University of Vermont
ScholarWorks @ UVM

Graduate College Dissertations and Theses | Dissertations and Theses

1-1-2014

Meta-Analysis Of Studies Investigation Of The Effect Of Smoking Cessation On Impatience

Miriam Claire Dash
University of Vermont, mikidash@gmail.com

Follow this and additional works at: http://scholarworks.uvm.edu/graddis

 Part of the Epidemiology Commons, and the Statistics and Probability Commons

Recommended Citation
Dash, Miriam Claire, "Meta-Analysis Of Studies Investigation Of The Effect Of Smoking Cessation On Impatience" (2014). *Graduate College Dissertations and Theses.* Paper 250.

This Thesis is brought to you for free and open access by the Dissertations and Theses at ScholarWorks @ UVM. It has been accepted for inclusion in Graduate College Dissertations and Theses by an authorized administrator of ScholarWorks @ UVM. For more information, please contact donna.omalley@uvm.edu.

META-ANALYSIS OF STUDIES INVESTIGATION OF THE EFFECT OF SMOKING CESSATION ON IMPATIENCE

A Thesis Presented

by

Miriam Claire Dash

to

The Faculty of the Graduate College

of

University of Vermont

In Partial Fulfillment of the Requirements
for the Degree of Master of Science
Specializing in Biostatistics

October, 2014

Accepted by the Faculty of the Graduate College, The University of Vermont, in partial fulfillment of the requirements for the degree of Master of Science, specializing in Biostatistics.

Thesis Examination Committee:

_____ **Advisor**

Peter W. Callas, Ph.D.

_____

Ruth M. Mickey, Ph.D.

_____ **Chairperson**

John R. Hughes, M.D.

_____ **Dean, Graduate College**

Cynthia J. Forehand, Ph.D.

Date: April 1, 2014

ABSTRACT

Background: Smoking cessation increases several symptoms, some of which appear to be due to nicotine withdrawal. One possible feature of withdrawal is impulsivity. Impulsivity is not currently included as a symptom of nicotine withdrawal neither in the Statistical Manual of Mental Disorders, 4th Edition, Text Revision (***DSM-IV-TR***) nor in withdrawal scales. However, a related term, "impatience" is listed in some nicotine withdrawal scales. (Hughes J. R., Measurements of the Effects of Abstinence from Tobacco: A Qualitative Review, 2007). Although impatience is not a synonym of impulsivity, both share the synonym "impetuous". Therefore, impatience can be considered a measure of impulsivity. Although some reviews of the effect of smoking cessation on impatience have occurred, we know of no quantitative review of prospective studies of whether smoking cessation increases impatience.

Purpose: To evaluate the effect of smoking cessation on impatience as measured by the Minnesota Nicotine Withdrawal Scale-Revised (MNWS).

Methods: A literature search of MEDLINE (PubMED), EMBASE, and PsychInfo was conducted. Articles containing relevant keywords were reviewed by two evaluators independently. To be considered for inclusion in the meta-analysis, studies had to be prospective studies, had to have pre-cessation impatience measurements, to include at least overnight abstinence, had to have smoking abstinence biochemically verified, and had to include effect size as an outcome measure.

Results: All pooled analyses were based on random-effects models. Seven trials met the selection criteria. The total number of subjects was 426. There was a significant level of heterogeneity among studies ($\chi^2 = 55.71$ (6), $p<0.0001$) and ($I^2 = 89\%$). The summary mean effect for impatience after tobacco cessation was an increase of .44 on a 0-3 scale (95% confidence interval [CI], 0.21-0.67) and a p-value<0.0001.

Conclusion: The meta-analysis shows that impulsivity increases post smoking cessation. These findings imply that smoking cessation may have an effect on decision making. Additionally higher rates of impulsivity have been associated with smoking relapse. (Doran, Spring, McChargue, Peradia, & Richmond, 2004). In order to better assist in the development of individual treatments, a better understanding is needed of how increased impulsivity influences cognitive behavior and relapse rates. These findings support the inclusion of impulsivity as a criterion for nicotine withdrawal.

Table of Contents

LIST OF TABLES iv

LIST OF FIGURES v

Why Perform a Meta-Analysis: 1

Generalized Statistical Approach 2

Fixed-Effect Model 3

Performing a Fixed-Effect Meta-Analysis 6

Identifying Heterogeneity: *Q* Statistic 8

Quantifying Heterogeneity: *T* and I^2 10

Random-Effects Model 12

Performing a Random-Effects Meta-Analysis 15

Forest Plot 17

Publication Bias 18

Identifying Publication Bias: The Funnel Plot 19

Assessing the Impact of Publication Bias: Fail-Safe N 21

THE META-ANALYSIS OF STUDIES INVESTIGATING THE EFFECT OF SMOKING CESSATION ON IMPATIENCE 23

Background and Literature Review 23

Methods 24
Definition of Terms 25
Initial Eligibility Criteria 26
Information Sources 26
Sample Search Strategy 27
Study Selection 27
Data Collection Process 30
Data Items 30
Risk of Bias within Individual Studies 31
Characteristics of Included Studies 34
Statistical Analysis and Results 36
Effect Size Based On Mean in a Pre-Post Design 36
Fixed-Effect Meta-Analysis 37
Discussion 41
Conclusion 43
APPENDIX 44
Meta-Analysis of Studies Investigation of the Effect of Smoking Cessation Impatience Performed Using Excel 2010 44

References 46

LIST OF TABLES

Table 1 Medline Search 27

Table 2 Cochrane Collaboration's Summary Assessments 32

Table 3 Risk of Bias Summary: Author's judgments about each risk of bias item for each included study. 33

Table 4 Comparisons' Characteristics 34

Table 5 Study Description and Design 35

Table 6 Fixed-Effects Meta-Analysis Results and Forest Plot 38

Table 7 Random-Effects Meta-Analysis Results and Forest Plot 38

LIST OF FIGURES

Figure 1 Fixed-Effect Model – True Effects and the Distribution of Sampling Error 4

Figure 2 Random-Effects Distribution..... 13

Figure 3 Example of a Forest Plot 18

Figure 4 Example of a Symmetrical Funnel Plot..... 20

Figure 5 Flow of information through the different phases of the systematic review..... 29

Figure 6 Author's judgments about each risk of bias item presented as percentages across all included studies..... 32

Figure 7 Funnel plot of effect size estimates for all individual comparisons in the meta-analysis..... 40

GENERALIZED META-ANALYSIS AND STATISTICAL ANALYSIS MODELING

Why Perform a Meta-Analysis:

Advantages

Synthesizing studies increases the power to detect a real effect as statistically significant if it exists. Primary studies may be small and by combining them in a meta-analysis the precision of the estimated effect is improved. Smaller studies have lower statistical power to reject the null hypothesis when it is false. For example, several small studies may not have significant p-values giving the impression they had small effects, in fact they may have larger effects than larger studies that have reached significance. The synthesizing of apparently conflicting studies allows for the evaluation of the statistical significance of the estimated effect. A meta-analysis is not only interested in the statistically significance of the effect but the magnitude and the direction of that effect The p-value only indicates that the estimated effect is not zero but tells us nothing about the magnitude of the effect, which is what is meaningful to researchers and clinicians. Additionally, a primary study is targeted to a very specific population resulting in an estimated effect that is limited to that population, whereas, a meta-analysis allows for the combination of heterogeneous populations to determine a consistency of effects which is more generalizable. (Borenstien, Hedges, Higgins, & Rothstein, 2009)

Disadvantages

Meta-analysis has limitations. There have been large randomized treatment studies performed studying the same question as a meta-analysis with a drastically different outcome. (LeLorier, Greoire, Benhaddad, Lapierre, & Derderian, 1997) A meta-analysis is only as good as its individual studies. If one of the large studies used in the meta-analysis was poorly constructed it may have an adverse effect on the estimated effect. A meta-analysis has several areas of potential bias, including inclusion/exclusion criteria used to select the studies and publication bias. Another area of possible bias, or at least another limitation of meta-analysis, is combining findings across studies that are so heterogeneous that they perhaps should not be combined. In these cases it can be misleading to present one average effect when maybe there are multiple true effects, none of which might be similar to the combined effect obtained from the meta-analysis. (Borenstien, Hedges, Higgins, & Rothstein, 2009)

Generalized Statistical Approach

The generalized statistical analysis follows the approach of Borenstein, Hedges, Higgins, and Rothstein, which begins with the calculation of the effect size for each study. Next, the combination of the individual estimates is used to generate a summary effect. Fixed-effects and random-effects models are used to fit the data. A compare and contrast between these models will be discussed in the following paragraphs.

Fixed-Effect Model

The purpose of a fixed effect model is to estimate the unknown common effect size, μ and measure the accuracy of that estimation. To estimate the common effect size, compute the summary effect which is the weighted mean of each study. Compute the weighted mean by multiplying each study's observed effect by its inverse variance.

Consider a model comparing effect sizes

$$Y_i = \mu + \varepsilon_i$$

Y_i = observed effect size of the $_i$*th* study.

μ = is the common effect size i.e. the underling population effect size when there is no sampling error.

ε_i = the within study sampling error for the $_i$*th* study.

The observation effect, Y_i for each study is comprised of two components: the unknown common "true" effect μ and the second component is the within study random sample error $\varepsilon_{i.}$

Figure 1 illustrates that the observed effect Y_i is assumed to be normally distributed about the unknown common effect size μ with the width of the curve based on the variance of the sampling error, σ_i^2.

