Title:

Tobacco smoking and meningococcal disease in adolescents and young adults: a systematic review and meta-analysis

Running Title:

Smoking and meningococcal disease: a systematic review

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Declarations of interest: none

Highlights

- Invasive meningococcal disease (IMD) is a significant cause of morbidity and mortality worldwide.
- Smoking is linked to meningococcal carriage and passive smoking to IMD in children.
- We conducted a systematic review searching multiple electronic databases.
- Active and passive smoking may be associated with IMD in adolescents and young adults.
- Smoking cessation may reduce transmission and disease incidence in all age groups.

Summary

Objectives: Systematically review the evidence on the association between active and passive tobacco smoking and invasive meningococcal disease (IMD) in adolescents and young adults aged 15-to-24-years.

Methods: Electronic searches were conducted in Ovid MEDLINE, EMBASE, and Web of Science to June 2020. Reference lists were hand-searched. Two independent reviewers screened articles for eligibility. Risk of bias was assessed using an adapted Risk of Bias in Non-Randomised Studies - of Interventions tool. Meta-analyses were conducted using random-effects models.

Results: Of 312 records identified, 13 studies were included. Five studies provided data on the association between active smoking and IMD in the target age group; pooled odds ratio (OR): 1.45 (95% CI: 0.93-2.26). The overall OR, including eight studies with a wider participant age range, was 1.45 (95% CI: 1.12-1.88). For passive smoking, the equivalent ORs were 1.56 (95% CI: 1.09-2.25) and 1.30 (95% CI: 1.06-1.59) respectively. All studies were at high risk of bias.

Conclusions: Active and passive smoking may be associated with IMD in adolescents and young adults. Since active smoking has also been linked to meningococcal carriage, and passive smoking to IMD in young children, smoking cessation should be encouraged to reduce transmission and IMD risk in all ages.

Keywords

Cigarette smoking, tobacco, invasive meningococcal disease, Meningococcal Infections, Neisseria meningitidis, adolescents, young adults, systematic review, meta-analysis

Introduction

Invasive meningococcal disease (IMD), presenting predominantly as meningitis and/or septicaemia, is a life-threatening condition resulting from infection with *Neisseria meningitidis*, otherwise known as the meningococcus. *N. meningitidis* colonises the pharyngeal mucosa and at any given time, around 10% of the population are estimated to be asymptomatic carriers of *N. meningitidis* (1). In a small proportion of carriers, *N. meningitidis* crosses the epithelial barrier and enters the bloodstream, giving rise to IMD. Six capsular groups (A, B, C, W, X, and Y) cause most IMD. The case fatality rate varies around 5-15% (2, 3) and complications of infection can persist beyond the period of acute illness, with hearing loss, visual impairment, and amputations reported in survivors of IMD (4).

Incidence worldwide is highest in the African 'meningitis belt' (5). Large, seasonal epidemics, with attack rates reaching 10-100 cases per 100,000 population, occur periodically in the belt and are a significant cause of morbidity and mortality. Incidence of IMD in other regions is lower, most countries recording annual rates well below 10 per 100,000 population (3, 4, 6). In industrialised countries, incidence is highest in young children, with a secondary disease peak observed in adolescents and young adults (4).

Vaccination remains the predominant method of preventing outbreaks of IMD. Protein-polysaccharide conjugate vaccines are widely used that protect against IMD due to serogroups A, C, W, and Y, and MenB protein vaccines have been introduced more recently to prevent serogroup B disease (3). Although conjugate vaccines are more effective as they can prevent carriage and lead to herd protection, most MenB vaccination to date has been given to infants and is unlikely to prevent IMD in older age groups (3, 7, 8). The continuing burden of IMD highlights the importance of understanding modifiable risk factors for disease.

In addition to age and close social contact, both active and passive tobacco smoking have been identified as risk factors for meningococcal carriage (9-11). Passive tobacco smoking has also been identified as a risk factor for IMD in young children (12, 13). However, it remains unclear if active tobacco smoking increases the risk of IMD. In a large multi-centre study involving 14,000 teenagers aged between 15 and 19 years, smoking one or more cigarettes per day and having other smokers in the home were positively associated with meningococcal carriage (9). Furthermore, in a recent systematic review, active tobacco

smoking was identified as a risk factor for meningococcal carriage in university students and new military recruits (10). Passive tobacco smoking has been identified as a risk factor for IMD in young children in systematic reviews by *Lee et al.* and *Murray et al.* (12, 13). *Lee et al.* found that that under 19-year-olds exposed to passive tobacco smoke were twice as likely than those unexposed to develop IMD (12). *Murray et al.* found similar results with second-hand smoke exposure in the home doubling the disease risk in children aged under 16 years; in children under the age of 5 years, second-hand smoke exposure was associated with a 2.5-fold increased risk of IMD (13). With the prevalence of tobacco smoking increasing in many countries in the 'meningitis belt', where incidence is highest, it is important to understand the role of tobacco smoking in the epidemiology of IMD (14).

