Severity of negative mood and anxiety symptoms occurring during acute abstinence from tobacco: A systematic review and meta-analysis

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Abstract

This review was conducted with the following goals: To quantify the severity of mood and anxiety symptoms emerging during acute abstinence from tobacco (1). To explore sex differences related to the experience of specific symptoms (2). To investigate the early time course of symptoms (3).

A meta-analysis was performed from 28 studies assessing mood and anxiety symptoms during the earliest phases of tobacco abstinence (up to 24hrs post-quit) conducted from 1999 to 2019. Results revealed a significant ($p<0.0001$) increase in 'anxiety', 'anger/irritability', 'depressed mood /sadness', and composite negative affect ('NA') in the 24 hours following smoking cessation. The largest effect size was detected for 'anxiety' (0.63). A qualitative analysis was performed to investigate sex differences and the time course of the specific symptoms. Results indicated that female smokers may experience worse mood symptoms compared to male smokers and that these symptoms may emerge within 3hrs post-quit. Smoking cessation programs should implement sex-tailored interventions in order to improve their effectiveness, while future research should focus on alternative methods of nicotine administration.

KEYWORDS: Acute abstinence; anger; anxiety; meta-analysis; depression; mood; negative affect; nicotine; tobacco; withdrawal.

1 Introduction

The World Health Organisation (WHO) describes tobacco smoking as "one of the biggest public health threats the world has ever faced" (WHO, 2019, p.1). Particularly, more than seven million individuals are reported to die each year because of tobacco induced and related diseases (WHO, 2019).

According to the WHO (2019), more than 1.1 billion individuals worldwide are currently tobacco smokers. In the US alone, 26 million adults above 18 years old are reported to be daily smokers (Wang et al., 2018). Addiction to tobacco is caused by nicotine, a highly addictive psychostimulant drug present in tobacco products (WHO, 2019). Despite the majority of smokers having an intention to quit (Babb et al, 2017), only 7% of smokers who attempt quitting remain abstinent (Babb et al, 2017). Research has estimated that "for many smokers it may take 30 or more quit attempts before being successful" (Chaiton et al., 2016, p.1), and that majority of relapses occur in the first few days following smoking cessation (Hughes, Kelly, & Naud, 2004 ; Zelle et al., 2017), with early lapses occurring several hours after quitting (Bolman et al., 2018; Brown et al., 2005;Deiches et al., 2013; Ferguson, Shiffman, & Blizzard, 2017; Franklin et al., 2018). Notably, smoking lapses and relapses have been related to negative mood and anxiety symptoms emerging during acute abstinence from tobacco by a consistent body of research (Allen et al., 2008; Doherty et al.,1995; Hall et al., 2015; Minami et al., 2014; Patterson et al., 2008; Piper & Curtin, 2006; Piper et al., 2011; Shiffman, West, & Gilbert, 2004; Zvolensky et al., 2009). After a quit attempt, smokers may resume their smoking habit to alleviate these symptoms through 'negative reinforcement' (Baker et al., 2004; Koob & LeMoal, 2005). In the context of drug addiction, 'negative reinforcement' is defined as "the motivational basis of addictive drug use by the reduction or avoidance of internal aversive states" (Baker et al., 2004, p.34). According to this paradigm, an addicted individual perpetuates in drug use in order to relieve negative affective symptoms emerging during drug withdrawal (Koob & LeMoal, 2005).

However, research conducted on young people and adolescents reported mild negative mood symptoms during abstinence from tobacco. Notably, these findings revealed that these symptoms may be less relevant in promoting relapses in comparison to adults (for a review see Lydon et al. 2014).

Abstinence from tobacco has been recently defined by Piper and colleagues (2019) as "abstinence from combustible tobacco products, smokeless tobacco products, and alternative products" (p.1). In the context of the current review, 'acute abstinence' refers to a time-period up to 24hrs since the last smoked cigarette and without utilizing any combustible or smokeless tobacco product, including alternative methods of nicotine administration (e.g. nicotine patches). Tobacco withdrawal symptoms such as negative mood (e.g. depressed mood, irritability) and anxiety may occur during this abstinence period (Hughes, 2007a).

Under a neurobehavioral perspective, the emergence of negative mood symptoms during acute drug abstinence (including abstinence from tobacco) and the consequent motivational effect on relapse has been related to 'opponent-process' theories of addiction (Solomon and Corbit, 1974; Poulos and Cappell, 1991). According to Solomon and Corbit (1974), the positive initial hedonic effect of a drug is counterbalanced by negative emotions that are caused by brain's homeostatic regulation. This opponent-process strengthen as dependence develops, causing negative mood symptoms to emerge as soon as the drug is removed (Solomon and Corbit, 1974). Koob (2001) developed further this paradigm by proposing the opponent-process as a component of an allostatic state caused by a dysregulation of brain's reward and stress systems that worsen progressively with the severity of drug dependence.

Negative mood concepts such as 'depressed mood', 'anxiety', and 'irritability' are well established and listed in the DSM-V (American Psychiatric Association, 2013) as a component of the 'Tobacco Withdrawal Syndrome'. Despite these guidelines, there is still uncertainty about the magnitude of severity of specific mood symptoms experienced by smokers during acute abstinence from tobacco and to their early time course (Hughes, 2007a). DSM-V is limited in reporting that "the most commonly endorsed signs and symptoms are anxiety, irritability, and difficulty concentrating, while the least commonly endorsed symptoms are depression and insomnia", and that "Tobacco withdrawal usually begins within 24 hours of stopping or cutting down on tobacco and peaks 2-3 days after abstinence" (American Psychiatric Association, 2013, p.576). However, several studies proposed that tobacco withdrawal symptoms may emerge as soon as 4 hrs post-quit (e.g. Hendricks et al., 2006). This has been further supported by recent neuroimaging findings that revealed disrupted neural processes in the mesocorticolimbic network following 4 hrs of smoking abstinence (Franklin et al., 2018).

Furthermore, little is known about possible sex differences related to the experience of specific mood symptoms. Data suggest lower long-term smoking abstinence rates for women compared to men regardless of treatments such as NRTs, Bupropion, nicotine patches, or counselling (Smith et al., 2015; Leventhal et al., 2007). Several studies investigated variables that could affect differentially smoking behavior and relapse in women compared to men, proposing attitudes towards cessation, social support during cessation, menstrual cycle, and nicotine reinforcement as possible risk factors (Leventhal et al., 2007; Etter, Prokhorov, & Preneger, 2002; Borrelli et al., 2001; Craig, Parrot, & Coomber, 1992, Murray et al., 1995). However, it has been proposed that negative affective symptoms emerging during acute tobacco abstinence may strongly "mediate relationships between sex and smoking behavior, such as cessation" (Leventhal et al.,2007, p.22). In fact, recent studies (Becker, McLellan, & Reed, 2017; Smith et al., 2016) proposed that female smokers may suffer more severe withdrawal symptoms and that may relapse more frequently in comparison to male smokers. Therefore, the investigation of possible sex-differences related to mood and anxiety symptoms emerging during acute tobacco abstinence would be of particular importance as it may improve sex-tailored smoking cessation treatments, and it may help to reduce sex disparities in smoking cessation rates.

No review, to our knowledge, has ever been conducted to quantify the severity of negative mood and anxiety symptoms emerging in the hours following smoking cessation, in addition to their early time course and to possible sex differences. Past reviews, such as those carried out by Taylor, McNeil, and Aveyard (2015) and by Lembke, Jhonson, and DeBattista (2007), focused on the decrease of negative affect symptoms during long-term abstinence (seven weeks to nine years), while other systematic reviews and meta-analyses focused on investigating the bi-directional relationship between smoking and symptoms of anxiety and depression, revealing contrasting results (Chaiton et al., 2009; Fluharty et al., 2017).

Findings from a review conducted on this topic would enhance current guidelines (e.g. DSM-V) by providing a quantitative estimate of the severity of negative mood symptoms experienced by daily smokers in the hours following smoking cessation. Additionally, it would contribute significantly to the existing literature by validating the role of sex in relation to the experience of negative mood symptoms during acute tobacco abstinence, and by outlining the early time course of the same symptoms.

A review was therefore conducted employing both meta-analytic and qualitative techniques with the following goals: 1) Provide a quantification of the severity of mood and anxiety symptoms emerging up to 24hrs during acute tobacco abstinence, 2) Investigate possible sex differences related to the experience of negative mood and anxiety symptoms emerging during acute tobacco abstinence, 3) Investigate the time course related to the manifestation of specific symptoms up to 24hrs during acute tobacco abstinence .

2 Methods

2.1 Search strategy

Pubmed, Psychinfo, Ovid Embase, and Cochrane Controlled Trials registry databases were used to detect studies conducted between 01/01/1999 and 01/01/2019. Notably, this review wasn't conducted to identify possible new symptoms occurring during acute tobacco abstinence. It was instead conducted to assess the magnitude of change among existing mood symptoms, thus a limit of 20 years was applied to encompass studies assessing established negative mood and anxiety symptoms as described in DSM-IV and DSM-V (American psychiatric association, 1994; 2013). The inclusion/exclusion criteria listed in Table 1 below was used for both qualitative and quantitative parts of this review.

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Studies employing a repeated-measures experimental design (ad. libitum smoking vs acute abstinence condition).	Studies testing participants taking any medication/treatment to aid smoking cessation during the abstinence period.
Studies verifying tobacco abstinence through objective measurements.	Studies testing participants enrolled in a smoking cessation treatment group/program or undergoing therapy/counselling to aid smoking cessation.
Studies testing human participants.	Studies testing pregnant participants.
Studies utilizing validated self-report measures of tobacco withdrawal, mood and anxiety*	Studies testing participants diagnosed with any co-morbid psychiatric disorder as described in DSM-V.
Studies measuring mood and anxiety symptoms at a single time point or at multiple time points during an acute tobacco abstinence period (up to 24hrs post smoking cessation) as reported by the tobacco withdrawal syndrome guidelines described in DSM-V **.	Studies testing participants diagnosed with any substance use disorder (SUD) other than tobacco use disorder as described in DSM-V.
Studies in all languages.	Studies manipulating participants' mood during tobacco abstinence (e.g. negative mood induction)-
Studies testing daily tobacco smokers.	Studies testing participants taking any psychoactive medication.
Studies testing participants from 15 to 60 years old.	Studies testing smokers who relapsed during acute abstinence.

Note. *: Validated self-report measures refer to psychometric scales with acceptable validity and reliability utilized to measure mood and anxiety symptoms of smokers during tobacco abstinence. The following scales were included (PANAS= Positive and Negative Affect Schedule; POMS=Profile of Mood States; MPSS=Mood and Physical Symptoms Scale ; WSWS=Wisconsin Smoking Withdrawal Scale ; MNWS=Minnesota Nicotine

Withdrawal Scale; WSC=Withdrawal Symptoms Checklist; Diener and Emmons Mood form);**: Studies measuring mood and anxiety symptoms at multiple time points within a timeframe exceeding 24hrs were also included, although only those measurements taken up to 24hrs post smoking cessation were considered for the current review. DSM-V= Diagnostic and Statistical Manual of Mental Disorders, fifth edition.

Studies employing a within-subjects/repeated measures experimental design in which groups of smoker participants were tested at baseline during *ad.libitum* smoking (freely available smoking for pleasure) and subsequently at a time single time point or at multiple time points during an acute abstinence condition (up to 24hrs post-quit) were selected to be included in the review. Studies employing a mixed within-subjects and between-subjects design were also included. However, only within-group mood measurements (*ad.libitum* smoking vs acute tobacco abstinence) from smoker participants randomized to receive a placebo treatment or no treatment at all were included in the analyses. Cohorts of smoker participants receiving any form of treatment during abstinence (e.g. NRTs) other than placebo were not included in the study.

The 'Preferred Reporting Items for Systematic Review and Meta-Analysis' (PRISMA) guidelines (Liberati et al., 2009) and the 'Meta-Analysis for Observational Studies in Epidemiology' (MOOSE) guidelines (Stroup et al., 2000) were utilised to aid the selection and subsequent assessment of the selected studies. The following search terms were used: (*affective state* OR negative affect* OR mood OR emotion*OR negative valence) AND (nicotine OR smoking OR tobacco) AND (acute OR initial) AND (withdrawal OR abstinence OR cessation OR quit OR deprivation).* The Research Domain Criteria (RDoC) matrix (Insel et al, 2010) was utilized to identify relevant units of analysis to insert as specific search terms in addition to the negative affective symptoms of 'tobacco withdrawal' listed in DSM-V (American Psychiatric Association, 2013). Both instruments were utilized as the RDoC Matrix does not contain a diagnostic tool for tobacco withdrawal. Therefore, the terms (*affective state* OR negative affect* OR mood OR emotion*OR negative valence)* were subsequently substituted with *(anhedonia OR decreased appetitive behavior OR apathy)*, with (*anxiety OR anxious arousal),* with *(depressed mood OR sadness OR depression),* and with *(anger OR irritability OR frustration).*

2.2 Analysis

The current review utilized both quantitative and qualitative methods of data analysis.

2.2.1 Data Extraction for Meta-Analysis

The primary outcome of the current meta-analysis consisted in quantifying the effect of acute tobacco abstinence (up to 24 hrs post-quit) on mood and anxiety symptoms identified through the RDoC Matrix (Insel et al., 2010) and the DSM-V (American Psychiatric Association, 2013) in daily tobacco smokers (see supplementary Table 1a). The secondary outcome consisted in assessing the impact of relevant moderator variables such as severity of tobacco dependence, sex, age, and hours of tobacco abstinence on the same symptoms.

It was possible to extract data to insert in the quantitative synthesis just for 'depressed mood/sadness', 'anxiety', and 'anger/irritability' symptoms , as these were the negative mood and anxiety constructs measured more frequently through the psychometric scales employed by the studies included in the review. Total scores from negative affect ('NA') measures were also extracted. This allowed to conduct a sensitivity analysis assessing the impact of acute tobacco abstinence on the composite 'NA' construct, which encompasses the afore-mentioned symptoms (see Supplementary Table 1b).

The Profile of Mood States (POMS) was the most utilized mood measure by the studies included in the meta-analysis (61%), followed by the Positive and Negative Affect Scale (PANAS) (22%), and by the Mood and Physical Symptom Scale (MPSS) (11%). The Wisconsin Smoking Withdrawal Scale (WSWS) was the least utilized measure (5%). All four scales measured the same outcome parameters such as 'depressed mood/sadness', 'anxiety', and 'anger/irritability' through 5-point Likert scales with equivalent directions. They differed in wording used and in the total number of items. The PANAS, POMS, and WSWS also provided scores for composite 'NA'. Particularly, the POMS (McNair, Lorr, & Droppleman, 1971/1981) constitutes of a 65 items scale with three subscales "most consistent with the negative affect observed as part of nicotine withdrawal (i.e., tension–anxiety, depression–dejection, and anger–hostility)" (Heffner et al., 2011,p. 245). These are measured through a 5-point Likert scale ranging from 'not at all' (0) to 'extremely'(4) . Similarly, the PANAS (Watson et al., 1988) consists of a 20 items

scale measuring positive and negative affect symptoms through a Likert scale ranging from 'not at all' (1) to 'very much' (5). The MPSS (West & Hajek, 2004) was specifically developed to measure mood and anxiety symptoms emerging during tobacco withdrawal. It measures negative affect symptoms through seven items including symptoms of 'anxiety', 'depressed mood', and 'irritability'. Scores are provided by rating a Likert scale ranging from 'not at all' (1) to 'extremely' (5). The WSWS (Welsch et al., 1999) is a 28 items scale that "produces a total score as well as scores on seven subscales: anger, anxiety, concentration, craving, hunger, sadness, and sleep. Participants rate each item on a scale from strongly disagree (0) to strongly agree (4)" (Castro et al., 2011, p.548).

Several studies compared the above mood and withdrawal measures revealing analogous psychometric properties. Particularly, a study conducted by West et al. (2006) revealed that both the MPPS and the WSWS showed high sensitivity in detecting changes in the 'irritability' construct during tobacco abstinence, with good reliability displayed for the other symptoms. Rossi and Pourtois (2006) conducted a systematic review comparing scales assessing rapid fluctuations in mood states such as POMS and PANAS. Their results showed that both POMS and PANAS provided "a reliable measure to capture rapid state-dependent variations in mood and anxiety" (Rossi & Pourtois, 2006, p.1)

The data necessary to compute effect sizes estimating symptoms' magnitude of change from baseline to acute tobacco abstinence consisted in Means (M) and Standard Deviations (SD) for scores on the above mood measures performed at baseline (*ad.libitum* smoking) and in Means (M) and Standard Deviations (SD) for scores on the same mood measures performed at a single time point or at multiple time points during acute tobacco abstinence (up to 24hrs post-quit). Studies' sample sizes and correlations between scores on mood measures performed at baseline and during abstinence were also required.

All pooled studies reported M and SD for scores on mood measures performed at baseline and at a single time point during abstinence (within 24hrs post-quit). No raw data were reported. Only two studies reported M and SD for mood measurements performed at multiple time points post smoking cessation, thus hampering the possibility to investigate quantitatively the moderating effect of different time points on specific mood symptoms. These were further investigated qualitatively as described in section 2.2.4. Two studies reported M and SD for separate subgroups (males VS females) and not for the overall

sample. No study reported pre/post correlations. Therefore, data extracted from the pooled studies consisted in Means (M) and Standard Deviations (SD) for scores on mood measures performed at baseline (*ad.libitum* smoking) and at a later single time point during acute tobacco abstinence (within 24hrs post-quit) by daily tobacco smokers. Studies' sample sizes were also extracted. Additionally, moderator variables such as severity of tobacco dependence ('dependence'), 'sex', hours of abstinence ('hours'), and 'age' were extracted from the pooled studies. The 'dependence' moderator consisted in numerical scores on subjective measures of tobacco dependence (e.g. FTND, HONC). The 'sex' moderator consisted in percentage of female and male smokers in each study sample. These variables were transformed prior to be included in the software as subsequently described in section 2.2.2.

2.2.2 Meta-Analysis

Meta-analytic calculations were performed using the Meta-Analysis Version III software (Borenstein et al., 2013). A random-effect model was preferred over a fixed-effect model to address plausible effect size variations between studies. Heterogeneity among the pooled studies was assessed by Cochran's *Q* and *I2* tests (Cochran, 1950; Higgins et al., 2003). Both tests were selected as Cochran's *Q* is considered to have low power when there is a small number of studies included in the analysis (Lee, 2018). The selected data entry format consisted in 'One group (Pre-post) data' (Borenstein et al., 2013).