The common effect size μ is constant for all studies, which means the sampled population for each study is identical and any differences between studies is attributed to random sampling error, ε_i.

	True Effect (μ)	Observed Effect (Y_i)
Study		
Combined		

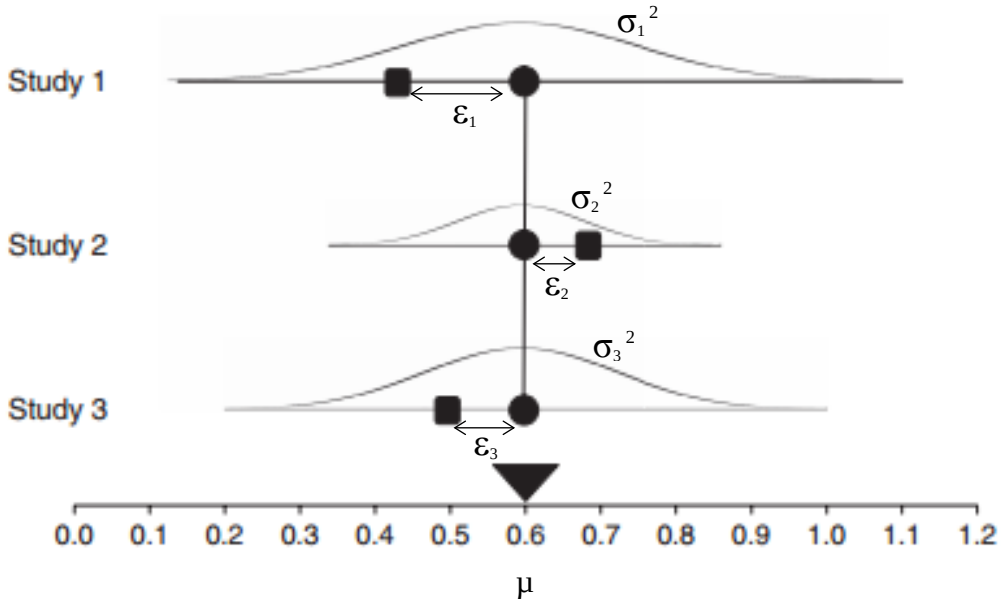


Figure 1 Fixed-Effect Model – True Effects and the Distribution of Sampling Error

Assumptions about the Fixed-Effects Model

$$Y_i \sim N(\mu, \sigma_i^2), \quad i = 1,..,k$$

Generally, the use of a fixed-effect model in a meta-analysis is inappropriate. Homogeneity among studies is essential for proper use of the fixed effects model. Although the studies in a meta-analysis are chosen because of their similarity to assume that each study is sampled from identical populations, i.e. same gender, same age, same race just to name a few characteristics is unrealistic.

Effect Size Significance Testing

In the fixed-effect model the null hypothesis is that there is zero effect in every study.

$$H_0: \mu = 0$$

Limitations of the Fixed-Effect Model

The inferences from a fixed-effects model are restricted to the studies in the model and do not test whether effect size varies from study to study. Researchers cannot illuminate if the intervention is impacted by the study sample.

Performing a Fixed-Effect Meta-Analysis

The goal of a fixed-effects meta-analysis is to estimate the common population effect, μ. Using the observed effects i.e. the collection of (Y_i), we estimate the common effect. To get the most precise estimate, i.e. to minimize the variance, a weighted mean is computed. Study weights are assigned to minimize the within study variance. A weight is assigned to each study, with more weight given to larger studies. The weight for a fixed-effect meta-analysis is

$$W_i = \frac{1}{V_{Y_i}}$$

where V_{Yi} is the estimate of within-study variance, σ_i^2. The weighted mean (M), which is referred to as the "summary effect", is then computed as

$$M = \frac{\sum_{i=1}^{k} W_i Y_i}{\sum_{i=1}^{k} W_i},$$

the sum of the products W_iY_i (the observed effect multiplied by the weight) divided by the sum of the weights.

The variance of the summary effect is estimated as the reciprocal of the weights and the estimated standard error of the summary effect is the square root of the variance.

$$V_M = \frac{1}{\sum_{i=1}^{k} W_i}$$

$$SE_M = \sqrt{V_M}$$

The 95% lower and upper limits for the summary effect are estimated as

$$LL_M = M - 1.96 \times SE_M$$

$$UL_M = M + 1.96 \times SE_M$$

To test $H_0 : \mu = 0$ namely, that the true effect μ is zero, a two sided Z test is performed.

$$Z = \frac{M}{SE_M}$$

Identifying Heterogeneity: *Q* Statistic

The *Q* statistic, also known as the χ^2 heterogeneity test, is a method of identifying the variation of true effect sizes μ from study to study. Heterogeneity of effect sizes is the variation of the true effect sizes.

In order to extract the between-study variation from the observed variation the following process is applied.

1. Compute total observed study to study variation.
2. Estimate how much the observed effects would be expected to vary between-studies if there were a true common effect.
3. The difference between the observed variation and the expected variation quantifies the real differences in effect size i.e. heterogeneity.

The *Q* statistic is used to analyze and partition the total observed variation.

Derivation of the *Q* statistic

Q is a weighted sum of squares. To compute *Q*, subtract each of the effect sizes (Y_i) from the mean (summary effect size *M*), square it, weight this by the inverse-variance (W_i) for

the study, and then sum these values over all studies to get the weighted sum of squares (*WSS*). (Borenstien, Hedges, Higgins, & Rothstein, 2009)

$$Q = \sum_{i=1}^{k} W_i \left(Y_i - M\right)^2$$

For easier computation

$$Q = \sum_{i=1}^{k} W_i Y_i^2 - \frac{\left(\sum_{i=1}^{k} W_i Y_i\right)^2}{\sum_{i=1}^{k} W_i}$$

Expected value of *Q*

The expected value of *Q* is based on the assumption that each study shares a common effect size μ and any variation is due to sampling error within studies. The expected value of *Q* is equal to the degrees of freedom (*df*). (Borenstien, Hedges, Higgins, & Rothstein, 2009)

$$Expected\left(Q\right) = df = k - 1,$$

where k is equal to the number of studies. When there is no heterogeneity in effect sizes, Q is distributed as χ^2 with *k*-1 (*df*).

The excess variation is computed by the observed WSS (Q) minus the expected WSS (df). This difference is the excess variation of the true effects attributed to the variation study to study, namely heterogeneity.

$$Q - df$$

Quantifying Heterogeneity: T and I^2

Whereas the Q statistic identifies the existence of heterogeneity, T^2 and T reflect the amount of heterogeneity. T^2 is an estimate of τ^2 the between-studies variance and T is the standard deviation of the true effects. In a meta-analysis it is important to report the summary effect and explain the dispersion of true effects (T) similar to a primary study where the mean and the standard deviation are reported.

To estimate the variance and the standard deviation T^2 and T use Q and remove the dependence on the number of studies returning it to the original metric. (Higgins & Green, 2011)

To compute T^2 and T

1. Take the difference ($Q - df$), which is standardized dispersion of the true effects
2. Divide by quantity C which puts the measurement back into original units and making it an average, rather than a sum of squared deviations

$$T = \sqrt{\frac{Q - df}{C}}$$

where

$$Q = \sum_{i=1}^{k} W_i Y_i^2 - \frac{\left(\sum_{i=1}^{k} W_i Y_i \right)^2}{\sum_{i=1}^{k} W_i}$$

$$df = k - 1$$

where k is the number of studies, and

$$C = \sum_{i=1}^{k} W_i - \frac{\sum_{i=1}^{k} W_i^2}{\sum_{i=1}^{k} W_i}$$

T^2 is in the same unit measurement (squared) as the effect size and represents the absolute amount of variation in that scale. (Borenstien, Hedges, Higgins, & Rothstein, 2009)

I^2 is a descriptive statistic that is the proportion of the real differences in effect size to the total variance. The term "real differences" refers to differences in effect size that is not attributed to random error. To compute I^2

$$I^2 = \frac{Variance_{Between}}{Variance_{Total}} = \left(\frac{Q - df}{Q}\right) \times 100\%$$

I^2 values of 25%, 50%, and 75% are considered low, moderate, and high proportions of heterogeneity, respectively.

Random-Effects Model

The purpose of a random-effects model is to estimate the mean distribution of the effect sizes, μ and measure the accuracy of that estimation. Unlike a fixed-effects model, for a random-effects model there is no assumption that each study is estimating the same effect size μ. To estimate the mean effect size compute the summary effect, this is the weighted mean of each study. Compute the weighted mean by multiplying each study's observed effect by its inverse variance. However, the variance in a random-effects model is calculated differently than a fixed-effects model and will be discussed in the following paragraphs.

Once again, consider a model comparing effect sizes

$$Y_i = \mu + \varsigma_i + \varepsilon_i$$

Y_i = observed effect size of the $_i$*th* study.

μ = is the mean of the population distribution of effect size.

ε_i = the within study sampling error for the *ith* study.

$\boldsymbol{\varsigma_i}$ = true effect of study$_i$.

Figure 2 illustrates the distribution of three studies drawn from the distribution of studies depicted by the normal curve. The observation effect, Y_i for each study is comprised of two components. The true effect μ plus the random true effect of study$_i$, $\boldsymbol{\varsigma_i}$, the second component is the within study random sampling error ε_i.

