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Worldwide relative smoking prevalence among people living with and without HIV: a systematic review and meta-analysis.

***Running Title**: SR of Relative Smoking Prevalence in PLH*

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Declaration of interests

We declare no competing interests

Abstract

Objective and design

People living with HIV (PLH) suffer disproportionately from the chronic diseases exacerbated by smoking tobacco. We performed a systematic review and meta-analysis to establish the relative prevalence of smoking among PLH.

Methods

We included observational studies reporting current smoking rates among PLH and comparators without HIV. We searched Medline, EMBASE, LILACS and SciELO from inception to 31.08.19. We excluded studies that recruited participants with smoking related illness. We used a random effects model to estimate the odds ratio for current smoking in PLH and people without HIV. We used the Newcastle-Ottawa scale to assess methodological bias. We performed subgroup analysis based on gender and World Health Organization (WHO) region. We quantified heterogeneity with meta-regression and predictive distributions. PROSPERO registration:CRD42016052608.

Results

We identified 6116 studies and included 37. Of 111,258 PLH compared with 10,961,217 HIV-negative participants pooled odds of smoking were 1.64 ((95% CI: 1.45-1.85)(95% PI: 0.66-4.10, I^2 98.1%)). Odds for men and women living with HIV were 1.68 ((95% CI: 1.44-1.95)(95% PI: 0.71-3.98, I^2 91.1%)) and 2.16 ((95% CI: 1.77-2.63)(95% PI: 0.92-5.07, I^2 81.7%)) respectively.

Conclusions

PLH are more likely to be smokers than people without HIV. This finding was true in sub-group analyses of males, females and in four of five WHO regions from which data were available. Meta-regression did not explain heterogeneity, which we attribute to the diversity of PLH populations worldwide. Smoking is a barrier to PLH achieving parity in life expectancy and an important co-variate in studies of HIV associated multi-morbidity.

72

73 **Key Words**

74 HIV; tobacco smoking; prevalence; systematic review; meta-analysis

Introduction

Combination anti-retroviral therapy (ART) has transformed HIV from a terminal illness into a chronic health condition. The life-expectancy of people living with HIV (PLH) is drawing closer to population averages, particularly in countries with well-resourced healthcare systems [1, 2]. The '90-90-90' targets adopted by the United Nations focus on ensuring that 90% of PLH know their serostatus, 90% of diagnosed PLH are receiving treatment and 90% of those on treatment achieve viral suppression [3]. Newer thinking extends beyond viral suppression toward a 'fourth 90'; optimising health related quality of life via effective prevention and management of co-morbidity [4, 5].

PLH are at increased risk of age related non-communicable diseases (NCD) associated with tobacco smoking including cardiovascular disease [6, 7], cancer [8, 9], and respiratory illness [10, 11]. HIV associated inflammation, direct viral effects, adverse effects of ART and prior AIDS events also contribute to the risk [12-14] but the impact of tobacco smoking is considerable [15]. PLH who smoke lose more life-years to smoking than to HIV in Europe and North America and have greater excess mortality from smoking than uninfected individuals [16]. PLH in LMIC who smoke are also affected; rising rates of smoking associated NCD are adding to the already high rates of tuberculosis and bacterial pneumonia, both of which are also increased in PLH who smoke [17-20]. Importantly, cessation of tobacco smoking is associated with improved health outcomes in PLH [21] and there is growing evidence supporting the efficacy of smoking cessation programmes in PLH using varenicline and other interventions [22, 23]. Smokeless tobacco consumption also has significant negative health consequences, increasing the risk of cancers of the head, neck, throat, oesophagus and oral cavity [24]. However, its use among PLH is far lower than tobacco smoking and its impact and the benefits of cessation in PLH are less well described [25, 26]. E-cigarettes or electronic nicotine delivery systems (ENDS) are not known to carry the risks of tobacco smoking and are instead a means used to quit [27, 28]. Data for their harm (or benefit) in PLH are also lacking [29]. Thus, a clear

appreciation of the prevalence of tobacco smoking among PLH must be the priority and is key to both understanding the mechanisms driving these co-morbidities and addressing their impact [30].

Whilst studies of HIV related co-morbidity frequently allude to a high smoking prevalence among PLH, citations are often based on data from large North American and European cohorts [31-33]. Most studies of smoking prevalence in HIV only include PLH in their sample and use general population estimates, which may not be contemporary either, as their comparator [34]. Furthermore, data that reflect the global distribution of PLH are limited. Mdege et al. (2017) used data from demographic and health surveys in LMIC to assess rates of tobacco use [25] but no study has systematically synthesised world-wide data comparing smoking prevalence in PLH with HIV uninfected individuals. This is likely to be particularly important with respect to gender differences in smoking; smoking prevalence is reported to be higher among women living with HIV in North American and European cohorts than elsewhere, but these regions have concentrated epidemics with significantly smaller proportions of women living with HIV than those areas of the globe with generalised HIV epidemics [35, 36]. Studies that include HIV negative populations in their samples will more adequately account for other factors determining the relative smoking prevalence in PLH according to gender category.

In this systematic review and meta-analysis we aim to establish whether there is a global trend for a difference in tobacco smoking prevalence among PLH to that among HIV-negative individuals. Our secondary aims are to determine whether differences apply to men and women living with HIV and individual WHO regions.

Methods

This was a systematic review and meta-analysis performed in accordance with PRISMA standards [37-41].

Inclusion/exclusion criteria

We included observational studies that reported the prevalence of current tobacco smoking in PLH and those without HIV infection. Populations of PLH and HIV seronegative comparators could comprise the same cohort or two existing cohorts combined for the purpose of the study. In studies that combined cohorts, it was essential that populations were contemporaneous and drawn from the same geographic location. In the absence of a universal definition of a 'current smoker', and with studies from various countries and populations, we took the pragmatic decision to accept the definitions of individual studies as indicative of smoking status, provided the same definitions were applied to PLH and HIV seronegative participants. Supplementary table 1 shows how smoking status was defined in each included study.

Smoking methods included any method of inhaling burned tobacco, such as via cigarettes, pipes, cigars or hookah. We did not include data from participants who used methods of tobacco consumption other than smoking (such as e-cigarettes or 'vaping', chewing tobacco or inhaling snuff) in our analysis. No lower or upper age limits for participants were set.

We excluded studies that selected participants on the basis of smoking status or that recruited on the basis of, or investigated for, a smoking related illness (e.g. lung cancer). Where data from the same cohort of patients were used in more than one article, only that which presented the largest, most complete and most up to date information was included.

Search strategy

We searched Medline and Excerpta Medica (EMBASE) via OVID, LILACS (Literatura Latino Americana em Ciências da Saúde) and SciELO (Scientific Electronic Library Online) from inception to 31st August 2019. The search strategy was developed for OVID (see supplementary table 5), and adapted for other databases. Reference lists of included papers were manually reviewed to identify further eligible studies. Where data regarding the gender of smokers were not published, the authors were contacted by SW or PJ.

Independent screening of titles and abstracts identified in the literature search was undertaken by SW and PC/PJ. Those not excluded at this stage were retrieved in full text format and scrutinised by SW/FP and PC/PJ for suitability for final inclusion. Disagreements were settled via discussion among reviewers to reach a consensus.

Data extraction and quality assessment

To measure the methodological quality of included papers for determining an association between HIV and smoking status, two reviewers (PC and FP) independently appraised the included studies using the Newcastle–Ottawa Quality Assessment Scale [42]. In the case of disagreement, consensus was reached through discussion. Studies with scores of greater than six on this scale were deemed to be of higher methodological quality.

We use the terms *HIV-seronegative, HIV uninfected* or *people without HIV* infection to describe participants who were not known to be living with HIV infection in each study. It should be noted that not all studies determined HIV status using a blood test. Where this was not the case, the background population prevalence of HIV infection was low (< 1%).

