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**Tables: 2**

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**Supplemental Figure: 1**

# The association between smoking prevalence and eating disorders:

# a systematic review and meta-analysis

**Running head:** smoking in eating disorders

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**Background and aims:** Cigarette smoking is associated with severe mental illness including schizophrenia and bipolar disorder, and with morbidity and mortality, but the association withanorexia (AN), bulimia nervosa (BN) and Binge Eating Disorder (BED), is unclear. This meta-analysis compared the odds of smoking in Eating Disorders (ED) (ED= AN or BN or BED) versus healthy controls (HC) and calculated the prevalence of smokers in people with ED.

**Methods:** Three independent authors searched PubMed,MEDLINE and Scopus from database inceptionuntil 12/31/2015 for studies reporting data on life-time or current smoking prevalence in BED, BN, and AN, with or without control group. Meta-analyses were

undertaken, calculating odds ratios (ORs) of life-time smoking in BED, BN, AN vs HCs, or prevalence of smoking in BED, BN, AN with 95% confidence intervals (CI).

**Results:** Thirty-one studies (ED=8,517, controls=68,335) were meta-analyzed. Compared with HCs, there were significantly more smokers among people with BN (life-time OR=2.165) and BED (life-time OR=1.792) but not AN (life-time OR=0.927). BED was associated with smoking the most (life-time prevalence=47.7%) followed by BN (life-time prevalence=39.4%) and AN (life-time prevalence=30.8%). In BN, life-time smoking prevalence was highest in Europe. In AN, higher age moderated both life-time and current smoking prevalence, and body mass index moderated higher life-time smoking prevalence. In BN, female sex moderated higher life-time smoking prevalence.

**Conclusions:** People with binge eating disorder and bulimia nervosa are significantly more likely to be life-time smokers than healthy controls, which is not the case for anorexia nervosa.

**Keywords:** smoking; anorexia nervosa; bulimia nervosa; binge eating disorder; eating disorders, meta-analysis, moderators.

**Introduction**

People with eating disorders often have comorbid psychiatric and substance use disorders (1,2).In particular, abuse of alcohol and illicit drugs has been highly associated with anorexia (AN), bulimia nervosa (BN) and Binge Eating Disorder (BED) (3,4);however, very little is known about cigarette smoking rates.

In mental illness smoking is highly prevalent, with values even higher than 50% when considering a life-time diagnosis of mental illness(5), and in the general population, smoking is a leading cause of premature mortality (6); there are a number of pertinent effects of cigarette smoking that could be particularly deleterious among people with ED, as both AN and BN typically have an onset in the teenage years(7), but surprisingly smoking prevalence in BED, BN and AN has not been considered in previous reviews.(5) Also, smoking is a relevant issue to anorexia (AN) and bulimia nervosa (BN), since smoking is a risk factor for higher oxidative stress and inflammatory levels (8,9), as well as for osteoporosis and fractures, which are often observed in AN (10). Furthermore, concomitant consequences of high levels of alcohol, nutritional deficiency and acidic damage due to self-induced vomiting already put people with AN and BN at higher risk of esophageal cancer(11), and smoking is an additional, established risk factor for esophageal cancer.(12) Moreover, pulmonary consequences of smoking in AN are well known; in a malnourished population often with associated emphysema-like changes, cigarette use could induce even worse damage, potentially leading to high lung cancer risk (13,14). Also, BED is often in comorbidity with obesity and metabolic syndrome, and smoking would further add to the increased cardiovascular risk profile.(15,16)

The relationship between smoking and ED appears to be complex. Smoking could be used as a weight-control strategy by women affected by ED(17). There appears to be a longstanding belief that nicotine suppresses appetite, and smoking has been shown to increase resting metabolic rate (18), which is why smoking is used for weight control(19,20). In individuals with ED, the perceived benefits of nicotine for weight-control and temporary stress reduction may outweigh any concerns about the long-term harms of smoking. Women's concerns about body shape and weight, and their belief that smoking helps to control appetite, have indeed been considered as factors which may influence initiation of smoking(21) and relapse after periods of abstinence(22,23). Finally, in the general population, smoking cessation has been associated with a mean increase of 4-5 kg in body weight after 12 months of abstinence, with a wide variation in weight change; 16% of quitters lose

weight and 13% gain more than 10 kg(16). Determining the prevalence of smoking among people with ED, and comparing it with the general population is an important public health issue; a meta-analytic approach is a reliable method to correctly estimate the prevalence of smokers in patients with ED.

