Comparative Effectiveness of Smoking Cessation Medications among Obese Smokers

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PROJECT SUMMARY

Tobacco use remains the largest preventable cause of mortality and morbidity in the United States, with considerable annual direct medical costs and potential life year lost (Centers for Disease Control and Prevention, 2008; US Department of Health and Human Services, 2010). Smoking cessation efforts among smokers should be part of routine preventive health care measures as tobacco-related disease is preventable (Corelli and Hudmon, 2002).

In the United States, the majority smokers who quit smoking gain weight (USDHHS, 1990; Parsons et al., 2009). Only 25% of former smokers maintain a normal post-cessation weight (Lycett et al., 2011). Therefore, there is a pervasive concern among smokers that quitting smoking is in general accompanied with weight gain; this weight gain can lessen some of the health benefits of quitting smoking (Audrain-McGovern and Benowitz, 2011; Lycett et al., 2010).

Cigarette smoking is associated with an increased risk of diabetes mellitus (Willi et al., 2007; Tonstad, 2009; Will et al., 2001; Hur et al., 2007); thus smoking cessation should decrease the risk of diabetes among current smokers. However, recent evidence suggests that smoking cessation could lead to a higher risk of developing diabetes in the short term, possibly because of post-cessation weight gain (Yeh et al., 2010).

Obesity is associated with an increased risk of type 2 diabetes (Ezzati et al., 2006; Whitmore, 2010). Approximately 90% of obese individuals also develop type 2 diabetes (World Health Organization, 2005). The risk of developing diabetes is greatly increased by early weight gain (Wannamethee and Shaper, 1999). There is strong evidence that weight loss in overweight and obese individuals can reduce the risk of diabetes (Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, 1998).

The US Public Health Service Clinical Practice Guidelines suggest that smoking cessation interventions should include at least one Food and Drug Administration (FDA)-approved medication, for example, bupropion and varenicline, to increase the likelihood of smoking cessation success (Fiore et al., 2008). Several trials have demonstrated less post cessation weight gain when using bupropion compared to placebo or varenicline (Parsons et al., 2009; Jorenby et al., 2006; Nides et al., 2006; Hurt et al., 1997). However, post-cessation weight gain is in general a concern among smokers, and particularly among weight-concerned smokers (Bush, 2008; Pomerleau et al., 2001). Moreover, cigarette smoking is perceived as helpful in controlling body weight (Audrain-McGovern and Benowitz, 2011). Considering that obese individuals already have an increased diabetes risk (Garber, 2011; Lycett et al., 2010), there is an increased concern of developing diabetes as a consequence of post smoking cessation weight gain. It is immensely important to compare the effectiveness of pharmacological smoking cessation strategies in achieving successful cessation and in protecting against post-cessation weight gain and diabetes among obese smokers attempting to quit. Therefore, the specific aims of this study will be:

Objective I: To compare the continuous abstinence rates of FDA-approved smoking cessation medication strategies during a) 3 months, b) 6 months, and b) 12 months follow up period among obese smokers.

Hypothesis (Ha): Abstinence rates among obese smokers using varenicline will be higher compared to obese smokers using bupropion during a)3, b)6, and c)12 month follow-up after treatment initiation.

Objective II: To compare the post-cessation weight gain between the two FDA-approved smoking cessation medications during: a) 3 months, b) 6 months, and c) 12 months of follow up period.

Hypothesis (Ha): Obese smokers using bupropion experience lesser weight gain compared to those obese smokers using varenicline during a)3, b)6, and c)12 month follow-up after treatment initiation.

Objective III: To compare the risk of developing diabetes following smoking cessation during the first year follow up among obese smokers between the FDA-approved smoking cessation medications (bupropion and varenicline).

Hypothesis (Ha): Obese smokers using bupropion are less likely to develop diabetes following smoking cessation during a 1-year follow up compared to those using varenicline.

BACKGROUND, SIGNIFICANCE AND RATIONALE

Burden of smoking

Tobacco use remains the primary preventable cause of death and disease in the United States, with an estimated 443,000 deaths from diseases including cardiovascular and respiratory diseases and cancer (Centers for Disease Control and Prevention, 2011). It was estimated that smoking cost the United States $193 billion in annual health-related expenditures between 2000 and 2004, $96 billion in direct medical costs and approximately $97 billion in lost productivity (Centers for Disease Control and Prevention, 2008). An estimated 46.5 million Americans smoke; of these, 70% report that they are willing to quit completely (Corelli and Hudmon, 2002). Approximately 52% of smokers in the United States make a serious attempt to quit; however, without receiving

proper assistance in smoking cessation, more than 94% and 98% failed to quit smoking at 1 month and 1 year after their initial quit date, respectively (USDHHS, 1990). In the United States, an estimated 19% of women and 23% of men are current smokers (Audrain-McGovern and Benowitz, 2011). Efforts to promote smoking cessation among smokers should be a routine preventive health care measure since tobacco-related disease is preventable (Corelli and Hudmon, 2002).

Tobacco induced health problem

Cigarette smoking results in approximately 5 million year of potential life lost in the United States each year and leads to multiple health consequences (US Department of Health and Human Services, 2010). It is reported that cigarette smoking has greatly increased the incidence of lung cancer and the risk of heart attacks and stroke (Walser et al., 2008; Lightwood and Glantz, 1997), with approximately 85% of lung cancer caused by smoking in the United States (US Department of Health and Human Services, 2010). Its use is also a risk factor for chronic obstructive pulmonary disease and cancers, including pharyngeal, esophageal, bladder, laryngeal, and pancreatic, mouth, throat, kidney, stomach, and cervix, as well as acute myeloid leukemia (Profita et al., 2010; Dennish and Castell, 1971; Van Hemelrijck et al., 2009; Fuchs et al., 1996, US Department of Health and Human Services, 2010). Evidence shows that cigarette smoking is associated with the onset of type 2 diabetes (Kawakami et al., 1997; Nakanishi et al., 2000; Manson et al., 2000; Wannamethee et al., 2001; Willi et al., 2007). In addition, smokers with diabetes are reported to have a higher risk of heart and kidney disease, amputation, and eye disease causing blindness (US Department of Health and Human Services, 2010).

Challenges to quit smoking

There are several challenges to quitting smoking; in the short-term after smoking cessation, withdrawal symptoms may appear including difficulty concentrating, insomnia, anger, depression, anxiety impatience, and restlessness. These symptoms usually peak within the first week and last 2–4 weeks (Hughes et al., 2004). Following smoking cessation when withdrawal symptoms peak, the greatest risk in the first few weeks is relapse. Relapse is a significant concern after smoking cessation which raises the highest risk of failure of quitting smoking (Coleman et al. 2010; Hughes et al., 2004). Those who maintain abstinence for the first 2 weeks are more likely to be abstinent 6 months later (Kenford et al., 1994). Although withdrawal symptoms may reduce and confidence in remaining abstinent may increase for those who maintain abstinence for the first few weeks, abstainers continue to relapse for months, even years following the quit attempts (Coleman et al., 2010). Meanwhile, weight gain has also been recognized as a distinguishing feature of nicotine withdrawal, which is opposed to other drug withdrawal syndromes (Hughes et al., 1994). Weight gain is one of the major cited reasons for continuity of smoking and relapse after smoking cessation, especially among women (Klesges et al., 1989; Klesges and Shumaker, 1992).

Weight gain after quitting

Cigarette smoking has been considered helpful in controlling body weight for many years (Audrain-McGovern and Benowitz, 2011). Female adolescents report initiating and continuing with cigarette smoking to control and lose weight (Fulkerson and French, 2003). Weight gain is one of the major reasons that hinder smoking cessation success (Meyers et al., 1997). Borrelli and Mermelstein (1998) noted that weight gain was associated with subsequent relapse (Borrelli and Mermelstein, 1998); Swan et al. (1993) found that “weight concern” female smokers were

more likely to relapse than any other group (Swan et al., 1993); Meyers et al. (1997) concluded a lower likelihood of quitting smoking among weight-concerned smokers than any other group (Meyers et al., 1997). Although most health care providers would agree that the benefits of the cessation significantly outweigh the health risks associated with post-cessation weight gain (Audrain-McGovern and Benowitz, 2011); nonetheless, post-cessation weight gain may contribute to an increased risk of type 2 diabetes (Yeh et al., 2010), hypertension (Janzon et al., 2004), and reduces the improvement of lung function (Chinn et al., 2005). The findings that the incidence of type 2 diabetes is increased by 50-100% in the first three years following cessation (Davey Smith et al., 2005; Yeh et al., 2010), that abstainers have a 30% increased risk of hypertension compared to continuing smoking (Gerace et al., 1991), and that the improvement in lung function of quitters decreased by 38% in men and 17% in women, are as a consequence of smoking cessation-related weight gain (Chinn et al., 2005).

