THE USE OF NICOTINE REPLACEMENT THERAPY (NRT) FOR PREGNANT 
WOMEN WHO SMOKE: A NARRATIVE REVIEW OF PLACEBO-
CONTROLLED RANDOMIZED CONTROLLED TRIALS TO EVALUATE 
EFFICACY AND SAFETY

BY

MATHEW CHRISTIAN BSc., MSc., PA-S

Supervisors: Annette Schultz PhD., RN & Drena Dunford BSc.(Hons), BSc.(Pharm), CDE

A capstone project submitted to the Faculty of Graduate Studies of The University of 
Manitoba in partial fulfillment of the requirements for the degree of MASTER OF 
PHYSICIAN ASSISTANT STUDIES

Physician Assistant Studies, University of Manitoba, Winnipeg

May 1, 2016
TABLE OF CONTENTS:

1. BACKGROUND: ........................................................................................................... 3
   1.1 Incidence of tobacco use during pregnancy in Manitoba: .................................... 3
   1.2 Risk factors for tobacco use in pregnancy: ......................................................... 4
   1.3 Adverse effects of tobacco use in pregnancy: ..................................................... 5
   1.4 Current guidelines for managing tobacco addiction in pregnancy: ..................... 6
   1.5 Efficacy of counseling for reducing tobacco use in pregnant smokers: .............. 7
   1.6 Efficacy and safety of nicotine replacement therapy in non-pregnant smokers: ...... 8
   1.7 Systematic review of NRT use in pregnant smokers: A call for placebo-controlled
       RCTs: ......................................................................................................................... 9
   1.8 Background summary: .......................................................................................... 9

2. OBJECTIVE: ................................................................................................................ 10

3. METHODS: .................................................................................................................. 11

4. RESULTS: .................................................................................................................... 12
   4.1 Process of study retrieval: ..................................................................................... 12
   4.2 Summary of study protocols: ............................................................................... 12
       Box 1: Summary of Study Protocols ...................................................................... 14
   4.3 Study demographics: ........................................................................................... 14
       Box 2: Summary of Study Demographics ............................................................... 15
   4.4 Efficacy outcome measures: .................................................................................. 16
   4.5 Safety outcome measures: .................................................................................... 17
   4.6 Methodological concerns- participant dropout & protocol adherence: .............. 18

5. DISCUSSION: .............................................................................................................. 19
   5.1 Narrative review summary: .................................................................................... 19
   5.2 Efficacy of NRT use in pregnant smokers: ......................................................... 19
       5.2.i. Cessation of tobacco use: ............................................................................... 19
       5.2.ii. Change in daily tobacco use levels: ............................................................... 21
       5.2.iii. The role of nicotine dependence.................................................................... 22
       5.2.iv. Nicotine withdrawal symptoms: ................................................................... 23
   5.3 Safety of NRT use in pregnant smokers: .............................................................. 24
   5.4 Limitations of included studies: ............................................................................ 26
       5.4.i. Risk of bias to study results: .......................................................................... 26
       5.4.ii. Statistical Power and risk of type II error: ...................................................... 26
   5.5. Future directions for research: ............................................................................ 27
       5.5.i. The limitations of nicotine patches, and the potential benefit of nicotine gum: 27
       5.5.ii. The potential benefit of combined NRT therapies ......................................... 28
       5.5.iii. Short and long-term safety profile ................................................................. 29
       5.5.iv. Addressing risk factors, not just nicotine addiction ...................................... 30

6. CONCLUSION: ............................................................................................................. 31

7. ACKNOWLEDGEMENTS: ......................................................................................... 33

8. BIBLIOGRAPHY: ........................................................................................................ 34

9. TABLES & FIGURES: .................................................................................................. 37
   Table 1: Study Demographics ..................................................................................... 37
   Table 2: Primary outcome measures .......................................................................... 38
   Table 3: Safety & Methodological Concerns .............................................................. 39
   Figure 1: Process of study retrieval ........................................................................... 40
Abstract:

Background: The use of tobacco during pregnancy is considered to be the most important preventable cause of pregnancy complications including pre-term labor and fetal growth restriction (3,9,10). Despite the potential for harmful effects, 10.5-23% of Canadian women smoke during pregnancy (4,5). While there is strong evidence that nicotine replacement therapy (NRT) is highly effective in reducing tobacco use in the general population (17), data supporting the use of NRT in pregnancy is limited.

Objective: We conducted a narrative review of placebo-controlled randomized-controlled trials (RCTs) to evaluate the safety and efficacy of NRT use for pregnant women who smoke.

Methods: A comprehensive review of the literature was performed using the Embase and Ovid MEDLINE database records from 1946 to December 2015. Articles were included if they were placebo-controlled RCTs testing the use of NRT in pregnant women who smoke. Primary outcome measures were daily tobacco use, cessation rates, and pregnancy complications.

Results: Of the 407 articles retrieved, five met the inclusion criteria (total n = 1,926 participants). All included RCTs provided cessation counseling to study participants in addition to NRT or placebo. In the RCTs that found a significant difference between NRT and placebo, NRT was associated with a significantly larger reduction in daily tobacco use (cigarettes/day), as well as a significant increase in mean birth weight and a reduced incidence of pre-term birth. NRT use did not have a significant effect on cessation rates, NICU admissions, or the incidence of fetal demise. There were no significant adverse effects associated with NRT use.

Conclusions: While additional research is still needed, the results of this narrative review suggest that NRT use may result in greater reductions in tobacco use than counseling alone. There is no evidence from this review that NRT increases the risk of fetal growth restriction, pre-term delivery, or NICU admissions.
1. Background:

1.1 Incidence of tobacco use during pregnancy in Manitoba:

Tobacco use is a leading cause of disability and death in Manitoba, with 1/5 of Manitobans over age 14 identifying as current smokers (1). For those that become long-term smokers, half will die as a direct result of their tobacco use. In Manitoba, this represents 1,400 preventable deaths annually (1). Female tobacco users at childbearing age are a particularly important population due to the potential harms that cigarettes pose during pregnancy. According to Statistics Canada, 14.8% of female Canadians were smokers in 2014, with a prevalence of 11.9% in female Manitobans (2). The use of tobacco during pregnancy is considered to be the most important preventable cause of adverse fetal outcomes (3). However, despite the widespread findings of adverse pregnancy outcomes, maternal smoking remains prevalent in Canada. In 2006, Statistics Canada conducted the Maternity Experience Survey (MES) on a representative sample of 6,421 females over 14 years of age that had given birth in the last year. The MES results showed that 10.5% of survey participants smoked during the third trimester of pregnancy and smoked an average of seven cigarettes per day. In Manitoba the prevalence was 14.6%, exceeded only by Saskatchewan, Prince Edward Island, and the Northern Territories (4). In a more recent Canadian Community Health Survey (CCHS) conducted from 2009-2010, the incidence of smoking during pregnancy was even more prevalent, with a national average of 23% overall. This survey population was considerably larger than the MES, consisting of 369,547 women over 14 years of age who had given birth within the last five years (5). Given that as much as one in five Canadian women smoke
during pregnancy, the treatment of tobacco dependence for pregnant women is a health priority.

