relatively steep slope at lower levels with relative risk reaching around 1.29 (95% CI: 1.19, 1.40) at 35 µg/m^3 $PM_{2.5}$, above which the slope continues to rise but becomes much shallower at around 200 µg/m^3 $PM_{2.5}$ at which point the predicted RR is 2.62 (1.83, 5.52). The curve does not flatten off completely, but has a shallow gradient that reaches 3.12 (95% CI: 2.30, 4.28) at the upper end of the exposure values shown in Figure 3.5, that is 600 µg/m^3.

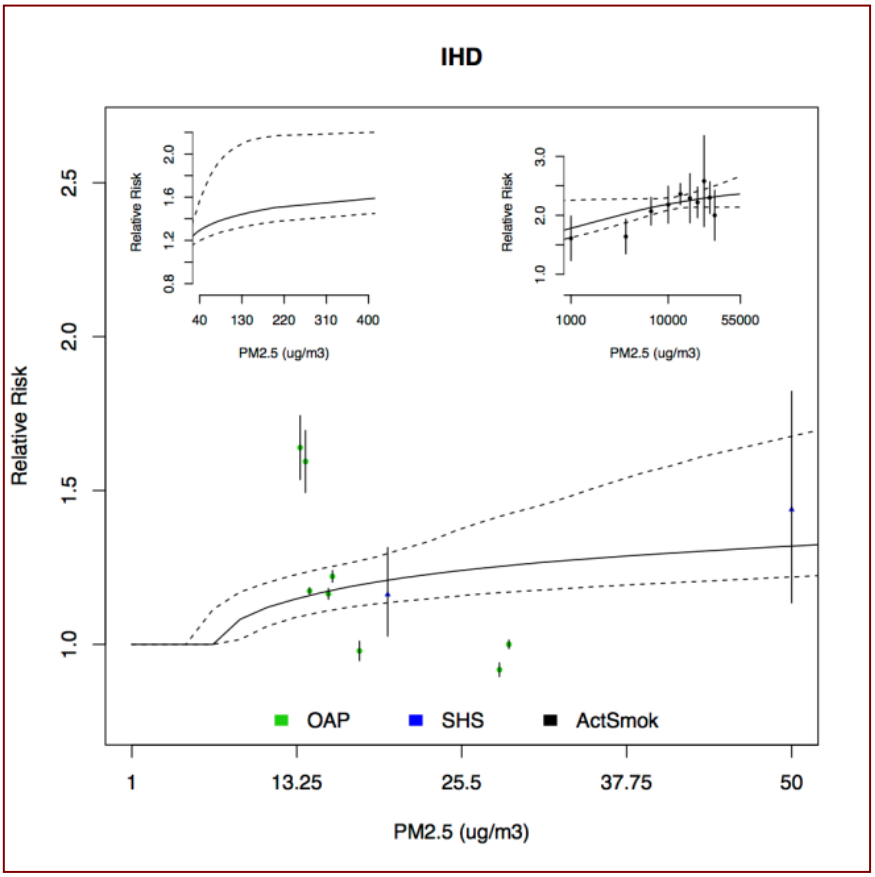
3.5.2 Other outcomes with IER models: IHD/stroke, COPD and lung cancer

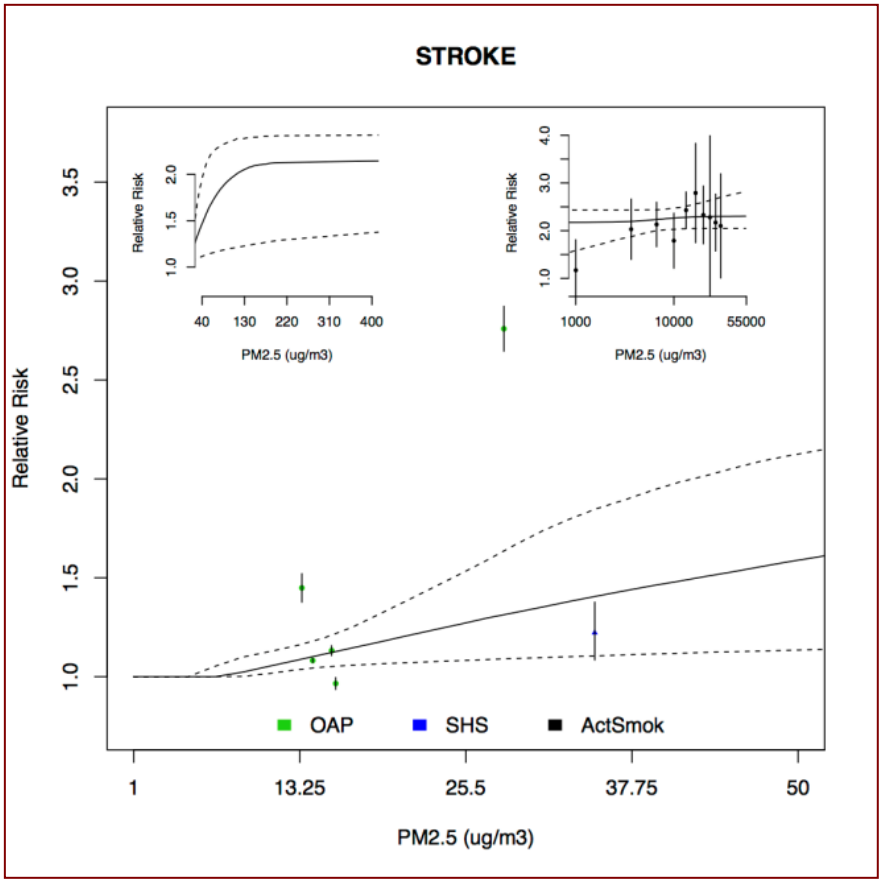
The IER functions for the other four outcomes are presented in Figure 3.6 to Figure 3.8 and employ an essentially similar approach and set of assumptions.

IHD and stroke

The predicted values of the IER models for IHD and stroke are shown in Figure 3.6 (a) and (b). The relative risk values are indicated by the solid line and 95% confidence interval by the dashed line. Relative risks (RR) by exposure-type (i.e. AAP, SHS, and AS) and 95% confidence intervals (error bars) drawn from the studies contributing to the model are presented (colour-coded by exposure type). The lower part of the graph includes data points for studies of AAP and SHS. For AAP, $PM_{2.5}$ exposure was determined in the studies from which risk estimates were obtained. For SHS, exposure was set at 20 µg/m^3 for low-moderate exposure and at 50 µg/m^3 for moderate-high exposure, these being categories for which RR estimates for IHD mortality were available; for stroke the mid-point of this range was used for the single SHS risk estimate used.

Figure 3.6: IER model predictions of risk for (a) [above] IHD and (b) [below] for stroke. Source: Brunett et al. 2014 *(188)*. See text for explanation.





The upper left hand insert graph represents household air pollution (HAP) concentration range, and it will be seen that no empirical risk estimates for IHD or stroke were available for this exposure type. The upper right hand insert graph depicts the active smoking concentration range, for which a large number of studies were available.

Exposure for AS was estimated on the assumption that smoking a single cigarette was equivalent to breathing a daily ambient concentration of $PM_{2.5}$ of 667 µg/m^3 assuming an average breathing rate of 18 m^3/day and inhaled dose of 12,000 µg $PM_{2.5}$ mass per cigarette. The counterfactual used for both of these outcomes, that is the $PM_{2.5}$ concentration for which the RR is assumed to be 1.0, is the TMRED, centered on (approximately) 7 µg/m^3.