PJ and FW/SW independently extracted information from included articles, including: number of PLH smoking compared with number of HIV uninfected people smoking, numbers smoking by gender (where available), publication year, country and World Health Organisation (WHO) region.

Meta-analysis

We used a random effects meta-analysis model to estimate pooled odds ratios with 95% confidence intervals (CI) and 95% prediction intervals (PI) [43]. We performed sensitivity analyses comparing the data from studies with Newcastle-Ottawa Scores ≤6 (high risk of methodological bias) with those > 6 (lower risk). The Newcastle Ottawa Scale is a validated tool that can be used to assess the representativeness of cases (PLH) and comparators to the wider population of these respective groups [42]. Points are awarded based on how comparable the groups of participants are to each other. We also performed subgroup analyses based on gender and WHO region.

We estimated the between-study standard deviation to quantify the extent of the heterogeneity and the I^2 statistic to assess the impact of heterogeneity (>75% high) [44]. We explored reasons for heterogeneity using meta-regression and subgroups analyses, and estimated 95% prediction intervals to quantify relative prevalence given unexplained heterogeneity. All analyses were performed using the freely available software package R [45]. This study was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) in December 2016: CRD42016052608.

Results

We retrieved 7207 articles from our literature search. 1091 were duplicate records. We screened 6116 titles and abstracts, of which 136 were included for full text review. We

excluded 99 of these after scrutiny, leaving 37 studies in the final analysis (Figure 1). Characteristics of included studies are summarised in Table 1.

Nine studies were from Europe (Denmark, France, Spain, United Kingdom) [46-54], seventeen were from the Americas (Brazil, Canada, Haiti, United States) [55-71] and seven studies were from Africa (Rwanda, South Africa, Tanzania, Uganda, Zimbabwe) [72-78]. Two studies drew participants from Western Pacific (Australia, and China) [79, 80]. One study contributed to South-East Asia (India) [81]. One study (Mdege et al., (2017)) contributed data from multiple WHO areas: Africa, Americas, South East Asia and Western Pacific [25].

Four studies included only male participants [55, 66, 71, 80] and five included only female participants [56, 59, 64, 70, 78]. Gerend et al. (2017) included cisgender men and transgender women [60]. Shariati et al. (2017) included all participants who identified as male including cisgender men and transgender men [68].

Overall, our analysis provided data for 111,258 PLH and 10,961,217 HIV-seronegative participants, with pooled meta-analysis of 18,241 male PLH and 298,334 HIV-seronegative males (15 studies), and 18,095 female PLH and 411,024 HIV-seronegative females (14 studies) (table 2, figure 2 and supplementary figures 1 and 2).

The pooled odds of smoking were greater in participants with HIV infection compared with people without HIV infection, OR 1.64 (95% CI: 1.45, 1.85). Heterogeneity suggested that the relative prevalence depends on the characteristics of individuals.

Heterogeneity between studies was generally mild and similar for males and females. However, the odds ratio for smoking for participants with HIV infection compared with people without HIV infection was greater for females OR 2.16 (95% CI: 1.77-2.63) than for males OR 1.68 (95% CI: 1.44-1.95).

Heterogeneity between studies within WHO regions was generally mild except for in Europe where it was moderate. Our analysis suggests an increased prevalence of smoking in PLH compared to individuals without HIV in all WHO regions other than the Western Pacific (supplementary figure 3). Although the relative prevalence of smoking in PLH and individuals without HIV depends on the characteristics of individuals, it is likely to be higher in the Americas and South-east Asia irrespective of individual characteristics. The meta-regression showed that participants from Africa had a lower relative smoking prevalence than participants from the Americas, but comparisons between other regions were not significant. (supplementary tables 2-4).

Fourteen studies had a higher risk of methodological bias (Newcastle Ottawa Scores ≤ 6).[46, 47, 50, 59, 60, 66-68, 71, 73, 76-79] Among these studies the odds ratio of current smoking in PLH was 2.06 (95% CI: 1.57-2.71). The remaining studies had a lower risk of methodological bias (>6), and these had a pooled odds ratio of current smoking in PLH of 1.54 (95% CI: 1.35-1.76) (supplementary figure 4). Thus, there was some evidence to suggest that lower quality studies were associated with a higher relative prevalence of smoking, although our findings remained statistically significant in both groups.

Discussion

This systematic review and meta-analysis is the first to synthesise all studies that directly compare worldwide smoking prevalence in PLH and people without HIV. The review

comprised a comprehensive, tailored search strategy, standardised data extraction, quality appraisal by multiple reviewers and *a priori* defined subgroup analyses. We show that PLH are more likely to be current tobacco smokers than HIV-seronegative individuals, a finding maintained among men and women and consistent in four of five WHO regions. Nevertheless, the relative prevalence of smoking in PLH compared to individuals without HIV also depends on other unmeasured and unknown characteristics.

Our findings confirm and reinforce previous observations of higher smoking rates among people living with HIV [16, 82-85]. Mdege et al. (2017) performed a meta-analysis of data from the health surveys of 28 low and middle-income countries which demonstrated that men and women with HIV had a higher risk of tobacco smoking than those without HIV infection [25]. The data from that study are included in the current review.

Our findings should be interpreted in the context of some limitations. The studies included in this systematic review differed in their research aims, and due to intrinsic differences in the makeup of populations of PLH when compared with a general population, study participants were infrequently matched. Populations of PLH are likely to differ from HIV seronegative comparators by virtue of the risk factors that are associated with HIV acquisition, for example socio-economic status, intravenous drug use, and sexual orientation. These factors are likely to contribute to the unexplained heterogeneity observed in this analysis. We were able to explore the effect of gender and region on relative prevalence, but could not perform sensitivity analyses for each variable associated with smoking risk.

Some of the studies from higher income settings compared groups of PLH containing high numbers of men who have sex with men (MSM) with HIV seronegative cohorts containing low or unspecified numbers of MSM (table 1) [46, 48, 51, 52, 54, 65, 66]. MSM have been identified as a group who are more likely to be smokers than heterosexuals [86, 87].

There were insufficient data on the sexual orientation and smoking status of individual participants to permit a sensitivity analysis across all studies. We were able to conduct a post-hoc subgroup analysis of four studies whose participants comprised only MSM in both HIV seropositive and HIV seronegative groups [55, 60, 68, 80]. We found that MSM who were also PLH had significantly higher odds of smoking than HIV seronegative MSM: OR 1.67 (95% CI 1.04-2.68) (supplementary figure 5). This suggests that in these studies at least, sexual orientation did not account for the observed difference in smoking prevalence between PLH and those who were HIV seronegative.

Previous studies and health surveys have defined a 'current smoker' in specific terms [88]. Initially this had been part of our protocol, but it became apparent that few papers provided sufficient information about the quantities of tobacco consumed to apply such definitions. We elected to take the pragmatic approach of accepting individual studies' reports of which participants were currently smoking. We accept that this means smokers might be determined differently between studies, but the internal validity of a comparison of smoking status within individual studies is unimpaired. Accurate recording of tobacco consumption should be a priority for future research, especially where co-morbidity is concerned. As ENDS become more widely used it will also be important to quantify novel modes of nicotine consumption alongside smoking status, and to determine whether PLH who are smokers use these devices to quit.

It is beyond the scope of this review to determine the reasons for increased smoking prevalence among PLH, but some hypotheses are useful to consider. A review by Nansseu et al. found that trends in tobacco smoking among PLH changed little over time, indicating a low quit rate [89]. An analysis of 184 PLH who smoked in San Francisco found high rates of psychological co-morbidity, unemployment and illicit drug use [90], all of which are positively

associated with tobacco consumption [91, 92]. A recent systematic review found a high prevalence of depressive disorders among PLH in Africa, which suggests that psychological co-morbidity may be a factor in this setting, too [93]. Regression analysis of health survey data from Sub-Saharan Africa indicates that low socio-economic status, male sex and lower educational attainment are risk factors for smoking among PLH [94]. A qualitative study indicated that PLH may perceive that their life expectancy is shortened and that the harms of smoking are therefore less important, but this research is dated [95]. There is a need for further studies to determine drivers of smoking among PLH in the present day.