1.2 Risk factors for tobacco use in pregnancy:

In the general population, the prevalence of tobacco use has decreased over the past decade. However, tobacco use in pregnancy has not shown the same degree of improvement. When the 2010 CCHS results are compared to previous CCHS findings from 2001, the demographic of women who smoked during their pregnancy showed a smaller reduction in the prevalence of smoking compared to non-pregnant females, 23.5% vs. 30.8% reduction respectively (6). Analysis of the CCHS results identified multiple risk factors that increase the likelihood of continued tobacco use during pregnancy. These include heavy tobacco use (>20 cigarettes/day), age <25 years, low socioeconomic status (i.e. low income and/or grade 12 or less education level), being unmarried and/or not living with their partner, lack of primary care provider for pre-natal care, and having at least one chronic or mental health disease (5). In addition to these CCHS findings, Schneider et al. conducted a systematic review of 19 studies published from 1997-2008 to identify predictors of smoking during pregnancy. Their results identified the same risk factors as the CCHS report. Additionally, they found an association with partner tobacco use (i.e. having a partner who was also a smoker), as well as an increased risk for multiparous women. They found that with each live birth the probability of quitting smoking decreased, potentially due to the experience of previous uncomplicated pregnancies that strengthened the denial of the risks of their smoking
behavior (7). These risk factors serve to provide insight into the prevalence of tobacco use during pregnancy, despite the increased risk of adverse pregnancy outcomes.

1.3 Adverse effects of tobacco use in pregnancy:

Maternal smoking during pregnancy has widespread consequences that continue throughout and beyond pregnancy, including increased risk of antenatal complications, neonatal morbidity and mortality, as well as long-term consequences throughout childhood. In addition to nicotine, which alters fetal blood flow and protein metabolism, smoking exposes both the mother and fetus to roughly 4,000 toxins that have multiple harmful effects (8,9). The Canadian Action Network for the Advancement, Dissemination and Adoption of Practice-informed Tobacco Treatment (CAN-ADAPTT) Canadian Smoking Cessation Guideline identifies multiple complications that are more likely to occur during the antenatal period as a result of cigarette smoking, including ectopic pregnancy, spontaneous abortion, pre-term labour, premature rupture of membranes, placenta previa and/or abruption, as well as fetal growth restriction (10).

In addition to increased antenatal complications, tobacco use during pregnancy also increases the risk of adverse effects in the neonate. Mothers who smoke are twice as likely to have babies who are small for their gestational age, and typically have babies that are ~200 grams smaller than non-smokers (9,10). Additionally, there is nearly a 50% increase in the odds of stillbirth, and the degree of risk is proportional to the number of cigarettes smoked per day (11). In addition to causing increased neonatal intensive care unit (NICU) admissions, neonatal tobacco exposure is the most common preventable cause of sudden infant death syndrome (SIDS) (9,10).
Beyond the neonate stage, maternal cigarette use has been associated with multiple long-term adverse effects. For example, smoking has been found to impair lung development and pulmonary function in the children of maternal smokers, resulting in short-term effects such as pneumonia, as well as chronic issues such as bronchitis and asthma (7). There is also an association with impaired learning and behavioral problems, with a four-fold increase in the risk of developing conduct disorders, as well as an increase in oppositional defiant disorder (9). Furthermore, children exposed to tobacco demonstrate 2.4-3.4 times higher rates of attention deficit hyperactivity disorder (ADHD) (9). Maternal smoking is also associated with an increased risk of non-Hodgkin’s lymphoma and a 33-60% increased likelihood of the child being overweight or obese (12,13). In addition to these complications, a systematic review by Hackshaw et al. concluded that maternal tobacco use was associated with an increased risk of multiple congenital defects including cardiovascular/heart, musculoskeletal, limb, face & eye, gastrointestinal, and urogenital defects (14).

1.4 Current guidelines for managing tobacco addiction in pregnancy:

In light of the numerous potential harmful effects of tobacco use during pregnancy, it is essential to develop an effective strategy for managing tobacco addiction in pregnancy. The CAN-ADAPTT clinic practice guideline recommends counseling as the first line treatment, with the goal of smoking cessation. If counseling alone is ineffective, nicotine replacement therapy (NRT) is recommended as a second line option. NRT methods that deliver an intermittent dose of nicotine (i.e. gum, lozenge, etc.) are preferred over continuous dosing methods (i.e. nicotine patch) based off the theoretical
belief that intermittent nicotine exposure is less harmful to the fetus (10). The Society of Obstetricians and Gynecologists of Canada (SOGC) provide the same recommendations that smoking cessation counseling should be considered the first line treatment and NRT should be used if counseling alone is ineffective (15). Both guidelines stress the importance of discussing the risks and benefits of NRT with the pregnant patient prior to use. While the CAN-ADAPTT guidelines for pregnancy stress caution with the use of NRT, the guidelines for the general population suggest that counseling and NRT have synergistic effects and both should be provided to patients motivated to stop smoking. The authors suggest that the difference in the treatment recommendations is due to the belief that more evidence is needed in order to adequately perform a risk/benefit analysis of NRT in pregnancy (10).

