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Parental Smoking and the Risk of Middle Ear Disease in Children

A Systematic Review and Meta-analysis

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Objectives: A systematic review and meta-analysis of studies of the association between passive smoking and middle ear disease (MED) in children.

Data Sources: MEDLINE, EMBASE and CAB Abstracts (to December 2010) and reference lists.

Study Selection: Sixty-one epidemiological studies of children assessing the effect of passive smoke exposure on outcomes of MED were included. Articles were reviewed, data extracted and synthesized by two researchers.

Main Outcome Exposures: Children's passive smoke exposure including: maternal smoking during and after pregnancy, paternal and household.

Main Outcome Measures: Middle ear disease in children.

Results: Living with a smoker was associated with an increased risk of MED in children; by an odds ratio (OR) of 1.62 (95% confidence interval (CI) 1.33 to 1.97) for maternal post-natal smoking and by 1.37 (95% CI 1.25 to 1.50) for any household member smoking. Pre-natal maternal smoking (OR 1.11, 95% CI 0.93 to 1.31) and paternal smoking (OR 1.24, 95% CI 0.98 to 1.57) were associated with a non-significant increase in the risk of MED in children. The strongest effect was on the risk of surgery for MED, where maternal post-natal smoking increased the risk by an OR of 1.86 (95% CI 1.31 to 2.63) and paternal smoking by 1.83 (95% CI 1.61 to 2.07).

Conclusions: Passive smoke exposure, particularly by the mother, significantly increases the risk of MED in childhood; this risk is particularly strong for MED requiring surgery. We have shown that 130,200 of child MED episodes per year are directly attributable to passive smoke exposure.

Middle ear disease (MED) is a common illness among children that accounts for a large number of physician visits, and which if untreated, can cause significant disability though hearing impairment.[1] It is estimated that around 10% of children have three episodes of acute otitis media (AOM) before their first birthday,[2] whilst middle ear effusion is the most common reason for admission of young children to hospitals for surgery, putting a heavy financial burden on health care services.[3] Furthermore, adenoidectomy and particularly adenotonsillectomy, which are surgical treatments for otitis media with effusion (OME), have been associated with significant morbidity and mortality, including that arising from surgery.[4] Middle ear effusion is associated with hearing loss in children, which may lead to delayed linguistic and cognitive development.[3] The prevalence of MED is higher among children with learning impairment.[5]

In 1998, a systematic review by Strachan and Cook of papers published up to 1996 found a significant association between parental smoking and MED.[6] However, the authors concluded that few studies had compared the effect of smoking by the mother and father and none had compared the effect of pre- and post-natal tobacco smoke exposure to MED. This original review was commissioned for a UK government Scientific Committee on Tobacco and Health (SCOTH),[7] and was subsequently updated as part of the 2006 US Surgeon General's report on the effects of involuntary exposure to tobacco smoke, which concluded that there was sufficient evidence to infer a causal relationship between parental smoking and otitis media in childhood.[8] Since these early reviews of papers published up until 2001, the evidence base on the association between parental smoking and MED in childhood has significantly increased. To date however, these new studies have not been subject to meta-analysis. We have therefore carried out a systematic review and meta-analysis of the epidemiological data to provide contemporary estimates of the effects of smoking by parents and other household members on the risk of middle ear disease in childhood. The work was carried out as part of a more extensive review of the effects of passive smoking in children, for the Royal College of Physicians.[9]

METHODS

Systematic review methods

Any analytical epidemiological study assessing the effect of passive smoke exposure (including household smoking, paternal[1] smoking, maternal smoking after during and after pregnancy) were included in the review. Outcomes of interest were MED, sub-divided into: middle ear infections (including acute otitis media, otitis media with effusion, recurrent otitis media, chronic otitis media); hearing impairment (including hearing loss, deafness, glue ear), and surgery related to MED (including adenotonsillectomy, tonsillectomy, adenoidectomy, and grommet insertion).

We searched MEDLINE, EMBASE and CAB Abstracts (from 1997 to December 2010), using the keywords *Tobacco smoke, cigarette smoking, passive smoking, parental smoking, maternal smoking, parental smoking, environmental tobacco smoking, second hand smoke, children, infants, adolescents, pediatric, otitis media with effusion, deafness, adenoidectomy, middle ear disease, adenotonsillectomy, acute otitis media, recurrent otitis media, middle ear*

[1] Please note that it was not possible in the current (or previous) study to identify studies that measured paternal smoking independently of maternal smoking i.e. father smokes but mother does not.

effusion, glue ear, otitis, tympanum, tonsil, otitis interna. Hand searching of reference lists was also performed. No language restrictions were imposed during the searches, however, to be consistent with the original review,[6] we report only those studies published in English.

Titles and abstracts from the identified studies were reviewed independently by two of three authors (AH & JLB or LLJ & JLB) to identify eligible studies. The full text of studies potentially eligible for inclusion were sought and assessed independently by two of the three authors. For included studies, two of the three authors independently extracted data using a standard data extraction form and assessed methodological quality using the Cochrane Collaboration Non-Randomized Studies Working Group recognized Newcastle-Ottawa Quality Assessment Scale[10] based on the following: selection of cases and controls, or cohort; comparability of the cases and controls, or cohort, and assessment of exposure/outcome. A score of six or more was chosen *a priori* to indicate higher methodological quality. In addition, all studies included in the previous review[6] were assessed for methodological quality using the same methods. Disagreements were resolved through discussion.

Statistical analysis

Where possible, the data extracted were unadjusted odds ratios (OR), or in preference, OR adjusted for potential confounding variables. Measures of uncertainty were also extracted either in the form of standard errors or 95% confidence intervals (CI). Pooled estimates of measures of association were estimated using random effect meta-analyses and presented as pooled OR with 95% CI. Heterogeneity was assessed using recognized methods (I^2).[11] Random effect meta-regression analyses were conducted to investigate the reasons for any heterogeneity between epidemiological studies based on definition of MED (middle ear infection, surgery and hearing impairment), methodological quality (higher versus lower), study design (cohort, cross-sectional and case-control), ascertainment of passive smoke exposure (biochemical vs. self-report) and by date of publication. Exposure was defined as household, paternal and maternal; maternal was split into pre- and post-natal. Data were analyzed using Review Manager, version 5.0.23 ((RevMan), Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration) and STATA MP/11.0 for Windows (StataCorp LP, 4905 Lakeway Drive, College Station, TX 77845, USA). P values less than 0.05 were considered statistically significant. The analysis was performed in accordance with the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[12]

Population attributable fraction estimation

We estimated the proportion of children in England who live in a household in which at least one person smokes using data from the Health Survey for England,[9] and used the formula *p(OR-1)/[p(OR-1)+1],* in which *p* is the proportion of the cohort exposed to passive smoking, and *OR* the odds ratio for MED in children where a member of the household smokes, to estimate the proportion of children whose MED is attributable to household smoking exposure. We then used national MED prevalence[9] data for England and Wales to estimate the number of disease episodes generated as a result of household passive smoke exposure.