We conducted the first meta-analysis investigating the prevalence of smoking among people with ED versus healthy controls (HCs). In particular, we compared (i) smoking rates in BED, BN, and AN vs HCs, calculating OR (ii) calculated the prevalence and moderators of smoking prevalence in each ED.

**Methods**

This systematic review adhered to the MOOSE guidelines (26) and PRISMA statement (27).

*Inclusion criteria*

Eligible studies had to meet the following criteria: (1) included participants of any age with a primary diagnosis of any ED (i.e., AN, BN, BED, eating disorder not otherwise specified (EDNOS) based on established criteria (e.g., DSM-III, DSM-IV, or ICD-10), (2) reported data about either current and/or life-time smoking status (through self-report, questionnaire or medical notes), (3) published in a peer reviewed journal, (4) had a control group for OR calculation, or either had or did not have a control group for prevalence calculation, and (5) was written in English. When we encountered mixed samples of ED, where it was not possible to stratify the results, the study was excluded due to significant clinical differences across ED that were expected to affect the risk of smoking .

*Information sources and searches*

Three authors (BS, NV, MS) independently searched PubMed, MEDLINE and Scopus from database inception until December, 31st 2015, using the following search strategy: ("eating disorder"

OR "anorexia" OR "bulimia" OR "binge eating disorders") AND ("smoke" OR "smoking" OR "cigarette" OR “tobacco” OR “nicotine”). We also checked the reference list of included articles and of relevant reviews(28). Any web references will be archived before citation using WebCite ® technology (http://www.webcitation.org).

*Study selection*

After removal of duplicates, three independent reviewers (CL, GS, DV) screened titles and abstracts of all potentially eligible articles. Three authors applied the eligibility criteria, considered the full texts and a final list of included articles was reached through consensus. A fourth reviewer (BS) was available for mediation.

*Outcomes*

Our primary outcome of interest was the odds ratios (ORs) of the relative prevalence of smokers between ED participants (AN, BN, EDNOS, BED) and HCs. For the aim of this work, both lifetime and current smoking were considered, without any pre-specified threshold in the number of cigarettes or years of smoking. Secondarily, we investigated the prevalence of smokers in ED according to type of ED (AN, BN, EDNOS, BED). We chose OR as outcome since the vast majority of studies have a cross-sectional design, making Relative Risk not appropriate.

*Data Extraction*

Two authors (NV, MS) independently extracted data using a predetermined extraction form, including: years of publication, country, setting, demographic characteristics for people with ED and the control groups (age, number of females, sample size, mean BMI values in each group), and if any matching criteria for age and sex were applied.

*Quality assessment*

As previously suggested (29) for reporting the methodological quality of observational studies, the quality of the included studies was assessed descriptively through five items, i.e. 1) clear description of participants (eligibility, setting, and methods of participant selection); 2) reporting data on mean duration of disease and diagnostic criteria in people with ED ; 3) clear definition of smoking; 4) reporting data about body mass index (BMI) or other body composition parameters; and 5) use of matching approach between ED patients and controls.

*Meta-analysis*

Due to the anticipated heterogeneity, we utilized random effects meta-analysis and calculated odds ratios (ORs) and 95% confidence intervals (CIs) as the effect size measure with comprehensive meta-analysis (CMA, version 3). The meta-analysis was conducted in the following steps. First, we calculated the OR statistic together with 95%CI to establish the difference in the proportion of smokers between each ED diagnostic group (AN, BN, EDNOS, BED) vs. HCs. Second, we calculated the prevalence of smokers in each ED group. Heterogeneity was assessed with the Cochrane Q and $I^2$ statistics for each analysis (30). We conducted meta-regression analyses with CMA for outcomes with high heterogeneity ($I^2 \geq 50\%$ and/or $p \leq 0.05$) and reported by at least 4 studies to investigate potential moderators of the results among people with ED compared with HCs, including country, setting, criteria for diagnosis of ED (DSM-IV vs. others), use of matching criteria (yes vs. no), methods for assessing smoking history (structural interview vs. self-reported), sample size, mean age, BMI, percentage of females in the ED and HC sample. Also, differences in mean age, BMI and in percentage of females were tested as potential moderators of the heterogeneity. All analyses were conducted for lifetime smoking and, if available, for current smoking status.

