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How robust is the association between smoking and depression in adults? A meta-analysis using linear mixed-effects models☆,☆☆

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HIGHLIGHTS

- Eighty-five studies investigating adult smoking and depression were reviewed.
- Few studies reported background information like smoking levels or abstinence length.
- Current smokers were more likely to be depressed than former or never smokers.
- Current smokers had greater odds of incident depression at follow-up.
- Smoking was associated with depression across a variety of moderators.

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ABSTRACT

Introduction: Our objective was to use meta-analytic techniques to assess the strength of the overall relationship and role of potential moderators in the association between smoking and depression in adults.
Methods: Two popular health and social science databases (PubMed and PsycINFO) were systematically searched to identify studies which examined the association between adult smoking behavior and major depressive disorder (MDD) or depressive symptoms. A total of 85 relevant studies were selected for inclusion. Studies were analyzed using a linear mixed effects modeling package ("lme4" for R) and the Comprehensive Meta-Analysis program version 2.
Results: Multiple nested linear mixed-effects models were compared. The best fitting models were those that included only random study effects and smoking status. In cross-sectional studies, current smokers were more likely to be depressed than never smokers ($OR = 1.50$, $CI = 1.39–1.60$), and current smokers were more likely to be depressed than former smokers ($OR = 1.76$, $CI = 1.48–2.09$). The few available prospective studies, that used the requisite statistical adjustments, also showed smokers at baseline had greater odds of incident depression at follow-up than never smokers ($OR = 1.62$, $CI = 1.10–2.40$).
Conclusions: In cross-sectional studies, smoking was associated with a nearly two-fold increased risk of depression relative to both never smokers and former smokers. In the smaller set of prospective studies, the odds of subsequent depression were also higher for current than never smokers. Attesting to its robustness, the relationship between smoking and depression was exhibited across several moderators. Findings could help health care providers to more effectively anticipate co-occurring health issues of their patients. Several methodological recommendations for future research are offered.

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Contents

1. Introduction

An association between depression and smoking, two important public health problems, has been documented in many cross-sectional studies of adults. Recent estimates suggest that 30% of patients with major depressive disorder are current smokers, and smokers with a history of depression are twice as likely to be nicotine dependent as those without a depression history (Ziedonis et al., 2008). Nevertheless, the magnitude and consistency of the smoking-depression relationship is not well-characterized in adults. Some reviews claim that current or past depression increases the probability of smoking two-fold (e.g., Mendelsohn, 2012); others refer to "robust" or "well-established" associations, but without any quantitative indices of magnitude or variability (e.g., Halperin, Smith, Heiligenstein, Brown, & Fleming, 2010; Morrell & Cohen, 2006; Wadsworth, Moss, Simpson, & Smith, 2004). The relationship is better characterized in adolescents (e.g., Audrain-McGovern, Rodriguez, & Kassel, 2009; Wang, Fitzhugh, Turner, Fu, & Westerfield, 1996). In a meta-analysis of longitudinal studies of adolescent smoking, Chaiton, Cohen, O'Loughlin, and Rehm (2009) found a risk of 1.71 for smoking and subsequent depression and a risk of 1.41 between depression and future smoking. The empirical interest in adolescence is understandable as smoking tends to begin during that time (USDHHS, 2012), yet a focus on adolescence presents an incomplete picture. Adolescent quitting is relatively infrequent so depression levels of former smokers cannot be established – making case-control investigations unfeasible. Optimally, a systematic review would provide quantitative indices of risk of depression in former smokers, current smokers and non-smokers, something that is afforded by an analysis in adults.

Beyond estimating the magnitude of the overall association between depression and smoking, it is important to assess whether the risk varies with demographic and measurement moderators. For example, the association, on occasion, has been reported to be stronger in women than in men (e.g., Frederick, Frerichs, & Clark, 1988; Son, Markovitz, Winders, & Smith, 1997). Self-reports of depressive symptoms constitute the measure of depression in some studies, while others used validated clinical interviews. The degree to which the magnitude of the association varies according to measurement is unknown, and in neither case has a systematic review been conducted to assess whether these or other moderators significantly affect the size of the association. The present quantitative review used a state-of-the-art meta-analytic approach (based on linear mixed-effects models) to establish the overall magnitude and variability of the cross-sectional association between depression and smoking in adults and to assess whether moderator variables (e.g., sample characteristics like gender or measurement variables such as method of assessing depression) significantly affect the size of the association.

A linear mixed-effects model meta-analytic approach was adopted to address a complication often ignored in conventional meta-analyses. Studies in this area vary widely in types of measures and the variables that serve as covariates (such as age or ethnicity). Biases in estimation can occur when studies using different covariates are aggregated meta-analytically. Fortunately, linear mixed-effects models allow each potential moderator to be tested simultaneously for its independent contribution to the overall effect.

An additional goal was to assess the directionality and magnitude of the longitudinal relationship between smoking and depression in adults. However, because there is a relatively small set of prospective studies and/or their designs or measurement often are not optimal to draw causal inferences, a more conventional meta-analytic approach was used to address the third aim. In fact, a close examination of the available adult literature indicated that only an assessment of the longitudinal association between baseline smoking and the risks of subsequent depression could be conducted, as too few studies on the association between baseline depression and subsequent smoking status using adult samples were available.

In sum, the aims of our review were:

Research Aim 1: To examine the overall magnitude of the association between smoking and depression using linear mixed-effects models meta-analytic techniques.

Research Aim 2: To investigate how moderators influence the magnitude of the association between smoking and depression.

Research Aim 3: To examine the magnitude of the prospective association between smoking and depression.

2. Methods

2.1. Selection process and inclusion criteria

We systematically searched the health and social science databases PubMed and PsycINFO for studies published from the earliest catalogued date in the database through December 2012 that examined the association between smoking behavior and major depressive disorder (MDD) or depressive symptoms. The terms for smoking used in the search were as follows: *smoking*, *cigarettes*, and *tobacco* while the terms for depression were: *depression*, *major depressive disorder*, *depressive symptoms*, and *mood*. Each smoking term was paired with each depression term for at least one search, ensuring that the maximum number of studies was

initially identified. Additionally, we identified potential articles that were referenced by the study being reviewed in order to identify those not indexed in the databases. Searching with these terms, removing duplicate studies, and retrieving non-indexed articles produced a total of 10,832 cross-sectional studies and 1,657 prospective studies for further review.

Multiple waves of review utilizing specific inclusion/exclusion criteria produced the final sample of studies included in the analyses (see Fig. 1).