RESULTS

From 360 titles published since 1997 identified in the literature search, 55 abstracts were deemed potentially eligible, and of these, 36 were included following the full-text review (Figure 1). The reasons for exclusion were: not having a comparative group without the outcome,[13-15] not assessing passive smoke as an exposure,[16] not assessing MED as an outcome,[17, 18] being published in a language other than English,[19-25] only reporting statistical significance (p value) of the result without data,[26-29] or only having passive smoking data as a confounder in the analysis.[30] Combining the results from this updated search with the previous review (25 studies) resulted in 61 epidemiological studies (Table 1, Figure 1).

Of the 61 studies included, 15[31-45] were a cross-sectional survey, 23[46-68] were case-control studies and 23[69-91] were cohort studies. Seventeen different disease outcomes were reported within these studies: acute infection and serious otitis media,[83] acute otitis media,[32, 35, 38, 68, 69, 72, 86, 87, 91] chronic suppurative otitis media,[59] earache,[82] glue each,[51] hearing loss,[70] middle ear disease,[46, 71] otitis media,[36, 39, 43, 48, 74, 81] otitis media with effusion,[31, 34, 40, 42, 44, 45, 47, 50, 53, 66, 67, 75, 76, 78, 80, 84, 90] otitis prone,[63] recurrent otitis media,[49, 60, 64, 73, 77, 79, 88, 89] suppurative otitis media,[33] surgery (adenoids/tonsils),[41] surgery (otitis media with effusion),[52, 57, 58, 61, 85] surgery (otitis media),[37, 55, 56] surgery (recurrent otitis media),[62] and surgery (tonsils).[54, 65]

Methodological Quality of Studies and Publication Bias

The methodological quality of the 61 studies included in the meta-analysis, as judged by the Newcastle-Ottawa scale score, is presented in Table 1. The overall median score was 5.5 (range 2 to 8). Using the *a priori* threshold of six to indicate high methodological quality, we judged 34 of the studies to be of high quality; the remaining 27 were deemed to be of lower quality primarily due to a combination of a lack of biochemical validation of passive smoke exposure, lack of representativeness of the study sample, and/or lack of adjusted analyses. There was no evidence of publication bias identified from funnel plots. The funnel plot for household exposure and the risk of MED is presented in Figure 2.

Effects of maternal post-natal smoking

Meta-analysis of the 20 studies of post-natal maternal smoking showed a statistically significant increase in the risk of MED in childhood by 1.62 (95% CI 1.33 to 1.97). High levels of heterogeneity were present in this analysis (I^2 = 93%). Pooled estimates for each of the outcome categories showed that the increase in risk of MED was driven predominantly by an increase in the risk of surgery for MED (OR 1.86, 95% CI 1.31 to 2.63; 5 studies; Figure 3) and to a lesser extent hearing impairment (OR 1.74, 95% CI 1.08 to 2.81; 1 study) and middle ear infection (OR 1.53, 95% CI 1.22 to 1.92; 14 studies). In a meta-regression based on method of ascertainment of passive smoke exposure, studies that used self-reported data showed a higher increase in disease risk (OR 1.70, 95% CI 1.29 to 2.25; 17 studies), than studies that used biochemical validation (OR 1.29, 95% CI 0.86 to 1.94; 3 studies). In a sub-group analysis based on study design, case-control studies showed a statistically significant increase in the risk of MED in children (OR 2.09, 95% 1.19 to 3.66; 10 studies), unlike cohort (OR 1.19, 95% CI 0.94 to 1.49; 6 studies) and cross-sectional (OR 1.28, 95% CI 0.88 to 1.86; 4 studies) study designs which were not statistically significantly associated with an increase in disease risk. Similar pooled estimates were also shown for the meta-regression analysis based on methodological quality and date of publication (see Table 2a). In a multiple meta-regression adjusting for study design, publication date, ascertainment and methodological quality, none of the factors independently predicted the odds ratio for maternal post-natal smoking.

Effects of maternal pre-natal smoking

All of the six studies of pre-natal maternal smoking were indentified from the updated search, as they were published after 1996. Pre-natal maternal smoking was not associated with a statistically significant increase in the risk of MED (OR 1.11, 95% CI 0.93 to 1.31; 6 studies); however, high levels of heterogeneity were seen between the studies (I^2 = 79%). Similarly, none statistically significant pooled estimates were also seen for meta-regression analyses stratified by study design, ascertainment of smoking status and methodological quality (see Table 2a).

Effects of paternal smoking

Exposure to paternal smoking was associated with a non-significant (p=0.07) increase in the odds of middle ear disease in childhood by 1.24 (95% CI 0.98 to 1.57; 12 studies). Very high levels of heterogeneity were seen in the analysis (I^2 = 87%). Sub-group analysis based on the definition of outcome showed that the increased risk of disease was due to a strong association between paternal passive smoke exposure and the risk of surgery for MED (OR 1.83, 95% CI 1.61 to 2.07; 4 studies; Figure 4). The association between paternal smoking and middle ear infection was not statistically significant (OR 1.06, 95% CI 0.91 to 1.24; 8 studies, p=0.47). Similar pooled estimates were also seen for meta-regression analyses stratified by study design, ascertainment of smoking status, date of publication and methodological quality (see Table 2b).

In a multiple meta-regression adjusting for study design, publication date, ascertainment and methodological quality, none of the factors independently predicted the odd ratio for paternal smoking.

Effects of household smoking

A pooled estimate derived from the 49 studies which defined exposure as household smoking (the study by Jacoby et al.[81] is shown in the Forest plot as two separate entries given the differing estimates reported for the two samples: aboriginal vs. non-aboriginal) demonstrated a statistically significant increase in the risk of middle ear disease by an OR of 1.37 (95% CI 1.25 to 1.50; 49 studies). High levels of heterogeneity were seen between the studies (I^2= 76%). Sub-group analysis based on the definition of outcome showed that the increase in risk was mainly attributable to a increase in risk of surgery for MED (OR 1.62, 95% CI 1.32 to 1.98; 11 studies; Figure 5) and to a lesser extent middle ear infection (OR 1.32, 95% CI 1.20 to 1.45; 38 studies). Meta-regression analysis based on study design showed varied pooled estimates, with case-control studies showing the highest increase in disease risk (OR 1.55, 95% CI 1.35 to 1.77; 18 studies), followed by cross sectional studies (OR 1.33, 95% CI 1.10 to 1.60; 13 studies) and cohort studies (OR 1.27, 95% CI 1.13 to 1.43; 18 studies). Similar pooled estimates were also seen for analyses stratified by ascertainment of smoking status, date of publication and methodological quality (see Table 2b). In a multiple meta-regression adjusting for study design, publication date, ascertainment and methodological quality, none of the factors independently predicted the odd ratio for household smoking.

Population attributable fraction

Health survey for England data indicate that in 2007, around 22% of children aged up to 15 years lived in a household in which someone smokes.{Royal College of Physicians, 2010 #561} Using the odds ratio for household smoking (1.37) as the estimated relative risk of developing MED, the proportion of children developing MED likely to be attributable to exposure to smoking in the home is estimated at 7.5%. In 2008 there were about 1,735,710 episodes of MED in children under the age of 16 years in the UK.[9] A 7.5% attributable fraction translates into approximately 130,200 new episodes of MED arising from exposure to smoking in the home in the UK.