Our results highlight the need for robust strategies to help worldwide populations of PLH quit smoking. Whilst buproprion interacts with commonly prescribed anti-retroviral drugs, two randomised control trials have shown varencicline to be superior to placebo at achieving sustained smoking cessation among PLH, with no concerns regarding safety or drug interaction [22, 96]. A 2016 Cochrane review examined smoking cessation strategies in PLH, encompassing psychotherapy and pharmacotherapy in combination or isolation. There was poor-quality evidence for the short-term success of any smoking cessation strategy, and no evidence was available for long-term success. All of the evidence considered came from high-income countries [23]. The development of effective strategies for smoking cessation is a clear priority, especially in low-resource settings.

Our review shows that PLH are more likely to smoke tobacco than people without HIV infection although other factors may affect this quantitatively and qualitatively. This is highly significant because HIV is independently associated with many of the chronic diseases exacerbated by smoking, and smoking has enhanced detrimental effects on PLH.

The 2020 Covid-19 pandemic places renewed focus on lung health. Whilst HIV itself may not yet appear to impact upon outcomes from SARS-CoV-2 infection, chronic obstructive pulmonary disease and smoking have been associated with increased risk of in-hospital death

[97]. At this time the community of HIV clinicians, researchers and policy makers need to be cognisant of smoking as a threat to PLH worldwide.

Tobacco consumption should be addressed as a routine aspect of HIV care, and we advocate the integration of smoking cessation within national treatment strategies. This will be a challenge in all settings, but particularly where demands on HIV care are overstretched and resources are limited. Research in to effective, scalable and affordable smoking cessation strategies is therefore urgently needed.

A final and important implication of this study is to alert researchers in the growing field of HIV associated co-morbidity. In order to evaluate the impact of HIV on the development of chronic conditions and to assess interventions, robust measures of tobacco consumption must be integral to study design.

Acknowledgements

SW, FP, PC and RH developed the initial study design. SW, PJ, FP and PC searched for and extracted data. PJ, MO and JS analysed the findings. PJ wrote the first draft of the manuscript. All authors discussed key decisions collaboratively throughout the course of the review, provided critical feedback on preliminary drafts and interpretation of results, and approved the final manuscript.

355 Figures and Tables (manuscript body)

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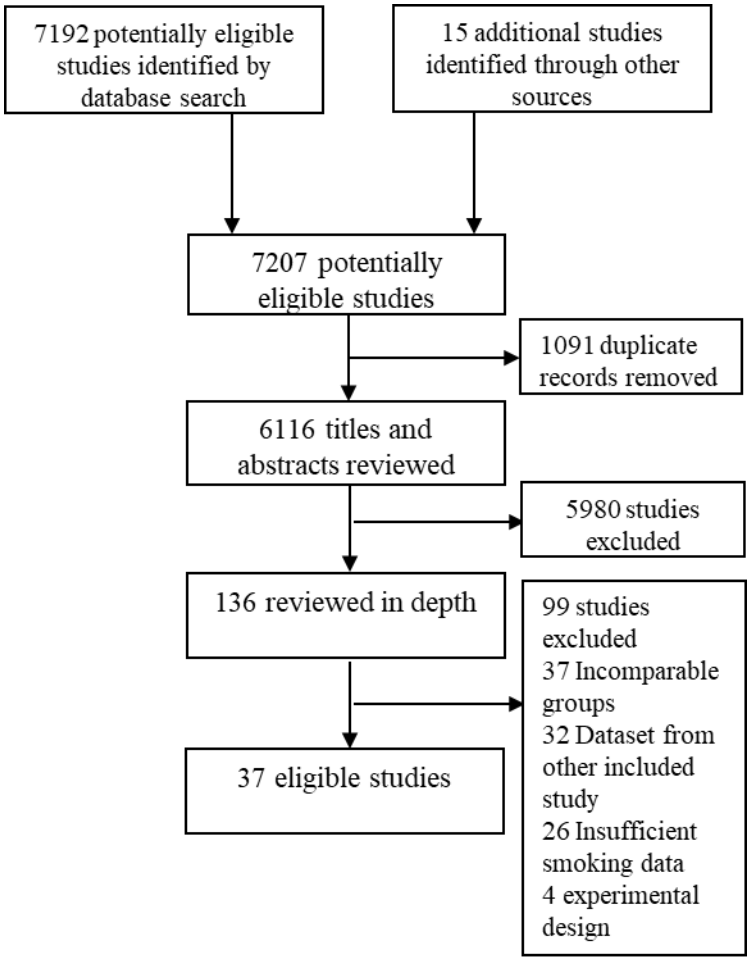

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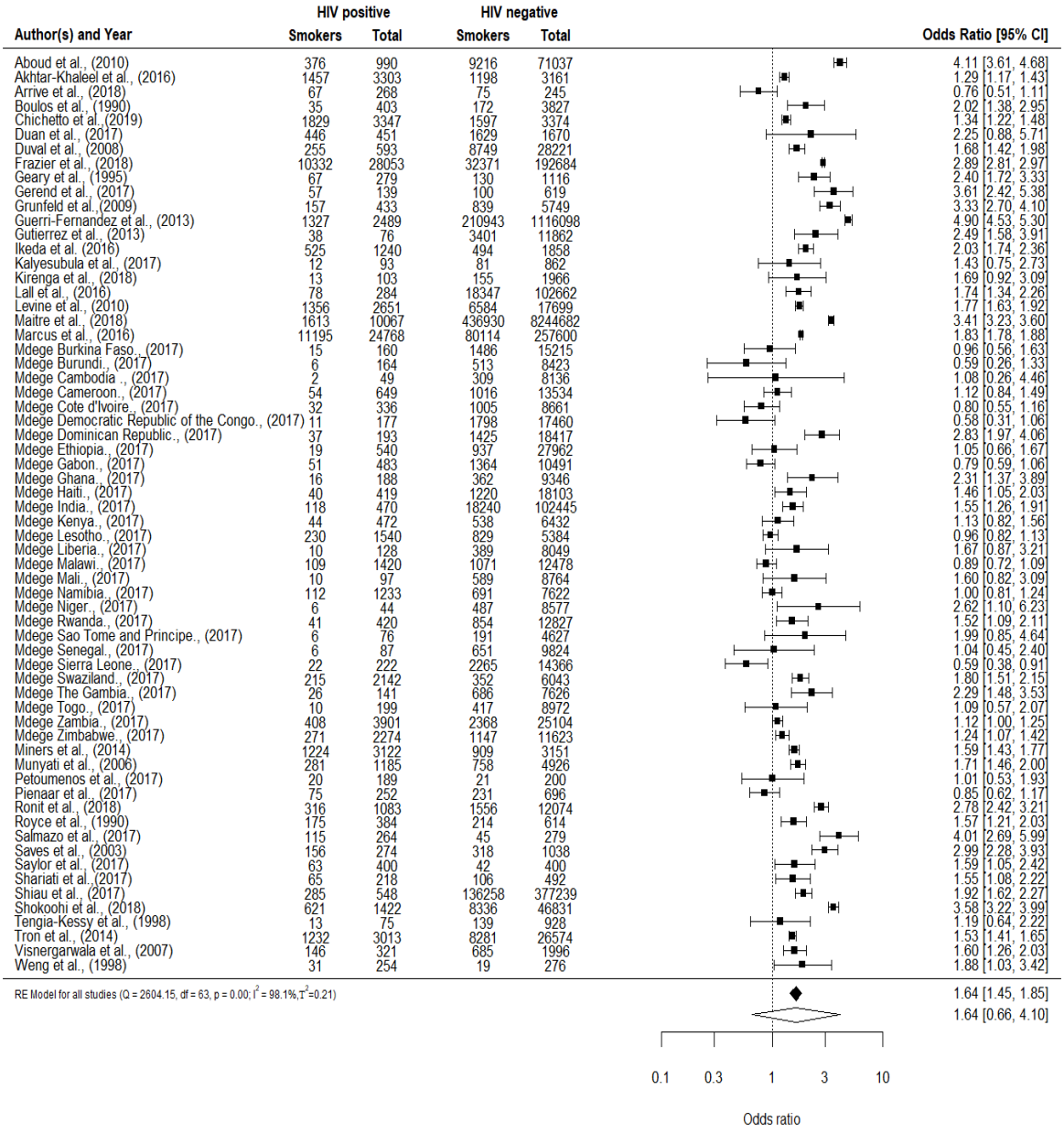
358 *Figure 1: Study selection*