1.5 Efficacy of counseling for reducing tobacco use in pregnant smokers:

Counseling is recommend as the first line modality for reducing tobacco use in the current Canadian guidelines for pregnant smokers. Therefore, it is important to evaluate the evidence for the efficacy of this treatment strategy. A meta-analysis by Fillion et al. examined eight randomized controlled trials (RCTs) that included 3,290 pregnant smokers to determine the efficacy of counseling by evaluating rates of cessation of tobacco use at six months after starting treatment. They found that within each trial the largest benefit over the control group was a 4% increase in cessation, and overall between the trials there was no significant difference in cessation rates between the counseling and control groups. They concluded that there is insufficient evidence to show a beneficial effect of counseling in isolation, and they suggested that future studies examine the use of
NRT in pregnant smokers (16). In contrast to these results, a Cochrane review of various interventions for tobacco use cessation in pregnancy found a significant, though modest effect, of a 5% increase in cessation rates in groups receiving counseling over controls, as well as a significant increase in mean birth weight. The review also found that 50% of participants in the counseling group reported cutting down on smoking. Interestingly, the trials that used NRT showed an effect on cessation rates equal to trials that used counseling interventions. However, there were only five studies of NRT use compared to 31 studies using counseling, so the data supporting the use of NRT was limited by comparison (3).

1.6 Efficacy and safety of nicotine replacement therapy in non-pregnant smokers:

The use of NRT in non-pregnant smokers has been well studied in numerous trials. In the 2012 Cochrane review of NRT for the use of smoking cessation 150 trials were reviewed and over 50,000 participants were included in the analysis. The review found that regardless of the treatment setting, the use of NRT increased the rate of quitting by 50-70% when compared to placebo or control. When comparing different types of NRT, the authors reported that nicotine patches increased quit rates by 64%, compared to 49% with nicotine gum, based off 43 and 55 trials respectively. With regards to the use of counseling, the authors concluded that the addition of counseling to NRT regimens increased the likelihood of quitting, but was not essential for NRT use to be effective (17).
1.7 Systematic review of NRT use in pregnant smokers: A call for placebo-controlled RCTs:

Two previous systematic reviews have been published on the use of NRT for pregnant women who smoke. In 2011, Coleman et al. concluded that non-placebo RCTs had a tendency to overestimate the effectiveness of NRT, and recommended that future trials adopt a placebo-controlled design to reduce the risk of bias when assessing the efficacy and safety of NRT in pregnancy. In addition to other study designs, that review included three placebo-controlled RCTs (18-20) and concluded that there was insufficient evidence to determine the level of safety or efficacy of NRT for promoting tobacco use cessation in pregnancy (21). The following year, Coleman et al. published a Cochrane Review which concluded that a separate analysis of placebo-controlled trials would be more representative of the actual efficacy of NRT use in pregnant smokers, due to reduced heterogeneity between studies (22). Similar to their previous review, they concluded that there was insufficient evidence to determine the efficacy and safety of NRT in pregnancy for promoting tobacco use cessation and improving birth outcomes (22).

1.8 Background summary:

Recent survey data indicates that up to 23% of Canadian women use tobacco during pregnancy (5). Female smokers who become pregnant are less likely to quit smoking if they are heavy smokers, have low socioeconomic status, lack adequate primary care, have a partner that smokes, are under 25 years of age, or have a history of multiparity (5,7). For women that smoke during pregnancy, there is an increased risk of antenatal complications, neonatal morbidity and mortality, as well as long-term
respiratory and neurological consequences throughout childhood. Current treatment guidelines for reducing tobacco use in pregnancy recommend a trial of counseling to promote cessation, followed by the use of NRT if counseling is unsuccessful (10). However, systematic reviews and meta-analyses of the use of counseling in pregnant smokers show conflicting levels of efficacy (3,16). Conversely, in non-pregnant populations there is strong evidence that NRT, with or without counseling, is highly effective in reducing tobacco use (17). Due to the perceived safety and ethical issues surrounding the use of pharmacological treatments during pregnancy in clinical trials, data supporting the use of NRT in pregnancy is limited. However, given that cigarettes expose the mother and fetus to roughly 4000 toxins in addition to nicotine, the use of controlled medicinal methods to deliver nicotine is likely safer than obtaining nicotine by smoking tobacco (8).

2. Objective:

Due to the importance of finding an effective method for reducing tobacco use during pregnancy, and the strong evidence for the efficacy of NRT in non-pregnant populations, it is essential to evaluate the applicability of NRT to pregnant smokers. The objective of this narrative review is to collect the highest quality evidence available (placebo-controlled RCTs) to determine if NRT use in pregnancy is effective for reducing tobacco use and to evaluate the safety of NRT use for both the mother and fetus.
3. Methods:

This narrative review was designed using the methodology outlined by Green et al. (23) and is intended to provide a comprehensive synthesis of previously published information. A review of the literature was performed using the following databases: Embase, Ovid Medline, Pubmed, CINAHL, and Scopus. The search was conducted in December 2015 and included any articles published prior to that date. The following groups of Medical Subject Heading (MeSH) terms were used: i) smoking; parental smoking; smoking habit; tobacco dependence; AND ii) pregnancy; pregnancy complication; pregnancy outcome; gestation period; pregnant women; perinatal care; AND iii) smoking cessation; nicotine; nicotine replacement therapy; nicotine gum; nicotine patch; transdermal patch; nicotinic agent. Database search limits were used for language (“English”), article type (“randomized controlled trial”), and subjects (“human”). Articles were included if they were randomized controlled trials (RCTs) of pregnant smokers comparing any form of nicotine replacement therapy (NRT) (i.e. patch, gum, lozenge, or inhaler) with or without any form of counseling to placebo NRT with the same level of counseling. Furthermore, the articles were required to be published in English but were not limited by year or country of publication in order to provide a comprehensive review of all placebo controlled RCTs that have been published to date. Conversely, articles that were not placebo controlled or published in English were excluded from this review. Additionally, RCTs that were unable to isolate the independent treatment effects to NRT (ex. control and treatment group receiving different levels of counseling) were also excluded. The rationale for limiting inclusion to placebo-controlled trials is based off the findings of a previously published systematic review by
Coleman et al., which found reduced heterogeneity between studies that were placebo controlled, compared to RCTs that did not use placebo. They suggested that due to a reduced risk of bias, a separate analysis of placebo-controlled trials would be more representative of the actual efficacy of NRT use in pregnant smokers (22).

4. Results:

4.1 Process of study retrieval:

The initial stage of the literature search was conducted using Embase and Ovid MEDLINE, which collectively had access to articles published since 1946. A detailed summary of the search results has been outlined in Figure 1. Using the MeSH terms and search limits outlined previously, 407 articles were retrieved. After title and abstract inspection, 43 randomized controlled trials (RCTs) on pregnant women who smoke were identified. Seven of these RCTs evaluated the use of NRT, four of which were placebo-controlled (8,19,20,24). After reviewing the references in these four articles, one additional article was found that met inclusion (18), resulting in a total of five articles that qualified for this narrative review. The second stage of the literature search involved utilizing the same methodology to search for articles in Pubmed (175 results), CINAHL (39 results), and Scopus (135 results). However, no additional articles were found in this secondary search that met the inclusion criteria.