Publication bias was assessed with a visual inspection of funnel plots and with the Begg-Mazumdar Kendall's tau (31) and Egger bias test(32). In order to test for publication bias, we calculated the trim and fill adjusted analysis (33) to remove the most extreme small studies from the positive side of the

funnel plot, and recalculated the effect size at each iteration, until the funnel plot was symmetric about the (new) effect size. Finally, we calculated the fail safe number of negative studies that would be required to nullify (i.e. make p>0.05) each of our comparative analyses(34).

*Search results*

The search identified 1,804 non-duplicated, potentially eligible studies. After excluding 1,711 papers through title and abstract review, 93 full text articles were examined, leading to the inclusion of 31 eligible studies in this meta-analysis (full details in **Figure 1**)(13,35–63).

*Characteristics of included studies and participants*

Study and patient characteristics are summarized in **Table S1** (comparative meta-analysis studies) and **Table S2** (prevalence studies (i.e., data from comparative and non-comparative studies)).The 31 studies included 76,852 participants (8,517 ED and 68,335 HCs). Of these, 2,033 participants were diagnosed with AN (mean age: 24.4±6.1 years; mean BMI: 16.8±2.4), 2,620 with BN (mean age: 23.5±5.3 years; mean BMI: 22.9±4.1), 3,528 with BED (mean age: 26.2±5.8 years; mean BMI: 23.4±4.1), and 336 with EDNOS (mean age: 22.6±9.0 years; no studies with BMI data). The mean age of the 68,335 HCs was 26.7±4.5 years with a BMI of 23.0±3.1 Kg/$m^2$. As reported in **Tables S1-2**, 13 studies used a structured interview for assessing smoking history, while the other 18 utilized a self-reported questionnaire.

Most studies were conducted in North America (18 studies), followed by 10 studies in Europe, and two in Oceania or Asia. All except six studies included only females and only five used matching criteria between ED and HCs. Full details of the included studies are reported in **Tables S1-2**.

*Study reporting quality and risk of bias*

Full details of study reporting quality are placed in **Table S3,** demonstrating that the most common sources of bias was the lack of matching between ED and HC and that several studies did not report data about BMI, other body composition parameters, and illness duration.

*Meta-analysis of smokers in ED and HCs*

As shown in **Table 1**, BN was associated with a significantly higher proportion of life-time smokers than HCs (OR=2.165; 95%CI: 1.642-2.855, p<0.0001; $I^2$=88.2%; studies=10; (35,39,40,48,50,54,55,61,62,64)), without any evidence of publication bias (Begg=-0.13, p=0.59, Egger=0.98, p=0.67). People with BED were also significantly more likely to be life-time smokers than HC (OR=1.792; 95%CI: 1.228-2.616, p=0.002; $I^2$=0%; studies=4; (40,54,59,60)).

Conversely, in 7 studies(26,27,30,31,34,36,39 )there was no evidence that people with AN are more likely to smoke in any period of their life than HC (OR=0.927; 95%CI: 0.650-1.320, p=0.67; $I^2$=70.4%). There was no evidence of publication bias (Egger=-1.69, p=0.18, Begg=-0.09, p=0.76). Only one comparative study reported smoking status in EDNOS and found no significant difference compared to HCs (35).

The trim and fill adjusted analyses remained unchanged for BN and BED. The trim and fill analysis for comparative studies including AN yielded an adjusted and increased OR of 1.14 (95%CI: 0.79-1.64), but the difference to HCs remained non-significant.

We also compared current smoking prevalence in AN and BN vs. HCs. AN did not differ significantly regarding current smokers compared to HCs (OR=0.783; 95%CI: 0.45-1.34; p=0.31; studies=7), while BN had higher proportions of current smokers than HCs (OR=2.32; 95%CI: 1.12-4.78; p=0.02; studies=4) (Table 1).

*Prevalence of smoking in ED*

**Table 2** reports the prevalence of life-time and current smokers according to type of ED and other sub-group analyses, including publication bias data. Key findings are briefly summarised below. Among all ED, the highest prevalence of smokers was observed in BED (47.73%, 95%CI: 34.80-60.97%; five studies; (40,54,59,65)), followed by BN (39.41%, 95%CI: 33.23-45.95%; 23 studies (35,37,39–41,44,46–52,54–57,61–64,66,67)), AN (22.45%, 95%CI: 17.07-28.95%; 16 studies (13,35–47,49,67)) and EDNOS (22.17%, 95%CI: 10.51-40.85%; 2 studies (35,49)). We also calculated prevalence of current smokers in AN (21.6%; 95%CI: 15.6-29.1; studies=15), in BN (36%; 95%CI: 28.9-43.8; studies=17) and in EDNOS (14.8%, 95%CI 2.7-51.9, studies=2).

