Clinical Infectious Diseases

REVIEW ARTICLE

Smoking as a Risk Factor of Invasive Fungal Disease: Systematic Review and Meta-Analysis

Annabelle Pourbaix,[1] Baptiste Lafont Rapnouil,[1] Romain Guéry,[1] Fanny Lanternier,[1,2] Olivier Lortholary,[1,2,*] and Jérémie F. Cohen[1,3,*]

[1]Necker-Pasteur Center for Infectious Diseases and Tropical Medicine, Necker-Enfants malades Hospital, APHP, Paris University, Sorbonne Paris Cité, Imagine Institute, Paris, France, [2]Institut Pasteur, Molecular Mycology Unit, National Reference Center for Invasive Mycoses and Antifungals, UMR 2000, CNRS, Paris, France, and [3]Inserm U1153, Centre of Research in Epidemiology and Statistics Sorbonne Paris Cité (CRESS), Paris University, Paris, France

To investigate the association between smoking and invasive fungal disease (IFD), we searched MEDLINE and Web of Science for studies published until September 2018. Two authors independently performed study selection and data extraction. Relative risks (RRs) were pooled using random-effects meta-analysis. We included 25 studies (18 171 participants; 2527 IFD cases). The meta-analysis showed an increased risk of IFD in smokers (RR 1.41 [95% confidence interval 1.09–1.81]; $P = .008$). The risk of IFD was higher in retrospective than in prospective studies (RR 1.93 [1.28–2.92] vs. 1.02 [0.78–1.34]; $P = .04$), in studies with multivariate adjustment compared to studies with univariate analysis (RR 2.15 [1.27–3.64] vs. 1.15 [0.88–1.51]; $P = .06$), and in studies published after 2002 (RR 2.08 [1.37–3.15] vs. 0.95 [0.75–1.22]; $P = .008$); other subgroup characteristics did not significantly influence the association in metaregression. Smoking cessation strategies should be implemented, especially in patients who are already at risk for IFD.

Keywords. invasive fungal disease; smoking; tobacco; systematic review; meta-analysis.

Invasive fungal disease (IFD) is a major cause of morbidity and mortality in immunocompromised hosts. The overall incidence of IFD was 27.2/100 000 patients per year in a large US health care network between 2006 and 2015, with a mean annual increase of 0.24/100 000 patients [1]. In France, the overall incidence of IFD was 5.9/100 000 population per year in the national hospital discharge database (2001–2010) [2]. Among IFDs, invasive candidiasis is the most frequent one, followed by aspergillosis and *Pneumocystis* pneumonia [1, 2]. Mortality rates, depending on the pathogen and underlying patient condition, remain as high as 25–50% [1, 2]. The main risk factors for IFD include hematological malignancies, prolonged neutropenia, human immunodeficiency virus (HIV) infection, primary immunodeficiencies, diabetes mellitus, chronic kidney disease, and corticosteroid treatment. Influenza infection and severe burns recently emerged as new risk factors for IFD [3, 4]. The general population may be at risk for IFD as well, as a result of specific environmental exposures, such as climate and agricultural profession, and lifestyle habits, such as smoking [5].

Several studies have assessed the association between smoking and infection. Smoking increases the risk of bacterial pneumonia and meningitis [6, 7] and second-hand smoke exposure is associated with increased risk of childhood invasive meningococcal disease [8]. Smoking is also associated with higher rates of oral candidiasis [9, 10] and has been reported as a risk factor of cryptococcal meningitis [11]. Smokers' alveolar macrophages have a reduced ability for phagocytosis and pathogen killing, are functionally impaired, and produce significantly lower levels of pro-inflammatory cytokines, compared to those of nonsmokers [12]. It was also demonstrated that tobacco and marijuana are heavily contaminated with fungal spores [13, 14]. Furthermore, the use of medicinal cannabis has increased in the past decade, following Food and Drug Administration (FDA) approval for its use in people living with HIV or cancer [15], who are already at high risk of IFD. Prevalence of tobacco smoking is higher among people living with HIV compared with the general population [16].

So far, several studies have assessed the association between smoking and IFD in specific patient populations, but a systematic review with meta-analysis is lacking. The aim of this systematic review was to determine whether smokers are at increased risk of IFD.

MATERIALS AND METHODS

The study protocol was registered with PROSPERO (CRD42018102724). We followed methodological guidance for conducting systematic reviews from the Centre for Reviews and Dissemination and the Cochrane Collaboration [17, 18]. We followed MOOSE and PRISMA for reporting [19, 20].

Received 14 August 2019; editorial decision 24 December 2019; accepted 1 January 2020; published online January 4, 2020.

*O. L and J. F. C. contributed equally to this work.

Correspondence: J. F. Cohen, Necker-Pasteur Center for Infectious Diseases and Tropical Medicine, Paris University, Paris, France (jeremie.cohen@inserm.fr).

Clinical Infectious Diseases® 2020;71(4):1106–19

DOI: 10.1093/cid/ciaa001

Eligibility Criteria

We included prospective and retrospective case-control and cohort studies that investigated the association between smoking and any IFD. We excluded case reports, case series without a comparative group, and cross-sectional studies.

Our target condition of interest was IFD, which included the following: (i) invasive aspergillosis or infection by other pathogenic molds (ie, *Mucorales*, *Fusarium* spp. or *Scedosporium/Lomentospora* spp.), defined according to EORTC/MSG 2008 criteria (proven or probable fungal disease) [21], or invasive aspergillosis in people living with HIV [22] or in diabetic patients (that met clinical and mycological criteria without host factors); (ii) invasive candidiasis (according to EORTC/MSG 2008 criteria or in critically ill patients); (iii) cryptococcal disease, defined as positive India ink preparation or culture of *Cryptococcus neoformans* or *Cryptococcus gattii* from any body site, detection of cryptococcal antigen in cerebrospinal fluid, or histopathological findings consistent with cryptococcosis; and cryptococcosis infection defined by an isolated positive cryptococcal antigen in blood; (iv) *Pneumocystis jirovecii* pneumonia (PJP), defined as detection of *P. jirovecii* on microscopic examination, immunofluorescence assay, or a positive polymerase chain reaction (PCR) result on samples of sputum or bronchoalveolar lavage fluid, consistent with clinical and radiological findings in a patient at risk for PJP; and (v) invasive fungal infections caused by dimorphic endemic pathogens (ie, coccidioidomycosis, paracoccidioidomycosis, blastomycosis, talaromycosis [or penicilliosis], sporotrichosis, and histoplasmosis).

We included studies that assessed the association between any kind of tobacco (eg, cigarette, pipe, cigar), cannabis (marijuana, hashish), crack cocaine, or opium smoking exposure and IFD. Timing of exposure was defined as current smokers or ever smokers (including current smokers and former smokers). In the case of studies defining the smoking group without mentioning whether the group included former smokers, we considered this group as current smokers in the analysis (ie, we considered former- and never-smoker patients combined as nonsmokers).

Studies were excluded if it was not possible to extract any measure of association (risk ratio [RR], hazard ratio [HR], or odds ratio [OR]) with its confidence interval [CI] or variance, and if it was not possible to recalculate any association measure based on raw data available in the study report. In the case of unclear or missing information, we attempted to contact study authors to obtain additional data.

In cases where overlap between studies was suspected, we avoided duplicate inclusion of data by selecting only the most complete report from each cohort.

Literature Searches and Study Selection

We searched MEDLINE (via PubMed) and Web of Science from inception onward using the strategy described in S1 Appendix. Articles that cited included studies were identified through PubMed and Google Scholar and assessed for inclusion. We also hand-searched the references of included articles. We included published and unpublished (eg, conference abstracts) studies without language restriction. Two review authors (A.P. and B.L.R.) independently conducted study selection. First, they excluded studies that were not related to IFD or smoking based on the titles and abstracts. Then they retrieved the full texts of relevant articles and evaluated them for inclusion.

Data Extraction

For each included study, the following data were extracted using a pro forma: (i) first author's last name, publication year, published/unpublished status, country, study period; (ii) study characteristics: study design, clinical setting, IFD case definition, inclusion criteria; (iii) exposure: definition of smoking timing (current, former, or never smoker), type of smoked product (tobacco, marijuana, crack cocaine, or opium); (iv) total number of participants, participant characteristics (mean or median age, sex (% males), comorbidities); (v) outcome: number of IFD cases; (vi) association between smoking and IFD: measure and strength of association (frequency of IFD in smokers vs nonsmokers, reported univariate and multivariate RR, HR, or OR with 95% CI and/or variance); (vii) assessment of confounding factors; (viii) blinding in outcome measurement, and (ix) data needed to assess study quality. Two review authors (A.P. and B.L.R.) independently conducted data extraction; one review author (J.F.C.) was solicited in case of disagreement.

