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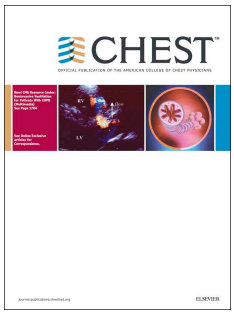

SmokeHaz: Systematic reviews and meta-analyses of the effects of smoking on respiratory health

Leah Jayes, Research Associate, Patricia L. Haslam, Emeritus Reader & Honorary Consultant, Christina G. Gratziou, Professor of Pulmonary Medicine, Pippa Powell, European Lung Foundation Director, John Britton, Professor of Epidemiology, Constantine Vardavas, Senior Research Scientist, Carlos Jimenez-Ruiz, Associate Professor of Medicine, Jo Leonardi-Bee, Professor of Medical Statistics and Epidemiology, on behalf of the Tobacco Control Committee of the European Respiratory Society

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Title: *SmokeHaz*: Systematic reviews and meta-analyses of the effects of smoking on respiratory health

Short running head: *SmokeHaz*: Effects of smoking on respiratory health

Authors: Leah Jayes [1], Patricia L Haslam [2,3], Christina G Gratziou [2,4], Pippa Powell [5], John Britton [1], Constantine Vardavas [2,6], Carlos Jimenez-Ruiz [2,7], and Jo Leonardi-Bee [1], on behalf of the Tobacco Control Committee of the European Respiratory Society

[1]UK Centre for Tobacco and Alcohol Studies, Division of Epidemiology and Public Health, University of Nottingham, City Hospital Campus NHS Trust, Hucknall Road, Nottingham, NG5 1PB, UK; [2]European Respiratory Society (ERS) Tobacco Control Committee, ERS EU Affairs Department, 49-51 Rue de Tréves, BE-1040 Brussels, Belgium; [3]National Heart & Lung Institute, Royal Brompton Campus, Imperial College, London SW3 6LY and Royal Brompton Hospital, London, SW3 6NP, UK; [4]Smoking Cessation Clinic, Asthma & Allergy Centre, Pulmonary & Intensive Care Department, Athens University, Evgenidio Hospital, 20 Papadiamantopoulou Street, 115 28 Athens, Greece; [5]European Lung Foundation (ELF), 442 Glossop Road, Sheffield, S10 2PX, UK; [6]Center for Global Tobacco Control, Department of Social and Behavioural Sciences, Harvard School of Public Health, 577 Huntington Avenue, Boston, MA 02115; [7] Smoking Cessation Service, Community of Madrid, C/ Santacruz del Marcenado, 9. Piso 2, 28015 Madrid, Spain

Leah Jayes, Research Associate; Patricia L Haslam, Emeritus Reader & Honorary Consultant; Christina G Gratziou, Professor of Pulmonary Medicine; Pippa Powell, European Lung Foundation Director; John Britton, Professor of Epidemiology; Constantine Vardavas, Senior Research Scientist; Carlos Jimenez-Ruiz, Associate Professor of Medicine, Jo Leonardi-Bee, Professor of Medical Statistics and Epidemiology.

Corresponding author: Professor Jo Leonardi-Bee, Professor of Medical Statistics and Epidemiology, UK Centre for Tobacco and Alcohol Studies, Division of Epidemiology and Public Health, University of Nottingham, City Hospital Campus NHS Trust, Hucknall Road, Nottingham, NG5 1PB, UK

Email: jo.leonardi-bee@nottingham.ac.uk

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Abstract

Background: Smoking tobacco increases the risk of respiratory disease in adults and children, but communicating the magnitude of these effects in a scientific manner that is accessible and usable by public and policymakers presents a challenge. We have therefore summarised scientific data on the impact of smoking on respiratory diseases to provide the content for a unique resource*, SmokeHaz*.

Methods: We conducted systematic reviews and meta-analyses of longitudinal studies (published to 2013) identified from electronic databases, grey literature, and experts. Random effect meta-analyses were used to pool the findings.

Results: We included 216 papers. Among adult smokers, we confirmed substantially increased risks of lung cancer (Risk Ratio (RR) 10.92, 95% CI 8.28-14.40; 34 studies), COPD (RR 4.01, 95% CI 3.18-5.05; 22 studies) and asthma (RR 1.61, 95% CI 1.07-2.42; 8 studies). Exposure to passive smoke significantly increased the risk of lung cancer in adult non-smokers; and increased the risks of asthma, wheeze, lower respiratory infections, and reduced lung function in children. Smoking significantly increased the risk of sleep apnoea, and asthma exacerbations in adult and pregnant populations; and active and passive smoking increased the risk of tuberculosis.

Conclusions: These findings have been translated into easily digestible content and published on the *SmokeHaz* website (*www.smokehaz.eu*).

Introduction

Tobacco smoking is the leading cause of preventable death in the European Union (EU), responsible for nearly 700,000 deaths every year; and around 50% of smokers die prematurely resulting in the loss of an average of 14 years of life (1). An estimated further 13 million people in the EU are living in poor health with chronic diseases as a result of smoking. Many forms of cancer, cardiovascular and respiratory diseases are linked to tobacco use, which causes more problems than alcohol, drugs, high blood pressure, excess weight or high cholesterol. Passive smoking is a significant health hazard to children as well as non-smoking adults, being responsible for causing excess cases of sudden infant death syndrome, asthma, middle ear infections, and meningitis (2). Thus, preventing smoking remains a key health priority. Since smoking prevention requires population-level policy measures as well as individual treatment interventions (3), it is important that accurate data on the effects of tobacco use on health are readily available to policymakers, policy advocates and the general public.

In this respect, one major difficulty is that the available evidence on smoking and health is extensive, disparate and at times conflicting. Therefore, it is particularly important that the evidence base is regularly captured, through systematic review, and synthesised to provide easily understandable and accurate summary estimates of effect.

This paper reports on the findings of the *SmokeHaz* project, which summarises the harms of smoking on respiratory health in a freely-accessible online resource for policy makers, researchers, students, healthcare professionals and the public (*www.smokehaz.eu*). *SmokeHaz* is a collaborative project between the UK Centre for Tobacco and Alcohol Studies, the European Respiratory Society, and the European Lung Foundation. In this project, all the available worldwide literature up to 2013 has been used to update a series of systematic reviews and meta-analyses on associations between tobacco smoking and a range of respiratory health outcomes. This manuscript presents the detailed scientific data for validation by independent peer review, and is designed to promote and strengthen public awareness of tobacco control issues as requested in Article 12 of the WHO Framework Convention on Tobacco Control (3).