A Standardized Mean Difference (SMD) effect size was calculated and selected as a statistical summary measure in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (Higgins & Green, 2011) as the pooled studies utilized different psychological rating scales to measure the same symptoms. The SMD "expresses the size of the intervention effect in each study relative to the variability observed in that study. Studies for which the difference in means is the same proportion of the standard deviation will have the same SMD, regardless of the actual scales used to make the measurements."(Higgins & Green,2011,p.1). The significance threshold was set at $p<0.05$ to reflect the 95% of probabilities of rejecting the null hypothesis (Cohen, 1988). Cohen's d (Cohen, 1988) was utilized as a benchmark-criteria for effect sizes to assess the magnitude of the impact of acute tobacco abstinence on mood and anxiety symptoms. Specifically, an effect size of 0.2 would have implied a 'small' effect size, an effect size of 0.5 would have implied a 'medium' effect size, and an effect size of

0.8 would have implied a ‘large’ effect size (Cohen, 1988). Calculations were performed to obtain combined group values for two studies reporting means and standard deviations only for separate subgroups (e.g. males vs females) and not for the overall sample. The following formulae were utilized.

Mean: $\frac{N1M1 + N2M2}{N1 + N2}$ (Higgins & Green, 2011)

Where

N1= sample size of group1

N2= sample size of group2

M1= mean value of group1

M2= mean value of group2

Standard deviation: ???????????? $\sqrt{(SD1^2 + SD2^2)/2}$ (Higgins & Green, 2011)
???? =

Where

SD1= standard deviation value of group1

SD2= standard deviation value of group2

Missing pre and post correlations were imputed at a value of 0.5. According to Fu et al. (2013), Balk et al (2012), and to Follman et al. (1992), imputing within-group correlation values at 0.5 does not introduce bias in the summary estimate of the treatment effect. Confirming this, sensitivity analyses assuming correlation values of 0 and 0.9 were carried out to corroborate the robustness of the analyses (Borenstein et al.,2009; Follman et al., 1992). Two sensitivity analyses were conducted for each mood construct ('anxiety', 'depressed mood/sadness', 'anger/irritability', and total 'NA') in order to estimate symptoms' magnitude of change from baseline (*ad.libitum* smoking) to acute tobacco abstinence (up to 24hrs post-quit). A random effect model was employed. The same data (M, SD, sample size) utilized to compute effect sizes with a pre/post correlation of 0.5 were inserted in the software. Analyses were conducted by substituting pre/post correlations of 0.5 with 0 and subsequently with 0.9, revealing no significant changes between effect size estimates. These results are described subsequently in section 3.1.6.

The ’dependence’ moderator was computed by converting the extracted numerical scores on subjective measures of tobacco dependence (e.g. FTND, HONC) reported in each study into categorical levels of dependence (e.g. ‘low’, ‘medium, ‘high’) according to the scoring guidelines of the respective instruments. This allowed additional subgroup analyses for each level of dependence and to display the results in forest plots. Regarding sex, percentages of female and male participants in each study sample were converted into decimal data and inserted as covariates in the software. The extracted data related to ‘hours’ and ‘age’ were also inserted as covariates.

Meta regressions were therefore conducted to assess the impact of each moderator variable on mood and anxiety symptoms emerging during acute tobacco abstinence. Particularly, four meta-regressions were conducted for each mood and anxiety symptom in addition to negative affect. This allowed to assess the possible impact of severity of tobacco dependence (‘dependence’), ‘sex’, hours of abstinence (‘hours’), and ‘age’ on each construct. Additionally, a multiple regression model was computed in order to assess the impact of each moderator variable on mood and anxiety symptoms while controlling for the other covariates.

2.2.3 Publication bias

Publication bias was assessed using Funnel Plot analyses and Fail-Safe N tests (Rosenthal, 1979). Funnel plots for each construct were visually inspected to exclude presence of bias (see supplementary figures 13-16). Additionally, Egger’s regression test (Egger et al., 1997) was carried out in order to address possible subjective misinterpretation of funnel plots’ asymmetry that may occur when there are few studies included in the meta-analysis (Simmonds, 2015). A non-significant ($p>0.05$) Egger’s regression test implies absence of publication bias despite perceived funnel plots’ asymmetry, which may result from inherent between-study heterogeneity (Lau et al., 2006). The Fail-Safe N represents the number of missing studies with effect size zero that are needed to render the meta-analysis non-significant ($p>0.05$) (Rosenthal, 1979). Fail safe N and Egger’s test results are subsequently depicted in Table 3.

2.2.4 Qualitative analysis

Additionally, a ‘narrative synthesis’ methodology (Dixon-Woods et al., 2005) was employed to summarize the findings of studies investigating sex differences related to the experience of negative mood symptoms during acute abstinence from tobacco, and of studies investigating the early time course of symptoms. In particular, two reviewers (AAC and AB) identified and pooled key results from each study and provided a descriptive summary of the findings. The summarized evidence was subsequently interpreted and a preliminary conclusion for the effect of sex on mood symptoms and on their early time course was drawn.

2.2.5 Assessment of study quality

The quality of the studies included in the review was assessed using the ‘Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group’ (Study Quality Assessment Tools, 2017) and for studies employing a within-subjects experimental design the ‘ Quality Assessment for Observational Cohort Studies’ (Study Quality Assessment Tools, 2017) for studies employing a mixed within-subjects and between-subjects experimental design. For both assessment tools, a ‘good’ study indicates a study presenting low risk of bias, a ‘fair’ study indicates a study presenting a moderate risk of bias but not sufficient to invalidate the results, and a ‘poor’ study indicates a study presenting high risk of bias, in addition to severe methodological flaws (Study Quality Assessment Tools, 2017).

Two reviewers (AAC and AB) assessed the internal and external validity of each study utilizing the afore-mentioned tools. Consensus was reached through discussion in case of a discordant opinion related to the assessment of a study.

3 Results

Of these 3529 identified studies, 1373 were duplicates and therefore excluded. Two thousand one hundred and fifty-six studies were subsequently inspected through title and abstract reading, leaving a total of 573 studies eligible for inclusion in the review. Once these papers were accessed a further 545 studies were excluded (see Figure 1 below). In total, 28 studies were included in this review. However, it was not possible to include all 28 studies in the quantitative synthesis. In fact, only two studies (Pang & Leventhal, 2013; Xu et al., 2008) reported means and standard deviations for scores on mood measures for both male and female subgroups, thus hampering the possibility of computing effect sizes for males vs females during acute tobacco abstinence. Similarly, two studies (Aguirre et al., 2015; Morrel et al., 2008) measured negative mood and anxiety symptoms at multiple time points within a 24hrs abstinence timeframe and reported means and standard deviations for each time point. Thus, studies investigating sex differences and the early time course of symptoms were inserted in the qualitative synthesis. In particular, 18 studies were included in the quantitative synthesis (Bello et al., 2016; Bidwell et al., 2013; Colby et al., 2010; Cook et al., 2004; Everson et al., 2006; Froeliger et al. 2015; Hendricks & Leventhal, 2013; Leventhal et al., 2010, 2013, 2014 ; Park et al., 2016; Quinn et al., 2014; West & Hajeck, 2004; Wong et al, 2014) , while 14 were included in the qualitative synthesis (Al Absi et al., 2002; Ashare & Kable, 2015; Brown et al., 2013; Bujarski et al., 2015; Hendricks et al., 2006; Jacobsen et al., 2005; Leventhal et al., 2007; Perkins et al., 2013; Sheets et al., 2015;Smith et al., 2009). Four studies (Aguirre et al., 2015; Morrel et al. 2008; Pang & Leventhal, 2013; Xu et al., 2008) were included in both quantitative and qualitative syntheses as they presented data valid for both types of analyses.

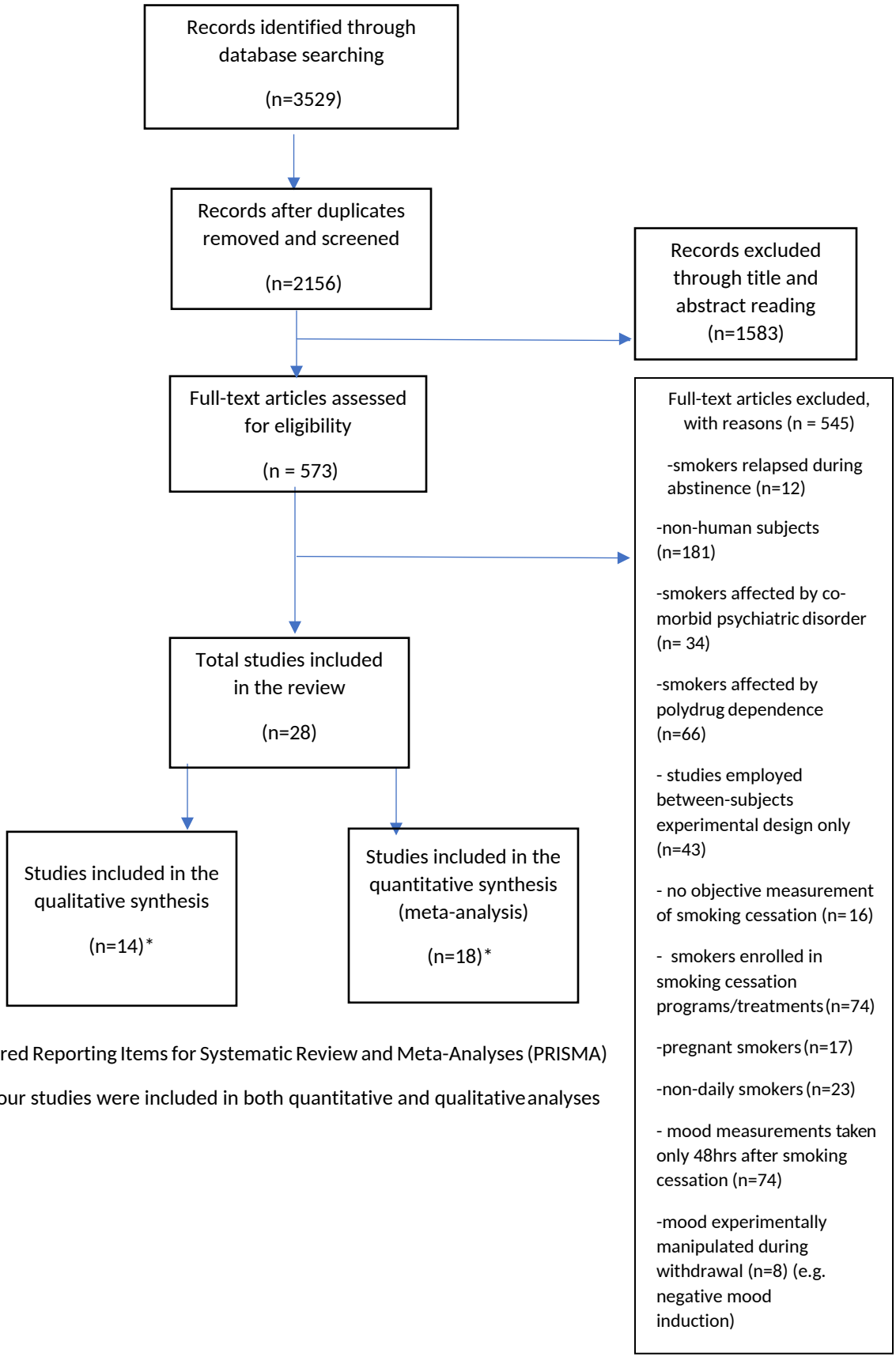

Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) 1999-2019; *: Four studies were included in both quantitative and qualitative analyses

3.1 Quantitative

Of the 18 studies included in the meta-analysis, 12 were classified as 'good' and six were classified as 'fair' according to the assessments of study quality listed in section 2.2.4. Fourteen studies employed a within-subjects experimental design, while the remaining four studies employed a mixed within-subjects and between-subjects experimental design. The mean hours of tobacco abstinence at which mood measurements were performed for the 18 pooled studies was 17hrs (SD=3.63), the median was 16hrs, the lowest was 12hrs, and the highest was 24hrs. All participants included in the analyses were abstinent during the acute abstinence condition as biochemically verified in each study (e.g. exhaled CO, salivary cotinine). Participants who failed to maintain abstinence were either excluded from the studies or rescheduled to another experimental session.

Demographic data and characteristics of studies included in the quantitative synthesis are shown in Table 2 below.

Table 2. Characteristics of studies assessing the impact of acute tobacco abstinence on mood and anxiety symptoms included in the meta-analysis.

Study (Country)	Study Quality	Intention to quit	Time points for mood and anxiety measurements in hours	Mood measures	Objective measure of acute tobacco abstinence	Level of Tobacco Dependence	Years of regular smoking (SD)	Mean cigarettes smoked per day (SD)	Sample size and sex (%)	Age in years (SD)	Study Design
Aguirre et al. 2015 (USA)	Good	No	1.0 And 17.0*	POMS	Breath Carbon Monoxide (CO)	FTND 5.3	24.5 (N/A)	16.7 (7.0)	286 (68% males, 32% females)	44.0 (10.5)	Within- subjects experimental design
Bello et al 2016 (USA)	Good	No	16.0	POMS	Breath Carbon Monoxide (CO)	FTND 5.4	24.9 (N/A)	16.8 (6.96)	324 (32.4% females, 67.6% males)	44.0 (10.6)	Within-subjects experimental design
Bidwell et al. 2013 (USA)	Good	No	12.0	PANAS	Breath Carbon Monoxide (CO) Salivary Cotinine	FTND 4.5	2 (N/A)	9.4 (N/A)	47 (61% females, 39% males)	16.4 (1.8)	Mixed between- and within-subjects experimental design**
Colby et al, 2010 (USA)	Good	No	15.0	PANAS	Breath Carbon Monoxide (CO)	SDI 14.5	2.6 (N/A)	10.5 (N/A)	31 (58 % females, 42% males)	15.6 (1.5)	Mixed between-subjects and within- subjects experimental design**
Cook et al.2004 (USA)	Fair	No	24.0	POMS	Breath Carbon Monoxide (CO)	FTND 5.6	17.5 (11.03)	N/A	35 (51% females, 49% males)	36.8 (11.74)	Within-subjects experimental design
Everson et al, 2006 (UK)	Fair	No	17.0	MPSS	Breath Carbon Monoxide (CO)	HONC 7	N/A	13.8 (3.72)	19 (53% females, 47.3% males)	17.8 (0.92)	Mixed within-subjects and between-subjects experimental design**

Froeliger et al 201 (USA)	Fair	No	24.0	PANAS	Breath Carbon Monoxide (CO)	FTND 6.4	17.6 (8.0)	15.4 (7.2)	17 (38% females, 62% males)	36.0 (9.6)	Mixed between- and within-subjects experimental design**
Hendricks & Leventhal 2013 (USA)	Good	No	16.0	POMS	Breath Carbon Monoxide (CO)	FTND 5.2	N/A	16.8 (6.98)	180 (67.8% males, 32.2% females)	44.5 (10.97)	Within- subjects experimental design
Leventhal et al 2014 (USA)	Good	No	16.0	POMS	Breath Carbon Monoxide (CO)	FTND 5.2	24.8 (N/A)	16.7 (7.0)	275 (69% males, 31% females)	44.2 (10.6)	Within- subjects experimental design
Leventhal et al. 2010 (USA)	Good	No	12.0	WSWS	Breath Carbon Monoxide (CO)	FTND 6.4	19.7 (10.3)	22.2 (6.61)	203 (49.8% males, 50.2% females)	36.7 (10.1)	Within- subjects experimental design
Leventhal et al. 2013 (USA)	Good	No	16.0	POMS	Breath Carbon Monoxide (CO)	FTND 5.3	27 (N/A)	19.3 (5.3)	187 (67% males, 33% females)	43.7 (10.3)	Within- subjects experimental design
Morrel et al.2008 (USA)	Fair	No	3.5 and 18.0*	POMS	Breath Carbon Monoxide (CO)	FTND 4.6	N/A	16.0 (N/A)	30 (73% males, 67% females)	27.0 (10.1)	within -subjects experimental design
Pang & Leventhal 2013 (USA)	Good	No	16.0	POMS	Breath Carbon Monoxide (CO)	FTND 5.3	24.1 (N/A)	16.7 (6.5)	199 (66% males, 34% females)	43.4 (10.2)	Within-subjects experimental design
Park et al. 2016 (USA)	Fair	No	16.0	POMS	Breath Carbon Monoxide (CO)	FTND 5.2	N/A	16.7 (6.98)	180 (68% males, 32% females)	44.5 (11.06)	Within subjects experimental design

Quinn et al 2014 (USA)	Good	No	16.0	POMS	Breath Carbon Monoxide (CO)	FTND 5.3	24.2 (N/A)	16.8 (6.41)	153 (66.0% males, 34% females)	43.7 (10.14)	within-subjects experimental design
West & Hajek 2004 (UK)	Fair	Yes	24.0	MPSS	Breath Carbon Monoxide (CO)	N/A	N/A	25.2 (8.70)	96 (41% males, 59% females)	39.8 (9.29)	Within- subjects experimental design
Wong et al., 2014 (USA)	Good	No	16.9	PANAS	Breath Carbon Monoxide (CO)	FTND 6.7	N/A	21.7 (N/A)	77 (22% males, 78% females)	38.2 (N/A)	Within-subjects experimental design
Xu et al. 2008 (USA)	Good	No	13.0	POMS	Breath Carbon Monoxide (CO)	FTND 5.2	17.1 (N/A)	20.4 (N/A)	64 (59% males, 41% females)	36.0 (N/A)	Within-subjects experimental design

Note*:It was only possible to insert in the meta-analysis one time point measurement for studies assessing mood and anxiety symptoms at multiple time points. For this reason, these studies were also included in the qualitative synthesis. **: Demographic characteristics and number of participants for nonsmoker controls or groups receiving a treatment other than placebo or no treatment at all that were reported in studies employing a mixed between-subjects and within-subjects experimental design were not included in the table as they were not considered for the current review. FTND= Fagerström Test of Nicotine Dependence (severity score: 0-2: Very low dependence, 3-4: Low dependence, 5: Medium dependence, 6-7:High dependence, 8-10: Very high Dependence); HONC=Hooked on Nicotine Checklist(severity score: 0 low to 10 very high); PANAS= Positive and Negative Affect Schedule ; POMS=Profile of Mood States ; MPSS=Mood and Physical Symptoms Scale ; WSWS=Wisconsin Smoking Withdrawal Scale; SDI=Stanford Dependence inventory(severity score: 5 low to 25 very high); SD=Standard Deviation, %=Percentage, N/A = Negative Affect

No statistically significant asymmetry was detected for each mood and anxiety symptom by inspecting Egger's regression tests ($p>0.05$). Fails-Safe N tests results revealed that a large number of non- statistically significant studies would have been needed to nullify the effect of acute tobacco abstinence on each symptom, therefore indicating the absence of publication bias in the current meta-analysis (Table 3). The assumption of homogeneity was not met for each mood and anxiety symptom as reported by Cochran's *Q* and *I2* tests (Table 3), thus justifying the application of a random effects model for the meta-analysis. In particular, the results of *Q* tests for each mood and anxiety symptom were found to be statistically significant ($p<0.05$) (Cochran, 1950). Additionally, *I2* tests' scores were over the 75% threshold (Higgins, 2003), thus indicating 'considerable heterogeneity' among the pooled studies (Higgins & Green, 2011).