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360 *Figure 2 Pooled odds of current smoking comparing all PLH with all HIV-seronegative participants. RE random effects, dF*
361 *degrees of freedom. Black diamond: pooled odds ratio. Empty Diamond: prediction interval.*

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363

364 *Table 1: Characteristics of included studies including: Author and (year of publication); WHO region and (country); gender of participants by HIV status (percentage female); average*
365 *participant age in years (mean or median as stated); study design and recruitment strategies; Newcastle-Ottawa Scale (NOS) score (0-10). Special populations: Men who have sex with men*
366 *(MSM) /Pregnant women /People who inject drugs (PWID) / Nosocomial acquisition of HIV / Vertically transmitted HIV*

Author / Year	Setting	Female Participants (PLH)	Female Participants (HIV-seronegative)	Age in years (PLH)	Age in years (HIV-seronegative)	Study design and target populations	NOS Score	Special populations
Aboud et al., (2010)[46]	European (UK)	26%	61%	Mean = 41	Mean = 52	Cross sectional PLH: outpatients attending for routine HIV care at two UK hospitals. HIV seronegative: recruited from UK General Practice population (Heart UK/Unilever study)	5	PLH: 315/990 MSM HIV seronegative: not reported
Akhtar-Khaleel et al., (2016)[55]	Americas (united States)	All male	All male	Mean = 34	Mean = 34.9	Prospective cohort PLH and HIV seronegative: recruited from Multicentre AIDS cohort study (MACS)	7	All MSM
Arrive et al., (2018)[47]	European (France)	53%	58%	Median = 23 Age restricted (18-30)	Median = 22.5 Age restricted (18-30)	Cross sectional PLH: adults with perinatally acquired HIV diagnosed <13 years of age. HIV seronegative: adults completing a national nutrition survey.	6	All PLH with perinatally-acquired HIV

Boulos et al., (1990)[56]	Americas (Haïti)	100%	100%	---	---	Cross sectional PLH and HIV seronegative: mothers of infants recruited whilst attending for a measles vaccine study.	7	None identified
Chichetto et al., (2019)[57]	Americas (United States)	5%	5%	Mean = 50	Mean = 50	Prospective cohort PLH and HIV seronegative: recruited from Veterans Aging Cohort Study (VACS). HIV seronegative age/race and site matched	9	None identified
Duan et al., (2017)[79]	Western Pacific (China)	4.4%	3.6%	---	---	Cross sectional PLH and HIV seronegative: former opiate users recruited from five methadone replacement clinics	6	All PWID
Duval et al., (2008)[48]	European (France)	30%	---	Mean = 45.1	No average reported Restricted to 18-75 years	Cross sectional PLH: recruited during a national survey of 82 units providing outpatient HIV care. HIV seronegative: taken from the 2005 French National Health Survey	8	PLH: 219/593 MSM HIV seronegative: not reported
Frazier et al., (2018)[58]	Americas (United States)	---	---	---	---	Cross sectional PLH: yearly, nationally representative estimates of HIV positive adults receiving care in the US	8	None identified

						HIV seronegative: annual, cross sectional survey of non-institutionalised US population		
Geary et al., (1995)[59]	Americas (United States)	100%	100%	---	---	Case control PLH and HIV seronegative: women giving birth at a large metropolitan hospital (1988-1992)	6	All pregnant women
Gerend et al., (2017)[60]	Americas (United States)	92% cisgender male; 6% transgender woman; 2% other		--- Restricted to 16-29 years	--- Restricted to 16-29 years	Longitudinal cohort: PLH and HIV seronegative: recruited from ongoing study of young MSM and transgender women	6	All MSM or transgender women
Grunfeld et al., (2009)[61]	Americas (United States)	30.5%	47.4%	Mean = 49	Mean = 61	Cross sectional PLH recruited from 16 infectious diseases clinics. HIV seronegative recruited from a cohort of young adults recruited to study visceral fat (not matched)	8	None identified
Güerri-Fernandez et al., (2013)[49]	European (Spain)	24.6%	52.2%	Mean = 50	Mean = 61.3	Retrospective cohort PLH and HIV seronegative: Electronic medical records from primary care attendances in Catalonia. ICD-10 codes used to identify PLH	7	None identified

Gutierrez et al., (2013)[62]	Americas (United States)	32%	54%	--- Restricted to 20-49 years	--- Restricted to 20-49 years	Retrospective cohort PLH and HIV seronegative: Adults from the 1999 to 2008 National Health and Nutrition Examination survey (NHANES).	7	None identified
Ikeda et al. (2016)[63]	Americas (Brazil)	49.4%	58.3%	Mean = 39.1	Mean = 43.9	Cross sectional PLH: consecutive patients referred for outpatient HIV care. HIV seronegative: population based cross-sectional study of alcohol consumption.	8	None identified
Kalyesubula et al., (2017)[72]	Africa (Uganda)	67%		Median = 31 (range 18-87)		Cross sectional PLH and HIV seronegative: Cross sectional community based survey with prospective determination of HIV serostatus	7	None identified
Kirenga et al., (2018)[73]	Africa (Uganda)	39%	61.2%	---	---	Cross sectional PLH and HIV seronegative: General population asthma survey. HIV status self-reported.	6	None identified
Lall et al., (2016)[81]	South-East Asia (India)	51.4%		--- Females aged 15-45, males aged 15-54		Cross sectional PLH and HIV seronegative: Survey of national and state	7	None identified

						level HIV prevalence. In areas suspected of high prevalence prospective HIV testing was undertaken .		
Levine et al., (2010)[64]	Americas (United States)	100%	100%	Median = 34.9	Median = 34.9	Cross sectional PLH: serologically confirmed members of a cohort study of women deemed at risk of HIV acquisition HIV seronegative: national survey investigating risk factors for health differences.	8	None identified
Maitre et al., (2018)[50]	European (France)	32%	52.5%	---	---	Retrospective PLH and HIV seronegative: extracted from electronic hospital discharge data over six year period.	5	None identified
Marcus et al., (2016)[65]	Americas (United States)	9.3%	9.3%	Mean = 40.7	Mean = 40.9	Retrospective cohort PLH with Kaiser Permanente membership in California, frequency matched by age and gender to members without HIV.	7	PLH: 16,781/24,768 PLH MSM 1734/24,768 PWID HIV seronegative: not reported
Mdege et al., (2017)[25]	Africa; Americas; South-East	Variable by country	Variable by country	Women aged 15-49, men	Women aged 15-49, men aged 15-54 (or	Cross sectional PLH and HIV seronegative: Demographic and health	9	None identified