Methods

Inclusion Criteria

We included longitudinal, cohort, or nested case-control studies that assessed the effect of active or passive tobacco smoking on the risk of developing respiratory diseases. Outcomes of interest included lung cancer, chronic obstructive pulmonary disease, asthma and wheeze, asthma exacerbations, sleep apnoea or tuberculosis in adults, and asthma and wheeze, asthma exacerbations, lung function, sleep apnoea, or lower respiratory tract infection in children. Where possible we used biochemically verified measures of smoking, for example exhaled carbon monoxide or saliva cotinine levels, in preference to self-reported smoking status. Active smoking was defined as ever smoker, current smoker, ex- or former smoker; and passive smoking was defined as being in contact with second hand smoke from any source; domestic, occupational, or other sources. Studies assessing levels of exposure to smoke based on cigarette consumption (pack years defined as number of packs smoked per day multiplied by number of years smoked, duration of smoking, or the number of cigarettes smoked per day) were also included. For passive smoking, we included studies which assessed effects either in non- or never-smokers or where the effect of active smoking was adjusted for in the statistical analyses. In addition to adult populations, studies focusing on *in utero*, infants, children and adolescents were also included. Where insufficient studies were identified for particular outcomes, we extended our searches to include studies reporting disease-specific mortality. Studies which only looked at passive smoke exposure relating to cooking fuels, and those looking at active or passive smoking from illegal substances were excluded. To ensure the strictest independence of the science as far as possible within the limits of disclosed knowledge, we omitted any primary studies with declared or identifiable involvement of the Tobacco Industry.

Search Strategy

Comprehensive literature searches in Medline, EMBASE and Web of Science were conducted from 1985 to 2013 (precise end dates varied for each health outcomes), with no language restrictions imposed. We also searched conference proceedings from major international tobacco control conferences and a range of websites hosted by relevant professional societies. Contact with experts in the field was made to identify further relevant published or unpublished research. References lists of all included studies were screened to identify further potentially eligible studies.

Study Selection and Data Extraction

Titles, abstracts and full text papers identified from the searches were screened by one reviewer (LJ) to select relevant articles. A second reviewer (JLB) independently screened a minimum of 10% of

titles and abstracts and 30% of full text papers. Two authors (LJ and JLB) independently extracted data from included studies using previously piloted data extraction forms and independently assessed the quality of the included studies using the Newcastle-Ottawa Scale (4) for primary studies and the Assessment of Multiple Systematic Reviews (AMSTAR) Scale for existing systematic reviews (5). A Newcastle-Ottawa Scale score of 7 or more indicated high quality in the primary studies. Disagreements and discrepancies in study selection and data extraction were resolved through discussion.

Statistical Analysis

We extracted measures of effect for the association between exposure to smoking and the risk of disease using either odds ratios (OR), risk ratios (RR), hazard ratios (HR) or incidence rate ratios (IRR), with 95% confidence intervals (CI). Estimates adjusted for potential confounders were used in preference to crude estimates. Pooled Relative Risk Ratios (RR) were estimated using random effect meta-analyses. Heterogeneity between the studies was assessed using the I^2 statistic (6). Subgroup analyses were performed to explore reasons for heterogeneity based on gender, age of children, country (Europe compared to the rest of the world), methodological quality, and level of exposure (for example, pack-years of active smoking). Evidence of publication bias was assessed using funnel plots.P values<0.05 were considered statistically significant. Statistical analysis was performed using STATA version 11 & Review Manager 5.3. The reviews adhered to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) (7) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (8) guidelines.

Results

The main findings from the systematic reviews and meta-analyses are presented. The characteristics of the studies included in the systematic reviews are presented in Table 1. Tables giving more information about the study populations, and wider data including funnel plots and additional figures containing more detailed data are available at *www.smokehaz.eu*.

Lung Cancer

Active smoking

Thirty-four studies assessing the effect of active smoking versus non-smoking on the development of lung cancer were eligible for inclusion in the review (9-42). Nineteen (56%) were deemed to be of high quality; and 13 were conducted in Europe.

Smokers were 11 times more likely than non-smokers to develop lung cancer (RR 10.92, 95% CI 8.28 to 14.40; I^2=95%; 34 studies; Figure 1) (9-42). The results were similar in both the higher and lower quality studies. Higher risks of developing lung cancer were seen in women (12 fold increase) compared to men (9 fold increase); however the test for subgroup differences was not statistically significant (p=0.40). Studies conducted in European countries tended to show higher risks of lung cancer (15 fold increase) among smokers than those conducted elsewhere (9 fold increase), but not reaching significance (p value for subgroup differences p=0.06). All the included studies reported that the incidence of lung cancer was consistently greater in those with higher cigarette consumption. A pooled analysis in the 13 comparisons from 11 studies (9-11, 15, 24, 25, 30-32, 34, 36) that reported pack years, found a significant dose response relationship between increasing risk (from 3 fold to 12 fold) of development of lung cancer with increasing exposure (<20 pack years: RR 3; 20-40 pack years: RR 7; 40-60 pack years: RR 11; >60 pack years: RR 12).

Passive smoking

Fifteen studies were included in the review, which assessed the effect of passive smoking on the risk of lung cancer (43-57). Six (40%) were deemed to be of higher quality. The main results are based on data from 13 of the studies (2 studies were excluded due to using duplicate data (44, 46)).

Exposure to passive smoke increased the risk of developing lung cancer by 1.41 fold (41%) compared to never smokers unexposed to passive smoke (RR 1.41, 95% CI 1.21 to 1.65; I^2=0%; 13 studies; Figure 1) (43, 45, 47-57). Most of this evidence was based on data from woman non-smokers who were exposed to passive smoke from their smoker husbands (11 of the studies). Similar risks of lung

cancer were seen in European countries compared to studies conducted elsewhere in the world, and in higher quality studies compared to lower quality studies. A meta-analysis to investigate the effect of levels of exposure to passive smoke was possible in 4 studies (47, 50, 51, 53), which found women whose husbands smoked >20 cigarettes per day had a 1.46 fold (46%) increased risk of lung cancer compared to women with non-smoker husbands (RR 1.46, 95% CI 1.10 to 1.44; 4 studies).

Chronic Obstructive Pulmonary Disease (COPD)

Active smoking

Twenty- four studies (58-81) assessing the effect of smoking on the risk of developing COPD were identified from a previous systematic review (82) and an updated search; however, only 22 of the studies provided sufficient data to be included in the meta-analysis. The majority (13) of the included studies used the GOLD criteria to define COPD based on forced expiratory volume in one minute (FEV_1)/forced vital capacity (VC) <70%. Only five of the studies (21%) were deemed to be of high quality.