First, we set search limits so that studies were eliminated if a) they contained only animal models of smoking and no human participants, b) had been published in a language other than English, or c) included only adolescent participants younger than 18 years. Second, we excluded studies that only measured smokeless tobacco use (as it is unclear whether the association is similar for cigarettes and smokeless tobacco products) or whose primary outcome was smoking cessation (as cessation may not generalize more broadly to the smoking-depression relationship and has already been the subject of prior meta-analytic review, e.g. Hitsman et al., 2013). Finally, we omitted studies that: a) utilized a non-validated measure of MDD or depressive symptoms ($N = 2$), b) only compared "ever smokers" to nonsmokers in analyses ($N = 3$), c) utilized a reference group other than never smokers (e.g., combined "former smokers" and never smokers in analyses)

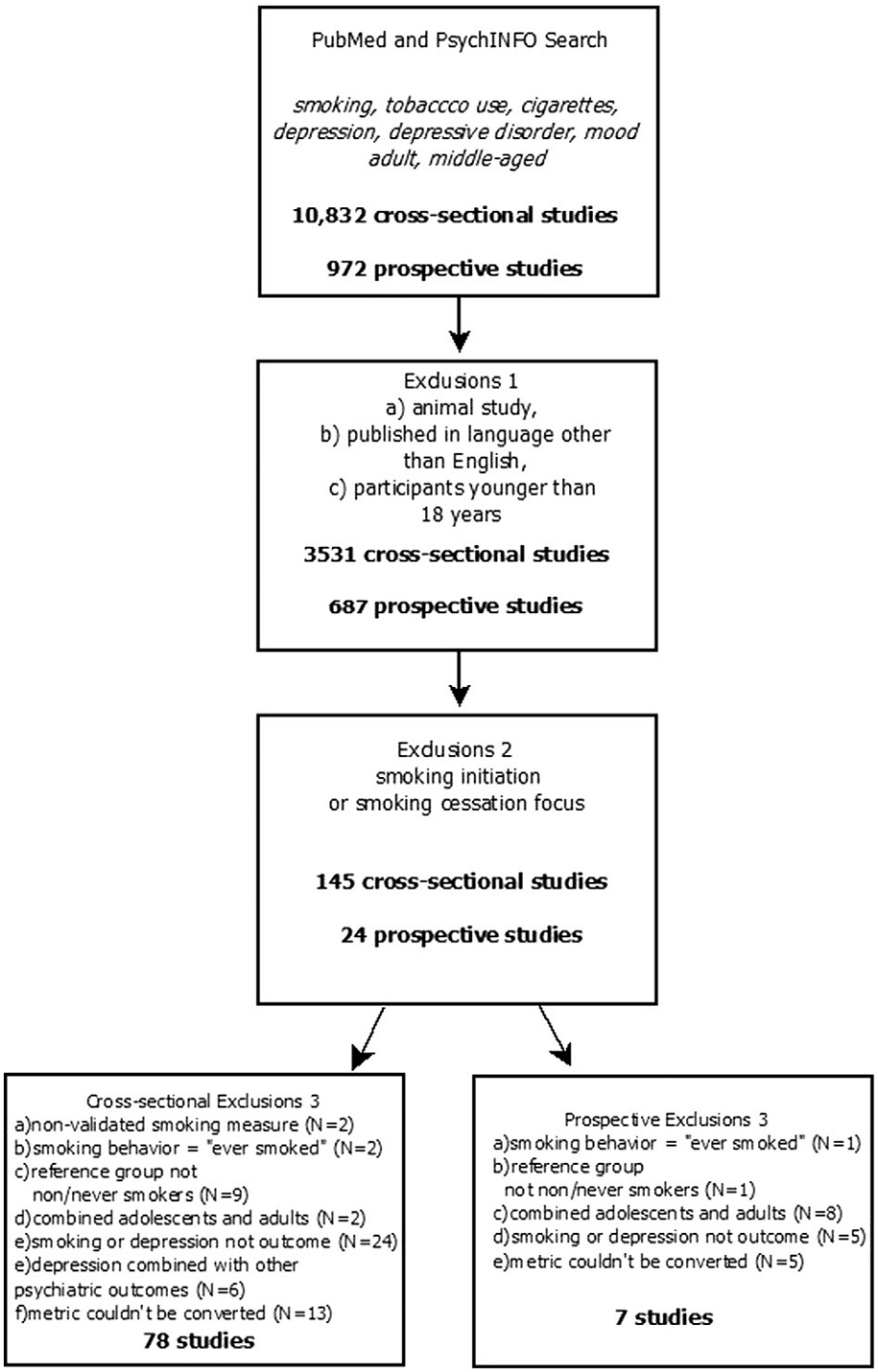

Fig. 1. Flow chart of study selection process.

Table 1
Cross-sectional study characteristics.