One exploratory study with a sample of 113 participants reported that 40% recruited female respondents expressed an unwillingness to gain any weight at all (Pomerleau and Kurth, 1996), however, it is estimated that 80% of smokers who quit smoking gain weight in the United States (USDHHS, 1990). Moreover, smokers gain weight differentially after quitting smoking (Moffatt and Owens, 1991; Stamford et al., 1986; Williamson et al., 1991). On average, smokers weigh 4-5 kilograms less than nonsmokers and gain 4.5 kilograms within 6-12 months after quitting smoking (Williamson et al., 1991). Smokers gain between 7 and 19 pounds within 8 years of their successful initial quitting, whereas those who continue to smoke gain an average of 4 to 5 pounds (Lycett et al., 2011; O'Hara et al., 1998). Williamson et al. (1991) reported that approximately 10% of smokers gained nearly 30 pounds in weight after quitting smoking (Williamson et al., 1991). Weight gain occurs greatest in the first 1-2 months and mostly within

the first 5 months, although continues to increase for 6 or more months of quitting smoking (Audrain-McGovern and Benowitz, 2011). Smokers who are either underweight or overweight appear to gain more weight than those who are normal weight after quitting smoking (Lycett et al., 2011). *Obese smokers gain most weight following quitting smoking*, while obese smokers continuing smoking habits are likely to remain stable or lose weight (Lycett et al., 2011). *Hence, obese quitters have the greatest need for interventions to ameliorate weight gain* (Lycett et al., 2011).

The physiological mechanisms of smoking decreasing body weight are complex and incompletely understood (Audrain-McGovern and Benowitz, 2011). Nicotine has many potential effects of regulating eating and energy consuming on the central nervous system; the release of hormones influences brain chemicals that suppress eating and decrease metabolic rate, including insulin resistance (Audrain-McGovern and Benowitz, 2011). Apart from decreased metabolic rate, one additional mechanism of weight gain after smoking cessation is increased caloric intake, which was affected by nicotine on appetite-suppressant effects on the brain and a food substitute for the rewarding effects of smoking (Audrain-McGovern and Benowitz, 2011).

Smoking cessation + diabetes risk

In the United States, the age-adjusted prevalence rates between 1997 and 2004 show that approximately 20-26% of adults diagnosed with diabetes were current smokers (Centers for Disease Control and Prevention, 2012). Recommendations for diabetes prevention from the American Diabetes Association Guidelines include increasing physical activity, maintaining a balanced diet, and stopping smoking, (Eyre et al., 2004). Smokers diagnosed with diabetes are listed as a target group for smoking cessation treatment owing to the increased health risks

associated with this disease and smoking by the US Clinical Guidelines for Treatment of Tobacco Dependence (2008) (Fiore et al., 2008).

Smokers with chronic diseases stated a high motivation to stop smoking compared to those who are healthy. However, the rates of smoking among patients diagnosed with diabetes do not appear to reduce (Tonstad, 2009; Twardella et al., 2006; Wilkes and Evans, 1999). Published literature shows evidence that there is an association of cigarette smoking with the development of type 2 diabetes (Tonstad, 2009; Will et al., 2001; Hur et al., 2007). Will et al. (2001) indicated that compared with non-smokers, smokers who take 2 packs of cigarettes a day or more at baseline had a significantly higher rate of developing diabetes, while smoking cessation equaled these rates after 5-10 years (Will et al., 2001). A previous study found a significantly higher risk of developing diabetes among current male smokers (OR: 1.49, 95% CI: 1.13-1.96) compared to non-smokers (Beziaud et al., 2004). However, some studies have reported an increased risk of diabetes after smoking cessation. Hur et al., (2007) found that both continuing smokers and former smokers had a higher adjusted risk ratio (OR: 1.60, 95% CI: 1.29-1.97 for continuing smokers; OR: 1.22, 95% CI: 0.96-1.55 for former smokers) of developing diabetes compared to non-smokers over an 8-year period, while an equal adjusted risk ratio over a 20-year period (Hur et al., 2007). Wannamethee et al. (2001) found that men who quit smoking in the first 5 years of follow-up had a significant mean weight gain and subsequently higher risk of developing diabetes (adjusted relative risk: 2.03, 95% CI: 1.22 – 3.37) than non-smokers (Wannamethee et al., 2001). Yeh et al. (2010) found that in the first 3 years of follow-up, compared with non-smokers, the hazard ratios of diabetes among former smokers, new quitters, and continuing smokers were 1.22 (95% CI: 0.99 – 1.50), 1.73 (95% CI: 1.19 – 2.53), and 1.31 (95% CI: 1.04 – 1.65), respectively, which means smoking cessation leads to higher short-term risk (Yeh et al.,

2010). Therefore, quitting smoking leading to a higher risk of developing diabetes is an overwhelming concern for smokers, especially for obese smokers, who have the potential to gain most weight following quitting smoking (Lycett et al., 2011), which is a risk factor for developing diabetes.

Obesity burden

The second leading cause of premature mortality and morbidity is overweight and obesity (Mokdad et al., 2004), with an estimated 97 million adults in the United States are overweight and obese (Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, 1998). Between 2003 and 2004, approximately 28.5% adults aged 20-39 years, while 36.8% adults aged 40-59 years old and 31% adults aged 60 years or older were obese in the United States (Ogden et al., 2006). Overweight and obesity peak at age between 45 and 64, which is also a period when smoking cessation is more likely to occur (Audrain-McGovern, 2011).

Obesity – diabetes risk

Obesity is associated with an increased risk of morbidity from cardiovascular disease (CVD), hypertension, type 2 diabetes, respiratory problems, musculoskeletal disorders, and certain cancers (Ezzati et al., 2006). Approximately 90% of obese individuals also develop type 2 diabetes (Stevens et al., 2001; World Health Organization, 2005). The risk of diabetes is greatly increased by weight gain (Wannamethee and Shaper, 1999). There is strong evidence that weight loss in obese individuals can reduce the risk of diabetes (Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, 1998).

The World Health Organization (WHO) predicts that the number of people diagnosed with type 2 diabetes will increase to more than 350 million worldwide in the next 20 years unless appropriate action is taken (World Health Organization, 2005). In 2003, an estimated prevalence of diabetes was 25.8 million, approximately 8.3% of the population in the United States. It is estimated that approximately 1.9 million Americans develop diabetes each year (Centers for Disease Control and Prevention, 2011). This incidence rate of diabetes reflects an increase in type 2 diabetes due to the epidemic increase in overweight/obesity in the United States populations (Mokdad et al., 2004). It has been estimated that 70% of type 2 diabetes risk are attributable to overweight/obesity in the United States (Eyre et al., 2004). More than 80% of adults diagnosed with diabetes are obese, indicating that obesity is one of the major risk factors in obese populations (Wannamethee, 2005; Waring, 2010). As each kilogram of weight gain over 10 years increases the risk by 4.5%, maintaining a healthy body weight is critical for the prevention and treatment of type 2 diabetes (Eyre et al., 2004).

Smoking cessation medication

The US Public Health Service Clinical Practice Guidelines suggest that smoking cessation interventions should include at least one FDA-approved medication in combination with tobacco dependence counseling if feasible and not medically contraindicated, to increase the likelihood of smoking cessation success (Fiore, 2000). Several smoking cessation pharmacotherapies have been evaluated to be effective and are available for preventing post-cessation weight gain for smokers. First-line smoking cessation medications, which are approved by the FDA, include nicotine agonists (also known as nicotine replacement therapies (NRTs)), nicotine antagonists (sustained-release bupropion hydrochloride <amfebutamone>), and nicotine partial agonists (varenicline <Chantix>). NRTs include nicotine gum, nicotine transdermal patches, nicotine

nasal spray, and nicotine inhaler (Table 1). The use of approved smoking cessation medications doubled the likelihood of quitting smoking (Fiore, 2000; West et al., 2000).

Several trials have demonstrated a lesser post cessation weight gain when using bupropion compared to varenicline or placebo (Parsons et al., 2009; Gadde and Xiong, 2007). At the end of treatment, participants taking bupropion were found to gain significantly less weight than those on varenicline (-0.51 kg (-0.09 to -0.93) (Gonzales et al., 2006; Nides et al., 2006; Jorenby et al., 2006) and placebo (-1.11kg (-1.47 to -076)) (Parsons et al., 2009). However, varenicline had no significant effect on post-cessation weight gain compared with placebo at the end of treatment (Nides et al., 2006; Jorenby et al., 2006; Gonzales et al., 2006). The weight gain was less with bupropion compared to placebo at 1-year (3.8 vs. 5.6kg) and 2-year follow-up (4.1 vs. 5.4kg) (Jorenby et al., 1999). However, no studies reported varenicline treatment differences versus placebo or bupropion in weight gain in the longer term follow up (Parsons et al., 2009). The pooled estimate of effect of varenicline on weight change was -0.52 kg (-.1.16 to 0.11) (Parsons et al., 2009). It is suggested that for smokers at risk for diabetes, smoking cessation interventions should be coupled with strategies for diabetes prevention (Yeh et al., 2010). There are randomized control trials (RCTs) and observational studies that show evidence that NRT, antidepressants (i.e., bupropion) and probably varenicline for smoking cessation all reduce weight gain after smoking cessation in the short term (Parsons et al., 2009). However, to date, there is no observational comparative effectiveness study to examine which pharmacological smoking cessation strategy is more effective regarding reducing post-cessation weight gain or decreasing the risk of diabetes among obese smokers.