Smokers were 4.01 times more likely to develop COPD compared to non-smokers (RR 4.01, 95% CI 3.18 to 5.05, I^2 = 87%, 22 studies; Figure 1) (58-67, 69, 71-81). Similar risks of COPD were seen between men and women, in higher and lower quality studies, and between studies conducted in Europe and the rest of the world.

Passive smoking

Three studies (71, 83, 84) assessing the effect of passive smoking on the risk of COPD were identified from two previous systematic reviews (85, 86) and an updated search. COPD was defined as either FEV_1 <65%, FEV_1/maximum VC <65% or percent predicted FEV_1 <75%, or as a clinical diagnosis of acute obstructive disease. None of the studies were deemed to be of high quality.

In adults, exposure to passive smoking for at least one hour per day was associated with a 1.44 fold (44%) increased risk of COPD compared to non-smokers (RR 1.44, 95% CI 1.02 to 2.01) (84); however, another study found no consistent effect of passive smoking on the development of COPD in non-smokers (71). Exposure to passive smoking during child and adulthood was associated with a 1.72 fold (72%) increased risk of developing COPD in adulthood (RR 1.72, 95% CI 1.31 to 2.23); however, no increased risk was seen in those only exposed during childhood (83).

Adult Asthma

Eight studies (87-94) assessing the effect of active smoking on the risk of asthma in adults were identified from a previous systematic review (95). Asthma was ascertained through physician reports in the majority of studies, while 2 studies relied on self-reports. Four of the studies (50%) were deemed to be of high quality. All but 2 of the included studies (90, 94) were conducted in Europe.

Smokers were 1.61 times (61%) more likely to develop asthma when compared to adults who had never smoked (RR 1.61, 95% CI 1.07 to 2.42; I^2=91%; 8 studies; Figure 1) (87-94). The high level of heterogeneity appeared to be related to a low quality study (90), which reported a significantly reduced risk of asthma in smokers. A sensitivity analysis excluding this study (90) found smokers were 1.81 times (81%) more likely to develop asthma when compared to people who never smoked (RR 1.81, 95% CI 1.37 to 2.38; I^2= 68%; 7 studies). The risk of developing asthma from active smoking was similar between European and non-European studies and between higher and lower quality studies.

Asthma Exacerbations

Five studies (96-100) were identified for inclusion which assessed the effect of active and passive smoking on exacerbations of asthma in adults, pregnant women or children. Three of the studies (60%) were deemed to be of high quality.

Active smoking

Two studies assessed the effect of active smoking on asthma exacerbations (96, 97). Adults with asthma who were current or ex-smokers had a 1.71 times higher risk of subsequent asthma exacerbations than adults with asthma who had never smoked (RR 1.71, 95% CI 1.48 to 1.97, 1 study) (96). A study of 80 pregnant women with asthma found that being a current smoker or ex-smoker significantly increased the number of severe asthma exacerbations per year, and being a current smoker also resulted in poorer asthma control, compared to those who never smoked (97).

Passive smoking

Three studies assessed the effect of passive smoking on asthma exacerbations (98-100). In non-smoking adults, exposure to passive smoke significantly increased the risk of being restricted in daily

activities (RR 1.61, 95% CI 1.06 to 2.46, 1 study) (99), but had no significant effect on increased risks of cough, shortness of breath or being awakened by asthma (90), or on admission to hospital for asthma (98). In a study of 140 children with asthma aged 3-15 years, exposure to passive smoke in the household or by the mother more than doubled the risk of multiple hospital admissions for asthma per year (RR 2.55, 95% CI 1.12-5.82; 1 study) and exposure to maternal smoking more than tripled the risk of multiple hospital admissions for asthma per year (RR 3.25, 95% CI 1.13-8.85) (100).

Tuberculosis (TB)

Five studies (101-105) assessing the effect of active and passive smoking on the risk of developing TB were identified from 4 previous systematic reviews (106-109) and an updated search. Four of the studies (80%) were deemed to be of high quality. None of the studies were conducted in Europe

Active smoking

Four studies assessed the effect of active smoking (101-104). People who smoked were 1.57 times (57%) more likely to develop TB when compared to those who had never smoked (RR 1.57, 95% CI 1.18 to 2.10; I^2=93%; 4 studies; Figure 1). Significantly higher risks of TB from smoking were seen the higher quality studies (2.2 times) compared to the study with a lower quality (1.1 times) (test for subgroup differences, p<0.00001); however similar risks were seen in studies of men and women. All of the studies reported an increased risk of TB with increasing numbers of cigarettes smoked per day.

Passive smoking

Two studies assessed the effect of passive smoking (103, 105). Exposure to household tobacco smoke increased the risk of developing TB by 1.44 times (44%) compared to people who were unexposed to household tobacco smoke (RR 1.44, 95% CI 1.02 to 2.04; I^2=0%; 2 studies). Both of the included studies were deemed to be of high quality, and similar results were seen for males and females. However, no significant trend was seen between the increased frequency of exposure to passive smoke (numbers of days per week exposed) and the risk of TB (p=0.74) (103).

Sleep Apnoea

Five studies (110-115) assessing the effect of active and passive smoking on the risk of sleep apnoea were identified from a previous review (116) and an updated search. None of the included studies were deemed to be of high quality.

Active smoking

Three studies assessed the effect of active smoking on the development of sleep apnoea in adults (111, 112, 115). Two of these studies reported numerical data, which found that people who smoke are twice as likely to have sleep apnoea than those that do not smoke (RR 1.97, 95% CI 1.02 to 3.82; 2 studies) (112, 115). Men and women were found to have similar risks of sleep apnoea from smoking (1.5 fold increase) when compared with non-smokers (115). One study investigated intensity of exposure and found a dose-dependent relationship where the greatest risk of sleep apnoea was associated with smoking at least 40 cigarettes per day (RR 8.38, 95% CI 1.68 to 41.94, 1 study) (112).

Passive smoking

Two studies assessed the effect of passive smoking on the risk of development of sleep apnoea in infants or young children (113, 114). Maternal smoking during pregnancy approximately doubled the risk of their infant developing sleep apnoea (age range from 1 day – 29 weeks) (RR 1.76, 95% CI 1.17 to 2.64, 1 study) (113). Maternal smoking after birth significantly increased the risk of developing sleep apnoea in children aged 6-18 months (RR 1.25, 95% CI 1.06 to 1.47, 1 study) (114). One study (113) also reported significantly more infants developed sleep apnoea where both parents had smoked during pregnancy compared to only mothers smoking during pregnancy (p=0.007).