Quality Assessment

We assessed risk of bias using a quality assessment tool based on the Joanna Briggs Institute checklist for cohort and case-control studies [23]. The main components of risk of bias were: selection of study participants and comparability of the groups, measurement of the exposure and outcomes, and identification and strategies to deal with confounding factors (S2 Appendix). For each study, the overall risk of bias was judged as high, low, or unclear, based on a simple combination of the main components of risk of bias (S2 Appendix).

Data Synthesis and Statistical Analysis

The RRs were used as the common measure of association across studies. HRs were considered as RRs. ORs were transformed into RRs using the formula $RR = OR/[(1- P_0) + (P_0 \times OR)]$, in which P_0 is the incidence of IFD in the nonsmoking group [24]. In cases where it was not possible to extract association measures from the report, we recalculated the OR and its variance using standard methods (S3 Appendix). Meta-analysis was performed using DerSimonian and Laird procedures for random-effects models. We pooled RR after logarithmic transformation. Forest plots were used to visually assess the RR estimates and

corresponding 95% CIs across studies. Heterogeneity was visualized through forest plots and statistically assessed by calculating the I^2 statistic.

Analyses were stratified by type of IFD (invasive mold diseases including invasive aspergillosis, cryptococcosis, PJP, dimorphic fungi, other), type of population (HIV/AIDS, hematologic malignancies, other), type of smoked product (tobacco, other) and timing of smoking exposure (current smokers, ever smokers), and study characteristics and epoch (published before vs after year 2002, which corresponds to first EORTC/MSG consensus criteria for IFD). Metaregression was performed to assess the effect of study-level variables on the association between smoking and IFD risk.

Publication bias was assessed through the visual inspection of funnel plots and by Egger test. Egger test detects funnel plot asymmetry by determining whether the intercept is significantly different from zero in a regression of the RR estimates against their standard error on a logarithmic scale. Sensitivity analysis was performed by repeating the meta-analysis on studies judged at low overall risk of bias. *P* values <.05 were regarded as significant, except in metaregression where a .10 cutoff was used. Statistical analysis involved the use of the *metan*, *metareg*, and *metabias* commands in Stata/SE version 15 (Stata Corp, College Station, TX, USA).

RESULTS

Literature Search

The literature search conducted on September 8, 2018, retrieved 1837 articles. Duplicates were removed, leaving 1697 potentially relevant articles. Of these, 1551 citations were excluded after screening based on titles, and 106 citations were excluded based on abstracts, leaving 40 articles for full-text assessment (Figure 1). Complementary searches identified ten additional references, for a total of 50 articles for full-text review. On full-text evaluation, 25 articles were excluded (S4 Appendix), leaving 25 studies for final inclusion in the systematic review and meta-analysis [11, 25–48].

Characteristics of Included Studies

The characteristics and main results of the included studies are shown in Tables 1 and 2. All but 1 study assessed tobacco smoking exposure, 2 assessed marijuana exposure in addition to tobacco of which one also assessed opium exposure, and 1 study assessed crack cocaine exposure. Sixteen studies compared current smokers to others, including former and never smokers; 3 studies compared ever smokers to never smokers. One study compared heavy smokers to others; this last study was considered as comparing current smokers to others. Five studies did not explicitly report the criteria used to define smokers; they were considered as current smokers in the analysis. Thirteen studies included people living with HIV, 7 included patients with hematological malignancies, and 5 included other populations.

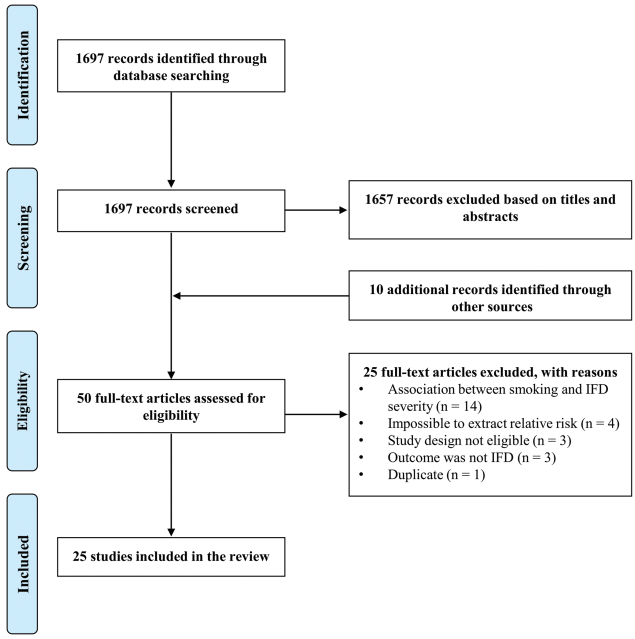

Figure 1. Flow of studies through the review. Abbreviation: IFD, invasive fungal disease.

The median number of participants per study was 240 (range 42–3455), for a total of 18 171 participants. The percentage of tobacco smokers ranged from 9% to 81%. Two studies reported the percentage of cannabis smokers (3% and 26%); 1 study reported the percentage of crack cocaine smokers (3%); 1 study reported the percentage of opium smokers (8%). The median number of IFD cases per study was 70 (range 8 to 538), for a total of 2527.

Quality assessment was impeded by poor reporting; judgment was difficult and items often scored as "unclear" (S5 Appendix). Twelve studies reported strategies to deal with confounding factors; only 9 studies reported adjusted risk measures for predefined confounders. Blinding to ascertain outcome was not explicitly reported in 22 of the included studies. Fourteen studies were judged at low overall risk of bias.

Risk of IFD for Smokers Compared With Nonsmokers

One study assessing 2 types of smoking exposure (tobacco and marijuana) and 2 types of IFD (mold and yeast diseases) was subdivided into 4 substudies [26]. Two studies assessing 2 types of IFD (PJP and histoplasmosis for one, PJP and cryptococcosis for the other) were subdivided into 2 substudies [27, 35]. One study assessing 3 types of smoking exposure (tobacco, marijuana, and opium) was subdivided into 3 substudies [28]. Thus, we included 32 study cohorts in the meta-analysis. Across study cohorts, RR varied from 0.29 to 9.11; 21 studies pointed to an increased risk of IFD in smokers (RR > 1). In

Table 1. Characteristics of Included Studies

Study	Publication Status	Country	Study Period	Study Design	Clinical Setting	IFD Case Definition	Inclusion Criteria	Exposure Type	Blinding
Yu 1986 [33].	Published	USA	1979–1982	Prospective Cohort Multicentric	University hospital	Invasive pulmonary aspergillosis (open lung biopsy or postmortem examination)	Patients in whom *Aspergillus* was isolated from sputum samples or the respiratory tract	Tobacco	No
Lowry 1989 [34].	Published	USA	1976–1985	Retrospective Case-control Multicentric	Population-based surveillance	*Blastomyces dermatitidis* infection (*B. dermatitidis* isolated from a culture specimen or identified in a tissue specimen)	*B. dermatitidis* infection, neighborhood controls (3:1) matched for sex, ethnicity, and age	Tobacco	No
Burns 1996 [35].	Published	USA	1990–1993	Prospective Cohort Multicentric	Outpatient	PJP and cryptococcosis	People with HIV	Tobacco	No
Conley 1996 [36].	Published	USA	1988–1992	Retrospective Cohort Multicentric	Outpatient	PJP	People with HIV among a cohort of homosexual and bisexual men	Tobacco	No
Chariyalertsak 1997 [28].	Published	Thailand	1993–1995	Prospective Case-control Monocentric	University hospital	*Talaromyces marneffei* infection (isolation from blood, skin biopsy specimen, or other clinical specimens on Sabouraud dextrose agar)	*T. marneffei* infection in people with HIV, AIDS controls (2:1) without *T. marneffei* infection	Tobacco, marijuana, opium	Yes
Olson 1997 [37].	Published	USA	1988–1995	Retrospective Case-control Monocentric	University hospital	Cryptococcosis	Cryptococcosis in people with HIV and CD4 cell count <100/mm^3, HIV controls (4:1) with CD4 cell count <100/mm^3	Tobacco	No
Galai 1997 [38].	Published	USA	1984–1993	Prospective Cohort Multicentric	Outpatient	PJP	People with HIV among a cohort of homosexual men	Tobacco	No
Hajjeh 1999 [11].	Published	USA	1992–1994	Retrospective Case-control Monocentric	Acute-care hospital	Cryptococcosis (isolation of *C. neoformans* from a normally sterile site)	Cryptococcosis in people with HIV, HIV controls (3:1) matched for CD4 cell count	Tobacco	No
Moorman 1999 [39].	Published	USA	1992–1995	Prospective Cohort Multicentric	Clinics	PJP	Ambulatory people with HIV	Tobacco	No
Leake 2000 [31].	Published	USA	1996–1997	Retrospective Case-control	Not reported	Acute symptomatic coccidioidomycosis: clinically compatible illness and laboratory criteria (culture, histopathology, serology, skin-test conversion)	Coccidioidomycosis patients ≥60 years, geographic matched controls[a] (1:1) ≥60 years	Tobacco	No
Woods 2000 [40].	Published	USA	1995–1997	Retrospective Case-control Multicentric	Population-based surveillance	Coccidioidomycosis (symptomatic and laboratory-confirmed)	Coccidioidomycosis in people with HIV, HIV controls (3:1) matched by county, sex, age, clinical status of HIV infection, and CD4 cell count	Tobacco	No
Dos Santos 2003 [46].	Published	Brazil	1999–2000	Retrospective Case-control Monocentric	University hospital	Chronic paracoccidioidomycosis: pathogen-positive histopathology, skin test or expectoration	Patients with chronic paracoccidioidomycosis (HIV excluded), controls without paracoccidioidomycosis matched for sex and selected from the same area	Tobacco	No
Miguez-Burbano 2003 [47].	Published	USA	1998–2000	Retrospective Case-control Monocentric	Outpatient	PJP	PJP in people with HIV, HIV controls matched for age, sex, ethnicity, socioeconomic level, and HIV status	Tobacco	No
Miguez-Burbano 2005 [48].	Published	USA	2001–2002	Prospective Case-control Monocentric	University hospital	PJP proven (*P. jirovecii* isolated in sputum with respiratory symptoms) or presumed	Adult people with HIV	Tobacco	No
Friedman 2006 [30].	Published	USA	1981–2000	Retrospective Case-control Monocentric	University hospital	Cryptococcosis (direct microscopy of CSF or biopsy material, culture or positive antigen test)	Cryptococcosis in people with HIV HIV controls (1:1) matched for age, sex, race, and date of AIDS diagnosis	Tobacco	No