4.2 Summary of study protocols:
A summary of the study protocols is presented in Box 1. All of the included studies examined the efficacy of NRT in combination with cessation counseling. In each study, the treatment and control group each received the same amount of counseling, while the treatment group also received NRT and the control group received a placebo. Each study provided multiple cessation counseling sessions, with the longest sessions occurring in the initial randomization visit. Counseling was reinforced at each follow up visit, resulting in a total of four counseling sessions in 3/5 studies (8,18,20) and seven counseling sessions in 2/5 studies (19,24). With regards to the use of NRT, all of the studies used nicotine patches except one, which used nicotine gum (19). The dose and duration of NRT was highly variable between studies. Of the studies that used nicotine patches, ¾ used a 16-hour patch (8,18,20) and ¼ used an 18-hour patch. Three studies used a tapered NRT dose schedule (18-20), one used a fixed dose (8), and one study used the salivary cotinine levels to tailor the dose for each participant (24). The study using nicotine gum used a 2mg dose, and instructed the participants to chew one piece for every cigarette they would usually smoke each day, up to a maximum of 20 pieces per day (19). The duration of the NRT intervention was limited to a maximum of 12 weeks for all of the studies except one, which provided NRT until the delivery date (24). All of the included studies used laboratory testing to confirm self-reported cessation, either by measuring salivary cotinine levels or exhaled carbon monoxide (CO) levels. Cotinine is the major metabolite of nicotine, and tobacco smoke contains CO, therefore both can be used to measure smoking levels (19,25). For studies that measured CO, an exhaled CO less than 8 ppm was considered to represent smoking cessation. For studies that measured
salivary cotinine, the cessation cutoff points were highly variable ranging from < 10 ng/mL to < 26 ng/mL, with one study failing to specify a cutoff value (8,18,20).

Box 1: Summary of Study Protocols

<table>
<thead>
<tr>
<th>Author</th>
<th>NRT Dose</th>
<th>NRT Tapering Schedule</th>
<th>NRT Duration</th>
<th>Counseling Frequency</th>
<th>Initial Counseling Session Duration</th>
<th>Lab Confirmed Cessation: Cutoff Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wisborg et al.</td>
<td>16 hr patch; 15 &amp; 10 mg</td>
<td>15mg x8 weeks, 10mg x3 weeks</td>
<td>11 weeks</td>
<td>4 sessions</td>
<td>45-60 mins</td>
<td>Saliva cotinine &lt; 26 ng/mL</td>
</tr>
<tr>
<td>Kapur et al.</td>
<td>18 hr patch; 15, 10, &amp; 5 mg</td>
<td>15mg x8 weeks, 10mg x2 weeks, 5mg x 2 weeks</td>
<td>12 weeks</td>
<td>4 sessions</td>
<td>Not specified</td>
<td>Cotinine cutoff point not stated</td>
</tr>
<tr>
<td>Oncken et al.</td>
<td>2 mg pieces; max 20/day</td>
<td>6 week taper period</td>
<td>12 weeks</td>
<td>7 sessions</td>
<td>35 mins</td>
<td>Exhaled CO &lt; 8 ppm</td>
</tr>
<tr>
<td>Coleman et al.</td>
<td>16 hr patch; 15 mg</td>
<td>None</td>
<td>4-8 weeks</td>
<td>4 sessions</td>
<td>60 mins</td>
<td>Exhaled CO &lt; 7 ppm; saliva cotinine &lt; 10 ng/mL</td>
</tr>
<tr>
<td>Berlin et al.</td>
<td>16 hr patch; 10-30 mg</td>
<td>Dose adjusted to saliva cotinine level</td>
<td>From quit date to delivery (up to 25 weeks)</td>
<td>7 sessions</td>
<td>60 mins</td>
<td>Exhaled CO ≤ 8 ppm</td>
</tr>
</tbody>
</table>

Overall, there was a high level of heterogeneity in the methodology between the studies. The NRT intervention varied in dose, duration, and the use of a tapering schedule. Additionally, the counseling intervention varied in frequency and duration between studies. While all of the studies confirmed self-reported tobacco use cessation with objective laboratory measures, the method of confirmation and cutoff values were inconsistent between studies.

4.3 Study demographics:
Study demographics of the five articles included in this review are summarized in Box 2 below and full details are presented in Table 1. Between all studies a total of 1,926 participants were recruited from five different countries: Denmark (20), Canada (18), USA (19), United Kingdom (8), and France (24). There was a wide range of sample sizes from 30 to 1050 participants. All participants were 16 years or older at inclusion. All studies recruited women who were already pregnant and interested in quitting smoking. While only two studies excluded women who were in their first trimester of pregnancy the majority of study participants were at least 12 weeks pregnant. Mean tobacco use at study inclusion was <15 cigarettes per day for all studies except one (18). In addition to having the highest average daily tobacco use (19.3 cig/day), the study by Kapur et al. had the smallest sample size (n=30) and the highest average age (33.4 years) (18).

**Box 2: Summary of Study Demographics**

<table>
<thead>
<tr>
<th></th>
<th>Sample Size (n)</th>
<th>Mean Age (years)</th>
<th>Gestational Age (weeks)</th>
<th>Initial Daily Cigarette Use (cig/day)</th>
<th>Multiparity (%)</th>
<th>Low Socio-economic Status (%)</th>
<th>Partner Smoking (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average</strong></td>
<td>385</td>
<td>28.3</td>
<td>16.8</td>
<td>13.4</td>
<td>61.2</td>
<td>61.2</td>
<td>72.9</td>
</tr>
<tr>
<td><strong>Lower Limit</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kapur</td>
<td>30</td>
<td>25.5</td>
<td>16.2</td>
<td>9.5</td>
<td>31.6</td>
<td>50</td>
<td>70.5</td>
</tr>
<tr>
<td>Oncken</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coleman</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Upper Limit</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coleman</td>
<td>1050</td>
<td>33.4</td>
<td>17.1</td>
<td>19.3</td>
<td>83.5</td>
<td>82.7</td>
<td>74.4</td>
</tr>
<tr>
<td>Kapur</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oncken</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Low socioeconomic status (SES), multiparity, and having a partner who smokes are all demographic features that have been previously identified as risk factors for continued tobacco use during pregnancy (7). In terms of the SES of participants, at least 50% of subjects in each study were either unemployed, had a low income, or had not completed high school (20). For studies that reported parity, the majority of participants
were multiparous in all studies except one (8). For studies that reported partner smoking, more than 75% of study participants had a partner who smokes (8,18,24).