Lower Respiratory Tract Infections (LRTI) in Childhood

Thirty-four studies (117-150) assessing the effect of passive smoking on the risk of LRTI in children under 2 years were identified from a previous review (151) and an updated search. Eighteen studies considered the effects of any household member smoking, six of both parents smoking, nine of paternal smoking, 16 of maternal smoking, and 11 of pre-natal maternal smoking (some studies covered more than one exposure). Sixteen (47%) were deemed to be of high quality, and 17 were conducted in Europe.

Infants exposed to smoking by any household member were 1.43 times (43%) more likely to develop LRTI compared to those not exposed to smoking in the home (RR 1.43, 95% CI 1.28 to 1.59; I^2=45%;

18 studies; Figure 2). Similar risks of LRTI were seen in European studies (1.42 times) and non-European studies (1.46 times), and in higher (1.49 times) and lower (1.35 times) quality studies.

Significant increased risks of developing LRTI were also seen in Infants exposed to both parents smoking (RR 1.82, 95% CI 1.51 to 2.19; I^2=45%; 6 studies), prenatal maternal smoking (RR 1.19, 95% CI 1.10 to 1.29; I^2=78%; 11 studies), maternal smoking in the postnatal period (RR 1.62, 95% CI 1.46 to 1.79; I^2=50%; 16 studies), but not to paternal smoking (RR 1.15, 95% CI 0.97 to 1.36; I^2=51%; 9 studies).

Childhood Asthma and Wheeze

Seventy-one studies assessing the effect of passive smoking in the risk of developing asthma or wheeze in childhood were identified from a recent systematic review (152). Thirty-one of the studies (44%) were deemed to be of high quality, and 32 were conducted in Europe.

Wheeze in childhood

Children aged ≤2 years who had been exposed to prenatal maternal smoking had a 1.41 times (41%) increased risk of developing wheeze compared to unexposed children (RR 1.41, 95% CI 1.19 to 1.67; Figure 3). Similar effects were observed for the relationship between prenatal maternal smoking and the incidence of wheeze in children aged 3 to 4 years (1.28 times) and 5 to 18 years (1.52 times). Similar effect sizes were seen in children aged 5-18 years who were exposed to paternal smoking (1.39 times) and in children exposed to household tobacco smoke (1.32 times).

The strongest impact on the incidence of wheeze was seen in children exposed to postnatal maternal smoking, where children under 5 years exposed to postnatal maternal smoking were 1.65 to 1.70 times (65-70%) more likely than unexposed children to develop wheeze (≤2 years: pooled RR 1.70, 95% CI 1.23 to 2.35; 3 to 4 years: RR 1.65, 95% CI 1.20 to 2.27).

For all sources of exposure to smoking (prenatal, postnatal, paternal, household), the effect size for the increased risk of wheeze were similar in sensitivity analyses based methodological quality and geographical location of the studies; except for the following sensitivity analyses: In European studies, the magnitudes of the risks of wheeze from prenatal maternal smoking in children aged 2 years or younger were larger (2.21 times) compared to all studies (1.41 times). For children aged 3-4 years, a larger magnitude of risk of household smoking on the risk of wheeze was seen in higher quality studies (1.20 times) compared to all studies (1.06 times).

Asthma in childhood

Children aged ≤2 years who were exposed to prenatal maternal smoke were 1.85 times (85%) more likely to develop asthma compared to unexposed children (RR 1.85, 95% CI 1.35 to 2.54; Figure 4). However, smaller magnitudes of risk were seen in children aged 3-4 years (1.30 times) and those aged 5-18 years (1.23 times). Across the age groups, children exposed to household smoking were 1.14 to 1.30 times (14-30%) more likely to develop asthma. However, exposure to postnatal maternal or paternal smoke did not appear to consistently increase the risk of developing asthma in any age group.

For all sources of exposure to smoking (prenatal, postnatal, paternal, household), the effect size for the increased risk of asthma were similar in sensitivity analyses based methodological quality and geographical location of the studies; except for the following sensitivity analyses: In European studies, the magnitudes of the risks of asthma from postnatal maternal smoking in children aged 5-18 years were larger (1.48 times) compared to all studies (1.20 times). In children aged 5-18 years, the magnitude of the risk of asthma from exposure to household smoking was larger (2.02 times) compared to all studies (1.30 times).

Lung Function in Childhood

Infants

Thirteen studies (153-165) assessing the effect of exposure to passive smoking on lung function in infants were identified from a previous review (2) and an updated search. Lung function measurements were assessed within 8 weeks of birth in all studies. Seven studies were conducted in Europe.

Pre-natal exposure: Seven of the studies assessed the effect of prenatal exposure of infants to maternal smoking on maximal flow at functional residual capacity (FRC), with the majority finding no significant reductions (154, 158, 159, 161, 165). However, the two remaining studies found prenatal maternal smoking significantly reduced maximal flow at FRC (157, 164). Prenatal maternal smoking had no significant effect on FRC at 8 weeks of age (155). Prenatal maternal smoking was significantly associated with reduced tidal breathing ratio (tPTEF:tE) in the infants within one week following birth (162) and in those born preterm at 37 weeks gestation (158), but no association between tidal breathing ratio in infants and maternal smoking was seen in the other studies (154-156). No apparent effect of prenatal smoking was seen on infant respiratory system compliance (C_{RS}) (155,

156, 158, 164), except for one study were C_{RS} was reduced in boys but not girls (160). Prenatal maternal smoking reduced lung function ($FEV_{0.5}$), in infants at 6 weeks of age (153).

Post-natal exposure: Postnatal maternal smoking significant reduced airflow during inspiration and expiration in their infants as measured by specific conductance, hence potentially increased susceptibility to asthma and/or COPD (156). However, maternal postnatal smoking was not associated with bronchial responsiveness in their infants (153, 154) or a reduction in lung volume (155, 157, 160). Paternal smoking during pregnancy had no significant impact on various measures of lung function (tidal volume, respiratory rate, minute ventilation and time to peak expiratory flow) (163).

School-aged children

Twelve studies (166-177) assessing the effect of passive smoking on lung function in school-aged children were identified from a previous review (2) and an updated search. None of the studies were deemed to be of high quality, and only four were conducted in Europe.