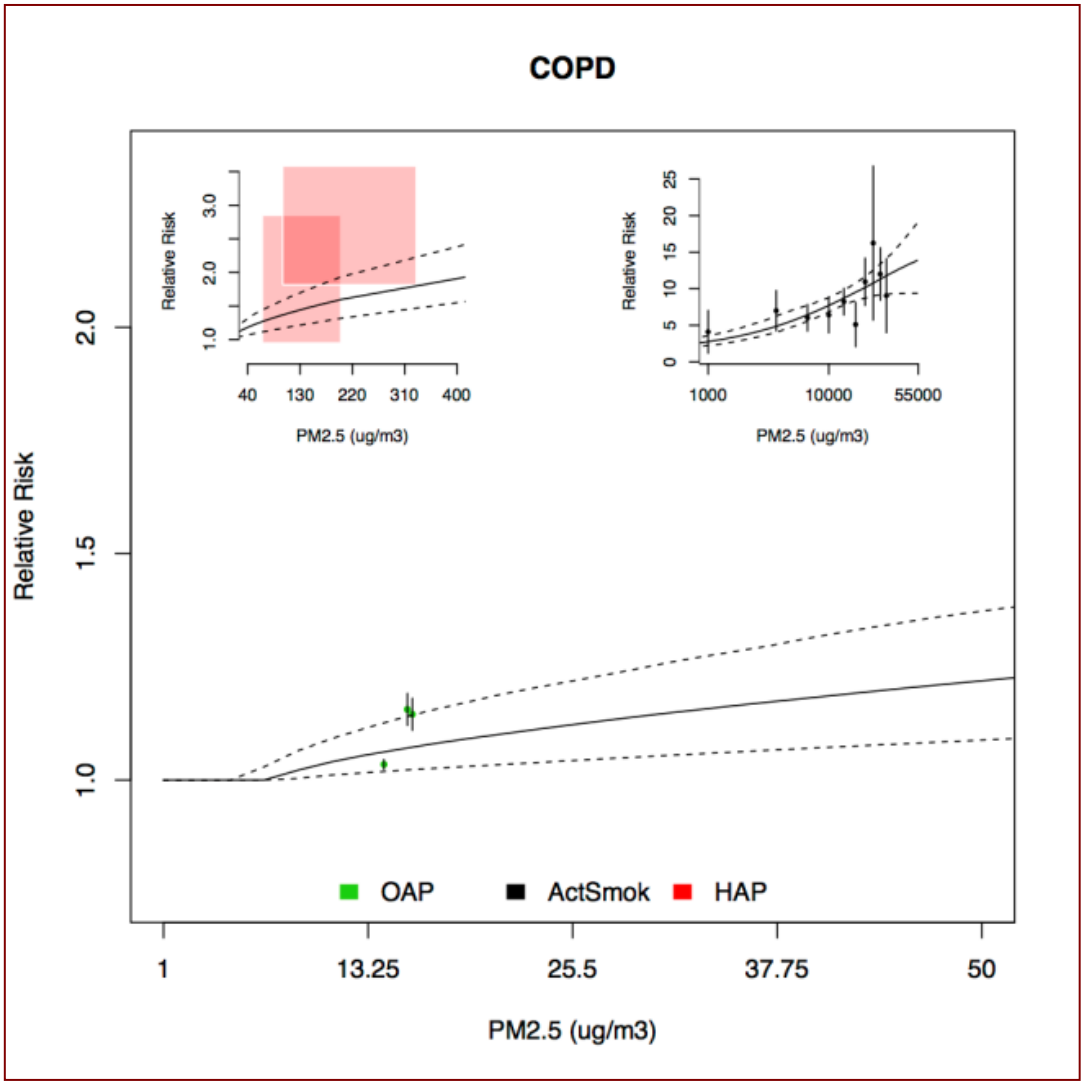
The curve for IHD is similar to that suggested by Pope et al. 2011, 'supralinear' in shape from low exposures and through the HAP exposure range, reaching an RR of 1.5 for high HAP exposure and a maximum of 2.5 for high AS exposure. The curve for stroke is similar, but appears to flatten off at levels well within the HAP range at a maximum RR of just over 2.0.

COPD

The predicted values of the IER model for COPD is shown in Figure 3.7. Explanation of the information included in the figure is the same as for IHD/stroke, except that (i) there was insufficient evidence to estimate a RR due to SHS exposure for COPD mortality, and (ii) for HAP shaded boxes indicate the exposure range and odds ratios obtained from the systematic review (Section 2.5.1). This method was used to display the HAP risk data since the source studies do not include measurements of exposure, and it is suspected that the 'unexposed' groups have levels of exposure well above the TMRED used as a counterfactual in the IER. Thus, $PM_{2.5}$ exposures were estimated at 300µg/m^3 and 200

µg/m^3 respectively for women and men in the 'exposed' groups of these studies, and at 100µg/m^3 and 65µg/m^3 respectively for men and women in the 'unexposed' groups. For each shaded box, the base represents the exposure contrast, and the height the associated risk; the higher values are for women.

Figure 3.7: IER model predictions of risk for COPD. Source: Brunett et al. 2014 *(188)*. See text for explanation.



It can be seen in Figure 3.7 that the risk estimates from the meta-analysis of COPD studies lie somewhat above the model curve; possible reasons for this are discussed in Section 3.5 below. In the model, the curve rises steadily across the HAP range, and continues to do so with increasing AS exposure to reach a RR of around 15 at the highest AS exposure.

Lung cancer

The predicted values of the IER model for COPD is shown in Figure 3.8. Explanation of the information included in the figure is similar to that for COPD, except that coal and biomass exposure treated as equitoxic for a given level of exposure to $PM_{2.5}$. Although this may be questioned, there is insufficient evidence to determine different levels of risk for these two fuel types. In addition, slightly different assumptions were made about the levels of $PM_{2.5}$ exposure in the source epidemiological studies, which – as with COPD – did not include exposure measurement. While values for the 'exposed' groups were assumed to be the

same as for COPD, those for the unexposed groups were set at 70 µg/m^3 and 45.5 µg/m^3 for women and men respectively. The interpretation of the shaded boxes is otherwise similar.

Figure 3.8: IER model predictions of risk for lung cancer. Source: Burnett et al. 2014 *(188)* See text for explanation.

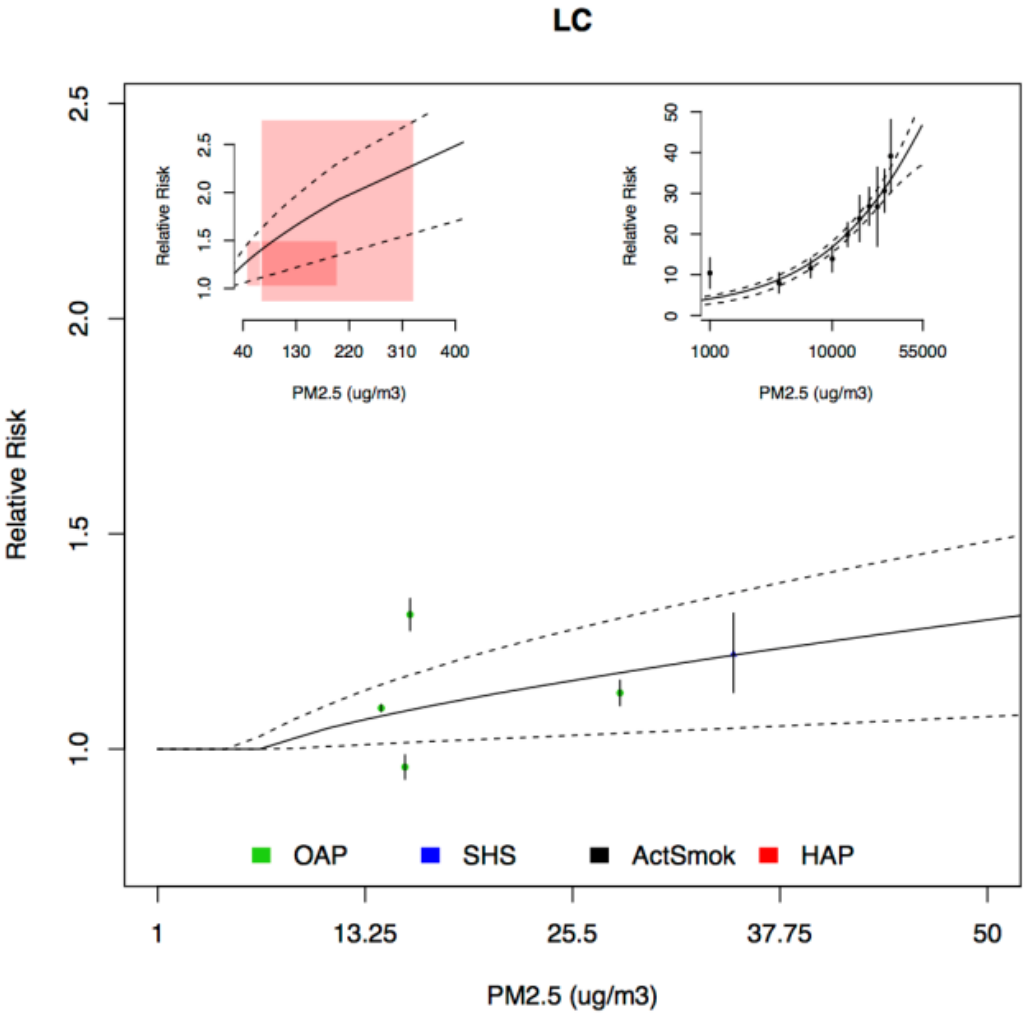


Figure 3.8 shows that the IER risk function for lung cancer is much closer to a linear relationship: RRs in the range 1.5 to 2.5 are seen across the HAP range, but reach more than 40 at the highest levels of AS exposure.

3.6 Assessment of strength of exposure-response evidence

Given the very limited amount of directly measured exposure-response evidence and the nature of the IER models, it is not appropriate to develop GEPHI profiles, but it remains useful to consider similar criteria in assessing the strength of this body of evidence including possible implications of the assumptions, and its suitability for developing recommendations. In doing this, a generic assessment of the evidence from the IER models is made, Table 3.2, followed by more specific discussion of the evidence available for child ALRI and other quality issues for IHD/Stroke and COPD.