Study	Sample Description	Sample Size/Age*	Percent Female	Percent Current Smoker	Percent Former Smoker	Percent Never Smoker	Depression Measure and Use	Effect Size (Odds Ratio and 95% Confidence Interval)
Acierno, Kilpatrick, Resnick, Saunders, & Best, 1996	U.S. female national sample	$N = 3.006/M = 46.10$	100%	24.10%	-	75.90%	*DSM-IV*, clinician diagnosis	$OR = 1.64$, $CI = 1.11–2.43$
Almeida & Pfaff, 2005	Australian general practice patients	$N = 1,030/M = 72.10$	57.20%	5.63%	48.35%	46.01%	*Center for Epidemiological Disease Studies* (*CES-D*), dimensional	*current* $OR = 1.75$, $CI = 1.06–2.87$ *former* $OR = 1.24$, $CI = 0.84–1.81$
Al-Subaie, 1998	Saudi university students	$N = 79/M = 21.80$	94.20%	16.47%	-	83.53%	*Hospital Anxiety and Depression Scale* (*HADS*), categorical	$OR = 1.41$, $CI = 1.11–1.78$
Allgöwer, Wardle, & Steptoe, 2001	European university students	$N = 5,529/M = 21.6$	62.18%	22.00%	-	78.00%	*Beck Depression Inventory* (*BDI*), categorical	$OR = 1.39$, $CI = 1.15–1.68$
Anda, Williamson, & Escobedo, 1990	National Health and Nutrition Examination Study (U.S.)	$N = 2,963/M = 24–74$ years	56.50%	39.39%	19.30%	41.31%	*CES-D*, categorical	*current* $OR = 2.02$, $CI = 1.64–2.48$ *former* $OR = 1.02$, $CI = 0.76–1.35$
Araya, Rojas, Fritsch, Acuña, & Lewis, 2001	Community members in Santiago, Chile	$N = 3,870/16–64$ years	33.00%	38.00%	11.40%	50.60%	*Clinical Interview Schedule-Revised* (*CIS-R*), clinician diagnosis	*current* $OR = 1.43$, $CI = 1.07–1.91$ *former* $OR = 0.79$, $CI = 0.49–1.27$
Benjet, Wagner, Borges, & Medina-Mora, 2004	Community-based sample in Mexico	$N = 1,935/18–64$ years	58.50%	25.43%	21.65%	52.92%	*CES-D*, categorical	*current*$OR = 1.24$, $CI = 0.91–1.69$ *former* $OR = 0.95$, $CI = 0.67–1.34$
Brown, Madden, Palenchar, & Cooper-Patrick, 2000	U.S. sample of primary care patients	$N = 526/18$ plus years	61.80%	38.40%	33.80%	44.70%	*CES-D*, categorical	*current* $OR = 1.67$, $CI = 0.86–3.23$ *former* $OR = 2.89$, $CI = 1.18–7.07$
Castilla-Puentes et al., 2008	Emergency department patients in Latin America	$N = 1,505/-$	-	-	-	-	*DSM-IV*, clinician diagnosis	$OR = 2.38$, $CI = 1.42–3.98$
Chwastiak, Rosenheck, & Kazis, 2011	Large Survey of Veteran Enrollees (U.S.)	$N = 501,161/M = 64.1$	51.00%	26.2%	-	73.8%	*ICD-9*, clinician diagnosis	$OR = 0.95$, $CI = 0.91–0.99$
Cooper, Rodríguez de Ybarra, Charter, & Blow, 2011	Hispanic college students from El Paso, TX/ Ciudad Juarez, Mexico	$N = 174/M = 19.6$	56.90%	42.53%	-	57.47%	*Primary Care Evaluation of Mental Disorders* (*PRIME-MD*), dimensional	$OR = 1.57$, $CI = 0.91–2.71$
Cranford, Eisenberg, & Serras, 2009	U.S. university students	$N = 5,021/-$	-	15.00%	-	85.00%	*Patient Health Questionnaire* (*PHQ*), categorical	$OR = 1.60$, $CI = 1.10–2.33$
Daniel, Cargo, Lifshay, & Green, 2004	Native American (First Nation) sample	$N = 187/M = 44.10$	66.80%	48.13%	-	51.87%	*Brief Screen for Depression* (*BSD*), dimensional	$OR = 2.43$, $CI = 1.43–4.12$
Dean, Sugar, Hellemann, & London, 2011	Los Angeles young adult sample	$N = 64/M = 20.00$	54.69%	40.63%	-	59.38%	*CES-D*, dimensional	$OR = 1.39$, $CI = 0.56–3.45$
Döme et al., 2005	Hungarian mental health outpatient sample	$N = 5,595/-$	55.30%	35.42%	-	64.58%	*DSM-IV*, clinician diagnosis	$OR = 1.34$, $CI = 1.14–1.58$
Edwards et al., 2006	North West England population survey	$N = 15,465/M = 46.45$	-	-	-	-	*General Health Questionnaire* (*GHQ*), categorical	$OR = 1.27$, $CI = 1.18–1.36$
Fishbain et al., 2007	U.S. sample of chronic pain patients	$N = 221/M = 41.1$	42.00%	36.65%	-	63.35%	*DSM-IV*, clinician diagnosis	$OR = 1.71$, $CI = 0.92–3.19$
Frerichs, Aneshensel, Clark, & Yokopenic, 1981	Los Angeles community survey	$N = 809/-$	61.06%	43.88%	23.49%	56.12%	*CES-D*, dimensional	$OR = 1.29$, $CI = 1.00–1.66$
Gallicchio, Schilling, Miller, Zacur, & Flaws, 2007	Post-menopausal sample in the U.S.	$N = 634/45–54$ years	100%	9.15%	38.80%	51.89%	*CES-D*, categorical	*current* $OR = 2.38$, $CI = 1.22–4.64$ *former* $OR = 0.89$, $CI = 0.57–1.39$
Gravely-Witte, Stewart, Suskin, & Grace, 2009	U.S. coronary artery disease outpatients	$N = 1498/M = 66.99$	28.60%	9.88%	32.44%	57.68%	*BDI*, dimensional	*current* $OR = 1.04$, $CI = 1.02–1.06$ *former* $OR = 1.02$, $CI = 1.00–1.04$
Güleç et al., 2005	Turkish military medical school students	$N = 684/M = 21.10$	3.80%	32.60%	-	65.06%	*BDI*, dimensional	$OR = 2.18$, $CI = 1.62–2.92$
Haas, Eng, Dowling, Schmitt, & Hall, 2005	U.S. sample of frail older adults	$N = 1,064/M = 77.68$	69.00%	6.95%	14.85%	75.66%	*Geriatric Depression Scale-Short Form* (*GDS-SF*), dimensional	*current* $OR = 0.65$, $CI = 0.42–1.00$ *former* $OR = 0.60$, $CI = 0.44–0.82$
Haire-Joshu, Heady, Thomas, Schechtman, & Fisher, 1994	Diabetic patients in the U.S.	$N = 186/M = 42.50$	54.80%	44.62%	-	55.38%	*BDI*, dimensional	$OR = 2.73$, $CI = 1.60–4.65$
Halperin et al., 2010	Sample of university health center users (college students)	$N = 2,091/18$ plus years	65.70%	-	-	-	*BDI*, categorical	$OR = 1.68$, $CI = 1.35–2.10$
Heffernan, O'Neill, & Moss, 2010	U.S. North Eastern university students	$N = 40/M = 25.2$	80.00%	45.00%	-	55.00%	*HADS*, dimensional	$OR = 2.45$, $CI = 0.78–7.70$
Holtrop et al., 2010	Medicaid-eligible pregnant women in Michigan	$N = 2,159/18$ plus years	100%	26.22%	17.00%	56.79%	*Edinburgh Postnatal Depression Screen*, categorical	*current* $OR = 2.05$, $CI = 1.66–2.53$ *former* $OR = 1.43$, $CI = 1.11–1.85$
Hooten, Shi, Gazelka, & Warner, 2011	Sample of chronic pain patients at Mayo Clinic	$N = 1,241/M = 44.5$	76.56%	25.22%	23.69%	51.09%	*CES-D*, dimensional	*current* $OR = 2.15$, $CI = 1.68–2.76$ *former* $OR = 1.18$, $CI = 0.92–1.52$
Ho-Yen, Bondevik, Eberhard-Gran, & Bjorvatn, 2007	Postnatal Nepalese sample	$N = 426/M = 24.50$	100%	4.24%	-	95.76%	*Edinburgh Postnatal Depression Screen*, categorical	$OR = 5.60$, $CI = 1.21–25.87$

(continued on next page)

Table 1 (*continued*)