Pre-natal exposure: Individual studies found smoking during pregnancy was significantly associated with the children having a 62 ml reduction in FEV_1 and 53 ml reduction in FVC at age 5 years (173), and significantly lowered peak expiratory flow at age 8 years (166); however, no significant effect on lung function was seen in other studies (167, 170).

Post-natal exposure: Any parental smoking significantly reduced FEV/FVC ratios by 0.67% and FEF_{25-75} by 2%, and significantly increase FVC by 0.58%, but had no effect on FEV_1 (2 studies; Figure 5) (170, 177). Data from individual studies showed postnatal maternal smoking had no significant effect on measures of lung function (166, 171, 172, 175); however, continual maternal smoking during and after pregnancy significantly reduced some measures of lung function (FEV/FVC and FEF_{25-75}), with similar magnitudes of reductions seen in boys and girls (170). Furthermore, both parents smoke resulted in significantly lower FEV_1/FVC ratios in boys, but not in girls; but no effect was seen for only exposure to paternal smoking (175). In another study, exposure to smoke measured using cotinine levels in hair resulted in significant decreases in PEF, but not FEV_1 (174).

Three of the included studies assessed the effect of exposure to smoking on lung growth (168, 169, 176); however, no consistent effect of parental or household smoking on lung function assessment of lung growth was demonstrated. Exposure to household smoking resulted in a significant increase in the growth by 7 ml in girls, but significantly reduced growth by 12 ml in boys (168). Having both parents smoke resulted in a significant reduction in lung growth in children aged 8-9 years, but no

effect was seen at older ages or in those with one parental smoker (169). However in another study, maternal smoking significantly reduced the expected annual lung growth (176).

Discussion

After decades of public scepticism amongst tobacco smokers, this millennium has seen major advances in public awareness that tobacco smoking poses a risk to health due to highly successful tobacco control policies and public information campaigns (3, 178-180). However, the battle to ensure the public fully understand the health risks of tobacco smoking is far from won. The public and policymakers are well aware that lung cancer is one of the greatest risks of tobacco smoking. However, there is little awareness of the risk of other diseases from active and passive smoking and few parents understand the damage their smoking can do to their children (179). This lack of knowledge remains a major challenge for policymakers. Without full understanding of the risks, smokers are less likely to have the motivation to quit even when effective smoking cessation measures are readily available (181, 182).

The data presented in our manuscript provides policymakers, the public, and health professionals with an easy 'one-stop shop' where they can find evidence-based meta-analyses of pooled data from studies published to 2013, on the relationship between tobacco smoking and increased risks of respiratory diseases in adults and in children. The main findings from our updated systematic reviews and meta-analyses are discussed below.

As previously mentioned, it is recognised that the public know smoking increases the risk of lung cancer (1); but they have little knowledge of the level of the risk, where **smokers are 11 times more likely to develop lung cancer, and there is no safe minimum number of cigarettes per day**. More education and publicity is needed to increase public awareness of these very high risks. **Exposure to passive smoke increased the risk of lung cancer in non-smokers by 1.41 times.** Raising public awareness about the disease of lung cancer is also important since motivation to quit may be improved through better awareness and knowledge about the symptoms of lung cancer; the lack of a curative treatment; the catastrophic effect on life expectancy with only 12.6% of patients being alive 5 years after diagnosis; and that lung cancer is now the leading cause of cancer deaths worldwide in both men and women (180).

It is estimated that 40-50% of life-long smokers will develop COPD (180); however, the exact mechanism by which tobacco smoking causes or promotes COPD is not known. Furthermore, the general public have little knowledge of this disease and its increased risk due to smoking. We found **smokers are 4.01 times more likely to develop COPD**, and **non-smokers exposed to passive smoking had 1.44 to 1.72 fold increased risk of developing COPD**. However, the latter finding is only based on data from three studies; therefore, **more research is needed to better define the**

relationship between passive smoking and the risk of development of COPD; and to establish whether there are differential effects based on whether passive smoke exposure occurs in childhood or adulthood.

Tobacco smoking is not generally thought of as a risk factor for asthma; therefore, the public should be made aware that **adult smokers are 1.61 times more likely to develop asthma**; and **adult smokers are 1.71 times more likely to have asthma exacerbations**. We found **pregnant women with asthma who smoke have more asthma exacerbations per year and poorer asthma control**; and **children exposed to passive smoke are more than twice as likely to have multiple hospital admissions**.

Although there has been a major reduction in the prevalence and incidence of TB in past decades, the threat of TB is now growing once again because of the emergence of new strains that are resistant to anti-TB drugs. With the inevitable threat of multi-drug resistant TB increasing across Europe, it is important for policymakers to learn of any preventative measures, large or small, that might contribute to reducing this emerging new threat. Therefore, it is important that we highlight the need to raise public awareness in relation to our findings that: i) **adults smokers are 1.57 times more likely to develop TB**; ii) **the risk of TB increases with increasing consumption of cigarettes per day for a longer period of time**; and iii) **non-smokers who are exposed to passive smoke have a 1.44 times increased risk of developing TB**. This evidence provides a motivator to ensure effective smoking-cessation programmes are provided for populations who live in regions identified as at especially high risk of TB.

The role of smoking on the risk of sleep apnoea is currently unclear. We found **adult smokers were 1.97 times as likely to develop sleep apnoea**, and the risk could be as great as **8.38 times where at least 40 cigarettes are smoked per day.** We also found **maternal smoking during pregnancy increased the risk of sleep apnoea in infants by 1.76 times**; and **postnatal maternal smoking increases the risk of sleep apnoea in childhood by 1.25 times**. Our review indicates that smoking is a significant contributory factor to sleep apnoea, but the evidence base is limited and needs strengthening. Therefore, efforts should be made to increase public awareness of the link between smoking and sleep apnoea.

Lower respiratory tract infections (LRTI) are an especial problem in childhood (180). We found **the risk of infants developing LRTI was significantly increased from their exposure to passive smoking within the household; where the largest increase in risk, 1.82 fold, was from both parents smoking**. We also found **prenatal exposure to maternal smoking increased the risk of LRTI by 1.19**

fold. Policymakers are already aware of the harm passive smoking can do to children, and they should be informed that smoke-free legislation has already led to a decrease in passive smoke exposure with a corresponding reduction in hospital admissions of children with respiratory tract infections (183).