In general, the typical study participant across the included studies was in their late twenties, at 16-17 weeks gestation, smoked more than 10 cigarettes/day, and had multiple risk factors related to tobacco use during pregnancy (i.e. multiparity, low socio-economic status, and/or smoking partner).

### 4.4 Efficacy outcome measures:

A summary of the main outcome measures is presented in Table 2. Smoking cessation was the primary outcome measure for all included studies for evaluating the efficacy of NRT. In addition to participant reporting of tobacco use, laboratory validation of tobacco use was performed in each study by measuring salivary cotinine levels and/or carbon monoxide (CO) levels in expired air. While some studies reported tobacco use cessation at multiple time points, all studies measured cessation between a GA of 34-36 weeks. There was no significant difference in self-reported or laboratory validated cessation rates between the NRT and placebo group in any of the included studies at 34-36 weeks GA (8,18-20,24). Cessation rates ranged from 5.1-28% across studies, with the two largest studies (n > 400) demonstrating an average of 7.6-9.4% (8) and 5.1-5.5% (24), respectively. For studies that reported average initial and final daily tobacco use, the NRT group averaged a 5.9-7.9 cigarette/day (50-72.8%) reduction in tobacco use, while the placebo group averaged a 3.5-7.7 cigarette/day (42-57.5%) reduction (19,20,24). However, only one study analyzed the statistical significance of the change in daily
tobacco use, which found that the NRT group had a significantly larger reduction in daily cigarette use vs. placebo (19).

4.5 Safety outcome measures:

The safety of the use of NRT in pregnancy was most consistently evaluated using three main fetal outcomes: pre-term delivery (<37 weeks), neonatal intensive care unit (NICU) admissions, and fetal demise (i.e. miscarriage, stillbirth, etc.). There were no statistically significant differences found between the NRT and placebo groups for rates of NICU admissions or fetal demise. One study found a significantly higher rate of pre-term deliveries in the placebo group (18.4%) compared to the NRT group (7.1%) (19). No other studies reported a significant difference in the rates of pre-term deliveries (8,20,24). Of note, the study by Kapur et al. did not report any results for birth outcomes or daily tobacco use levels (18).

In addition to evaluating the safety of NRT use via fetal outcomes, side effects reported by participants served to provide further insight for the safety of NRT use in pregnancy. Common side effects are presented in Table 3. There were no significant differences in adverse effects between NRT and placebo groups, with the exception of one study that found a small but significant increase in diastolic blood pressure of 0.02mmHg/day in the NRT group (24). Reported side effects for both the treatment and control groups included: skin irritation, headache, palpitations, dizziness, heartburn, and emesis (19,20,24). One study reported that 8.8% of NRT participants and 6% of placebo participants withdrew from the study due to unspecified adverse events, but the difference between groups was not significant (8).
4.6 Methodological concerns- participant dropout & protocol adherence:

Participant dropout and protocol adherence rates are presented in Table 3. With regards to participant dropout, two studies reported high dropout rates (18,24). In the study by Kapur et al., 77% of the NRT subjects and 100% of the placebo subjects withdrew from the study after three weeks. Since the authors did not report data on side effects, it is unclear whether participant dropout was due to adverse effects of patch use or due to other unknown factors (18). In the study by Berlin et al., 46% of the NRT subjects and 57% of the placebo subjects withdrew from the study. The authors did not discuss the potential cause of these high dropout rates, but did state that there were no significant differences in withdrawal symptoms or the number of adverse events between groups (24). The remaining studies that reported dropout had rates of 5.5% or less (8,19). For all included studies, dropout rates were higher in the placebo group than the NRT group, however the difference was only statistically significant in one study with 78% and 64% attendance to the last pre-natal visit for the NRT and placebo group, respectively (19).

Adherence to NRT/placebo use protocol was generally poor in most studies, with a trend towards better adherence to NRT use, however the difference was only statistically significant in one study (24). In two studies <20% of the participants used all of the patches they were provided (8,20), and in the nicotine gum study the average duration of gum use was <6 weeks despite a target of 12 weeks (19). The study by Berlin et al. demonstrated the highest compliance with patch use, with 85% compliance in the NRT group and 83% in the placebo group (24).
5. Discussion:

5.1 Narrative review summary:

This narrative review of five placebo-controlled RCTs evaluating the use of NRT in pregnant smokers is the first review on the subject to exclusively include placebo-controlled RCTs. While results of this review confirm the findings of previous studies that there is insufficient evidence to support the claim that NRT is effective for increasing tobacco use cessation rates (22), the results suggest that NRT can be effective for promoting significant reductions in daily tobacco use compared to counseling alone. By defining the efficacy of NRT in terms of reduction in tobacco use, rather than solely cessation, this review provides a unique perspective when considering the potential beneficial effects of NRT use in pregnancy for reducing exposure to cigarette smoke for both the mother and fetus. With the exception of one study, which found a small increase in diastolic blood pressure in the NRT group participants (24), there is no evidence to suggest any safety concerns for mother or fetus. The results of this review suggest that NRT use in pregnancy has the potential to improve pregnancy outcomes such as increased birth weight and reduced pre-term deliveries.

5.2 Efficacy of NRT use in pregnant smokers:

5.2.i. Cessation of tobacco use:

The two previously published systematic reviews on the use of NRT for pregnant women who smoke both concluded that there was insufficient evidence to determine the level of efficacy of NRT use for promoting tobacco use cessation (21,22). Those findings
are consistent with the current review, which did not find any significant difference in cessation rates between the NRT and placebo groups. One study reported significantly higher cessation rates four weeks after starting NRT, but by the end of the trial the difference was no longer significant (8).