	True Effect (μ)	Observed Effect (Y_i)
Study	●	■
Combined	▼	

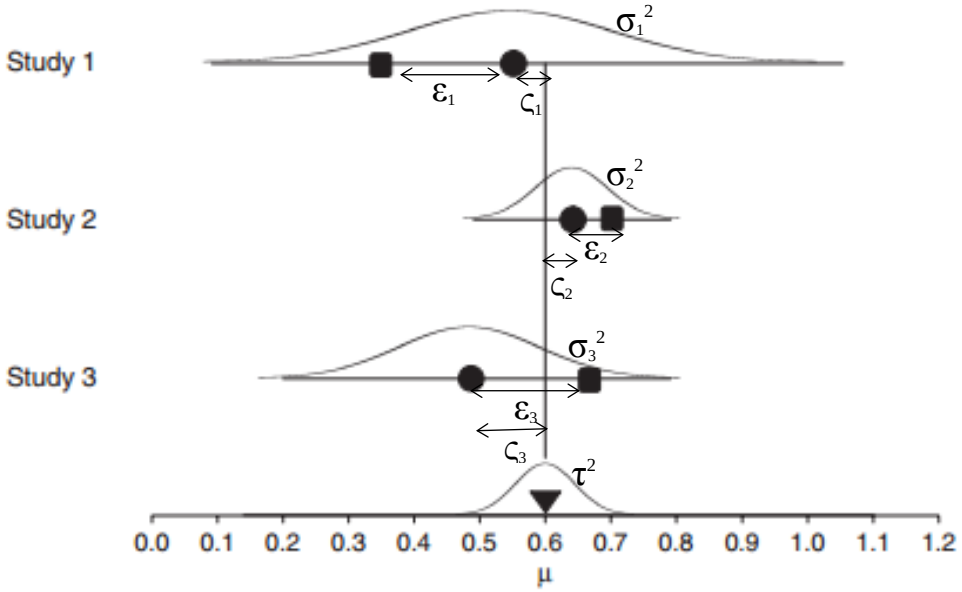


Figure 2 Random-Effects Distribution

Assumptions about the Random-Effects Model

$$\varepsilon_i \sim N(0, \sigma_i^2), \quad i = 1,..,k$$

$$\varsigma_i \sim N(0, \tau^2), \quad i = 1,..,k$$

Random-effects meta-analysis sampling is a two stage process. First, a random sample of studies is acquired from a larger population of studies whose true effects can be different for each study. The true effect is sampled from a distribution with mean μ and variance τ^2. In the second stage, a random sample of subjects is selected from a larger population of subjects. Y_i is sampled from a distribution of the true effects and variance σ_i^2. (Cooper, Hedges, & Valentine, 2009)

$$\text{Variance}\ (Y_i) = \sigma_i^2 + \tau^2$$

Effect Size Significance Testing

In the random-effect model the null hypothesis is that there is zero average effect across studies.

$$H_o: \mu = 0$$

Limitations of the Random-Effects Model

The studies in the model may be too heterogeneous to combine in a meta-analysis rendering any summary effect non-informative.

Performing a Random-Effects Meta-Analysis

The goal of the random-effects meta-analysis is to estimate the range of population effects. In the random-effects model the summary effect is used to estimate the mean distribution population effect. To get the most precise estimate, i.e. to minimize the variance a weighted mean is computed. A weight is assigned to each study. This is the reciprocal of the study's total variance. Unlike the fixed-effects model, larger studies are not assigned more relative weight and smaller studies are not assigned less relative weight because each study in the analysis represents a unique population. (*) denotes random-effects model. The weight for a random-effects meta-analysis

$$W_i^* = \frac{1}{V_{Yi}^*}$$

Where V^*_{Yi} is the sum of the estimate of within-study variance (V_{Yi}) and the estimate of the between study variance (T^2).

$$V_{Yi}^{*} = V_{Yi} + T^{2}$$

where, $Estimate\ of\ \sigma^2 = V_{Y_i}$

$$Estimate\ of\ \tau^2 = T^2$$

The weighted mean (*M*), which is referred to as the "summary effect", is then computed as

$$M^{*} = \frac{\sum_{i=1}^{k} W_i^{*} Y_i}{\sum_{i=1}^{k} W_i^{*}}$$

the sum of the products $W_i Y_i$ (the observed effect multiplied by the weight) divided by the sum of the weights.

The variance of the summary effect is estimated as the reciprocal of the weights and the estimated standard error of the summary effect is the square root of the variance.

$$V_{M*} = \frac{1}{\sum_{i=1}^{k} W_i^{*}}$$

$$SE_{M*} = \sqrt{V_{M*}}$$

The 95% lower and upper limits for the summary effect are estimated as

$$LL_{M^*} = M^* - 1.96 \times SE_{M^*}$$

$$UL_{M^*} = M^* + 1.96 \times SE_{M^*}$$

To test $H_0 : \mu = 0$ namely that the true effect μ is zero a two sided Z test is performed.

$$Z^* = \frac{M^*}{SE_{M^*}}$$

Forest Plot

A Forest Plot is a graphical representation of the meta-analysis results. To illustrate, suppose a meta-analysis is performed using four studies A, B, C, and D. In Figure 4, there are four squares with a horizontal line representing the four individual studies in the analysis. The size of the square is proportional (in area) to that study's weight in the analysis. The diamond represents the summary effect from the analysis. The vertical line centered at zero represents a null effect. The horizontal lines represents the confidence interval for each study. The length of the line illustrates the precision or imprecision of the point estimate. If the horizontal line crosses the vertical line then that study has an insignificant result. Studies C and D cross the vertical line and therefore contains the null

result. The middle of the diamond is the summary effect and its width is the confidence interval.

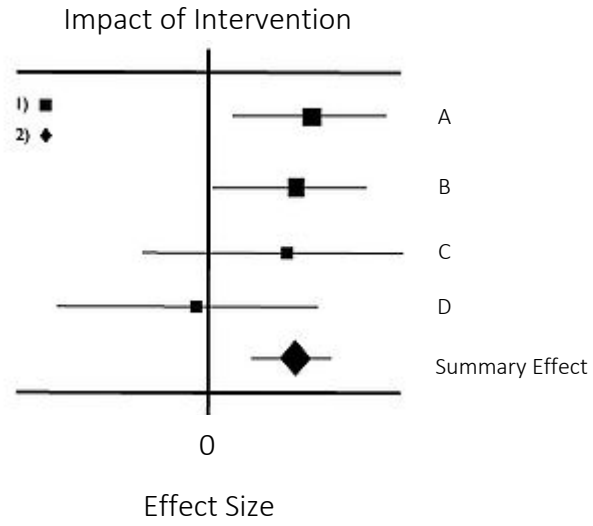


Figure 3 Example of a Forest Plot

Publication Bias

Publication bias can be a serious problem in health research and systematic reviews. Not all studies are published. Published and unpublished studies frequently have different results. It is accepted knowledge that larger studies and studies with statistically significant results are more likely to be published than smaller studies and studies with statistically non-significant results (Cooper, Hedges, & Valentine, 2009). Compounding this problem is that well designed and conducted research tends to produce more statistically non-significant results; hence less likely to be published. If published

research is a biased sample of all conducted research then the validity of the resulting inferences will be questionable, usually overestimating the true effect size because the studies are unrepresentative of the research population. (Sciences)

Identifying Publication Bias: The Funnel Plot

A funnel plot is a graphical method of detecting publication bias. It is a plot of estimates of effects versus measures of their precision for each of the primary studies in the meta-analysis. It is called the "funnel" plot because studies of smaller size (less precision) will have a wider distribution of results than studies of larger size, due to a higher variation. If publication bias is absent you should expect a symmetrical funnel about the true population effect size where less precise studies should be scattered to either side of the more precise studies. (Song, Khan, Dinnes, & Sutton, 2002)