Table 1. Continued

Study	Publication Status	Country	Study Period	Study Design	Clinical Setting	IFD Case Definition	Inclusion Criteria	Exposure Type	Blinding
Nacher 2009 [27].	Published	French Guiana	1996–2007	Retrospective Cohort Multicentric	General hospitals	Disseminated histoplasmosis, pneumocystosis, cryptococcal meningitis	People with HIV	Crack cocaine	No
Mukherjee 2011 [32].	Conference abstract	USA	1994–2009	Retrospective Cohort Monocentric	Clinic	Proven/probable IFD (modified EORTC/MSG 2008[b])	AML patients treated with cytarabine-based induction chemotherapy	Tobacco	No
Blum 2012 [41].	Published	Austria	NR	Prospective Cohort Monocentric	University hospital	Invasive mold disease (EORTC/MSG 2008)	Patients treated for hematological malignancies or underwent SOT	Tobacco	Yes
Sivgin 2013 [42].	Published	Turkey	2004–2010	Retrospective Case-control Monocentric	University hospital	Proven/probable invasive fungal pneumonia (EORTC/MSG 2008)	Allo-HCT recipients who were diagnosed with pneumonia (fungal or nonfungal) in the posttransplant period	Tobacco	No
Stanzani 2013 [43].	Published	Italy	2005–2012	Retrospective Cohort Monocentric	University hospital	Proven/probable invasive mold disease (EORTC/MSG 2008)	Consecutive hospital admissions of patients with hematological malignancies	Tobacco	No
Caira 2015 [26].	Published	Italy	2010–2012	Prospective Cohort Multicentric	Tertiary care hospital	Proven/probable invasive mold or yeast disease (EORTC/MSG 2008)	AML patients who received their first course of conventional intensive chemotherapy	Tobacco, marijuana	No
Garnica 2015 [44].	Published	Brazil	2007–2009	Prospective Case-control Multicentric	Tertiary care hospital	Proven/probable invasive fusariosis (EORTC/MSG 2008)	Patients with AML or MDS undergoing induction chemotherapy	Tobacco	Yes
Blount 2017 [45].	Published	USA	2008–2011	Prospective Cohort Monocentric	General hospital	Laboratory confirmed PJP by modified Giemsa staining of BAL fluid	Confirmed PJP in people with HIV, HIV controls who underwent bronchoscopy with BAL for suspected PJP (PJP ruled out)	Tobacco	No
Mehdi 2017 [25].	Published	USA	2004–2010	Retrospective Cohort Monocentric	Clinic	Proven/probable IFD (EORTC/MSG 2008)	Patients who received myeloablative allo-HCT	Tobacco Heavy smokers (>20 pack-years)	No
Kashef Hamadani 2018 [29].	Published	USA	2000–2017	Retrospective Case-control Monocentric	University hospital	*Cryptococcus* infection: positive culture or positive serum cryptococcal antigen from any specimen (pleural, CSF, blood, synovial, bronchoalveolar lavage, peritoneal fluid and tissue)	Patients with cryptococcal infection, controls (2:1) selected from the same hospital without cryptococcal infection matched for age, sex, and specimen collection date	Tobacco	No

Abbreviations: AML, acute myeloid leukemia; BAL, bronchoalveolar lavage; CSF, cerebrospinal fluid; EORTC/MSG, European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group; HCT, hematopoietic cell transplant; HIV, human immunodeficiency virus; IFD, invasive fungal disease; NR, not reported; MDS, myelodysplasia; PJP, *Pneumocystis jirovecii* pneumonia; SOT, solid organ transplantation.

[a]In this study, 2 control groups were selected (geographic controls and laboratory-negative controls). We arbitrarily considered geographic controls only.

[b]Modified EORTC/MSG 2008: Proven cases required confirmation of a fungal pathogen; probable IFD cases were defined using the modified criteria as immunocompromised host with clinically compatible illness including typical radiologic signs but without any definite proof of fungal pathogen (ie, host factor and clinical criteria, without mycological criteria).

Table 2. Main Results of Included Studies

Study	No. of Participants[a]	Participant Characteristics	No. of IFD Cases	IFD incidence by Smoking Status, No./Total (%)		Confounding Risk Factors in Multivariate Analysis	Published Measure of Association	Published Association Between Smoking and IFD (OR, HR, or RR with 95% CI)[b]	
				Smokers	Nonsmokers			Univariate	Multivariate
Yu 1986 [33].	72	Mean age: 57 years Neutropenia/leukemia: 24% Solid tumor/lymphoma: 29% Corticosteroid therapy: 43%	20	8/50 (16)	12/22 (54.5)	Neutropenia, immunosuppression, COPD, fever, and prior antibiotic usage	OR	Not reported	Not reported ($P < .05$)
Lowry 1989 [34].	86	Not reported	22	8/22 (36.4)	14/64 (21.9)	Not reported	OR	2 (.6–6.5)	Not reported
Burns 1996 [35].	3221	Mean age: 37 years Male: 83% Mean CD4 cell count: 295/mm^3 Current smokers: 57%	PJP: 387 Cryptococcosis: 47	PJP: 181/1843 (9.8) Cryptococcosis: 16/1843 (0.8)	PJP: 206/1378 (14.9) Cryptococcosis: 31/1378 (2.2)	CD4 count, age, gender, ethnicity, HIV risk behavior, prior opportunistic events, Karnofsky score, alcohol and drugs, ARV, PJP prophylaxis	HR	Not reported	Not reported
Conley 1996 [36].	232	Median age: 37 years Male: 100% Current smokers: 46%	36	12/106 (11.3)	24/126 (19)	Not reported	RR	0.6 (.3–1.19)	Not reported
Chariyalertsak 1997 [28].	240	Male: 83% CD4 cell count <50/mm^3: 55% CD4 cell count >100/mm^3: 8%	80	Cigarettes: 53/169 (31.4) Marijuana: 25/63 (39.7) Opium: 8/19 (42.1)	Cigarettes: 27/71 (38) Marijuana: 55/177 (31.1) Opium: 72/221 (32.6)	Not reported	OR	Cigarettes: 0.74 (.4–1.38) Marijuana: 1.46 (.77–2.76) Opium: 1.51 (.53–4.26)	Not reported
Olson 1997 [37].	85	CD4 cell count <100/mm^3	17	11/33 (33.3)	6/52 (11.5)	Not reported	OR	3.83 (1.1–14.2)	Not reported
Galai 1997 [38].	2499	Male: 100% Current smokers: 39%	538	184/973 (18.9)	354/1526 (23.2)	CD4 count, HIV-related medications	HR	Not reported	1.03 (.81–1.3)
Hajjeh 1999 [11].	581	Age: 495 participants 20–44 years (85%) Male: 91% CD4 cell count <100/mm^3: 521 (90%)	158	64/160 (40.0)	94/421 (22.3)	Fluconazole in the last 3 months, Outdoor building or landscaping	OR	1.8 (1.1–2.8)	1.9 (1.1–3.3)
Moorman 1999 [39].	1459	Age <36 years: 42% Male: 87% Current smokers: 39%	80	Not reported	Not reported	Not reported	HR	0.9 (.54–1.49)	Not reported
Leake 2000 [31].	180	Median age: 74 years Male: 56%	89	64/112 (57.1)	25/68 (36.8)	Duration of Arizona residence, age, sex, income category, congestive heart failure, chronic lung disease, cancer, and corticosteroid use	OR	2.4 (1.3–4.5)	3.7 (1.4–9.6)
Woods 2000 [40].	446	Median age: 38 years Male: 85% Median CD4 cell count: 54/mm^3	97	47/170 (27.6)	50/200 (25)	Not reported	OR	1.0 (.6–1.7)	Not reported
Dos Santos 2003 [46].	250	Mean age: 55 years Male: 98%	70	65/150 (43.3)	5/100 (5)	Not reported	OR	14.5 (5.6 – 37.7)	Not reported
Miguez-Burbano 2003 [47].	42	Male: 80% Median CD4 cell count: 358/mm3	15	15/34 (44.1)	0/8 (0)	Antiretroviral therapy	RR	∞ ($P = .001$)	1.56 ($P = .02$)
Miguez-Burbano 2005 [48].	520	Mean age: 43 years Male: 58% Mean CD4 cell count: 172/mm^3	65	53/328 (16.2)[c]	12/192 (6.3)[c]	Antiretroviral therapy, and viral load	OR	2.55 (1.27–4.77)	3.5 ($P = .000$)
Friedman 2006 [30].	146	Mean age: cases 46.3 years, controls 45.8 years	73 (65 meningitis, 6 pneumonia, 1 in blood, 1 in stool)	16/37 (43.2)	57/109 (52.3)	CD4 cell count, race	OR	0.57 (.24–1.32)	0.69 (.13–3.78)
Nacher 2009 [27].	2275	76 crack cocaine users (3.3%)	Disseminated histoplasmosis: 141 PJP: 94	Incidence rate per 100 person-years: Histoplasmosis 27.5 PJP 5.5	Incidence rate per 100 person-years: Histoplasmosis 3.2 PJP 1.5	CD4 and CD8 counts, HAART, sex, nationality, and age	HR	Not reported	Histoplasmosis: 5.4 (3–9.7) PJP: 5 (1.5–16.4)