Study	Sample Description	Sample Size/Age*	Percent Female	Percent Current Smoker	Percent Former Smoker	Percent Never Smoker	Depression Measure and Use	Effect Size (Odds Ratio and 95% Confidence Interval)
Husky, Mazure, Paliwal, & McKee, 2008	Population-based sample in U.S.	$N = 43.093$/-	52.10%	23.22%	19.50%	56.00%	*Alcohol Use Disorders and Associated Disabilities Interview Schedule (AUDADIS)*, clinician diagnosis	*current OR* = 2.31, *CI* = 2.08–2.57 *former OR* = 1.49, *CI* = 1.29–1.72
Johnson & Breslau, 2006	Community-based U.S. sample	$N = 4,858$/53–54 years	-	17.6%	-	82.4%	*Composite International Diagnostic Interview (CIDI)*, clinician diagnosis	*OR* = 1.40, *CI* = 1.09–1.79
Kabali et al., 2011	Sample of HIV patients	$N = 462$/21–71 years	23.00%	77.49%	-	22.51%	*CES-D*, dimensional	*OR* = 2.04, *CI* = 1.29–3.22
Kao, Liu, Cheng, & Chou, 2011	Taiwanese mental health outpatients	$N = 95/M = 35.87$	53.00%	65.26%	-	34.74%	*BDI*, dimensional	*OR* = 2.36, *CI* = 1.07–5.19
Kenney, Holahan, North, & Holahan, 2006	National U.S. sample	$N = 2,593/M = 46.37$	51.00%	-	-	-	*BDI*, categorical	*OR* = 2.14, *CI* = 1.35–3.38
Khaled, Bulloch, Exner & Patten, 2009	Population based sample in Canada	$N = 10,236$/-	-	23.93%	39.28%	36.79%	*CIDI*, clinician diagnosis	*current OR* = 2.99, *CI* = 2.71–3.29 *former OR* = 1.37, *CI* = 1.24–1.51
Kick & Cooley, 1997	U.S. internal medicine outpatients	$N = 370/M = 50.10$	65.14%	32.97%	-	67.03%	*Sheehan Patient-Rated Anxiety Scale*, dimensional	*OR* = 1.05, *CI* = 1.02–1.08
Klonoff & Landrine, 2001	U.S. community sample of Black adults	$N = 520/M = 28.20$	53.27%	19.62%	20.00%	60.38%	*Symptom Checklist-58*, dimensional	*OR* = 0.79, *CI* = 0.52–1.18
Lam et al., 2004	Elderly Chinese in Hong Kong	$N = 56,167$/65 years or older	66.70%	9.45%	18.90%	71.65%	*Geriatric Depression Scale*, categorical	*current OR* = 1.51, *CI* = 1.33–1.72 *former OR* = 1.25, *CI* = 1.12–1.39
Launay et al., 2010	National survey of French teachers	$N = 6633/M = 44.13$	62.40%	20.23%	27.80%	51.97%	*CIDI*, clinician diagnosis	*current OR* = 1.40, *CI* = 1.16–1.68 *former OR* = 0.91, *CI* = 0.75–1.10
Leventhal et al., 2010	U.S. National Epidemiologic Survey on Alcohol and Related Conditions	$N = 41,654$/18 plus years	-	26.13%	-	73.87%	*AUDADIS-IV*, categorical	*OR* = 1.97, *CI* = 1.83–2.12
Lopes et al., 2002	Mental health outpatients in Brazil	$N = 330/M = 35.10$	66.20%	25.76%	23.03%	50.91%	*Structured Clinical Interview for DSM-IV (SCID)*, clinician diagnosis	*current OR* = 1.24, *CI* = 0.57–2.71 *former OR* = 1.03, *CI* = 0.44–2.40
Luk & Tsoh, 2010	Community sample of Chinese Americans	$N = 1393/M = 40.50$	43.80%	53.40%	7.30%	39.90%	*CES-D*, dimensional	*current OR* = 1.30, *CI* = 1.07–1.59 *former OR* = 1.66, *CI* = 1.13–2.43
Lyvers, Thorberg, Dobie, Huang, & Reginald, 2008	Community-based sample in Australia	$N = 219/M = 28.11$	60.30%	43.84%	-	56.16%	*Depression Anxiety Stress Scale (DASS)*, dimensional	*OR* = 2.04, *CI* = 1.25–3.33
Massak & Graham, 2008	Canadian national sample	$N = 14,063$/-	57.27%	25.90%	26.40%	47.70%	*CIDI*, clinician diagnosis	*OR* = 1.89, *CI* = 1.69–2.11
Murphy et al., 2003	Canadian population survedy	$N = 3,600$/-	-	60.22%	-	39.78%	*DPAX*, clinician diagnosis	*current OR* = 1.55, *CI* = 0.77–3.12 *former OR* = 1.90, *CI* = 1.12–3.21
Mykletun, Overland, Aarø, Liabø, & Stewart, 2008	Population-based sample in Norway	$N = 60,814$/20–89 years	52.70%	29.00%	29.00%	42.00%	*HADS*, categorical	*current OR* = 1.10, *CI* = 0.99–1.22 *former OR* = 1.03, *CI* = 0.93–1.14
Nakata et al., 2008	Japanese community-based sample	$N = 2,770/M = 44.63$	33.60%	46.46%	11.37%	42.17%	*CES-D*, categorical	*current OR* = 1.65, *CI* = 1.30–2.09 *former OR* = 1.10, *CI* = 0.79–1.53
Parchman, 1991	U.S. family practice patients	$N = 704$/-	-	32.90%	-	67.10%	*BDI*, categorical	*OR* = 1.77, *CI* = 1.19–2.62
Pasco et al., 2008	Australian population-based sample	$N = 1,043$/-	100%	32.79%	-	99.67%	*SCID*, clinician diagnosis	*OR* = 1.02, *CI* = 0.84–1.24
Pomerleau, Zucker, & Stewart, 2003	National U.S. sample	$N = 931$/18–45 years	100%	39.26%	22.75%	37.99%	*CES-D*, dimensional	*current OR* = 1.75, *CI* = 1.34–2.28 *former OR* = 1.58, *CI* = 1.16–2.16