Forty-five effect size measurements were computed: 10 for 'anxiety', 11 for 'anger/irritability', 12 for 'depressed mood/sadness', and 12 for composite negative affect ('NA'). These are summarized in Table 3 below. Another 45 effect size measurements were computed by running separate analyses for each level of tobacco dependence for all mood and anxiety symptoms. Ninety effect sizes are reported in Supplementary Figures 1-8. Meta regressions testing the impact of each moderator on specific mood and anxiety symptoms were also conducted as indicated in section 2.2.2.

Table 3. Pooled effect sizes for the severity of mood and anxiety symptoms experienced by daily smokers during acute abstinence from tobacco.

			Effect size and 95% confidence interval					Test of null(2tail)		Heterogeneity			Publication bias	
Mood and anxiety symptoms	N[1]	Studies[2]	Hours of abstinence[3]	Effect Size[4]	SE[5]	Lower limit[6]	Upper Limit[7]	Z[8]	P for Z[9]	Q[10]	P for Q[11]	I^2[12]	Fail safe N[13]	P for Egger's Test[14]
Anxiety	1448	10	15.5	0.63	0.06	0.50	0.77	9.2	0.00	45.1	0.00	80.06	1061	0.34
Anger/irritability	1533	11	16.1	0.51	0.06	0.38	0.64	7.6	0.00	54.2	0.00	81.5	829	0.24
Depressed mood/sadness	1499	12	14.0	0.27	0.05	0.16	0.39	4.7	0.00	47.4	0.00	76.8	282	0.32
Negative Affect (NA)	1737	12	16.5	0.47	0.08	0.30	0.64	5.5	0.00	106.6	0.00	89.6	722	0.12

1=Number of daily smokers ;2=Number of pooled studies; 3= Mean hours of tobacco abstinence at which mood measurements were taken;4=Cohen's d effect size;5=Standard error; 6= Lower limit of the 95% confidence interval for the effect size; 7= Upper limit of the 95% confidence interval for the effect size; 8= One sample Z Statistic; 9= Probability that Z Statistics is significantly different than 0; 10= Q statistic; 11= Probability that Q statistics significantly different than 0; 12= *I2* statistic; 13= Classic Fail safe N; 14=Probability that Egger's test is significantly different than 0.

3.1.1 Anxiety

For ‘anxiety’, a significant effect size ($p<0.0001$) was detected for the acute tobacco abstinence condition in comparison to the *ad.libitum* smoking condition (see Table 3 above and Supplementary Figure 1). Subgroup analyses revealed a major impact of acute abstinence from tobacco on ‘anxiety’ for studies reporting a ‘high’ level of tobacco dependence (SMD=1.016, Z=13.805, $p<0.0001$) in comparison to studies reporting a ‘medium’ level of dependence (SMD=0.519, Z=15.923, $p<0.0001$), and in comparison to the study reporting a ‘low’ level of dependence (SMD=0.671, Z=3.322, $p=0.001$) for the respective samples (see Supplementary Figure 2).

3.1.2 Anger/irritability

For ‘anger/irritability’, a significant ($p<0.0001$) and medium effect size was detected for the acute tobacco abstinence condition in comparison to the *ad.libitum* smoking condition (See Table 3 above and Supplementary Figure 3). Subgroup analyses revealed a major impact of acute abstinence from tobacco on ‘anger/irritability’ for studies reporting a ‘high’ level of tobacco dependence (SMD=0.712, Z=4.453, $p<0.0001$) in comparison to studies reporting a ‘medium’ level of dependence (SMD=0.379, Z=11.643, $p<0.0001$) (see Supplementary Figure 4).

3.1.3 Depressed mood/sadness

For ‘depressed mood/sadness’, a significant ($p<0.0001$) and small effect size was detected for the acute tobacco abstinence condition in comparison to the *ad.libitum* smoking condition (see Table 3 above and Supplementary Figure 5). Subgroup analyses revealed a major impact of acute abstinence from tobacco on ‘depressed mood/sadness’ for studies reporting a ‘high’ level of tobacco dependence (SMD=0.603, Z=9.246 , $p<0.0001$) in comparison to studies reporting a ‘medium’ level of dependence (SMD=0.166, Z=5.557, $p<0.0001$), and in comparison to the study reporting a ‘low’ level of dependence (SMD=0.135 , Z=0.735 , $p=0.462$) (see Supplementary Figure 6).

3.1.4 Composite Negative Affect ('NA')

For composite 'NA', a significant ($p<0.0001$) and medium effect size was detected for the acute tobacco abstinence condition in comparison to the *ad.libitum* smoking condition (see Table 3 above and Supplementary Figure 7). Subgroup analyses revealed a major impact of acute abstinence from tobacco on composite 'NA' for studies reporting a 'high' level of tobacco dependence (SMD=1.005 , Z=8.702, $p<0.0001$) in comparison to studies reporting a 'medium' level of dependence (SMD=0.277 , Z=9.452 , $p<0.0001$), and in comparison to the study reporting a 'low' level of dependence (SMD=0.368 , Z=2.442 , $p=0.015$) for the respective samples (see Supplementary Figure 8).

3.1.5 Meta-regression

A significant effect was detected for sex on 'anxiety' (slope Z=2.94, $p=0.003$), on 'anger/irritability' (slope Z=4.52, $p<0.0001$), on 'depressed mood/sadness' (slope Z=2.84, $p=0.004$), and on composite 'NA' (slope Z=4.35, $p<0.0001$), with samples consisting of a higher percentage of female smokers reporting more severe mood and anxiety symptoms in comparison to samples with a smaller percentage of female smokers (see supplementary Figures 9-12). The effect of sex remained significant ($p<0.05$) on 'anxiety' and 'anger/irritability' after controlling for levels of tobacco dependence, hours of abstinence, and age in a meta-regression model as illustrated in supplementary Table 2. No effect for 'age' was detected ($P>0.05$). The same regression model revealed a possible effect for hours of abstinence on 'anxiety' ($p<0.05$) and on 'anger /irritability' ($p=0.001$) symptoms while holding constant the other moderator variables (see supplementary Table 2). Symptoms of 'anxiety' and of 'anger/irritability' were most severe at 12hrs post-quit in comparison to the other time points, suggesting a possible earlier peak in comparison to symptoms of 'depressed mood/sadness'.

A significant effect was detected for levels of tobacco dependence on all mood and anxiety symptoms and on composite 'NA' ($p<0.05$), thus providing support to the previously described subgroup analyses.

3.1.6 Sensitivity analysis

Sensitivity analyses conducted with pre/post correlation values of 0 detected a significant effect for the acute tobacco abstinence condition in comparison to the *ad.libitum* smoking condition on 'anxiety', (SMD=0.639, p<0.0001), 'anger/irritability' (SMD=0.522, p<0.0001), 'depressed mood/sadness' (SMD=0.272, p<0.0001), and total 'NA' (SMD=0.479, p<0.0001). Similarly, sensitivity analyses conducted with a pre/post correlation value of 0.9 revealed a significant effect for the acute tobacco abstinence condition in comparison to the *ad.libitum* smoking condition on 'anxiety', (SMD=0.569, p<0.0001), 'anger/irritability' (SMD=0.451, p<0.0001), 'depressed mood/sadness' (SMD=0.261, p<0.0001), and total 'NA' (SMD=0.396, p<0.0001) (forest plots are available on request from the corresponding author).

3.2 Qualitative

A total of 14 studies were included in the qualitative review. Seven of these studies assessed sex differences related to negative mood and anxiety symptoms experienced during acute tobacco abstinence (Al'Absi et al, 2002; Ashare & Kable, 2015; Jacobsen et al, 2005; Levental et al, 2007; Perkins et al, 2013; Pang & Leventhal, 2013; Xu et al, 2008), while another seven studies assessed the impact of acute tobacco abstinence on negative mood and anxiety symptoms at multiple time points within a 24hrs timeframe (Aguirre et al, 2015; Brown et al, 2013; Bujarski et al, 2015; Hendricks et al, 2006; Morrel et al, 2008; Sheets et al, 2015; Smith et al, 2009). Study characteristics and demographic data are shown in Tables 4a and 4b.

Table 4a. Characteristics of studies assessing sex differences related to the experience of negative mood and anxiety symptoms during acute tobacco abstinence.

Study (Country)	Study Quality	Intention to quit	Time points for mood and anxiety measurements in hours	Mood measures	Objective measure of acute tobacco abstinence	Level of Tobacco Dependence	Years of regular smoking (SD)	Mean cigarettes smoked per day (SD)	Sample size and sex (%)	Age in years (SD)	Study Design
Ashare & Kable, 2015 (USA)	Good	No	24.0	PANAS	Breath Carbon Monoxide (CO)	FTND 4.7(1.6)	N/A	16.4 (11)	33 (63% males, 37% females)	38.5 (13.8)	Within- subjects experimental design
Al'Absi et al 2002 (USA)	Fair	No	18.0	WSC	Breath Carbon Monoxide (CO) Systolic BP Diastolic BP Heart rate	FTND 5.3	4.0 (N/A)	19.5 (N/A)	30 (50% females, 50% males)	24.5 (N/A)	Within-subjects experimental design
Jacobsen et al.2005 (USA)	Fair	No	24.0	POMS	Breath Carbon Monoxide (CO) Urinary Cotinine	FTND 2.6	3.9 (N/A)	11.7 (6.7)	41 (65% females, 35% males)	17.0 (1.1)	Mixed between Subjects and within subjects experimental design**
Leventhal et al. 2007 (USA)	Good	No	12.0	PANAS	Breath Carbon Monoxide (CO)	FTND 6.47	19.7 (10.3)	22.2 (6.61)	203 (50% males, 50% females)	36.7 (10.1)	Within- subjects experimental design

Pang & Leventhal 2013 (USA)	Good	No	16.0	POMS	Breath Carbon Monoxide (CO)	FTND 5.3	24.2 (N/A)	16.7 (6.5)	199 (66% males, 34% females)	43.4 (10.2)	Within-subjects experimental design
Perkins et al.2013 (USA)	Fair	No	12.0	Diener & Emmons (1984) Mood Form	Breath Carbon Monoxide (CO)	FTND 4.8	N/A	19.5 (N/A)	105 (40% females, 60% males)	27.3 (N/A)	Within-subjects experimental design
Xu et al. 2008 (USA)	Good	No	13.0	POMS	Breath Carbon Monoxide (CO)	FTND 5.2	17.2 (N/A)	20.4 (N/A)	64 (59% males, 41% females)	36.1 (N/A)	Within-subjects experimental design

Note. **: Demographic characteristics and number of participants for nonsmoker controls or groups receiving a treatment other than placebo or no treatment at all that were reported in studies employing a mixed between-subjects and within-subjects experimental design were not included in the table as they were not considered for the current review. CO= Carbon Monoxide; FTND= Fagerström Test of Nicotine Dependence (with severity score: 0-2: Very low dependence, 3-4: Low dependence, 5: Medium dependence, 6-7: High dependence, 8-10: Very high Dependence); hrs= hours; PANAS= Positive and Negative Affect Schedule; POMS=Profile of Mood States;;WSC=Withdrawal Symptoms Checklist; SD=Standard deviation; %=Percentage . N/A = Negative Affect.

Table 4b. Characteristics of studies assessing the early time course of mood and anxiety symptoms during acute tobacco abstinence.

Study (Country)	Study Quality	Intention To quit	Time points for mood and anxiety measurements in hours	Mood measures	Objective measure of acute tobacco abstinence	Level of Tobacco Dependence	Years of regular smoking (SD)	Mean cigarettes smoked per day (SD)	Sample size and sex (%)	Age (SD)	Study Design
Aguirre et al. 2015 (USA)	Good	No	1.0 17.0	POMS	Breath Carbon Monoxide (CO)	FTND 5.3	24.5 (N/A)	16.7 (7.0)	286 (68% males, 32% females)	44.0 (10.5)	Within- subjects experimental design
Brown et al, 2013 (UK)	Good	No	0.5 2.0 4.0 6.0	MPSS	Breath Carbon Monoxide (CO)	N/A	19.0 (N/A)	23.1 (N/A)	66 (51.5% females, 49.5% males)	34.3 (N/A)	Mixed within subject and between-subjects experimental design**
Bujarski et al 2015 (USA)	Fair	No	Hourly during a 24hrs period	EMA measure items taken from POMS **And** MNWS	Breath Carbon Monoxide (CO) Urinary cotinine	FTND Moderate smokers: 5.6 Heavy smokers: 8.3	N/A	Moderate smokers: 9.5 (2.4) Heavy smokers: 19.1 (2.7)	30 (30% females,70% males)	Moderate smokers: 36.7(11.7) Heavy smokers: 38.3 (13.1)	Mixed within-subject and between -subjects experimental design
Hendricks et al. 2006 (USA)	Fair	No	0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0.	WSWS	Breath Carbon Monoxide (CO) Heart Rate (HR)	FTND 5.4	12.8 (8.1)	23.5 (4.7)	50(58% females, 42% males)	29.2 (8.3)	Within- subjects experimental design
Morrel et al.2008 (USA)	Fair	No	3.5 18.0	POMS	Breath Carbon Monoxide (CO)	FTND 4.6	N/A	16.0 (N/A)	30(74% males, 26% females)	27.0 (10.1)	within -subjects experimental design

Sheets et al., 2015 (USA)	Fair	No	Hourly during a 24hrs period	EMA measure items taken from POMS and MNWS	Breath Carbon Monoxide (CO) Urinary cotinine	FTND Moderate smokers: 5.6 Heavy smokers: 8.3)	N/A	Moderate smokers:9.5 (2.4) Heavy smokers:19.1 (2.7)	30 (30% females, 70% males)	Moderate smokers: 36.7 (11.7) Heavy smokers: 38.3 (13.1)	Mixed within-subjects and between- subjects experimental design
Smith et al. 2009 (USA)	Good	No	1.5 3.5 14.5 17.5 20.0 22.5	POMS	Breath Carbon Monoxide (CO) Salivary Cotinine	FTND 4.0	2.5 (N/A)	13.0 (N/A)	55 (49% females, 51% males)	16.4 (1.3)	Mixed between-subjects and within-subjects experimental design**

Note. **: Demographic characteristics and number of participants for nonsmoker controls or groups receiving a treatment other than placebo or no treatment at all that were reported in studies employing a mixed between-subjects and within-subjects experimental design were not included in the table as they were not considered for the current review. CO= Carbon Monoxide; FTND= Fagerström Test of Nicotine Dependence (with severity score: 0-2: Very low dependence, 3-4: Low dependence, 5: Medium dependence, 6-7: High dependence, 8-10: Very high Dependence); hrs= hours; MNWS=Minnesota Nicotine Withdrawal Scale; POMS=Profile of Mood States; MPSS=Mood and Physical Symptoms Scale; WSWS=Wisconsin Smoking Withdrawal Scale; EMA=Ecological Momentary Assessment; SD=Standard deviation; %=Percentage, N/A = Negative Affect.

3.2.1 Sex differences

Overall, five of the seven studies revealed significant differences between female and male smokers.

The study conducted by Pang and Leventhal (2013) revealed that female smokers suffered more severe abstinence-induced effects on negative affect constructs such as ‘anger’, ‘anxiety’, ‘depression’ and composite ‘NA’ in comparison to male smokers. After applying a Bonferroni-Holm correction for type 1 error, these authors revealed that sex differences remained significant for the ‘anxiety’ and composite ‘NA’ constructs. Similar findings were reported in the study conducted by Xu et al. (2008) in which female smokers experienced worse anger and anxiety symptoms during acute abstinence from tobacco (13hrs) in comparison to male smokers. The study conducted by Al’Absi et al. (2002) reported higher anxiety and irritability 18hrs after smoking cessation in comparison to male smokers.

Leventhal et al. (2007) conducted a study to specifically investigate sex differences on objective (physiological) and subjective (affective) measures of tobacco withdrawal during an acute abstinence period of 12hrs. According to their findings “women consistently reported larger abstinence-induced increases in negative affect (i.e., anger, anxiety, sadness, irritability, tension, restlessness, impatience) and greater desire to relieve withdrawal distress by smoking than men”(73, p.1). Jacobsen et al. (2005) showed that symptoms of ‘anxiety’ increased significantly just for adolescent female smokers during a 24hrs abstinence period. However, studies conducted by Perkins et al. (2013) and by Ashare & Kable (2015) did not reveal any main effect of sex on negative mood and anxiety symptoms experienced by smokers during acute abstinence from tobacco.

Considering that these studies utilized an analogous experimental design, it can be inferred that female smokers may experience more severe mood and anxiety symptoms in comparison to male smokers (with similar levels of tobacco dependence) up to 24 hrs post smoking cessation. This may be especially relevant for 'anger/irritability', and 'anxiety' symptoms as reported by the aforementioned studies (Al'Absi et al., 2002; Jacobsen et al., 2005; Leventhal et al., 2007; Xu et al. 2008). These findings provide support to the meta-regression results as described in section 3.1.5.

3.2.2 Time course

Studies that explored the time course of negative mood and anxiety symptoms up to 24hrs post smoking cessation (Aguirre et al., 2015; Brown et al., 2013; Bujarski et al., 2015; Hendricks et al., 2006; Morrel et al., 2008 ; Sheets et al., 2015; Smith et al., 2008) revealed that symptoms manifested during acute abstinence (as soon as 1hr post-quit) and that their severity increased as the length of the abstinence period increased.

In particular, Hendricks et al. (2006) revealed that 'anger' symptoms manifested significantly at 1 hr post-smoking cessation, followed by 'anxiety' (2hrs) and 'sadness' (3hrs) symptoms in a sample of 50 daily smokers. Similarly, a study conducted by Morrel et al. (2008) on 30 daily smokers with a medium level of tobacco dependence showed that symptoms of 'anxiety' manifested significantly ($p<0.05$) at 3.5 hrs post-quit, while symptoms of 'depression' manifested significantly ($p<0.05$) only at 18hrs post-smoking cessation. Symptoms of 'anxiety' peaked at 18hrs of abstinence. Brown et al. (2013) assessed the time course of mood symptoms by testing smokers randomized to receive a placebo treatment during temporary abstinence in a naturalistic setting (a train journey). Their findings revealed that symptoms of 'irritability' and 'anxiety' manifested significantly ($p<0.05$) at 3hrs post-smoking cessation. The severity of these symptoms

increased modestly over a 6 hrs time period. Symptoms of ‘depression’ showed a slower increase in comparison to symptoms of ‘anxiety’ and ‘irritability’. Smith et al. (2008) revealed that 50 adolescent smokers (mean age=16.4 yrs) with a moderate level of tobacco dependence experienced a slight increase in ‘anger’ during an acute tobacco abstinence period ranging from 1hr to 24hrs.