DISCUSSION

Middle ear disease is a significant cause of morbidities in children and has been shown to be associated with parental passive smoke exposure.[6] This relationship has been further explored in the current systematic review and meta-analysis, providing novel findings which suggest that maternal post-natal smoking, rather than maternal pre-natal or paternal smoking has the strongest influence on disease risk. This may suggest that the effect is due to ambient smoke pollution from the child's close proximity to the primary caregiver, not to development effects. However, it important to consider that only six pre-natal studies met the inclusion criteria in the current study and hence may be underpowered to detect an association. Therefore, further well-conducted research studies are needed. We additionally found that smoking by any household member was statistically significantly associated with an increased risk of disease in children, which translates to an additional 130,200 episodes of MED per year in the UK, which are directly attributable to passive smoking.

From meta-regression analysis exploring the different MED outcomes (middle ear infection, surgery for middle ear infection, hearing impairment or hearing loss), we found that the effect of passive smoke exposure was strongest for surgery for MED, with an increased risk of 1.86 for maternal post-natal, 1.83 for paternal and 1.62 for household smoking. In addition, maternal post-natal smoking was shown to increase the risk of hearing impairment by an odds of 1.74 (95% CI 1.08 to 2.81), although this estimate is based on only one study of high methodological quality.[51]

Our findings are likely to be representative estimates of the true effects of passive smoking on the risk of MED in children since they are based on results of a comprehensive search, including data identified through hand searching of reference lists and previous reviews. However, there are limitations to this review. We elected to keep methods consistent with the original strategy[6] and only included studies written in English in the meta-analyses. Additionally, we were inevitably limited in the range of confounding factors that could be adjusted for in our analyses. Although the high quality studies generally adjusted for maternal age and socioeconomic status; other potential confounders, such as smoking by other individuals in the household, were not consistently adjusted for in the analyses of the individual effects of paternal and maternal smoking. A further limitation of this meta-analysis was that high levels of heterogeneity were observed for some comparisons, which suggests that there are unexplained reasons for variation in the findings between studies over and above chance, which may result in potentially misleading summary estimates. We investigated reasons for heterogeneity by performing meta-regression analyses; however, these analyses revealed relatively consistent findings. Generally, the pooled results did not differ appreciably between studies of different methodological quality, publication date or study design.

CONCLUSIONS

This study confirms that household smoking, in particular, maternal post-natal smoking causes a statistically significant increase in the risk of MED in childhood, and identifies that one of the main consequences of children's exposure to passive smoke is the significant increase in risk of having to have surgery for chronic MED. Surgical treatments for otitis media, such as grommet insertion, have been shown to be questionable in their effectiveness, high risk and resource and cost intensive.[92]Therefore, primary prevention through the reduction of risk factors such as exposure to passive smoke, are key to reducing the burden of MED in childhood. Although evidence is emerging to suggest that the incidence of MED has been declining in recent years in England,[93] perhaps as a reflection of a reduction in the number of parents who smoke, MED is still a major public and child health concern, with a total of 1.74 million episodes estimated in the UK each year.[9] We have shown that 7.5% of these episodes (130,200) are directly attributable to passive smoke exposure in the home, all of which are avoidable. The findings from this study should encourage renewed efforts to promote smoke free environments for children.

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Author Contributions: Dr Leonardi-Bee had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Britton and Leonardi-Bee. *Acquisition of data:* Jones, Hassanien and Leonardi-Bee. *Analysis and interpretation of data:* Jones and Leonardi-Bee. *Drafting of the manuscript:* Jones, Hassanien and Leonardi-Bee. *Critical revision of the manuscript for important intellectual content: Jones, Hassanien, Cook, Britton and Leonardi-Bee*. *Statistical analysis:* Leonardi-Bee. *Administrative, technical, and material support:* Jones and Leonardi-Bee. *Study supervision:* Jones and Leonardi-Bee.

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FIGURE TITLES AND LEGENDS

Figure 1. Flow diagram of included and excluded studies

Figure 2. Funnel plot for household second hand smoke exposure against middle ear disease.

(Plot shows the standard error of the odds ratio versus odds ratio for each study (random effects model). Vertical dotted lines indicate pooled effect estimate; and dots, individual studies).

Figure 3. Relationship between passive smoke exposure by maternal smoking after birth and the risk of middle ear disease using a meta-analysis of comparative epidemiologic studies (Data are presented as odds ratios sub-grouped by the definition of middle ear disease outcome).

(Squares denote the odds ratio (OR) for a single study with horizontal lines denoting 95% confidence intervals. The centre of the diamond denotes the pooled OR and the corners the 95% confidence intervals. An OR >1 indicates a higher risk of the outcome in those exposed to passive smoke).

Figure 4. Relationship between paternal passive smoke exposure and the risk of middle ear disease using a meta-analysis of comparative epidemiologic studies (Data are presented as odds ratios sub-grouped by the definition of middle ear disease outcome).

(Squares denote the odds ratio (OR) for a single study with horizontal lines denoting 95% confidence intervals. The centre of the diamond denotes the pooled OR and the corners the 95% confidence intervals. An OR >1 indicates a higher risk of the outcome in those exposed to passive smoke).

Figure 5. Relationship between passive smoke exposure by any household member and the risk of middle ear disease using a meta-analysis of comparative epidemiologic studies (Data are presented as odds ratios sub-grouped by the definition of middle ear disease outcome).

(Squares denote the odds ratio (OR) for a single study with horizontal lines denoting 95% confidence intervals. The centre of the diamond denotes the pooled OR and the corners the 95% confidence intervals. An OR >1 indicates a higher risk of the outcome in those exposed to passive smoke).

TABLES

Table 1 Summary of studies included in the meta-analysis

Study	Year of Publication*	Study Design	Study Location	Ascertainment	Exposure	Outcome	Methodological Quality†
Adair-Bischoff[46]	1998	Case control	Canada	Biochemical and self-report	Maternal post-natal, paternal, household	Middle ear disease	8
Alho[69]	1993	Cohort	Finland	Biochemical	Household	Acute otitis media	8
Apostolopoulos[31]	1998	Cross sectional	Greece	Self-report	Household	Otitis media with effusion	6
Barr[47]	1992	Case control	United Kingdom	Self-report	Maternal pre-natal, household	Otitis media with effusion	5
Bener[70]	2005	Cohort	Qatar	Self-report	Maternal pre-natal	Hearing loss	7
Bennett[71]	1998	Cohort	United Kingdom	Self-report	Maternal post-natal	Middle ear disease	6
Bentdal[72]	2007	Cohort	Norway	Self-report	Household	Acute otitis media	7
Collet[73]	1995	Cohort	Canada	Self-report	Household	Recurrent otitis media	6
da Costa[48]	2004	Case control	Mozambique	Self-report	Household	Otitis media	8
Daigler[49]	1991	Case control	United States	Self-report	Maternal post-natal, paternal	Recurrent otitis media	8