When interpreting these results, it is important to consider the demographics of the study population. In general, becoming pregnant is associated with exceptionally high cessation rates, up to eight times higher than the general population. For women who smoked before pregnancy, up to 45% will quit by their first pre-natal visit (3). The studies included in this review specifically selected for the remaining 55% of women who continued to smoke beyond the first trimester of pregnancy despite a desire to quit. This represents a key demographic of women who continue to use tobacco at a time when tobacco users are most likely to quit. Previous epidemiological studies have identified important characteristics of this population, including high tobacco use level (>20 cigarettes/day), low socioeconomic status (SES), multiparity, and having a partner who smokes (7). Therefore, it is important to recognize that the majority of the participants across all of the included studies had at least one of these risk factors for continued smoking during pregnancy. When the results are reviewed in this context, the conclusion that NRT use does not increase cessation rates is not completely unexpected. These women share common psychosocial factors that are not addressed simply by providing nicotine to manage the biological mechanism of their tobacco addiction (26).

While NRT use did not increase cessation rates compared to placebo, 5-28% of participants across the included studies did manage to quit smoking during their pregnancy regardless of which treatment group they were randomized to. These findings
indicate that the intervention both groups were exposed to, tobacco use counseling, could play an important role in reducing tobacco use in pregnancy by addressing key psychosocial issues in this population that are not addressed by providing NRT alone.

5.2.ii. Change in daily tobacco use levels:

The results of this review indicate that while NRT does not increase tobacco use cessation rates in pregnant women, it has the potential to increase mean birth weight and reduce the rate of pre-term delivery (19,20). As a result, complete cessation may not be necessary to improve fetal outcomes. Smoking cessation is considered the ideal outcome because it eliminates tobacco exposure entirely, however a reduction in daily tobacco use (i.e. number of cigarettes smoked per day) likely still provides benefits for pregnant women who smoke. Surprisingly, while all studies reported cessation rates, only 2/5 studies reported daily tobacco use levels before and after the NRT intervention (19,20,24).

Of the two studies that reported a significant difference in mean birth weight, only one study reported a statistical analysis for changes in daily tobacco use levels. Oncken et al. found that participants in the NRT group smoked 5.7 fewer cigarettes at the last prenatal visit compared to baseline levels, which was a significant reduction compared to the placebo group which smoked 3.5 fewer cigarettes per day (19). Berlin et al. also presented data on the change in daily tobacco use and found that 42% of the NRT group and 37% of the placebo cut their daily tobacco use in half by the last pre-natal visit, however there was no significant difference between groups (24).
While the results of this review do not support the notion that NRT increases cessation rates in pregnancy, there is some evidence to suggest NRT can help pregnant women who smoke cut down their daily tobacco use levels. Given that 40-60% of quit attempts for tobacco users start with cutting down (27), NRT has the potential to help pregnant smokers make strides towards quitting. Furthermore, while cessation may be the ideal outcome, there is some evidence to suggest that reducing daily tobacco use by 55% or more can still result in a reduced risk of pregnancy complications (19).

5.2.iii. The role of nicotine dependence

While salivary cotinine and exhaled carbon monoxide levels are useful objective measures of tobacco use, subjective measures of nicotine dependence can also be useful for evaluating nicotine dependence. The Fagerstrom test for nicotine dependence (FTND) is a six-item questionnaire used to measure the degree of physical dependence on nicotine. In addition to quantifying the number of cigarettes smoked per day, it also provides insight into smoking habits such as the need to smoke soon after waking and the urge to smoke despite being ill or in a place where smoking is prohibited (28). Four of the five included studies reported using a nicotine dependence questionnaire, however only two reported questionnaire results (19,24). Of the two studies that reported subjective nicotine dependence results, the study with the lower average Fagerstrom scores reported higher efficacy of NRT for daily tobacco use and birth weight (19). Given that individuals with higher tobacco dependence levels are less likely to stop smoking, lower Fagerstrom scores could provide insight into the increased efficacy of NRT in one study when compared to another (7). Unfortunately, since only two of the included studies
reported FTND scores, it is difficult to make further comparisons between studies based on reported nicotine dependence.

5.2.iv. Nicotine withdrawal symptoms:

When evaluating the efficacy of NRT to reduce tobacco use in pregnancy, it is important to measure the degree to which NRT mediates nicotine withdrawal symptoms. The Minnesota Nicotine Withdrawal Scale (MNWS) is a questionnaire evaluating the presence of the eight most common symptoms of nicotine withdrawal, such as cravings, mood changes, and sleep disturbance (29). Similar to nicotine dependence levels, only two of the studies in this review reported measuring withdrawal symptoms, with both using the MWNS (19,24). One trial reported a decrease in withdrawal symptoms for both the NRT and placebo groups with no significant difference between groups (24), and the other trial reported using the MNWS in their methods but did not present any results (19). Nicotine is metabolized faster in pregnancy, so it is possible that the standard dose of NRT would be insufficient to achieve adequate serum cotinine levels and control withdrawal symptoms (22). However, in the single study that reported MNWS scores, serum cotinine was measured at each follow up and the NRT dose was adjusted accordingly, so nicotine metabolism was not a likely factor that caused the NRT group to report the same level of withdrawal symptoms as the placebo group (24). Unfortunately, since most of the studies included in this review did not measure or report withdrawal symptoms, it is difficult to determine the efficacy of NRT to reduce withdrawal symptoms in pregnancy and whether or not withdrawal symptoms were related to tobacco use levels, participant dropout, or protocol adherence.
5.3 Safety of NRT use in pregnant smokers:

Tobacco use during pregnancy is associated with an increased risk of multiple complications including pre-term labour, fetal growth restriction, fetal demise, and neonatal intensive care unit (NICU) admissions (10,11). Nicotine has been shown to alter fetal protein metabolism and blood flow, which is a potential cause of fetal growth restriction and reduced birth weight (9). As a result, there is concern about the safety of NRT use in pregnancy because it exposes the fetus to nicotine. This concern is the basis for current practice guidelines to suggest that NRT methods that provide intermittent nicotine doses (i.e. gum) are preferred over continuous dose methods (i.e. patch) in order to limit nicotine exposure during pregnancy (10). However, there are no RCTs comparing fetal outcomes for nicotine patch vs. gum use, so this recommendation is based off a theoretical premise. In an observational study of 15,796 Danish women who smoked during pregnancy there was no association between the use of NRT and birth weight, regardless of the type of NRT used (i.e. gum vs. patch). For women who used more than one NRT product simultaneously there was a trend for reduced birth weight, however this was not statistically significant (30).