Bujarski et al. (2015) revealed that composite ‘NA’ symptoms manifested significantly ($p<0.05$) at 3hrs post-smoking cessation in 30 daily smokers and peaked at 24hrs of abstinence. Similarly, the studies conducted by Sheets et al. (2015) and by Aguirre et al. (2015), showed that symptoms of composite ‘NA’ started at 1hr post-quit, steadily increasing until their latest mood measurements performed at 24hrs (Sheets et al., 2015), and at 17hrs (Aguirre et al., 2015).

Besides reporting changes on mood and anxiety symptoms at different time points, the studies conducted by Aguirre et al. (2015), Bujarski et al. (2015), and by Sheets et al. (2015) also assessed the interaction between severity of tobacco dependence and hours of tobacco abstinence. Specifically, the study conducted by Aguirre et al. (2015) revealed that levels of tobacco dependence (as reported by the FTND) predicted significantly ($p<0.001$) composite ‘NA’. Additionally, Bujarski et al. (2015) showed a difference in relation to the progression of ‘NA’ symptoms between moderate and heavy smokers in the earliest phases of withdrawal as “post-hoc tests revealed significant group ($p<0.05$) difference beginning 3 hours after the last cigarette such that heavy smokers had significantly ($p<0.05$) greater withdrawal/NA as compared to moderate smokers starting 3 hours after the last cigarette and lasting until the end of the day”(72, p.1). Likewise, Sheets et al. (2015) revealed that heavy smokers experienced worse negative emotions compared to light smokers during an acute abstinence period ranging from 1hr to24 hrs.

In summary, these findings suggest that negative mood and anxiety symptoms emerge within the first 3 hours post-smoking cessation, and that the severity of these symptoms increase steadily over a 24hrs period of abstinence without receiving any form of treatment. This seems to be

especially relevant for ‘anxiety’ and ‘anger/irritability’. Furthermore, smokers with severe tobacco dependence seem to experience worse mood symptoms. These results provide further support to the quantitative analysis conducted in Section 3.1.

4 Discussion

The current review was conducted to 1) provide a quantification of the severity of negative mood and anxiety symptoms occurring up to 24hrs during acute tobacco abstinence, 2) to investigate possible sex differences related to the experience of specific symptoms, and 3) to investigate the early time course of symptoms.

Results from quantitative analyses revealed a significant ($p<0.0001$) increase in ‘anxiety’, ‘anger/irritability’, ‘depressed mood /sadness’, and a significant increase in composite ‘NA’ ($p=0.015$) within a mean time period of 17hrs (SD=3.63) post-smoking cessation. These findings provide support to the DSM-V guidelines related to the ‘Tobacco Withdrawal Syndrome’ and to a previous review conducted by McLaughlin, Dani, & De Biasi (2015) that proposed the emergence of an aversive tobacco abstinence syndrome at 4hrs-24hrs post-quit.

Uniquely, this review proposes ‘anxiety’ as the most severe affective symptom (SMD=0.63) experienced by daily smokers during the acute abstinence period, followed by ‘anger/irritability’ (SMD=0.51). Results from the qualitative analysis suggest that these symptoms may emerge as early as 3hrs post-smoking cessation and increase steadily in the following hours. These findings are in contrast to previous studies showing affective symptoms to not peak significantly below than 24 hrs post abstinence (Hatsukami et al, 1989). Symptoms of depressed mood are milder (SMD=0.27) and appear late compared to symptoms of anxiety and irritability, thus supporting the findings of another review (Hughes, 2007b) in which depression and dysphoric mood symptoms were found to increase with the length of abstinence, and to peak at 1-3 weeks post

cessation.

Results from both quantitative and qualitative analyses confirm that female smokers suffer more severe mood and anxiety symptoms during an acute abstinence period compared to male smokers, thus endorsing the strong impact of sex in the experience of negative affect during acute abstinence from tobacco. This finding is in line with a literature review conducted recently by Becker et al (2017). According to these authors, sex and gender differences occur in all stages of the drug addiction cycle. Specific to the abstinence phase, there is evidence from the literature that women suffer more severe negative affect compared to men. This occurs with the majorities of drugs of abuse, including tobacco. Becker and colleagues (2017) provided a comprehensive explanation of the possible physiological causes of this phenomenon, revealing that the menstrual cycle and the production of ovarian hormones may exacerbate the subjective effects of drug intake and abstinence in women.

The current review also proposes a relationship between the severity of tobacco dependence and the experience of mood and anxiety symptoms during acute tobacco abstinence for daily smokers. In particular, meta-regression results revealed that levels of tobacco dependence may predict significantly ($p<0.0001$) the emergence of mood and anxiety symptoms in the hours following smoking cessation. Additionally, ‘anxiety’, ‘anger/irritability’, ‘depressed mood’, and composite ‘NA’ symptoms were found to be more severe for daily smokers reporting a high level of tobacco dependence compared to daily smokers reporting a medium or low level of tobacco dependence as revealed by our subgroup analyses (see section 3.1).

This relationship could be explained through the allostasis theory of Koob (2001). According to Koob and Le Moal (2005), the affective and motivational changes experienced during acute drug abstinence are related to a neurobiological opponent-process mechanism within the brain’s reward circuitry that is dysregulated by chronic drug intake. In particular, “as dependence and withdrawal episodes occur, the brain anti- reward systems including corticotropin releasing factor (CRF),

norepinephrine and dynorphin are recruited. These neurotransmitter systems are activated during the development of excessive drug taking, and this activation is manifest when the drug in removed" (Koob & LeMoal,2005, p.1). The recruitment of these anti-reward systems in combination with decreases in reward-linked neurotransmitter function is thought to cause the emergence of negative affective states during drug abstinence, which in turn may motivate lapse or relapse (i.e. negative reinforcement) (Koob & Le Moal, 2005). A review conducted by Hughes (2007a) provided further support to this statement by revealing 'anxiety', 'anger/irritability', and 'depressed mood' to be true, time limited tobacco abstinence effects and not "offset effects".

4.1 Strengths and limitations

The current review has a number of strengths such as the stringent database search methodology encompassing keywords from both DSM-V and the RDoC matrix. The utilization of the RDoC matrix allowed the inclusion of relevant units of analysis as alternative search terms to the main mood symptoms listed in DSM-V. Additionally, the inclusion/exclusion criteria were rigorous, thus enabling the exclusion of confounders such as daily smokers affected by psychiatric disorders, dependency on other drugs, or subjects enrolled in smoking cessation treatment/programs. Furthermore, only samples of smokers receiving a placebo treatment or no treatment at all were included in the quantitative and qualitative syntheses. Samples of smokers receiving any form of treatment (e.g. NRTs, counselling) were not included in the current review, thus allowing the assessment of mood symptoms that daily smokers are likely to suffer during unassisted quit attempts. This is important considering that majority of smokers attempt to quit without utilizing any form of treatment or medication (Edwards et al., 2014; Smith et al., 2015).

Methodological strengths encompass the exclusion of studies employing a between-subjects experimental design only (e.g. smokers vs nonsmokers) from the current review. Notably, they present greater between-subjects variability (Shiffman, West, & Gilbert, 2004) and lower internal validity compared to studies employing a within-subjects experimental design (Hughes et al.,

2018). Studies employing a within-subjects design are considered optimal to test the effect of tobacco abstinence on withdrawal symptoms (Shiffman, West, & Gilbert, 2004). Additionally, only within-group measurements were extracted from studies employing a mixed method within-subjects and between-subjects experimental design.

The concurrent investigation of relevant moderator variables such as 'sex', 'severity of dependence', and 'hours of abstinence' on the experience of negative mood symptoms emerging during acute tobacco abstinence could be considered another strength of the current review. In particular, the utilization of both quantitative and qualitative analysis techniques allowed to validate the impact of 'sex', and 'hours of abstinence' on specific mood symptoms. The insertion of other moderator variables such as 'years of smoking', and 'cigarettes smoked per day' was taken in consideration, although a study conducted by Donny et al. (2008) revealed that 'cigarette smoked per day' and 'years of smoking' accounted for just <6% of the variance in the severity of tobacco dependence in 489 daily smokers. Thus, scales of tobacco and nicotine dependence with high internal validity and reliability such as The Fagerström Test for Nicotine Dependence ('FTND') (Heaterton et al., 1991) may constitute a more appropriate moderator and were therefore utilized to compute the 'severity of dependence' covariate.

The current review also presents several potential limitations. In particular, it was not possible to investigate thoroughly the 'age' moderator variable as only a few studies tested adolescent daily smokers (Bidwell et al., 2013; Colby et al, 2010; Everson et al, 2006; Smith et al. 2009). As introduced previously, it has been proposed that adolescent smokers may experience less severe withdrawal symptoms during abstinence in comparison to adult smokers (Lydon et al., 2014). Furthermore, it has been proposed that smokers with the intention to quit for good may suffer more severe withdrawal symptoms in comparison to smokers with no intention to quit (Perkins, Stitzer, & Lerman, 2006). Only one study of those included in the review tested smokers who intended to quit (West & Hajek, 2004), thus it was not possible to include 'intention to quit' as a

moderator in both quantitative and qualitative analyses. Consequently, the magnitude of abstinence effects on mood symptoms revealed by the current review could be underestimated.

Another potential limitation could be related to the CO cut-off values necessary to distinguish smokers from nonsmokers within 24hrs of acute abstinence used by the studies included in the review. In fact, while the majority of studies (75%) who reported CO values used a cut-off criteria of 8-10ppm as described by the SRNT subcommittee on Biochemical Verification (2002), a study conducted by Cropsey et al. (2014) revealed that this cut-off value may be too high and may produce high false-negative rates (up to 20%). Thus, several smoking participants could have been misclassified as abstinent by the studies included in the review.

The inability to test the impact of acute tobacco abstinence on 'Anhedonia', which has been recently proposed as a novel affective symptom of the tobacco withdrawal syndrome (Hughes et al, 2018), could be considered another limitation of the current review. The relationship between negative affective symptoms and craving, which has a significant impact on smoking lapse and relapse, was also not investigated as it was beyond the scope of this study. Additionally, this review did not explore racial/ethnic differences in mood and anxiety symptoms emerging during acute abstinence from tobacco. In fact, recent studies proposed differences related to the experience of withdrawal symptoms and smoking cessation outcomes across different racial/ethnic groups (e.g. Weinberger et al., 2017; Bello et al., 2015). Moreover, the current review focused on tobacco smoking, excluding investigation of aversive mood symptoms occurring during the first few hours of abstinence from alternative methods of nicotine administration (e.g. e-cigarettes).

Finally, results from the quantitative analysis should be interpreted with caution as considerable heterogeneity was found among the studies pooled for each mood and anxiety symptom. This could be related to methodological procedures such as the utilization of different mood measures. A random-effect model was selected to take into account possible sources of heterogeneity between studies. According to Higgins and Green (2011), the random-effect model "involves an assumption that the effects being estimated in the different studies are not

identical but follow some distribution. However, the validity of this distributional assumption it is difficult to determine" (Higgins & Green, 2011, p.1).

4.2 Clinical Relevance

The clinical relevance of the current review resides in the quantification of the severity of negative mood and anxiety symptoms occurring during acute abstinence from tobacco, in addition to sex differences and to their early time course. In particular, a strong relationship between sex and the severity of negative mood and anxiety symptoms experienced during acute tobacco abstinence should motivate researchers and clinicians to identify and provide sex- tailored interventions targeting relevant negative mood symptoms. This would be of importance considering the strong association between negative affective symptoms and lapses/relapses (e.g. Ferguson et al., 2017; Minami et al., 2014; Patterson et al., 2008), and that women who lapse early exhibit heightened negative mood symptoms immediately after quitting (Cofta-Woerpel et al., 2011). Furthermore, a recent review conducted by Smith et al. (2016), that explored sex variations in smoking cessation, revealed that women have more difficulty maintaining long-term abstinence and relapse more frequently compared to men (Smith et al., 2016).

Smoking cessation treatments should also consider the severity of specific mood symptoms experienced by smokers with different levels of tobacco dependence during acute abstinence, in addition to their early manifestation and time course. This could be done by providing targeted mood related counselling and/or medications to alleviate the distress of daily smokers as soon as they quit. This would allow a timely and effective targeting of symptoms such as 'anxiety' and 'anger/irritability', which appear to manifest and to peak earlier in comparison to symptoms of 'depressed mood/sadness'. A timely targeting of negative mood symptoms would prevent smoking reinstatement as early lapses may occur few hours following smoking cessation (Bolman et al., 2018; Brown et al., 2005; Deiches et al., 2013 ; Franklin et al.,2018;).Additionally, a recent study

conducted by Zuo, Rabinovich, and Gilbert (2017) revealed that "slower dissipation of negative affect, especially anxiety and anger, represents a greater risk for relapse to smoking beyond that predicted by craving during early abstinence. Thus, temporal profiles of the affective symptoms convey unique motivational significance in relapse. Reduction in NA during early abstinence may be a valid target for interventions to increase long-term cessation success rates" (p.761).

The current review has also underlined the utility of subjective scales of tobacco dependence (e.g. FTND). In particular, considering the possible relationship between scores on scales of tobacco dependence and the severity of mood and anxiety symptoms experienced by daily smokers during acute abstinence, these could be used by healthcare providers to predict the intensity of negative mood symptoms that daily smokers are likely to experience following smoking cessation.

5 Conclusion

The current review has quantified the severity of mood and anxiety symptoms emerging during acute tobacco abstinence by revealing a significant increase ($p<0.0001$) in 'anxiety', 'anger/irritability', and 'depressed mood/sadness' within 24 hours following smoking cessation. It showed 'anxiety' to be the most severe symptom (SMD=0.63) experienced by daily smokers during acute abstinence, and 'depressed mood/sadness' to be the mildest symptom (SMD=0.27). Additionally, this review confirmed that female smokers suffer worse mood and anxiety symptoms in comparison to male smokers during acute tobacco abstinence. These symptoms manifest within 3hrs post-quit and increase steadily over a 24hrs period.

Considering the strong impact of acute tobacco abstinence on mood and anxiety symptoms and their early manifestation, future research should focus on investigating the severity and time-course of the same symptoms occurring during acute abstinence from alternative methods of nicotine administration such as vaporizers and e-cigarettes, which remain under-investigated.

Furthermore, considering that the current review included only four studies testing adolescent daily smokers, and that there is a lack of summarized empirical evidence in the literature, future reviews and meta-analyses should explore the impact of acute abstinence on mood symptoms in smokers from younger age groups. This would be of importance considering that tobacco addiction is mainly established in adolescence due to the vulnerability of adolescents' brain. Finally, the current review has underlined the importance of implementing sex-tailored interventions targeting mood symptoms in smoking cessation programs. These might reduce early lapses and relapses in female smokers, and consequently reduce sex disparities in smoking cessation rates.

Conflicts of Interest

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References

Aguirre, C. G., Madrid, J., & Leventhal, A. M. (2015). Tobacco withdrawal symptoms mediate motivation to reinstate smoking during abstinence. J. Abnorm. Psychol., 124(3), 623. https://psycnet.apa.org/doi/10.1037/abn0000060

al'Absi, M., Amunrud, T., & Wittmers, L. E. (2002). Psychophysiological effects of nicotine abstinence and behavioral challenges in habitual smokers. Pharmacol. Biochem. Behav., 72(3), 707-716. https://doi.org/10.1016/S0091-3057(02)00739-6

Allen, S. S., Bade, T., Hatsukami, D., & Center, B. (2008). Craving, withdrawal, and smoking urges on days immediately prior to smoking relapse. Nicotine Tob. Res., 10(1), 35-45. https://doi.org/10.1080/14622200701705076

American Psychiatric Association. (1994). Diagnostic and statistical manual of mental disorders (4th ed.).

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

Ashare, R. L., & Kable, J. W. (2015). Sex differences in time perception during smoking abstinence. Nicotine Tob. Res., 17(4), 449-454. https://doi.org/10.1093/ntr/ntu260

Babb, S. (2017). Quitting smoking among adults—United States, 2000–2015. MMWR. Morbidity and mortality weekly report, 65. http://dx.doi.org/10.15585/mmwr.mm6552a1

Baker, T. B., Piper, M. E., McCarthy, D. E., Majeskie, M. R., & Fiore, M. C. (2004). Addiction motivation reformulated: an affective processing model of negative reinforcement. Psychol. Rev., 111(1), 33. doi: 10.1037/0033-295X.111.1.33

Balk, E. M., Earley, A., Patel, K., Trikalinos, T. A., & Dahabreh, I. J. (2012). Empirical assessment of within-arm correlation imputation in trials of continuous outcomes. Available from: https://www.ncbi.nlm.nih.gov/books/NBK115797/

Becker, J. B., McClellan, M. L., & Reed, B. G. (2017). Sex differences, gender and addiction. J.Neurosci. Res., 95(1-2), 136-147. https://doi.org/10.1002/jnr.23963

Bello, M. S., Pang, R. D., Cropsey, K. L., Zvolensky, M. J., Reitzel, L. R., Huh, J., & Leventhal, A. M. (2015). Tobacco withdrawal amongst African American, Hispanic, and white smokers. Nicotine Tob. Res., 18(6), 1479-1487. https://doi.org/10.1093/ntr/ntv231

Bidwell, L. C., Leventhal, A. M., Tidey, J. W., Brazil, L., Niaura, R. S., & Colby, S. M. (2012). Effects of abstinence in adolescent tobacco smokers: Withdrawal symptoms, urge, affect, and cue reactivity. Nicotine Tob. Res., 15(2), 457-464. https://doi.org/10.1093/ntr/nts155

Bolman, C., Verboon, P., Thewissen, V., Boonen, V., Soons, K., & Jacobs, N. (2018). Predicting smoking lapses in the first week of quitting: an ecological momentary assessment study. J. Addict. Med., 12(1), 65.doi:10.1097/ADM.0000000000000365

Borenstein, M., Cooper, H., Hedges, L., & Valentine, J. (2009). Effect sizes for continuous data. The handbook of research synthesis and meta-analysis, 2, 221-235.

Borenstein, M., Hedges, L., Higgins, J., & Rothstein, H. *Comprehensive Meta-Analysis Version 3* Biostat, Englewood, NJ 2013.