Regarding childhood asthma and wheeze, **exposure to passive smoking in the home environment significantly increased the risk of developing asthma and/or wheeze, where the largest increases in risk seemed to be from maternal prenatal smoking on asthma in infants under 2 years (1.85 fold) and maternal postnatal smoking on wheeze in children under 5 years (up to 1.70 fold)**. The findings indicate that passive smoking has a greater effect on the risk of wheeze in children across all age groups than on the risk of asthma, where children under 2 years old are at greater risk. More research is needed to understand the mechanisms underlying these effects and the components of tobacco smoke involved. It is encouraging that adoption of comprehensive smoke-free legislation has led to a significant reduction in the rate of hospital admissions for childhood asthma (184).

Regarding lung function, we found **exposure to passive smoking can decrease lung function in infants within 8 weeks of birth and in school-aged children**. The findings of these studies were variable and most lung function measurements were normal. The only findings of note were that exposure of infants to maternal smoking after birth is associated with reduced airflow, which may reflect the reported increased susceptibility of children to the various airways diseases discussed above; and that maternal smoking during pregnancy and parental smoking after birth may have a detrimental effect on lung function in school-aged children. However, there is currently insufficient evidence to reach firm conclusions on the effect of prenatal and postnatal parental smoking on lung function of their children.

The strength of our systematic reviews is that methodological quality of the evidence within the systematic reviews was generally good, with the majority of the more recent studies providing adjusted effect estimates, thereby reducing the potential for confounding within our pooled estimates. We are confident that our search strategies were comprehensive and we were able to identify further eligible studies through contact with experts with an interest in tobacco control within the respiratory medicine field. A limitation of the systematic reviews relates to the high levels of heterogeneity found within some comparisons; however, we performed exploration analyses using subgroup and sensitivity analyses to assess whether the association varied by participant level characteristics (age and gender) and study level characteristics (geographical location and methodological quality); and found relatively consistent findings across these subgroups.

In conclusion, the *SmokeHaz* study provides a useful resource enabling policymakers and others to rapidly view the available evidence-based scientific data on the increased risk of development of respiratory diseases in adults and children caused by active and passive tobacco smoking. The high levels of risk reported support smoke-free legislation, and justify its continuance and expansion, not only in public places, but also in the home and other confined spaces, such as cars, to protect children. All governmental efforts against smoking should be strengthened, with the ultimate aim of phasing-out tobacco use. Because of the now indisputable health hazards, measures to help all current smokers to quit should be widely available to the general public, and to patients suffering from smoking related diseases ensuring cost is not a barrier. Education to disseminate information to increase public awareness of the many health risks of smoking should be improved; and education and training on the health risks and in smoking cessation methods should be included in the curricula of all health professionals and medical students. The *SmokeHaz* systematic review of respiratory health risks of smoking, and its companion free public website (*www.smokehaz.eu*), are ideal as educational resources since they aim to promote and strengthen public awareness of tobacco control issues, thus complying with Article 12, 'Education, communication, training and public awareness', of the WHO Framework Convention on Tobacco Control (3).

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Author contributions: JLB had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. LJ, PLH, CGG, and JLB made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data, and drafted the submitted article. PP, JB, CV and CJR contributed substantially to the study design, data analysis and interpretation, and revised the manuscript critically for important intellectual content. All authors have provided final approval of the version of the manuscript to be published, and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Table legends

Table 1 Characteristics of studies included in the systematic reviews

Figure legends

Figure 1 Summary estimates from meta-analyses assessing the effect of active and passive smoking on the risk of lung cancer, COPD, asthma, sleep apnoea, and tuberculosis in adults

Figure 2 Summary estimates from meta-analysis assessing the effect of passive smoking on the risk of lower respiratory tract infection in infants

Figure 3 Summary estimates from meta-analyses assessing the effect of exposure to passive smoking on the risk of developing wheeze in children

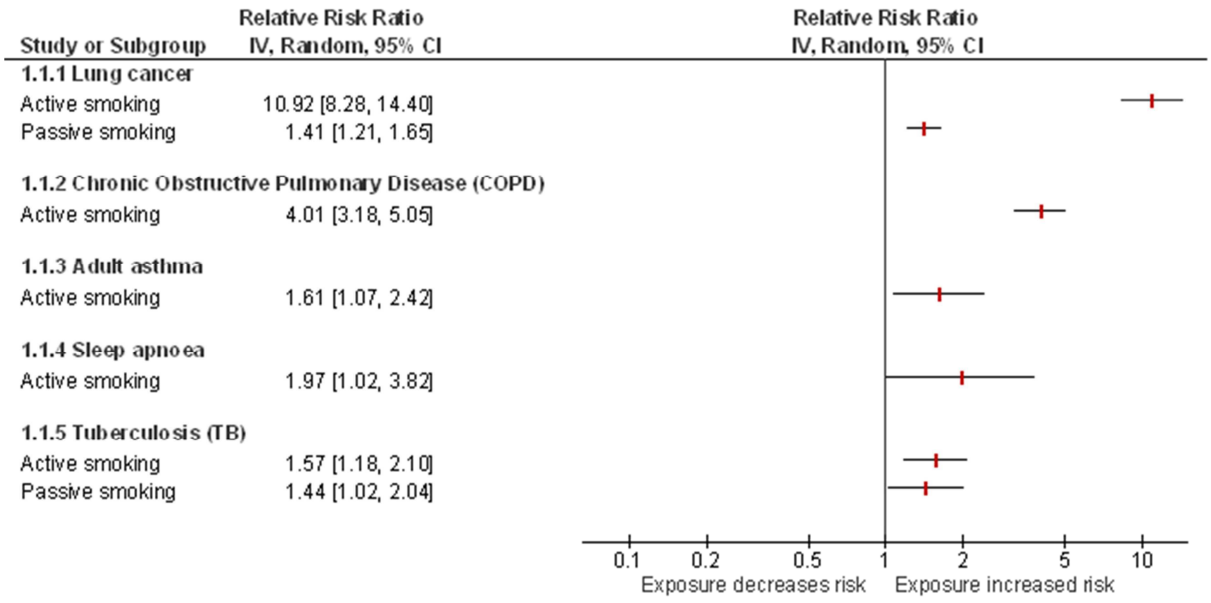
Figure 4 Summary estimates from meta-analyses assessing the effect of exposure to passive smoking on the risk of developing asthma in children