Table 3.2: Generic issues relating to the IER functions:

Criterion	Assessment
Number of studies	A good number of studies are available for each outcome in the models, and for each source of exposure, with the exception of ALRI (all HAP risk estimates are based on the RESPIRE study, but see below for further discussion of consistency with systematic review of solid fuel use and ALRI), and IHD/stroke for which no studies were available at the time of model development, also discussed separately below.
Risk of bias	Studies have generally used adjusted risk estimates, although some residual confounding is possible. Age-adjustment was carried out for IHD and stroke to account for the reduction in risk with increasing age. The main source of bias may come from estimates of the true exposure, with the exception of the RESPIRE study which measured this directly, albeit via a single pollutant (CO) as a proxy. Thus, exposure levels in SHS have been estimated and may not be accurate, and furthermore those exposed to SHS may also be exposed to AAP, and vice-versa.
Indirectness	Studies providing risk estimates have direct measures of risk of the outcomes of interest. Some indirectness may result from combining sources of $PM_{2.5}$ and the assumption that risk of $PM_{2.5}$ exposure increases with dose, independent of the source; at the current state of knowledge, however, there is insufficient evidence to suggest this is not the case. There is some suggestion reported in foregoing sections that wood smoke may be associated with a higher risk of COPD than coal, and that coal exposure may have a higher risk of lung cancer than wood. In both cases, however, the respective 95% CIs overlap, and other sources of heterogeneity may contribute
Imprecision	The 95% CIs have been calculated for the functions, and are shown in Figure 3.5 (a) and (b). There is generally greater precision for exposure from active smoking compared to the other sources, reflecting the extent of epidemiological evidence and precision of the component studies. This does however mean that the 'high end' of the IER functions are relatively well estimated, which in turn lends some more precision to the upper end of the HAP range of exposure. The exception is child ALRI for which no risk data are available for AS.
Inconsistency	The alternative models were assessed by AIC and BIC, and the IER version performed best in terms of fitting the data. Figures 3.6 to 3.8 illustrate the estimates from all contributing studies for the four adult disease conditions, and for all sources of $PM_{2.5}$. These show the degree of inconsistency, which is quite substantial in some cases, especially at the lower levels of exposure associated with AAP and SHS, although much less so for high exposure resulting from AS. For HAP, there were no estimates for IHD and Stroke, and although more than 20 studies are available for COPD, the meta-analysis estimates did not fit well (see discussion below).
Publication bias	Publication bias was assessed in the systematic reviews carried out for HAP risks for the CRA. There was no strong evidence of publication bias for the reviews of child ALRI or for lung cancer with exposure to coal and biomass. For COPD there was evidence of publication bias and could be contributing to over-estimation of the risk estimates, but the available reviews are not entirely consistent on this finding (see discussion in Section 2.5.1)

ALRI

As noted above, child ALRI has the most direct exposure-response data for HAP, and is a very important outcome in a vulnerable population group. Consequently, there is a good case for giving this special attention in term of the recommendations. In addition to the generic issues concerning quality of this evidence, there are a number of specific issues regarding the strength of evidence for the ALRI IER function. As there are no estimates from AS, the 'upper' bound of the curve is dependent on HAP, which is derived from a single study. On the other hand, a strong aspect of this evidence is that the HAP data points are

based on direct individual subject (child) exposure measurement, which is not available for any other source or outcome in the IERs. Some additional uncertainty arises from the possibility that the epidemiology of ALRI may differ between AAP and SHS results (all developed countries) and HAP (developing countries, also high altitude).

The consistency of the IER function with the systematic review and meta-analysis of child ALRI reported in Section 3 of this review can also be assessed. That review provided a pooled OR of 0.63 (95% CI: 0.53, 0.75) for all ALRI, and the exposure contrast in these studies is estimated to be around 300 μg/m^3 $PM_{2.5}$ for the 'exposed' groups which used traditional solid fuel fires and stoves, and around 50-75 μg/m^3 $PM_{2.5}$ for the 'unexposed' groups consistent with what has been measured in studies of clean fuel users in developing country settings (see Reviews 5 and 6). The child ALRI IER function predicts an increase in RR from 1.64 (1.36, 1.96) to 2.88 (2.03, 3.84) as exposure increases from 65 to 300 μg/m^3 $PM_{2.5}$; this is equivalent to a RR ratio of 1.76, and indicates a good level of consistency between the IER and the available epidemiologic evidence on solid fuel use and ALRI risk.

IHD/Stroke

For IHD/Stroke, the two studies published subsequently are described in Section 2 of this review; one was unadjusted and hence not useful for comparison, the other reported ORs of 2.58 (1.53, 4.32) for CVD and 1.60 (0.80, 3.21) for stroke, when comparing ever use of solid fuels (coal, biomass) for cooking and/or heating with never use. Although actual long-term average exposures in these groups are not known, the CVD estimate appears somewhat high compared to the HAP range of the IER model (although within the 95% confidence intervals), while the stroke estimate is more consistent.

COPD

The poorer fit of the HAP estimates for COPD may result from the fact that exposure begins very early in life (in utero), compared to late teenage years or early adulthood for smoking, so risk could be expected to be higher for a given level of exposure due to longer duration, and possibly exposure during critical periods of life and lung development.

Summary

Direct, quantified evidence on exposure-response relationships are limited to two studies for one outcome (child ALRI), and these two sets of data could not easily be combined. Some exposure-response evidence is available for other outcomes, and was reviewed in Section 2 of this review, and while useful for establishing causation, is not quantified in terms of exposure. The IERs are a relatively new approach and have some important assumptions, but are mostly based on an extensive and broad evidence base. That for child ALRI has the only directly assessed individual exposure data, and shows consistency between the IER and pooled estimate for the predominantly observational epidemiological studies available.

3.7 Conclusions and implications for policy

The shape of the exposure-response functions described here have important implications for the expected impacts of different stove technologies and fuels, and hence for policy.

The IER for child ALRI is considered especially important in that regard, and indicates that while reductions of 50% or so in exposure from the levels experienced in homes using traditional solid fuels and stove can be expected to result in small reductions in risk, the very clear message is that much larger reductions down to levels close to the WHO IT-1 of 35 μg/m^3 $PM_{2.5}$ for long term average exposure are needed to prevent most of the ALRI cases attributed to HAP.

The IER functions for IHD and stroke are comparable to that for child ALRI, with similar implications for expected health benefits.

The IER for COPD is currently less clear across the HAP range but the high exposure area from AS shows that risk continues to rise with exposure to high levels. This suggests less of a plateau effect as seen with ALRI, IHD and stroke, and that reduction in exposure across the HAP range may lead to more proportionate reductions in risk. There is some evidence to support this, albeit from a coal-using area, in that a large cohort study in Xuanwei (an area where chimney stoves had been widely adopted) found that long-term users of improved chimney stoves (which are unlikely to have delivered very low levels of HAP and exposure, although this was not measured in the study) were associated with adjusted hazard ratios of 0.58 (95% CI: 0.49, 0.70; P < 0.001) in men and 0.75 (0.62 to 0.92, P = 0.005) in women, with risk reduction becoming unequivocal in both sexes after around 10 years with the improved stove *(191)*.

For lung cancer, the IER is more clearly linear and consistent with the HAP meta-analysis estimates. This has similar implications for benefit as suggested for COPD, and again some evidence is available to support this from the same coal-burning area of China. Another large cohort study in Xuanwei found risk ratios (RRs) for lung cancer after stove improvement to be 0.59 (95% CI: 0.49, 0.71) in men and 0.54 (95% CI: 0.44, 0.65) in women, with P<0.001 for both sexes *(127)*. As with COPD, incidence reduction became unequivocal about 10 years after stove improvement. The authors report that HAP levels in chimney stove homes were less than 35% of those with unvented combustion, although these data were obtained from a sample of just 13 homes in which 5-day sampling was carried out with and without the chimney blocked. More representative data on the levels of HAP and reductions achieved in NISP areas are reported in Review 6, which suggest that in general levels of HAP may not have been reduced by as much as 35%.

While the IERs and limited supportive evidence from the two cohort studies for lung cancer and COPD suggest that risk reduction could be more proportionate to exposure reduction, this is clearly not the case for child ALRI, and maybe also for IHD and stroke. Policy needs to protect all members of the population, and especially young children, and for that reason recommendations should be driven by the evidence for this age group. Furthermore, in the absence of exposure-response evidence for other important child (e.g. low birth weight) and adult (e.g. TB, cataract) outcomes, it should probably be assumed that the non-linear functions could apply.

4. Health risks from household use of gaseous fuels

4.1 Summary

Background
Gas, along with electricity, is the dominant household fuel in developed countries, and is a potentially important clean fuel option for household in developing countries currently using more polluting fuels. Household combustion of gas results in emission of a range of pollutants known to impact health, including particulate matter (PM), carbon monoxide (CO) and nitrogen dioxide (NO_2).

Objective and key questions
The objective of this review is to summarise the evidence available on health risks from combustion emissions from household use of gas. The specific questions addressed by the main systematic review reported are the risks for childhood asthma and wheezing from exposure to gas cooking, and to elevated levels of NO_2.

Methods
A narrative review of prior evidence is presented, including that used for the published WHO air quality guideline for NO_2. A summary is provided of a recently published systematic review and meta-analysis which investigates the risks for childhood asthma and wheeze.

Results
Pollutant emissions from gas cooking can exceed WHO air quality guidelines, but this usually results from poor equipment, poor maintenance, and inadequate ventilation. There is evidence that gas cooking increases the risk of childhood asthma (OR=1.32; 95% CI: 1.18, 1.48), and that a 15 ppb increase in NO_2 is associated with an increased risk of wheeze (OR=1.12; 95% CI: 1.04, 1.21). Findings for other health outcomes are inconsistent and weak.

Conclusions
There is evidence that gas cooking, and the associated increases in NO_2 exposure, can increase the risk of asthma and/or wheeze in children, but elevated levels of pollutants are more likely with poor quality equipment and maintenance, and inadequate ventilation. Gas represents an important cleaner fuel option for many households, but its promotion should be accompanied by proper maintenance and ventilation. Safety (prevention of leaks and explosions) is also important, and is addressed eleswhere in these guidelines.