Pritchard, 1994	Pregnant women in Scotland	*N* = 395/-	100%	30.1%	-	69.9%	*HADS*, categorical	*OR* = 2.65, *CI* = 1.14–6.15
Rabois & Haaga, 1997	Community-based U.S. sample	*N* = 87/*M* = 29.63	-	47.13%	-	52.87%	*Inventory to Diagnose Depression (IDD)*, dimensional	*OR* = 2.11, *CI* = 0.75–5.94
Ridner, Staten, & Danner, 2005	U.S. university students	*N* = 895/18–24 years	61.00%	28.04%	-	71.96%	*CES-D*, categorical	*OR* = 1.34, *CI* = 1.03–1.74
Roberts, Glod, Kim, & Hounchell, 2010	U.S. North East university students	*N* = 428/18 plus years	63.00%	32.00%	-	68.00%	*BDI*, categorical	*OR* = 5.02, *CI* = 3.06–8.23
Salive & Blazer, 1993	Community-based U.S. sample	*N* = 3960/65 plus years	-	8.84%	13.03%	31.97%	*CES-D*, categorical	*current OR* = 4.14, *CI* = 0.93–18.36 *former OR* = 1.04, *CI* = 0.78–1.39
Smith, Colwell, Ahn, & Ory, 2012	Texas community sample	*N* = 593/*M* = 60.5	100%	16.69%	23.95%	59.36%	*CES-D*, dimensional	*OR* = 0.83, *CI* = 0.75–0.93
Strine et al., 2008	U.S. population-based sample	*N* = 217,379/-	-	-	-	-	*PHQ*, categorical	*OR* = 2.10, *CI* = 1.74–2.53
Takeuchi, Nakao, & Yano, 2004	Japanese workers	*N* = 1,060/*M* = 35.00	31.10%	17.17%	9.53%	73.30%	*DSM-IV*, clinician diagnosis	*current OR* = 2.54, *CI* = 1.23–5.27 *former OR* = 1.88, *CI* = 0.69–5.09
Tamburrino, Lynch, Nagel, Stadler, & Pauling, 1994	Female U.S. family practice patients	*N* = 695/*M* = 45.00	100%	28.06%	-	71.94%	*CES-D*, categorical	*OR* = 2.24, *CI* = 1.68–3.00
Tan et al., 2011	Sample of pregnant women from Washington D.C.	*N* = 929/*M* = 25.63	100%	26.91%	22.82%	50.27%	*BDI*, categorical	*OR* = 1.84, *CI* = 1.28–2.66
Tanskanen et al., 1999	Finnish mental health in- and outpatients	*N* = 1,217/*M* = 41.00	56.00%	-	-	-	*BDI*, categorical	*OR* = 1.40, *CI* = 1.02–1.93
Tekbas, Ceylan, Hamzaoglu, & Hasde, 2003	Turkish new army recruits	*N* = 2,910/*M* = 20.70	0.00%	60.62%	-	35.40%	*BDI*, categorical	*OR* = 1.57, *CI* = 1.32–1.87
Tselebis, Papaleftheris, Balis, Theotoka, & Ilias, 2003	Greek physicians and surgeons	*N* = 80/*M* = 34.20	41.30%	48.75%	17.50%	33.75%	*BDI*, dimensional	*current OR* = 2.80, *CI* = 1.13–6.94 *former OR* = 1.35, *CI* = 0.42–4.36
Tsoh, Lam, Delucchi, & Hall, 2003	Chinese Americans	*N* = 199/-	-	100.00%	-	0.00%	*CES-D*, dimensional	*OR* = 10.53, *CI* = 1.89–58.60
Urbán, Kugler, Oláh, & Szilágyi, 2006	Hungarian military recruits	*N* = 574/*M* = 20.70	0.00%	70.03%	5.57%	24.39%	*BDI*, dimensional	*OR* = 1.62, *CI* = 1.17–2.25
Vander Weg, Ward, Scarinci, Read, & Evans, 2004	U.S., low-income pregnant women	*N* = 245/*M* = 25.64	100.00%	73.00%	27.00%	0.00%	*CES-D*, dimensional	*OR* = 1.98, *CI* = 1.24–3.15
Vickers et al., 2003	U.S. undergraduates	*N* = 656/*M* = 19.50	74.00%	46.00%	-	54.00%	*CES-D*, categorical	*OR* = 1.34, *CI* = 1.00–1.80
Wadsworth et al., 2004	British community-based sample	*N* = 7,979/*M* = 45.61	58.00%	21.00%	-	79.00%	*HADS*, categorical	*OR* = 1.88, *CI* = 1.39–2.54
Webb, Vanable, Carey, & Blair, 2007	Sample of HIV + patients attending a health clinic	*N* = 212/*M* = 41.0	43.00%	73.58%	-	26.42%	*CES-D*, dimensional	*OR* = 2.50, *CI* = 1.36–4.61
Wewers et al., 2012	Sample of rural women from Appalachian Ohio	*N* = 570/*M* = 18 plus years	100%	27.37%	20.53%	52.11%	*CES-D*, categorical	*current OR* = 2.96, *CI* = 1.96–4.46 *former OR* = 0.93, *CI* = 0.56–1.55
Weyerer et al., 2008	Elderly German general practice patients	*N* = 3,242/*M* = 80.20	65.60%	7.53%	-	92.35%	*GDS*, categorical	*OR* = 1.60, *CI* = 1.03–2.49
Whitaker, Orzol, & Kahn, 2007	U.S. mothers 15 months after delivery	*N* = 4,365/-	100.00%	26.53%	-	73.20%	*CIDI*, clinician diagnosis	*OR* = 1.54, *CI* = 1.27–1.87
White, Young, Morris, & Lawford, 2011	Sample of Australian university students	*N* = 132/*M* = 19.44	53.03%	35.61%	-	64.39%	*BDI*, categorical	*OR* = 2.97, *CI* = 1.25–7.10
Whitlock, Ferry, Burchette, & Abbey, 1995	U.S. female military veterans	*N* = 409/*M* = 53.00	100%	32.50%	28.90%	38.60%	*CES-D*, categorical	*current OR* = 1.55, *CI* = 1.00–2.41 *former OR* = 1.59, *CI* = 1.00–2.52
Whooley et al., 2008	Sample of San Francisco cardiac disease outpatients	*N* = 1017/-	-	19.47%	49.36%	30.10%	*PHQ*, categorical	*current OR* = 0.32, *CI* = 0.19–0.54 *former OR* = 0.40, *CI* = 0.23–0.68
Widome et al., 2009	Population-based of Washington and Idaho	*N* = 4,956/*M* = 52.1	100%	10.61%	-	89.39%	*PHQ*, categorical	*OR* = 2.13, *CI* = 1.13–4.02
Yazici, 2008	Turkish technical school students	*N* = 626/*M* = 21.01	38.40%	59.42%	-	40.58%	*BDI*, dimensional	*OR* = 2.53, *CI* = 1.89–3.40
Zhao, Xu, Lai, Che, & Zhou, 2012	Sample of Chinese patients with hepatitis B	*N* = 181/*M* = 39.2	0.00%	29.83%	-	70.17%	*HADS*, dimensional	*OR* = 27.47, *CI* = 14.05–53.73

* Mean age or age range reported.

Table 2
AIC values for full mixed model.