Abstinence rates using smoking cessation medications among obese smokers

Abstinence rate is one of the important measures for evaluating the success of smoking cessation (NAQC Issue Paper, 2009). Evidence shows that all the FDA approved smoking cessation medications have higher abstinence rates than placebos for short-term and long-term use. In addition, varenicline has a higher abstinence rate as compared to bupropion or NRT. The adjusted risk ratio (RR) of continuous abstinence at 52 weeks is 1.3 to 2.3 times higher by using varenicline than that of bupropion (Gonzales et al., 2006: RR: 1.36, 95% CI: 0.99 – 1.86; Jorenby et al., 2006: RR: 1.57, 95% CI: 1.14 – 2.17; Nides et al., 2006: RR: 2.27, 95% CI: 1.02 – 5.03) and NRT (Aubin et al., 2008, RR: 1.31, 95% CI: 1.01 – 1.71). However, as is mentioned above, varenicline has limited effectiveness of preventing post-cessation weight gain compared to bupropion. Therefore, which smoking cessation intervention will result in better abstinence and what is the abstinence rate of each intervention are important to be explored among obese smokers.

Significance

Both cigarette smoking and obesity are the highest ranked preventable causes of morbidity and mortality with a significant economic burden in the United States (Corelli and Hudmon, 2002, Mokdad et al., 2004). Both smoking and obesity are associated with an increased risk of type 2 diabetes (Ezzati et al., 2006; Kawakami et al., 1997; Nakanishi et al., 2000; Manson et al., 2000; Wannamethee et al., 2001; Willi et al., 2007); therefore, smoking cessation should help decrease the risk of diabetes among smokers. However, Yeh et al. (2010) reported that although cigarette smoking leads to higher risk of development of type 2 diabetes, quitting smoking may increase such risk. Moreover, evidence that smoking cessation leads to higher risk of developing diabetes in the short term compared to the long term, possibly as a consequence of substantial post-

cessation weight gain (O'Hara et al., 1998; Balkau et al., 2006), which could counteract the reduced risk of diabetes. Meanwhile, the risk of diabetes is greatly increased by early weight gain (Wannamethee and Shaper, 1999). There is strong evidence that weight loss can help obese individuals reduce the risk of diabetes (Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, 1998). Hence, post-cessation weight gain and diabetes risk might be a considerable concern among obese smokers attempting to quit.

Despite the fact that several pharmacotherapies have been evaluated to be effective (measured by continuous abstinence rate) and are available for smokers for preventing post-cessation weight gain, none of these studies were conducted among obese smokers where risk of weight gain is highest. It is not clear which smoking cessation strategy is more effective in terms of providing a higher abstinence rate, reducing weight gain, and reducing the risk of developing diabetes following cessation among obese smokers. To better assess the effectiveness of each smoking cessation strategy, it is primarily essential to understand which FDA approved smoking cessation strategy can provide better abstinence rates among obese smokers. Furthermore, the effect of adding NRT might improve the abstinence rate of each strategy. In addition, it is important to know which smoking cessation strategy among obese smokers is more likely to attenuate weight gain and risk of developing diabetes. Knowledge gained from this study will provide additional information on the effectiveness and benefit of smoking cessation medications among obese adult smokers. Results will help the policy-makers and clinicians optimize drug regimen to treat obese smokers.

MANUSCRIPT 1

Comparison of Abstinence Rates of Smoking Cessation Medications among Obese Smokers

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Abstract

OBJECTIVE: To compare abstinence rates of different Food and Drug Administration (FDA)-approved smoking cessation medication strategies among obese smokers.

METHODS: A population-based retrospective cohort study was conducted using the General Electric (GE) electronic medical record database (2006 – 2011). The cohort consisted of obese adult smokers newly initiating use of an FDA-approved smoking cessation medication (bupropion vs. varenicline). A more specific cohort of morbid obese (Body Mass Index (BMI) $\geqslant$ 40) adult smokers was further investigated. The outcome variable was abstinent vs. not at 3, 6, or 12 months following first prescription. Descriptive analyses and chi-square tests were conducted to assess the frequency distribution of sample characteristics and their association with the smoking cessation medication use. Multivariate logistic regression models were carried out to identify predictors of abstinence at 3, 6 and 12 months after assessing multicolinearity between independent variables, with the use of multiple imputation to account for missing data for covariates. Backward elimination was used to arrive at the final models.

RESULTS: The abstinence rate of using any smoking cessation medication among obese smokers was 17.01% (n = 3,106) at 3 months, 20.58% (n = 4,714) at 6 months, and 22.86 % (n = 7,021) at 12 months. While previous literature among adults reports higher abstinence rates with varenicline compared to bupropion, our findings among obese smokers indicate slightly higher abstinence rates for those using bupropion compared to those using varenicline (bupropion vs. varenicline: 19.65% vs. 17.01% at 3 months ($p < 0.05$); 22.39% vs. 20.58% at 6 months ($p = 0.16$); 24.15% vs. 22.86% at 12 months ($p = 0.28$)). Significant predictors of successful abstinence included: demographic characteristic factors (age, race, region, payment type,

specialty group, and baseline BMI value), disease (hypertension), and utilization factors (weight influencing medications which may cause weight reduction, number of cigarettes smoked per day, smoking counseling, and alcohol dependence).

CONCLUSIONS: Abstinence rates were higher among obese smokers taking bupropion vs. those taking varenicline. Predictors identified in this study should be considered when designing smoking cessation interventions among the high risk population of obese smokers.

Key Words: Comparative effectiveness, Smoking cessation, Abstinence rate, Obesity, Varenicline, Bupropion

INTRODUCTION

Tobacco use and obesity remain the primary and second leading cause of mortality and morbidity in the United States (US), with an estimated 443,000 deaths caused by smoking and an annual 300,000 deaths caused by obesity (Centers for Disease Control and Prevention, 2011; Mokdad et al, 2004). In the US, it was estimated that approximately 9 million smokers were also obese in the last 10 years (Healton et al., 2006).

There are several challenges to quitting smoking; in the short-term after smoking cessation, withdrawal symptoms can occur including impatience, anger, difficulty concentrating, depression, anxiety, insomnia, and restlessness. These symptoms usually peak within the first week and last 2–4 weeks (Hughes et al., 2004). The greatest risk of relapse following smoking cessation is when withdrawal symptoms peak in the first few weeks. Relapse is a significant concern after smoking cessation as it leads to failure of the cessation attempt (Coleman et al. 2010; Hughes et al., 2004). Those who maintain abstinence for the first 2 weeks are more likely to be abstinent 6 months later (Kenford et al., 1994). Although withdrawal symptoms may reduce and confidence in remaining abstinent may increase for those who maintain abstinence for the first few weeks, abstainers continue to relapse for months, even years following the quit attempts (Coleman et al., 2010).

Efforts to promote smoking cessation among smokers should be a routine preventive health care measure since tobacco-related disease is preventable (Corelli and Hudmon, 2002). The US Public Health Service Clinical Practice Guidelines suggest that smoking cessation interventions should include at least one Food and Drug Administration (FDA)-approved medication in combination with tobacco dependence counseling, to increase the likelihood of smoking

cessation success (Fiore, 2000). Several smoking cessation pharmacotherapies have been evaluated to be effective for quitting smoking. First-line FDA-approved smoking cessation medications include nicotine replacement therapies (NRTs), sustained-release bupropion hydrochloride, and varenicline. The use of approved smoking cessation medications has been reported to double the likelihood of quitting smoking (Fiore, 2000).

Abstinence rate is the primary measure for evaluating the success of smoking cessation (NAQC Issue Paper, 2009). Evidence shows that all the FDA approved smoking cessation medications have higher abstinence rates compared to placebo for short-term and long-term use. In addition, varenicline has a higher abstinence rate as compared to bupropion or NRT (Cahill et al., 2012). The adjusted risk ratio (RR) of continuous abstinence at 52 weeks is 1.3 to 2.3 times higher by using varenicline than that of bupropion (Gonzales et al., 2006: RR: 1.36, 95% CI: 0.99 – 1.86; Jorenby et al., 2006: RR: 1.57, 95% CI: 1.14 – 2.17; Nides et al., 2006: RR: 2.27, 95% CI: 1.02 – 5.03) and NRT (Aubin et al., 2008, RR: 1.31, 95% CI: 1.01 – 1.71).