4.2 Introduction

In the past decades, natural gas, liquefied petroleum gas (LPG) and electricity replaced biomass, kerosene, coal and charcoal as the main household cooking fuels at the top of the energy ladder, with the majority of users in developed countries. Natural gas and LPG are in themselves relatively non-toxic but combustion products during cooking have been linked to adverse health effects in humans. Those products include nitrogen dioxide (NO_2), nitric oxide, nitrous acid, volatile organic compounds, particulate matter, carbon monoxide and sulphur dioxide *(192)*. The most extensively studied product is NO_2, partly because a convenient, portable, cost-efficient but accurate method for sampling indoor NO_2 has been well developed *(193)* and sampling has been done in a sufficient number of household locations.

The health risks of indoor NO_2 exposure were extensively reviewed during preparation of the WHO indoor air quality guidelines on specific pollutants, drawing on studies of all sources of NO_2, including gas cooking and heating *(8)*. Indoor NO_2 from gas cookers in kitchens often exceeds the WHO air quality guideline value of 200 μg/m^3 in 1 hour and has the potential to delete tissue antioxidant defenses, induce cytotoxicity, change lung metabolism, structure and function, cause inflammation and increase susceptibility to pulmonary infections. *(8)*. The 2010 WHO guidelines concluded that in controlled exposure studies where concentrations reached several hundred μg/m^3 NO_2 over several hours, there was strong evidence of acute respiratory health effects. For epidemiological studies, there was limited or suggestive evidence that NO2, at levels currently experienced in populations, for reported respiratory symptoms in children and adults, and an increase in symptoms and severity following viral infections among children with asthma. Only one study was reported which provided some evidence that LPG (bottled gas) users in Italy had higher symptoms prevalence than natural gas (piped) users, and it was suggested this was caused by less complete combustion of the former. No evidence was cited for an increased risk of ALRI or other important health outcomes reviewed here.

This summary report builds on this foundation of evidence, and focuses on the health effects of gas cooking and indoor NO_2 with gas cookers in home, drawing on the main published reviews, and a recently conducted systematic review with meta-analysis by Lin et al. *(194)*.

Research into the health effects of gas cooking exposure was carried out particularly in children by during the 1970s and early 1980s in Europe and the USA, where the comparison fuel generally was electricity. Although the link between respiratory diseases and unvented gas cookers (and high concentrations of NO_2) was widely accepted, the results of many of these studies were in fact contradictory. Studies on larger population groups or smaller scale studies focusing on subgroups with high levels of exposure were therefore suggested *(195)*. In the late 1980s to 1990s, substantial numbers of studies of infants, children and adults and infants were conducted. The 1992 Hasselblad meta-analysis *(196)* became a benchmark review for the relationship between indoor NO_2 and respiratory illness in children, and was considered as an important reference for the outdoor NO_2 air quality guideline value in 1997 *(197)*. Since then, numerous reviews *(8, 198-205)* and further studies of household gas cooking and indoor NO_2 exposure and health effects have been published. There is no shortage of recent reviews in this field, although few have provided quantitative risk estimates *(198, 206)*.

4.2 Causes of indoor air pollution related to gas cooking

4.2.1 Poor-quality or ill-maintained gas stoves

Elevated levels of pollutants related to emissions from gas, particularly NO_2, particulate matter and carbon monoxide (CO) usually result from poorly maintained gas stoves. For example, in a study of 270 homes in the UK, 18% exceeded the mean World Health Organization 8-hour indoor air quality guideline for CO of 8.6 ppm (10 mg/m^3), and 9.4% exceeded the 1-hour level of 26 ppm (35 mg/m^3). Further investigation carried out by qualified gas engineers found that these exceedences were mostly due to older, poorly-maintained gas cookers and incorrect installation *(207)*.

4.2.2 Inefficient or inadequate ventilation

Gas stoves with ventilation to the exterior of the home should result in only minimal combustion pollutants in the indoor air, but clearly this can only be realized if the ventilation system is functioning well. Unvented gas appliances, including stoves and ovens, can give

rise to substantial quantities of NO_2, ultrafine particles and CO *(207-208)*. In a study of 319 women in Hong Kong, personal NO_2 levels were found to be 11% higher when they did not have adequate ventilation in the kitchen *(209)*.

4.3 Main findings from epidemiological studies

4.3.1 Asthma and asthma symptoms (wheeze/short of breath)

Jones et al. *(200)* concluded that indoor NO_2 from gas cooking along with other indoor pollution may be an important risk for asthma, although this 1998 review focused on only two studies. A subsequent review by the same authors *(210)* addressed the same question, and included discussion of the mechanism by which indoor NO_2 might cause asthma, and drew similar conclusions. A review by Strachan et al. of large studies from Europe and North America in 1991-1999, *(201)* found that the role of gas cooking in initiating asthma remained uncertain due to inconsistent findings. Belanger et al.*(192)* reviewed studies conducted mostly after the year 2000, and concluded that evidence for a relationship between gas cooking (and indoor NO_2) and asthma prevalence or asthma symptoms was inconsistent, although the findings were more consistent for children than among adults. A recent review by Heinrich*(205)* sought to assess the evidence for causality for gas cooking (and indoor NO_2) and childhood asthma using four-level criteria, and concluded that the current evidence was insufficient to support causality.

The inconsistency among studies may be due to variation in the exposure metrics used, which include presence of gas cookers in some and direct NO_2 sampling in others. However, even when restricted to studies using only quantitative NO_2 measurement, Weichenthal et al. *(203)* did not find consistent evidence for an association between indoor NO_2 and asthma. Despite these inconsistencies, the few quantitative reviews do suggest an association between gas cooking and childhood asthma and wheeze in children. Nitschke et al. *(198)* conducted a meta-analysis of three studies in children which indicated a significant increase of 20% in asthma and 12% in wheezing with exposure to gas cooking. The most recent and comprehensive systematic review and meta-analysis of this topic was carried out by Lin et al. *(194)*, and this is summarized and discussed below.

Systematic review of risk of childhood wheeze and asthma with gas cooking

This systematic review, which was published in 2013, examined the risks for wheezing and asthma in children, with exposure to gas cooking, and also to elevated NO_2. The reader is referred to the published paper for full details of the methods, which are summarized in Box 4.1 and the flow chart in Figure 4.1. The key questions for this review were:

1. What are the risks for childhood asthma and wheezing from exposure to gas cooking?
2. What are the risks for childhood asthma and wheezinfg with a 15 ppb increase in NO_2 levels in the home?

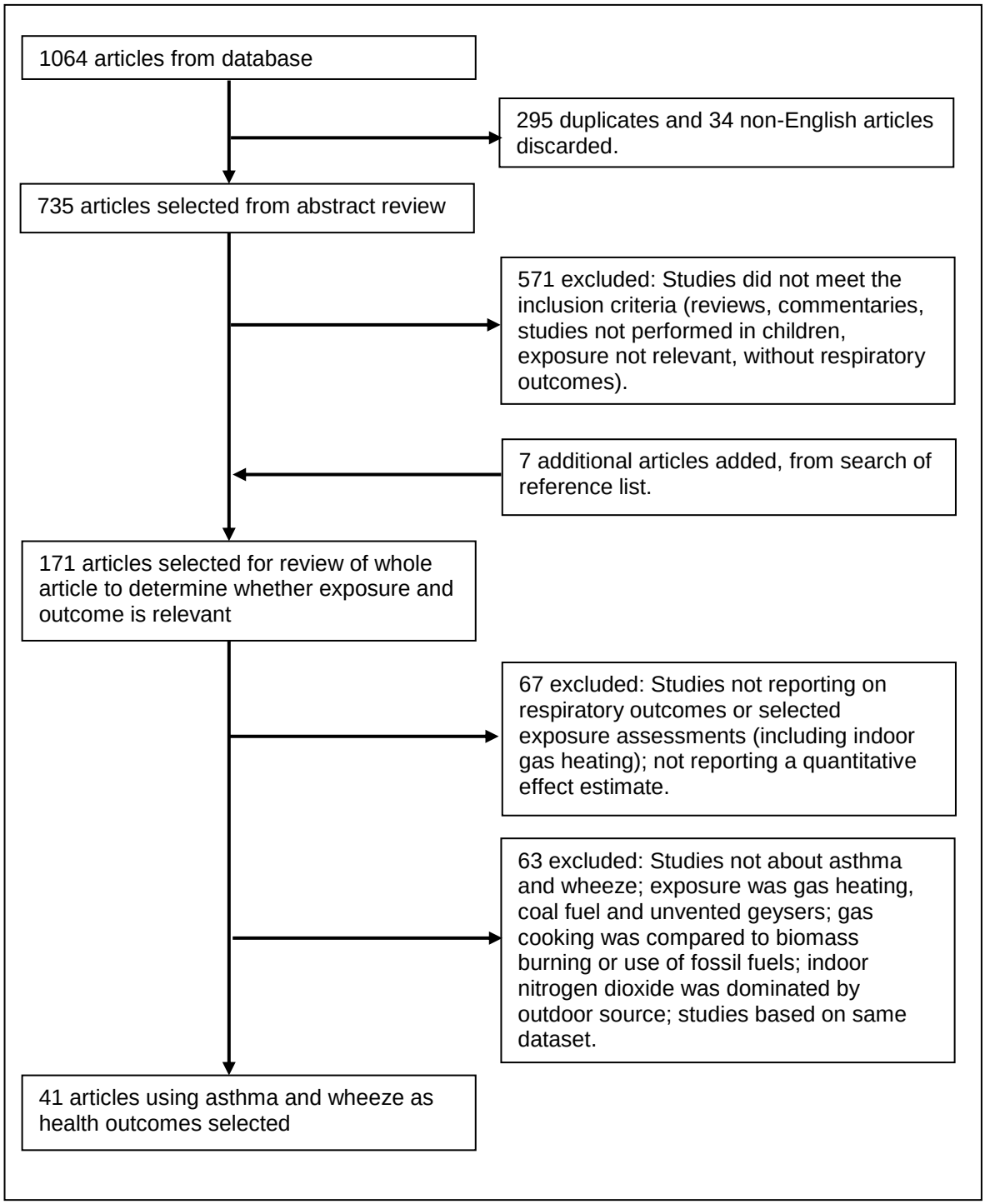
The search terms used were (i) indoor nitrogen dioxide and children; (ii) personal nitrogen dioxide and children; (iii) gas cooking and children; (iv) gas appliance and children; (v) unvented and children; (vi) gas heating and children; and (vii) gas heater and children. The seven search results were combined with the Boolean operator ‘or’.