Borrelli, B., Spring, B., Niaura, R., Hitsman, B., & Papandonatos, G. (2001). Influences of gender and weight gain on short-term relapse to smoking in a cessation trial. J Consult Clin. Psychol, 69(3), 511. https://psycnet.apa.org/doi/10.1037/0022-006X.69.3.511

Brown, J., Hajek, P., McRobbie, H., Locker, J., Gillison, F., McEwen, A., ... & West, R. (2013). Cigarette craving and withdrawal symptoms during temporary abstinence and the effect of nicotine gum. Psychopharmacol., 229(1), 209-218. https://doi.org/10.1007/s00213-013-3100-2

Brown, R. A., Lejuez, C. W., Kahler, C. W., Strong, D. R., & Zvolensky, M. J. (2005). Distress tolerance and early smoking lapse. Clin. Psychol. Rev., 25(6), 713-733. https://doi.org/10.1016/j.cpr.2005.05.003

Bujarski, S., Roche, D. J., Sheets, E. S., Krull, J. L., Guzman, I., & Ray, L. A. (2015). Modeling naturalistic craving, withdrawal, and affect during early nicotine abstinence: A pilot

ecological momentary assessment study. Exp. Clin. Psychopharmacol., 23(2), 81. https://psycnet.apa.org/doi/10.1037/a0038861

Castro, Y., Kendzor, D. E., Businelle, M. S., Mazas, C. A., Cofta-Woerpel, L., Cinciripini, P. M., & Wetter, D. W. (2011). Structural and predictive equivalency of the Wisconsin Smoking Withdrawal Scale across three racial/ethnic groups. Nicotine Tob Res, 13(7), 548-555. https://doi.org/10.1093/ntr/ntr039

Chaiton, M. O., Cohen, J. E., O'Loughlin, J., & Rehm, J. (2009). A systematic review of longitudinal studies on the association between depression and smoking in adolescents. BMC public health, 9(1), 356. https://doi.org/10.1186/1471-2458-9-356

Chaiton, M., Diemert, L., Cohen, J. E., Bondy, S. J., Selby, P., Philipneri, A., & Schwartz, R. (2016). Estimating the number of quit attempts it takes to quit smoking successfully in a longitudinal cohort of smokers. BMJ open, 6(6), e011045. doi: 10.1136/bmjopen-2016-011045.

Cochran, W.G., 1950. The comparison of percentages in matched samples. Biometrika 37(3/4), 256–266. https://doi.org/10.2307/2332378.

Cofta-Woerpel, L., McClure, J. B., Li, Y., Urbauer, D., Cinciripini, P. M., & Wetter, D. W. (2011). Early cessation success or failure among women attempting to quit smoking: Trajectories and volatility of urge and negative mood during the first postcessation week. J.Abnorm. Psychol., 120(3), 596. https://psycnet.apa.org/doi/10.1037/a0023755

Cohen J. 1988. *Statistical power analysis for the social sciences*.

Colby, S. M., Leventhal, A. M., Brazil, L., Lewis-Esquerre, J., Stein, L. A. R., Rohsenow, D. J., ... & Niaura, R. S. (2009). Smoking abstinence and reinstatement effects in adolescent cigarette smokers. Nicotine Tob. Res., 12(1), 19-28. https://doi.org/10.1093/ntr/ntp167

Cook, J. W., Spring, B., McChargue, D., & Hedeker, D. (2004). Hedonic capacity, cigarette craving, and diminished positive mood. Nicotine Tob. Res., 6(1), 39-47. https://doi.org/10.1080/14622200310001656849

Craig, D., Parrott, A., & Coomber, J. A. (1992). Smoking cessation in women: Effects of the menstrual cycle. Int J Addict, 27(6), 697-706. https://doi.org/10.3109/10826089209068761

Cropsey, K. L., Trent, L. R., Clark, C. B., Stevens, E. N., Lahti, A. C., & Hendricks, P. S. (2014). How low should you go? Determining the optimal cutoff for exhaled carbon monoxide to confirm smoking abstinence when using cotinine as reference. Nicotine Tob Res, 16(10), 1348-1355. https://doi.org/10.1093/ntr/ntu085

Deiches, J. F., Baker, T. B., Lanza, S., & Piper, M. E. (2013). Early lapses in a cessation attempt: lapse contexts, cessation success, and predictors of early lapse. Nicotine Tob. Res., 15(11), 1883-1891. https://doi.org/10.1093/ntr/ntt074

Dixon-Woods, M., Agarwal, S., Jones, D., Young, B., & Sutton, A. (2005). Synthesising qualitative and quantitative evidence: a review of possible methods. Journal of health services research & policy, 10(1), 45-53. https://doi.org/10.1177%2F135581960501000110

Doherty, K., Kinnunen, T., Militello, F. S., & Garvey, A. J. (1995). Urges to smoke during the first month of abstinence: relationship to relapse and predictors. Psychopharmacol., 119(2), 171-178. https://doi.org/10.1007/BF02246158

Donny, E. C., Griffin, K. M., Shiffman, S., & Sayette, M. A. (2008). The relationship between cigarette use, nicotine dependence, and craving in laboratory volunteers. Nicotine Tob. Res., 10(3), 447-455. https://doi.org/10.1080/14622200801901906

Edwards, S. A., Bondy, S. J., Callaghan, R. C., & Mann, R. E. (2014). Prevalence of unassisted quit attempts in population-based studies: a systematic review of the literature. Addictive Behaviors, 39(3), 512-519. https://doi.org/10.1016/j.addbeh.2013.10.036

Egger, M., Smith, G. D., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. Bmj, 315(7109), 629-634. https://doi.org/10.1136/bmj.315.7109.629

Etter, J. F., Prokhorov, A. V., & Perneger, T. V. (2002). Gender differences in the psychological determinants of cigarette smoking. Addiction, 97(6), 733-743. https://doi.org/10.1046/j.1360-0443.2002.00135.x

Everson, E. S., Daley, A. J., & Ussher, M. (2006). Does exercise have an acute effect on desire to smoke, mood and withdrawal symptoms in abstaining adolescent smokers?. Addict.Behav., 31(9), 1547-1558. https://doi.org/10.1016/j.addbeh.2005.11.007

Ferguson, S. G., Shiffman, S., & Blizzard, L. (2017). Triggers of smoking lapses over the course of a quit attempt. J.Smoking Cessat., 12(4), 205-212. https://doi.org/10.1017/jsc.2016.21

Fluharty, M., Taylor, A. E., Grabski, M., & Munafò, M. R. (2016). The association of cigarette smoking with depression and anxiety: a systematic review. Nicotine Tob. Res., 19(1), 3-13. https://doi.org/10.1093/ntr/ntw140

Follmann, D., Elliott, P., Suh, I. L., & Cutler, J. (1992). Variance imputation for overviews of clinical trials with continuous response. J. Clin. Epidemiol., 45(7), 769-773. https://doi.org/10.1016/0895-4356(92)90054-Q

Franklin, T. R., Jagannathan, K., Hager, N., Fang, Z., Xu, S., Wong, J., ... & Wetherill, R. (2018). Brain substrates of early (4 h) cigarette abstinence: Identification of treatment targets. Drug Alcohol Depend., 182, 78-85. https://doi.org/10.1016/j.drugalcdep.2017.10.010

Froeliger, B., McConnell, P. A., Stankeviciute, N., McClure, E. A., Kalivas, P. W., & Gray, K. M. (2015). The effects of N-acetylcysteine on frontostriatal resting-state functional connectivity, withdrawal symptoms and smoking abstinence: a double-blind, placebo-controlled fMRI pilot study. Drug Alcohol Depend., 156, 234-242. https://doi.org/10.1016/j.drugalcdep.2015.09.021

Fu, R., Vandermeer, B. W., Shamliyan, T. A., O'Neil, M. E., Yazdi, F., Fox, S. H., & Morton, S. C. (2013). Handling continuous outcomes in quantitative synthesis. In Methods Guide for Effectiveness and Comparative Effectiveness Reviews [Internet]. Agency for Healthcare Research and Quality (US).

Hall, F. S., Der-Avakian, A., Gould, T. J., Markou, A., Shoaib, M., & Young, J. W. (2015). Negative affective states and cognitive impairments in nicotine dependence. Neurosci.Biobehav. Rev., 58, 168-185. https://doi.org/10.1016/j.neubiorev.2015.06.004

Hatsukami, D., Fletcher, L., Morgan, S., Keenan, R., & Amble, P. P. (1989). The effects of varying cigarette deprivation duration on cognitive and performance tasks. J. Subst. Abuse. https://psycnet.apa.org/record/1997-73134-001

Heatherton, T. F., Kozlowski, L. T., Frecker, R. C., & FAGERSTROM, K. O. (1991). The Fagerström test for nicotine dependence: a revision of the Fagerstrom Tolerance Questionnaire. Brit J Addict., 86(9), 1119-1127. https://doi.org/10.1111/j.1360-0443.1991.tb01879.x

Heffner, J. L., Mingione, C., Blom, T. J., & Anthenelli, R. M. (2011). Smoking history, nicotine dependence, and changes in craving and mood during short-term smoking abstinence in alcohol dependent vs. control smokers. Addict Behav, 36(3), 244-247. https://doi.org/10.1016/j.addbeh.2010.10.008

Hendricks, P. S., & Leventhal, A. M. (2013). Abstinence-related expectancies predict smoking withdrawal effects: Implications for possible causal mechanisms. Psychopharmacol., 230(3), 363-373. https://doi.org/10.1007/s00213-013-3169-7

Hendricks, P. S., Ditre, J. W., Drobes, D. J., & Brandon, T. H. (2006). The early time course of smoking withdrawal effects. Psychopharmacol., 187(3), 385-396. https://doi.org/10.1007/s00213-006-0429-9

Higgins, J.P., Thompson, S.G., Deeks, J.J., Altman, D.G., (2003). Measuring inconsistency in meta-analyses. BMJ Br. Med. J. 327 (7414), 557. https://dx.doi.org/10.1136%

Higgins, J. P., & Green, S. (Eds.). (2011). Cochrane handbook for systematic reviews of interventions (Vol. 4). John Wiley & Sons.

Hughes, J. R. (2007a). Effects of abstinence from tobacco: valid symptoms and time course. Nicotine Tob. Res., 9(3), 315-327. https://doi.org/10.1080/14622200701188919

Hughes, J. R. (2007b). Effects of abstinence from tobacco: etiology, animal models, epidemiology, and significance: a subjective review. Nicotine Tob. Res., 9(3), 329-339. https://doi.org/10.1080/14622200701188927

Hughes, J. R., Keely, J., & Naud, S. (2004). Shape of the relapse curve and long-term abstinence among untreated smokers. Addiction, 99(1), 29-38. https://doi.org/10.1111/j.1360-0443.2004.00540.x

Hughes, J. R., Klemperer, E. M., & Peasley-Miklus, C. (2018). Possible New Symptoms of Tobacco Withdrawal II: Anhedonia—A Systematic Review. Nicotine Tob. Res. https://doi.org/10.1093/ntr/nty171

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., ... & Wang, P. (2010). Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. https://doi.org/10.1176/appi.ajp.2010.09091379

Jacobsen, L. K., Krystal, J. H., Mencl, W. E., Westerveld, M., Frost, S. J., & Pugh, K. R. (2005). Effects of smoking and smoking abstinence on cognition in adolescent tobacco smokers. Biol. Psych., 57(1), 56-66. https://doi.org/10.1016/j.biopsych.2004.10.022

Koob, G. F., & Le Moal, M. (2001). Drug addiction, dysregulation of reward, and allostasis. Neuropsychopharmacology, 24(2), 97. https://doi.org/10.1016/S0893-133X(00)00195-0

Koob, G. F., & Le Moal, M. (2005). Plasticity of reward neurocircuitry and the'dark side'of drug addiction. Nat Neurosci, 8(11), 1442. https://doi.org/10.1038/nn1105-1442

Lau, J., Ioannidis, J. P., Terrin, N., Schmid, C. H., & Olkin, I. (2006). The case of the misleading funnel plot. *Bmj*, *333*(7568), 597-600.

Lee Y. H. (2018). An overview of meta-analysis for clinicians. Korean J Intern Med, 33(2), 277–283. https://doi.org/10.3904/kjim.2016.195

Lembke, A., Johnson, K., & DeBattista, C. (2007). Depression and smoking cessation: does the evidence support psychiatric practice?.Neuropsychiatr. Dis. Treat., 3(4), 487.

Leventhal, A. M., Ameringer, K. J., Osborn, E., Zvolensky, M. J., & Langdon, K. J. (2013). Anxiety and depressive symptoms and affective patterns of tobacco withdrawal. Drug Alcohol Depend., 133(2), 324-329.

Leventhal, A. M., Trujillo, M., Ameringer, K. J., Tidey, J. W., Sussman, S., & Kahler, C. W. (2014). Anhedonia and the relative reward value of drug and nondrug reinforcers in cigarette smokers. J. Abnorm. Psychol., 123(2), 375. https://psycnet.apa.org/doi/10.1037/a0036384

Leventhal, A. M., Waters, A. J., Boyd, S., Moolchan, E. T., Lerman, C., & Pickworth, W. B. (2007). Gender differences in acute tobacco withdrawal: Effects on subjective, cognitive, and physiological measures. Exp. Clin. Psychopharm., 15(1), 21. https://psycnet.apa.org/doi/10.1037/1064-1297.15.1.21

Leventhal, A. M., Waters, A. J., Moolchan, E. T., Heishman, S. J., & Pickworth, W. B. (2010). A quantitative analysis of subjective, cognitive, and physiological manifestations of the acute tobacco abstinence syndrome. Addict. Behav., 35(12), 1120-1130. https://doi.org/10.1016/j.addbeh.2010.08.007

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P., ... & Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS med., 6(7), e1000100. https://doi.org/10.1371/journal.pmed.1000100

Lydon, D. M., Wilson, S. J., Child, A., & Geier, C. F. (2014). Adolescent brain maturation and smoking: what we know and where we're headed. Neurosci. Biobehav. Rev., 45, 323-342. https://doi.org/10.1016/j.neubiorev.2014.07.003

McLaughlin, I., Dani, J. A., & De Biasi, M. (2015). Nicotine withdrawal. In The Neuropharmacology of Nicotine Dependence (pp. 99-123). Springer, Cham. https://doi.org/10.1007/978-3-319-13482-6_4

McNair, D. M., Lorr, M., & Droppleman, L. F. (1971). Manual for the profile of mood states (POMS). San Diego: Educational and Industrial Testing Service.

McNair, D. M., Lorr, M., & Droppleman, L. (1981). Profile of mood states questionnaire. EDITS, San Diego, CA.

Miech, R., Johnston, L., O'Malley, P. M., Bachman, J. G., & Patrick, M. E. (2019). Trends in Adolescent Vaping, 2017–2019. 381(15), 1490-1491. doi:10.1056/NEJMc1910739

Minami, H., Yeh, V. M., Bold, K. W., Chapman, G. B., & McCarthy, D. E. (2014). Relations among affect, abstinence motivation and confidence, and daily smoking lapse risk. Psychol. Addict. Behav., 28(2), 376. https://psycnet.apa.org/doi/10.1037/a0034445

Morrell, H. E., Cohen, L. M., & Al'Absi, M. (2008). Physiological and psychological symptoms and predictors in early nicotine withdrawal. Pharmacol. Biochem. Behav. 89(3), 272-278.

https://doi.org/10.1016/j.pbb.2007.12.020
Murray, R. P., Johnston, J. J., Dolce, J. J., Lee, W. W., & O'Hara, P. (1995). Social support for smoking cessation and abstinence: The Lung Health Study. Addict Behav, 20(2), 159-170. https://doi.org/10.1016/S0306-4603(99)80001-X
Pang, R. D., & Leventhal, A. M. (2013). Sex differences in negative affect and lapse behavior during acute tobacco abstinence: A laboratory study. Exp. Clin. Psychopharmacol., 21(4), 269. https://psycnet.apa.org/doi/10.1037/a0033429
Park, A. D., Farrahi, L. N., Pang, R. D., Guillot, C. R., Aguirre, C. G., & Leventhal, A. M. (2016). Negative urgency is associated with heightened negative affect and urge during tobacco abstinence in regular smokers. J. Sud Alcohol Drugs,77(5), 766-773. https://doi.org/10.15288/jsad.2016.77.766
Patterson, F., Kerrin, K., Wileyto, E. P., & Lerman, C. (2008). Increase in anger symptoms after smoking cessation predicts relapse. Drug Alcohol Depend, 95(1-2), 173-176. https://doi.org/10.1016/j.drugalcdep.2008.01.013
Perkins, K. A., Karelitz, J. L., Giedgowd, G. E., & Conklin, C. A. (2013). Negative mood effects on craving to smoke in women versus men. Addict. Behav., 38(2), 1527-1531. https://doi.org/10.1016/j.addbeh.2012.06.002
Perkins, K. A., Stitzer, M., & Lerman, C. (2006). Medication screening for smoking cessation: a proposal for new methodologies. Psychopharmacol., 184(3-4), 628-636. https://doi.org/10.1007/s00213-005-0105-5
Piper, M. E., & Curtin, J. J. (2006). Tobacco withdrawal and negative affect: An analysis of initial emotional response intensity and voluntary emotion regulation. J. Abnorm. Psychol., 115(1), 96. doi:10.1037/0021-843X.115.1.96
Piper, M. E., Bullen, C., Krishnan-Sarin, S., Rigotti, N. A., Steinberg, M. L., Streck, J. M., & Joseph, A. M. (2019). Defining and measuring abstinence in clinical trials of smoking cessation interventions: An updated review. Nicotine & Tob Res. https://doi.org/10.1093/ntr/ntz110
Piper, M. E., Schlam, T. R., Cook, J. W., Sheffer, M. A., Smith, S. S., Loh, W. Y., ... & Baker, T. B. (2011). Tobacco withdrawal components and their relations with cessation success. Psychopharmacol., 216(4), 569-578. https://doi.org/10.1007/s00213-011-2250-3
Poulos, C. X., & Cappell, H. (1991). Homeostatic theory of drug tolerance: a general model of physiological adaptation. Psychol rev, 98(3), 390. https://psycnet.apa.org/doi/10.1037/0033-295X.98.3.390
Quinn, A., Sekimura, S., Pang, R., Trujillo, M., Kahler, C. W., & Leventhal, A. M. (2013). Hostility as a predictor of affective changes during acute tobacco withdrawal. Nicotine Tob. Res., 16(3), 335-342. https://doi.org/10.1093/ntr/ntt151.
Rosenthal, R. (1979). The file drawer problem and tolerance for null results. Psychol. bulletin, 86(3), 638. https://psycnet.apa.org/doi/10.1037/0033-2909.86.3.638
Rossi, V., & Pourtois, G. (2012). Transient state-dependent fluctuations in anxiety measured using STAI, POMS, PANAS or VAS: a comparative review. Anxiety, Stress & Coping, 25(6), 603-645. https://doi.org/10.1080/10615806.2011.582948
Sheets, E. S., Bujarski, S., Leventhal, A. M., & Ray, L. A. (2015). Emotion differentiation and intensity during acute tobacco abstinence: A comparison of heavy and light smokers. Addict. Behav., 47, 70-73. https://doi.org/10.1016/j.addbeh.2015.03.024
Shiffman, S., West, R. J., & Gilbert, D. G. (2004). Recommendation for the assessment of tobacco craving and withdrawal in smoking cessation trials. Nicotine Tob. Res., 6(4), 599-614. https://doi.org/10.1080/14622200410001734067
Simmonds, M. (2015). Quantifying the risk of error when interpreting funnel plots. Syst.Rev., 4(1), 24. https://doi.org/10.1186/s13643-015-0004-8
Smith, A. E., Cavallo, D. A., Dahl, T., Wu, R., George, T. P., & Krishnan-Sarin, S. (2008). Effects of acute tobacco abstinence in adolescent smokers compared with nonsmokers. J.Adol. Health, 43(1), 46-54. https://doi.org/10.1016/j.jadohealth.2007.12.004
Smith, A. L., Carter, S. M., Dunlop, S. M., Freeman, B., & Chapman, S. (2015). The views and experiences of smokers who quit smoking unassisted. A systematic review of the qualitative evidence. PloS one, 10(5), e0127144.