	Asia; Western Pacific			aged 15-54 (or 59, dependent on country)	59, dependent on country)	survey data from 28 low and Middle income countries where tobacco use and HIV test data were made public		
Miners et al., (2014)[51]	European (United Kingdom)	19%	56%	Median = 45.2	Median = 49	Cross sectional PLH: survey of attendees at outpatient clinics in the UK. HIV seronegative: Health Survey for England (HSE) measure of health related behaviours in the general population	8	PLH: 2209/ 3151 MSM HIV seronegative: 58/7424 MSM
Munyati et al., (2006)[74]	African (Zimbabwe)	---	---	---	---	Cross sectional PLH and HIV seronegative: Employees from 22 businesses were tested for HIV and underwent an interview	8	None identified
Petoumenos et al., (2017)[80]	South Pacific (Australia)	All male	All male	Median = 65 (>55 only)	Median = 62 (> 55 only)	Cross sectional PLH and HIV seronegative: recruited from General Practices, sexual health clinics and referral hospitals, through advertisements	7	All MSM
Pienaar et al., (2017)[75]	Africa (South Africa)	76%	79%	---	---	Cross sectional PLH and HIV seronegative: identified from same rural and urban populations. HIV	8	None identified

						serostatus determined on study entry		
Ronit et al., (2018)[52]	European (Denmark)	14.3%	18.4%	Mean = 50.6	Mean = 52.8	Cross sectional PLH: from existing cohort study of co-morbidity in HIV infection. HIV seronegative recruited from cohort study serving same population (age and sex matched)	7	PLH: 771/1083 MSM 16/1083 former PWID HIV seronegative: not reported
Royce et al., (1990)[66]	Americas (United States)	All male	All male	--- Restricted to 24-55 years	--- Restricted to 24-55 years	Prospective cohort PLH and HIV seronegative: recruited from a population based cohort of single Men in San Francisco	6	PLH:all MSM or bisexual. HIV seronegative: 410/614 MSM / bisexual
Salmazo et al., (2017)[67]	Americas (Brazil)	47.3%	51.6%	Mean = 43.2	Mean = 37.9	Cross sectional PLH: recruited from outpatient clinics PLH and HIV seronegative: prospectively included (no matching or detail as to how recruited)	5	None identified
Savès et al., (2003)[53]	European (France)	19%	49%	--- Restricted to 35-44 years	--- Restricted to 35-44 years	Nested cross sectional PLH: started on protease inhibitors in outpatient settings HIV seronegative: population based pre-existing cohort stratified by age and sex with the	7	None identified

						stratum most closely matching the ages of PLH included		
Saylor et al., (2017)[76]	Africa (Uganda)	47%	48%	Mean = 35	Mean = 35	Cross sectional PLH and HIV seronegative: drawn from a community cohort study in which PLH were age and sex matched to adults in the same district	6	None identified
Shariati et al., (2017)[68]	Americas (Canada)	All identified as male	All identified as male	Median = 34		Prospective cohort PLH and HIV seronegative: adults having had sex with a man in the last 6 months, identifying as male (including trans male) and living in Vancouver.	6	All MSM.
Shiau et al., (2017)[69]	Americas (United States)	20%	52%	---	---	Cross sectional. PLH and HIV seronegative: from National survey of drug and alcohol use – randomly selected households invited for interview	7	PLH: high reported illicit drug use. No data regarding PWID
Shokoohi et al., (2018)[70]	Americas (Canada)	100%	100%	---	Standardisation performed to make ages comparable before analysis	Cross sectional PLH: Community based study of female PLH in Qebec, Ontario and British Columbia. HIV seronegative: drawn from nationwide cross	9	PLH: high reported illicit drug use. No data regarding PWID

						sectional community health survey		
Tengia-Kessy et al., (1998) *[77]*	Africa (Tanzania)	53.5%	46.5%	--- Restricted to 15-24 years	--- Restricted to 15-24 years	Cross sectional PLH and HIV seronegative: Four wards randomly selected from district, then two villages selected from each ward with survey of all 15-24 year olds	6	None identified
Tron et al., (2014)[54]	European (France)	34%	58.1	--- Range 15-84	--- Range 15-85	Cross sectional PLH: recruited from national survey conducted across 73 hospital outpatient departments. HIV seronegative: recruited from French national health survey	9	PLH: 1016/ 3013 MSM. 404/3013 PWID. HIV seronegative: not reported
Visnergarwala et al., (2007)[71]	Americas (United States)	All male	All male	---	---	Cross sectional PLH all participants of a multicentre randomised trial comparing HIV treatment strategies. HIV seronegative: National Health survey (1992-2002) age restricted to 20-59 years	6	None identified
Weng et al., (1998)[78]	Africa (Rwanda)	100%	100%	Mean = 26	Mean = 28	Prospective cohort PLH: selected at random from pregnant women attending a health centre. HIV seronegative: randomly	6	All pregnant women

						selected from women attending on same day as each PLH recruited		

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369 *Table 2: pooled odds of smoking by HIV status*

	Studies	PLH	HIV negative	Pooled Odds Risk (95% CI)	Prediction Interval (95% PI)	I^2
All	37	111,258	10,961,217	1.64 (1.45-1.85)	1.64 (0.66-4.10)	98.1%
Male	15	18,241	298,334	1.68 (1.44-1.95)	1.68 (0.71-3.98)	91.1%
Female	14	18,095	411,024	2.16 (1.77-2.63)	2.16 (0.92-5.07)	81.7%

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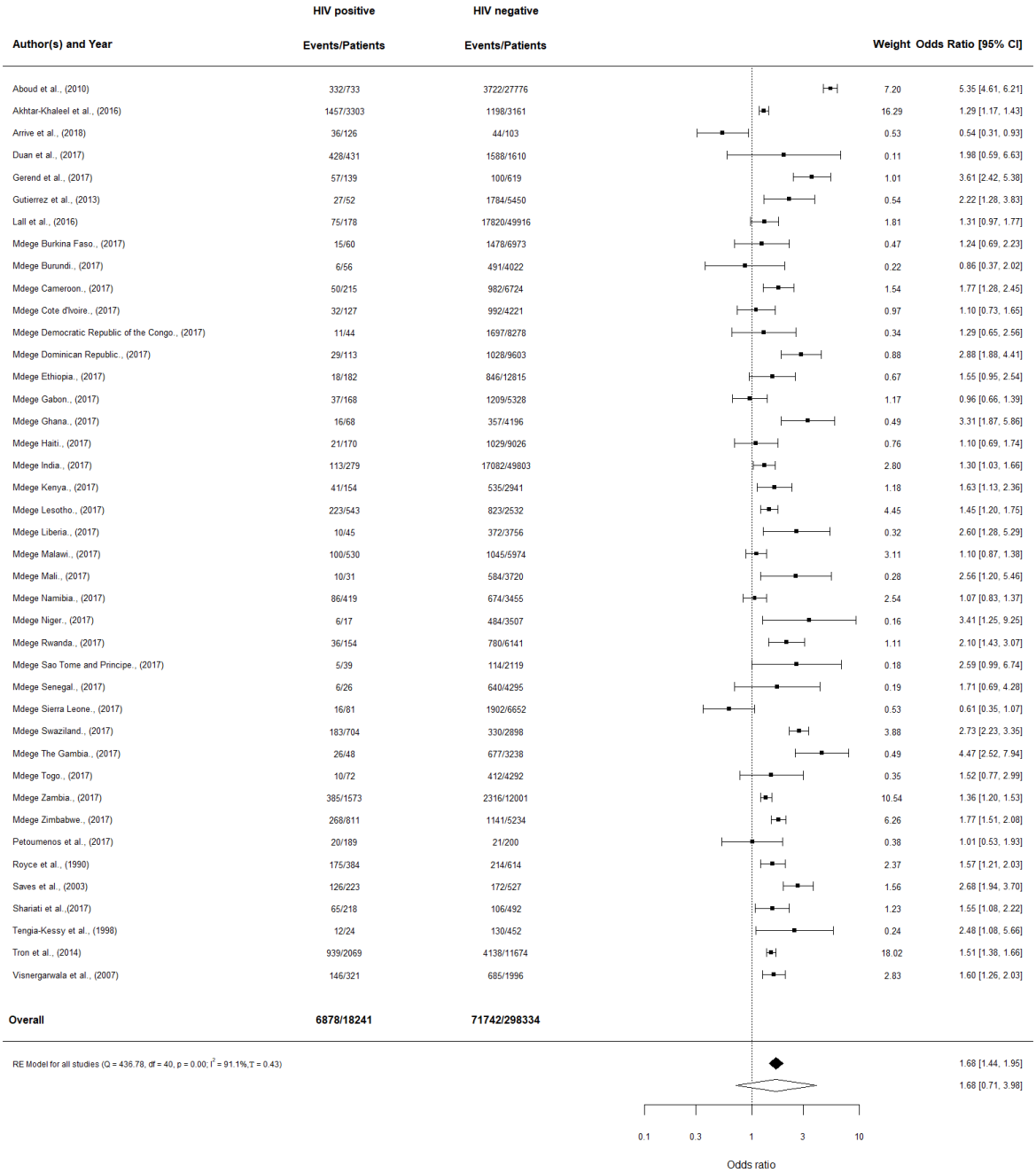
Figures (supplementary material)



Supplementary Figure 1 pooled odds of current smoking among men living with HIV and HIV-seronegative men. RE random effects, dF degrees of freedom. Black diamond: pooled odds ratio. Empty Diamond: prediction interval.