Box 4.1: Summary of methods for Lin et al. (2013)

- Period of search: 1977 to 31 March 2013
- Databases: PubMed, ISI web of knowledge.
- Inclusion criteria: (i) exposure to gas cooking, gas heating, measured NO_2 levels within family houses; (ii) respiratory disease in infancy or in childhood; (iii) report an odds ratio or sufficient data to estimate them
- Number of studies: 41
- Languages: English

The search identified 41 studies of childhood asthma or wheeze published from 1979 to 2013 that had either indoor NO_2 or the use of gas for cooking as the exposure metric. The report created a new classification for asthma and wheeze based on the time of occurrence in order to deal with the variable definitions used in each independent study, that is, current /lifetime asthma, and current/lifetime wheeze. “Current” was defined as having incident asthma (or wheeze) and the symptoms occurred within the past 12 months before the questionnaire. “Lifetime asthma” was defined as ever having been diagnosed with asthma by a doctor. “Lifetime wheeze” was defined as wheeze ever.

Figure 4.1: Flow chart for systematic review by Lin et al. 2013.*(194)* Reproduced with permission



Results

A total of 41 eligible studies were included, although fewer studies were available for sub-categories of exposure (gas cooking or NO_2) and outcome (asthma or wheeze, and sub-sets of these). More studies were available for wheeze than for asthma, and for gas cooking than for elevated NO_2, see Tables 4.1 (a) and (b). Sixteen of the studies were cross-sectional designs, 18 cohort studies, and 7 case-control studies; there were no randomized trials or other interventions-based studies.

The main findings are summarized in Tables 4.1 (a) and (b), including I^2 results for heterogeneity which were statistically significant only for current and all asthma with exposure to gas cooking. Random and fixed effects meta-analysis results are provided for all main analyses. Forest plots are provided in the published paper. There was no evidence of publication bias.

Asthma

The review found that household gas cooking was associated with significantly increased odds of current asthma (1.42; 95% CI, 1.23-1.64), and lifetime asthma (1.24; 95% CI, 1.05-1.47) in children. The overall risk for asthma (current + lifetime) and gas cooking exposure was 1.32 (95% CI, 1.18-1.48), and for a 15 ppb increase in NO_2 was 1.09 (95% CI, 0.91-1.31).

The estimates varied little by age (≤6 years, 6-10 years and >10 years). For wheeze, there was a significant association with indoor NO_2 (1.12; 95% CI, 1.04-1.21), but not with gas cooking exposure (1.06; 95% CI, 0.99-1.13).

Table 4.1: Summary of main results from systematic review of (a) asthma and (b) wheeze risk with exposure to gas cooking and elevated NO_2 levels *(194)*.

(a) Asthma:

Exposure	Outcome	Number of estimates	Heterogeneity (I^2%, p-value)	Odds ratio (95% CI)	
				Random effects	Fixed effects
Gas	Current asthma	13	2.9%; p=0.417	1.42 (1.23, 1.64)	1.42 (1.24, 1.63)
	Lifetime asthma	8	31.1%; p=0.180	1.24 (1.04, 1.47)	1.24 (1.11, 1.38)
	All asthma	21	19.8%; p=0.204	1.32 (1.18, 1.48)	1.30 (1.20, 1.42)
15 ppb increase in NO_2	Current asthma	2	71.5%; p=0.061	1.36 (0.57, 3.29)	1.33 (0.83, 2.12)
	Lifetime asthma	3	0.3%; p=0.367	1.08 (0.95, 1.23)	1.08 (0.95, 1.23)
	All asthma	5	35.5%; p=0.185	1.09 (0.91, 1.31)	1.10 (0.97, 1.24)

(b) Wheeze:

Exposure	Outcome	Number of estimates	Heterogeneity (I^2%, p-value)	Odds ratio (95% CI)	
				Random effects	Fixed effects
Gas	Current wheeze	27	50.4%; p=0.002	1.07 (0.99, 1.15)	1.05 (1.01, 1.10)
	Lifetime wheeze	6	0.0%; p=0.654	1.02 (0.90, 1.16)	1.02 (0.90, 1.16)
	All wheeze	33	42.8%; p=0.006	1.06 (0.99, 1.13)	1.05 (1.01, 1.09)
15 ppb increase in NO_2	Current wheeze	10	5.0%; p=0.395	1.15 (1.06, 1.25)	1.15 (1.06, 1.24)
	Lifetime wheeze	1	N/A	1.04 (0.92, 1.17)	1.04 (0.92, 1.17)
	All wheeze	11	11.3%; p=0.337	1.12 (1.04, 1.21)	1.11 (1.04, 1.19)

Findings from sensitivity analysis

Detailed sensitivity analysis was carried out with the following main findings. Restricting to studies with adjustment for confounding made little difference to the overall results, and the estimates varied little by age (≤6 years, 6-10 years and >10years). Studies in which <30% of the participants were cooking on gas tended to have higher risk, possibly (although this was not suggested by the authors) as may have been more residual use of other fuels, including solid fuels, and other sources of pollution).

The timing of the research appeared to have some effect, as studies published after 2000 tended to have lower risk, possibly (as suggested by the authors) due to more use of microwaves, better gas cookers, and more ventilation in kitchens. There was also some evidence of geographical variation, studies from Europe and Asia-Pacific higher risk than North America, but no explanation offered for this by the authors.

Discussion and conclusion

A number of reasons for the inconsistency between findings for asthma and wheeze for the two types of exposure are considered by the authors, and also in an accompanying commentary on the review by Vrijheid *(211)*.

The authors first note that wheeze and asthma can be considered as somewhat distinct outcomes, and that definitions vary including that one-time wheeze is used in many of the studies. It is also noted that gas emits more pollutants than just NO_2, including for example ultrafine particles, which could explain some of the different findings between gas cooking and elevated NO2 exposure. Residual confounding from factors associated with gas cooking are also considered, but the review authors think this is unlikely as most studies included adjustment for factors known to increase the risk of asthma. Vrijheid also considers this explanation and suggests that gas-using homes may differ from those using electricity with respect to asthma risk factors. Finally, the review authors also point out that there could have been insufficient power to detect a relationship for asthma with exposure to elevated NO_2, as there were fewer studies (five in total).

The conclusion reached by the authors is that the review provides quantitative evidence that, in children, gas cooking increases the risk of asthma, and indoor NO_2 increases the risk of wheeze. In the commentary, Vrijheid concurs by calling for effective control measures of gas cooking-related emissions, but also sounds a note of caution about the need to assess co-exposures and co-risk factors.

The overall assessment of risk from gas cooking is considered further in the conclusions to this review.

4.3.2 Lower respiratory tract illnesses

The systematic review and meta-analysis by Hasselblad et al. *(196)* referred to above, included 11 studies conducted in the United Kingdom, the Netherlands and the USA, and concluded that a 15 ppb increase in long-term indoor NO_2 exposure is associated with a 18% [95% CI: 11%, 25%] increase in the risk of lower respiratory tract illness (LRI) in children. In these studies, LRI was a broad definition that included any symptoms of colds going to chest, chronic wheeze and cough, bronchitis, chest cough with phlegm and shortness of breath. All but one of the studies reported an increased risk of LRI with higher exposure.

4.3.3 Upper respiratory tract infection

A few studies have examined the relationship between gas cooking and upper respiratory infections, mainly in infants *(212-213)*, but no significant association has been reported.

4.3.4 Chronic cough

Several studies have suggested that children exposed to gas cooking and indoor NO_2 may have a higher risk of chronic cough without colds, *(214-216)* cough in morning, *(214-215)* cough during the day and the night *(215)*. Several other studies, however, have not reported an increased risk *(217-220)*.

4.3.5 Lung function and Bronchial hyperreactivity (BHR)

Findings on the effects of gas cooking (and indoor NO_2) on lung function are inconsistent. Thus, Moshammer et al. *(221)* and Gillespie-Bennett et al. *(222)* found significantly reduced FEV_1 in children, while others found no effect *(223-227)*. It appears that current evidence does not provide sufficient support for an association between gas cooking (and indoor NO_2) and reduced lung function. Two studies have reported an association between gas cooking and indoor NO_2 and increased BHR in children, although there were conflicting findings for atopic and non-atopic children *(228-229)*.