Considering AN, setting, region in which the study was performed, and study type (with or without control group) did not affect the prevalence of life-time or current smokers. Conversely, BN studies conducted in Europe reported a significantly higher prevalence of life-time smokers (45.79%; 95%CI: 35.05-56.93) compared with studies from other continents ($p<0.001$).

Publication bias was evident for the main analyses in AN, and for studies conducted in North America among AN. After accounting for this issue, the trim and fill procedure suggested that the prevalence of life-time smokers was higher in AN in general (30.8%, 95%CI: 24.6-37.8%, 6 studies trimmed) as well as in the subgroup of North American studies (29.1%; 95%CI: 21.4-38.3%, 5 studies trimmed).

*Meta-regression of moderators of smokers in ED*

Meta-regression analyses for the prevalence of smokers in AN identified that a higher prevalence of smokers was moderated by a higher mean age of participants (life-time smokers: $\beta$=0.06; 95%CI: 0.01 to 0.11, p=0.02, $R^2$=0.38; current smokers: $\beta$=0.33; 95%CI: 0.08 to 0.59, p=0.01, $R^2$=0.66 ) and a higher mean BMI (life-time smokers: $\beta$=0.33; 95%CI: 0.00 to 0.63, p=0.03, $R^2$=0.10).

Regarding BN participants, the prevalence of life-time or current smokers was not moderated by either higher mean age, or mean BMI . However, a higher proportion of females was

significantly associated with a higher prevalence of life-time smokers with BN (β=0.05; 95%CI: 0.02 to 0.09, p=0.005, $R^2$=0.27).

**Discussion**

The current meta-analysis of 31 studies demonstrated that people with BED and even more so with BN, but not those with AN, were significantly more likely to have a lifetime history of smoking than HCs. Odds ratios indicated that BN and BED were around twice as likely to smoke as HCs. Meta-analysis of prevalence rates demonstrated that almost half of BED smoked, and almost 40% of the BN patients and 30% of people with AN smoked. Meta-regression analyses identified that higher mean age and BMI moderate life-time smoking rates in AN, with higher age moderating also current smoking in people with AN, whereas a higher percentage of females moderated the prevalence of life-time smokers in BN.

The high prevalence of smoking among BN could be due to the fact that smoking might be considered a compensatory behavior, since nicotine suppresses appetite, stimulates metabolism, and might control weight or modulate eating (19,68,69). Moreover smoking could be linked to both impulsive and compulsive personality traits and behaviors, which are known to be part of the relational and behavioral pattern in BN(70). Furthermore, smoking is associated with higher use of marijuana and alcohol(71), and different substance use is related in turn to increased incidence of attempted suicide, stealing, and sexual intercourse(42). Hence, much attention should be paid to the high smoking prevalence in patients with BN. However, among all ED, BED seem to have the highest presence of smokers. This is a concern, since these people are at increased risk of cardiovascular diseases due to higher presence of obesity(72), diabetes(73) and hypercholesterolemia(74). Hence, routine smoking assessment and smoking cessation treatment is warranted for those with BED and BN.

Conversely, our results suggest that AN is not associated with higher smoking frequencies than in HCs. Patients with AN likely pay more attention to their ability to exercise and focus more on details (75), which may lead them to contemplate the health consequences of smoking more than other EDs. However, as suggested by our meta-regression analysis, it should be noted that in AN higher BMI moderated higher prevalence of smokers, suggesting that also in this ED, tobacco smoking might be being used as compensatory behavior to lose weight. Unfortunately, among AN, uptake of outpatient services related to concerns about their health are poor, which would be an opportunity to explain the potential risks associated with cigarette use and initiate smoking cessation interventions (76).However, there is evidence that smoking cessation may exacerbate AN symptoms, and eating behavior should be carefully monitored in patients with lifetime AN who are attempting to quit smoking(77). Finally, the lower smoking prevalence in AN could also be due to a reporting bias in that patients with AN may be more likely to underreport unhealthy behaviors, similarly as for other self-reported information(78). Further studies should clarify smoking frequency in AN compared with HCs.

Considering the high prevalence of tobacco use in ED, in particular in patients with BN and BED, and in light of previous evidence suggesting that smoking is associated with alcohol abuse, poorer physical quality of life, increased risk of metabolic syndrome and cardiovascular risk factors, alongside with depressive symptoms in BED (79,80); clinicians should ask people with ED about their smoking status, and provide appropriate counseling and interventions (81).