Table 1 Continued

Study	Year of Publication*	Study Design	Study Location	Ascertainment	Exposure	Outcome	Methodological Quality†
Daly[74]	2007	Cohort	United States	Self-report	Maternal post-natal, household	Otitis media	6
Engel[75]	1999	Cohort	Netherlands	Self-report	Household	Otitis media with effusion	7
Etzel[76]	1992	Cohort	United States	Biochemical	Household	Otitis media with effusion	8
Ey[77]	1995	Cohort	United States	Biochemical	Maternal post-natal	Recurrent Otitis media	8
Froom[32]	2001	Cross sectional	United States, Canada, United Kingdom, Netherlands	Self-report	Household	Acute otitis media	4
Gliddon[78]	2001	Cohort	United Kingdom	Self-report	Maternal post-natal, household	Otitis media with effusion	3
Green[50]	1991	Case control	Germany	Self-report	Maternal post-natal, paternal	Otitis media with effusion	5
Gryczynska[33]	1999	Cross sectional	Poland	Self-report	Household	Suppurative otitis media	2
Gultekin[66]	2010	Case control	Turkey	Self-report	Maternal post-natal, paternal, household	Otitis media with effusion	6

Table 1 continued

Study	Year of Publication*	Study Design	Study Location	Ascertainment	Exposure	Outcome	Methodological Quality†
Haberg[91]	2010	Cohort	Norway	Self-report	Maternal pre-natal, maternal post-natal, household	Acute otitis media	4
Haggard[51]	2002	Case control	United Kingdom	Self-report	Maternal post-natal	glue ear	6
Hammaren-Malmi[34]	2005	Cross sectional	Finland	Self-report	Maternal post-natal, paternal	Otitis media with effusion	4
Hammaren-Malmi[79]	2007	Cohort	Finland	Self-report	Maternal post-natal, paternal	Recurrent otitis media	8
Hinton[53]	1988	Case control	United Kingdom	Self-report	Household	Otitis media with effusion	4
Hinton[52]	1989	Case control	United Kingdom	Self-report	Household	Surgery (otitis media with effusion)	2
Hinton[54]	1993	Case control	United Kingdom	Self-report	Maternal post-natal, paternal, household	Surgery (tonsils)	6
Homoe[35]	1999	Cross sectional	Greenland	Self-report	Household	Acute otitis media	4

Table 1 continued

Study	Year of Publication*	Study Design	Study Location	Ascertainment	Exposure	Outcome	Methodological Quality†
Ilicali[55]	1999	Case control	Turkey	Self-report	Maternal post-natal, paternal, household	Surgery (otitis media)	3
Ilicali[56]	2001	Case control	Turkey	Biochemical and self-report	Household	Surgery (otitis media)	5
Iversen[80]	1985	Cohort	Denmark	Self-report	Household	Otitis media with effusion	6
Jacoby[81]	2008	Cohort	United States	Self-report	Household	Otitis media	8
Kitchens[57]	1995	Case control	United States	Self-report	Maternal post-natal, paternal, household	Surgery (otitis media with effusion)	5
Kraemer[58]	1983	Case control	United States	Self-report	Household	Surgery (otitis media with effusion)	6
Lasisi[59]	2007	Case control	Nigeria	Self-report	Household	Chronic suppurative otitis media	6
Lee[82]	2003	Cohort	United States	Self-report	Household	Earache	4

Table 1 continued

Study	Year of Publication*	Study Design	Study Location	Ascertainment	Exposure	Outcome	Methodological Quality†
Lieu[36]	2002	Cross sectional	United States	Biochemical and self-report	Maternal pre-natal, maternal post-natal, household	Otitis media	7
Lister[37]	1998	Cross sectional	Australia	Self-report	Maternal post-natal	Surgery (otitis media)	4
Lubianca[38]	1999	Cross sectional	Brazil	Self-report	Household	Acute otitis media	4
MacIntyre[68]	2010	Case control	Canada	Self-report	Maternal pre-natal	Acute otitis media	7
Noakes[83]	2007	Cohort	Australia	Biochemical	Maternal pre-natal	Acute infection and serious otitis media	4
Paradise[84]	1997	Cohort	United States	Self-report	Household	Otitis media with effusion	6
Pukander[60]	1985	Case control	Finland	Self-report	Household	Recurrent otitis media	5
Rasmussen[85]	1993	Cohort	Sweden	Biochemical	Household	Surgery (otitis media with effusion)	7
Rowe-Jones[61]	1992	Case control	United Kingdom	Self-report	Household	Surgery (otitis media with effusion)	3

Table 1 continued

Study	Year of Publication*	Study Design	Study Location	Ascertainment	Exposure	Outcome	Methodological Quality†
Rylander[39]	2000	Cross sectional	Switzerland	Self-report	Household	Otitis media	4
Safavi Naini[40]	2002	Cross sectional	Iran	Self-report	Household	Otitis media with effusion	4
Said[41]	1978	Cross sectional	France	Self-report	Maternal post-natal, paternal, household	Surgery (adenoids/tonsils)	3
Saim[42]	1997	Cross sectional	Malaysia	Self-report	Household	Otitis media with effusion	4
Salazar[86]	1997	Cohort	United States	Self-report	Household	Acute otitis media	7
Shiva[43]	2003	Cross sectional	Iran	Self-report	Household	Otitis media	3
Sophia[67]	2010	Case control	India	Self-report	Household	Otitis media with effusion	7
Ståhlberg[62]	1986	Case control	Finland	Self-report	Household	Surgery (recurrent otitis media)	4
Stathis[87]	1999	Cohort	Australia	Self-report	Maternal pre-natal, household	Acute otitis media	7
Stenstrom[64]	1993	Case control	Canada	Self-report	Household	Recurrent otitis media	6

Table 1 continued

Study	Year of Publication*	Study Design	Study Location	Ascertainment	Exposure	Outcome	Methodological Quality†
Stenstrom[63]	1997	Case control	Sweden	Self-report	Maternal post-natal, paternal	Otitis prone	5
Strachan[44]	1990	Cross sectional	United Kingdom	Self-report	Household	Otitis media with effusion	6
Tainio[88]	1988	Cohort	Finland	Biochemical	Household	Recurrent otitis media	8
Teele[89]	1989	Cohort	United States	Biochemical	Household	Recurrent otitis media	7
Willatt[65]	1986	Case control	United Kingdom	Self-report	Household	Surgery (tonsils)	6
Xenellis[45]	2005	Cross sectional	Greece	Self-report	Household	Otitis media with effusion	2
Zielhuis[90]	1989	Cohort	Netherlands	Biochemical	Household	Otitis media with effusion	6

*Studies published prior to 1996 from previous Strachan and Cook review[6]

†Methodological quality of the studies are based on the Newcastle-Ottawa Quality Assessment Scale[10]

Table 2a Summary of overall effect and meta-regression analysis of maternal pre- and post-natal passive smoke exposure on the risk of middle ear disease in childhood