Model	K	AIC	ΔAIC	AIC weight
Random effect + smoking status	4	285.82	0.00	0.49
Random effect + smoking status + disorder vs. symptoms	5	295.93	0.11	0.46
Random effect + smoking status + disorder vs. symptoms + depression measure	9	290.89	5.07	0.04
Random effect + smoking status + disorder vs. symptoms + depression measure + dimensional vs. categorical use	11	293.63	7.81	0.00
Random effect + smoking status + Disorder vs. symptoms + depression measure + dimensional vs. categorical use + sample type (community vs. clinical)	12	295.63	9.81	0.00
Random effect	3	302.35	16.53	0.00
Random effect + smoking status + Disorder vs. symptoms + depression measure + dimensional vs. categorical use + sample type (community vs. clinical) + covariates (age, sex, race, SES, BMI, exercise, drink alcohol, caffeine intake, physical health, psychological health, living situation, social support)	23	305.23	19.41	0.00

Table 3
AIC values for mean age model.

Model	K	AIC	ΔAIC	AIC Weight
Random effect + smoking status	4	112.11	0.00	0.42
Random effect + smoking status + mean age	5	112.83	0.72	0.29
Random effect + smoking status + mean age + depression measure + dimensional vs. categorical use + sample type (community vs. clinical)	9	115.13	3.02	0.09
Random effect	3	115.16	3.05	0.09
Random effect + smoking status + mean age + depression measure	7	115.66	3.56	0.07
Random effect + smoking status + mean age + depression measure + dimensional vs. categorical use	8	117.50	5.39	0.03
Random effect + smoking status + depression measure + dimensional vs. categorical use + sample type (community vs. clinical) + covariates (sex, SES, drink alcohol)	12	121.44	9.33	0.00

Table 4
AIC values for gender model.

Model	K	AIC	ΔAIC	AIC Weight
Random effect + smoking status	4	211.26	0.00	0.60
Random effect + smoking status + gender	5	212.88	1.63	0.26
Random effect + smoking status + gender + disorder vs. symptoms	6	214.37	3.11	0.13
Random effect + smoking status + gender + disorder vs. symptoms + depression measure	10	220.88	9.63	0.00
Random effect + smoking status + gender + disorder vs. symptoms + depression measure + dimensional vs. categorical use + sample type (community vs. clinical	13	221.58	10.32	0.00
Random effect	3	222.86	11.61	0.00
Random effect + smoking status + gender + disorder vs. symptoms + depression measure + dimensional vs. categorical use	12	224.56	13.30	0.00
Random effect + smoking status + gender + disorder vs. symptoms + depression measure + dimensional vs. categorical use + sample type (community vs. clinical) + covariates (age, sex, race, SES, BMI, exercise, drink alcohol, caffeine intake, physical health, psychological health, living situation)	24	227.27	16.01	0.00

Table 5
AIC values for direct current/former comparison.

Model	K	AIC	ΔAIC	AIC Weight
Smoking status	2	30.19	0.00	0.53
Smoking status + disorder vs. symptoms	3	31.81	1.62	0.23
Smoking status + disorder vs. symptoms + depression measure + dimensional vs. categorical use	8	32.84	2.64	0.14
Smoking status + disorder vs. symptoms + depression measure	6	33.55	3.36	0.10

($N = 10$), d) combined adults and adolescents in the sample ($N = 10$), e) only examined smoking or depression in its relationship to another outcome (e.g., aggression, diabetes control) ($N = 29$), or f) combined depression with other psychiatric outcomes (e.g. bipolar disorder, anxiety) ($N = 6$). Finally, some studies reported data in a metric that could not be converted directly to an odds ratio ($N = 18$) such as a hazard ratio. After these exclusions, a total of 78 cross-sectional studies and seven prospective studies comprised the final sample.

2.2. Effects and moderator coding

To assess whether moderators (participant characteristics or measurement variations) contribute to the association between smoking and depression, the lead researcher (TML) coded studies for the effect size and a variety of moderators. In order to ensure reliability, an additional author (JS) coded a random selection of one-third of the studies. Agreement between the coders was high (86%).

Table 6
AIC values for current smoking as dependent variable.

Model	K	AIC	ΔAIC	AIC Weight
General depression + disorder vs. symptoms + depression measure	7	10.34	0.00	0.40
General depression	2	10.46	0.12	0.38
General depression + disorder vs. symptoms	3	11.60	1.27	0.21

Table 7
Prospective study characteristics.

Study	Sample Description	Sample Size/Age*	Percent Female	Percent Current Smoker (Baseline)	Percent Former Smoker (Baseline)	Percent Non-Smoker (Baseline)	Depression Measure and Use	Time to Follow-Up Measurement	Effect Size (Odds Ratio and 95% Confidence Interval)
Breslau, Peterson, Schultz, Chilcoat, & Andreski, 1998	U.S. sample from a Michigan HMO	$N = 974$/21–30 years	62.00%	28.90%	-	35.60%	*DSM-IV*, clinician diagnosis, incident depression	5 years	$OR = 1.50$, $CI = 0.82–2.74$
Goodwin et al., 2013	Sample of Ohio National Guard soldiers	$N = 1770$/18 plus years	12.40%	24.80%	20.68%	33.11%	*PHQ*, categorical, incident depression	3 years	$OR = 2.00$, $CI = 0.64–1.81$
Green et al., 1992	U.K. community-based sample	$N = 1{,}070/M = 74$	62.00%	-	-	-	*Geriatric Mental State*, cut-off, incident depression	3 years	$OR = 1.30$, $CI = 1.04–1.61$
Kang & Lee, 2010	Population-based sample in South Korea	$N = 13{,}764$/20 plus years	60.95%	22.81%	-	77.19%	*CES-D*, categorical, controls for baseline depression, incident depression	1 year	$OR = 1.38$, $CI = 0.99–1.94$
Mojtabai & Crum, 2013	Population-based sample in U.S.	$N = 33{,}154$/18 plus years	48.32%	17.49%	26.84%	55.66%	*AUDADIS*, categorical, controls for baseline depression, incident depression	2 years	$OR = 1.36$, $CI = 1.12–1.67$
van Gool et al., 2003	Dutch community-based sample	$N = 1{,}280$/55–85 years	-	12.27%	-	87.73%	*CES-D*, dimensional, controls for baseline depression	6 years	$OR = 1.25$, $CI = 0.95–1.63$
Xu, Anderson, & Courtney, 2010	Community sample of women in South East Queensland, Australia	$N = 556/M = 54.95$	100%	10.79%	20.06%	61.15%	*Greene Climacteric Scale (GCS)*, dimensional, controls for baseline depression	5 years	$OR = 5.77$, $CI = 4.13–8.05$

* Mean Age or Age Range reported.