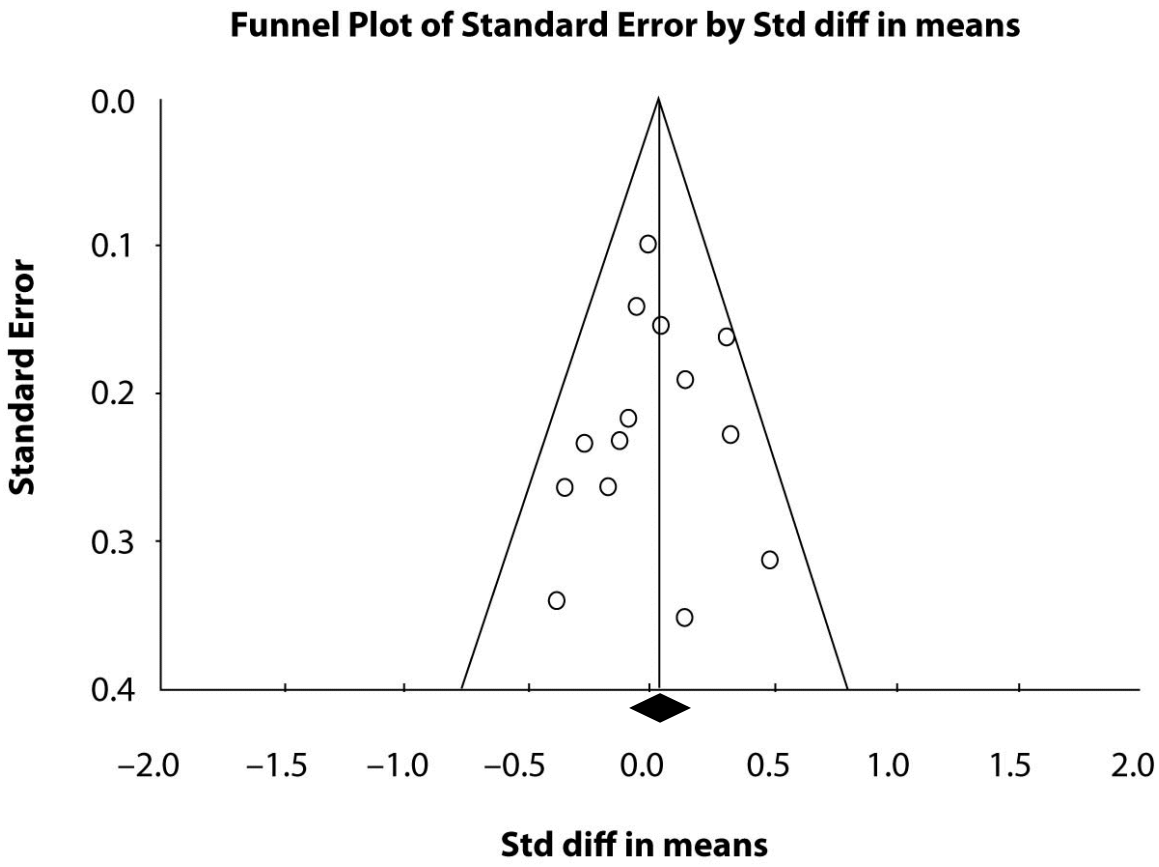


Figure 4 Example of a Symmetrical Funnel Plot

However; if a funnel plot is asymmetrical there may be other explanations other than publication bias. If a meta-analysis consists of a small number of studies or high heterogeneity between studies an inaccurate or asymmetrical funnel plot may be generated.

The objective of the Fail-Safe N method is to determine the number of unpublished research (k_0) with an average null effect of zero that would bring the overall summary effect to statistical non-significance i.e. $p \geq 0.05$. If it is determined that k_0 is so large that it is implausible there is that much unpublished research in existence then we can be confident that the statistical significance of the observed effects is likely to be true. To determine if k_0 is realistically achievable it should not exceed a calculated tolerance level. (Cooper, Hedges, & Valentine, 2009) To compute k_0 and the appropriate tolerance level

$$Z = \frac{\sum_1^k Z_i}{\sqrt{k}}$$

where k is the number of studies

$$\frac{\sum_1^k Z_i}{\sqrt{k + k_0}} < Z_{\propto/2}$$

that is

$$k_0 > -k + \frac{\left(\sum_1^k Z_i\right)^2}{\left(Z_{\propto/2}\right)^2}$$

with a tolerance level

$$5k + 10$$

So $k_0 \geq 5k + 10$, implies that if "5k + 10" or more studies are un-retrieved with zero effect, (compared to the published studies used in the research), on average, the meta-analysis would not reach statistical significance at the five percent level of significance. (Borenstien, Hedges, Higgins, & Rothstein, 2009)

There are several drawbacks to the Fail Safe N method: it does not consider sample size; it assumes a zero null effect for the unpublished studies, where the average effect may really be a non-zero effect; and the heterogeneity among studies is not considered, to name a few. Therefore, this method should be viewed as a useful, simple but rough method of assessing the impact of publication bias.

THE META-ANALYSIS OF STUDIES INVESTIGATING THE EFFECT OF SMOKING CESSATION ON IMPATIENCE

Background and Literature Review

Smoking cessation increases several symptoms, some of which appear to be due to nicotine withdrawal. (Shiffman, West, & Gilbert, August 2004) One possible feature of withdrawal is impulsivity.

Impulsivity is a broad concept that has been defined and measured differently by authors. The most widely included measures are self-reports of the adjective "impulsivity" or high scores on multi-item scales of impulsivity (Ashare & Hawk Jr., 2012) such as:

Delay discounting which is a measure of the degree to which an individual is driven by immediate gratification vs. the prospect of larger, but delayed rewards in either hypothetical or real delay scenarios. (Reynolds, Ortengren, Richards, & de Wit, 2006)

Response inhibition, often defined as an inability to inhibit false positive responses on a vigilance task i.e. the inability to suppress actions that are inappropriate in a given context and that interfere with goal-driven behavior. (Logan, Schachar, & Tannock, 1997).

Pre-pulse inhibition is the ability of a weak warning stimulus to reduce the impulsive reaction to a strong stimulus. (Ashare, Hawk, & Mazzullo, 2007)

Impulsivity is not currently included as a symptom of nicotine withdrawal neither in the Statistical Manual of Mental Disorders, 4th Edition, Text Revision (***DSM-IV-TR***) [American Psychiatric Association], International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) nor in withdrawal scales. However, a related term, "impatience" is listed in some nicotine withdrawal scales. (Hughes J. R., 2007) Although impatience is not a synonym of impulsivity, both share the synonym "impetuous". Therefore, impatience can be considered a measure of impulsivity.

Although some reviews of the effect of smoking abstinence on impatience, delay discounting, and response inhibition have occurred, we know of no quantitative review of prospective studies of whether smoking cessation increases one of the above measures of impulsivity. A meta-analysis of literature findings would be useful to strengthen the evidence of an association between smoking cessation or smoking deprivation and increased impulsivity.

Methods

The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions was used in the reporting of the research methodology and its results. (Liberati Alessandro, 2009)

Definition of Terms

There are several terms in the literature that are used interchangeably to describe the discontinuation of tobacco: abstinence, cessation, deprivation, quitting, and stopping. For simplicity and clarity, this research will use the Hughes, 2007 recommended terms: abstinence, cessation, and quitting referring to smokers who are trying to stop smoking permanently and use of deprivation to refer to experimenter-instructed temporary discontinuation of tobacco use in smokers not trying to stop tobacco use permanently.

In addition to withdrawal effects there is another post-cessation phenomenon called offset effect. The distinction between withdrawal effects and offset effects is that withdrawal effects are a time limited pattern of symptoms that may increase or decrease. "Whereas, offset effects are abstinence effects with a unidirectional change from the typical values of a smoker i.e. the simple termination of the chronic effects of tobacco." (Hughes J. R., p. 128). For example, once a smoker comes out of withdrawal the continuation of a symptom may be the return to the original state of that individual prior to smoking; and it is that original state of being that may have led to the need to begin smoking i.e. an anxious individual may have begun smoking to reduce their anxiety. Therefore, smoking has a calming effect and reduces anxiety, the discontinuation of smoking may increase anxiety and "level off "at pre-smoking levels. That "level off" is the offset effect.

Lastly, impatience is the only measure of impulsivity that is included in this meta-analysis. This is because, as described below, there were an insufficient number of studies that measured ratings of "impulsiveness," delay discounting, response inhibition or pre-pulse inhibition.

Initial Eligibility Criteria

Prospective studies of smoking cessation or smoking deprivation that measured self-reported impatience, at least once during smoking and once during abstinence within the same participants. The cessation could be experimenter or subject-induced. Smokers could or could not be trying to stop for good. Analyses could be based on all participants or only those who successfully abstained. Studies in any language and any year were eligible. Unpublished studies were eligible. Participants had to be current daily smokers greater than 18 years old. Participants could not have received a treatment. Abstinence duration must be more than overnight abstinence and abstinence verification less than two weeks after smoking cessation begins.

Information Sources

A reference librarian independently searched CINAHL, Medline, and PsychInfo. Authors used supplementary approaches to identify such as hand searching journals, and checking reference lists. Search terms included “cigarettes, nicotine, smoking, or tobacco” AND “abstain, abstinence, cease, cessation, quit, or stop,” AND “impulsivity, response inhibition, delay discounting, restless”, and their stems in the title or abstract or keywords and MESH terms. All years were included. We added to this, articles already obtained by authors, and relevant citations in the texts obtained. The total number of articles examined was 726 (which include overlap across multiple databases).

Sample Search Strategy

Table 1 Medline Search

Ovid MEDLINE(R) Complete (1946 - present)

#	Searches	Results	Search Type
1	exp *Smoking Cessation/	12272	Advanced
2	exp *Smoking/pc [Prevention & Control]	8176	Advanced
3	exp *Smoking/th [Therapy]	634	Advanced
4	2 or 3	8803	Advanced
5	limit 4 to yr="1968 - 1992"	2843	Advanced
6	exp *"Tobacco Use Cessation"/	12748	Advanced
7	exp *"Tobacco Use Disorder"/	5486	Advanced
8	(smok$ or tobacco$ or nicotin$ or cigar$).tw.	249561	Advanced
9	(discontin$ or abstain$ or abstinen$ or ceas$ or cessation$ or quit$ or stop$).tw.	315326	Advanced
10	7 or 8	249703	Advanced
11	9 and 10	28132	Advanced
12	1 or 5 or 6 or 11	32707	Advanced
13	*Impulsive Behavior/	2221	Advanced
14	impulsiv$.tw.	9971	Advanced
15	impatien$.tw.	866	Advanced
16	*"Inhibition (Psychology)"/	3997	Advanced
17	inhibit$.tw.	1569980	Advanced
18	inhibitor$1.tw.	831221	Advanced
19	17 not 18	738759	Advanced
20	respons$ inhibit$.tw.	2518	Advanced
21	delay$ discount$.tw.	428	Advanced
22	restless$.tw.	5259	Advanced
23	13 or 14 or 15 or 16 or 19 or 20 or 21 or 22	756911	Advanced
24	12 and 23	684	Advanced
25	limit 24 to humans	507	Advanced

Study Selection

The author and rater (MD and JH) independently examined titles to decide which papers to proceed to reading of their abstracts. This eliminated 639 articles. Kappa for Inter-rater agreement reviewing titles was 0.83. The raters then independently read abstracts searching for key study criteria,: abstinence greater than 12 hours, prospective study, baseline and post abstinence impulsivity measurement, verification of abstinence, and adult participants who smoked at least ten cigarettes per day to independently decide which papers to proceed to reading the entire articles Disagreements were resolved by mutual consent. This eliminated another 59 articles Kappa for inter-rater agreement on

complete papers to review include was 0.80. .Finally, the raters independently read entire articles and decided which papers would be included in the meta-analysis (Figure 1). This eliminated another 19 articles. Kappa for inter-rater agreement for papers to include in the meta-analysis was 1.00.