Table 2. Continued

Study	No. of Participants[a]	Participant Characteristics	No. of IFD Cases	IFD incidence by Smoking Status, No./Total (%)		Confounding Risk Factors in Multivariate Analysis	Published Measure of Association	Published Association Between Smoking and IFD (OR, HR, or RR with 95% CI)[b]	
				Smokers	Nonsmokers			Univariate	Multivariate
Mukherjee 2011 [32].	604	Mean age: 58 years Male: 55% Current smokers: 24% Past smokers: 18% Marijuana users: 3%	97	67/180 (37.2)	30/424 (7.1)	Age, gender, WBC at diagnosis, AML etiology or classification, cytogenetics, BMT, day from diagnosis to induction, and achievement of complete remission	OR	Not reported	12.26 (5.28–28.46)
Blum 2012 [41].	234	Mean age: 49.4 years Male: 62.4% Hematological malignancies: 49.6% SOT recipients: 50.4%	18	5/44 (11.4)	13/190 (6.8)	No	Not reported	Not reported (P = .310)	Not reported
Sivgin 2013 [42].	73	Male: 56% AML: 47%	35	16/34 (47.1)	19/39 (48.7)	Not reported	OR	Not reported (P = .665)	Not reported
Stanzani 2013 [43].	3455	Median age: 52 years Male: 60% AML/MDS: 31% Lymphoma: 30%	114	33/994 (3.3)	81/2461 (3.3)	Not reported	Not reported	Not reported	Not reported
Caira 2015 [26].	744	Median age: 58 years Male: 49%	77 IFD (54 mold and 23 yeast infections)	Cigarettes smoker: mold infection 24/228 (10.5) yeast infection 8/228 (3.5) Marijuana smoker: mold infection 1/21 (4.8) yeast infection 1/21 (4.8)	Cigarette nonsmoker: mold infection 30/516 (5.8) yeast infection 15/516 (2.9) Marijuana nonsmoker: mold infection 53/723 (7.3) yeast infection 22/723 (3.0)	PS, house renovation, high exposure job, higher body weight, COPD, days of neutropenia, esophagitis, central venous catheter, posaconazole prophylaxis	OR	Not reported Cigarettes and mold: P = .02 Cigarettes and yeast: P = .57 Marijuana and mold: P = .66 Marijuana and yeast: P = .67	Not reported ("NS")
Garnica 2015 [44].	212	Not reported	8	4/29 (13.8)	4/183 (2.2)	Not reported	HR	9.11 (2.04–40.71)	Not reported
Blount 2017 [45].	81	Median age: 46 years Male: 89% Median CD4 cell count: 51/mm^3	47	19/34 (55.9)	26/43 (60.5)	Not reported	OR	Not reported (P = .69)	Not reported
Mehdi 2017 [25].	267	Antifungal prophylaxis: 100% Current smokers: 9% Former smokers: 21%	47	Not reported	Not reported	Not reported	HR	2.54 (.98–6.58)	Not reported
Kashef Hamadani 2018 [29].	167	Mean age: 55 years Male: 80% HIV patients: 38%	55	11/38 (28.9)	44/129 (34.1)	Headaches, respiratory symptoms, hyponatremia, lung disease, altered mental status, corticosteroids, diabetes mellitus, hypertension, and peripheral monocytosis	OR	Not reported (P = .75)	0.46 (.14–1.45)

Abbreviations: AML, acute myeloid leukemia; ART, antiretroviral therapy; BMT, bone marrow transplant; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HAART, highly active antiretroviral therapy; HCT, hematopoietic cell transplant; HIV, human immunodeficiency virus; HR, hazard ratio; IFD, invasive fungal disease; MDS, myelodysplasia; NS, not significant; OR, odds ratio; PJP, *Pneumocystis jirovecii* pneumonia; PS, performance status according to ECOG scale; RR, relative risk; SOT, solid organ transplant; WBC, white blood cell count.

[a]The number of participants per study corresponds of the number of people for whom smoking status is reported.

[b]In case of discrepancy in the study, we considered the most conservative value of association (ie, the weakest measure of association).

[c]Additional unpublished data provided by Dr. Miguez-Burbano.

meta-analysis, smokers had an increased risk of IFD compared with nonsmokers, with a pooled RR of 1.41 (95% CI 1.09–1.81; $P = .008$) (Figure 2). There was evidence of statistical heterogeneity of RRs across studies (I^2 81%, $P < .001$).

Stratified Analysis With Metaregression

The results of stratified analysis with metaregression are presented in Table 3, Figures 3, 4 and S6 Appendix. The pooled RR for the association between smoking and IFD seemed higher for dimorphic fungi (8 study cohorts, pooled RR 1.90 [1.11–3.24], $P = .02$, Figure 3), in patients with hematologic malignancies (10 study cohorts, pooled RR 1.86 [1.14–3.03], $P = .013$, Figure 4), for smoking exposures other than tobacco (6 study cohorts, pooled RR 2.11 [1.01–4.38], $P = .046$). However, metaregression showed that type of IFD, type of population, and type of smoking product did not significantly influence the association between smoking and IFD ($P > .10$ for all).

Stratified analysis by methodological variables showed higher pooled RR for the association between smoking and IFD in retrospective studies (16 study cohorts, pooled RR 1.93 [1.28–2.92], $P = .02$), in case-control studies (15 study cohorts, pooled RR 1.60 [1.15–2.22], $P = .005$), in studies with multivariate adjustment (10 study cohort, pooled RR 2.15 [1.27–3.64], $P = .004$), and in most recent studies (18 study cohorts, pooled RR 2.08 [1.37–3.15], $P = .001$). Metaregression confirmed that the risk of IFD was higher in retrospective than in prospective studies ($P = .04$), in studies with multivariate adjustment compared to studies with univariate analysis ($P = .06$), and in studies published after year 2002 ($P = .008$); other methodological characteristics did not alter the association between smoking and IFD ($P > .10$ for all).

Additional Analyses

The funnel plot is represented in Figure 5. Egger test provided evidence of a small study effect (bias 1.94, $P = .01$). Thus, we undertook a sensitivity analysis using the trim and fill method, which imputes potentially missing studies that cause funnel plot asymmetry. However, the trim and fill algorithm failed to perform study imputation, and the data remained unchanged.