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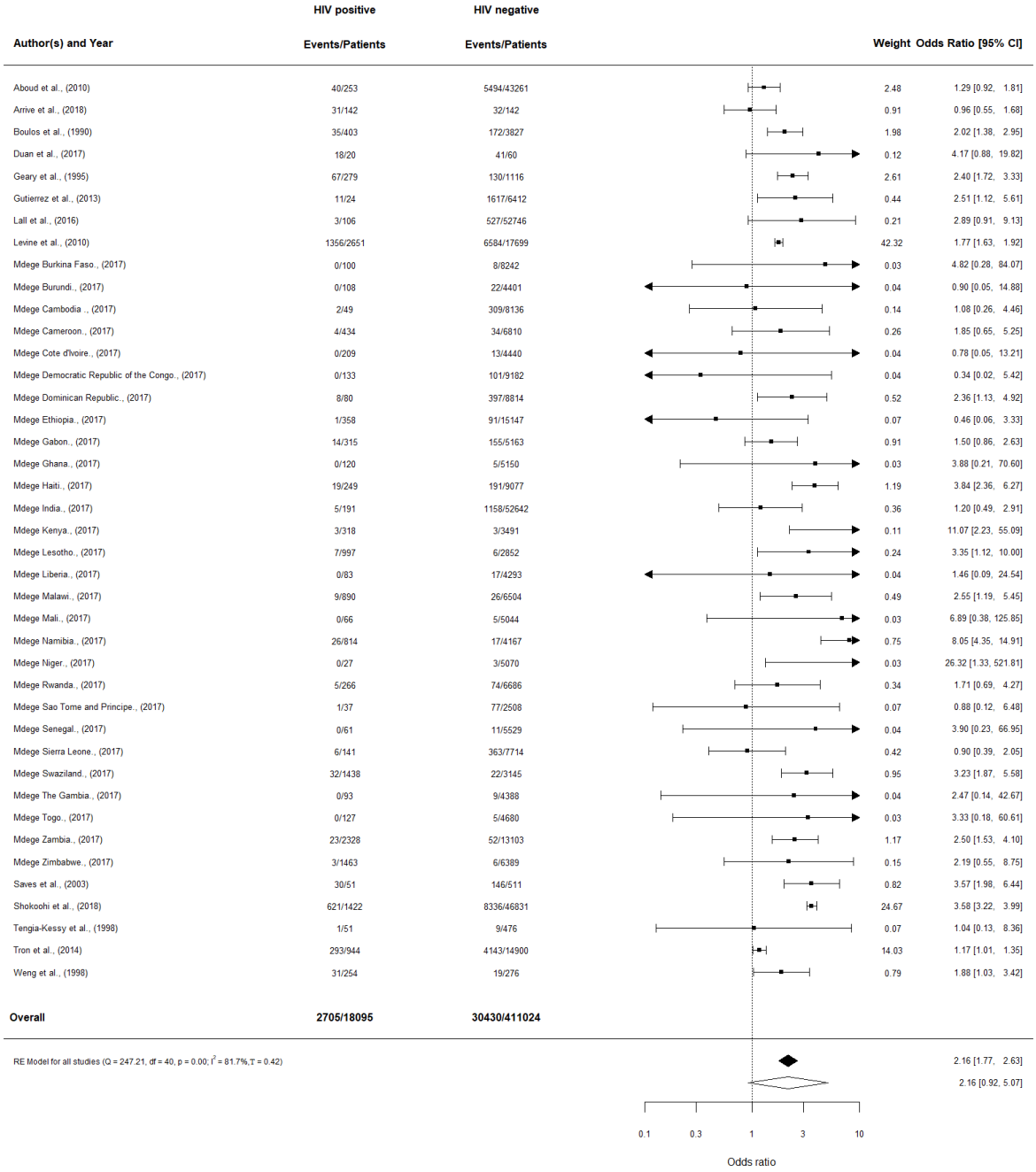

Supplementary Figure 2 pooled odds of current smoking among women living with HIV and HIV-seronegative women. RE random effects, dF degrees of freedom. Black diamond: pooled odds ratio. Empty Diamond: prediction interval.