Both smoking and obesity are associated with an increased risk of type 2 diabetes (Ezzati et al., 2006; Willi et al. 2007); therefore, smoking cessation should help decrease the risk of diabetes among smokers. However, quitting smoking may increase risk of developing diabetes (Yeh et al., 2010), possibly as a consequence of substantial post-cessation weight gain (O'Hara et al., 1998). There is strong evidence that weight loss can help obese individuals reduce the risk of diabetes (Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, 1998). Hence, post-cessation weight gain might be a considerable concern among obese smokers who are at a higher risk of developing diabetes even before quitting.

While varenicline is reported to have a higher abstinence rate compared to bupropion and placebo among smokers of all weight levels, several trials have demonstrated a lesser post cessation weight gain when using bupropion compared to varenicline or placebo (Parsons et al., 2009; Gadde and Xiong, 2007). Varenicline does not seem to have a significant effect on post-cessation weight gain at the end of treatment (Nides et al., 2006; Jorenby et al., 2006; Gonzales et al., 2006), and bupropion has been shown to attenuate post cessation weight gain. As a considerable concern among obese smokers, post cessation weight gain may potentially influence the abstinence rate among such a population. Obese smokers gain most weight following quitting smoking, while obese smokers continuing smoking habits are likely to remain stable or lose weight (Lycett et al., 2011). Hence, obese quitters have the greatest need for interventions to ameliorate weight gain (Lycett et al., 2011).

Despite the fact that several pharmacotherapies have been evaluated to be effective (measured by continuous abstinence rate), it is not clear which smoking cessation strategy is more effective in terms of providing a higher abstinence rate following cessation among obese smokers. Therefore, the primary objective of study was to compare the abstinence rates of FDA-approved smoking cessation medication strategies during a) 3-month, b) 6-month, and c) 12-month follow up period among obese smokers. Knowledge gained from this study will provide additional information on the effectiveness and benefit of smoking cessation medications among obese adult smokers. That will aid both policy-makers and clinicians in optimizing drug regimens to treat this high risk population.

METHODS

Study Design and Data Sources

This study was a population-based retrospective cohort study using General Electric (GE) healthcare clinical data. It is a real-world observational, daily-updated and nationally representative clinical data, rich in information of millions of patients in the ambulatory primary care setting in the US. It had approximately 20 million unique patients as of 2011. GE healthcare clinical data has the results of lab tests (in both numeric and test form), vital signs such as height and weight, calculations such as Body Mass Index (BMI), and other clinical findings associated with patient care like pain scores, smoking status that are not available in other databases.

The uniqueness and the features of the GE healthcare clinical data mentioned above make it the optimal clinical database to be used for conducting this study. GE clinical data set has been widely used in the literature to study obesity and smoking (McAdam-Marx et al., 2011; McAdam-Marx et al., 2010; Brixner et al., 2009; Horton et al., 2010). For example, one of the studies was designed to assess effectiveness of different statins among diabetes mellitus patients with one of the covariates of smoking status (Fox et al., 2007).

The G-power 3.1.4 statistical software was used for sample size calculation with a 0.05 α-level, 80% power. A medium effect size for abstinence rate of 0.30 (that is, 1.30 odds ratio), with a binominal distribution, two-tails z-test for multiple logistic regression model would need a number of 3,677 observations. Based upon the preliminary analysis, the differences with a small to medium effect size can be detected using GE database.

Measures

The outcome variable was abstinence from smoking vs. not at 3-, 6-, and 12-month follow up times.

The *Body Mass Index* is a simple index of weight-for-height that is commonly used to classify underweight, overweight and obesity in adults. It was defined as the weight in kilograms divided by the square of height in meters (kg/m^2) and was rounded to the nearest tenth.

Obesity was classified according to BMI by the World Health Organization (WHO). Individuals whose BMI is greater than 30 are classified as obese, while those whose BMI is greater than 40 are classified as morbid obese (Seidell, JC, 2007).

Smoking status was classified as *never smoked*, *formerly smoked*, *not currently smoking*, and *currently smoking*, which are dummy variables of *smoking status* in GE healthcare clinical data. *Never smoker* was defined as an individual who has not smoked 100 or more cigarettes during his/her lifetime; *former smoker* or *not current smoker* was defined as an individual who has smoked at least 100 cigarettes during his/her lifetime, but not currently smoke; *current smoker* was defined as an individual who has smoked at least 100 cigarettes during his/her lifetime and still regularly smokes every day or periodically.

Study Population

Inclusion criteria

The study cohort was identified using the following inclusion criteria: 1) obese, 2) aged 18 years or older, 3) enrolled in the GE healthcare clinical data in the United States between January 2006 and December 2011 (Bupropion was first approved by FDA as the non-nicotine medication for

smoking cessation in 1997, while varenicline was first approved in 2006), and 4) received at least one smoking cessation medication (bupropion HCL or varenicline tartrate).

The index date was defined as the first day of being prescribed smoking cessation medication. Wash-out period was defined as not receiving any smoking cessation medication 6 months before the index date (Chatterjee et al., 2012). New users were defined as taking at least one smoking cessation medication between July 1st 2006 and December 31 2011, while not taking any smoking cessation medication during wash-out period.

Exclusion criteria

Patients were excluded if they were: 1) missing data on smoking status at baseline and follow up, and 2) received any of the smoking cessation medication under study during the 6 months of pre-index period.

Statistical Analyses

The cohort consisted of obese smokers newly initiating use of at least one of the FDA-approved smoking cessation medications (bupropion vs. varenicline). Abstinence was defined as being reported as 'not current' or 'former' smoker at any point of the follow up period; being reported as 'current' smoker throughout the follow up period was categorized as non-abstinence. Once identified as being abstinent, abstinence status was sustained until throughout the follow up. The abstinence rate was assessed as number of abstinent smokers divided by overall obese smokers for each medication strategy.

Smoking status of the study population was measured during 3 months, 6 months, and 12 months, to compute the abstinence rates. The outcome measure – abstinence rate – was followed up by

three different timelines: 3-month (end of active treatment effect), 6-month (sustained effect, short term), and 12-month (sustained effect, long term) after the index date. The reason for taking three different follow-up time periods was that smoking cessation medications are usually required for a 3-month treatment; thus, monitoring the status of smoking 3 months after the treatment can help understand the end of treatment effect of the smoking cessation medications. On the other hand, smoking cessation medication may also have a short-term and long-term effect on influencing the decision of smoking. A 6-month and 12-month follow up time periods are acceptable for assessing the short-term and long-term effect of smoking cessation medications on abstinence rates (Gilpin et al., 1997).

Descriptive analyses were conducted to assess the frequency distribution of sample demographic characteristics at baseline. Student t-tests were conducted among obese smokers for continuous variables to assess the differences of mean values across the smoking cessation medication strategies, while chi-square tests were conducted for categorical variables to assess the differences in covariates and frequencies of abstinence rates across the smoking cessation medication strategies at the different follow-up times. Univariate analyses of participant characteristics were carried out with the three outcome variables, and results were presented as unadjusted odds ratios (OR) with 95% confidence intervals (CI). Three multivariate logistic regression models were carried out to assess the association between the outcome variable (abstinence vs. not) and independent variables after assessing multicolinearity and interaction. Multivariate logistic regression model results were presented as adjusted ORs with 95% CIs. The major independent variable was type of smoking cessation medication prescribed (bupropion and varenicline). Other patient characteristics identified as independent variables and potential confounders for the analysis included the following: age (categorized as 18 – 40/41 – 64/≥65),

sex (female/male), race (white/non-white), region (Midwest/Northeast/South/West), payment type (commercial /government/self-paid), specialty group (primary care/specialty care), BMI at baseline, comorbidities (smoking attributed diseases including hypertension, hyperlipidemia, lung cancer, stroke, chronic obstructive pulmonary disease (COPD), and acute myocardial infarction (AMI)), NRT use (using NRT between index date and follow up), weight counseling (no/yes), smoking counseling (no/yes), weight control medications (including medications which may cause weight reduction and weight gain, respectively), number of cigarettes smoked per day (no/yes), alcohol dependence (no/yes), and alcohol consumption (no/yes). Backward elimination was used to arrive at the final models that included smoking cessation medication (bupropion vs. varenicline), and any significant variable ($p<0.05$).