https://doi.org/10.1371/journal.pone.0127144
Smith, P. H., Kasza, K. A., Hyland, A., Fong, G. T., Borland, R., Brady, K., ... & McKee, S. A. (2015). Gender differences in medication use and cigarette smoking cessation: results from the International Tobacco Control Four Country Survey. Nicotine Tob. Res., 17(4), 463-472. https://doi.org/10.1093/ntr/ntu212
Smith, P. H., Bessette, A. J., Weinberger, A. H., Sheffer, C. E., & McKee, S. A. (2016). Sex/gender differences in smoking cessation: a review. Prev. Med., 92, 135-140. https://doi.org/10.1016/j.ypmed.2016.07.013
Solomon, R. L., & Corbit, J. D. (1974). An opponent-process theory of motivation: I. Temporal dynamics of affect. Psychol rev, 81(2), 119. https://psycnet.apa.org/doi/10.1037/h0036128
Solomon, R. L., & Corbit, J. D. (1974). An opponent-process theory of motivation: I. Temporal dynamics of affect. Psychol rev, 81(2), 119. https://psycnet.apa.org/doi/10.1037/h0036128
SRNT Subcommittee on Biochemical Verification. (2002). Biochemical verification of tobacco use and cessation. Nicotine & Tobacco Research, 4(2), 149-159
Stroup, D. F., Berlin, J. A., Morton, S. C., Olkin, I., Williamson, G. D., Rennie, D., ... & Thacker, S. B. (2000). Meta-analysis of observational studies in epidemiology: a proposal for reporting. Jama, 283(15), 2008-2012. doi:10.1001/jama.283.15.2008
Study Quality Assessment Tools. National Heart, Lung, and Blood Institute website. https://www.nhlbi.nih.gov/health- topics/study-quality-assessment-tools
Taylor, G., McNeill, A., & Aveyard, P. (2015). Does deterioration in mental health after smoking cessation predict relapse to smoking?. BMC pub. health, 15(1), 1150. https://doi.org/10.1186/s12889-015-2473-z
Wang, T. W., Asman, K., Gentzke, A. S., Cullen, K. A., Holder-Hayes, E., Reyes-Guzman, C., ... & King, B. A. (2018). Tobacco product use among adults—United States, 2017.Morbidity and Mortality Weekly Report, 67(44), 1225. doi: 10.15585/mmwr.mm6744a2
Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol, 54(6), 1063. http://dx.doi.org/10.1037/0022-3514.54.6.1063
Weinberger, A. H., Kashan, R. S., Shpigel, D. M., Esan, H., Taha, F., Lee, C. J., ... & Goodwin, R. D. (2017). Depression and cigarette smoking behavior: a critical review of population-based studies. The American journal of drug and alcohol abuse, 43(4), 416-431. https://doi.org/10.3109/00952990.2016.1171327
Welsch SK, Smith SS, Wetter DW, Jorenby DE, Fiore MC, Baker TB. Development and validation of the Wisconsin Smoking Withdrawal Scale. Exp Clin Psychopharm. 1999;7:354–361. doi:10.1037/1064-1297.7.4.354. https://psycnet.apa.org/doi/10.1037/1064-1297.7.4.354
West, R., & Hajek, P. (2004). Evaluation of the mood and physical symptoms scale (MPSS) toassess cigarette withdrawal. Psychopharmacol., 177(1-2), 195-199. https://doi.org/10.1007/s00213-004-1923-6
West, R., Ussher, M., Evans, M., & Rashid, M. (2006). Assessing DSM-IV nicotine withdrawal symptoms: a comparison and evaluation of five different scales. Psychopharmacol, 184(3-4), 619-627. https://doi.org/10.1007/s00213-005-0216-z
Wong, J. A., Pickworth, W. B., Waters, A. J., al'Absi, M., & Leventhal, A. M. (2014). Cortisol levels decrease after acute tobacco abstinence in regular smokers. Hum.Psychopharma.Clin. , 29(2), 152-162. https://doi.org/10.1002/hup.2382
World Health Organisation, Tobacco.https://www.who.int/news-room/fact-sheets/detail/tobacco. Accessed 3 September 2019
Xu, J., Azizian, A., Monterosso, J., Domier, C. P., Brody, A. L., London, E. D., & Fong, T. W. (2008). Gender effects on mood and cigarette craving during early abstinence and resumption of smoking. Nicotine Tob. Res., 10(11), 1653-1661. https://doi.org/10.1080/14622200802412929
Zelle, S. L., Gates, K. M., Fiez, J. A., Sayette, M. A., & Wilson, S. J. (2017). The first day is

always the hardest: Functional connectivity during cue exposure and the ability to resist smoking in the initial hours of a quit attempt. NeuroImage, 151, 24-32. https://doi.org/10.1016/j.neuroimage.2016.03.015

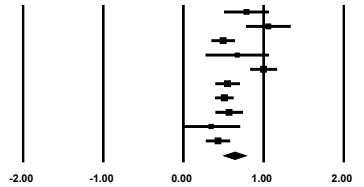
Zuo, Y., Rabinovich, N. E., & Gilbert, D. G. (2017). Negative affect subtypes and craving differentially predict long-term cessation success among smokers achieving initial abstinence. Psychopharmacol., 234(5), 761-771. https://doi.org/10.1007/s00213-016-4509-1

Zvolensky, M. J., Stewart, S. H., Vujanovic, A. A., Gavric, D., & Steeves, D. (2009). Anxiety sensitivity and anxiety and depressive symptoms in the prediction of early smoking lapse and relapse during smoking cessation treatment. Nicotine Tob. Res., 11(3), 323-331. https://doi.org/10.1093/ntr/ntn037

- Anxiety, depression, and anger symptoms emerge during acute tobacco abstinence
- Negative mood symptoms emerge as soon as 3hrs post smoking cessation
- Anxiety is the most severe symptom experienced by smokers during acute abstinence
- Female smokers experience worse mood symptoms compared to male smokers

Anxiety

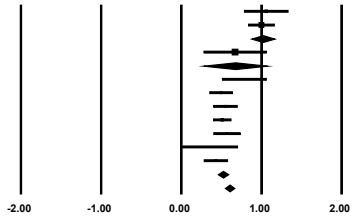
Study name	Outcome	Age	Hours	Dependence	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Xu et al, 2009	POMS	36	13	Medium	0.787	0.143	0.020	0.507	1.068	5.503	0.000
Wong et al, 2014	PANAS	38	17	High	1.060	0.142	0.020	0.780	1.339	7.441	0.000
Pang & Leventhal, 2013	POMS	43	16	Medium	0.497	0.075	0.006	0.349	0.644	6.612	0.000
Morrel et al, 2008	POMS	27	18	Low	0.671	0.202	0.041	0.275	1.068	3.322	0.001
Leventhal et al,2010	WSWS	36	12	High	1.000	0.086	0.007	0.832	1.168	11.633	0.000
Leventhal et al, 2013	POMS	43	16	Medium	0.551	0.078	0.006	0.397	0.705	7.021	0.000
Bello et al,2016	POMS	44	16	Medium	0.511	0.059	0.003	0.395	0.627	8.647	0.000
Quinn et al,2014	POMS	43	16	Medium	0.570	0.087	0.008	0.399	0.741	6.541	0.000
Colby et al,2010	PANAS	15	15	Medium	0.346	0.185	0.034	-0.016	0.709	1.873	0.061
Hendricks&Leventhal,2013	POMS	44	16	Medium	0.431	0.078	0.006	0.279	0.584	5.536	0.000
					0.636	0.069	0.005	0.501	0.771	9.231	0.000



Supplementary Figure 1. Anxiety forest plot (std diff= standard difference; Z value=one sample z statistics; p value= probability that Z statistics is significantly different than 0; Lower limit= lower limit of the 95% confidence interval for the effect size; Upper limit= upper limit of the 95% confidence interval for the effect size; POMS=profile of mood states; WSWS= Wisconsin smoking withdrawal scale; PANAS= positive and negative affect schedule).

Anxiety

Group by Dependence	Study name	Outcome	Age	Hours	Dependence	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
High	Wong et al, 2014	PANAS	38	17	High	1.060	0.142	0.020	0.780	1.339	7.441	0.000
High	Leventhal et al,2010	WSWS	36	12	High	1.000	0.086	0.007	0.832	1.168	11.633	0.000
High						1.016	0.074	0.005	0.872	1.160	13.805	0.000
Low	Morrel et al, 2008	POMS	27	18	Low	0.671	0.202	0.041	0.275	1.068	3.322	0.001
Low						0.671	0.202	0.041	0.275	1.068	3.322	0.001
Medium	Xu et al, 2009	POMS	36	13	Medium	0.787	0.143	0.020	0.507	1.068	5.503	0.000
Medium	Pang & Leventhal, 2013	POMS	43	16	Medium	0.497	0.075	0.006	0.349	0.644	6.612	0.000
Medium	Leventhal et al, 2013	POMS	43	16	Medium	0.551	0.078	0.006	0.397	0.705	7.021	0.000
Medium	Bello et al,2016	POMS	44	16	Medium	0.511	0.059	0.003	0.395	0.627	8.647	0.000
Medium	Quinn et al,2014	POMS	43	16	Medium	0.570	0.087	0.008	0.399	0.741	6.541	0.000
Medium	Colby et al,2010	PANAS	15	15	Medium	0.346	0.185	0.034	-0.016	0.709	1.873	0.061
Medium	Hendricks&Leventhal,2013	POMS	44	16	Medium	0.431	0.078	0.006	0.279	0.584	5.536	0.000
Medium						0.519	0.033	0.001	0.455	0.583	15.923	0.000
Overall						0.602	0.029	0.001	0.544	0.659	20.417	0.000

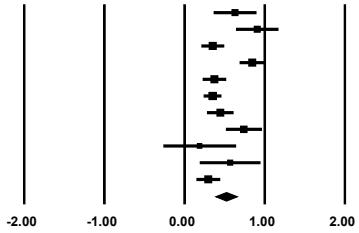


ad lib.smoking abstinence

Supplementary Figure 2. Anxiety subgroup analysis forest plot (std diff= standard difference; Z value=one sample z statistics; p value= probability that Z statistics is significantly different than 0; Lower limit= lower limit of the 95% confidence interval for the effect size; Upper limit= upper limit of the 95% confidence interval for the effect size; POMS=profile of mood states; WSWS= Wisconsin smoking withdrawal scale; PANAS= positive and negative affect schedule).

Anger/irritability

Study name	Outcome	Std diff in means	Standard error	Age	Hours	Dependence	Variance	Lower limit	Upper limit	Z-Value	p-Value
Xu et al, 2009	POMS	0.629	0.137	36	13	Medium	0.019	0.361	0.898	4.600	0.000
Wong et al, 2014	PANAS	0.908	0.135	38	17	High	0.018	0.642	1.173	6.704	0.000
Pang & Leventhal, 2013	POMS	0.352	0.073	43	16	Medium	0.005	0.208	0.495	4.813	0.000
Leventhal et al,2010	WSWS	0.845	0.082	36	12	High	0.007	0.685	1.006	10.338	0.000
Leventhal et al, 2013	POMS	0.372	0.076	43	16	Medium	0.006	0.224	0.520	4.919	0.000
Bello et al,2016	POMS	0.349	0.057	44	16	Medium	0.003	0.236	0.461	6.092	0.000
Quinn et al,2014	POMS	0.446	0.085	43	16	Medium	0.007	0.279	0.612	5.256	0.000
West &Hajek,2004	MPSS	0.740	0.115	39	24	N/A	0.013	0.515	0.966	6.426	0.000
Everson et al, 2006	MPSS	0.189	0.231	17	17	High	0.054	-0.265	0.643	0.816	0.414
Colby et al,2010	PANAS	0.568	0.194	15	15	Medium	0.037	0.189	0.948	2.936	0.003
Hendricks &Leventhal,2013	POMS	0.296	0.076	44	16	Medium	0.006	0.147	0.445	3.887	0.000
		0.516	0.068				0.005	0.384	0.649	7.636	0.000

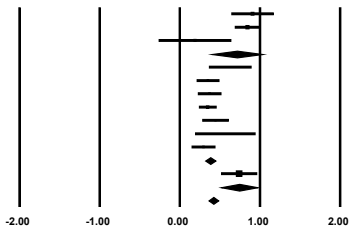


ad lib.smoking abstinence

Supplementary Figure 3. Anger/irritability forest plot (std diff= standard difference; Z value=one sample z statistics; p value= probability that Z statistics is significantly different than 0; Lower limit= lower limit of the 95% confidence interval for the effect size; Upper limit= upper limit of the 95% confidence interval for the effect size; POMS=profile of mood states; WSWS= Wisconsin smoking withdrawal scale; PANAS= positive and negative affect schedule).

Anger/irritability

Group by Dependence	Study name	Outcome	Std diff in means	Standard error	Age	Hours	Dependence	Variance	Lower limit	Upper limit	Z-Value	p-Value
High	Wong et al, 2014	PANAS	0.908	0.135	38	17	High	0.018	0.642	1.173	6.704	0.000
High	Leventhal et al,2010	WSWS	0.845	0.082	36	12	High	0.007	0.685	1.006	10.338	0.000
High	Everson et al, 2006	MPSS	0.189	0.231	17	17	High	0.054	-0.265	0.643	0.816	0.414
High			0.712	0.160				0.026	0.399	1.026	4.453	0.000
Medium	Xu et al, 2009	POMS	0.629	0.137	36	13	Medium	0.019	0.361	0.898	4.600	0.000
Medium	Pang & Leventhal, 2013	POMS	0.352	0.073	43	16	Medium	0.005	0.208	0.495	4.813	0.000
Medium	Leventhal et al, 2013	POMS	0.372	0.076	43	16	Medium	0.006	0.224	0.520	4.919	0.000
Medium	Bello et al,2016	POMS	0.349	0.057	44	16	Medium	0.003	0.236	0.461	6.092	0.000
Medium	Quinn et al,2014	POMS	0.446	0.085	43	16	Medium	0.007	0.279	0.612	5.256	0.000
Medium	Colby et al,2010	PANAS	0.568	0.194	15	15	Medium	0.037	0.189	0.948	2.936	0.003
Medium	Hendricks &Leventhal,2013	POMS	0.296	0.076	44	16	Medium	0.006	0.147	0.445	3.887	0.000
Medium			0.379	0.033				0.001	0.315	0.443	11.643	0.000
N/A	West &Hajek,2004	MPSS	0.740	0.115	39	24	N/A	0.013	0.515	0.966	6.426	0.000
N/A			0.740	0.115				0.013	0.515	0.966	6.426	0.000
Overall			0.417	0.031				0.001	0.357	0.477	13.566	0.000



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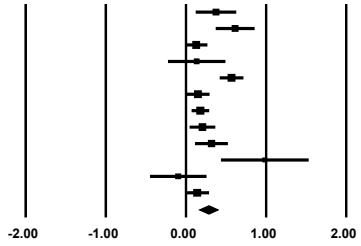
Supplementary Figure 4. Anger/irritability subgroup analysis forest plot (std diff= standard difference; Z value=one sample z statistics; p value= probability that Z statistics is significantly different than 0; Lower limit= lower limit of the 95% confidence interval for the effect size; Upper limit= upper limit of the 95% confidence interval for the effect size; POMS=profile of mood states; WSWS= Wisconsin smoking withdrawal scale; PANAS= positive and negative affect schedule).

Depressed mood/sadness

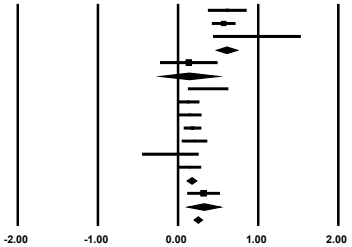
Study name	Outcome	Std diff in means	Age	Hours	Dependence	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Xu et al, 2009	POMS	0.375	36	13	Medium	0.129	0.017	0.122	0.628	2.900	0.004
Wong et al, 2014	PANAS	0.613	38	17	High	0.124	0.015	0.370	0.857	4.938	0.000
Pang & Leventhal, 2013	POMS	0.128	43	16	Medium	0.071	0.005	-0.011	0.268	1.799	0.072
Morrel et al, 2008	POMS	0.135	27	4	Low	0.183	0.034	-0.225	0.494	0.735	0.462
Leventhal et al,2010	WSWS	0.569	36	12	High	0.076	0.006	0.421	0.717	7.523	0.000
Leventhal et al, 2013	POMS	0.150	43	16	Medium	0.074	0.005	0.006	0.294	2.041	0.041
Bello et al,2016	POMS	0.180	44	16	Medium	0.056	0.003	0.071	0.290	3.219	0.001
Quinn et al,2014	POMS	0.206	43	16	Medium	0.082	0.007	0.046	0.366	2.522	0.012
West &Hajek,2004	MPSS	0.319	36	24	N/A	0.105	0.011	0.114	0.524	3.046	0.002
Everson et al, 2006	MPSS	0.984	17	17	High	0.279	0.078	0.436	1.531	3.520	0.000
Colby et al, 2010	POMS	-0.096	15	15	Medium	0.180	0.032	-0.448	0.257	-0.531	0.595
Hendricks & Leventhal,2013	POMS	0.141	44	16	Medium	0.075	0.006	-0.006	0.288	1.882	0.060
		0.278				0.058	0.003	0.164	0.392	4.776	0.000



Supplementary Figure 5. Depressed mood/sadness forest plot (std diff= standard difference; Z value=one sample z statistics; p value= probability that Z statistics is significantly different than 0; Lower limit= lower limit of the 95% confidence interval for the effect size; Upper limit= upper limit of the 95% confidence interval for the effect size; POMS=profile of mood states; WSWS= Wisconsin smoking withdrawal scale; PANAS= positive and negative affect schedule).