4.3.6 Diarrhoea

In a review of epidemiological studies examining links between indoor NO_2 and diarrhoea in infants, Farrow et al. reported two British studies that showed significant associations *(230)*. One hypothesis for this finding is that nitrogen oxides may break the balance of the nitrate/nitrite pathway that can increase the likelihood of gastrointestinal infection and diarrhoea.

4.4 Discussion

Many of the studies reviewed have shown wide variability in health risks among infants, children and adults as a result of gas cooking exposure. Knowledge of which factors are responsible for this heterogeneity is important for determination of causality and for future study design. Although susceptibility and physiologic maturation of the respiratory system can account for part of this inconsistency, a number of methodological factors could be operating, such as differing definitions of health outcomes (e.g., incident vs. prevalent asthma), presence or absence of ventilation in kitchens, condition and maintenance of cooking/heating equipment, duration of indoor NO_2 sampling, and the role of other indoor co-pollutants.

Gas cooking is undoubtedly a major source of indoor NO_2, but the question arises as to whether this serves as an adequate measure of NO_2 exposure. Many studies have categorized personal NO_2 exposure on the basis of the presence of gas cooking, gas heating, other some other source of fuel combustion in home, as well as traffic-related NO_2 from outdoors. Various of the reviews have indicated that normal use of a vented gas stove can result in NO_2 above background concentrations in the home, that the presence of gas stoves contributed a much higher concentration of indoor NO_2 compared to electric stoves *(210)*, and that indoor NO_2 was highly correlated with personal NO_2 in the presence of gas stoves *(197)*. Taken together, this evidence suggests that gas cooking may act as a reasonable surrogate for personal exposure to NO_2. Nevertheless, some other authors have expressed skepticism about the prediction of indoor and/or personal NO_2 exposure according to the presence of gas stoves *(203, 231)*. It is, however, generally accepted that gas cooking is a better surrogate of peak NO_2 exposure than average levels.

Given that the available evidence strongly suggests health risks from use of gas stoves, particularly for wheeze and asthma among children and where ventilation and condition of the equipment are sub-optimal, another important question arises in respect of whether gas

can serve as a clean fuel standard in comparison with solid fuel, not only for research, but most importantly, in respect of household energy intervention programmes. Numerous studies of indoor NO_2 concentrations have found that use of gas stoves generated more NO_2 and ultrafine particles than use of electric stoves; indeed, a controlled experiment on electric versus gas stoves found that no NO_2 was produced during the use of electric cookers *(208)*. While electric cooking is undoubtedly the cleanest option at the point of use (not considering the emissions and health risks through the full life cycles of these fuels which is outside the scope of these Guidelines, although nevertheless important), risk associated with well-vented gas cookers that are correctly installed and maintained, would appear to be minimal. Given the relatively high costs to households of electricity for cooking in many low and middle income countries, there seems to be little question that gas (whether natural piped gas, or more easily transported liquefied petroleum gas), represents one of the best clean fuel options to reduce household pollution in these countries *(232)*.

4.5 Conclusion

There is good evidence that use of gas for cooking and heating can result in levels of pollutants including NO_2, CO and $PM_{2.5}$ that exceed WHO indoor air quality guidelines, but this appears to be mainly the result of equipment that is poorly fitted or maintained, and with inadequate ventilation. The evidence linking exposure above guideline levels to health outcomes has been extensively reviewed in prior WHO air quality guidelines [WHO 2005 and 2010], and these health risk associations are assumed to be causal. It can therefore be expected that sub-optimal use of gas for cooking and heating will have associated health risks. The major reviews described for LRI *(196)*, and for asthma and wheezing illness in children *(194)*, do provide evidence of increased risks of asthma with gas cooking compared with electricity, and wheeze with increased levels of NO_2. It is not possible to determine from these studies the extent to which the observed risks are the result of technical issues (poor equipment, maintenance and ventilation) or other sources of pollution, but related evidence does suggest that these factors are likely to be important. .

While, as a source of energy in the home, gas may not be as clean as electricity (at the point of use), it appears to carry a very low excess risk of adverse health outcomes when used optimally. In promoting gas as a household fuel, efforts should therefore be made to ensure that gas cookers and heaters function correctly, and are adequately ventilated.

5. Effects of smoke in reducing risk of vector-borne disease

5.1 Summary

Background
A number of factors relating to household fuel combustion and household air pollution levels may affect insect disease vector behavior. Smoke is known to be an insect repellant, including for mosquitoes; openings in the home, for example eaves spaces, can impact on the numbers of insects in the home, and; various components of smoke might impact the effectiveness of insecticide treated nets.

Objectives and key questions
The objective of this review was to summarize the available evidence on how measures to reduce smoke pollution in the home might impact on vector-borne disease. In practice, investigation on this issue has been more or less restricted to mosquitoes and malaria. The key questions for the systematic review were:

1. What are the impacts of lower levels of smoke on rates of biting by mosquitoes?
2. What are the impacts of increased ventilation on biting rates by mosquitoes?
3. What are the impacts of biomass smoke on the effectiveness of insecticide treated nets?

Methods
A summary of a systematic review carried out to answer these questions, and reported in 2008, is provided. Searches of PubMed and the Global Health archive were carried out to June 2006, and supplemented with request for additional publications from experts in the field. Meta-analysis was not carried out.

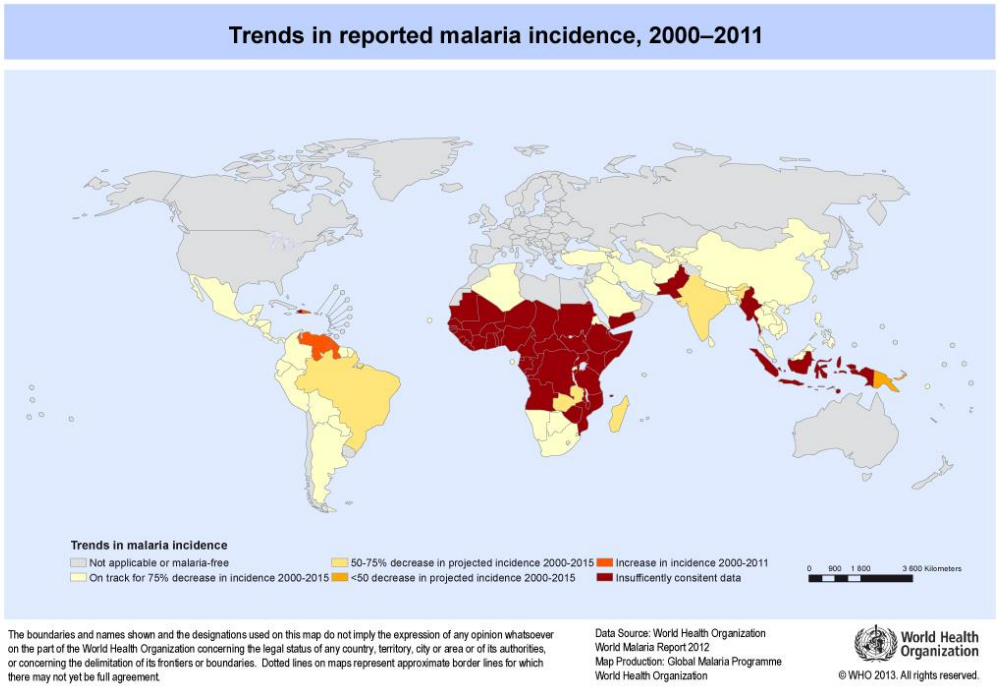
Main findings
A range of studies were found addressing the questions, including some controlled experiments, but no randomized clinical trials. Wood smoke has been found to reduce the rate of biting by mosquitoes among volunteers, but to date there is no strong evidence of any impact of smoke on malaria transmission. Eaves spaces increase the density of mosquitoes, and there is some evidence that homes with close eaves spaces are associated with a significantly lower risk of malaria, but there is concern about confounding among these latter studies. There was no evidence that smoke affects the effectiveness of insecticide treated nets. A further concern with the evidence reviewed is that none have measured levels of smoke pollutants.

Conclusions
While there is evidence that smoke can reduce biting, and that close eaves may reduce insect density and possibly malaria transmission, there is current no strong evidence that reducing smoke pollution levels in the home increases the risk of malaria, and by implication some other insect vector-borne diseases. It is recommended that this systematic review be updated, and if sufficient additional, robust studies are not available, further investigation should be carried out ideally using randomized experimental designs and including air pollutant measurement.

5.2 Introduction

Many of the homes relying on solid household fuels are in parts of the world where insect-borne diseases are common. Figures 5.1 illustrates the trends in malaria incidence by country, and shows the concordance of countries with a high percentage of solid fuel use [see Figure 2.1(a)] and those for which malaria is an ongoing public health concern.

Figure 5.1: Trends in reported malaria incidence 2000-2011 (representing malaria affected countries) [to obtain malaria incidence/mortality] Source WHO/GHO[5].



Given that smoke from the combustion of biomass and other solid fuel has insect repellant properties, the question has arisen regarding the effect that stoves and other interventions such as increased ventilation through eaves spaces might have on the transmission of malaria and other insect vector-borne diseases. An additional issue is the possible impact of smoke pollutants on insecticide-treated nets (ITNs). A systematic review to investigate these issues was conducted for WHO, and a summary reported here.