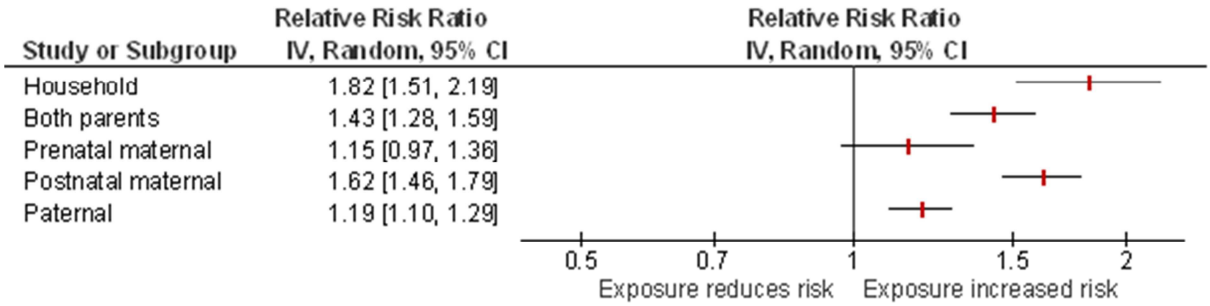
Figure 5 Meta-analysis for the effect of passive smoke exposure on lung function in school-aged children

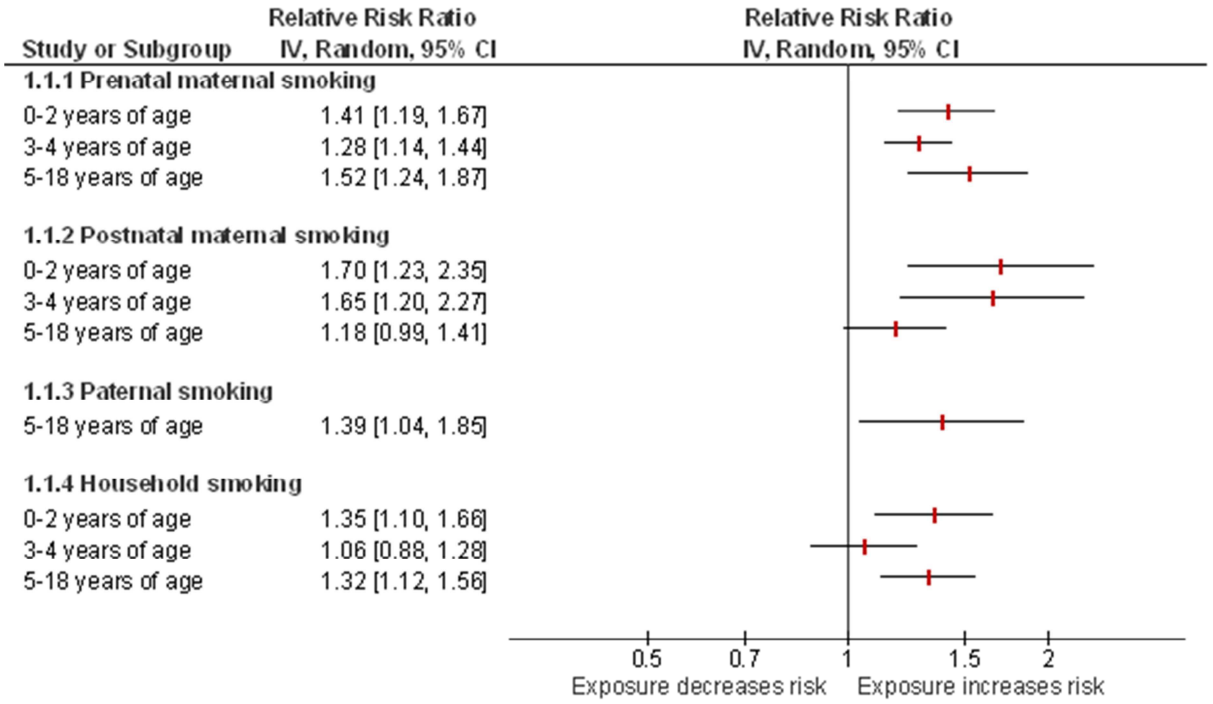
Table 1 Characteristics of studies included in the systematic reviews

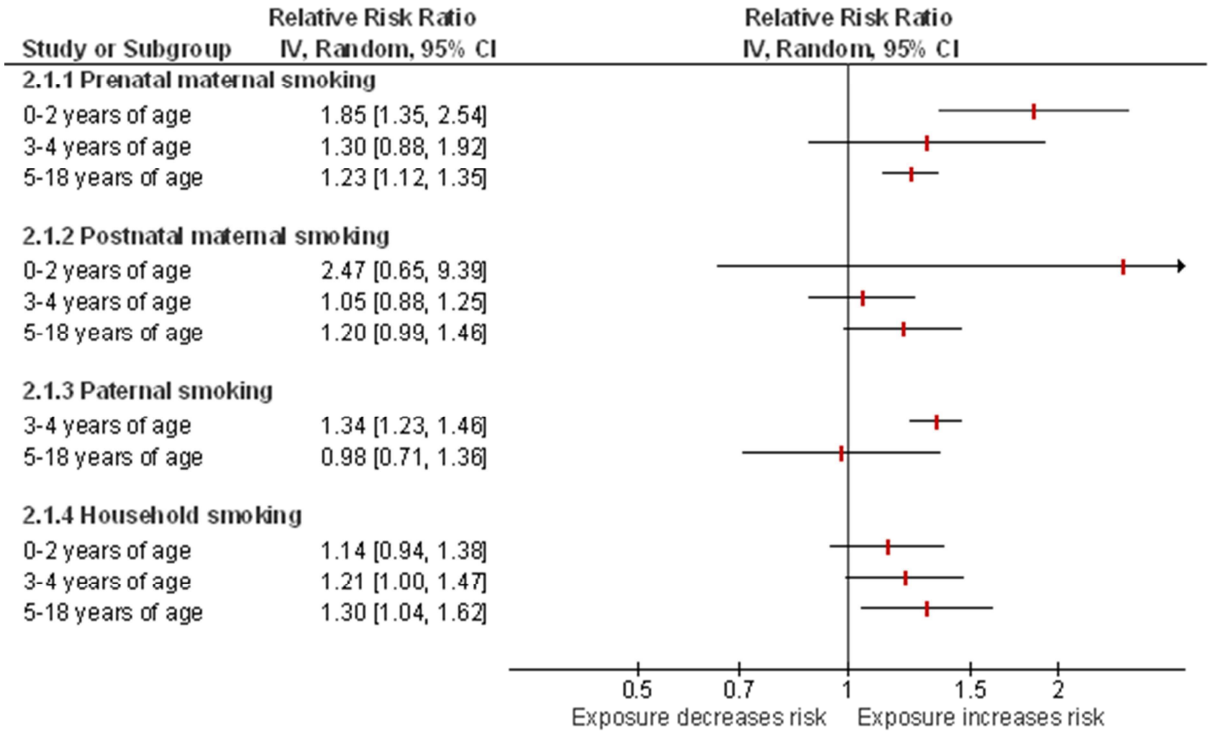
Diseases	Tobacco smoking	Number of studies	References	Used a cohort design	Conducted in Europe	Assessed as high quality	Published since 2000
Adult:							
Lung cancer	Active	34	[9-42]	27 (79%)	13 (38%)	19 (56%)	22 (65%)
	Passive	15	[43-57]	13 (91%)	4 (27%)	6 (40%)	8 (53%)
COPD	Active	24	[58-81]	22 (92%)	15 (63%)	5 (21%)	20 (83%)
	Passive	3	[71, 83, 84]	3 (100%)	1 (33%)	0 (0%)	0 (0%)
Asthma	Active	8	[87-94]	8 (100%)	6 (75%)	4 (50%)	3 (38%)
Asthma exacerbations	Active	2	[96-97]	1 (50%)	1 (50%)	2 (100%)	2 (100%)
	Passive	3	[98-100]	3 (100%)	2 (67%)†	1 (33%)	2 (67%)
Tuberculosis	Active	4	[101-104]	4 (100%)	0 (100%)	3 (75%)	4 (100%)
	Passive	2	[103, 105]	2 (100%)	0 (100%)	2 (100%)	2 (100%)
Sleep apnoea	Active	3	[111-112, 115]	3 (100%)	2 (67%)	0 (0%)	1 (33%)
	Passive	2	[113-114]	2 (100%)	2 (100%)	0 (0%)	1 (50%)
Childhood:							
LRTI	Passive	34	[117-150]	34 (100)%	17 (50%)	16 (47%)	16 (47%)
Asthma/wheeze	Passive	71	[152]	71 (100%)	32 (45%)	31 (44%)	55 (77%)
Lung function in infants	Passive	13	[153-165]	13 (100%)	7 (57%)	6 (46%)‡	5 (38%)
Lung function in school-aged children	Passive	12	[166-177]	12 (100%)	4 (33%)	0 (0%)	6 (50%)