Whilst our meta-analysis is the first to comprehensively assess smoking prevalence's in people with different kind of EDs, the findings should be considered within the study's limitations. First, we were not able to meta-analyze more detailed quantitative data (e.g. number of cigarettes, duration of smoking etc.) about smoking in patients with ED. Such data would have been relevant since several medical conditions (like cancer) show a dose-response with the number of cigarettes smoked. Further, nor did we have data on current smoking rates, especially not confirmed with

biochemical measures, such as expired carbon monoxide or cotinine. Second, we were not able to distinguish restrictive AN (RAN) from binge-purge AN (BPAN). This is an important limitation, since from a clinical and impulsivity-related perspective patients with BPAN are closer to BN than RAN, Therefore, smoking status in these two subgroups should be compared in future studies. Third, most of the meta-analyzed studies included females, and it remains unclear if the same results are evident in males with ED. However, our meta-regression analysis suggests that being female was at least related to a higher prevalence of smokers in BN. Further studies including males in ED are warranted to better clarify a potential effect of sex. Fourth, in several studies BMI or other relevant anthropometric measures were not reported. The effect of smoking on adiposity in ED remains to be confirmed with better designed studies. Finally, another potential bias could be due to the lack of matching between ED and HCs in most studies. On the other hand, notable strengths of this meta-analysis, besides it being the first on this important topic, are: (a) the large number of included studies (n=31) and(b) the large sample size (over 70,000 participants).

In conclusion, smoking is highly prevalent in ED, in particular among people with BED and BN. Further, high-quality studies are needed to assess the time course of ED and smoking, the impact of smoking on the onset and development of medical complications in eating disorders, and, most importantly, the effectiveness of interventions aimed at promoting smoking cessation in people with ED.

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**Table 1**: Meta-analysis of smoking rates in patients with eating disorders versus controls

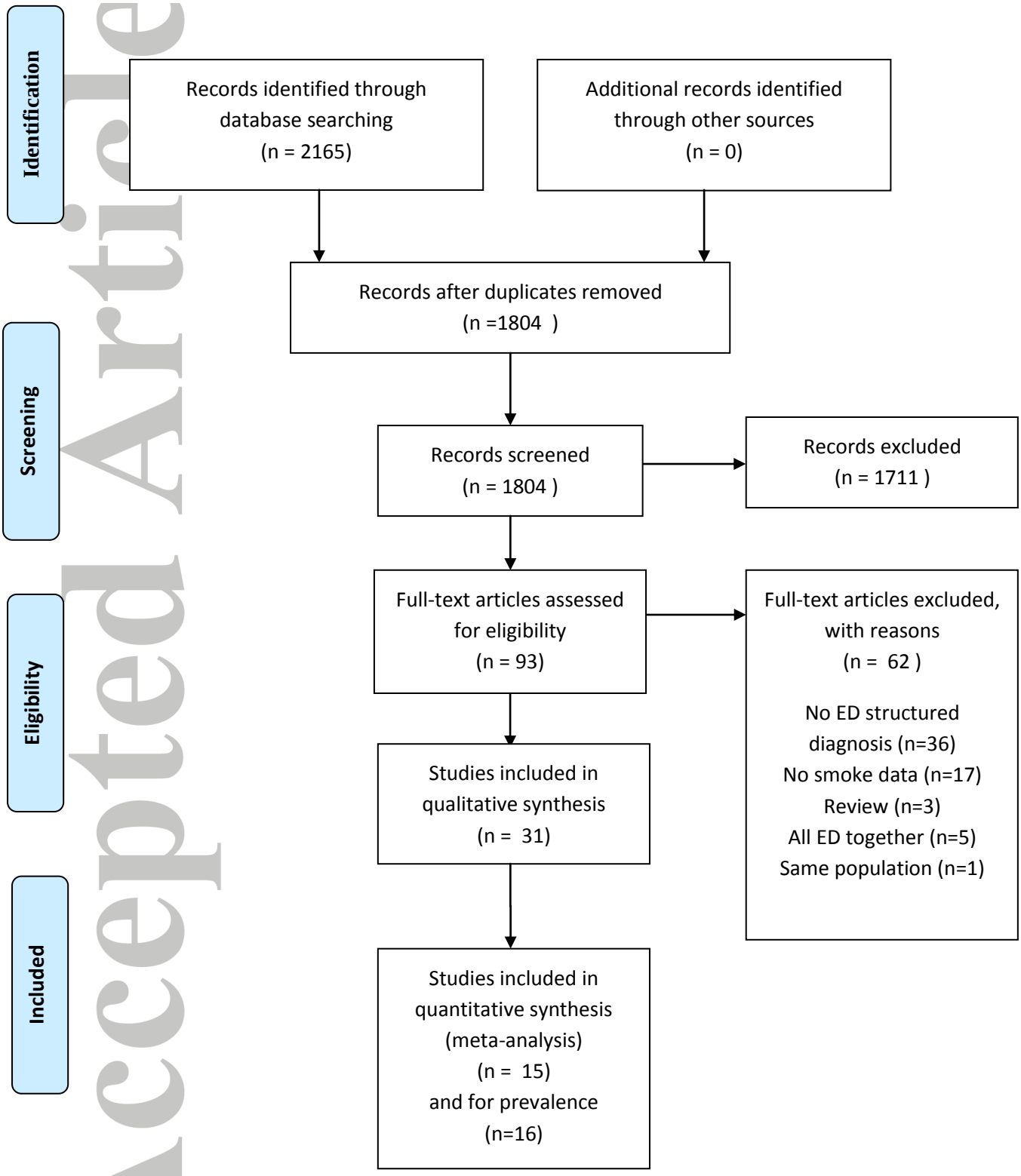
| Analysis | Number of studies | Number participants | | Meta-analysis | | | | Heterogeneity | Publication bias | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | ED | HC | OR | 95% CI | | P value | $I^2$ | Egger bias & p value | Trim and fill (95% CI) [NR studies trimmed] |
| **Life-time Smokers** | | | | | | | | | | |
| *Anorexia Nervosa* | 7 | 1617 | 1350 | 0.93 | 0.65 | 1.32 | 0.674 | 70.4 | -1.69, p=0.18 | 1.14 (0.79 to 1.64) [2] |
| *Bulimia Nervosa* | 10 | 149 | 139 | 2.16 | 1.64 | 2.85 | **<0.0001** | 88.2 | 0.98, p=0.67 | Unchanged |
| *BED* | 4 | 3425 | 4313 | 1.79 | 1.23 | 2.62 | **0.002** | 0 | 0.90, p=0.31 | Unchanged |
| **Current Smokers** | | | | | | | | | | |
| *Anorexia Nervosa* | 7 | 578 | 2131 | 0.78 | 0.45 | 1.34 | 0.31 | 83.3 | -1.02, p=0.27 | Unchanged |
| *Bulimia Nervosa* | 4 | 322 | 592 | 2.32 | 1.12 | 4.78 | **0.02** | 61.3 | 0.67, p=0.71 | Unchanged |