The aim of this systematic review and meta-analysis was to determine if active tobacco smoking in adolescents and young adults, aged between 15 and 24 years, is associated with an increased risk of IMD. Passive tobacco smoke exposure was investigated as a secondary exposure of interest. It is important to understand modifiable risk factors for disease in this age group to inform IMD prevention policies and programmes.

Methods

Our manuscript follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (15). A review protocol is available from the corresponding author on request.

Eligibility Criteria

Studies with a case-control, cohort, or cross-sectional design were considered for inclusion. There was no language restriction.

The **PECO** framework was used to develop the eligibility criteria. The **P**opulation of interest was adolescents and young adults aged between 15 and 24 years. The primary **E**xposure of interest was active tobacco smoking. The secondary exposure of interest was passive tobacco smoke exposure. All sources of passive tobacco smoke exposure were included, as were studies that did not distinguish between active and passive smoking in their analyses. The **C**omparator group was adolescents and young adults aged between 15 and 24 years who had not been exposed to active or passive tobacco smoking. Studies were excluded if no measure of relative risk for the exposure of interest was reported and it was not possible

to calculate one from the study data. The **O**utcome of interest was clinically diagnosed or laboratory confirmed IMD.

Studies that presented data on active tobacco smoking from a wide age range of participants that overlapped with our population of interest, without performing an age subgroup analysis, were considered eligible for inclusion provided controls were matched for age. This was because it was assumed that active tobacco smoking would not be relevant to younger children, and that participants exposed to active tobacco smoking would be largely aged 15 years or over. It was also assumed that as IMD is less common in adults over 24 years, a large proportion of cases and controls would fall within our population of interest (16). For passive tobacco smoke, we assumed that all age groups were at risk of exposure, so that studies investigating passive smoking in a wider age range of participants were only included if the lower limit of their population fell within our target age range (i.e. were at least 15 years old).

Search Strategy

Electronic searches were conducted in Ovid MEDLINE, EMBASE, and Web of Science, from the inception of each database to 28th June 2020. Full electronic search strategies are presented in **Supplementary Figure 1**. No restriction was placed on language, country, or publication status. Reference lists of all relevant studies, including those that did not meet the criteria for full text screening, were hand-searched for additional studies. Search results were stored and managed in EndNote X9.

Study selection

Abstracts and titles of identified studies were independently screened for eligibility by EP and JS. Reference lists of relevant studies were hand-searched by EP. Full texts of all potentially eligible studies were screened for eligibility by EP and JS and the reasons for exclusion of studies at this stage were documented. Disagreements regarding eligibility were resolved by discussion with CF.

Data extraction and synthesis

The data extraction form was a custom spreadsheet developed by EP. Data was extracted by EP and double-checked by CF. Data extracted included: author and year of publication, study design, study country and setting, study period, study population, exposures, method of IMD

ascertainment, and key findings. Effect estimates were relatively homogeneous; 11 studies reported odds ratios and associated confidence intervals which were extracted, one study presented data from which unmatched odds ratios and confidence intervals were calculated, and one study reported odds ratios and p-values from which the associated confidence intervals were calculated (17). Unadjusted odds ratios were extracted if adjusted odds ratios were not presented.

Random-effects meta-analyses were conducted to obtain pooled effect estimates for active and passive tobacco smoke exposure. This method was chosen as there were differences in study populations, as well as the quantity and frequency of the exposure assessed, and therefore between-study variance was to be expected. Effect estimates derived from studies with the specific population of interest and those with a wider age range of participants were analysed as separate sub-groups. A post-hoc sensitivity analysis was conducted to exclude one study in which the population was deemed to be considerably different. Statistical heterogeneity was examined using the Cochran's Q statistic and the I^2 statistic which assesses the percentage of variability between studies that is due to heterogeneity rather than sampling error. Meta-analyses were conducted using the metan package in Stata (version 16.1) and data presented in forest plots.

Risk of bias assessments

Risk of bias in included studies was assessed using an adapted version of the ROBINS-I (Risk of Bias in Non-Randomised Studies - of Interventions) tool (18). Domain 3 "Bias in classification of interventions" was adapted to "Bias in classification of exposures" and Domain 4 "Bias due to deviations from intended interventions" was omitted as it was not relevant for exposure studies. The risk of bias was assessed across six risk of bias domains and the domain-level assessments were used to inform an overall risk of bias assessment. If a study presented data on both active and passive tobacco smoke exposure, separate assessments were made for each effect estimate presented. If multivariate analysis had been performed, but an adjusted odds ratio was not presented, a risk of bias assessment was made for the unadjusted effect estimate. In order to assess the risk of bias due to confounding it was decided that studies, at a minimum, should have controlled for age, sex, and a measure of close contact with others, such as intimate kissing contacts or pub/club/disco attendance. Risk of bias assessments were visualised using the *robvis* tool (19). ROBINS-I is not designed

to assess bias due to sources of funding or conflicts of interests, therefore, we also made an informal assessment of potential biases due to conflicts of interests of study authors or funders.