To further compare the risk factors of being abstinent from smoking among morbid obese smokers who were prescribed bupropion vs. varenicline, three multivariate logistic regression models were carried out among morbid obese smokers. Considering that missing value might have an impact on the model's fit, missing value analyses by using multiple imputation method were performed after assuming that these values were missing at random (Sterne et al., 2009). Unlike the single imputation procedure, where each missing value is replaced by a single value, the multiple imputation procedure replaced each missing value with a set of plausible values, so that the uncertainty about the right value to impute can be accounted for (Little and Rubin, 2002). The multiple imputed data were considered as complete data and analyzed by using standard procedures. The results from each imputation were then combined. The imputed models were then compared with the multivariate logistic regression models which missing values were considered as incomplete cases and deleted from the analyses.

Considering weight change at each follow up might be a causal determinant variable of abstinence and smoking cessation medication use (varenicline or bupropion) might be a causal determinant variable of weight change; in other words, weight change is a predictor hypothesized to lie on the causal pathway between smoking cessation medication use and abstinence, and thus to confound the effects of smoking cessation medication on abstinence, analyses which controlled for weight change were carried out to assess the direct effect of weight change on smoking cessation medication and abstinence. Univariate regression analyses were carried out to identify whether weight change is a confounder, followed by multivariate regression analyses to assess the percentage changes of coefficients of smoking cessation medications. A change of 10% or more in coefficients was considered as confounding effects. Figure 1 shows the directed acyclic graph (DAG) representing the effects of smoking cessation medication use and weight change on abstinence.

All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC) statistical package at a priori significance level of 0.05. GE healthcare clinical data has de-identified patient variables and the protocol was reviewed and approved by the relevant Committee for the Protection of Human Subjects at the University of Houston.

RESULTS

Baseline Sample Characteristics

The total sample consisted of 87,065 obese smokers utilizing at least one FDA-approved smoking cessation medication from July 2006 to December 2011. Figure 2 shows the schematic diagram for study cohort. The mean age of the cohort was 45.41 years (± SD: 12.19), while the mean BMI was 35.36 (± SD: 5.43). The mean age of the abstinent at 3 months, 6 months, and 12

months were 43.53 (± SD: 12.00), 43.96 (± SD: 12.14), and 44.32 (± SD: 12.21), respectively, while the mean BMI for each follow up were 35.46 (± SD: 5.41), 35.51 (± SD: 5.48), and 35.52 (± SD: 5.52). An overall abstinence rate at each follow up was 17.01% (n = 3,106), 20.58% (n = 4,714), and 22.86% (n = 7,021), respectively. Figure 3 presents the overall abstinence rate at each follow up. In terms of follow up at 3 months, the abstinence rate was 16.90% (n = 2,958) for obese smokers who were prescribed varenicline, while 19.65% (n = 148) for those who were prescribed bupropion ($p < .05$); in terms of follow up at 6 months, the abstinence rate was 20.51% (n = 4,506) for those who were prescribed varenicline, while 22.39% (n = 208) for those who were prescribed bupropion ($p = 0.16$); in terms of follow up at 12 months, the abstinence rate was 22.81% (n = 6,730) for those who were prescribed varenicline, while 22.81% (n = 291) for those who were prescribed bupropion ($p = 0.28$). Figure 4 presents the abstinence rate of each pharmacotherapy intervention at different follow up times. Table 1 summarizes the results of patients' characteristics and chi-square tests with the three outcome variables. Results from multiple imputation missing value analyses showed consistent results compared to the baseline models (data not shown).

Logistic Regression Analyses

Table 2 summarizes the results of univariate logistic regression and multivariate logistic regression of abstinence rate at each follow up period. Multicollinearity analysis and interaction assessment showed that there was no multicollinearity or interaction among the independent variables.

Obese smokers aged between 40 and 64 years (OR: 1.10, 95% CI: 1.01 – 1.20 in model 2; OR: 1.16, 95% CI: 1.05 – 1.28 in model 3) and 65 years or older (OR: 1.58, 95% CI: 1.21 – 2.06 in model 1; OR: 2.02, 95% CI: 1.70 – 2.39 in model 2; OR: 1.79, 95% CI: 1.46 – 2.20 in model 3)

were more likely to be abstinent than those who were aged between 18 and 39 years old. Non-white (OR: 0.86, 95% CI: 0.76 – 0.96 in model 1; OR: 0.88, 95% CI: 0.81 – 0.95 in model 2; OR: 0.86, 95% CI: 0.78 – 0.94 in model 3) were less likely to be abstinent than White. Obese smokers who were from the Northeast (OR: 1.21, 95% CI: 1.01 – 1.45 in model 1; OR: 1.37, 95% CI: 1.22 – 1.54 in model 2; OR: 1.30, 95% CI: 1.15 – 1.48 in model 3), Southern (OR: 1.20, 95% CI: 1.07 – 1.33 in model 2), and Western United States (OR: 1.34, 95% CI: 1.12 – 1.60 in model 1; OR: 1.56, 95% CI: 1.39 – 1.75 in model 2; OR: 1.44, 95% CI: 1.24 – 1.66 in model 3) were more likely to be abstinent than those who were from Midwest. Obese smokers who were diagnosed with hypertension (OR: 1.25, 95% CI: 1.06 – 1.47 in model 1; OR: 1.14, 95% CI: 1.02 – 1.28 in model 2), were more likely to be abstinent than those who were not. In contrast, obese smokers who were diagnosed with alcohol dependence were less likely to be abstinent than those who did not (OR: 0.64, 95% CI: 0.57 – 0.72 in model 1; OR: 0.68, 95% CI: 0.63 – 0.74 in model 2; OR: 0.77, 95% CI: 0.70 – 0.85 in model 3). Obese smokers who were prescribed weight influencing medications which may cause weight reduction were more likely to be abstinent than those who did not (OR: 1.51, 95% CI: 1.25 – 1.83 in model 1; OR: 1.36, 95% CI: 1.20 – 1.55 in model 2; OR: 1.50, 95% CI: 1.30 – 1.73 in model 3). Obese smokers who were offered smoking counseling were less likely to be abstinent than those who were not (OR: 0.50, 95% CI: 0.45 – 0.57 in model 1; OR: 0.52, 95% CI: 0.48 – 0.57 in model 2; OR: 0.59, 95% CI: 0.54 – 0.65 in model 3). Obese smokers who were identified to smoke at least one cigarette per day were less likely to be abstinent than those who were not (OR: 0.83, 95% CI: 0.74 – 0.93 in model 1; OR: 0.81, 95% CI: 0.75 – 0.87 in model 2; OR: 0.89 95% CI: 0.81 – 0.97 in model 3). In addition, each unit increase of BMI at baseline resulted in 2% more likelihood to be abstinent (OR: 1.02,

95% CI: 1.01 – 1.03 in model 1; OR: 1.02, 95% CI: 1.01 – 1.02 in model 2; OR: 1.02, 95% CI: 1.01 – 1.02 in model 3).

Some associations were found only in one model out of the three models: Obese smokers who received a specialty care were more likely to be abstinent than those who received a primary care (OR: 1.36, 95% CI: 1.15 – 1.61 in model 1). Obese smokers who paid insurance out of pocket were less likely to be abstinent than those who had a commercial insurance (OR: 0.71, 95% CI: 0.58 – 0.86 in model 3).

Morbid Obese Smokers

An overall abstinence rate at each follow up was 17.65% (n = 415), 20.90% (n = 610), and 21.91% (n = 3,793), respectively. The current study also showed that at 3 months, the abstinence rate was 17.48% (n = 393) for obese smokers who were prescribed varenicline and 21.36% (n = 22) for those who were prescribed bupropion (p = 0.31). Similarly, at 6 months follow-up, the abstinence rate was 20.71% (n = 579) for those who were prescribed varenicline and 25.20% (n = 31) for those who were prescribed bupropion (p = 0.23). In addition, abstinence rates of 21.75% (n=790) among those who were prescribed varenicline and 25.47% (n= 41) among those who were prescribed bupropion were observed at 12 months follow-up (p- 0.26). Table 3 shows the results of multivariate logistic regression models of abstinence rates at each follow up period among morbid obese smokers. Male morbid obese smokers were less likely to be abstinent than female morbid smokes (OR: 0.69, 95% CI: 0.55 – 0.88 in model 1; OR: 0.78, 95% CI: 0.64 – 0.94 in model 2). Morbid obese smokers aged between 40 and 64 years (OR: 1.26, 95% CI: 1.01 – 1.58 in model 3) and 65 years or older (OR: 1.96, 95% CI: 1.14 – 3.38 in model 2; OR: 2.09, 95% CI: 1.13 – 3.86 in model 3) were more likely to be abstinent than those who were aged