		Maternal pre-natal					Maternal post-natal				
		OR	**95% CI**	**Studies**	**I^2**	**p‡**	**OR**	**95% CI**	**Studies**	**I^2**	**p‡**
Overall effect		1.11	0.93 to 1.31	6	79	N/A	1.62	1.33 to 1.97	20	93	N/A
Outcome	Middle ear infection	1.15	0.98 to 1.35	5	79	0.36	1.53	1.22 to 1.92	16	94	0.63
	Surgery for middle ear disease	N/A	N/A	0	N/A		1.86	1.31 to 2.63	5	73	
	Hearing loss	0.61	0.35 to 1.08	1	N/A		N/A	N/A	0	N/A	
	Hearing impairment	N/A	N/A	0	N/A		1.74	1.08 to 2.81	1	N/A	
Study Design	Cohort	1.97	0.51 to 2.24	4	85	0.94	1.19	0.94 to 1.49	6	76	0.14
	Cross sectional	1.07	0.97 to 1.18	1	N/A		1.28	0.88 to 1.86	4	94	
	Case-control	1.16	1.09 to 1.23	1	N/A		2.09	1.19 to 3.66	10	92	
Methodological Quality	High	1.17	0.95 to 1.44	4	85	0.49	1.83	1.21 to 2.76	10	96	0.47
	Low	0.74	0.24 to 2.27	2	41		1.47	1.12 to 1.94	10	88	
Publication Date	Prior to 1996	N/A	N/A	0	N/A	N/A	1.48	1.22 to 1.80	7	31	0.58
	Post 1996	1.11	0.93 to 1.31	6	79		1.72	1.35 to 2.21	13	95	
Ascertainment	Self-report	1.17	0.87 to 1.57	4	85	0.56	1.70	1.29 to 2.25	17	94	0.56
	Biochemical	0.75	0.22 to 2.61	2	47		1.29	0.86 to 1.94	3	82	

OR = odds ratio

95% CI = 95% confidence interval

I2 = percentage of heterogeneity

N/A = not applicable

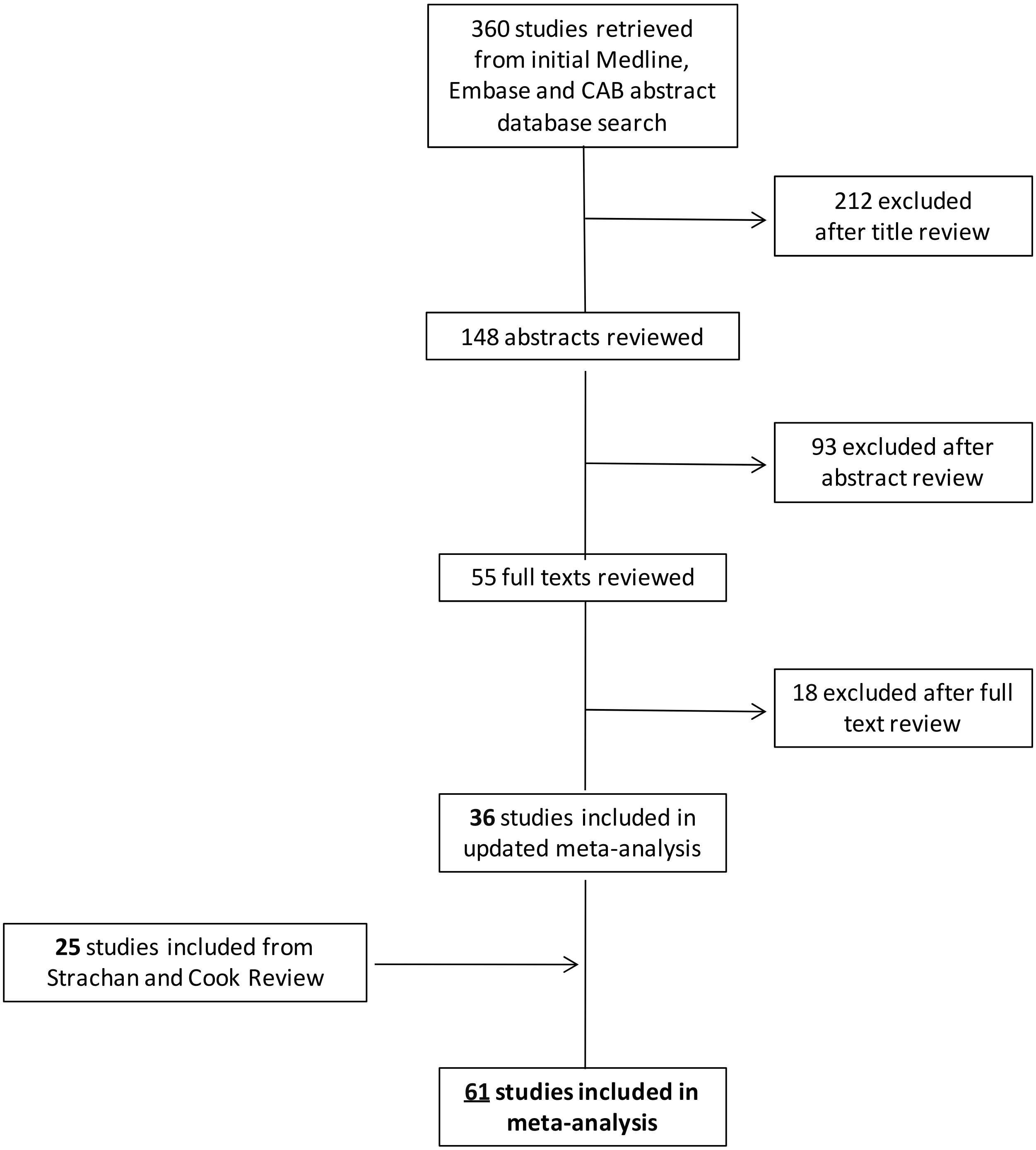
p‡ = p value from random effect meta-regression analysis

Table 2b Summary of overall effect and meta-regression analysis of household and paternal passive smoke exposure on the risk of middle ear disease in childhood

		Household					Paternal				
		OR	**95% CI**	**Studies**	**I^2**	**p‡**	**OR**	**95% CI**	**Studies**	**I^2**	**p‡**
Overall effect		1.37	1.25 to 1.50	49	76	N/A	1.24	0.98 to 1.57	12	87	N/A
Outcome	Middle ear infection	1.32	1.20 to 1.45	38	73	0.11	1.06	0.91 to 1.24	8	33	<0.001
	Surgery for middle ear disease	1.62	1.32 to 1.98	11	41		1.83	1.61 to 2.07	4	0	
	Hearing loss	N/A	N/A	0	N/A		N/A	N/A	0	N/A	
	Hearing impairment	N/A	N/A	0	N/A		N/A	N/A	0	N/A	
Study Design	Cohort	1.27	1.13 to 1.43	18	46	0.25	2.45	0.85 to 7.07	1		0.28
	Cross sectional	1.33	1.10 to 1.60	13	90		1.51	0.82 to 2.78	2	66	
	Case-control	1.55	1.35 to 1.77	18	25		1.14	0.90 to 1.44	7	39	
Methodological Quality	High	1.30	1.19 to 1.43	28	67	0.40	1.19	0.94 to 1.50	5	8	0.82
	Low	1.41	1.18 to 1.68	21	71		1.25	0.91 to 1.74	7	92	
Publication Date	Prior to 1996	1.46	1.26 to 1.70	21	60	0.27	1.40	1.01 to 1.94	5	64	0.22
	Post 1996	1.31	1.17 to 1.46	28	77		1.11	0.92 to 1.35	7	49	
Ascertainment	Self-report	1.40	1.25 to 1.56	40	74	0.32	1.25	0.97 to 1.62	11	88	0.74
	Biochemical	1.22	1.03 to 1.45	9	66		1.11	0.76 to 1.63	1	N/A	

OR = odds ratio
95% CI = 95% confidence interval
I2 = percentage of heterogeneity
N/A = not applicable
p‡ = p value from random effect meta-regression analysis