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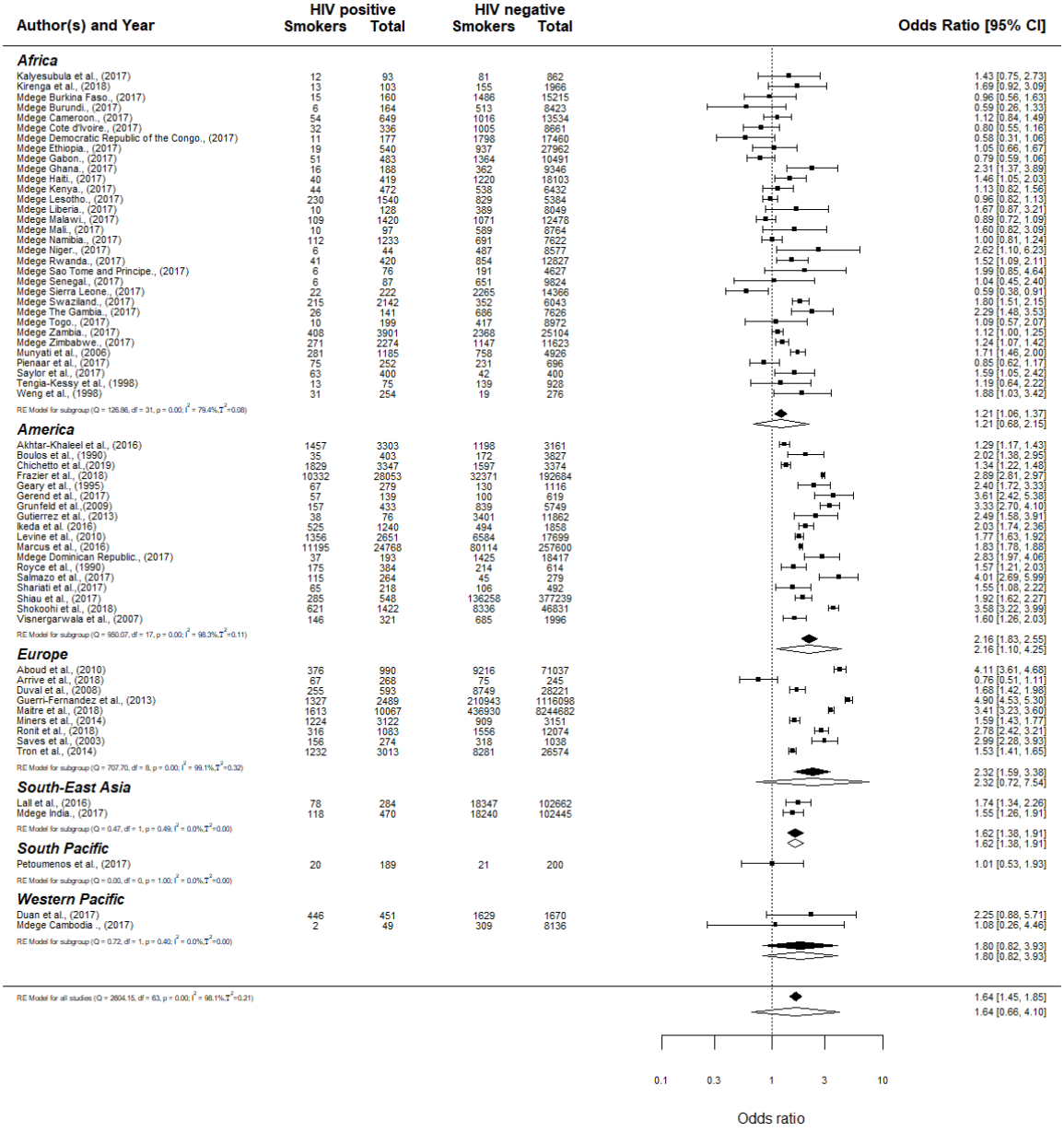
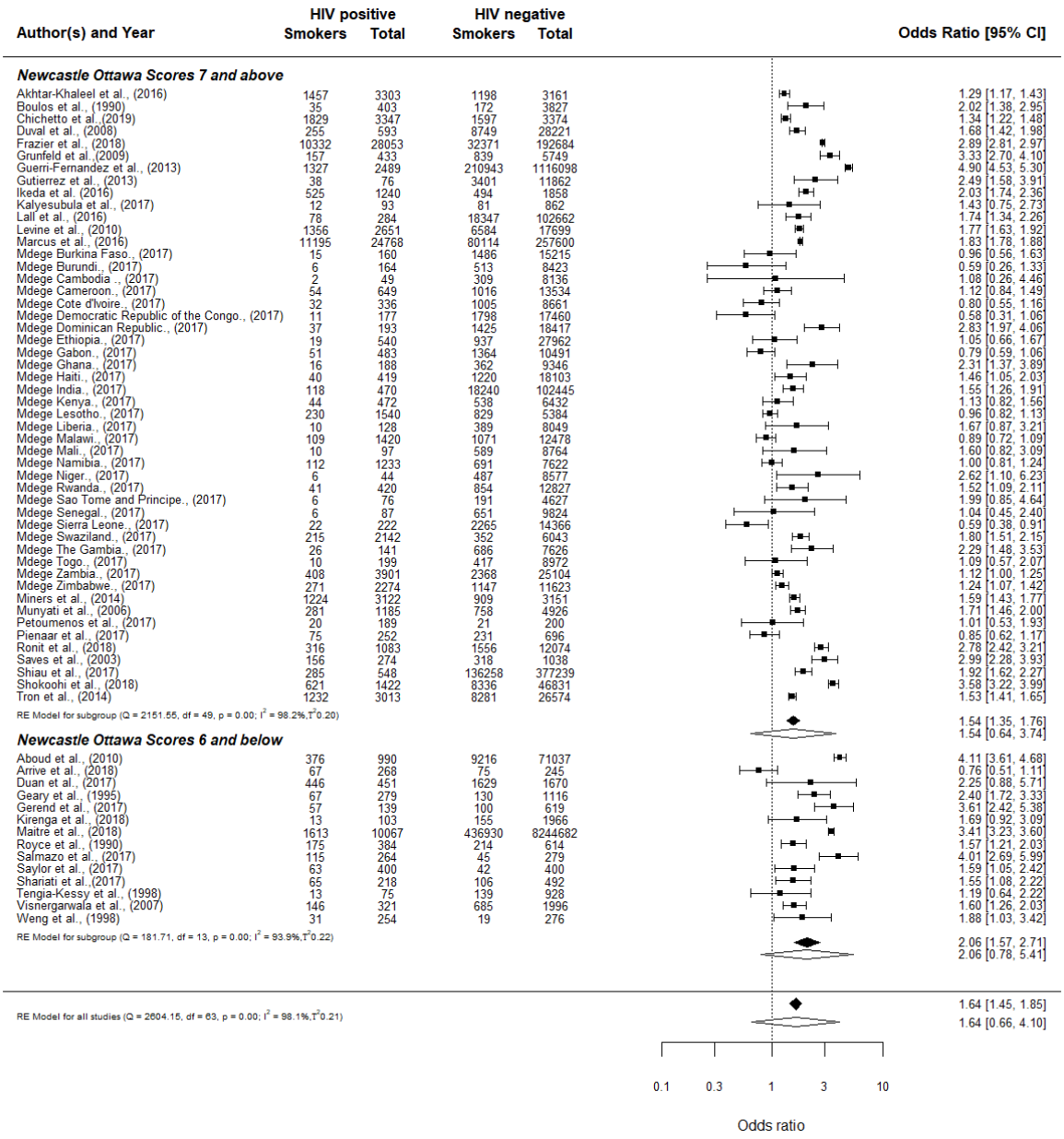
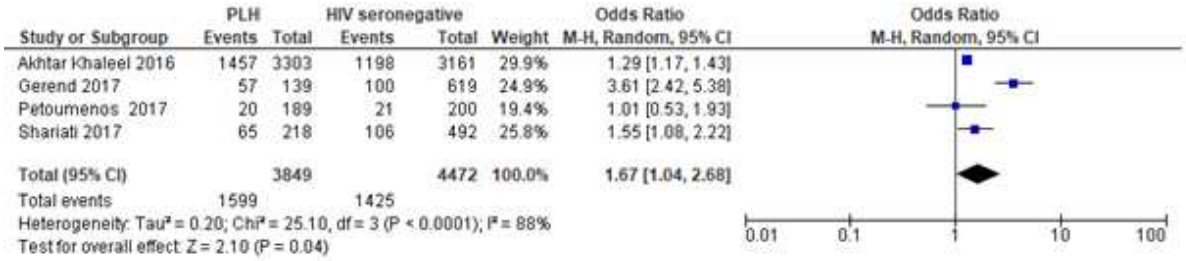


Supplemental Figure 3 pooled odds of smoking prevalence among PLH and HIV-seronegative participants by WHO region. RE random effects, dF degrees of freedom. Black diamond: pooled odds ratio. Empty diamond: prediction interval



Supplementary Figure 4 pooled odds of smoking prevalence by HIV-serostatus for studies of higher methodological quality (NOS > 6) and lower methodological quality (NOS ≤ 6) . RE random effects, dF degrees of freedom. Black diamond: pooled odds ratio. Empty Diamond: prediction interval.



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389 *Supplementary Figure 5 pooled odds of smoking prevalence by HIV-serostatus for studies comprised entirely of Men who*
390 *have sex with men (MSM). RE random effects. Black diamond: pooled odds ratio*

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392 *Supplementary table 1 Means of determining smoking status in included studies*

Author	'Smoker' definition
Aboud et al., (2010)	"Current smoking" as compared with "recent" smoking (within 5 years). No formal description of how current smoking was defined
Akhtar-Khaleel et al., (2016)	Current smoker = 'do you smoke cigarettes now?' = yes (interview)
Arrive et al., (2018)	Self-administered questionnaire and data collected in examination centres Consuming tobacco 'every day' vs 'not every day' vs 'in the past' vs never'. This review included those who consumed tobacco 'ever day'.
Boulos et al., (1990)	'detailed interviews' including numbers of cigarettes per day This review included all smokers of any number of cigarettes ≥ 1 per day
Chichetto et al., (2019)	Self-report: of 'past and current smoking' (definitions not supplied) This review included 'current smokers'
Duan et al., (2017)	Face to face interviews. Ever smokers = 100 cigarettes per lifetime. Current smokers also smoked in the month prior to interview
Duval et al., (2008)	Self-administered multiple-choice questionnaire. This review included regular tobacco smokers (one or more cigarettes per day for at least one year)
Frazier et al., (2018)	Combination of self-report and interviews. Current smokers had smoked more than 100 cigarettes in a lifetime and were smoking some days or every day
Frazier et al., (2018)	"Have you ever smoked cigarettes?" Response options = never, once or twice, occasionally but not regularly, regularly in the past, regularly now. "Regularly now" were classified as current smokers
Geary et al., (1995)	This study gave no clear definitions, participants were either a 'smoker' or not a smoker
Gerend et al., (2017)	At interview, participants were asked "Have you ever smoked cigarettes?" Those responding 'regularly now' were included in this review as current smokers
Grunfeld et al., (2009)	Structured questionnaires administered but no formal details as to how a smoker or non-smoker were determined in this.
Güerri-Fernandez et al., (2013)	Structured questionnaire, but defined limits of a current smoker not defined