Results

Description of studies

After the removal of duplicates, electronic database searching identified 307 potentially eligible records. A further five were identified through hand-searching reference lists. After screening titles and abstracts for eligibility, 32 studies met the criteria for full-text screening (**Figure 1**). Full-text screening identified 13 matched case-control studies eligible for inclusion in the review. Six studies originated from the United States, one from Argentina, one from Ghana, one from the Czech Republic, two from Australia, and two from the UK. Three studies analysed risk factors for IMD in university students and one study was a school-based study. The remainder were population-based studies. Sample sizes ranged from 40 to 1010 participants. Effect estimates for active tobacco smoking were extracted from all 13 studies; 11 studies presented matched odds ratios, one presented an unmatched odds ratio, and one study presented data from which unmatched odds ratios were calculated. In total, 15 effect estimates for active tobacco smoking were extracted. Nine effect estimates were extracted from the eight studies on passive tobacco smoke exposure. Eight of the summary statistics were matched odds ratios and one was an unmatched odds ratio. The full summary of included studies can be found in **Table 1.**

Risk of bias

Of the 15 active tobacco smoking effect estimates, 14 were at “Critical” risk of bias overall; one was considered to be at “Serious” risk of bias (**Supplementary Figure 2**). Of the nine passive tobacco smoking effect estimates, seven were at “Critical” risk of bias and two at “Serious” risk of bias overall (**Supplementary Figure 3**). This was mostly due to a lack of adjustment for confounding. Risk of bias in classification of exposures was also an issue, with six active and one passive tobacco smoking effect estimate considered to be at “Critical” risk of bias and nine active and eight passive tobacco smoking effect estimates at “Serious” risk of bias. Studies were classified at “Critical” risk of bias in this domain if exposure status was determined a long time after onset of case illness. All were considered to be at “Low” risk of

bias in the measurement of outcomes and at "Low" risk of bias due to selection of participants. All were at "Moderate" risk of bias in selection of the reported result. Two passive tobacco smoking effect estimates were considered to be at "Serious" risk of bias due to missing data, and there was insufficient information to determine the extent of missing data for two of the active tobacco smoking effect estimates. We did not find any studies to be at risk of bias based on sources of funding or conflicts of interests reported by the study authors.

Study Results

Active tobacco smoking as a risk factor for IMD

13 studies reported on the association between active tobacco smoking and IMD (**Figure 2**). *Stuart et al*. contributed two effect estimates as exposure in cases was compared to exposure in two separate control groups and *Křížová et al.* analysed active tobacco smoking in two separate age subgroups, thus making 15 effect estimates in total (**Table 1**).

In the five studies that investigated active tobacco smoking in 15-24-year olds, the pooled odds ratio (OR) was 1.45 (95% CI: 0.93-2.26). Between-study heterogeneity was low (I^2: 6.7%, p-value: 0.368). For the 15 effect estimates obtained from all 13 eligible studies, including those with a wider age range, the pooled OR was the same but with narrower confidence intervals that did not overlap with 1 (OR 1.45 (95% CI 1.12-1.88). There was no evidence of heterogeneity (I^2: 0.0%, p-value: 0.779).

Ridpath et al. was identified as being considerably different from the other studies with regards to population and comparator (20). A sensitivity analysis was performed in which *Ridpath et al.* was excluded from the meta-analysis; this had little impact on the magnitude or direction of the pooled effect estimates.

13 of the 15 effect estimates were not adjusted for confounding. *Ridpath et al.* had adjusted for HIV infection (20). *Fischer et al.* had controlled for some confounders, although these variables were not explicitly stated (21). Four studies (*Robinson et al.*, *McCall et al.*, *Imrey et al.* and *Tully et al.*) performed multivariate analyses but did not present adjusted odds ratios (22-25).

Passive tobacco smoking as a risk factor for IMD

Eight studies reported on the association between passive tobacco smoke exposure and IMD (**Figure 3**). All studies contributed one effect estimate apart from *Robinson et al.* who investigated two passive smoking variables (**Table 1**).

The combined estimate from the four studies among the 15-24-year-old age group showed that passive tobacco smoking was associated with increased odds of IMD (OR: 1.56, 95% CI: 1.09-2.25) with no evidence of heterogeneity (I^2: 0.0%, p-value: 0.732). When all nine effect estimates, including the wider age range, were combined the OR was 1.30 (95% CI: 1.06-1.59), with low between-study heterogeneity (I^2: 12.3%, p-value: 0.332).

Two effect estimates were adjusted for confounding, although it was unclear which confounders had been adjusted for (21, 24). Three studies (*Harrison et al*., *Tully et al., and McCall et al.)* performed multivariate analyses but did not present adjusted odds ratios (23, 25, 26).

Discussion

Our systematic review and meta-analysis found slightly increased odds of IMD in adolescents and young adults who were exposed to active and passive tobacco smoking. In our target age group, the evidence for an association between active tobacco smoking and IMD was weak; the odds ratio, although elevated, had wide confidence intervals that included a negative effect. However, when studies with a broader age range were included, the lower limit of confidence also became positive. Sub-group analyses showed that the summary estimates for this wider age range were very similar to those for our target population, therefore, this change likely reflects greater precision. These findings of a potential association between tobacco smoking and IMD are consistent with previous reviews showing an association between passive tobacco smoke exposure and IMD in young children (12, 13), and tie in with the findings of a systematic review which found increased levels of meningococcal carriage among university students and other high-risk groups who reported smoking (10). However, the studies included in this review were at high risk of bias, and therefore our findings must be interpreted with caution.