**Key**: SMD = standardised mean difference, CI = confidence interval, EDNOS= eating disorder not otherwise specified, BED= binge eating disorder

**Table 2.Life-time and current** prevalence of smokers in each eating disorder subcategory

| Analysis | Number of studies | Number participants | Meta-analysis | | | Heterogeneity | Publication bias | |
|---|---|---|---|---|---|---|---|---|
| | | ED | Prevalence | 95% CI | | $I^2$ | Egger bias & p value | Trim and fill (95% CI) [Number studies trimmed] |
| **LIFE-TIME SMOKERS** | | | | | | | | |
| *Anorexia Nervosa* | 16 | 2033 | 22.45 | 17.07 | 28.95 | 84.9 | -2.8, p<0.05 | 30.8 (24.6 to 37.8) [6] |
| *Bulimia Nervosa* | 23 | 2620 | 39.41 | 33.23 | 45.95 | 89.2 | -1.6, p=0.27 | unchanged |
| *EDNOS* | 2 | 336 | 22.17 | 10.51 | 40.85 | 97.5 | N/A | N/A |
| *BED* | 5 | 3528 | 47.73 | 34.80 | 60.97 | 96.9 | -5.6, p=0.26 | 56.2 (44.2 to 67.6) [2] |
| **CURRENT SMOKERS** | | | | | | | | |
| *Anorexia Nervosa* | 15 | 1168 | 21.6 | 15.6 | 29.1 | 89.7 | -1.1, p-0.45 | Unchanged |
| *Bulimia Nervosa* | 17 | 1557 | 36.04 | 28.9 | 43.8 | 86.6 | 0.78, p=0.61 | Unchanged |
| EDNOS | 2 | 304 | 14.8 | 2.7 | 51.9 | 92.7 | N/A | N/A |

**Figure 1. PRISMA flow-chart**




*Key: ED= Eating Disorders*