Figure 1



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212 excluded after title review
148 abstracts reviewed
93 excluded after abstract review
55 full texts reviewed
18 excluded after full text review
36 studies included in updated meta-analysis
25 studies included from Strachan and Cook Review
61 studies included in meta-analysis

Figure 2

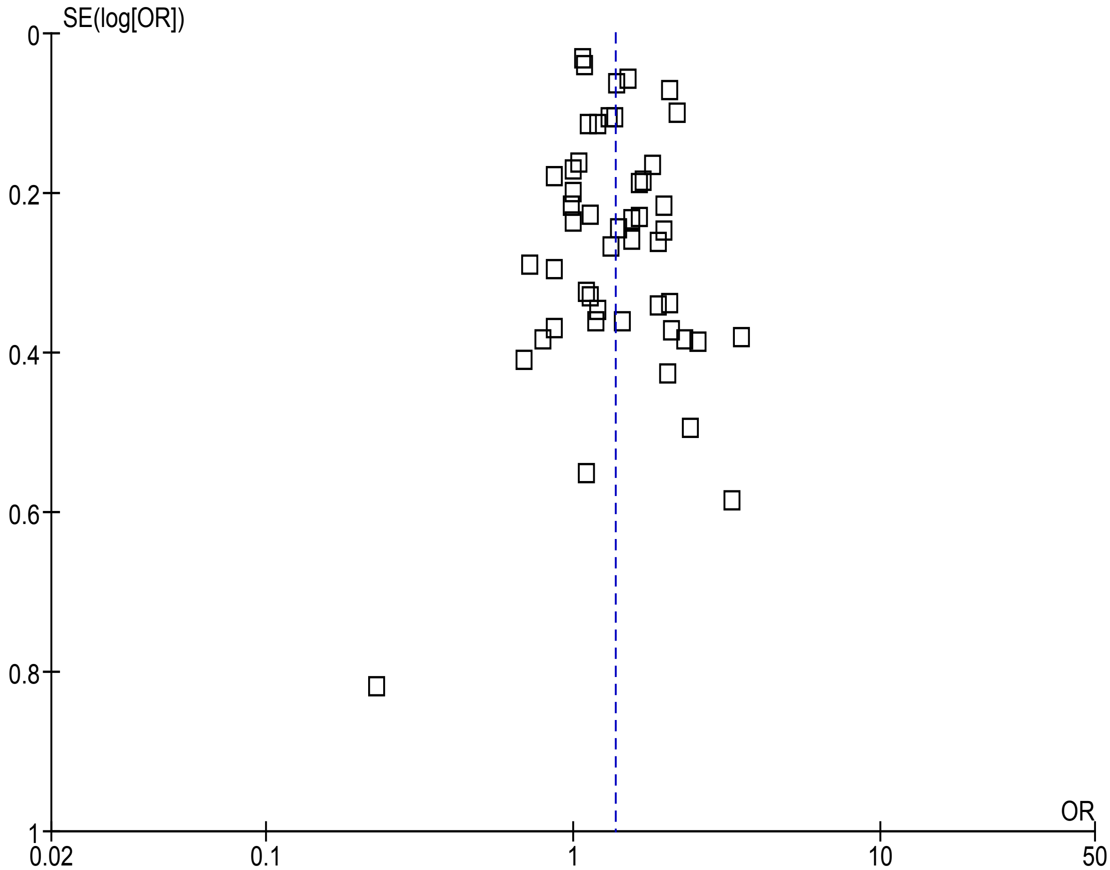


Figure 3

Study or Subgroup	Odds Ratio IV, Random, 95% CI
11.1.1 Middle ear infection	
Adair-Bischoff 1998	1.89 [1.23, 2.91]
Barr 1992	1.23 [0.70, 2.15]
Bennett 1998	1.31 [1.14, 1.51]
Daigler 1991	0.90 [0.54, 1.50]
Daly 2007	0.89 [0.50, 1.58]
Ey 1995	1.33 [0.91, 1.95]
Gliddon 2001	0.51 [0.09, 2.85]
Green 1991	1.92 [1.20, 3.06]
Gultekin 2010	13.64 [9.29, 20.03]
Haberg 2010	1.00 [0.94, 1.06]
Hammaren-Malmi 2005	1.25 [0.57, 2.73]
Hammaren-Malmi 2007	4.15 [1.45, 11.89]
Lieu 2002	0.97 [0.91, 1.03]
Stenstrom 1997	1.32 [0.91, 1.93]
Subtotal (95% CI)	**1.53 [1.22, 1.92]**
Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 214.55$, df = 13 ($P < 0.00001$); $I^2 = 94\%$	
Test for overall effect: Z = 3.66 (P = 0.0003)	
11.1.2 Surgery for middle ear disease	
Hinton 1993	2.29 [1.02, 5.14]
Ilicali 1999	3.93 [2.41, 6.41]
Kitchens 1995	1.28 [0.65, 2.54]
Lister 1998	1.31 [0.95, 1.80]
Said 1978	1.68 [1.45, 1.95]
Subtotal (95% CI)	**1.86 [1.31, 2.63]**
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 15.07$, df = 4 (P = 0.005); $I^2 = 73\%$	
Test for overall effect: Z = 3.48 (P = 0.0005)	
11.1.3 Hearing impairment	
Haaggard 2002	1.74 [1.08, 2.81]
Subtotal (95% CI)	**1.74 [1.08, 2.81]**
Heterogeneity: Not applicable	
Test for overall effect: Z = 2.26 (P = 0.02)	
Total (95% CI)	**1.62 [1.33, 1.97]**
Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 284.12$, df = 19 ($P < 0.00001$); $I^2 = 93\%$	
Test for overall effect: Z = 4.82 ($P < 0.00001$)	
Test for subgroup differences: $Chi^2 = 54.49$, df = 2 ($P < 0.00001$), $I^2 = 96.3\%$	