With regards to fetal outcomes after birth, maternal smoking has been associated with an increased risk of developmental impairment, including congenital defects, impaired lung function, impaired learning, and behavioral problems (7,9,14). In order to determine if NRT use during pregnancy was associated with an increased risk of developmental impairment, Cooper et al. conducted a two-year follow-up of the trial by Coleman et al. (8) that included 1,050 pregnant smokers randomized to NRT patch or placebo. They found that parents in the placebo group were more likely to report
impairment than the NRT group (Odds ratio 1.40; p = 0.023) (31). These findings suggest that NRT use may play a role in preventing developmental impairment in children of mothers who smoked during pregnancy.

For the studies included in this review, there was no evidence that fetal exposure to NRT reduced birth weight. In fact, two studies demonstrated significantly higher average birth weights (+186g; +337g) in the NRT group vs. the placebo group (19,20). In regards to pre-term delivery (<37 weeks gestation), NRT use did not demonstrate an increase in pre-term deliveries, and one study found a significant reduction compared to placebo (19). Furthermore, there were no significant differences in NICU admission rates or fetal demise between the NRT and placebo groups in any of the included studies. However, regarding NICU admissions, it is important to note that each of the included studies were conducted in different countries which likely have varying protocols regarding NICU admission criteria. As a result, comparison of NICU admission rates between studies is limited by the heterogeneity of neonatal healthcare practices between countries.

In regards to the safety of NRT for pregnant women, there were no significant differences in the incidence of adverse effects between NRT and placebo groups, with the exception of one study that found a significant increase in diastolic blood pressure of 0.02mmHg/day in the NRT group (24). Based off the results of the studies in this review, there is no evidence to support the claim that NRT use during pregnancy increases the risk of adverse effects to the mother or fetus. Furthermore, there is some evidence to suggest that for pregnant women who smoke NRT use results in increased fetal birth weight and reduced incidence of pre-term delivery (19,20). However, due to variability
between studies in the dose and duration of NRT use, as well as variable protocol adherence, it is difficult to determine which NRT regimen has the lowest risk of adverse effects.

5.4 Limitations of included studies:

5.4.i. Risk of bias to study results:

Since only placebo-controlled RCTs were included in this review, heterogeneity between the included studies is reduced and the risk of selection, performance, and detection bias is considered low when interpreting these results (22). The study by Kapur et al. had the highest potential risk of reporting bias due to the lack of reporting of results regarding daily tobacco use, birth outcomes, and side effects (18). The study by Wisborg et al., 2000 had the highest potential risk of attrition bias due to the lack of reporting of participant dropout results (20).

5.4.ii. Statistical Power and risk of type II error:

Statistical power is an important consideration for each of the included studies when evaluating for potential type II error based off sample size. Based off the power analyses presented in each of these articles, three of the five included studies were underpowered to detect a significant difference between the NRT and placebo groups, either due to inadequate recruitment or high dropout rates (18,19,24). Furthermore, while the study by Wisborg et al. was able to recruit a large enough sample size to achieve 80% power, the authors did not report participant dropout rates, therefore it is difficult to determine if the
cohort was large enough at the end of study to achieve the desired 80% power level (20). However, despite failing to recruit the target sample size to achieve a projected 80% power level, the Oncken et al. study reported a significant difference in birth weight and daily tobacco use between the NRT and placebo groups (19).

In summary, of the three studies that failed to detect a significant difference in tobacco use in cessation rates or birth weight between treatment groups, two were significantly underpowered and therefore at higher risk of type II error (18,24). However, despite having a power level >90%, the trial with the largest cohort still failed to detect any significant difference between groups (8).

5.5. Future directions for research:

5.5.i. The limitations of nicotine patches, and the potential benefit of nicotine gum:

In the most recently published systematic review of the use of NRT in pregnancy, Coleman et al. suggested that due to the encouraging, but non-significant effects of NRT demonstrated in previous studies, placebo-controlled RCTs using higher doses of NRT should be conducted (8). Subsequently, Berlin et al. conducted a trial using a regimen of NRT with a longer duration and doses that were matched to participant cotinine levels as high as 30mg patches, double the dose used in previous studies. Despite the higher doses of NRT, this trial did not find any significant effect of NRT. However, due to participant dropout levels of 46% in the NRT group and 57% in the placebo group, these findings were underpowered to detect a benefit of NRT (24). Therefore, there is still room for future research to assess the potential benefit of high dose NRT.
Alternatively, the use of short-acting NRT such as nicotine gum is another possible means of providing higher doses of NRT, since multiple doses of nicotine can be administered in a day, as opposed to one high dose patch. The use of nicotine gum in pregnant smokers also requires further study, given that only one placebo-controlled RCT using gum was found in this review. Furthermore, the nicotine gum trial showed the greatest benefit of NRT, with significant improvement in daily tobacco use, mean birth weight, and pre-term deliveries compared to placebo (19). Therefore, it is possible that nicotine gum may be a more effective form of NRT than patches for pregnant smokers. Given that the current Canadian guidelines for the use of NRT in pregnancy suggest that short-acting NRT products (i.e. gum, lozenge, inhaler) are preferred over long-acting NRT products (i.e. patches), future studies should focus on the use of nicotine gum alone and/or in direct comparison with patches (10).

5.5.ii. The potential benefit of combined NRT therapies

The availability of NRT in different forms provides the flexibility of long lasting (16-18 hour) baseline doses of nicotine from patches as well as on-demand short-term doses from gum. While both forms of NRT have been studied in pregnant smokers, the combined use of nicotine patches and gum has yet to be studied in placebo-controlled RCTs. In a Cochrane review of NRT use for non-pregnant smokers, combination therapy of patches with short-term dosing methods such as nicotine gum showed beneficial effects (17). In a correlational study of pregnant smokers in England, the combined use of a nicotine patch and a faster acting form of NRT (i.e. gum) was associated with increased odds of quitting after four weeks compared to no NRT (odds ratio =1.93; p=0.016). This
study included 3,880 pregnant smokers enrolled in the English Stop Smoking Services between 2009-2011 (32). While these results are encouraging, the study did not evaluate pregnancy outcomes so the safety profile of combined NRT use is unknown. In an observational study of 1,753 Danish women who used NRT during pregnancy, the simultaneous use of more than one form of NRT was associated with reduced birth weight, however this association was not statistically significant (30). Therefore, while the combined used of a long-acting patch for constant nicotine dosing and a short-acting gum for breakthrough cravings has the potential to reduce tobacco use during pregnancy, placebo-controlled NRTs are required before the practice can be considered safe. However, the argument can be made that in terms of safety, the use of combined forms of NRT is likely less harmful than smoking cigarettes which contain thousands of additional potentially toxic chemicals (32).