Depressed mood/sadness

Group by Dependence	Study name	Outcome	Std diff in means	Age	Hours	Dependence	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
High	Wong et al, 2014	PANAS	0.613	38	17	High	0.124	0.015	0.370	0.857	4.938	0.000
High	Leventhal et al,2010	WSWS	0.569	36	12	High	0.076	0.006	0.421	0.717	7.523	0.000
High	Everson et al, 2006	MPSS	0.984	17	17	High	0.279	0.078	0.436	1.531	3.520	0.000
High			0.603				0.065	0.004	0.476	0.731	9.246	0.000
Low	Morrel et al, 2008	POMS	0.135	27	4	Low	0.183	0.034	-0.225	0.494	0.735	0.462
Low			0.135				0.183	0.034	-0.225	0.494	0.735	0.462
Medium	Xu et al, 2009	POMS	0.375	36	13	Medium	0.129	0.017	0.122	0.628	2.900	0.004
Medium	Pang & Leventhal, 2013	POMS	0.128	43	16	Medium	0.071	0.005	-0.011	0.268	1.799	0.072
Medium	Leventhal et al, 2013	POMS	0.150	43	16	Medium	0.074	0.005	0.006	0.294	2.041	0.041
Medium	Bello et al,2016	POMS	0.180	44	16	Medium	0.056	0.003	0.071	0.290	3.219	0.001
Medium	Quinn et al,2014	POMS	0.206	43	16	Medium	0.082	0.007	0.046	0.366	2.522	0.012
Medium	Colby et al, 2010	POMS	-0.096	15	15	Medium	0.180	0.032	-0.448	0.257	-0.531	0.595
Medium	Hendricks & Leventhal,2013	POMS	0.141	44	16	Medium	0.075	0.006	-0.006	0.288	1.882	0.060
Medium			0.166				0.030	0.001	0.108	0.225	5.557	0.000
N/A	West &Hajek,2004	MPSS	0.319	36	24	N/A	0.105	0.011	0.114	0.524	3.046	0.002
N/A			0.319				0.105	0.011	0.114	0.524	3.046	0.002
Overall			0.244				0.026	0.001	0.193	0.295	9.391	0.000

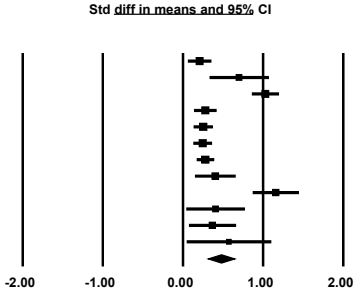


ad lib.smoking abstinence

Supplementary Figure 6. Depressed mood/sadness subgroup analysis forest plot (std diff= standard difference; Z value=one sample z statistics; p value= probability that Z statistics is significantly different than 0; Lower limit= lower limit of the 95% confidence interval for the effect size; Upper limit= upper limit of the 95% confidence interval for the effect size; POMS=profile of mood states; WSWS= Wisconsin smoking withdrawal scale; PANAS= positive and negative affect schedule; MPSS=mood and physical symptoms scale).

Composite Negative Affect

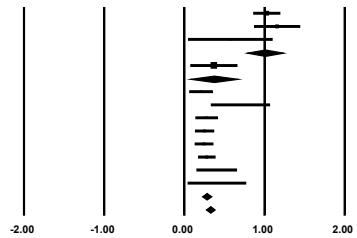
Study name	Outcome	Std diff in means	Standard error	Variance	Age	Hours	Dependence	Lower limit	Upper limit	Z-Value	p-Value
Park et al,2016	POMS	0.208	0.075	0.006	44	16	Medium	0.060	0.356	2.760	0.006
Cook et al,2004	POMS	0.700	0.189	0.036	36	24	Medium	0.330	1.070	3.711	0.000
Leventhal et al,2010	WSWS	1.029	0.087	0.008	36	12	High	0.859	1.199	11.855	0.000
Pang & Leventhal2013	POMS	0.279	0.072	0.005	43	16	Medium	0.137	0.420	3.856	0.000
Leventhal et al,2014	POMS	0.253	0.061	0.004	44	16	Medium	0.133	0.373	4.131	0.000
Aguirre et al,2015	POMS	0.247	0.060	0.004	44	17	Medium	0.129	0.364	4.108	0.000
Bello et al,2016	POMS	0.280	0.057	0.003	44	16	Medium	0.169	0.391	4.948	0.000
Xu et al,2009	POMS	0.404	0.130	0.017	36	13	Medium	0.149	0.659	3.107	0.002
Wong et al,2014	PANAS	1.158	0.147	0.022	38	17	High	0.870	1.447	7.863	0.000
Colby et al,2010	PANAS	0.407	0.187	0.035	15	15	Medium	0.040	0.773	2.176	0.030
Bidwell et al, 2013	PANAS	0.368	0.151	0.023	16	12	Low	0.073	0.663	2.442	0.015
Froeliger et al,2015	PANAS	0.574	0.270	0.073	38	24	High	0.045	1.102	2.126	0.034
		0.474	0.085	0.007				0.308	0.641	5.589	0.000



Supplementary Figure 7. Negative affect forest plot (std diff= standard difference; Z value=one sample z statistics; p value= probability that Z statistics is significantly different than 0; Lower limit= lower limit of the 95% confidence interval for the effect size; Upper limit= upper limit of the 95% confidence interval for the effect size; POMS=profile of mood states; WSWS= Wisconsin smoking withdrawal scale; PANAS= positive and negative affect schedule).

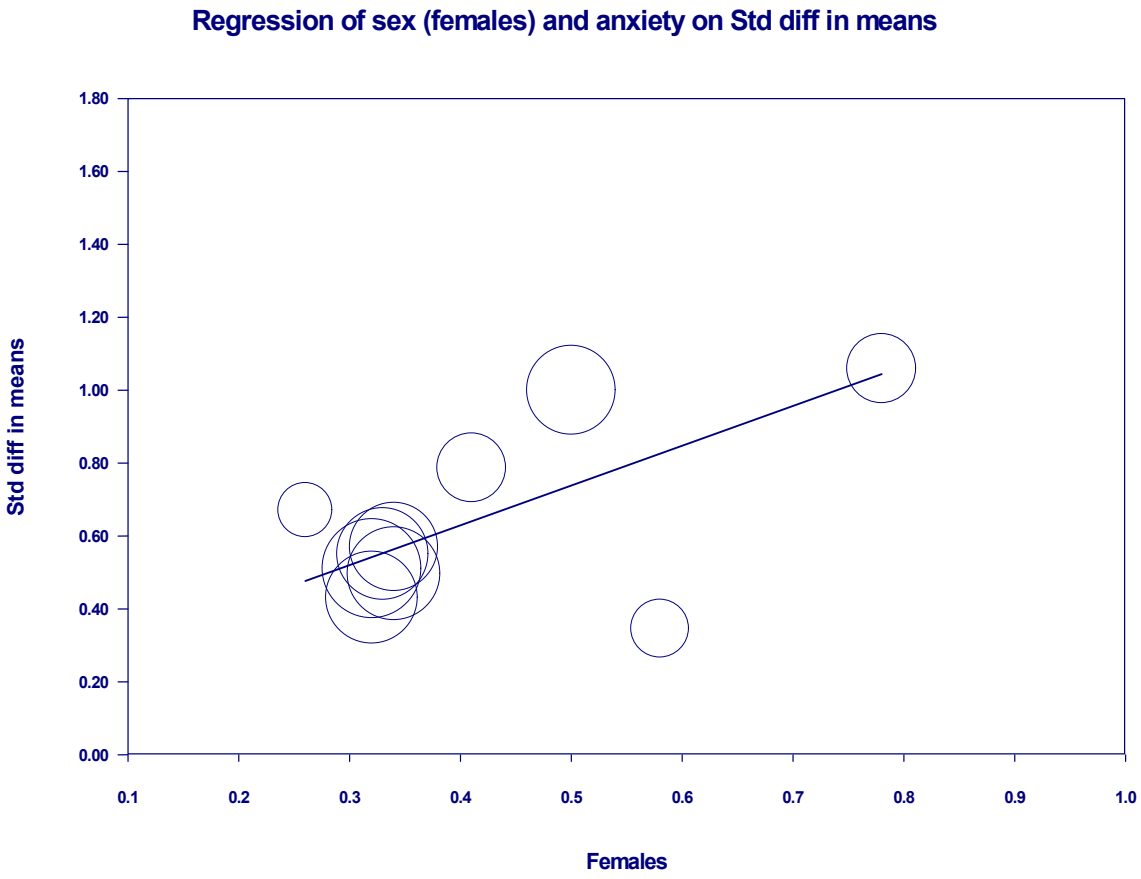
Composite Negative Affect

Group by Dependence	Study name	Outcome	Std diff in means	Standard error	Variance	Age	Hours	Dependence	Lower limit	Upper limit	Z-Value	p-Value
High	Leventhal et al,2010	WSWS	1.029	0.087	0.008	36	12	High	0.859	1.199	11.855	0.000
High	Wong et al,2014	PANAS	1.158	0.147	0.022	38	17	High	0.870	1.447	7.863	0.000
High	Froeliger et al,2015	PANAS	0.574	0.270	0.073	38	24	High	0.045	1.102	2.126	0.034
High			1.005	0.116	0.013				0.779	1.232	8.702	0.000
Low	Bidwell et al, 2013	PANAS	0.368	0.151	0.023	16	12	Low	0.073	0.663	2.442	0.015
Low			0.368	0.151	0.023				0.073	0.663	2.442	0.015
Medium	Park et al,2016	POMS	0.208	0.075	0.006	44	16	Medium	0.060	0.356	2.760	0.006
Medium	Cook et al,2004	POMS	0.700	0.189	0.036	36	24	Medium	0.330	1.070	3.711	0.000
Medium	Pang & Leventhal2013	POMS	0.279	0.072	0.005	43	16	Medium	0.137	0.420	3.856	0.000
Medium	Leventhal et al,2014	POMS	0.253	0.061	0.004	44	16	Medium	0.133	0.373	4.131	0.000
Medium	Aguirre et al,2015	POMS	0.247	0.060	0.004	44	17	Medium	0.129	0.364	4.108	0.000
Medium	Bello et al,2016	POMS	0.280	0.057	0.003	44	16	Medium	0.169	0.391	4.948	0.000
Medium	Xu et al,2009	POMS	0.404	0.130	0.017	36	13	Medium	0.149	0.659	3.107	0.002
Medium	Colby et al,2010	PANAS	0.407	0.187	0.035	15	15	Medium	0.040	0.773	2.176	0.030
Medium			0.277	0.029	0.001				0.220	0.335	9.452	0.000
Overall			0.323	0.028	0.001				0.268	0.378	11.559	0.000

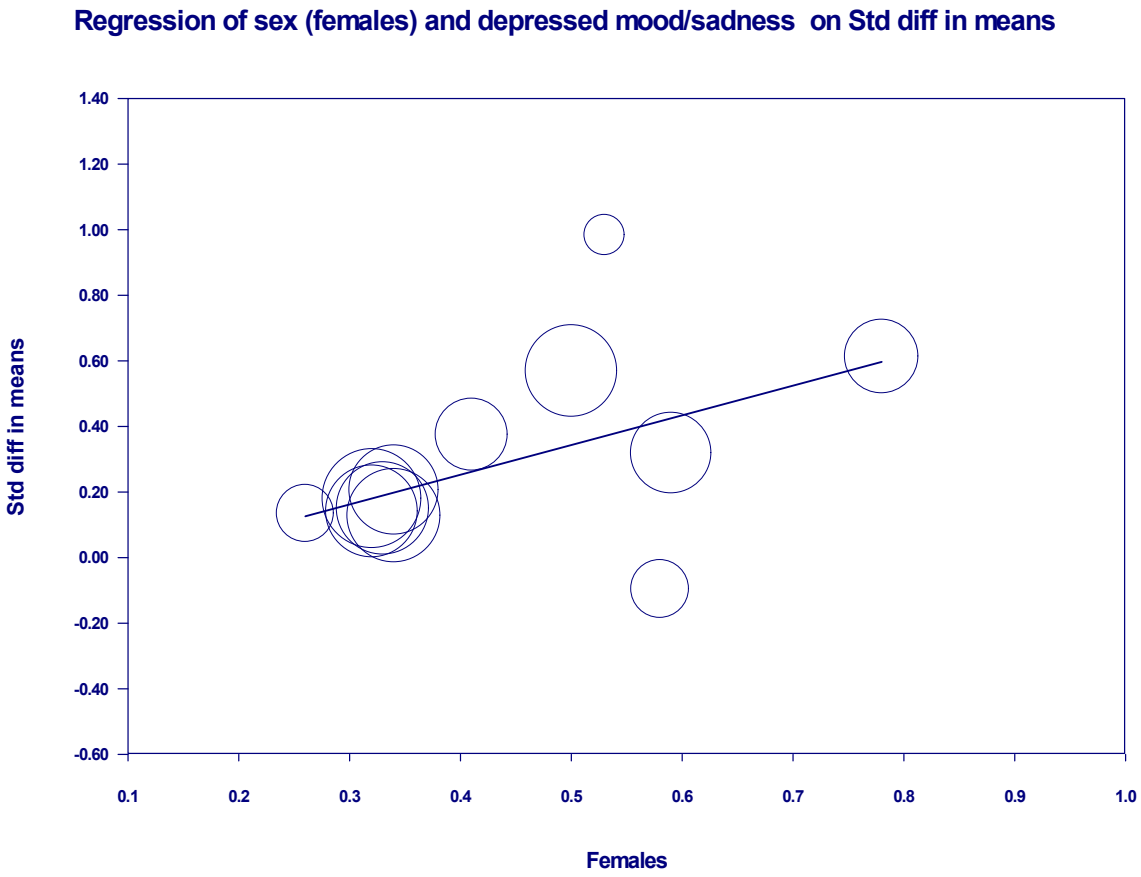


ad lib.smoking abstinence

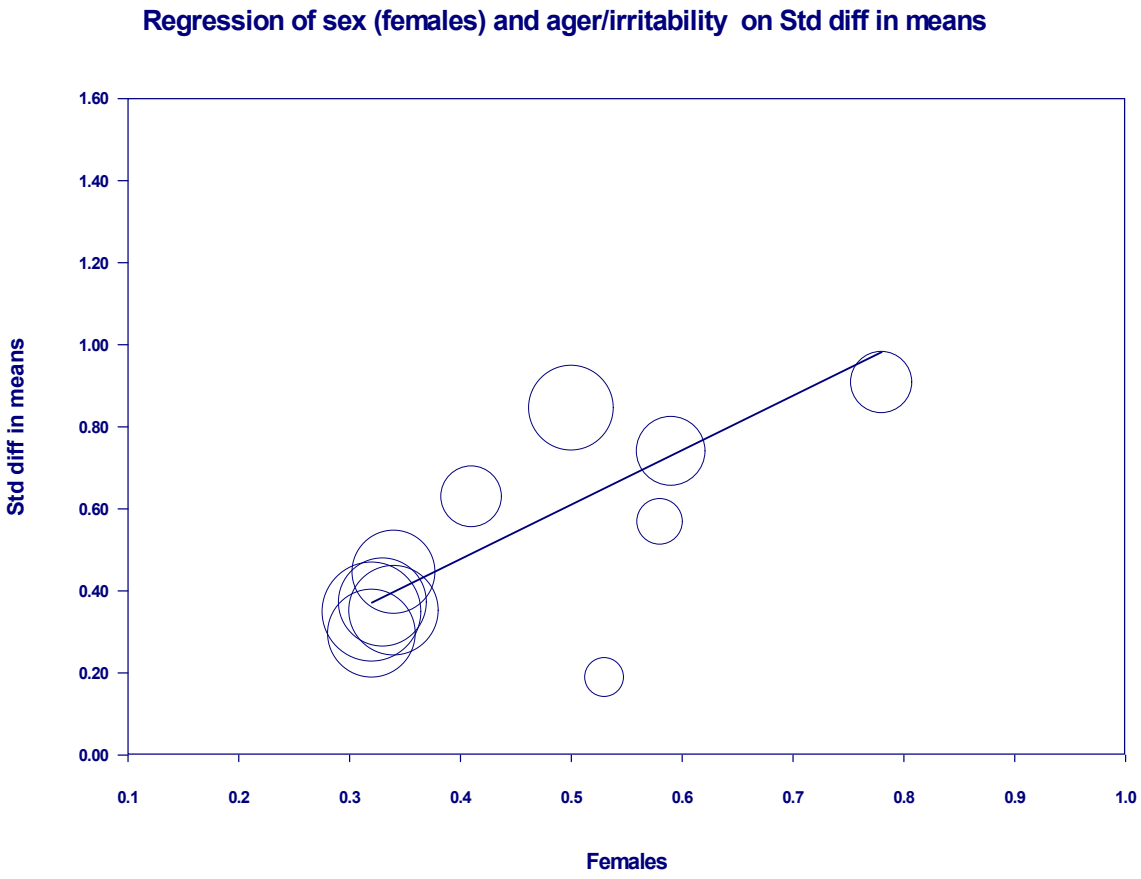
Supplementary Figure 8. Negative affect subgroup analysis forest plot (std diff= standard difference; Z value=one sample z statistics; p value= probability that Z statistics is significantly different than 0; Lower limit= lower limit of the 95% confidence interval for the effect size; Upper limit= upper limit of the 95% confidence interval for the effect size; POMS=profile of mood states; WSWS= Wisconsin smoking withdrawal scale; PANAS= positive and negative affect schedule).