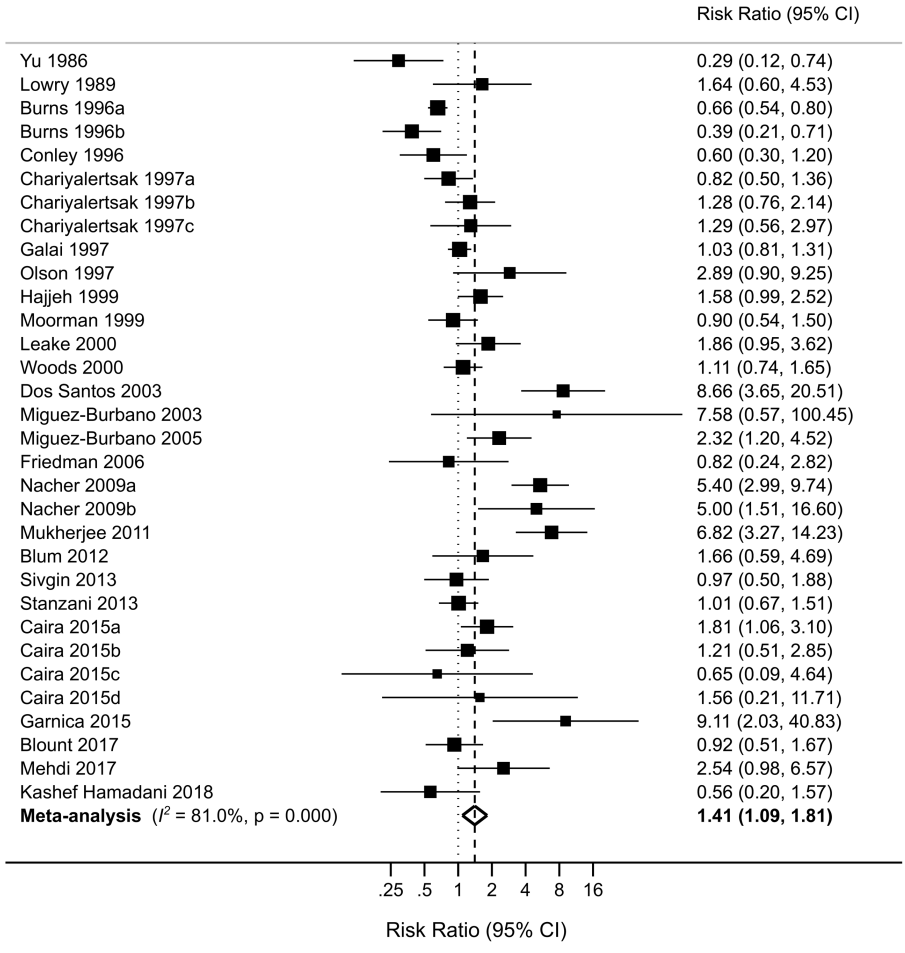

Figure 2. Relative risk of invasive fungal disease for smokers compared with nonsmokers. Squares indicate risk ratios (RR) from primary studies, with sizes reflecting the statistical weight of the study in random-effects meta-analysis. The horizontal lines indicate 95% CIs. Diamonds represent the summary RR and its 95% confidence interval. The vertical dashed line is aligned with the summary RR. The vertical dotted line shows the line of no effect (RR = 1). I^2 is the variation in RR attributable to heterogeneity rather than chance. Abbreviation: CI, confidence interval.

Table 3. Risk of IFD for Smokers Compared With Nonsmokers: Stratified Analysis With Metaregression

Stratified Analysis	No. of Study Cohorts	Pooled RR (95% CI)	Metaregression *P*-value
Target IFD			.49
Molds	6	1.25 (.63–2.47)	
Cryptococcosis	5	.93 (.44–2.00)	
PJP	8	1.08 (.75–1.55)	
Dimorphic fungi	8	1.90 (1.11–3.24)	
Other	5	2.05 (.88–4.75)	
Population			.52
HIV	17	1.21 (.90–1.63)	
Hematology	10	1.86 (1.14–3.03)	
Other population	5	1.36 (.45–4.14)	
Smoking exposure type			.26
Tobacco	26	1.29 (.99–1.68)	
Other	6	2.11 (1.01–4.38)	
Timing of exposure			.56
Current smokers	27	1.35 (1.02–1.77)	
Ever smokers	5	1.72 (.88–1.81)	
Study type			.35
Cohort	17	1.25 (.87–1.78)	
Case-control	15	1.60 (1.15–2.22)	
Study design			.04
Prospective	16	1.02 (.78–1.34)	
Retrospective	16	1.93 (1.28–2.92)	
Blinding			.81
No	27	1.39 (1.05–1.85)	
Yes	5	1.42 (.83–2.42)	
Adjustment method			.06
Univariate	22	1.15 (.88–1.51)	
Multivariate	10	2.15 (1.27–3.64)	
Study epoch			.008
Before 2002	14	.95 (.75–1.22)	
After 2002	18	2.08 (1.37–3.15)	
Overall	32	1.41 (1.09–1.81)	

Abbreviations: HIV, human immunodeficiency virus; IFD, invasive fungal disease; PJP, *Pneumocystis jirovecii* pneumonia; RR, risk ratio.

Following risk of bias assessment, 21 study cohorts were judged at low overall risk of bias. Sensitivity analysis showed that the association between smoking and IFD was of lower magnitude and no more significant in low risk of bias studies (RR 1.25 [0.96–1.64], $P = .098$) (S7 Appendix).

DISCUSSION

Smoking is a major modifiable risk factor for pulmonary, cardiovascular, and infectious morbidity, as well as overall mortality. This systematic review and meta-analysis identified an increased risk of IFD among smokers compared to nonsmokers, with a pooled RR of 1.41 (95% CI 1.09–1.81). Type of IFD, type of population, and type and timing of smoking exposure did not significantly influence the results.

In this systematic review, the risk of IFD was higher for invasive dimorphic fungal disease than for other IFD. These infections typically occur after inhalation of airborne conidia. Many noncomparative studies reported a high percentage of smokers among patients with dimorphic fungal infections. In studies investigating cases of paracoccidioidomycosis, between 50 and 100% of patients were smokers [46, 49–52]. In other dimorphic fungal infections such as histoplasmosis, coccidioidomycosis, and blastomycosis, between 27 and 61% of patients were smokers [53–55], which is much higher than estimates in the general population [54].

Despite evidence supporting a link between smoking and aspergillosis, the risk of invasive mold disease was not significantly increased in smokers, for a pooled RR of 1.25 (0.63–2.47). Many opportunistic molds are also common plant pathogens. Kagen demonstrated the presence of *Aspergillus* in 11 of 12 marijuana samples and showed that spores passed easily through contaminated cigarettes, and most marijuana smokers had precipitins against *Aspergillus* [13]. The association between marijuana smoking and invasive aspergillosis has been reported in several case reports in immunosuppressed patients [56–59] but also in immunocompetent patients [60]. In some cases, authors reported positive fungal cultures of samples of the patient's marijuana or tobacco [56–58].

Similarly, the meta-analysis showed no increased risk of PJP among smokers (1.08, 95% CI .75–1.55; Table 3). All included studies assessed the risk of PJP among people living with HIV, but even though CD4 cell count is an obvious confounder, only 1 study reported an adjusted measure of association. Some studies showed that tobacco and marijuana smoking were associated with a lower increase of CD4 cell count over time [61, 62]. It has also been suggested that cigarette smoking is associated with poor adherence to antiretroviral treatment [63], although this remains controversial [62]. Otherwise, Nieman et al showed that PJP occurred significantly earlier in smokers than in nonsmokers [64].

Although several studies have reported the association between smoking and oral candidiasis, we identified no study assessing the association between smoking and invasive candidiasis.

Smoking acts as a modifier of the immune system through several mechanisms, affecting both innate and adaptive responses, and both humoral and cell-mediated immunity. Immunosuppressive properties of smoke are mainly caused by the particulate phase of smoke. Cigarette smoking is associated with reduced interferon (IFN) response (IFN-β and IFN-γ), reduced antigen-presenting activity, reduced circulating immunoglobulins, reduced T-cell activity, reduced neutrophil activity, and inhibition of inflammatory cytokines [65, 66]. Smoking affects mainly the immune system of the respiratory tract, through altered mucociliary clearance, disruption of the respiratory epithelium, and inhibition of phagocytic and pro-inflammatory activities of alveolar macrophages [66]. Beyond the respiratory tract, smoking also increases the risk of extrapulmonary infections [7].