between 18 and 39 years old. Morbid obese smokers who were from the Northeast (OR: 1.51, 95% CI: 1.14 – 1.99 in model 2), Southern (OR: 1.37, 95% CI: 1.01 – 1.85 in model 1; OR: 1.38, 95% CI: 1.07 – 1.79 in model 2), and Western United States (OR: 1.59, 95% CI: 1.15 – 2.20 in model 1; OR: 1.63, 95% CI: 1.23 – 2.15 in model 2) were more likely to be abstinent than those who were from the Midwest. Morbid obese smokers who were diagnosed with alcohol dependence were less likely to be abstinent than those who did not (OR: 0.51, 95% CI: 0.45 – 0.70 in model 1; OR: 0.68, 95% CI: 0.56 – 0.82 in model 2). Morbid obese smokers who were prescribed weight influencing medications which may cause weight reduction (OR: 1.77, 95% CI: 1.32 – 2.36 in model 1; OR: 1.47, 95% CI: 1.14 – 1.90 in model 2; OR: 1.63, 95% CI: 1.23 – 2.15 in model 3) and weight gain (OR: 1.30, 95% CI: 1.03 – 1.64 in model 2) respectively were more likely to be abstinent than those who did not. Morbid obese smokers who were offered smoking counseling were less likely to be abstinent than those who were not (OR: 0.46, 95% CI: 0.37 – 0.58 in model 1; OR: 0.51, 95% CI: 0.42 – 0.62 in model 2; OR: 0.56, 95% CI: 0.45 – 0.70 in model 3). Morbid obese smokers who were identified to smoke at least one cigarette per day were less likely to be abstinent than those who did not smoke cigarettes (OR: 0.79, 95% CI: 0.66 – 0.95 in model 2). In addition, each unit increase of BMI at baseline resulted in 2% more likelihood to be abstinent (OR: 1.03, 95% CI: 1.01 – 1.05 in model 1; OR: 1.03, 95% CI: 1.01 – 1.04 in model 2; OR: 1.03, 95% CI: 1.01 – 1.05 in model 3).

Analyses for Confounding

Among obese adult smokers, univariate analyses indicated that smoking cessation medication was a significant predictive factor of abstinence at 3-month follow up (unadjusted OR: 1.20, 95% CI: 1.00 – 1.45 in model 1, unadjusted OR: 1.12, 95% CI: 0.96 – 1.31 in model 2, unadjusted OR: 1.08, 95% CI: 0.94 – 1.23 in model 3). However, it was not a significant factor of weight change

at each follow up (p = 0.29 in model 1, p = 0.05 in model 2, p = 0.15 in model 3). Moreover, weight change was not a significant predictor of abstinence, either (OR: 1.01, 95% CI: 1.00 – 1.01 in model 1, OR: 1.01, 95% CI: 1.01 – 1.02 in model 2, OR: 1.01, 95% CI: 1.01 – 1.02 in model 3). Therefore, weight change was not a confounder lying on the pathway between smoking cessation medication use and abstinence among obese adult smokers. The coefficients of smoking cessation medication use had a substantial change when weight change was added in the models compared to the ones without weight change (ORs: 0.77 vs. 1.06 in model 1, 1.02 vs. 1.04 in model 2, 0.73 vs. 0.96 in model3).

Among morbid obese smokers, univariate analyses indicated that smoking cessation medication was neither a significant predictive factor of abstinence at 3-month follow up (unadjusted OR: 1.28, 95% CI: 0.79 – 2.08 in model 1, unadjusted OR: 1.29, 95% CI: 0.79 – 1.96 in model 2, unadjusted OR: 1.23, 95% CI: 0.85 – 1.77 in model 3), nor a significant factor of weight change at each follow up (p = 0.06 in model 1, p = 0.45 in model 2, p = 0.65 in model 3). Moreover, weight change was not a significant predictor of abstinence, either (OR: 1.00, 95% CI: 1.00 – 1.01 in model 1,2, and 3). Therefore, weight change was not a confounder lying on the pathway between smoking cessation medication use and abstinence among morbid obese smokers. The coefficients of smoking cessation medication use had a substantial change when weight change was added in the models compared to the ones without weight change (ORs: 0.59 vs. 1.02 in model 1, 0.99 vs. 1.11 in model 2, 0.69 vs. 0.98 in model3).

DISCUSSION

An overall abstinence rate of between approximately 18% and 23% from 3-month to 12-month follow up following smoking cessation medication intervention was found among obese smokers

in this study. For obese smokers who were prescribed varenicline, abstinence rate increased from nearly 17% at 3-month follow up to nearly 23% at 12-month follow up, whereas for those who were prescribed bupropion, abstinence rates increased from nearly 21% at 3-month follow up to 25% at 12-month follow up. Our finding is consistent with the study conducted by Chatkin et al. (2004), which found an estimated continuous abstinence rate of 23.2% at 12-month follow up among a Brazilian cohort of non-obese smokers (Chatkin et al., 2004). As compared to the clinical trial conducted by Jorenby et al. (2006), the 12-month follow up abstinence rate of our study is similar for varenicline, while 10% more for bupropion (Jorenby et al., 2006). To be noted, however, study conducted by Jorenby et al. (2006) was a clinical study with small sample size, general population of obese and non-obese participants.

Most studies reported that varenicline had a higher abstinence rate as compared to bupropion. (Gonzales et al., 2006; Jorenby et al., 2006; Nides et al., 2006; Rankin and Jones, 2011; Xenakis, 2011; Casella, 2010), with an adjusted RR ranged between 1.3 and 2.3 at 1-year follow up (Cahill et al., 2012). However, this study found that obese smokers who were prescribed bupropion had a statistically significant higher abstinence rate than those who were prescribed varenicline at 3-month follow up, while there is no statistically significant difference at 6-month and 12-month follow up. Moreover, although not statistically significant, we found that morbid obese smokers who were prescribed bupropion had higher abstinence rate than those who were prescribed varenicline at each follow up. A possible explanation for this improved abstinence with bupropion could be related to less post-cessation weight gain for bupropion users compared to varenicline or placebo users (Parsons et al., 2009; Gadde and Xiong, 2007). Varenicline is not reported to decrease post-cessation weight gain, although a higher abstinence rate was reported by clinical trials conducted with participants of all weight levels (Nides et al., 2006; Jorenby et

al., 2006; Gonzales et al., 2006). Weight gain has been recognized as a distinguishing feature of nicotine withdrawal (Hughes et al., 1994). Weight gain is one of the major cited reasons for continuity of smoking and relapse after smoking cessation, especially among women (Klesges et al., 1989; Klesges and Shumaker, 1992). The risk of diabetes can also increase by early weight gain (Wannamethee and Shaper, 1999). Hence, post-cessation weight gain might be a considerable concern among obese smokers wanting to quit smoking without an increased risk of developing diabetes. As bupropion is reported to significantly attenuate post cessation weight gain, it might be a better choice among obese smokers and might affect the abstinence rate among such population. Our finding is consistent with the study conducted by Jiménez Ruiz et al. (2012), which found no statistically significant differences on continuous abstinence rate up to 6 months between COPD smokers who were prescribed varenicline and who were prescribed bupropion (Jiménez Ruiz et al., 2012). Our study results varied from the latest Cochrane meta-analyses, which have found that both varenicline and bupropion improved smoking cessation rate; the pooled relative risk for continuous abstinence at 12-month follow up for varenicline versus bupropion was 1.52 (95% CI: 1.22 – 1.88), analyzing from 3 clinical trials with a total of 1,622 participants (Cahill et al., 2012).This however was based on participants of all weight levels, while our study included only obese smokers expected to gain most weight gain following cessation (Lycett et al., 2011). In addition, the analyses for confounder among obese adult smokers and morbid obese smokers indicated that weight change had a substantial effect on smoking cessation medication use in predicting abstinence.

To be noted, the frequency distribution of varenicline (n = 6,730) vs. bupropion (n = 291) use at 12-month follow up showed that the majority of obese smokers were prescribed varenicline. This finding is consistent with the Cochrane systematic review based on clinical trials results, which

concluded that more people quit smoking with varenicline than with bupropion (Cahill et al., 2012). This finding is also consistent with the study conducted by Jiménez Ruiz et al. (2012), which had 190 consecutive smokers diagnosed with severe or very severe COPD who utilized varenicline, while 45 had bupropion (Jiménez Ruiz et al., 2012). One study conducted in England concluded that the use of varenicline for smoking cessation increased following the publication of the National Institute for Clinical Excellence (NICE) guidance, however, the increased use of varenicline did not appear to substitute for use of bupropion (Kotz et al., 2011). Although both varenicline and bupropion are approved as first line smoking cessation medications, varenicline is far more prescribed to smokers by physicians as compared to bupropion (Kotz et al., 2011); such utilization pattern and trend might be due to physician preferences and marketing. Those concerned about weight may be more motivated to use bupropion than other smoking cessation medications since bupropion has been shown to attenuate the weight gain following smoking cessation (Hays and Ebbert, 2003). Moreover, serious adverse effect may occur in patients who taking varenicline, such as nausea, headache, difficulty sleeping, and abnormal dreams. Hence, it was suggested that health benefits of quitting smoking should be weighed against risk of adverse events associated with the use of varenicline for smoking cessation (Rankin and Jones, 2011). The reasons for prescribing a certain smoking cessation medication vs. another should be further evaluated in future research.