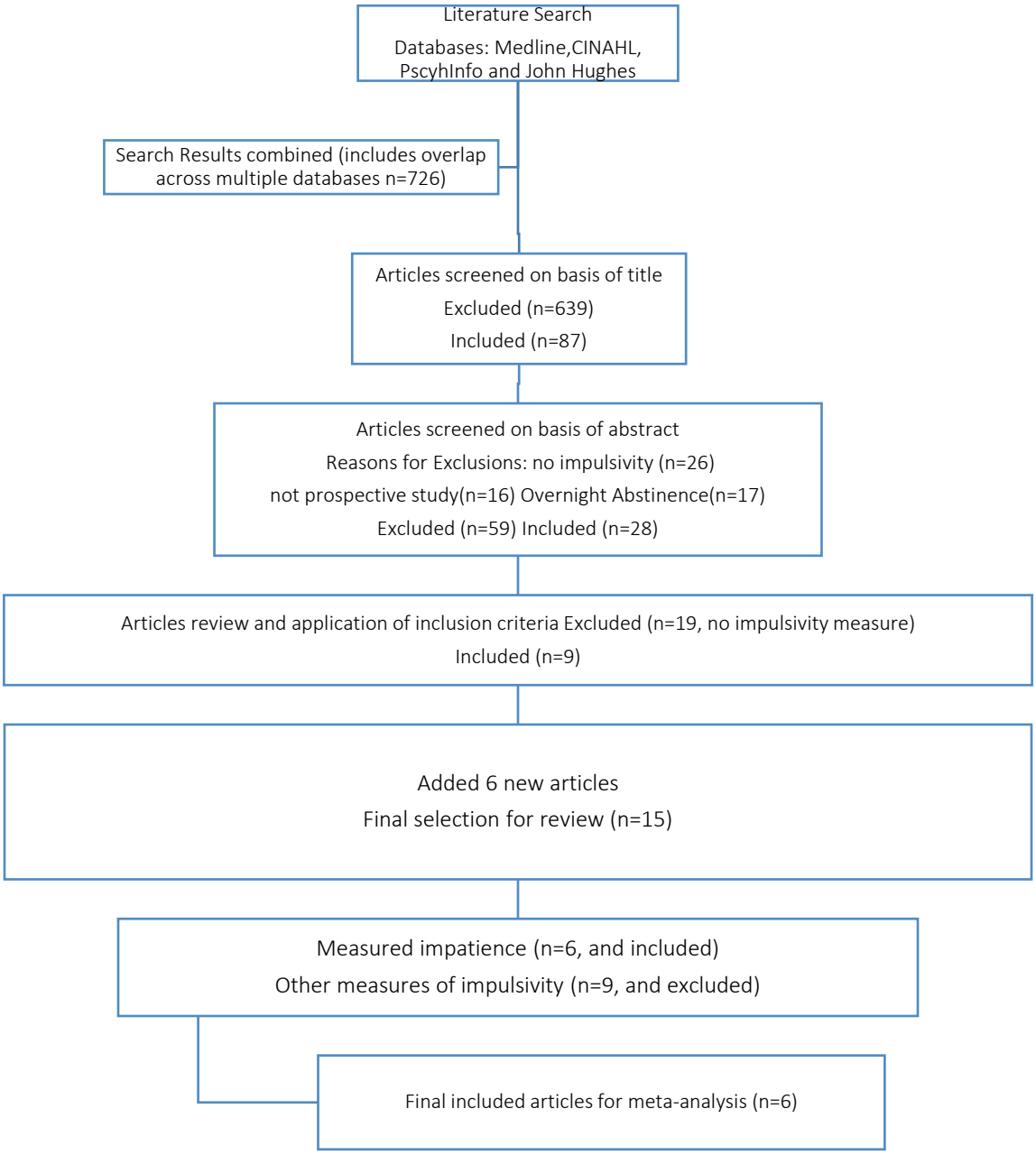


Figure 5 Flow of information through the different phases of the systematic review

After reviewing selected articles (n=9), the authors decided to expand the search criteria because there were not enough studies in any particular category of impulsivity for a meta-analysis. The authors reviewed and now included (if appropriate) the following type

of articles: abstracts that had been excluded for ‘overnight abstinence’, abstracts that were excluded because they lacked impulsivity measurement but had an “impatience” measurement. In addition, the raters located an additional 6 articles from the reference section of reviewed articles.

With these changes, there were still too few studies of self-rated impulsivity, response inhibition, delay discounting or pre-pulse inhibition that used sufficiently similar measures to undertake a meta-analysis. However, there were six studies that met the criteria and used similar measures of impatience. One study included two groups (pregnant and non-pregnant smokers) which were analyzed separately, so there were a total of seven pre/post comparisons available for the meta-analysis.

Data Collection Process

A data extraction sheet to code information for the six included studies was created. One review author extracted the following data from the included studies and the second author checked the extracted data. Disagreements were resolved by discussion between the two review authors.

Data Items

Information was extracted from each study on: characteristics of study participants (including mean age, gender, race, mean Fagerstrom Test for Nicotine Dependence (FTND) score) trial’s inclusion and exclusion criteria; duration of smoking cessation, frequency of the Minnesota Nicotine Withdrawal Scale-Revised (MNWS)

measurements, whether a special population was used, pre/post impatience score, their change score and its standard error of the mean, and length of follow up.

For four of the seven comparisons, standard deviations for the pre and post impatience scores were presented but not the standard deviation for the within-subject differences in impatience. As a result, the standard deviation for the within subject differences was estimated from the between subject standard deviation and the estimated within subject correlation (r). (Cooper, Hedges, & Valentine, 2009, pp. 229-230) The meta-analysis was performed both using $r = 0.6$ for the studies that did not report the standard deviation for the change in impatience.

Risk of Bias within Individual Studies

In a meta-analysis to be confident that the reported intervention effects are accurate depends on the validity of the included studies. To ascertain the validity of eligible randomized studies the author determined the adequacy of randomization, and concealment of allocation, blinding of participants and data collectors; and the extent loss to follow-up using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials. (Higgins, Altman, Gotzche, & Juni, 2011)

Table 2 Cochrane Collaboration's Summary Assessments

Risk of bias	Interpretation	Within a study	Across studies
Low risk of bias	Plausible bias unlikely to seriously alter the results.	Low risk of bias for all key domains.	Most information is from studies at low risk of bias.
Unclear risk of bias	Plausible bias that raises some doubt about the results	Unclear risk of bias for one or more key domains.	Most information is from studies at low or unclear risk of bias
High risk of bias	Plausible bias that seriously weakens confidence in the results.	High risk of bias for one or more key domains.	The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of the results

Figure 6 Author's judgments about each risk of bias item presented as percentages across all included studies.

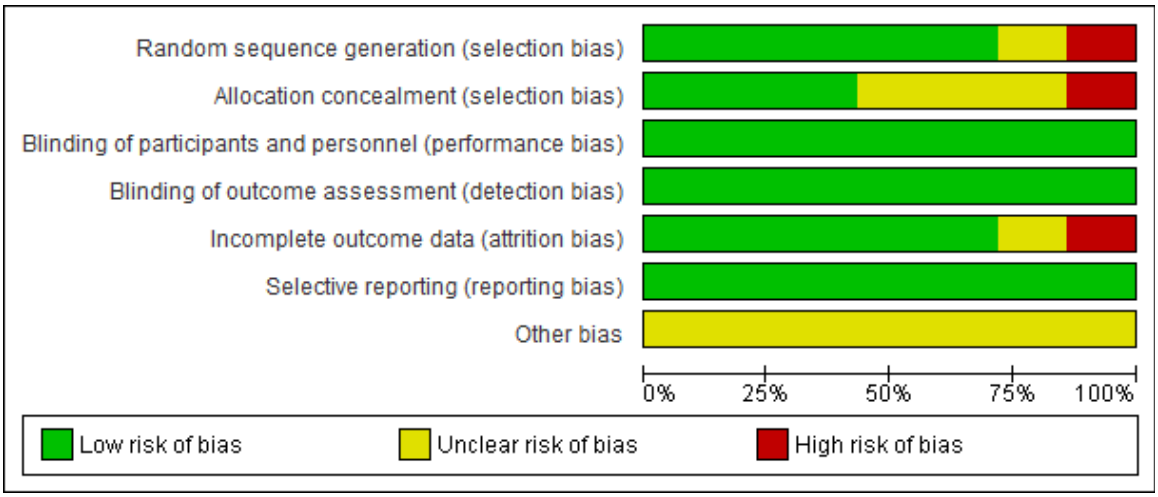


Table 3 Risk of Bias Summary: Author's judgments about each risk of bias item for each included study.