Gutierrez et al. (2013)	Face to face interview, with those who were smokers at the time of interview considered to be current smokers
Ikeda et al., (2016)	Standardised questionnaires. Smoking > 100 cigarettes or more in a lifetime = current or former smoker (no mention of how current and former were distinguished but able to glean this from data presentation)
Kalyesubula et al., (2017)	WHO STEPS questionnaire administered via face to face interviews https://www.who.int/ncds/surveillance/steps/STEPS_Instrument_v2.1.pdf Not stated: used 'a standardised questionnaire adapted from WHO health survey'
Kirenga et al., (2018)	Not stated: used 'a standardised questionnaire adapted from WHO health survey'
Lall et al., (2016)	Differentiated between tobacco consumption and 'smoking' due to high prevalence of chewing tobacco. For SR include current smokers of cigarettes / bidis / pipes / cigars
Levine et al., (2010)	Never / former and current smoking Only article to include pack years broken down by HIV serostatus (current smokers with HIV had slightly higher pack years than HIV negative)
Maitre et al., (2018)	Encoded in main or associated diagnoses (i.e. smoker).
Marcus et al., (2016)	extracted from electronic health record (ICD 9 smoking/tobacco use) defined as ever smokers from 2 years before baseline to the end of follow up
Mdege et al., (2017)	3 questions answered yes/no 1) smoke cigarettes? 2) use other form of tobacco? 3) what type of tobacco currently smoked or used (including country specific tobacco products) "Tobacco smoker" = 'yes' to smoking cigarettes, pipes, or country specific smoking product.
Miners et al., (2014)	Self administered questionnaire and data collected in medical examination centres. Status = consuming tobacco 'every day' 'not every day' 'in the past' and 'never'. This review included those consuming tobacco 'every day'
Munyati et al., (2006)	smokers = lifetime consumption of at least 20 cigarettes, or equivalent in pipe tobacco, current smokers = at least one occasion in the last month
Petoumenos et al., (2017)	self reported (pack years calculated) not stated how they determined whether current / ever / never smokers SR = current smokers
Pienaar et al., (2017)	health questionnaire adapted from one developed for the Prospective Urban Rural Epidemiology (PURE) – instrument not available to current authors

Ronit et al., (2018)	self report. Questions not given. Divided in to 'current' 'former' 'never' For SR: 'current smokers'
Royce et al., (1990)	Interview data: current, occasional, past and never. Occasional smokers (< 1 cigarette per day) classed as non-smokers for data purposes.
Salmazo et al., (2017)	'Active smoking': no indication as to how this was defined
Savès et al., (2003)	Those who smoked in the 12 months before recruitment
Saylor et al., (2017)	Participants completed a 'sociodemographic interview' to determine whether they were smokers, but no further ascertainment details given
Shariati et al., (2017	Our review included 'daily smokers'. This was based on a computer assisted self-interview which placed participants in to four groups 'never smoker' 'non-daily smoker', 'daily smoker' and 'former smoker'
Shiau et al., (2017)	Dichotomous yes/no to cigarettes / tobacco for 1) lifetime use 2) past year use 3) past month use. For the review we included those with use in the past month
Shokoohi et al., (2018)	Our review included daily smokers (of more than one cigarette per day or 30 in a month)
Tengia-Kessy et al., (1998)	Questionnaire – no mention of how smoking status was defined Standardized questionnaire delivered face to face.
Tron et al., (2014)	Included current smokers as those who were regular smokers > 1 cigarette per day
Visnergarwala et al., (2007)	The percentage of participants described as 'smoking' were included as smokers in this review
Weng et al., (1998)	Smokers of ≥ 1 cigarette per day included as 'current smokers'

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395 *Supplementary Table 2: meta-regression, all studies*

Variable	Coefficient	P-Value	Confidence interval	OR
Intercept	0.7276 (0.1127)	<.0001	[0.5068, 0.9484]	2.0701
Proportion male	-0.0029 (0.0023)	0.213	[-0.0073, 0.0016]	0.9971
Africa	-0.5810 (0.1412)	<.0001	[-0.8577, -0.3042]	0.5593
Europe	-0.1059 (0.2044)	0.6042	[-0.5065, 0.2946]	0.8995
South East Asia	-0.2298 (0.2886)	0.4258	[-0.7955, 0.3358]	0.7947
West Pacific	-0.3484 (0.3644)	0.339	[-1.0625, 0.3657]	0.7058
Summary statistics				
τ	0.3562			
I^2	89.99%			
N = 48				

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397 *Supplementary Table 3: meta-regression, lower methodological quality studies*

Variable	Coefficient	P-Value	Confidence interval	OR
Intercept	0.6828 (0.1343)	<.0001	[0.4196, 0.9460]	1.9794
Proportion male	-0.0034 (0.0030)	0.2545	[-0.0093, 0.0025]	0.9966
Africa	-0.5521 (0.1544)	0.0003	[-0.8546, -0.2496]	0.5757
Europe	-0.0911 (0.2270)	0.6881	[-0.5361, 0.3538]	0.9129
South East Asia	-0.1846 (0.2722)	0.4977	[-0.7181, 0.3489]	0.8314
West Pacific	-0.5628 (0.4311)	0.1917	[-1.4077, 0.2821]	0.5696
Summary statistics				
τ	0.3115			
I^2	87.52%			
N = 38				

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399 *Supplementary Table 4: meta-regression, higher methodological quality studies*

Variable	Coefficient	P-Value	Confidence interval	OR
Intercept	0.8106 (0.3600)	0.0243	[0.1051, 1.5161]	2.2493
Proportion male	-0.0035 (0.0067)	0.6027	[-0.0167, 0.0097]	0.9965
Africa	-0.4892 (0.6809)	0.4724	[-1.8237, 0.8452]	0.6131
Europe	-0.2262 (0.5884)	0.7006	[-1.3796, 0.9271]	0.7976
West Pacific	0.1694 (0.8357)	0.8394	[-1.4685, 1.8073]	1.1846
Summary statistics				
τ	0.615			
I^2	93.26%			
N = 10				

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412 *Supplementary Table 5. Search terms*

	Search area	**Search terms** (adapted from Cochrane review group search strategies)
1	HIV	exp HIV/
2		exp HIV Infections/
3		1 or 2
4		(aids or hiv or (human* adj2 (immunodefic* or (immun* adj2 defic*)))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
5		3 or 4
6	Prevalence	exp Epidemiology/
7		exp Epidemiologic Studies/
8		exp Morbidity/ or exp Incidence/ or exp Prevalence/
9		6 or 7 or 8
10	Smoking	exp Smoking/ or exp Smoking Cessation/
11		"Tobacco Use"/
12		Cannabis/
13		exp "Tobacco Use Disorder"/

14		exp Tobacco Products/
15		((smok* or cigar* or tobacco* or nicotin* or cannabis or marijuana) adj2 (use* or abuse* or disord* or depend* or cessat*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
16		10 or 11 or 12 or 13 or 14 or 15
17		5 and 9 and 16

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