We observed a similar magnitude of effect for active and passive smoking among the studies included in our review. If exposure to tobacco smoke increases susceptibility to

invasive disease, a higher odds ratio for active than passive smoking might have been expected (27), and the observed associations in our review could be due to unadjusted confounding factors and other biases in the eligible studies. However, a similar risk of IMD from active and passive smoking is consistent with the findings of a study in UK teenagers (28) suggesting that a higher risk of invasive disease may be linked to increased meningococcal acquisition among cigarette smokers and a higher risk of transmission to their contacts than to a direct effect of smoke on susceptibility to disease. While it is possible that any exposure to cigarette smoke is sufficient to increase the risk of IMD independently of dose, a clear dose response relationship has been observed in studies of cigarette smoke exposure in children with IMD (21) and in adults with other respiratory tract infections (27, 29).

A limitation of the available evidence is that due to the small number of exposed cases and controls, many studies were underpowered to detect small differences in effect size. The risk of bias was high in all studies particularly due to a lack of adjustment for confounding and ascertainment of the exposure which may be subject to recall bias. Furthermore, not all matched studies conducted matched analyses and the unmatched odds ratios may be at risk of bias due to sparse data (30). A matched analysis may not have been necessary if these studies had only matched for a few simple confounding factors, such as age and sex, however these studies also matched for medical practice and one also for address. We conducted a comprehensive systematic review, searching multiple electronic databases and hand searching relevant reference lists. However, we recognise that some relevant studies (such as those unpublished) may have been missed and publication bias may therefore be a concern. Due to the relatively small number of studies included in the meta-analysis we did not test for funnel plot asymmetry (31). Meanwhile, in the absence of a tool specifically designed to assess the risk of bias in non-randomised studies of exposures, an adapted ROBINS-I tool was selected as the most appropriate instrument though we recognise that it may have some limitations in assessing risk of bias in studies of exposures. For this reason, domain-level assessments were made without the use of the intra-domain signalling questions, an approach that has been previously used (32). We included laboratory confirmed and clinically diagnosed outcomes. Whilst not as reliable as a laboratory confirmation, clinical diagnoses are the predominant means of diagnosing IMD in resource limited settings and we did not want to exclude studies from countries with lower testing capacity.

To conclude, both active and passive tobacco smoke exposure may be linked to an increased risk of IMD in adolescents and young adults. The evidence is uncertain due to the low strength of association observed and the high risk of bias in included studies. In many high-income countries, tobacco use is declining in young people and smoke-free legislation has reduced passive tobacco smoke exposure (33, 34). However, the prevalence of tobacco smoking is increasing in sub-Saharan Africa, highlighting the importance of understanding tobacco smoking as a risk factor for IMD in countries in the 'meningitis belt' (14). Large well-designed studies that control for key confounders are needed. Furthermore, in view of the replacement of cigarette smoking by vaping and the rising prevalence of cannabis use in some countries, future studies on IMD risk should also include e-cigarettes and exposure to tobacco in other inhaled substances (35, 36). Reducing the number of smokers nevertheless remains an important public health measure in all countries as it may reduce incidence of IMD in all age groups.