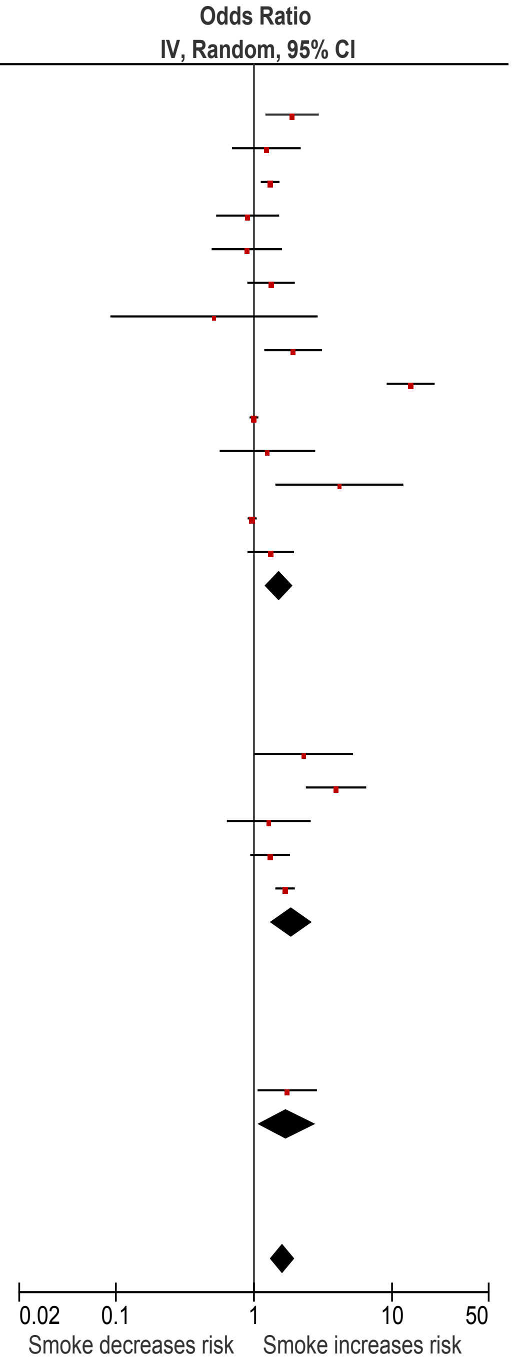


Figure 4

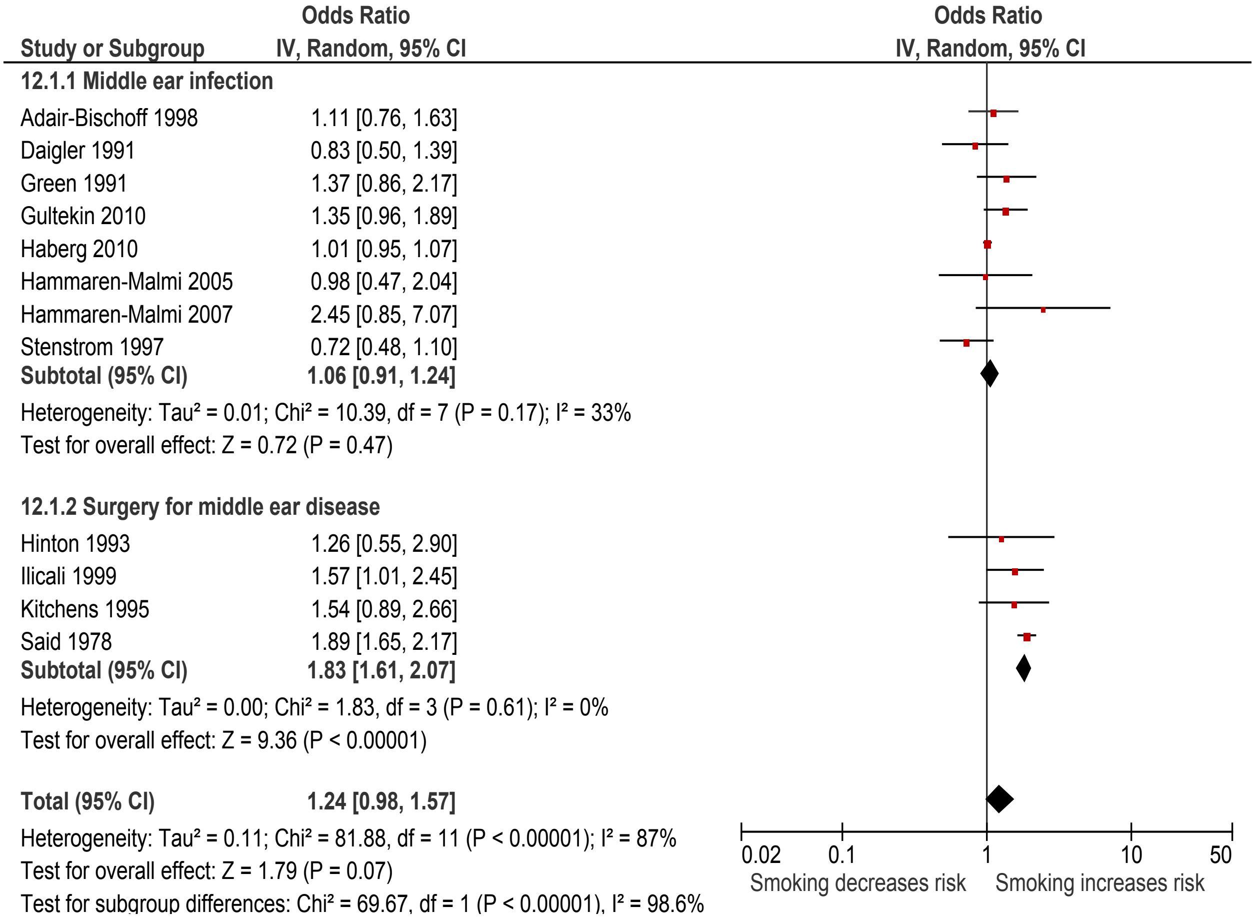
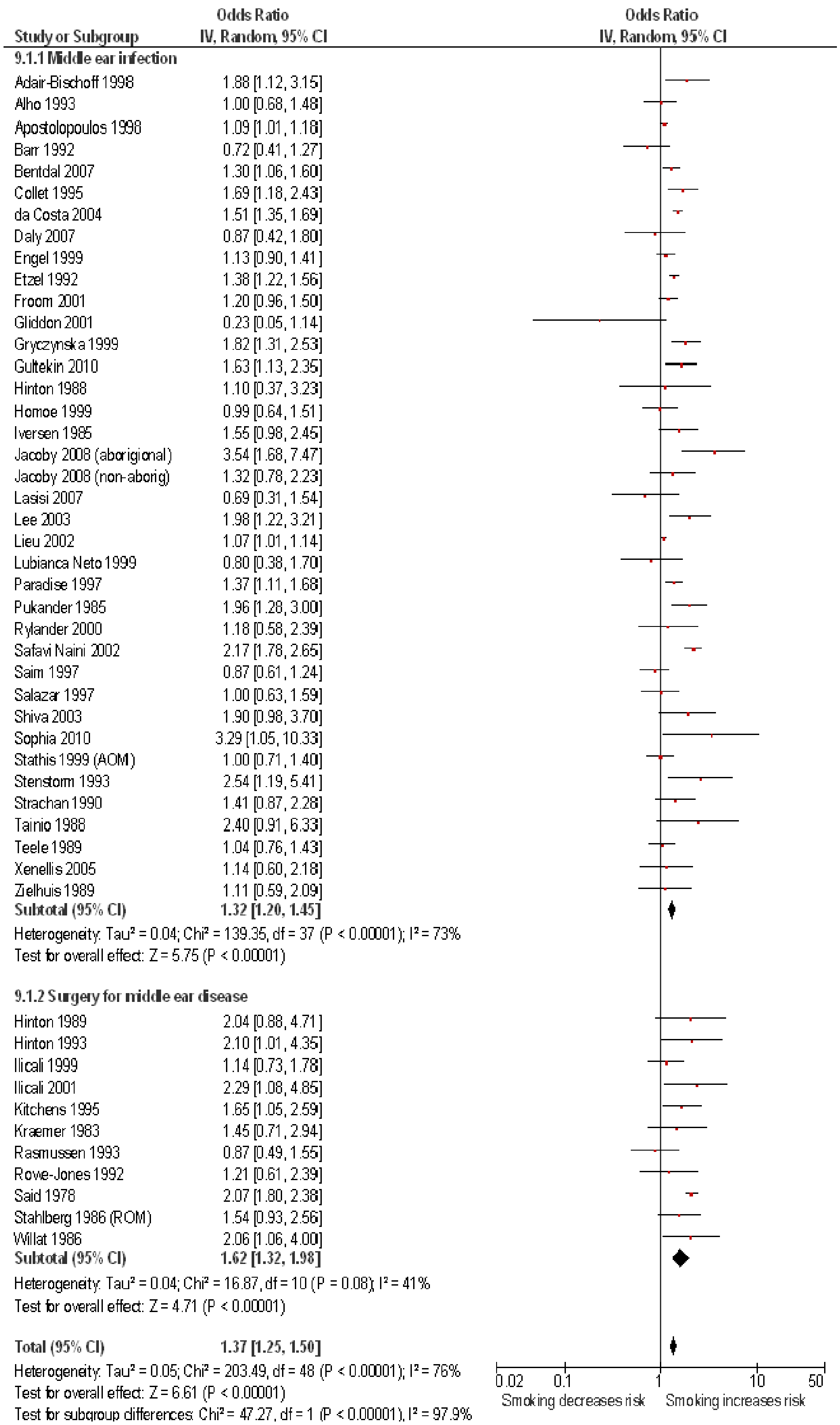