In this study, we found that smoking cessation medication type was not found to be a significant predictor of abstinence from smoking at any of the follow up times. Both varenicline and bupropion were found effective in helping quitting smoking up to 1 year follow up (Cahill et al., 2012); however, the adjusted results showed in this study indicated that there is no statistically significant difference of using varenicline and bupropion for smoking cessation at different

follow up times. It is important to note that studies included in the previous systematic review were all clinical trials, and independent cohort observational studies in smokers with varying comorbidities are needed. In addition, the cohorts of all the selected studies included individuals with various weights; hence, different populations may result in different abstinence rates. Our study suggests an improved abstinence with bupropion among obese smokers and the significant advantage of varenicline disappeared when only obese smokers were examined. At the same time, we found the following demographic characteristics of the cohort were significant predictors of successful abstinence from smoking: age, race, region, payment type, and specialty group.

Our finding that age was a predictor of abstinence is consistent with the study conducted by Dale et al. (1997), which found that older age were more likely to be abstinent than smokers at younger age (Dale et al., 1997). Older aged smokers tend to be concerned more about their health than younger aged smokers (Yang et al., 2012), particularly among obese smokers, who might have more health problems due to cigarette smoking and obesity.

We found that both race and region were significant predictors of abstinence from smoking. Nonwhites were less likely to be abstinence than whites among obese smokers who were prescribed smoking cessation medications. Cokkinides et al. (2008) concluded that there were racial and ethnic disparities in receiving smoking-cessation interventions (Cokkindides et al., 2008). Our study shows that minorities receiving smoking cessation medications also showed lower abstinence. Both the geographic variation and racial disparity, affecting simultaneously the abstinence rate among obese smokers, highlight the importance of exploring and understanding the underlying causes of disparities within and across regions (McClure et al., 2011).

In terms of insurance status, only obese smokers who were self-payers had less likelihood of being abstinent than those who had commercial insurance for the 12 months outcome. This finding might be due to the fact that self-pay patients may not want to continue with the medication. Our finding is consistent with the study conducted by Bouvy et al. (2003), who found that having health insurance was associated with tobacco abstinence at 3 months follow up (Biazzo et al., 2010); also, private insurance status was associated with a higher successful abstinence rate (Bouvy et al., 2003).

Those who were offered specialty care were more likely to be abstinent than those who were offered a primary care for the 3 months outcome. Specialists may be more influential in convincing patients. This finding was similar with the study conducted by Brose et al., which found that specialist clinics settings were more successful in terms of effective smoking cessation intervention than primary care (Brose et al., 2011). Obese smokers who were diagnosed with hypertension were more likely to be abstinent than those who were not. This finding is reasonable as hypertension is related to cigarette smoking; therefore, stopping smoking maybe necessary to improve the health status of obese smokers. In addition, the higher the BMI of the obese smokers, the more they were likely to be abstinent from smoking. This is possibly related to the concern that the health condition tends to worsen with a higher BMI. However, none of the diseases like hypertension was found to be a significant risk factor of being abstinent among morbid obese smokers. As morbid obese smokers are at an even higher risk of comorbidity diagnosis like hypertension compared to those who were not morbid obese smokers, the benefit of quitting may be more difficult to envision in this group.

Obese smokers who were also alcohol dependent were less likely to be abstinent from smoking; consistent with previous reports showing that smoking cessation failure is highly correlated with

alcohol consumption (Cook et al., 2012). The co-occurrence of cigarette smoking and alcohol consumption has been well documented and was well known among the public (Dawson, 2000; Falk et al., 2006). Individuals who are smokers are more likely to be alcoholics at the same time than non-smokers; moreover, smokers tend to consume alcohol more frequently and heavily than nonsmokers (Dawson, 2000; Falk et al., 2006; Piasecki et al., 2011). On the other hand, more than 60% of alcohol dependents are also cigarette smokers (Falk et al., 2006), and approximately 80% of these alcohol dependents are heavy smokers (Dierker and Donny, 2008).

Obese smokers who were prescribed weight influencing medications which may cause weight reduction were more likely to be abstinent than those who did not. An obese smoker's health is expected to be of high concern to physicians, and patients are usually advised to stop smoking and lose weight. Weight-concerned smokers may prefer taking weight control drugs along with quitting smoking. By taking weight control drugs along with cessation, obese smokers might be able to have more control of post cessation weight gain, thus they might be more inclined to continue with cessation, as the increased weight might cause relapse after smoking cessation (Klesges et al., 1989; Klesges and Shumaker, 1992).

Obese smokers who were offered smoking counseling were less likely to be abstinent from smoking than those who were not. This result was not expected. A possible explanation could be that obese smokers who were offered smoking counseling were more addicted to nicotine. Although smoking counseling was offered, it is not easy to stop smoking by counseling only. Previous studies showed that smoking cessation interventions with both pharmacological and behavioral intervention are more effective than pharmacological or behavioral interventions only (Stead and Lancaster, 2012). However, our finding is not consistent with most of the studies which stated that smoking cessation is more likely to be successful when smoking counseling is

offered. Another plausible explanation is that discussing potential weight gain in counseling might have deterred patients from a successful cessation.

Obese smokers who smoked at least one cigarette per day were less likely to be abstinent from smoking compared to those who did not. As one of the factors associated with nicotine dependence, the group of obese smokers who smoked at least one cigarette per day were more likely to be smokers with high level nicotine dependence, thus had more difficulty stopping smoking. Our study was consistent with the finding from another study, which found that smokers who had smoking history were less likely to be abstinence in a long-term time period (Curry et al., 1989).

The major difference regarding predictors of abstinence among morbid obese smokers from obese smokers is that male morbid obese smokers were less likely to be abstinent than female morbid obese smokes at 3-, and 6-month follow up. Since morbid obese smokers are those who have BMI greater than 40 and have obesity-related health problems, it is possible that females are more concerned about their health-related risks than men because women often play the role of nurturer and care provider of the family (Siegrist, 2000).

Strengths and Limitations

There are certain limitations in this study. This observational cohort study limits us from drawing a causal relationship of identified predictors of successful abstinence at different follow up times. Other limitations in this study are mainly related to using EMR data. Data for smoking and obesity may not be completely recorded and the diagnosis codes in the EMR data may not match those in the administrative claims data. Some of the independent variables that have been found in previous studies and could be a predictor of the outcome measure are not available in GE

database, including: Fagerstrom Tolerance Questionnaire (FTQ) (Fagerstrom and Schneider, 1989), marital status, educational level, others smokers in the household, age that respondents started smoking, longest duration of previous abstinence, readiness to stop, physician visits, number of prior serious attempts, prior NRT use, prior use of hypnotism, and prior use of group therapy sessions; thus, it is one of the limitations in this study. In addition, selection bias, including self-selection bias by physicians' and patients' choices may exist. Furthermore, prescription data were identified by physician orders, which did not guarantee that the patients actually filled the prescription and persistence cannot be accounted for. Some confounders such as eating habits and education cannot be controlled for in the analysis as this information is lacking.

Although these foregoing deficiencies may belie the precision of the finding, the overall research perspective provided by the database, due to its sample size and representativeness of outpatient practice, and availability of BMI and smoking information, serves as an important strength. Our study has other strengths: the follow up times was from 3 months to 12 months. It was suggested that for longitudinal studies, 3-month follow up may be a reasonable time period to assess intermediate success of smoking cessation, while the optimal estimate of success smoking cessation rate is the 12-month continuous abstinence rate, for 12-month data are available for many interventions (Gilpin et al., 1997).

Future study

The study compared the effectiveness of the available prescription cessation medications among a high risk population of obese smokers. Future research should take the findings into

consideration to help obese smokers achieve successful cessation and provide an improvement to the future health of the American society.

Since personalized medicine and targeted therapy are more and more widely used in clinical practice, personalized smoking cessation is also currently under investigation in many perspectives (Rose et al., 2010). Individualizing smokers' cessation intervention should be a promising approach for better abstinent results.

CONCLUSIONS

An overall abstinence rate of 18-23% from 6- to 12-month follow up was found among obese smokers. Abstinence rates were higher among obese smokers who were taking bupropion vs. those who were taking varenicline at 3-, 6-, and 12-month follow up. While many studies reported better abstinence with varenicline compared to bupropion, we found no such difference among obese smokers after adjusting for other covariates. This might be related to the anti-obesity effects of bupropion. Predictors identified in this study included: age, race, region, payment type, specialty group, morbidities including hypertension, alcohol dependence, weight influencing medications which may cause weight reduction, smoking counseling, number of cigarettes smoked per day, and BMI value at baseline, whereas smoking cessation medications were not found to be a significant predictor of abstinence from smoking at any follow up time. Predictors identified in this study should be considered when designing smoking cessation interventions among the high risk population of obese smokers.