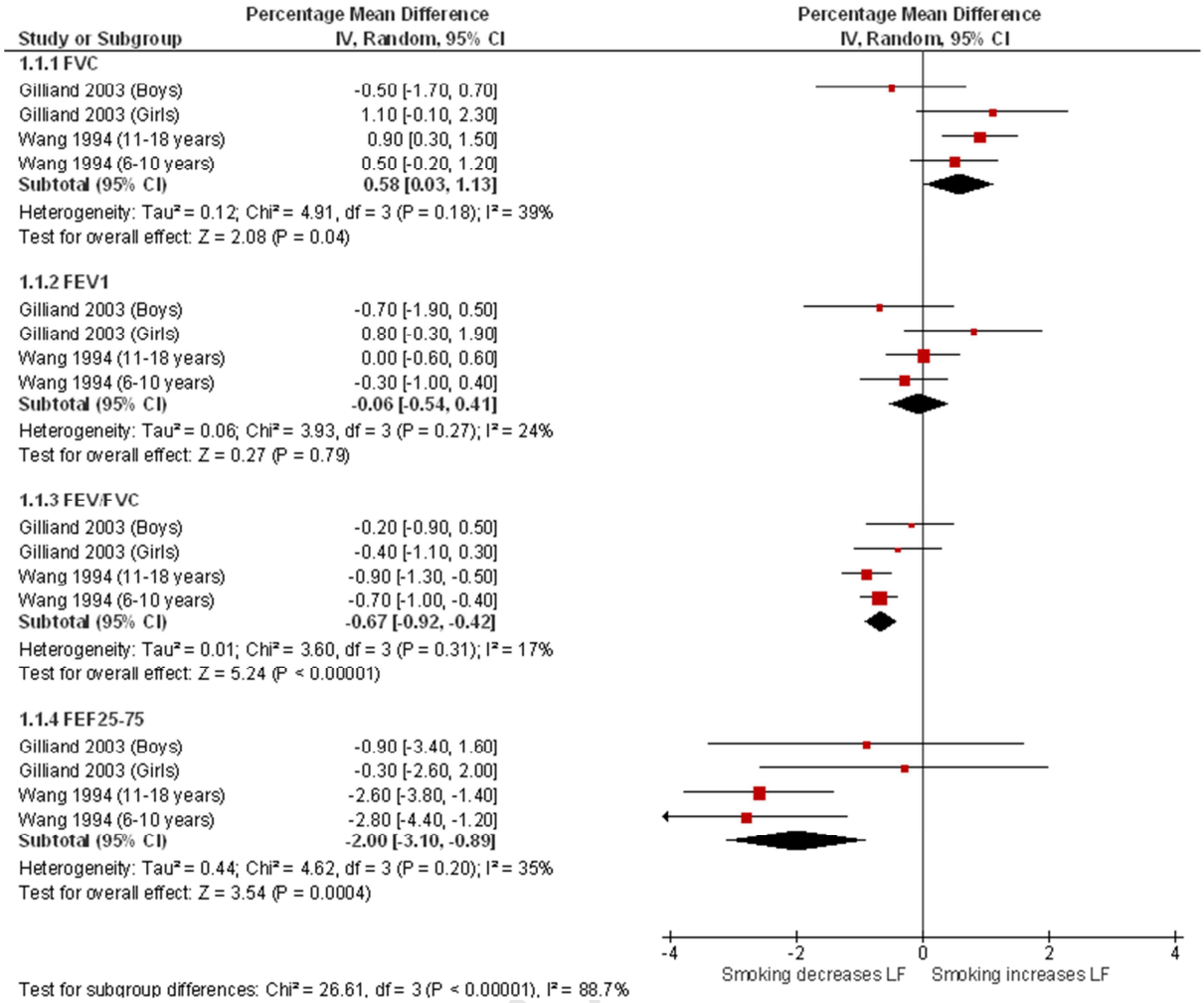
COPD Chronic Obstructive Pulmonary Disease; LRTI Lower Respiratory Tract Infection; †one study was conducted in both the UK and US; ‡assessed based on adjustment for confounders











Abbreviations

COPD	Chronic Obstructive Pulmonary Disease
CI	Confidence Interval
CRS	Respiratory System Compliance
EU	European Union
FEF_{25-75}	Forced Expiratory Flow during the mid-portion of the FVC
FEV_1	Forced Expiratory Volume in one second
FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
LRTI	Lower Respiratory Tract Infection
PEF	Peak Expiratory Flow
RR	Risk Ratio