Information gleaned from the literature included a) authors and citations, b) the odds ratio (the adjusted ratio was used if both unadjusted and adjusted were available) or information that could be used to calculate the odds ratio, and the following moderators: c) operationalization of depression as a condition/disorder (MDD) or as levels of depressive symptoms (disorder vs. symptoms), d) the specific validated depression measure used, e) whether the measure used a cut point to classify participants (categorical) or was expressed on a continuum (dimensional), f) participant characteristics (sample size, mean age, percent female, smoking status [current or former smoker]), g) community or clinical sample based upon the description of where the sample was derived (e.g., national telephone survey vs. mental health inpatients), and h) individual study covariates (study sample information for which the study authors had adjusted their individual effects, e.g., gender, alcohol use).

2.3. Statistical analysis

Cross-sectional effect sizes were computed and aggregated with R statistical software package version 2.15.1 (R Core Team, 2012). We selected the odds ratio for the primary effect size as many of the studies summarized their data in this manner or in a comparable metric. The fail-safe N was calculated in order to assess publication bias. It is loosely defined as the number of "null result" or negative effect studies that would need to be published to change the statistical significance of a meta-analysis (Rosenthal, 1979).

Heterogeneity in effect size estimates was assumed *a priori* because of the variety of measures and samples in the included studies. Thus, we constructed linear mixed-effects models with the R package 'lme4' (Sarkar, 2008) to assess the contribution of moderators. First, the effects of the 66 studies that structured their study design (and demographic covariates) to reflect depression as an outcome were analyzed. As stepwise predictor selection methods may bias parameter estimates (Sarkar, Midi, & Rana, 2010), we decided to utilize an information-theoretic model selection approach (Bolker et al., 2009). A series of nested models were tested in which the coded moderators (i.e., smoking status, depression measure/survey, etc.) were included in the model as fixed effects. Moderators were introduced to the model according to proposed empirical importance as well as pragmatic considerations with smoking status first, followed by disorder vs. symptoms, specific depression measure used, dimensional or categorical use of measure, clinical vs. community sample, and whether the study controlled for each demographic covariate. Thus, a total of six models were constructed. Individual studies were modeled as a random effect. We compared the Akaike Information Criterion (AIC) value for each nested model using the R package 'AICcmodavg' (Mazerolle, 2012). The best fitting model was determined to be that with the lowest AIC value and highest AIC weight (Johnson & Omland, 2004; Wagenmakers & Farrell, 2004). Confidence intervals were calculated by hand for the fixed effects parameters of the best fitting model.

To examine age and gender, subgroup analyses were necessary as few studies reported this information. In addition, in age and gender sub-analyses, certain moderators (such as caffeine use) were completely confounded with other variables in the model, preventing the R statistics package from estimating the fixed effects. In these instances, the confounded moderator was dropped so that only independent variables were included in the series of models. A list of the included moderators for each set of analyses can be found in Tables 2–8. Finally, a subset of studies had structured their cross-sectional analyses (and control of demographic covariates) to reflect smoking as an outcome rather than a predictor ($N = 12$). Thus, a final cross-sectional analysis compared a series of three nested linear models in which depression predicted smoking outcome.

As previously mentioned, few prospective studies examined smoking and depression among adults. In addition, many studies did not measure the outcome of interest at baseline (whether it was follow-up smoking or

Table 8
Recommendations for future studies.

knowledge Gap/potential research questions	Recommendations
1. Are current vs. former smoker characteristics contributing to differences seen in depression levels?	1a. Collect background/baseline information on current and former smokers such as gender, age, smoking levels, resilience, depression levels, and length of abstinence. 1b. Prospective studies should follow both current and former smokers to measure changes in characteristics.
2. What is the direction of the smoking-depression relationship in adults?	2a. Prospective studies should be designed to capture adult smoking initiation as compared to persistent smoking. 2b. Ideally, prospective studies should measure and report baseline and follow-up outcomes to assess change in the behavior over time.
3. What is the relationship between smoking and depression in occasional or intermittent smokers (i.e., "chippers")?	3a. Studies should refine their categorization of smokers so that comparisons can be made between current, occasional/intermittent, former, and never smokers.

follow-up depression), which prevented a systematic review of change in that variable over time. Finally, because there were few prospective studies fulfilling the inclusion criteria, analysis of moderator effects with a linear mixed-effects model was not permissible. As an alternative analytic approach, a summary effect size was calculated using Comprehensive Meta-Analysis (CMA) version 2 software program (Biostat, Inc., 2006). Sensitivity analyses were then conducted to examine summary effects for only those studies that reported both baseline and follow-up outcomes.

3. Results

3.1. Cross-sectional studies

Table 1 presents a description of the 78 studies included in the cross-sectional analyses.

In the 66 studies that treated depression as the outcome, a comparison of AIC values indicated that the best fitting model was that which included only random study effects and smoking status. Thus, the relationship between smoking and depression did not significantly change when additional moderators were included in the model. The AIC values for each of the nested models can be found in Table 2.

Examination of the fixed effects parameters showed that current smokers were more likely to be depressed than never smokers (OR = 1.50, CI = 1.39–1.60). Similarly, former smokers were more likely to be depressed than never smokers (OR = 1.21, CI = 1.13–1.30). The fail-safe N indicated that 8,839 "null result" studies would have to be published to change the statistical significance of the combined effect (i.e., change the point estimate to 1.00).

In the age subgroup analysis, the AIC values again indicated that the best fitting model was that which included only random study effects and smoking status (see Table 3).

In the gender subgroup analysis, the AIC values again suggested that the best fitting model included only random study effects and smoking status (see Table 4).

When current smokers were directly compared to former smokers, the AIC values indicated that the best fitting model was the intercept-only model representing the comparison of smoking status without any additional moderators (see Table 5).

Examination of the intercept showed that current smokers were more likely to be depressed than former smokers (OR = 1.76, CI = 1.48–2.09).

In the subgroup of studies that treated smoking as an outcome (rather than a predictor), the AIC values indicated that the best fitting model included the moderators of disorder vs. symptoms and specific measure of depression (see Table 6).

However, examination of the model showed that depression was the only statistically significant predictor, such that individuals with depression were more likely than persons without depression to be current smokers (OR = 1.40, CI = 1.17–1.68).

3.2. Prospective studies

Table 7 presents a description of the seven prospective studies.