5.5.iii. Short and long-term safety profile

In this review, none of the studies indicated that NRT increases the risk of pregnancy complications such as low birth weight, pre-term delivery, NICU admissions, or fetal demise. However, for the studies included in this review, the average gestational age at randomization ranged from 16-18 weeks. As a result, the birth outcomes reported are limited to pregnant smokers that did not start using NRT until the second trimester of pregnancy. Given that a large proportion of fetal development occurs in the first trimester, it is possible that pregnancy complications could occur if NRT is used early in pregnancy (9). Future studies using NRT in the first trimester would help provide further insight into the safety profile of NRT in the different stages of pregnancy.
When evaluating the safety profile of NRT in pregnancy it is also important to consider the sample size in relation to the incidence of pregnancy complications. For example, depending on the region being studied, stillbirth rates can be as low as two per every 1000 live births (11). Given that if all of the studies in this review were combined there would still be less than 2000 subjects, therefore the sample size is likely too small to show a significant effect of NRT on rates of fetal demise. As a result, continued research is required to create a large enough sample to provide complete assurance that NRT use in pregnancy is safe. Furthermore, in regards to the evaluation of the safety profile of NRT in pregnancy, long-term follow-up studies have the potential to provide insight to the effects on early childhood development. For example, in a two-year follow-up of the placebo-controlled RCT by Coleman et al., despite not finding any significant effect of the use of NRT during pregnancy, infants of mothers in the NRT group were less likely to show signs of cognitive or physical impairment at two years of age compared to the placebo group (31). These results suggest that the use of NRT by pregnant smokers may have a protective effect on the development of their children. However, additional studies are required to support these findings.

5.5.iv. Addressing risk factors, not just nicotine addiction

In this review, the demographics of the participants included women who were unable to quit smoking in the first trimester of pregnancy and shared the common risk factors for persistent tobacco use including multiparity, having a partner who smokes, and/or low socioeconomic status (SES). These common traits suggest that there are important psychosocial factors that influence maternal smoking habits, as opposed to
solely nicotine addiction. Previous studies have attempted to address these factors using peer support interventions and programs targeted at partner smoking habits. In a systematic review by Ford et al., seven studies were reviewed that provided peer support interventions for pregnant smokers. However, only three studies showed a moderate effect on cessation rates and none of the studies showed a beneficial effect beyond six months (33). In regards to partner smoking and support, a systematic review of nine studies found that only two studies demonstrated an increase in partner smoking cessation, while three studies showed an increase in cessation attempts by the partner (34). Despite the relatively low success rate of studies that sought to decrease tobacco use during pregnancy by addressing psychosocial risk factors, it is possible that the use of NRT combined with peer support could increase the efficacy of both interventions. Future studies that compare NRT to peer support to NRT plus peer support have the potential to provide insight to the synergistic roles of these interventions.

6. Conclusion:

The use of tobacco during pregnancy is considered to be the most important preventable cause of pregnancy complications including pre-term labor, fetal growth restriction, fetal demise (spontaneous abortion, stillbirth), and NICU admissions (3,9,10). Despite the potential for harmful effects, 10.5-23% of Canadian women smoke during pregnancy (4,5). The current Canadian practice guidelines recommend cessation counseling as the first line therapy, and the use of NRT as a second line therapy if counseling is ineffective (10). The results of this narrative review support the use of counseling for pregnant women who smoke, and suggest that the use of NRT may result
in greater reductions in daily tobacco use levels than counseling alone. There is no
evidence from this review that NRT increases the risk of fetal growth restriction, pre-term
delivery, or NICU admissions. Furthermore, the results suggest that NRT may reduce the
risk of these outcomes, and the risk of developmental complications after birth (31).
While this review did not reveal any safety concerns, continued research is required to
create a large enough sample to provide complete assurance that NRT use in pregnancy is
safe. There is currently insufficient evidence to determine the effect of NRT on
withdrawal symptoms, and the role of nicotine dependence levels on NRT efficacy in
pregnancy. There is some evidence that nicotine gum may be more effective than patch,
but more placebo-controlled studies are needed, including trials that directly compare the
efficacy of gum with patches. Furthermore, observational studies suggest that the
combination of patch and gum NRT may have synergistic effects for reducing tobacco
use, however the safety profile of combined NRT in pregnancy needs further study (32).
Despite the combined use of counseling and NRT, the majority of the study participants
continued to use tobacco during their pregnancy. There are multiple identified risk factors
that are associated with tobacco use during pregnancy, and programs that aim to address
these issues, such as peer support interventions, used in combination with NRT and
counseling may be a worthwhile strategy for future investigation. In summary, while
additional research is still needed, the use of NRT for pregnant women who smoke shows
more signs of benefit than harm and has the potential to improve outcomes for both
mother and fetus.
7. Acknowledgements:

To my advisors Annette Schultz & Drena Dunford, thank you for your support, guidance and insight. Together you know more about tobacco addiction and pharmacology than I ever will and I am grateful that you joined forces to take the time to educate me.

Thank you to the University of Manitoba Health Sciences librarians for your help with the technical aspects of this project. Specifically, thank you Me-Linh Le for your helpful instruction regarding the use of article databases and selecting the appropriate MeSH terms, and thank you Hal Loewen for your instruction regarding the use of Refworks reference managing software.

I would also like to thank Ian Jones, the Master’s of Physician Assistant Studies (MPAS) program director, for connecting me with Annette and Drena, and providing guidance throughout the process of completing this study. Furthermore, thank you to the MPAS faculty for their hard work and dedication to providing a nurturing learning environment for my classmates and I.

Last, but not least, a heartfelt thanks to my wife Amanda. As always you have supported me through all of the late nights, early mornings, and time in between. You are the common thread connecting all of my accomplishments over the last ten years. You’re a constant inspiration, thank you for being you.
8. Bibliography:


(22) Coleman T, Chamberlain C, Davey M, Cooper SE, Leonardi-Bee J. Pharmacological interventions for promoting smoking cessation during pregnancy. Cochrane Database of Systematic Reviews 2012(9).