Tables and Figures

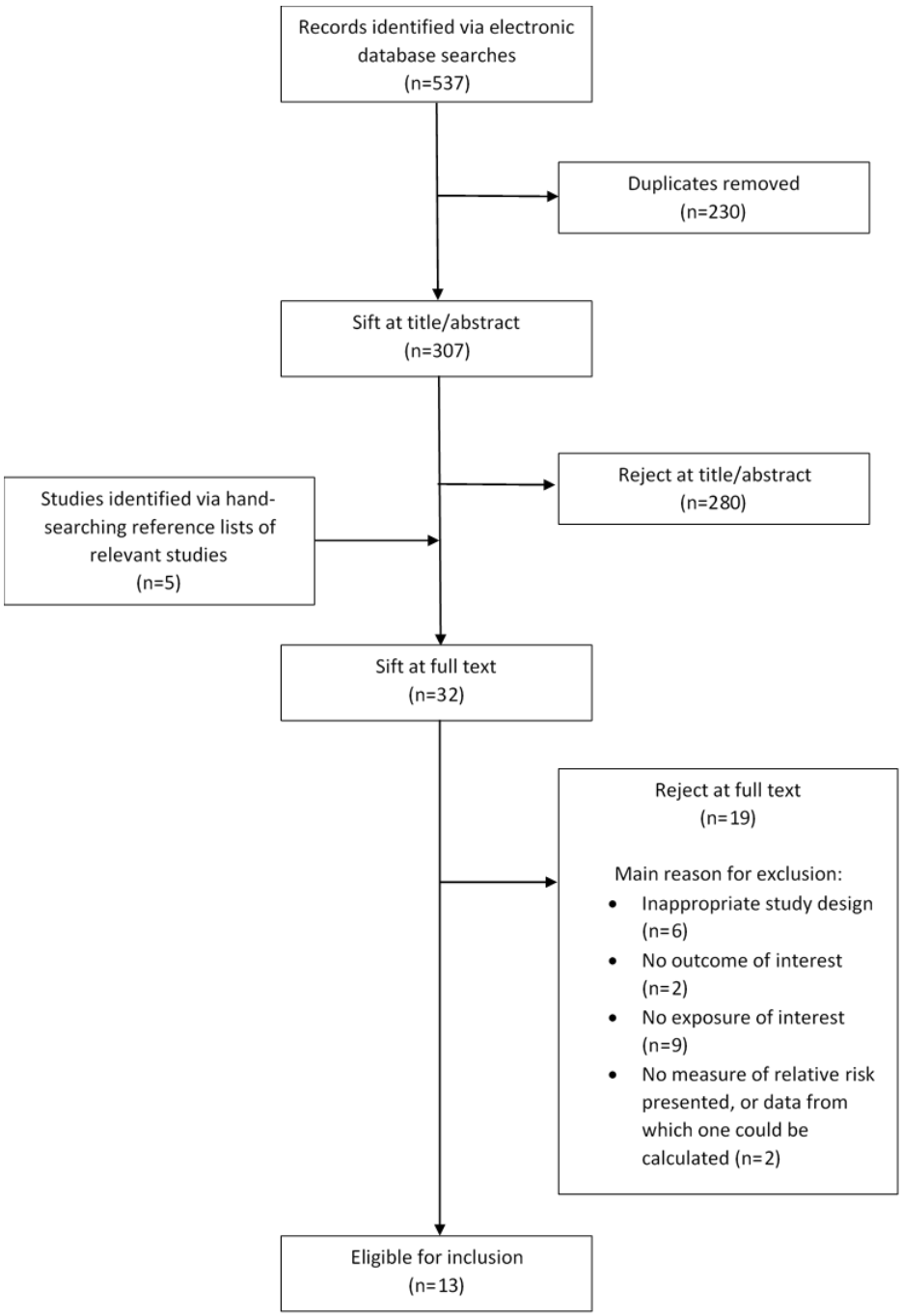

Figure 1: Study selection flow chart

Table 1: Characteristics of included studies

First author, year	Study design	Study country and setting	Study period	Study population	Exposure assessed	IMD ascertainment	Key findings
Bruce, 2001 (37)	Case-control	United States, university-based	September 1998 – April 1999	50 cases (18-24 years) and 148 controls matched for sex, college, and undergraduate vs. graduate status	Active (smoking "at least half a pack per day") and passive (no definition given) tobacco smoke exposure in the month preceding onset of illness in cases	Laboratory confirmation	Univariate matched ORs for the association between tobacco smoking and IMD: - Active smoking: 1.5 (95% CI: 0.5-4.0), p=0.45 - Passive smoking: 1.2 (95% CI: 0.6-2.4), p=0.52
Cookson, 1998 (38)	Case-control	Argentina, population-based	August 1996	8 cases (15-45 years) and 32 controls matched for sex and age (within 2 years). Controls were neighbourhood school controls (if cases attended school) or neighbourhood block controls	Active (smoking >=one cigarette per day day) and passive (no definition given) tobacco smoke exposure in the two weeks preceding onset of illness in cases	Laboratory confirmation	Univariate matched ORs for the association between tobacco smoking and IMD: - Active smoking: 6.0 (95% CI: 0.6-50.0), p=0.077 - Passive smoking: 1.6 (95% CI: 0.2-11.2), p=0.49
Fischer, 1997 (21)	Case-control	United States, population-based	January - December 1994	129 cases and 274 controls matched for age group and area. 45 cases and 99 controls were aged >=18 years	Active (regularly smoking >=one cigarette per day) and passive ("regular exposure to other people's cigarette smoke in or out of the home") tobacco smoke exposure in the month preceding onset of illness in cases	Laboratory confirmation	Adjusted ORs for the association between tobacco smoking and IMD in adults >= 18 years: - Active smoking: 2.4 (95% CI: 0.9-6.6), p=0.10 - Passive smoking: 2.5 (95% CI: 0.9-6.9), p=0.07 It is unclear which variables were adjusted for
Harrison, 2008 (26)	Case-control	United States, school-based	July 2002-December 2005	49 cases (14-19 years) and 185 controls matched for homeroom class (or another shared class if the student did not have a homeroom)	Active (no definition given) and passive (no definition given) tobacco smoke exposure in the month preceding onset of illness in cases	Laboratory confirmation	Univariate matched ORs for the association between tobacco smoking and IMD: - Active smoking: 1.65 (95% CI: 0.70-3.87), p=0.25