No studies which examined baseline depression's association with follow-up smoking measured the outcome (smoking) at both time points, an inclusion criterion. As a result, our prospective analyses were unidirectional (baseline smoking's relationship to follow-up depression). First, when all studies were included, baseline smoking was significantly associated with increased odds of incident depression (developing a new diagnosis of depression or presentation of depressive symptoms when none was present at baseline) at follow-up (OR = 1.62, CI = 1.10–2.40). Second, when only those "ideal" studies that reported both baseline and follow-up depression were examined, baseline smoking was again significantly associated with increased odds of incident depression at follow-up (OR = 1.32, CI = 1.02–1.71).

4. Discussion

4.1. Smoking and depression

Meta-analysis of the empirical literature showed greater odds of depression associated with both current and former smoking versus never smoking in cross-sectional studies. In addition, current smokers were more likely to be depressed than former smokers. On the basis of a smaller literature, smoking at baseline was also found to be prospectively associated with greater odds of future incident depression.

In terms of robustness, the best fitting model included only smoking status. This suggests that the coded moderators did not meaningfully contribute to the estimate of the relationship between smoking and depression. Smoking status is robustly associated with depression (or depressive symptomatology) at 1 ½ to 2 times the risk of nonsmoking across a variety of study designs, depression measurements, and participant populations.

According to the convention for odds ratios (*small* OR = 1.5, *medium* OR = 3.5, *large* OR = 9.0) (Cohen, 1988), we found that a small-to-medium association exists between smoking and depression. The magnitude of association is comparable to other evaluations of depression's relationship to alcohol abuse (OR = 2.24, CI = 1.74–2.88) (Grant & Harford, 1995), diabetes (OR = 2.00, CI = 1.80–2.20) (Anderson, Freedland, Clouse, & Lustman, 2001), obesity (OR = 1.73, CI = 1.04–2.87) (Roberts, Kaplan, Shema, & Strawbridge, 2000), migraines (OR = 2.84, CI = 2.19–3.70) (McWilliams, Goodwin, & Cox, 2004), and cardiac disease (OR = 1.76, CI = 1.27–2.43) (Barth, Schumacher, & Herrmann-Lingen, 2004).

In cross-sectional studies, former smokers were still at higher odds of depression than never smokers, but at lower odds than current smokers. The implication is that smoking often precipitates depression because former smokers exhibit lower odds of depression than those who still smoke. While nicotine withdrawal during a period of abstinence is known to be associated with acute distress and dysphoria

(Hughes, Stead, & Lancaster, 2007), results from the present meta-analysis suggest that the risk of depression is likely to lessen with time following cessation, a finding which is consistent with prior studies of the time course of depression and other nicotine withdrawal symptoms (Hughes et al., 2007). Therefore, it would behoove providers to recommend to patients who currently smoke to try to quit, despite the risk of acutely elevated depressed mood during withdrawal. Nevertheless, additional prospective data would help to better elucidate the temporal association between smoking cessation and depression.

A caveat is that between-group differences in related characteristics could have contributed to these findings. For example, former smokers may simply be less depressed originally than current smokers, which enabled them to quit more easily. Alternatively, former smokers may be more resilient or tolerant of distress and better able to adapt to the discomfort that withdrawal symptoms produce. This, too, might account for the difference in the odds of depression between current and former smokers. Former smokers also may have smoked less in the past than smokers currently do, which could have influenced both withdrawal symptoms and ability to quit. In order to truly explicate the mechanisms of the smoking-depression relationship, additional longitudinal studies are necessary. However, few of the longitudinal studies included in our meta-analysis (discussed below) collected and/or reported this important information regarding individual characteristics, such as level of former smoking or length of abstinence.

Prospective analyses showed that smokers at baseline had greater odds of developing incident depression than never smokers. In an earlier meta-analysis, Chaiton et al. (2009) found that the odds of adolescent smokers developing depression over time were 1.73 ($CI = 1.32–2.40$) times greater than for nonsmokers, which is slightly higher than we found for adults. More investigations of adult smokers seem warranted to determine if the relationship to depression in adults does, in fact, meaningfully differ from adolescent smokers. In addition, Chaiton et al. (2009) found a reciprocal relationship between smoking and depression in adolescents. However, we were unable to examine depression's effect on smoking in adults, as few studies measured baseline smoking in order to accurately assess change in smoking over time. Additional prospective studies of smoking initiation in adults should contribute to knowledge of the directionality of the smoking-depression relationship in this population.

4.2. Limitations and recommendations

A summary of our recommendations for future studies can be found in Table 8.

One major limitation of the current systematic review was the lack of consistent methodology among studies. Although we adopted the random effects model, which is advised under such circumstances (Borenstein, Hedges, Higgins, & Rothstein, 2009), some subgroup analyses were not possible. Frequently, researchers failed to report sufficient data on potentially important covariates, such as gender or duration of smoking, limiting the number that could be included in the subgroup analyses. Finally, due to limited information available in the original studies, we were unable to distinguish between those who had smoked on a limited number of occasions in the past (i.e., experimental smokers), but who did not meet study criteria for being a current or former smoker, versus those who never used cigarettes on even a single occasion. Consequently, there may be variability in the odds of depression among those categorized as never smokers related to differences in their smoking history.

Many of the studies utilized data from large, epidemiologic samples that are representative and highly statistically powered, but often did not collect information about smokers' individual differences such as level of smoking and duration of abstinence. These variables are crucial to identifying the cause(s) of the cross-sectional difference in the odds of depression between current and former smokers.

A perhaps more important limitation of the current meta-analysis is the small number of prospective studies that reported sufficient data to assess change and the lack of follow-up of former smokers. Additionally, prospective studies are needed to assess individual difference variables in both current and former smokers over time. The measurement of variations in current and former smoking levels might elucidate the differences between these groups and lead to a greater understanding of how smoking behavior affects and is affected by depression. A fuller understanding will require observational studies, experimental studies and animal models.

4.3. Conclusion

The current meta-analytic study systematically examined cigarette smoking's relationship to depression. Although the association between depression/depressive symptoms and smoking is well-recognized, the present quantitative review provides an overall estimate of the magnitude and robustness of the association in adults, which until the present, has not been available. The size of the relationship is comparable to other risk factors, such as alcohol abuse, and seems to be independent of moderators like sample characteristics or measurement variations. Thus, this may signal to health providers that one behavioral health issue is likely accompanied by another, suggesting that providers solicit information about both smoking behavior and depression/depressive symptoms from patients of any background.

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Contributors

Drs. Luger, Suls, and Vander Weg determined the inclusion/exclusion criteria. Dr. Luger determined articles appropriate for review. Drs. Luger and Suls reviewed the articles for inclusion and coded the articles for moderators. Dr. Luger conducted the quantitative analysis. Drs. Luger, Suls, and Vander Weg wrote, reviewed, and revised versions of the manuscript. All authors have approved the final version submitted.

Conflict of interest

Drs. Luger, Suls, and Vander Weg declare that they have no conflicts of interest.

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