5.3 Methods for systematic review

A systematic review of this issue was carried out and published in 2007 *(233)*, and prepared as a WHO Report published in 2008 *(234)*. As these documents are available, a summary is described here. Some eighty percent of the burden of insect-borne diseases and ninety percent of the resulting deaths are due to malaria and the review therefore focused on this disease. The key questions for the review, which sought evidence relating to interventions that may be used to reduce HAP exposure (e.g. increased ventilation, improved stoves, etc.), were as follows:

1. What are the impacts of lower levels of smoke on rates of biting by mosquitoes?
2. What are the impacts of increased ventilation on biting rates by mosquitoes?
3. What are the impacts of biomass smoke on the effectiveness of insecticide treated nets?

The methods used for the systematic review are summarized in Box 5.1 *(234)*.

[5] http://www.who.int/gho/en/

The search terms used were as follows: 'exposure' terms biomass, burn, combust*, cook*, dung, fire*, indoor air pollution, smoke, stove*, fuel, coal and charcoal were combined with the 'outcome' terms aedes, anopheles*, culex*, culicidae, malaria*, mosquito*, ochlerotatus, vector*, vector-borne, bite, biting, blood meal, feeding behaviour, feeding pattern*, resting behaviour and resting pattern*.

Individual studies included in the review have not been referenced in this summary, and the reader is referred to the published work for these details.

Box 5.1: Systematic review of solid fuel smoke and risk of malaria

- Period of search: To June 2006
- Databases and sources: PubMed, Global Health Archive (1920-1972); contact with experts.
- Inclusion criteria: (i) exposure to solid fuel smoke and increased ventilation through eaves spaces, (ii) biting and transmission of malaria, and (iii) effectiveness of ITN.
- Number of studies: smoke and malaria risk and biting (15); ventilation (7, 9); effectiveness of ITNs (2).
- Languages: English only

5.4 Impact of smoke in repelling mosquitoes and preventing malaria

Seven early (pre-1940) observational studies were identified relating to the effects of smoke from household fuel use. Three of these (none from Africa) suggested that smoke from domestic fires can deter mosquitoes from resting or hibernating in houses. By contrast three African studies reported no effect of cooking smoke on mosquito numbers observed in houses. A fourth African study found no difference in numbers of mosquitoes caught between houses with a separate kitchen and those without. A recent observational study from Ethiopia actually reported a significantly greater risk of childhood malaria in (presumably smokier) households without separate kitchens. One experimental study of the effect of firewood smoke as a mosquito repellent, found no significant difference in the proportion of females that blood-fed on humans between two rooms one of which was exposed to wood smoke for four hours, the other not. The study concluded that smoke from household fires deterred resting by *Angambiae* species mosquitoes but did not significantly affect the feeding success of mosquitoes on humans.

In addition, eight experimental field studies were found which investigated the effects of smoke from a variety of traditional mosquito-repellent plant materials, by measuring the number of insect landings on volunteers. These showed that for the mosquito species involved, including *Aedes*, *Culex* and *Mansonia* species as well as *Anopheles* malaria vectors, the degree to which the plant materials were repellent varied according to the species of plant and the species of mosquito. Those materials that did significantly reduce biting brought about reductions ranging from 21% to 84%. While these studies show that smoke from various plant species can deter landings and by implication biting, they do not provide evidence on the impact on disease transmission.

Insect vectors show species-specific variation in feeding behavior in terms of peak biting times and preference for indoor or outdoor feeding. Most of the world's important malaria vector species, including those in Africa where 90% of deaths due to malaria occur, have biting peaks late at night and in the early hours of the morning, outside the likely peak times for fuel use. This means that in Africa the potential for protection against malaria vectors offered by smoke from domestic fuel use would probably be minimal.

5.5 Effect of increased ventilation on risk of malaria

Improved household ventilation through the provision or enlargement of eaves spaces has been proposed as one intervention to help remove smoke from the household environment. On the other hand, eaves spaces have been found to be an important entry point for vector mosquito species and a number of studies have suggested that eaves spaces are associated with higher mosquito densities and an increased risk of malaria. Eaves spaces can to some extent be protected against mosquito entry by the use of screens or curtains. The protection against malaria is increased if the materials used are treated with insecticide.

Seven studies were identified which reviewed of the effects of eaves spaces, and all were observational. These studies are liable to confounding and are unable to provide reliable evidence for causal relationships. The extent to which effective ventilation is diminished by protecting eaves with screens in this way is not clear.

Nine other studies were identified which investigated the risk of malaria with close eaves spaces. Five of these studies reported statistically significant odds ratios or relative risks in the range 0.36 to 0.54 (indicating that close eaves spaces reduced the risk of malaria). The remaining four studies in this series reported non-significant increased or decreased risks. Confounding was judged to be a concern with these studies, as the fact of open or closed eaves was thought likely to be associated with other potentially influential factors for risk of malaria.

Overall, the evidence on increased ventilation through eaves spaces is judged to be very weak and needs to be strengthened through well designed randomized experimental studies.

5.6 Effect of soot/HAP on the effectiveness of ITNs

Insecticide-treated bed nets (ITNs) are a widely used and effective intervention to prevent malaria transmission. Indoor smoke deposits a layer of soot on the bed net fabric. Based on the two studies reviewed to date, the presence of a sooty layer has no detectable impact on the effectiveness of the insecticide but does increase the frequency with which ITNs are washed. It was noted, however, than in one study by Kayedi et al. nets were exposed to 'intense hay smoke' for only three minutes on one occasion, which seems unlikely to mimic typical repeated daily exposures from cooking. It is also reported that long-lasting impregnated nets retain their insecticidal properties after repeated washing, the concern here being that sooty nets may be washed more frequently.

5.7 Conclusions and assessment of evidence

The evidence on the impacts of household air pollution on malaria, and potentially other insect (vector) borne diseases is weak. Almost all studies of biomass smoke and insect numbers in homes are observational, with one experimental study. Most have not studied malaria as the outcome, rather the number of insects in the home. One study reporting malaria incidence in children showed higher rates in homes without separate kitchens, which (although speculative as exposure data were not available), might be assumed to be more polluted. As with many studies in this field, actual measurements of HAP levels have not been made. Based on the available evidence, HAP seems likely to reduce insect numbers in the home and biting, but there is as yet no good evidence of any impact on disease transmission.

6. Research needs

An assessment of research gaps and needs, based on a workshop hosted by the National Institutes for Health in May 2011, has recently been reported by Martin et al.(2013) *(235)*. This considers the urgent need for evaluation of health impacts as the current momentum to expand access to improved household energy grows, key gaps in the evidence on health effects across a wide range of health outcomes, and related issues such as the importance of developing capacity for high quality research in this field in countries and regions where the health burdens are greatest. Since the assessment of health research priorities in this field is expected to evolve further over the coming months and years, a brief summary of major issues and the pointers to the direction of this research are provided here.

6.1 Evidence gaps

The reviews summarized here, together with the discussion paper by Martin et al. (2013), clearly show a number of important limitations in the evidence linking HAP to a range of health outcomes; for some this is more a question of confidence in effect size, for others causality is still uncertain. While there is already ample evidence on risks for important child and adult health outcomes to justify concerted efforts to deal with pollution from household fuel combustion, stronger and more precise evidence on the risk for outcomes including severe/fatal child pneumonia, pre-term birth, IHD, TB, asthma, cancer of the uterine cervix (and other cancers) and child cognitive development would have important implications for priority action by programmes dealing with these conditions. Indeed, it has been noted that given the similarities between emissions from smoking and those from burning of biomass in the home, many – if not all – of the disease conditions linked to smoking can be expected to result from HAP exposure.

A second and critical area of uncertainty lies with exposure-response relationships: while the emerging empirical evidence and work on integrated exposure-response functions reported in Section 4 provides a sufficient basis for assessing the form of these relationship and basis for policy guidance, the assumptions employed and resulting uncertainties demand that strengthening this evidence be a research priority.

6.2 Issues for future intervention-based research

Relatively few intervention studies are currently available to this field, although several are in progress (see Section 2.6). Intervention-based research will play an important part in strengthening evidence, especially with respect to causal inference. A number of issues concerning the development, implementation and interpretation of intervention studies have been discussed by Martin et al. *(235)*. Critical in the development of prospective intervention studies has been ensuring that the stove(s) are well accepted by households, will more or less completely replace use of the traditional stove(s), and deliver large reductions in emissions and consequently low levels of HAP and exposure in practice. In addition to paying the usual attention to outcome definitions and assessment, it is also important to conduct thorough exposure assessment, as not only will this confirm the performance of the intervention in practice, but also provides the opportunity to contribute to understanding of exposure-response functions.

Randomized trials have multiple strengths, but may not reflect the actual impacts of programmes implemented at scale due to the special conditions that often accompany such carefully managed studies, although this may be possible through, for example, providing the intervention through ante-natal care in an attempt to reach a key at-risk group (pregnant women).

In future, it will also be important to conduct more evaluation studies on the impacts of programmes implemented through more 'natural' (e.g. market-based) diffusion, although this does present challenges for obtaining robust comparisons between the intervention and traditional technologies and fuels.