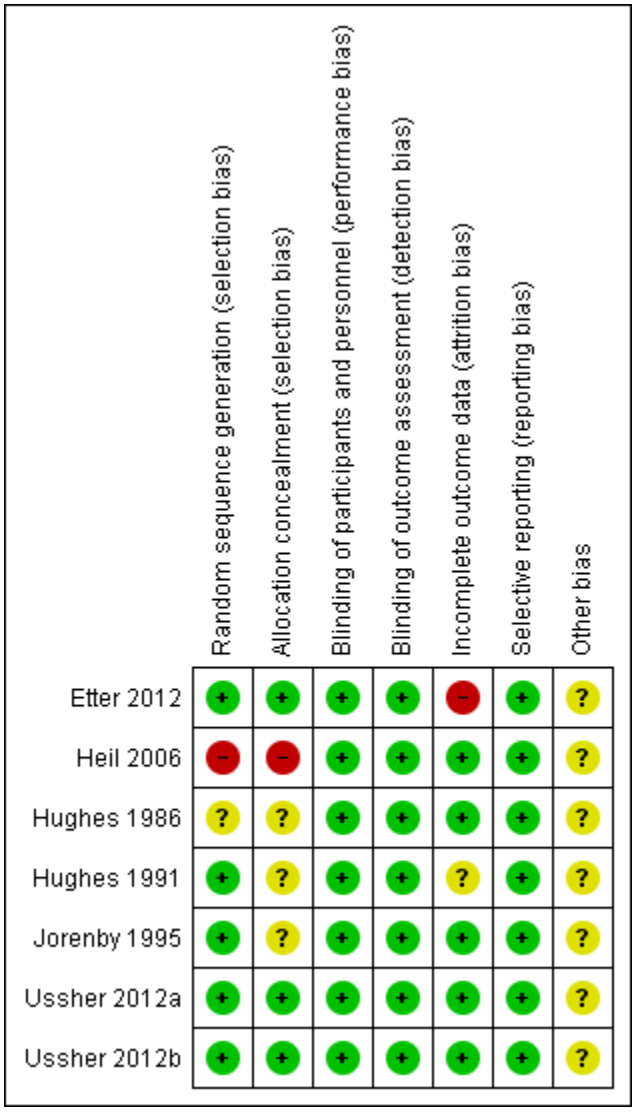


Table 4 Comparisons' Characteristics

Study	Sample (N)	Mean Age	%Female	%Minority	Cigarettes per day	What treatments were used to induce abstinence 0 = None; 2 = Money; 3 = Other
Etter	65	37	66%	_	15	0
Heil	27	25	100%	4%	7	3
Hughes, 1986	50	38	54%	_	_	3
Hughes, 1991	105	36	59%	_	29	3
Jorenby	106	42	52%	3%	29	3
Ussher, Preg	20	29	100%	94%	14	0
Ussher, non-Preg	95	29	100%	94%	15	0

	Special Population: 0=No,1=High Impulsivity Score 2=Psychiatric Disorder, 3= Pregnant	Fagerstrom Test of Nicotine Ddependence	Abstinence Verified 1=Yes, 0=No	No. hours after abstinence was the first measure of impatience	Was Placebo used during abstinence period? 1 = yes; 0 = no	Percent of subjects dropped out before last measure within 2 week period
Etter	0	4.6	0	168	0	76%
Heil	3	_	1	120	0	44%
Hughes, 1986	0	_	1	144	1	0%
Hughes, 1991	0	5.8	1	168	1	22%
Jorenby	0	6.8	1	168	1	39%
Ussher, Preg	3	5.2	0	24	0	49%
Ussher, non-Preg	0	4.6	0	24	0	49%

Table 5Study Description and Design

Study	Description
Etter, Jean, et al. 2012	In an internet-based study, daily smokers were assigned randomly to continue to smoke for 2 weeks (n=539) or to stop smoking (n=297). Only the latter group was included in the meta-analysis). Participants answered followed up surveys 1, 3, and 7 days after their target quit date. The study measured tobacco withdrawal symptoms using Minnesota Nicotine Withdrawal Scale. Impatience significantly decreased. The authors did not expect that abstinence would have significantly decreased impatience. (Etter, Ussher, & Hughes, 2012)
Heil, Sarah, et al. 2006	The aim of this study was to characterize nicotine withdrawal and craving in pregnant cigarette smokers. Participants self-selected into the abstainer or smoker categories. The authors examined results from the Minnesota Nicotine Withdrawal Scale in abstainers (n=27 this group was included in the meta-analysis) and smokers (n=21). Participants attended daily abstinence monitoring sessions during the first five days of the quit attempt. Impatience significantly increased more in abstainers than smokers. The results suggest that pregnant smokers generally may have elevated baseline levels of withdrawal. (Heil, Higgins, Mongeon, Badger, & Bernstein, 2006)
Hughes, John, et al. 1986	Smokers were randomly assigned to receive placebo gum (n=50 this group was included in the meta-analysis) or nicotine gum during a double blind study of the effect of nicotine gum on the self-reported using the Minnesota Nicotine Withdrawal Scale. Smokers were counseled about smoking cessation for less than ten minutes. Impatience significantly increased after smoking cessation in the placebo group. (Hughes & Hatsukami, Signs and Symptoms of Tobacco Withdrawal, 1986)
Hughes, John, et al. 1991	Smokers were randomly assigned to receive placebo gum (n= 105 this group was included in the meta-analysis) or nicotine gum (n=210) during a double blind study of the effect of nicotine gum on the self-reported using the Minnesota Nicotine Withdrawal. The self-reports were collected 1-2 weeks, 1 month, and 6 months. Impatience significantly increased post tobacco cessation. (Hughes, Gust, Skoog, Keenan, & Fenwick, 1991)
Jorenby, Douglas, et. al. 1996	This was a 5 week multi-site, double-blind nicotine vs placebo gum controlled trial. Participants were randomly assigned to either active (n=105) or placebo treatment gum (n= 106 this group was included in the meta-analysis). Adjuvant treatment consisted of group counseling lasting 1 hour. In addition to the pre-quit visit, groups met three times in each of the two weeks following the quit date, and twice in both the third and fourth week post quit for a total of 11 sessions. The study examined smoker's self-reported withdrawal symptoms using the Minnesota Nicotine Withdrawal Scale. Impatience significantly increased in the placebo and active group after smoking cessation. (Jorenby, et al., 1996)
Ussher, Michael, et al. 2012	For the meta-analysis the pregnant abstainers (n=20) and the non-pregnant abstainers (n=95) were analyzed as two separate analyses, Ussher, 2012a and Ussher, 2012b, respectively. This study compared tobacco withdrawal using the Minnesota Nicotine Withdrawal Scale in pregnant and non-pregnant smokers that abstained for 24 hours. Participants were randomized to either abstain from smoking for 24 hours or smoke as usual. Impatience significantly increased with smoking cessation. (Ussher, Etter, Giatras, & Coleman, 2012)

Statistical Analysis and Results

Effect Size Based On Mean in a Pre-Post Design

This analysis used the raw unstandardized mean difference because the reported outcome for all the included studies used the Minnesota Nicotine Withdrawal Scale-Revised (MNWS) and performing the analysis directly on the raw mean difference was intuitively meaningful and the use of the MNWS scale is widespread. This analysis used the 0-3 MNWS scale. Those studies that provided a 0-4 MNWS were converted to the 0-3 MNWS scale along with their associated standard deviations. This analysis used the average of the post cessation MNWS repeated measurements as a single score.

Effect size was the mean difference between pre and post cessation impatience scores. The true population means of the pre-post design is μ_1 and μ_2 and the population mean difference is defined as

$$\mu = (\mu_2 - \mu_1)$$

The unbiased estimator of μ is Y_i the sample mean difference.

For fixed-effect meta-analysis, the effect sizes for each study are fixed and are unknown constants. In a random-effects meta-analysis, the true effect size for each study is different and normally distributed and independent.

$$Y_i \sim N(\mu + \varsigma_i, \sigma_i^2),\ i = 1, \ldots, k$$

The goal of this analysis was to determine if there is a significant change in the impatience score post smoking cessation, as well as provide a confidence interval for that change score. The mean difference with 95% CIs were calculated for the pooled estimates. A mean difference > 0 indicates that impatience increased and a mean difference < 0 indicates that impatience decreased. Heterogeneity was assessed by examining the forest plots of the seven comparisons, by performing the χ^2 heterogeneity test, and I^2 statistics. Data management and analysis were carried out in Review Manager 5.2. and verified using excel 2010.

Prior to any statistical analysis the random-effects model was chosen because the subject populations varied study to study and the timing and number of post cessation impatience measurements vastly differed among studies (see Table 6). For the sake of analytical comparison we also performed analysis using the fixed-effects model.