First author, year	Study design	Study country and setting	Study period	Study population	Exposure assessed	IMD ascertainment	Key findings
							- Passive smoking: 1.86 (95% CI: 0.93-3.70), p=0.08 Variables with a p-value <0.20 in the univariate analysis were included in the multivariate analysis, however an adjusted OR for passive smoking was not presented
Hodgson, 2001 (39)	Case-control	Ghana, population-based	Cases that had occurred during the 1997 epidemic period and their controls were enrolled in mid-1999	505 cases (2-73 years) and 505 controls (2-74 years) matched for age (±10%), sex, and area. Age range of cases and controls obtained from (40)	Active (no definition given) tobacco smoking. Passive smoking data not extracted as wide age range of study participants with no age subgroup analysis. The time-period over which exposure was measured was not given	Clinical diagnosis and/or laboratory confirmation	Univariate matched OR for the association between active tobacco smoking and IMD: 1.07 (95% CI: 0.49-2.32), p=1.00
Imrey, 1996 (22)	Case-control	United States, university-based	February 1991 - April 1992	6 cases (18-22 years) and 117 controls matched for college, sex, and year in school	Active (no definition given) tobacco smoking in the two weeks preceding onset of illness in cases. Passive smoking was not asked directly	Laboratory confirmation	Univariate matched ORs for the association between active tobacco smoking and IMD: 7.8 (95% CI: 1.3-64.4), p=0.012. It was reported that active tobacco smoking became "marginally non-significant" in a multivariate analysis but an adjusted OR was not presented
Křížová, 1999 (41)	Case-control	Czech Republic, population-based	October 1996-May 1998	107 cases and 211 controls matched for age, sex, district, and urban-rural place of residence.	Active (no definition given) tobacco smoking. The time period over which exposure was measured was not given.	Clinical diagnosis and/or	Univariate matched ORs for the association between active tobacco smoking and IMD:

First author, year	Study design	Study country and setting	Study period	Study population	Exposure assessed	IMD ascertainment	Key findings
				Subgroup analyses were performed for adolescents (10-19 years) and adults (20+ years)	Passive smoking data not extracted as wide age range of study participants and no age subgroup analysis for our specific population of interest	laboratory confirmation	- Adolescents: 1.30 (95% CI: 0.12-14.26), p=0.841 - Adults: 2.04 (95% CI: 0.44-9.56), p=0.372
Mandal, 2013 (42)	Case-control	United States, university-based	January 2008 -November 2010	7 cases (19-20 years) and 35 controls (18-21 years) matched for academic year at the time of onset of illness in cases	Active (smoking >= one cigarette per day on average) and passive (no definition given) tobacco smoke exposure in the 30 days preceding onset of illness in cases	Laboratory confirmation	Univariate matched ORs for the association between tobacco smoking and IMD: - Active smoking: 3.45 (95% CI: 0.22-53.02), p>0.05 - Passive smoking: 4.73 (95% CI: 0.46-244.1), p>0.05
McCall, 2004 (23)	Case-control	Australia, population-based	January 2000 -December 2001	45 cases and 79 controls matched for age-group and medical practice. 62 cases (4 weeks-75 years) and 79 controls were interviewed. 36 cases and 45 controls were aged >= 15 years	Active (smoking "at least one cigarette in the four weeks before interview") and passive ("exposure to tobacco smoke for at least one hour per day") tobacco smoke exposure in the four weeks preceding interview	Laboratory confirmation	Unmatched and matched ORs were calculated with little difference between the two values observed (data not presented). Univariate unmatched ORs for the association between tobacco smoking and IMD in participants >=15 years: - Active smoking: 2.1 (95% CI: 0.6-7.3), p=0.18 - Passive smoking: 2.3 (0.7-8.3), p=0.15 Variables with a p-value <0.25 were included in a multivariate analysis, however adjusted ORs were not presented

First author, year	Study design	Study country and setting	Study period	Study population	Exposure assessed	IMD ascertainment	Key findings
Ridpath, 2015 (20)	Case-control	United States, population-based	January 2012 -February 2013	Men who have sex with men (MSM). 17 cases (21-59 years) and 51 controls (22-59 years). Controls were MSM given a diagnosis of infection with *Giardia lamblia* or *Entamoeba histolytica*. Controls were matched for age at disease diagnosis (±5 years) and diagnosis date (±1 month)	Active (no definition given) tobacco smoking in the 30 days preceding onset of illness for cases and controls	Laboratory confirmation	Multivariate matched OR for the association between active smoking and IMD after adjusting for HIV infection: 0.9 (95% CI: 0.2-3.3), p>0.05
Robinson, 2001 (24)	Case-control	Australia, population-based	January - December 1997	87 cases and 174 controls matched for age and gender. 40 cases and 80 controls were >=16 years	Active (smoking "at least one cigarette in the previous month") and passive (participating in "smoky indoor activities" and having a "smoker amongst intimate contacts") tobacco smoke exposure in the 2 weeks preceding onset of illness in the cases	Clinical diagnosis and/or laboratory confirmation	Univariate matched ORs for the association between tobacco smoking and IMD in participants >= 16 years: - Active smoking: 2.2 (95% CI: 0.8-5.8), p=0.11 - Participating in smoky indoor behaviour: 1.1 (95% CI: 1.0-1.2), p=0.16 Adjusted OR for the association between having a parent or partner who smokes and IMD in participants >= 16 years: 1.84 (95% CI: 0.6-5.7), p=0.29. Active tobacco smoking was not "statistically significant" in the multivariate analysis. However, an adjusted OR was not presented