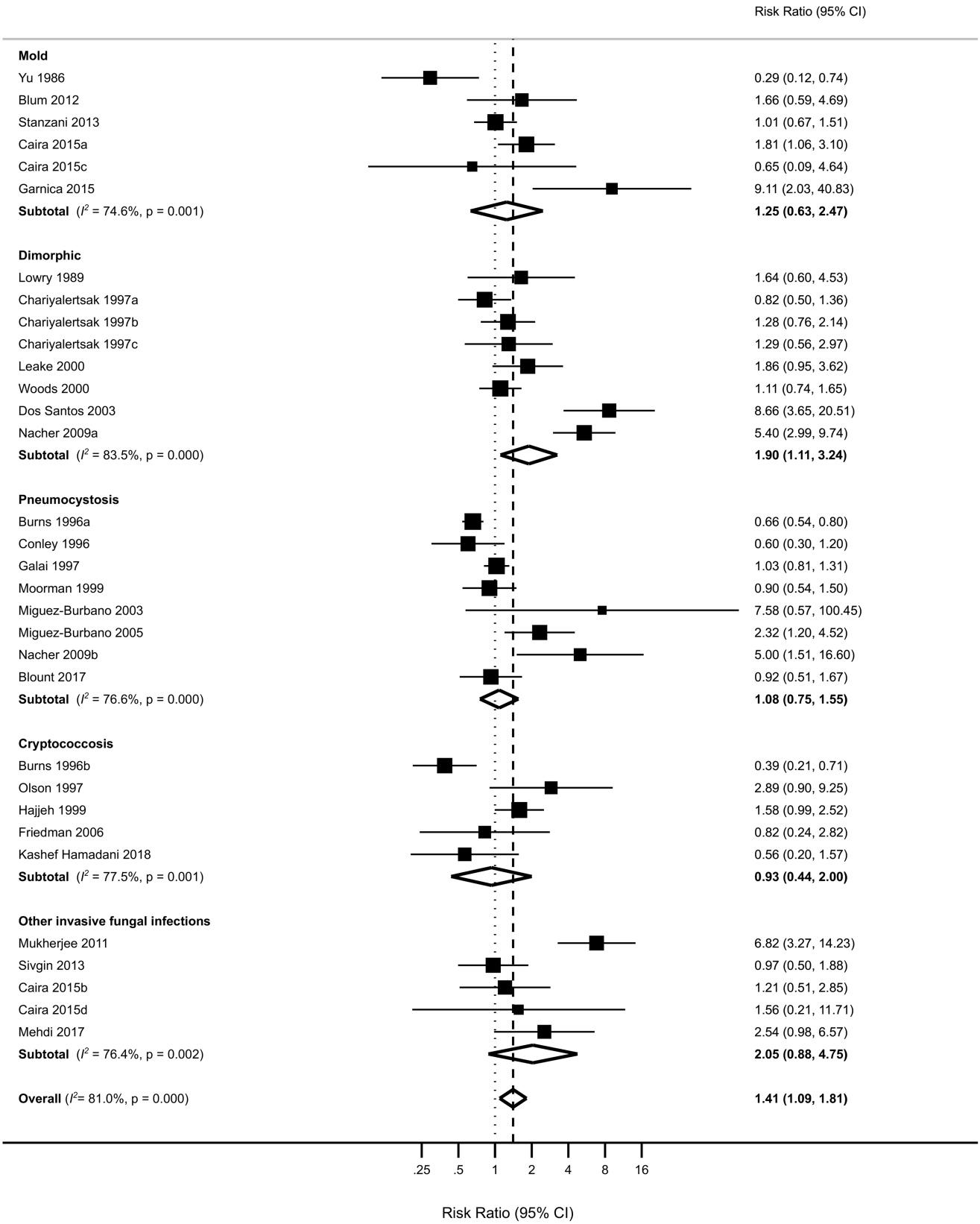

Figure 3. Stratified analysis by type of invasive fungal disease. Squares indicate risk ratios (RR) from primary studies, with sizes reflecting the statistical weight of the study in random-effects meta-analysis. The horizontal lines indicate 95% confidence intervals. Diamonds represent the summary RR and its 95%CI. The vertical dashed line is aligned with the summary RR. The vertical dotted line shows the line of no effect (RR = 1). I^2 is the variation in RR attributable to heterogeneity rather than chance. Abbreviation: CI, confidence interval.

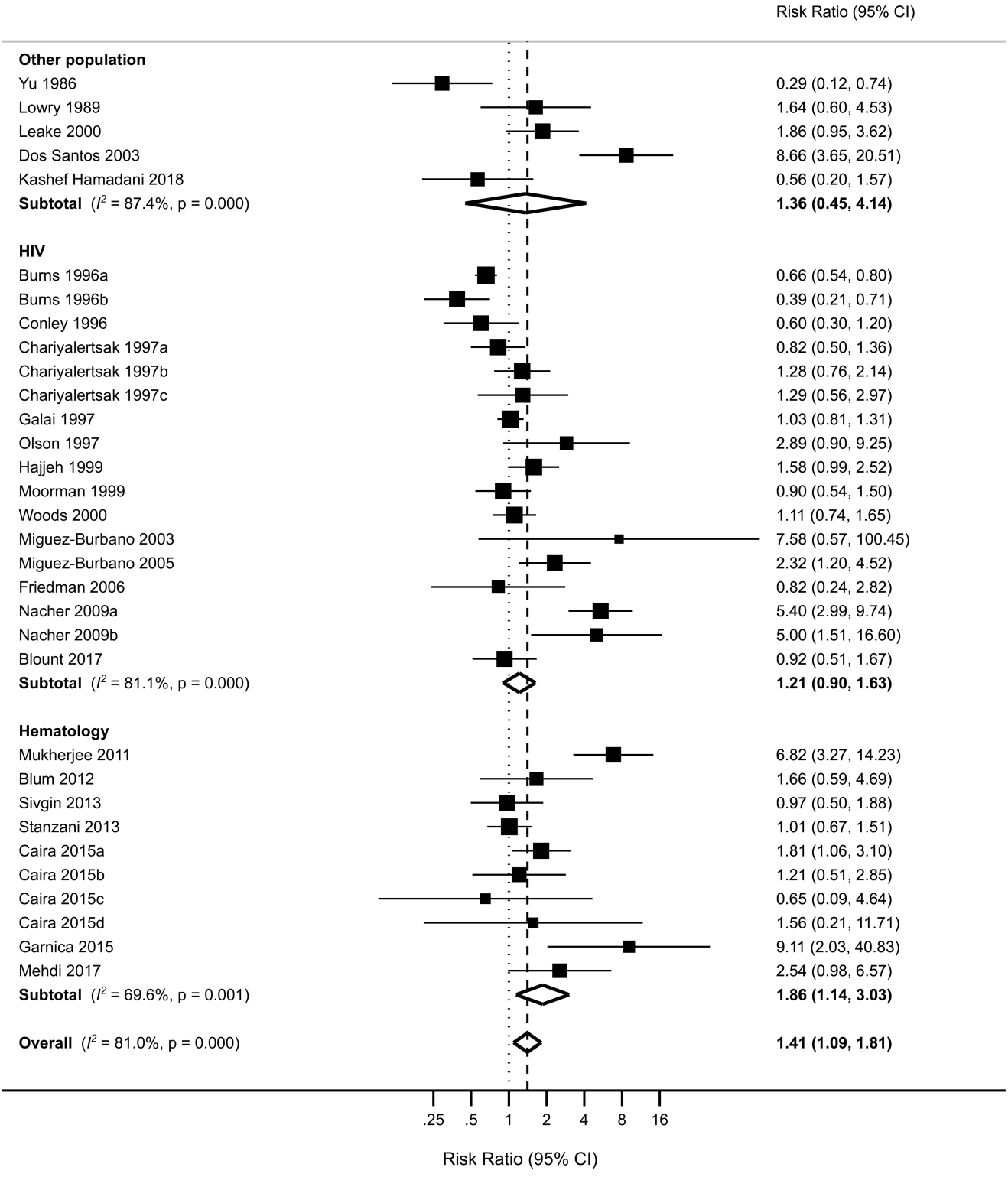

Figure 4. Stratified analysis by type of population. Squares indicate risk ratios (RR) from primary studies, with sizes reflecting the statistical weight of the study in random-effects meta-analysis. The horizontal lines indicate 95% CIs. Diamonds represent the summary RR and its 95% CI. The vertical dashed line is aligned with the summary RR. The vertical dotted line shows the line of no effect (RR = 1). *I2* is the variation in RR attributable to heterogeneity rather than chance. Abbreviation: CI, confidence interval.

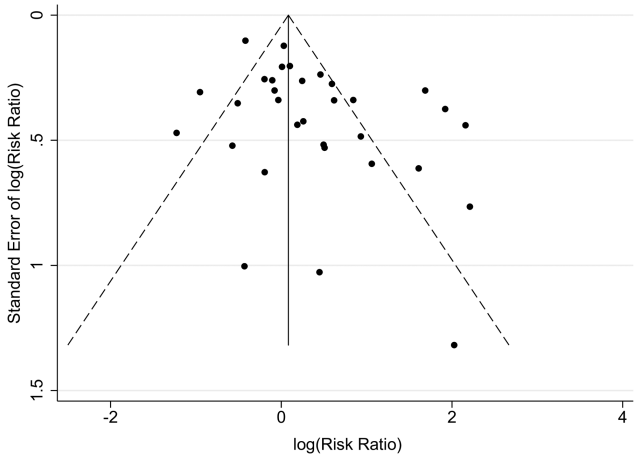

Figure 5. Funnel plot.