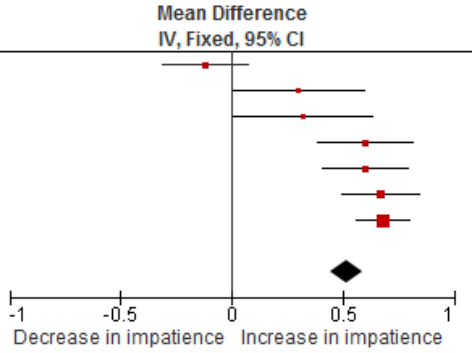
Fixed-Effect Meta-Analysis

The summary common effect for impatience after tobacco cessation was an increase of 0.51 on a 0-3 scale (95% CI [0.44, 0.59]). There was a significant level of heterogeneity ($\chi^2 = 55.71$ (6), $p<0.0001$) indicating using the random-effects model for this meta-analysis was more appropriate (see Table 6).

Table 6 Fixed-Effects Meta-Analysis Results and Forest Plot

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Etter 2012	-0.12	0.1	13.0%	-0.12 [-0.32, 0.08]
Ussher 2012a	0.3	0.15	5.8%	0.30 [0.01, 0.59]
Heil 2006	0.32	0.16	5.1%	0.32 [0.01, 0.63]
Hughes 1991	0.6	0.11	10.8%	0.60 [0.38, 0.82]
Hughes 1986	0.6	0.1	13.0%	0.60 [0.40, 0.80]
Jorenby 1995	0.67	0.09	16.1%	0.67 [0.49, 0.85]
Ussher 2012b	0.68	0.06	36.2%	0.68 [0.56, 0.80]
Total (95% CI)			**100.0%**	**0.51 [0.44, 0.59]**

Heterogeneity: Chi² = 55.71, df = 6 (P < 0.00001); I² = 89%
Test for overall effect: Z = 14.26 (P < 0.00001)

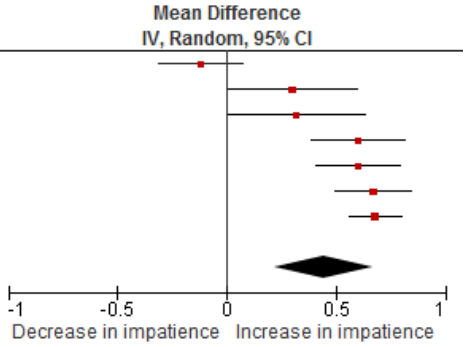


The summary effect for impatience after tobacco cessation in the random effects model was an average increase of 0.44 on a 0-3 scale, $p < 0.00001$ [95% CI [0.22, 0.67]. (Table 7)

Table 7 Random-Effects Meta-Analysis Results and Forest Plot

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Random, 95% CI
Etter 2012	-0.12	0.1	14.7%	-0.12 [-0.32, 0.08]
Ussher 2012a	0.3	0.15	12.9%	0.30 [0.01, 0.59]
Heil 2006	0.32	0.16	12.6%	0.32 [0.01, 0.63]
Hughes 1991	0.6	0.11	14.4%	0.60 [0.38, 0.82]
Hughes 1986	0.6	0.1	14.7%	0.60 [0.40, 0.80]
Jorenby 1995	0.67	0.09	15.0%	0.67 [0.49, 0.85]
Ussher 2012b	0.68	0.06	15.8%	0.68 [0.56, 0.80]
Total (95% CI)			**100.0%**	**0.44 [0.22, 0.67]**

Heterogeneity: Tau² = 0.08; Chi² = 55.71, df = 6 (P < 0.00001); I² = 89%
Test for overall effect: Z = 3.82 (P = 0.0001)



Six of the seven comparisons showed a significant increase in impatience with smoking cessation. The remaining comparison Etter, 2012 showed a non-significant decrease in impatience. There was considerable heterogeneity between studies $I^2 = 89\%$. This heterogeneity was substantially attributed to the Etter, 2012 study. This was the only

study that showed a decrease in impatience, albeit a statistically insignificant decrease, ([-0.12, 95% CI [-0.32, 0.08]). As a sensitivity analysis, the Etter, 2012 study was removed from the data and heterogeneity was reassessed on the remaining data with the following results: (0.58, 95%CI [0.46, 0.69]); $T^2 = 0.01$; $\chi^2 = 9.38$ (5), (p = 0.09); $I^2 = 47\%$ and Z = 10.02 (p < 0.00001). Removing the Etter, 2012 study increased the effect size estimate and reduced heterogeneity to a statistically insignificant level while maintaining a significant summary effect confirming it as a major source of variation.

The confidence interval tells us how confident we can be in the effect size. Ideally, the narrower the interval the more confident we should be in the effect size estimate. The confidence interval for the random-effects analysis [0.22, 0.67] was wider than the fixed-effects analysis [0.44, 0.59] because the summary effect is a less precise estimate because of the increase variation due to heterogeneity. This same information is presented graphically in Table 7 and Table 8. Each study is represented by a box and bounded by a confidence interval and the combined results and confidence interval is shown by the diamond.

Assessing publication bias was addressed using the funnel plot and the fail-safe N methods. Figure 7 is asymmetric funnel plot and gives the appearance of potential publication bias; however, with only seven comparisons in this meta-analysis and I^2 of 89% an asymmetrical funnel plot is not unexpected regardless of the possibility of publication bias.

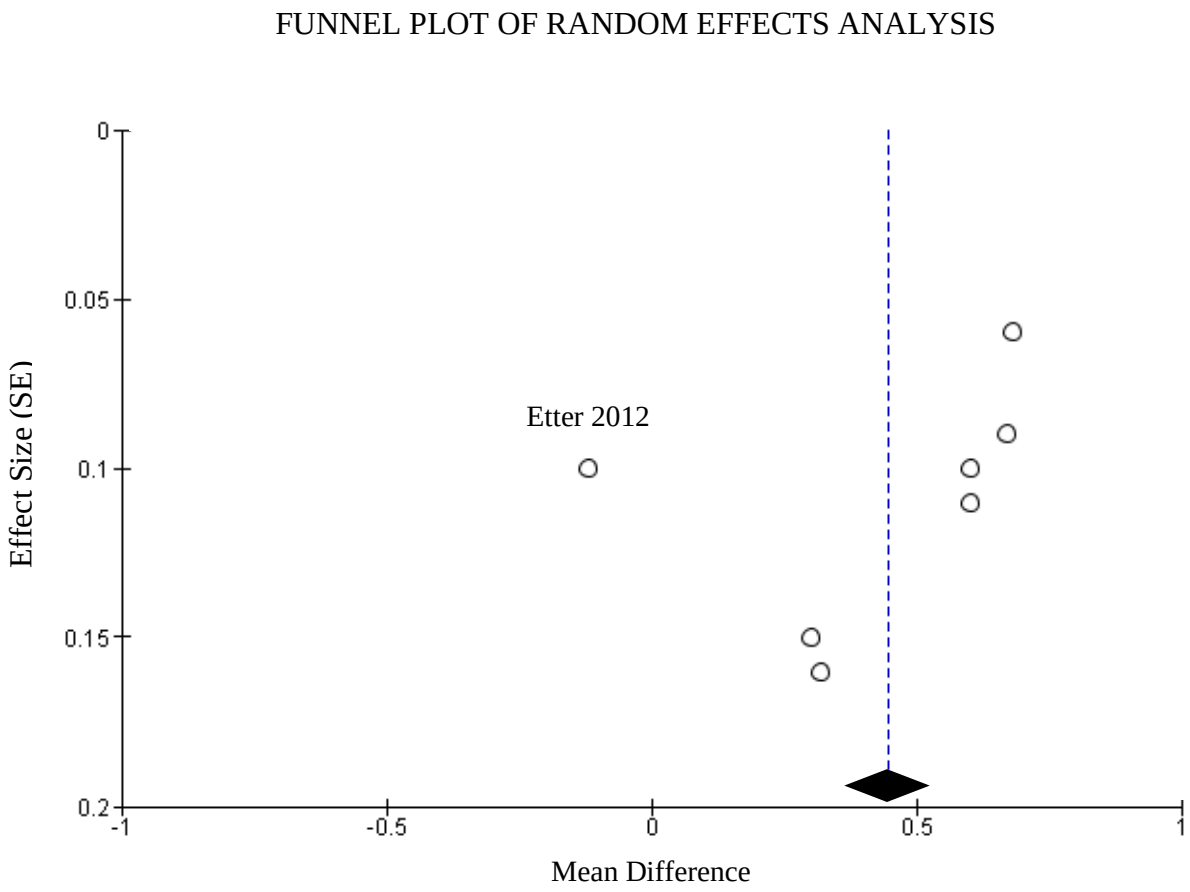


Figure 7 Funnel plot of effect size estimates for all individual comparisons in the meta-analysis

Next, to assess the potential for publication bias to have influenced the results of this meta-analysis we calculated the 'fail-safe N', the number of additional 'negative' studies (studies in which the intervention average effect is zero) that would be needed to increase the P value for the meta-analysis to above 0.05. To that end, individual z scores were computed by dividing the effect size by the corresponding standard errors. This lead to $\sum z_i = 12.49$; $k_0 > -7 + (33.03/1.96)^2$ leading to $k_0 \geq 277$. If there were 277 unpublished studies with the mean null effect of zero than the results of the meta-analysis would be reversed; However 277 unpublished studies far exceeds the tolerance level of $5k + 10 = 45$ and it can be inferred that it is unrealistic to believe there are 277 un-retrievable studies therefore; the result of the observed effects were not affected by publication bias.

Discussion

The meta-analysis revealed that nicotine withdrawal significantly increases impulsivity as measured by a significant increase of impatience over baseline ratings.