Annex Table A1: GEPHI Assessments

Table A1.1(a): Non-fatal ALRI

		Importance of outcome: Important (6)									
Design	**No. of studies**	**Risk of bias**	**Inconsistency (heterogeneity)**	**Indirectness (external validity)**	**Imprecision (power)**	**Publication bias**	**Other considerations (specify)***	**Number of events**		**Relative effect and 95% CI**	**Quality**
								Intervention	**Control**		
RCTs	1	No	No	No	Yes (-1)	No	No	149	180	0·78 (0·59–1·06)	Moderate
Observational	20	Yes (-1)	Yes (-1)	No	No	No	No	11,331 events		0.63 (0.53, 0.75)	Very low
Intermediate score										Very low	
Final score		Despite statistical heterogeneity in the systematic review, overall consistency of effect is demonstrated through sensitivity analysis (+1)								**Moderate**	
		Evidence on effects of exposures to ambient air pollution and second-hand tobacco smoke (+1)									

*Only large effect (relative risk estimate >2) is used for upgrading if the group of studies is downgraded for any reason

Table A1.1(b): Severe ALRI

		Importance of outcome: Critical (9)									
Design	**No. of studies**	**Risk of bias**	**Inconsistency (heterogeneity)**	**Indirectness (external validity)**	**Imprecision (power)**	**Publication bias**	**Other considerations (specify)***	**Number of events**		**Relative effect and 95% CI**	**Quality**
								Intervention	**Control**		
RCTs	1	No	No	No	No	No	Exposure-response (+1)	72	101	0·67 (0·45–0·98)	High
Observational	3	Yes (-1)	No	No	No	No	Large effect (+1)	331 events		0.40 (0.25, 0.67)	Low
Intermediate score										Low	
Final score		Insufficient evidence to upgrade for overall consistency of effect								**Low**	
		No analogous evidence available yet of larger risk for severe pneumonia									

Table A1.1(c): Fatal ALRI

		Importance of outcome: Critical (9)									
Design	**No. of studies**	**Risk of bias**	**Inconsistency (heterogeneity)**	**Indirectness (external validity)**	**Imprecision (power)**	**Publication bias**	**Other considerations (specify)***	**Number of events****		**Relative effect and 95% CI**	**Quality**
								Intervention	**Control**		
RCTs	1	No	No	No	Yes (-1)	No	No (NS)	3	6	0.48 (0.12, 1.91)	[Moderate]
Observational	3	Yes (-1)	No	No	No	No	Large effect (+1)	659 events		0.34 (0.22, 0.55)	Low
Intermediate score										Low	
Final score		Insufficient evidence to upgrade for overall consistency of effect								**Low**	
		No analogous evidence available yet of larger risk for fatal pneumonia									

Table A1.2: Low birth weight

		Importance of outcome: Important (6)									
Design	**No. of studies**	**Risk of bias**	**Inconsistency (heterogeneity)**	**Indirectness (external validity)**	**Imprecision (power)**	**Publication bias**	**Other considerations (specify)***	**Number of events**		**Relative effect and 95% CI**	**Quality**
								Intervention	**Control**		
RCTs	1	No	No	No	Yes (-1)	No	No	13	26	0.74 (0.33-1.66)	Moderate
Observational	6	No	No	No	No	No	No	5,670 events		0.71 (0.64, 0.79)	Low
Intermediate score										Low	
Final score		The remarkable consistency across studies and settings could lead to upgrading, but this was not done as only 7 studies are available								**Moderate**	
		Good analogous evidence from other combustion sources, especially smoking									

Table A1.3: Stillbirth

		Importance of outcome: Critical (9)									
Design	**No. of studies**	**Risk of bias**	**Inconsistency (heterogeneity)**	**Indirectness (external validity)**	**Imprecision (power)**	**Publication bias**	**Other considerations (specify)***	**Number of events**		**Relative effect and 95% CI**	**Quality**
								Intervention	**Control**		
Observational	4	No	No	No	No	No	No	3,345 events		0.66 (0.54, 0.81)	LOW
Intermediate score										Low	
Final score										**Low**	

Table A1.4: Stunting (all observational designs)

		Importance of outcome: Important (6)									
Design	**No. of studies**	**Risk of bias**	**Inconsistency (heterogeneity)**	**Indirectness (external validity)**	**Imprecision (power)**	**Publication bias**	**Other considerations (specify)***	**Number of events**		**Relative effect and 95% CI**	**Quality**
								Intervention	**Control**		
Stunting	2	No	No	No	No	No	No	7,109 events		0.79 (0.70, 0.89)	LOW
Severe stunting	2	No	Yes (-1)	No	No	No	No	8,157 events		0.64 (0.43, 0.96)	VERY LOW
Intermediate score										Low	
Final score		Insufficient evidence to upgrade for overall consistency of effect								**Moderate stunting: Low**	
		Analogous evidence from maternal smoking (including from Kyu et al. 2009) for severe stunting								**Severe stunting: Low**	

Table A1.5: All cause child mortality

		Importance of outcome: Critical (9)								
Design	**No. of studies**	**Risk of bias**	**Inconsistency (heterogeneity)**	**Indirectness (external validity)**	**Imprecision (power)**	**Publication bias**	**Other considerations (specify)***	**Number of events**		**Relative effect and 95% CI**	**Quality**
								Intervention	**Control**		
Observational	5	No	Yes (-1)	No	No	Possible	No	8,446 events		0.79 (0.70, 0.89)	VERY LOW
Intermediate score										Low	
Final score		Insufficient evidence to upgrade for overall consistency of effect									
		[To check whether there is analogous evidence available yet risk for all cause child mortality]								**Low**	

Table A1.6: COPD

		Importance of outcome: Important (6)								
Design	**No. of studies**	**Risk of bias**	**Inconsistency (heterogeneity)**	**Indirectness (external validity)**	**Imprecision (power)**	**Publication bias**	**Other considerations (specify)***	**Number of events**		**Relative effect and 95% CI**	**Quality**
								Intervention	**Control**		
Observational	24	Yes (-1)	Yes (-1)	No	No	Yes (-1)	Large effect for women (+1)	24,870 events		F: 0.43 (0.33, 0.58) M: 0.53 (0.32, 0.87)	VERY LOW
Intermediate score										Very low	
Final score		Despite statistical heterogeneity in the systematic review, overall consistency of effect is demonstrated through sensitivity analysis (+1)									
		Evidence on effects of exposures to ambient air pollution, second-hand tobacco smoke and active smoking (+1)								**Low**	

Table A1.7: Lung cancer with exposure to household coal use

		Importance of outcome: Important (9)								
Design	**No. of studies**	**Risk of bias**	**Inconsistency (heterogeneity)**	**Indirectness (external validity)**	**Imprecision (power)**	**Publication bias**	**Other considerations (specify)***	**Number of events**		**Relative effect and 95% CI**	**Quality**
								Intervention	**Control**		
Observational	25	No	Yes (-1)	No	No	No	Large effect (+1) D/response (but can't upgrade)	10,142 events		0.46 (0.35, 0.62)	LOW
Intermediate score										Low	
Final score		Evidence that risk does vary by setting, possibly due in part to type of coal									
		Evidence on effects of exposures to other sources of coal combustion pollution (+1)								**Moderate**	

Table A1.8: Lung cancer with exposure to household biomass use

(a) Men:

		Importance of outcome: Important (9)								
Design	**No. of studies**	**Risk of bias***	**Inconsistency (heterogeneity)**	**Indirectness (external validity)**	**Imprecision (power)**	**Publication bias**	**Other considerations (specify)**	**Number of events**		**Relative effect and 95% CI**	**Quality**
								Intervention	**Control**		
Observational	3	Yes (-1)	No	No	No	No	Exposure-response (+1)	4005 events		0.82 (0.73, 0.93)	LOW
Intermediate score										Low	
Final score		Too few studies to assess consistency across settings								**Moderate**	
		Evidence on effects of exposures to biomass from second-hand and active smoking (+1)									

*Almost all evidence for men is from Europe and North America and this estimate may not be reliable for higher exposures with open fires/stoves in developing countries

(a) Women:

		Importance of outcome: Important (9)								
Design	**No. of studies**	**Risk of bias**	**Inconsistency (heterogeneity)**	**Indirectness (external validity)**	**Imprecision (power)**	**Publication bias**	**Other considerations (specify)**	**Number of events**		**Relative effect and 95% CI**	**Quality**
								Intervention	**Control**		
Observational	6	No	Yes (-1)	No	No	No	No	4311 events		0.63 (0.43, 0.93)	VERY LOW
Intermediate score										Very low	
Final score		Lack of consistency for largest group across Asia and Mexico								**Low**	
		Evidence on effects of exposures to biomass from second-hand and active smoking (+1)									

Table A1.9: Cataract with exposure to household solid fuel use

		Importance of outcome: Important (9)								
Design	**No. of studies**	**Risk of bias**	**Inconsistency (heterogeneity)**	**Indirectness (external validity)**	**Imprecision (power)**	**Publication bias**	**Other considerations (specify)***	**Number of events**		**Relative effect and 95% CI**	**Quality**
								Intervention	**Control**		
Observational	7	No	Yes (-1)	No	No	No	Large effect (+1)	3170 events		0.41 (0.29, 0.57)	LOW
Intermediate score										Low	
Final score		Although the studies show reasonable consistency, all were conducted in the same region								(Women only) **Moderate**	
		Evidence on effects of exposures to smoking (+1)									

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