Otherwise, we identified evidence of more severe IFD in smokers compared to nonsmokers [67–70], with higher mortality rates, especially for PJP [68, 69], but such studies were very heterogeneous and were not in the scope of this review.

LIMITATIONS

The quality of individual studies included in the review was suboptimal and often challenging to evaluate because of poor reporting. Additional analyses suggested that the association between smoking and IFD might be driven by methodological weaknesses such as retrospective design, overall risk of bias, and small study effects. Because of heterogeneous study designs and corresponding association measures, we had to convert ORs into RRs, which potentially led to inflated risk estimates in the meta-analysis. We performed a meta-analysis combining cohort and case-control studies, and crude and adjusted RR estimates, which remains controversial. There was substantial statistical heterogeneity across studies. However, heterogeneity did not decrease in stratified analyses, suggesting that the factors we explored could not explain the observed variability across studies. Furthermore, except for retrospective design, multivariate adjustment, and epoch, metaregression did not identify factors explaining variability in RR across subgroups. A reason could be that, although robust, metaregression often lacks statistical power [71]. Our study did not allow us to explore a dose-response relationship between smoking and the risk of IFD, or the duration of exposure prior to IFD, because smoking exposure was not clearly measured and most of the time reported in a binary way. Also, because most studies only assessed tobacco smoking, we cannot rule out exposure to other smoking products in some patients, thus leading to potential residual confounding. Poor reporting also hampered the assessment of potential changes in IFD definitions over time (S8 Appendix). Another limitation is that known risk factors of IFD (eg, prolonged neutropenia and corticosteroid use) were often not precisely measured nor reported in the included studies. There is an urgent need for large and high-quality studies in order to establish whether the association between smoking and IFD is true or artifactual.

CONCLUSIONS

This review and meta-analysis showed an increased risk of IFD among smokers, with a stable association across a variety of clinical subgroups. This provides new evidence supporting the implementation of smoking cessation strategies, including tobacco, marijuana, opium, and crack cocaine, especially in people with HIV and patients with hematological malignancies who are already at higher risk for IFD.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

S1 Appendix. Search strategy. 1a. Search strategy in MEDLINE. 1b. Search strategy in Web of Science.

S2 Appendix. Quality assessment tool for primary studies.

S3 Appendix. Methods for calculating the odds ratio and its variance.

S4 Appendix. Studies excluded after full-text evaluation.

S5 Appendix. Study quality assessment.

S6 Appendix. Forest plots of stratified analyses. 6a. Stratified analysis by type of smoking exposure. 6b. Stratified analysis by timing of smoking exposure. 6c. Stratified analysis by study type: cohort vs. case-control. 6d. Stratified analysis by study design: prospective vs. retrospective. 6e. Stratified analysis by blinding criteria. 6f. Stratified analysis by adjustment method. 6g. Stratified analysis by epoch.

S7 Appendix. Sensitivity analysis: studies with low overall risk of bias.

S8 Appendix. Detailed diagnostic criteria for IFD across included studies.

Notes

Acknowledgments. The authors thank Dr Miguez-Burbano for having shared additional unpublished data.

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Webb BJ, Ferraro JP, Rea S, Kaufusi S, Goodman BE, Spalding J. Epidemiology and clinical features of invasive fungal infection in a US Health Care Network. Open Forum Infect Dis **2018**; 5:ofy187.
2. Bitar D, Lortholary O, Le Strat Y, et al. Population-based analysis of invasive fungal infections, France, 2001–2010. Emerg Infect Dis **2014**; 20:1149–55.
3. Garcia-Vidal C, Barba P, Arnan M, et al. Invasive aspergillosis complicating pandemic influenza A (H1N1) infection in severely immunocompromised patients. Clin Infect Dis **2011**; 53:e16–9.
4. Schaal JV, Leclerc T, Soler C, et al. Epidemiology of filamentous fungal infections in burned patients: a French retrospective study. Burns **2015**; 41:853–63.
5. Sipsas NV, Kontoyiannis DP. Occupation, lifestyle, diet, and invasive fungal infections. Infection **2008**; 36:515–25.
6. Nuorti JP, Butler JC, Farley MM, et al. Cigarette smoking and invasive pneumococcal disease. Active Bacterial Core Surveillance Team. N Engl J Med **2000**; 342:681–9.
7. Gold R. Epidemiology of bacterial meningitis. Infect Dis Clin North Am **1999**; 13:515–25, v.