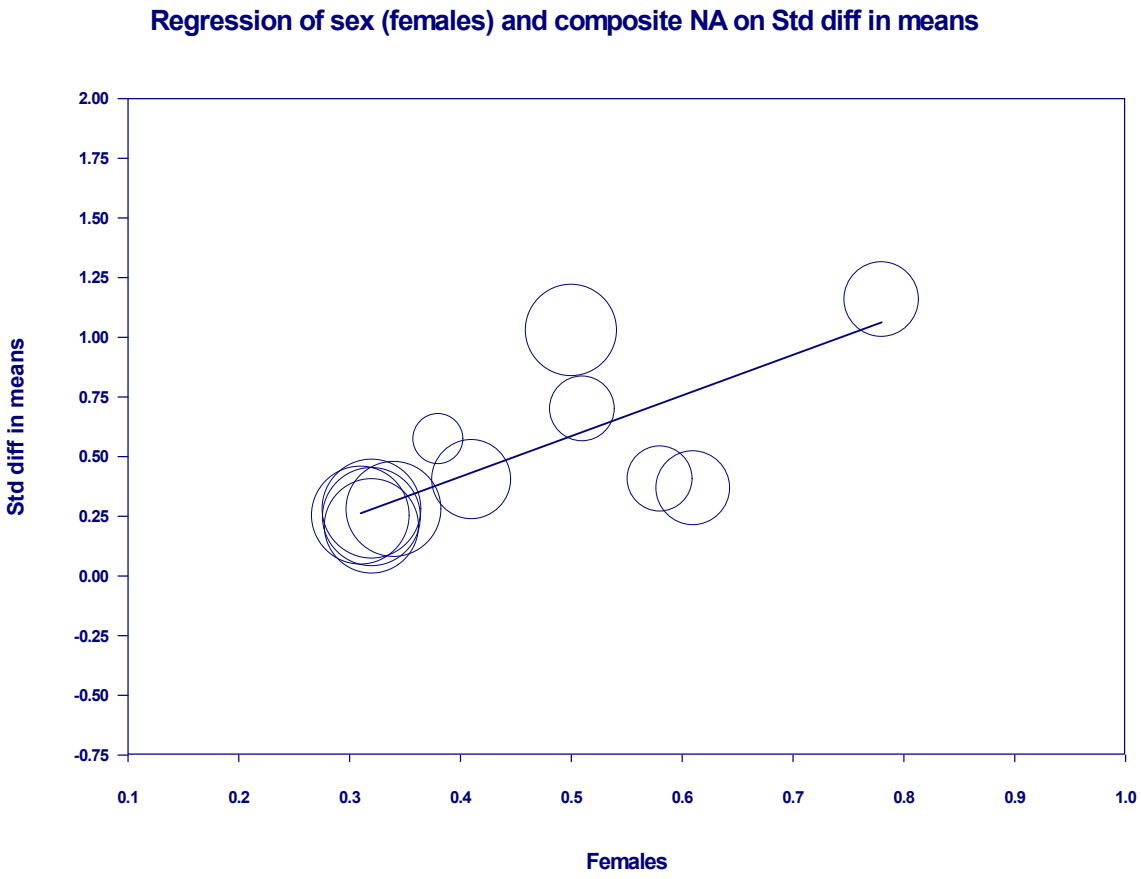
Supplementary Figure 9. Regression of sex (females) and anxiety on Std difference in means



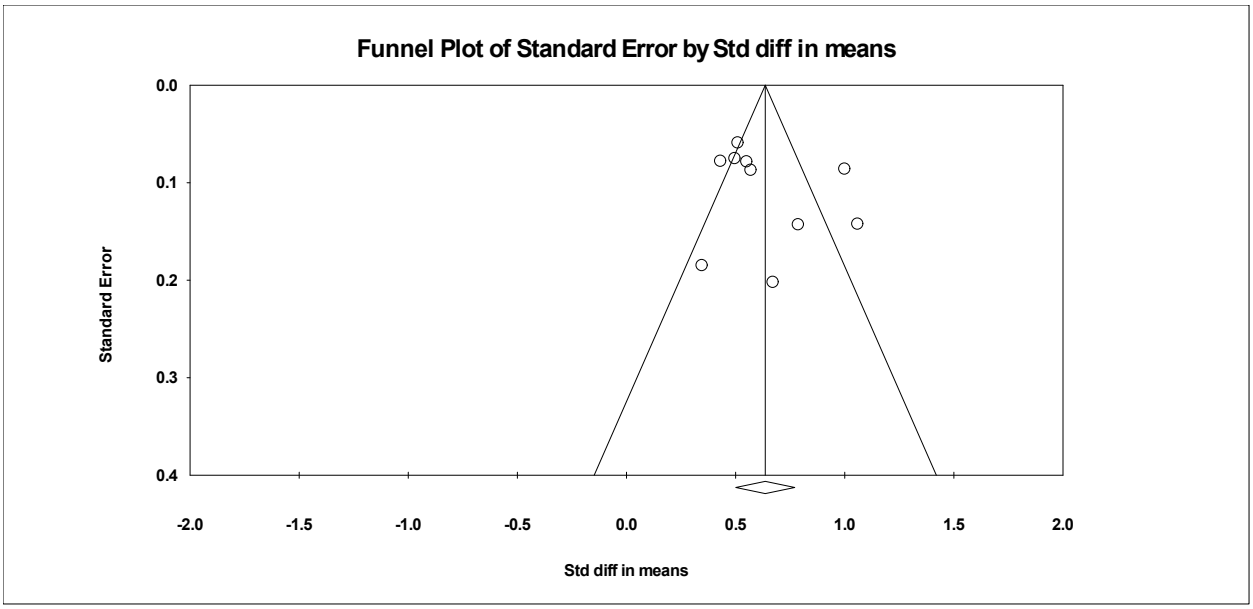
Supplementary Figure 10. Regression of sex (females) and depressed mood/sadness on Std difference in means



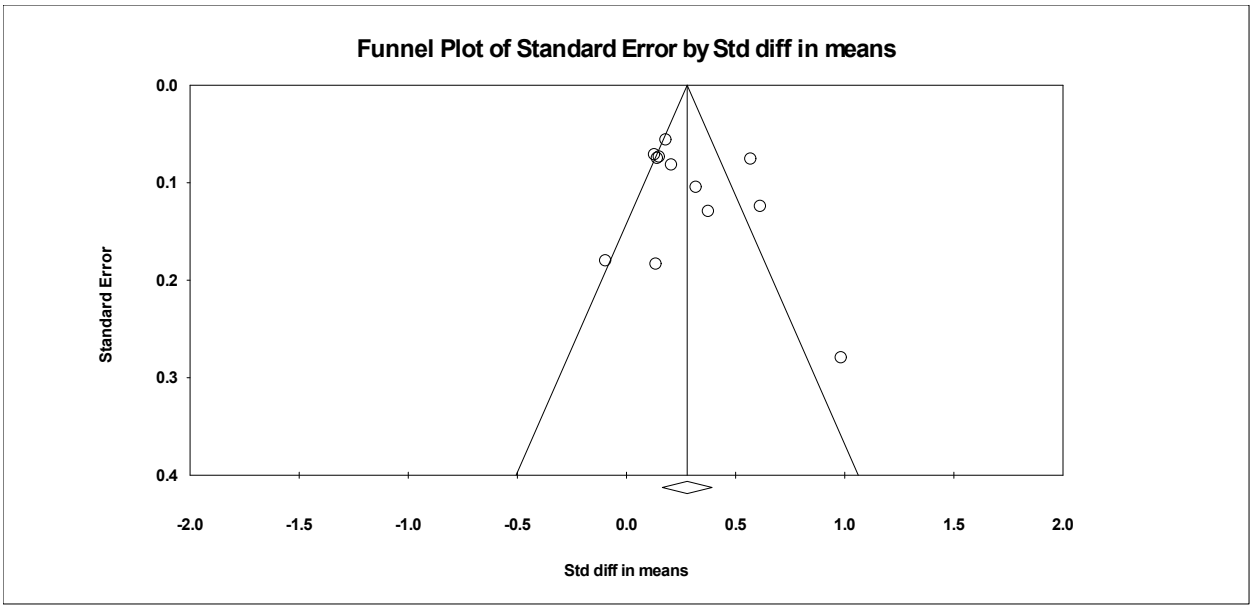
Supplementary Figure 11. Regression of sex(females) and anger/irritability on Std difference in means.



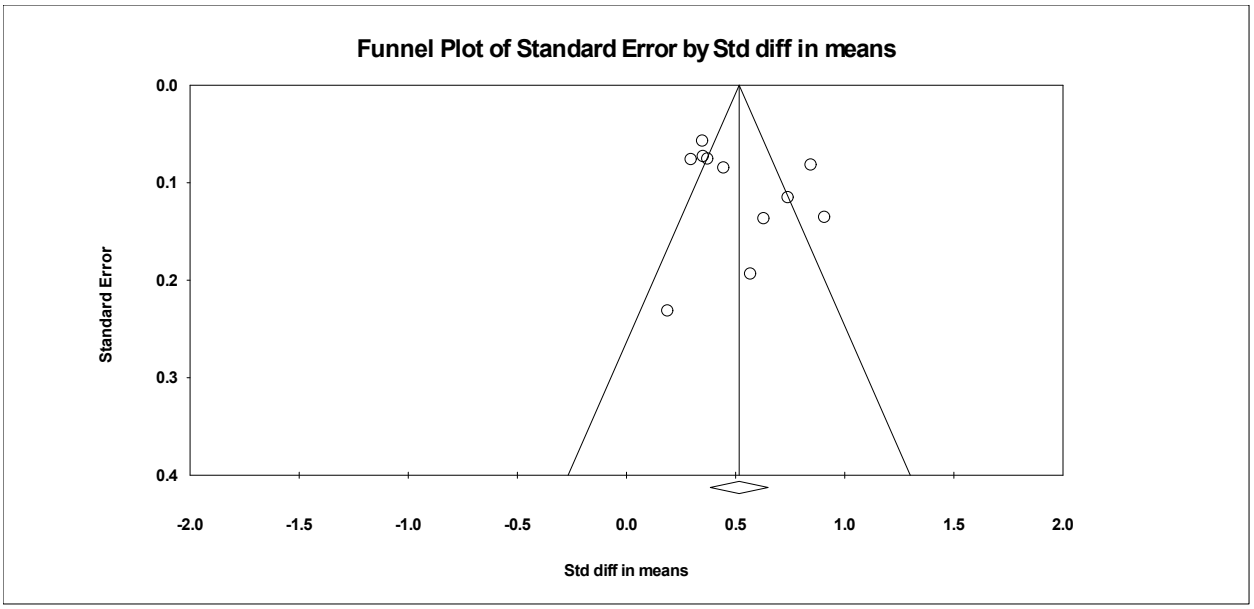
Supplementary Figure 12. Regression of sex(females) and composite NA on Std difference in means



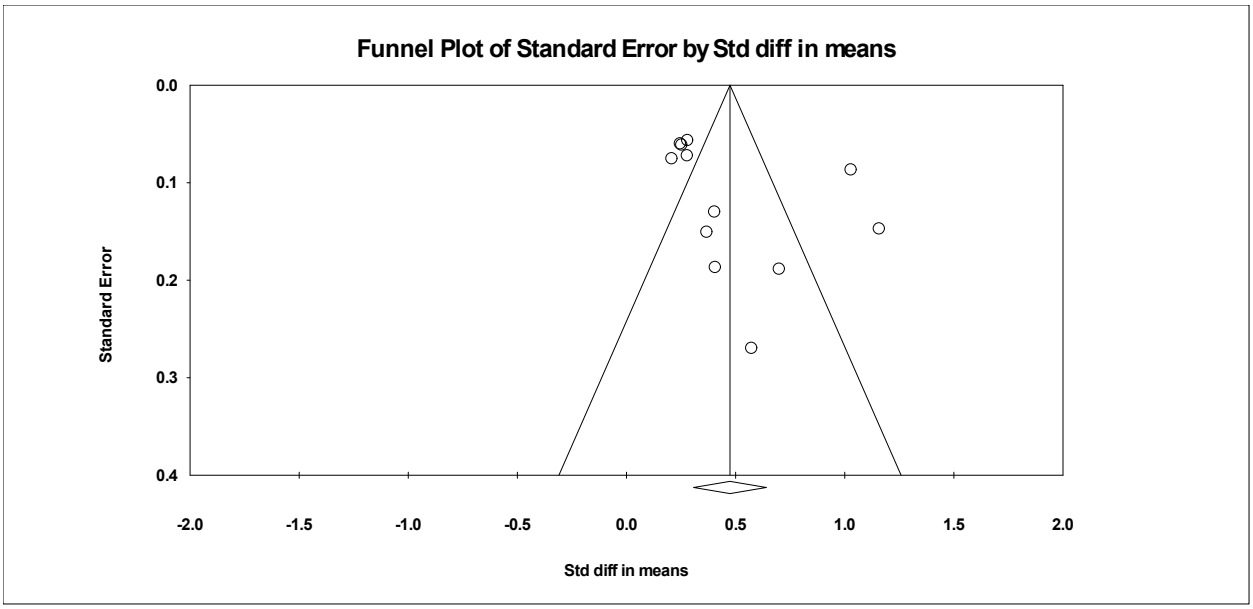
Supplementary Figure 13. Anxiety Funnel plot



Supplementary Figure 14. Depressed mood/sadness Funnel plot



Supplementary Figure 15. Anger/irritability Funnel plot



Supplementary Figure 16. Composite 'NA' Funnel plot

Supplementary Table 1a. Mood and anxiety symptoms inserted as specific and alternative search terms during database searching.

Mood and anxiety symptoms of Tobacco withdrawal as listed in DSM-V	Definition
Anxiety	According to the DSM-V (American Psychiatric Association, 2013): "The apprehensive anticipation of future danger or misfortune accompanied by a feeling of worry, distress, and/or somatic symptoms of tension. The focus of anticipated danger may be internal or external" (p.818)
Irritability, Anger, or Frustration	According to Stringaris et al. (2018): Irritability: "Increased proneness to anger compared with peers at same development level, and defining mood of Disruptive Mood Dysregulation Disorder (DMDD). As a symptom it is present in the criteria of several psychiatric disorders, including generalized anxiety disorder (GAD), depression, and post-traumatic stress disorder (PTSD)" (p.722) Anger: "The emotion that characterizes irritability. It is often a feeling, i.e. consciously processed. It has received considerable research in psychology (Blair, 2012), but is not classified separately in the DSM" (p.722) Frustration: "The emotional state induced by blocked goal attainment, analogous to frustrative nonreward which elicits increased aggression and activity in animals (Amsel, 1958; Brotman et al., 2017). Often used synonymously to irritability and anger in clinical practice" (p.722)
Depressed Mood	According to De Zwart et al. (2018): "A state of low mood and aversion to activity. It can affect a person's thoughts, behavior, motivation, feelings, and sense of well-being. It may feature sadness, difficulty in thinking and concentration and a significant increase/decrease in appetite and time spent sleeping" (p.2)

Units of analysis related to mood and anxiety symptoms as listed in the RDoC matrix

Mood and anxiety symptoms	Definition
Anxious arousal	According to Grisanzio et al. (2018): "inability to concentrate and impaired ability to control thoughts. Physical symptoms include a racing heart, sweating, and feeling stressed." (p.1)
Anhedonia/decreased appetitive behavior	According to the DSM-V (American Psychiatric Association, 2013): "Lack of enjoyment from, engagement in, or energy for life's experiences; deficits in the capacity to feel pleasure and take interest in things." (p.817)
Sadness	According to Horwitz and Wakefield (207): "Experience of sad feelings, difficulty to concentrate, and reduced appetite" (p.1)
Apathy	According to Van Reekum, Stuss, and Ostrander (1988): "lack of interest or emotion" (p.2)

Note. Operational definitions for the above symptoms were extracted from DSM-V or from relevant publications if definitions for the above symptoms were not listed in DSM-V. The above symptoms relate to mood disturbances occurring during abstinence from tobacco and may not necessary meet the criteria for disorders as listed in DSM-V.

Supplementary Table 1b. Mood and anxiety symptoms measured by studies included in the review.

Negative Affect (NA)	According to the DSM-V (American Psychiatric Association, 2013): "intense experiences of high levels of a wide range of negative emotions (e.g., anxiety, depression, guilt/shame, worry, anger), and their behavioral (e.g., self-harm) and interpersonal (e.g., dependency) manifestations." (p.825)
Anxiety	According to the DSM-V (American Psychiatric Association, 2013): "The apprehensive anticipation of future danger or misfortune accompanied by a feeling of worry, distress, and/or somatic symptoms of tension. The focus of anticipated danger may be internal or external" (p.818)
Anger/Irritability	According to Stringaris et al. (2018): Irritability: "Increased proneness to anger compared with peers at same development level, and defining mood of Disruptive Mood Dysregulation Disorder (DMDD). As a symptom it is present in the criteria of several psychiatric disorders, including generalized anxiety disorder (GAD), depression, and post-traumatic stress disorder (PTSD)"(p.722) Anger: "The emotion that characterizes irritability. It is often a feeling, i.e. consciously processed. It has received considerable research in psychology (Blair, 2012), but is not classified separately in the DSM"(p.722)
Depressed mood/sadness	According to De Zwart et al. (2018): Depressed mood "A state of low mood and aversion to activity. It can affect a person's thoughts, behavior, motivation, feelings, and sense of well-being. It may feature sadness, difficulty in thinking and concentration and a significant increase/decrease in appetite and time spent sleeping" (p.2) According to Horwitz and Wakefield (2007): Sadness: "Experience of sad feelings, difficulty to concentrate, and reduced appetite" (p.1)

Note: Operational definitions for the above symptoms were extracted from DSM-V or from relevant publications if definitions for the above symptoms were not listed in DSM-V. The above symptoms relate to mood disturbances occurring during abstinence from tobacco and may not necessary meet the criteria for disorders as listed in DSM-V.

Bibliography:

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

De Zwart PL, Jeronimus BF, De Jonge P. Empirical evidence for definitions of episode, remission, recovery, relapse and recurrence in depression: a systematic review. *Epidemiol Psychiatr Sci* . 2018:1-9.

Grisanzio KA, Goldstein-Piekarski AN, Wang MY, Ahmed AP, Samara Z, Williams LM. Transdiagnostic symptom clusters and associations with brain, behavior, and daily function in mood, anxiety, and trauma disorders. *JAMA Psychiatry* . 2018;75(2):201-9.

Horwitz AV, Wakefield JC. The loss of sadness: How psychiatry transformed normal sorrow into depressive disorder. Oxford University Press; 2007 Jun 18.

Stringaris A, Vidal-Ribas P, Brotman MA, Leibenluft E. Practitioner review: definition, recognition, and treatment challenges of irritability in young people. *J Child Psychol Psychiatry*. 2018 ;59(7):721-39.

Van Reekum R, Stuss DT, Ostrander L. Apathy: why care?.*J Neuropsychiatry Clin Neurosci*.2005 ;17(1):7-19.

Supplementary Table 2. Meta regression model predicting anxiety, anger/irritability, depressed mood/sadness, and composite NA from levels of tobacco dependence, age, sex, and hours of tobacco abstinence.

Symptom	Variables		B	SE	95% CI	*p*
Anxiety	Intercept		1.37	0.56	0.26,0.48	0.01*
	Dependence[1]:	High	-1.00	0.66	-2.31,0.30	0.00**
		Medium	-0.93	0.42	-1.76,-0.10	
	Age		0.02	0.01	0, 0.05	0.06
	Hours of abstinence		-0.10	0.05	-0.20, -0.00	0.03*
	Sex (female)		1.93	0.97		0.04*
Anger/irritability	Intercept		01.37	0.62	0.09,2.56	0.03*
	Dependence[1]:	High	-0.75	0.30	-1.35,-0.15	0.00**
		Medium	-0.67	0.23	-1.13,-0.21	
	Age		0.01	0.00	-0.00,0.02	0.08
	Hours of abstinence		-0.08	0.02	-0.14,-0.03	0.00**
	Sex (female)		1.75	0.56	0.64,2.85	0.00**
Depresssed mood/sadness	Intercept		0.15	0.33	-0.49,0.80	0.63
	Dependence[1]:	High	0.40	0.17	0.05,0.75	0.00**
		Medium	-0.10	0.12	-0.34,0.13	
	Age		0.00	0.00	-0.01,0.01	0.99
	Hours of abstinence		0.01	0.01	-0.02,0.04	0.51
	Sex (female)		-0.17	0.59	-1.33,0.97	0.76

Negative affect (NA)	Intercept		-0.23	0.42	-1.07,0.59	0.57
	Dependence[1]:	High	0.70	0.22	0.27,1.14	0.000***
		Medium	0.20	0.22	-0.24,0.64	
	Age		0.00	0.00	-0.01,0.01	0.92
	Hours of abstinence		-0.00	0.01	-0.03,0.02	0.75
	Sex (female)		1.06	0.54	-0.00,2.13	0.05

Note. ***: p<0.0001, **: p<0.001, *: p<0.05, B: Beta coefficient, CI: Confidence interval, 1: Dependence included as a set with high and medium levels of dependence included as dummy coded variables.