First author, year	Study design	Study country and setting	Study period	Study population	Exposure assessed	IMD ascertainment	Key findings
Stuart, 1988 (43)	Case-control	United Kingdom, population-based	January 1982 – April 1986	105 cases, 105 district controls, and 105 neighbourhood controls. Two controls enrolled per case; one matched for sex, local authority district, and nearest date of birth (district control) and the other for year of birth, sex, general practitioner, and nearest address (neighbourhood control). 47 cases (and matched controls) were aged 12-19 years. 18 cases (and matched controls) were aged 20+	Active (no definition given) tobacco smoke exposure. Controls were interviewed about the same month and year as their matched case. Active tobacco smoking exposure status was only determined for cases and matched controls over age 12 years. There was insufficient data presented in the paper from which unmatched ORs for passive tobacco smoke exposure could be calculated	Clinical diagnosis and/or laboratory confirmation	Univariate unmatched ORs for the association between active tobacco smoking and IMD: - Comparing cases to neighbourhood controls: 1.31 (95% CI: 0.60-2.87), p=0.58 - Comparing cases to district controls: 1.07 (95% CI: 0.49-2.31), p=1.00
Tully, 2006 (25)	Case-control	United Kingdom, population-based	January 1999 -June 2000	114 cases (15-19 years) and 114 controls matched for age and sex	Active (smoking >=one cigarette per day) and passive (having "multiple close contacts who smoked") tobacco smoke exposure in the two weeks prior to hospital admission (cases) or interview (controls)	Laboratory confirmation	Univariate matched ORs for the association between tobacco smoking and IMD: - Active smoking: 1.1 (95% CI: 0.6-1.8), p=0.80 - Passive smoking: 1.6 (95% CI: 0.9-2.7), p=0.11 Neither active nor passive tobacco smoke exposure were associated with an increased risk of IMD in the multivariate analysis although adjusted ORs were not presented