8. Murray RL, Britton J, Leonardi-Bee J. Secondhand smoke exposure and the risk of invasive meningococcal disease in children: systematic review and meta-analysis. BMC Public Health **2012**; 12:1062.
9. Barr C, Friedmann P, Desjarlais D. Smoking is a significant factor in HIV-related oral candidiasis. J Dent Res **1998**; 77:155.
10. Versteeg PA, Slot DE, van der Velden U, van der Weijden GA. Effect of cannabis usage on the oral environment: a review. Int J Dent Hyg **2008**; 6:315–20.
11. Hajjeh RA, Conn LA, Stephens DS, et al. Cryptococcosis: population-based multistate active surveillance and risk factors in human immunodeficiency virus-infected persons. Cryptococcal Active Surveillance Group. J Infect Dis **1999**; 179:449–54.
12. Sopori M. Effects of cigarette smoke on the immune system. Nat Rev Immunol **2002**; 2:372–7.
13. Kagen SL. *Aspergillus*: an inhalable contaminant of marihuana. N Engl J Med **1981**; 304:483–4.
14. Verweij PE, Kerremans JJ, Voss A, Meis JF. Fungal contamination of tobacco and marijuana. JAMA **2000**; 284:2875.
15. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: a systematic review and meta-analysis. JAMA **2015**; 313:2456–73.
16. Mdege ND, Shah S, Ayo-Yusuf OA, Hakim J, Siddiqi K. Tobacco use among people living with HIV: analysis of data from demographic and health surveys from 28 low-income and middle-income countries. Lancet Glob Health **2017**; 5:e578–92.
17. Systematic Reviews: CRD's guidance for undertaking reviews in health care: 294.
18. Cochrane Handbook for Systematic Reviews of Interventions [Internet]. Available at: http://handbook-5-1.cochrane.org/. Accessed February 2018.
19. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. JAMA **2000**; 283:2008–12.
20. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med **2009**; 6:e1000100.
21. De Pauw B, Walsh TJ, Donnelly JP, et al; European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group; National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis **2008**; 46:1813–21.
22. Denis B, Guiguet M, de Castro N, et al; French Hospital Database on HIV National Agency for Research on AIDS and Viral Hepatitis, France CO4. Relevance of EORTC Criteria for the diagnosis of invasive aspergillosis in HIV-infected patients, and survival trends over a 20-year period in France. Clin Infect Dis **2015**; 61:1273–80.
23. Critical appraisal tools - JBI [Internet]. Available at: https://joannabriggs.org/ebp/critical_appraisal_tools. Accessed February 2018.
24. Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J. Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. JAMA **2007**; 298:2654–64.
25. Mehdi A, Rybicki L, Mossad S, et al. Impact of cigarette smoking on survival after myeloablative allogeneic hematopoietic stem cell transplantation and contribution of invasive fungal infection. Bone Marrow Transplant **2017**; 52:1665–7.
26. Caira M, Candoni A, Verga L, et al; SEIFEM Group (Sorveglianza Epidemiologica Infezioni Fungine in Emopatie Maligne). Pre-chemotherapy risk factors for invasive fungal diseases: prospective analysis of 1192 patients with newly diagnosed acute myeloid leukemia (SEIFEM 2010-a multicenter study). Haematologica **2015**; 100:284–92.
27. Nacher M, Adenis A, Hanf M, et al. Crack cocaine use increases the incidence of AIDS-defining events in French Guiana. AIDS **2009**; 23:2223–6.
28. Chariyalertsak S, Sirisanthana T, Supparatpinyo K, Praparattanapan J, Nelson KE. Case-control study of risk factors for *Penicillium marneffei* infection in human immunodeficiency virus-infected patients in northern Thailand. Clin Infect Dis **1997**; 24:1080–6.
29. Kashef Hamadani BH, Franco-Paredes C, McCollister B, Shapiro L, Beckham JD, Henao-Martínez AF. Cryptococcosis and cryptococcal meningitis: new predictors and clinical outcomes at a United States academic medical centre. Mycoses **2018**; 61:314–20.
30. Friedman GD, Fessel J, Udaltsova N, Hurley LB. Smoking and cryptococcosis in AIDS patients. Mycoses **2006**; 49:68–9.
31. Leake JA, Mosley DG, England B, et al. Risk factors for acute symptomatic coccidioidomycosis among elderly persons in Arizona, 1996–1997. J Infect Dis **2000**; 181:1435–40.
32. Mukherjee S, Fu AZ, Mansour M, et al. Cigarette smoking significantly increases the risk of invasive fungal disease (IFD) in acute myeloid leukemia (AML) patients undergoing induction chemotherapy. Blood **2011**; 118:1534–5.
33. Yu VL, Muder RR, Poorsattar A. Significance of isolation of *Aspergillus* from the respiratory tract in diagnosis of invasive pulmonary aspergillosis: results from a three-year prospective study. Am J Med **1986**; 81:249–54.
34. Lowry PW, Kelso KY, McFarland LM. Blastomycosis in Washington Parish, Louisiana, 1976–1985. Am J Epidemiol **1989**; 130:151–9.
35. Burns DN, Hillman D, Neaton JD, et al. Cigarette smoking, bacterial pneumonia, and other clinical outcomes in HIV-1 infection. Terry Beirn Community Programs for Clinical Research on AIDS. J Acquir Immune Defic Syndr Hum Retrovirol **1996**; 13:374–83.
36. Conley LJ, Bush TJ, Buchbinder SP, Penley KA, Judson FN, Holmberg SD. The association between cigarette smoking and selected HIV-related medical conditions. AIDS **1996**; 10:1121–6.
37. Olson PE, Earhart KC, Rossetti RJ, Newton JA, Wallace MR. Smoking and risk of cryptococcosis in patients with AIDS. JAMA **1997**; 277:629–30.
38. Galai N, Park LP, Wesch J, Visscher B, Riddler S, Margolick JB. Effect of smoking on the clinical progression of HIV-1 infection. J Acquir Immune Defic Syndr Hum Retrovirol **1997**; 14:451–8.
39. Moorman AC, Holmberg SD, Marlowe SI, et al. Changing conditions and treatments in a dynamic cohort of ambulatory HIV patients: the HIV outpatient study (HOPS). Ann Epidemiol **1999**; 9:349–57.
40. Woods CW, McRill C, Plikaytis BD, et al. Coccidioidomycosis in human immunodeficiency virus-infected persons in Arizona, 1994–1997: incidence, risk factors, and prevention. J Infect Dis **2000**; 181:1428–34.
41. Blum G, Eschertzhuber S, Auberger J, et al. Airborne fungus exposure prior to hospitalisation as risk factor for mould infections in immunocompromised patients. Mycoses **2012**; 55:237–43.
42. Sivgin S, Baldane S, Kaynar L, et al. Pretransplant iron overload may be associated with increased risk of invasive fungal pneumonia (IFP) in patients that underwent allogeneic hematopoietic stem cell transplantation (alloHSCT). Transfus Apher Sci **2013**; 48:103–8.
43. Stanzani M, Lewis RE, Fiacchini M, et al. A risk prediction score for invasive mold disease in patients with hematological malignancies. PLoS One **2013**; 8:e75531.
44. Garnica M, da Cunha MO, Portugal R, Maiolino A, Colombo AL, Nucci M. Risk factors for invasive fusariosis in patients with acute myeloid leukemia and in hematopoietic cell transplant recipients. Clin Infect Dis **2015**; 60:875–80.
45. Blount RJ, Daly KR, Fong S, et al. Effects of clinical and environmental factors on bronchoalveolar antibody responses to *Pneumocystis jirovecii*: a prospective cohort study of HIV+ patients. PLoS One **2017**; 12:e0180212.
46. dos Santos WA, da Silva BM, Passos ED, Zandonade E, Falqueto A. Association between smoking and paracoccidioidomycosis: a case-control study in the State of Espírito Santo, Brazil. Cad Saude Publica **2003**; 19:245–53.
47. Miguez-Burbano MJ, Burbano X, Ashkin D, et al. Impact of tobacco use on the development of opportunistic respiratory infections in HIV seropositive patients on antiretroviral therapy. Addict Biol **2003**; 8:39–43.
48. Miguez-Burbano MJ, Ashkin D, Rodriguez A, et al. Increased risk of *Pneumocystis carinii* and community-acquired pneumonia with tobacco use in HIV disease. Int J Infect Dis **2005**; 9:208–17.
49. Bellissimo-Rodrigues F, Machado AA, Martinez R. Paracoccidioidomycosis epidemiological features of a 1000-cases series from a hyperendemic area on the southeast of Brazil. Am J Trop Med Hyg **2011**; 85:546–50.
50. Costa AN, Benard G, Albuquerque AL, et al. The lung in paracoccidioidomycosis: new insights into old problems. Clinics (Sao Paulo) **2013**; 68:441–8.
51. Freitas RM, Prado R, Prado FL, et al. Pulmonary paracoccidioidomycosis: radiology and clinical-epidemiological evaluation. Rev Soc Bras Med Trop **2010**; 43:651–6.
52. Girardi FM, Scroferneker ML, Gava V, Pruinelli R. Head and neck manifestations of paracoccidioidomycosis: an epidemiological study of 36 cases in Brazil. Mycopathologia **2012**; 173:139–44.
53. Faiolla RC, Coelho MC, Santana Rde C, Martinez R. Histoplasmosis in immunocompetent individuals living in an endemic area in the Brazilian Southeast. Rev Soc Bras Med Trop **2013**; 46:461–5.
54. Dalcin D, Ahmed SZ. Blastomycosis in northwestern Ontario, 2004 to 2014. Can J Infect Dis Med Microbiol **2015**; 26:259–62.
55. Shekhel TA, Ricciotti RW, Blair JE, Colby TV, Sobonya RE, Larsen BT. Surgical pathology of pleural coccidioidomycosis: a clinicopathological study of 36 cases. Hum Pathol **2014**; 45:961–9.
56. Szyper-Kravitz M, Lang R, Manor Y, Lahav M. Early invasive pulmonary aspergillosis in a leukemia patient linked to *Aspergillus* contaminated marijuana smoking. Leuk Lymphoma **2001**; 42:1433–7.

57. Cescon DW, Page AV, Richardson S, Moore MJ, Boerner S, Gold WL. Invasive pulmonary aspergillosis associated with marijuana use in a man with colorectal cancer. J Clin Oncol **2008**; 26:2214–5.
58. Hamadeh R, Ardehali A, Locksley RM, York MK. Fatal aspergillosis associated with smoking contaminated marijuana, in a marrow transplant recipient. Chest **1988**; 94:432–3.
59. Marks WH, Florence L, Lieberman J, et al. Successfully treated invasive pulmonary aspergillosis associated with smoking marijuana in a renal transplant recipient. Transplantation **1996**; 61:1771–4.
60. Cary RM, Bragg C, Mukherjee J. Pleuritic chest pain and fluid levels on imaging in a heavy cannabis smoker. BMJ Case Rep **2015**; 2015 pii:bcr2014208064.
61. Montarroyos UR, Miranda-Filho DB, César CC, et al. Factors related to changes in CD4+ T-cell counts over time in patients living with HIV/AIDS: a multilevel analysis. PLoS One **2014**; 9:e84276.
62. Feldman JG, Minkoff H, Schneider MF, et al. Association of cigarette smoking with HIV prognosis among women in the HAART era: a report from the women's interagency HIV study. Am J Public Health **2006**; 96:1060–5.
63. Shuter J, Bernstein SL. Cigarette smoking is an independent predictor of nonadherence in HIV-infected individuals receiving highly active antiretroviral therapy. Nicotine Tob Res **2008**; 10:731–6.
64. Nieman RB, Fleming J, Coker RJ, Harris JR, Mitchell DM. The effect of cigarette smoking on the development of AIDS in HIV-1-seropositive individuals. AIDS **1993**; 7:705–10.
65. Arnson Y, Shoenfeld Y, Amital H. Effects of tobacco smoke on immunity, inflammation and autoimmunity. J Autoimmun **2010**; 34:J258–65.
66. Feldman C, Anderson R. Cigarette smoking and mechanisms of susceptibility to infections of the respiratory tract and other organ systems. J Infect **2013**; 67:169–84.
67. Rosenstein NE, Emery KW, Werner SB, et al. Risk factors for severe pulmonary and disseminated coccidioidomycosis: Kern County, California, 1995–1996. Clin Infect Dis **2001**; 32:708–15.
68. Kim SJ, Lee J, Cho YJ, et al. Prognostic factors of *Pneumocystis jirovecii* pneumonia in patients without HIV infection. J Infect **2014**; 69:88–95.
69. Fei MW, Kim EJ, Sant CA, et al. Predicting mortality from HIV-associated *Pneumocystis* pneumonia at illness presentation: an observational cohort study. Thorax **2009**; 64:1070–6.
70. Phillips P, Galanis E, MacDougall L, et al; British Columbia *Cryptococcus gattii* Study Group. Longitudinal clinical findings and outcome among patients with *Cryptococcus gattii* infection in British Columbia. Clin Infect Dis **2015**; 60:1368–76.
71. Hardy RJ, Thompson SG. Detecting and describing heterogeneity in meta-analysis. Stat Med **1998**; 17:841–56.