Study or Subgroup
Odds Ratio
IV, Random, 95% CI
Odds Ratio
IV, Random, 95% CI
12.1.1 Middle ear infection
Adair-Bischoff 1998 1.11 [0.76, 1.63]
Daigler 1991 0.83 [0.50, 1.39]
Green 1991 1.37 [0.86, 2.17]
Gultekin 2010 1.35 [0.96, 1.89]
Haberg 2010 1.01 [0.95, 1.07]
Hammaren-Malmi 2005 0.98 [0.47, 2.04]
Hammaren-Malmi 2007 2.45 [0.85, 7.07]
Stenstrom 1997 0.72 [0.48, 1.10]
Subtotal (95% CI) 1.06 [0.91, 1.24]
Heterogeneity: Tau² = 0.01; Chi² = 10.39, df = 7 (P = 0.17); I² = 33%
Test for overall effect: Z = 0.72 (P = 0.47)
12.1.2 Surgery for middle ear disease
Hinton 1993 1.26 [0.55, 2.90]
Ilicali 1999 1.57 [1.01, 2.45]
Kitchens 1995 1.54 [0.89, 2.66]
Said 1978 1.89 [1.65, 2.17]
Subtotal (95% CI) 1.83 [1.61, 2.07]
Heterogeneity: Tau² = 0.00; Chi² = 1.83, df = 3 (P = 0.61); I² = 0%
Test for overall effect: Z = 9.36 (P < 0.00001)
Total (95% CI) 1.24 [0.98, 1.57]
Heterogeneity: Tau² = 0.11; Chi² = 81.88, df = 11 (P < 0.00001); I² = 87%
Test for overall effect: Z = 1.79 (P = 0.07)
Test for subgroup differences: Chi² = 69.67, df = 1 (P < 0.00001), I² = 98.6%
0.02
0.1
1
10
50
Smoking decreases risk
Smoking increases risk

Figure 5


Study or Subgroup
Odds Ratio IV, Random, 95% CI
Odds Ratio IV, Random, 95% CI
9.1.1 Middle ear infection
Adair-Bischoff 1998 1.88 [1.12, 3.15]
Alho 1993 1.00 [0.68, 1.48]
Apostolopoulos 1998 1.09 [1.01, 1.18]
Barr 1992 0.72 [0.41, 1.27]
Bentdal 2007 1.30 [1.06, 1.60]
Collet 1995 1.69 [1.18, 2.43]
da Costa 2004 1.51 [1.35, 1.69]
Daly 2007 0.87 [0.42, 1.80]
Engel 1999 1.13 [0.90, 1.41]
Etzel 1992 1.38 [1.22, 1.56]
Froom 2001 1.20 [0.96, 1.50]
Gliddon 2001 0.23 [0.05, 1.14]
Gryczynska 1999 1.82 [1.31, 2.53]
Gultekin 2010 1.63 [1.13, 2.35]
Hinton 1988 1.10 [0.37, 3.23]
Homoe 1999 0.99 [0.64, 1.51]
Iversen 1985 1.55 [0.98, 2.45]
Jacoby 2008 (aborigional) 3.54 [1.68, 7.47]
Jacoby 2008 (non-aborig) 1.32 [0.78, 2.23]
Lasisi 2007 0.69 [0.31, 1.54]
Lee 2003 1.98 [1.22, 3.21]
Lieu 2002 1.07 [1.01, 1.14]
Lubianca Neto 1999 0.80 [0.38, 1.70]
Paradise 1997 1.37 [1.11, 1.68]
Pukander 1985 1.96 [1.28, 3.00]
Rylander 2000 1.18 [0.58, 2.39]
Safavi Naini 2002 2.17 [1.78, 2.65]
Saim 1997 0.87 [0.61, 1.24]
Salazar 1997 1.00 [0.63, 1.59]
Shiva 2003 1.90 [0.98, 3.70]
Sophia 2010 3.29 [1.05, 10.33]
Stathis 1999 (AOM) 1.00 [0.71, 1.40]
Stenstorm 1993 2.54 [1.19, 5.41]
Strachan 1990 1.41 [0.87, 2.28]
Tainio 1988 2.40 [0.91, 6.33]
Teele 1989 1.04 [0.76, 1.43]
Xenellis 2005 1.14 [0.60, 2.18]
Zielhuis 1989 1.11 [0.59, 2.09]
Subtotal (95% CI) 1.32 [1.20, 1.45]
Heterogeneity: Tau² = 0.04; Chi² = 139.35, df = 37 (P < 0.00001); I² = 73%
Test for overall effect: Z = 5.75 (P < 0.00001)
9.1.2 Surgery for middle ear disease
Hinton 1989 2.04 [0.88, 4.71]
Hinton 1993 2.10 [1.01, 4.35]
Ilicali 1999 1.14 [0.73, 1.78]
Ilicali 2001 2.29 [1.08, 4.85]
Kitchens 1995 1.65 [1.05, 2.59]
Kraemer 1983 1.45 [0.71, 2.94]
Rasmussen 1993 0.87 [0.49, 1.55]
Rowe-Jones 1992 1.21 [0.61, 2.39]
Said 1978 2.07 [1.80, 2.38]
Stahlberg 1986 (ROM) 1.54 [0.93, 2.56]
Willat 1986 2.06 [1.06, 4.00]
Subtotal (95% CI) 1.62 [1.32, 1.98]
Heterogeneity: Tau² = 0.04; Chi² = 16.87, df = 10 (P = 0.08); I² = 41%
Test for overall effect: Z = 4.71 (P < 0.00001)
Total (95% CI) 1.37 [1.25, 1.50]
Heterogeneity: Tau² = 0.05; Chi² = 203.49, df = 48 (P < 0.00001); I² = 76%
Test for overall effect: Z = 6.61 (P < 0.00001)
Test for subgroup differences: Chi² = 47.27, df = 1 (P < 0.00001), I² = 97.9%
0.02
0.1
1
10
50
Smoking decreases risk
Smoking increases risk