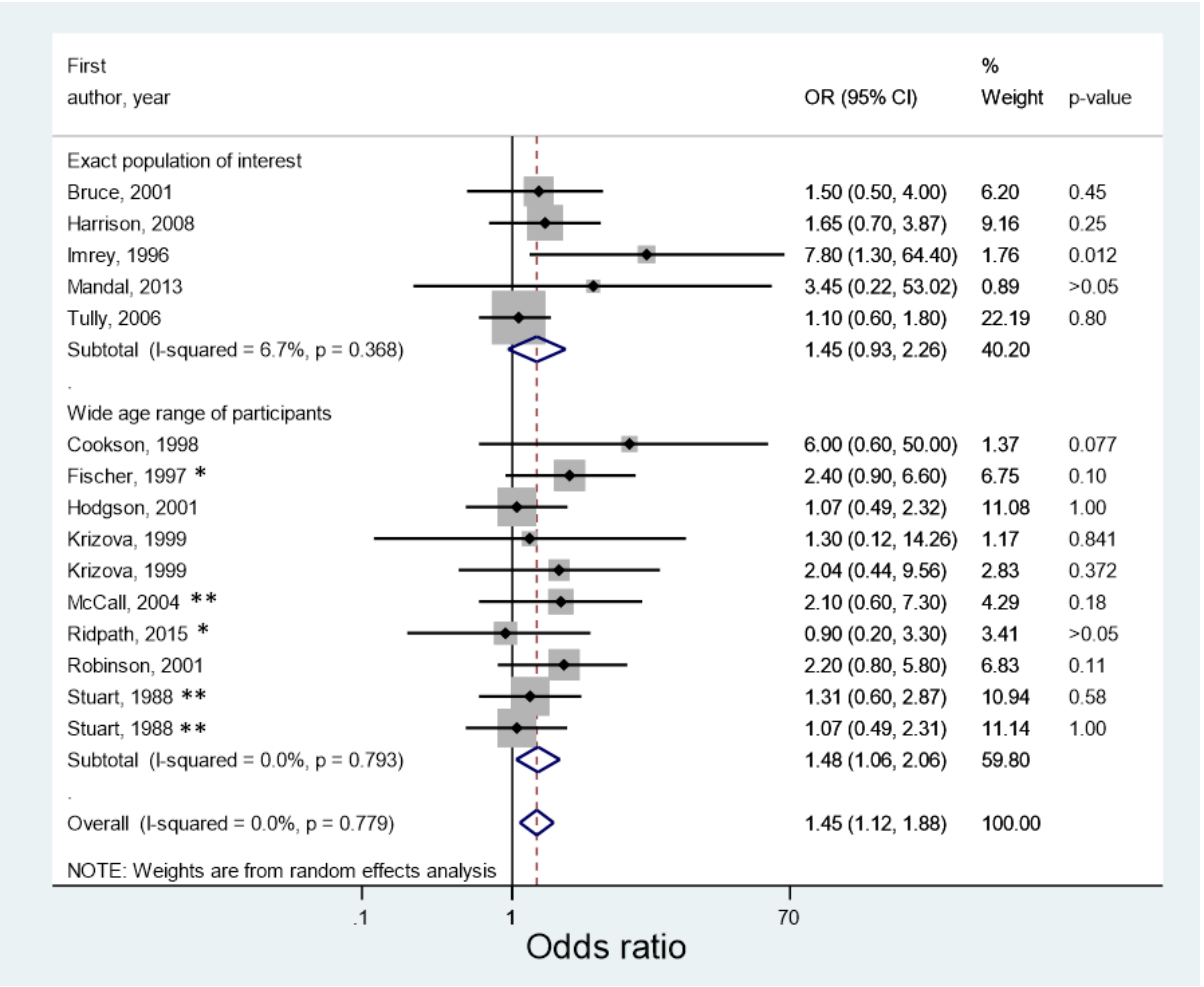

Figure 2*:* Forest plot of the association between active tobacco smoking and IMD. * : adjusted OR. **: unmatched OR (all other ORs presented are matched ORs).[a]

[a]Two studies (*Křížová, 1999* and *Stuart, 1988*) provided more than one effect estimate due to the use of multiple control groups/age group analyses.

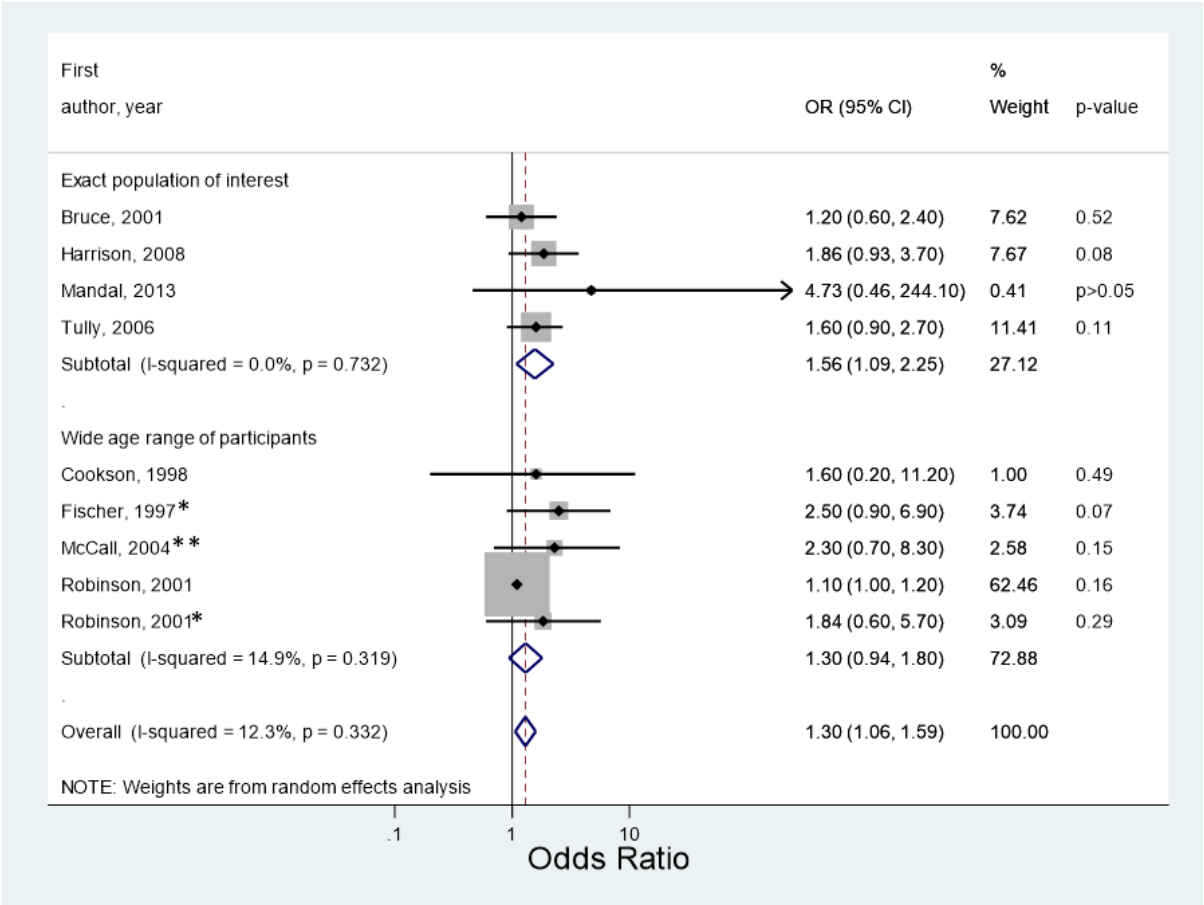

Figure 3: Forest plot of the association between passive tobacco smoke exposure and IMD. * : adjusted OR. **: unmatched OR (all other ORs presented are matched ORs).[a]

[a]*Robinson, 2001* provided two effect estimates as two passive tobacco smoking variables were analysed.

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Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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