This meta-analysis has several strengths and some limitations that deserve mention. The strengths include the comprehensive search strategy that improved the likelihood of identifying all relevant studies. Over 700 citations were searched and 28 articles were read. An independent parallel process for selecting studies and the extraction of data reduced the potential for bias. The included studies used a well-established scale to measure impulsivity. Six of the seven comparisons were randomized trials which would have reduced the likelihood of systematic error.

Fail Safe N method suggests the summary effect was not influenced by publication bias and did not contribute to the asymmetry of the funnel plot and is not the cause of any unexplained heterogeneity.

Limitations

The meta-analysis had a relatively small sample size which limited our options for statistical analysis. There was statistical evidence of substantial heterogeneity. The major source of the heterogeneity and funnel plot asymmetry was the inclusion of the Etter, 2012 study. This study found a statistically insignificant decrease in impatience after smoking cessation compared with the pre-cessation impatience score. Etter explains that the unexpected result was attributed to the fact that it was an internet study which may have caused a reactivity effect; i.e. repeated self-measures may modify symptoms and behaviors. A meta-analysis excluding this study resulted in an increase in the estimate and the heterogeneity was reduced to statistical non-significance. It is this author's belief that the Etter, 2012 study was an outlier and is inconsistent with other impulsivity research outcomes.

The meta-analysis had some "unclear risk" of selection bias. The Cochrane Collaboration tool for assessing risk of bias of randomized trials sets a high bar. Few published studies report or make available the necessary information to objectively assess the risk of bias for all categories of interest. This was especially true for this meta-analysis, few studies discussed allocation concealment which refers to "techniques used to implement the allocation sequence, not to generate it" (Higgins, Altman, Gotzche, & Juni, 2011).

In general, high risk of bias was not an issue for this meta-analysis, even though Heil 2006 was not a randomized trial and Etter, 2012 had substantial loss to follow up, which according to its author is common for internet studies.

Lastly, the meta-analysis could not address "offset effects" because that distinction was not discussed in the included studies.

Conclusion

The meta-analysis shows that impulsivity increases post smoking cessation. These findings imply that smoking cessation may have an effect on decision making. Additionally higher rates of impulsivity have been associated with smoking relapse. (Doran, Spring, McChargue, Peradia, & Richmond, 2004). In order to assist better in the development of individual treatments, a better understanding is needed of how increased impulsivity influences cognitive behavior and relapse rates. These findings support the inclusion of impulsivity as a criterion for nicotine withdrawal.

APPENDIX

Meta-Analysis of Studies Investigation of the Effect of Smoking Cessation Impatience Performed Using Excel 2010

Study	Events	Sample size	es	$SD_{Diff\,(r=.6)}$	SE_D	Var_D	w	w*es	$w*(es^2)$	w^2		w_v	w_v*es	$w_v*(es^2)$	w_v^2
Etter, Jean-Francois		65	-0.12	0.82	0.10	0.01	95.99	-11.84	1.46	9,215.00		11.19	-1.38	0.17	125.21
Heil, Sarah		27	0.32	0.83	0.16	0.03	39.38	12.52	3.98	1,550.79		9.58	3.05	0.97	91.85
Hughes, John (1986)		50	0.60	0.70	0.10	0.01	102.04	61.22	36.73	10,412.33		11.27	6.76	4.06	126.96
Hughes, John (1991)		91	0.60	1.08	0.11	0.01	78.02	46.81	28.09	6,086.78		10.90	6.54	3.92	118.75
Jorenby, Douglas		78	0.67	0.80	0.09	0.01	123.41	82.69	55.40	15,230.73		11.49	7.70	5.16	131.96
Ussher, Michael Preg		20	0.30	0.67	0.15	0.02	44.44	13.33	4.00	1,975.31		9.86	2.96	0.89	97.16
Ussher, Michael non-Preg		95	0.68	0.54	0.06	0.00	329.86	222.66	150.29	108,808.35		12.20	8.23	5.56	148.79
k	7					Sums:	813.15	427.39	279.96	153279.30		76.48	33.85	20.72	840.66
df	6														
												Tau^2	0.078951		
Q	55.32			Q_v		5.74									
I^2	89.15			I^2_v		-4.62									
es(fixed) effect summary	0.53			es(random)		0.44									
SEes(fixed)	0.04			SEes(random)		0.11									
CI (fixed)	0.46	0.59		CI (random)		0.22	0.67								
Fixed Effect				Random Effects											
M (weighted Mean)	0.53			M_v	0.44										
variance of summary effe	0.00			V_{Mv}	0.01										
SE_M	0.04			SE_{Mv}	0.11										
LL_M	0.46			LL_{Mv}	0.22										
UL_M	0.59			UL_{Mv}	0.67										
Z	14.99			Z_M	3.87										
Q	55.32														
C	624.65														

References

Ashare, R. L., & Hawk Jr., L. W. (2012). Effects of smoking abstinence on impulsive behavior. *Psychopharmacology*, 537–547.

Ashare, R., Hawk, L., & Mazzullo, R. (2007). Motivated attention:incentive effects on attentional modification of prepulse inhibition. *Psychophysiology*, 839–845.

Borenstien, M., Hedges, L. V., Higgins, J. P., & Rothstein, H. R. (2009). *Introduction to Meta-Analysis.* Chichester: John Wiley & Sons Ltd.

Cooper, H., Hedges, L., & Valentine, J. (2009). *The Handbook of Research Synthesis and Meta-Analysis.* New York: Russell Sage Foundation.

Dawkins, L., Powell, J., West, R., Powell, J., & Pickering, A. (2007). A double-blind placebo-controlled experimental study of nicotine:ill-effects on response inhibition and executive functioning. *Psychopharmacology*, 457–467.

Doran, N., Spring, B., McChargue, D., Peradia, M., & Richmond, M. (2004). Impulsivity and Smoking Relapse. *Nicotine and Tobacco Research*, 641-647.

Etter, F.-J., Ussher, M., & Hughes, J. H. (2012). A test of proposed new tobacco withdrawal symptoms. *Addiction*, 50-59.

Field, M., Santarcangelo, M., Sumnall, H., Goudie, A., & Cole, J. ((2006)). Delay discounting and the behavioural economics of cigarette. *Psychopharmacology* , 255–263.

Heil, S. H., Higgins, S. T., Mongeon, J. A., Badger, G. J., & Bernstein, I. M. (2006). Characterizing Nicotine Withdrawal in Pregnant Cigarette Smokers. *Experimental and Clinical Psychopharmacology*, 165-170.

Higgins, J. P., Altman, D. G., Gotzche, P. C., & Juni, P. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomized trials. *BMJ*, 343:d5928.

Higgins, J., & Green, S. (. (2011). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0[updated March 2011]*. Retrieved from The Cochrane Collaboration: www.cochrane-handbook.org.

Hughes, J. R. (2007). Measurements of the Effects of Abstinence from Tobacco: A Qualitative Review. *Psychology of Addictive Behaviors*, 127-133.

Hughes, J. R. (2007). Measurements of the Effects of Abstinence from Tobacco: A Qualitative Review. *Psychology of Addictive Behaviors*, 127-137.

Hughes, J. R., & Hatsukami, D. (1986). Signs and Symptoms of Tobacco Withdrawal. *Archives of General Psychiatry*, 289-294.

Hughes, J. R., Gust, S. W., Skoog, K., Keenan, R. M., & Fenwick, J. W. (1991). Symptoms of Tobacco Withdrawal. *Archives of General Psychiatry*, 52-59.

Jorenby, D. E., Hatsukami, D. K., Smith, S. S., Fiore, M. C., Sllen, S., Jensen, J., & Baker, T. B. (1996). Characterization of tobacco withdrawal symptoms:

transdermal nicotine reduces hunger and wight gain. *Psychopharmacology*, 130-138.

LeLorier, J., Greoire, G., Benhaddad, A., Lapierre, J., & Derderian, F. (1997). Discrepancies Between Meta-Analyses and Subsequent Large Randomized, Controlled Trials. *New England Journal of Medicine*, 536-542.

Liberati Alessandro, A. D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* , 339:b2700.

Logan, G., Schachar, R., & Tannock, R. (1997). Impulsivity and inhibitory Control. *Psychological Science*, 60-66.

Reynolds, B., Ortengren, A., Richards, J., & de Wit, H. (2006). Dimensions of impulsive behavior: personality and behavioral measures. *Personality and Individual Differences*, 305–315.

Sciences, D. o. (n.d.). *University of York.* Retrieved from http://www-users.york.ac.uk/~mb55/msc/systrev/week7/pub_text.pdf

Series, N. I. (n.d.). What Are the Medical Consequences of Tobacco Use? *Tobacco Addiction*, 1.

Shiffman, S., West, R. J., & Gilbert, D. G. (August 2004). Recommendation for the assessment of tobacco craving and withdrawal in smoking cessation trials. *Nicotine & Tobacco Research*, 599–614.

Song, F., Khan, K. S., Dinnes, J., & Sutton, A. J. (2002). Asymetric funnel plots and publication in meta-analyses of diagnostic accuracy. *International Journal of Epidedemiology*, 88-95.

Ussher, M., Etter, J.-F., Giatras, N., & Coleman, T. (2012). Tobacco withdrwal symptoms and urges to smoke in pregnant versus non-prenant smokers. *Addictive Behaviors*, 1353-1357.