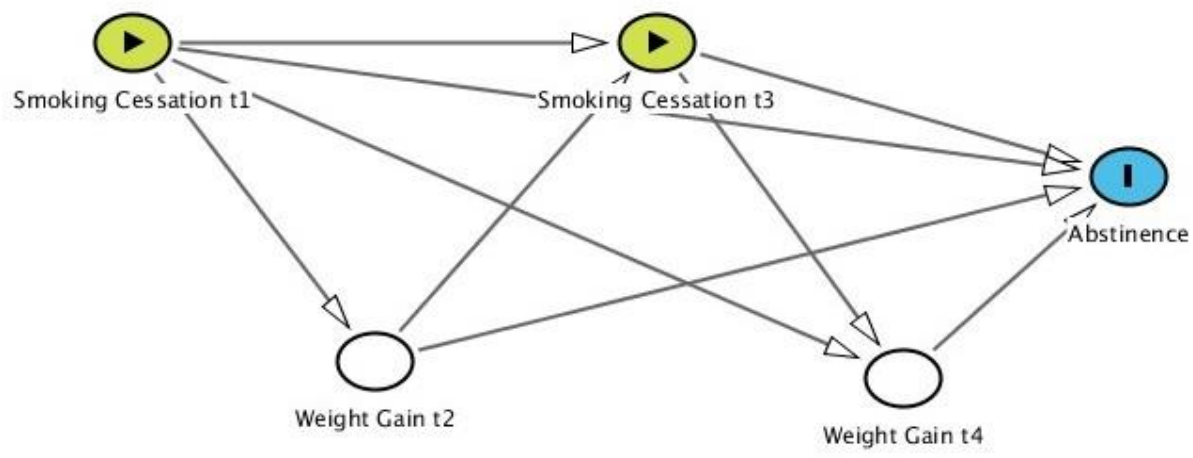

Figure 1

Directed Acyclic Graph (DAG) of Effect of Smoking Cessation and Weight Change on Abstinence

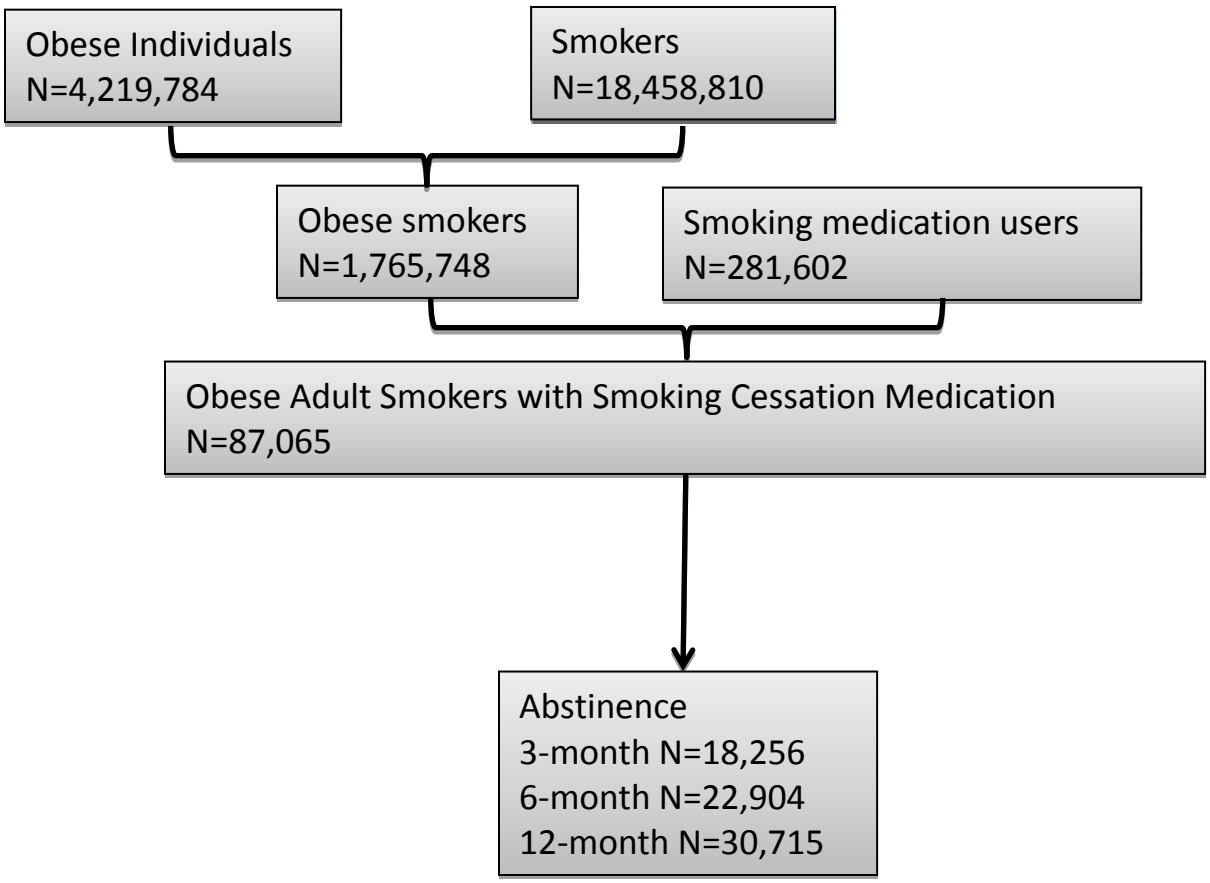

Figure 2

Schematic Diagram for Study Cohort

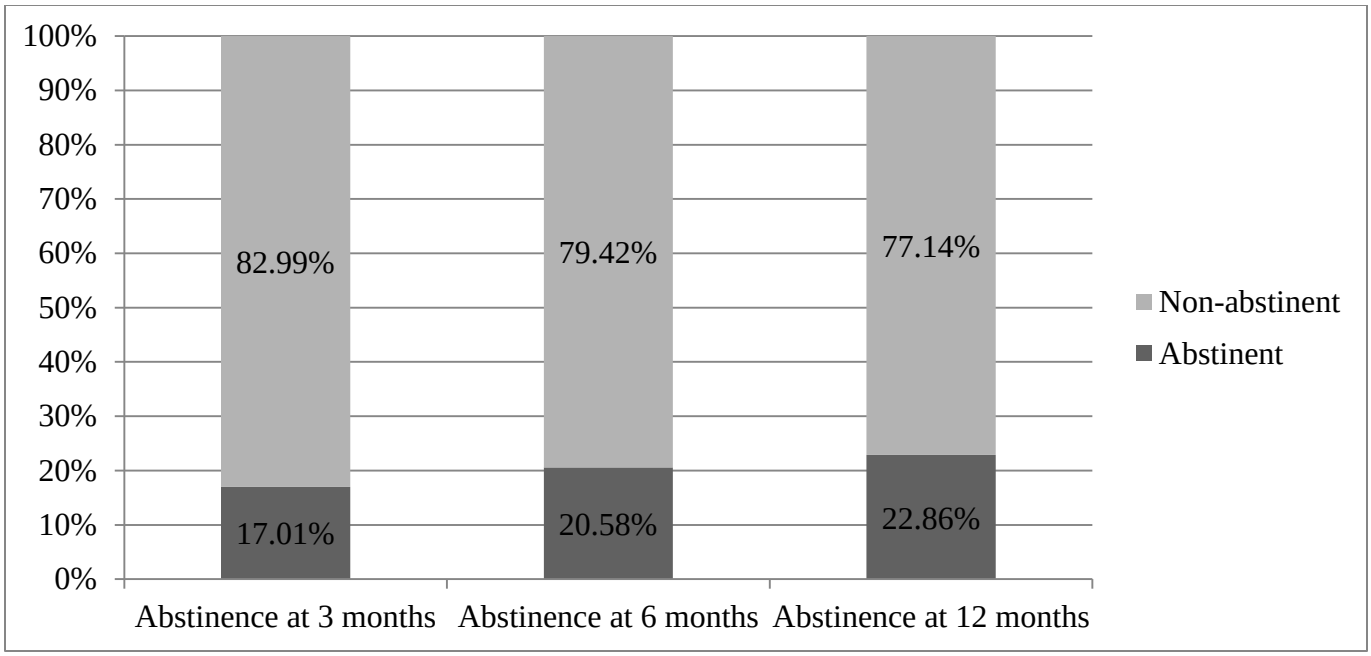

Figure 3

Abstinence Rate for Obese Adult Smokers Who Were Prescribed Any Smoking Cessation Medication At 3-, 6-, and 12-month Follow Up Time Period

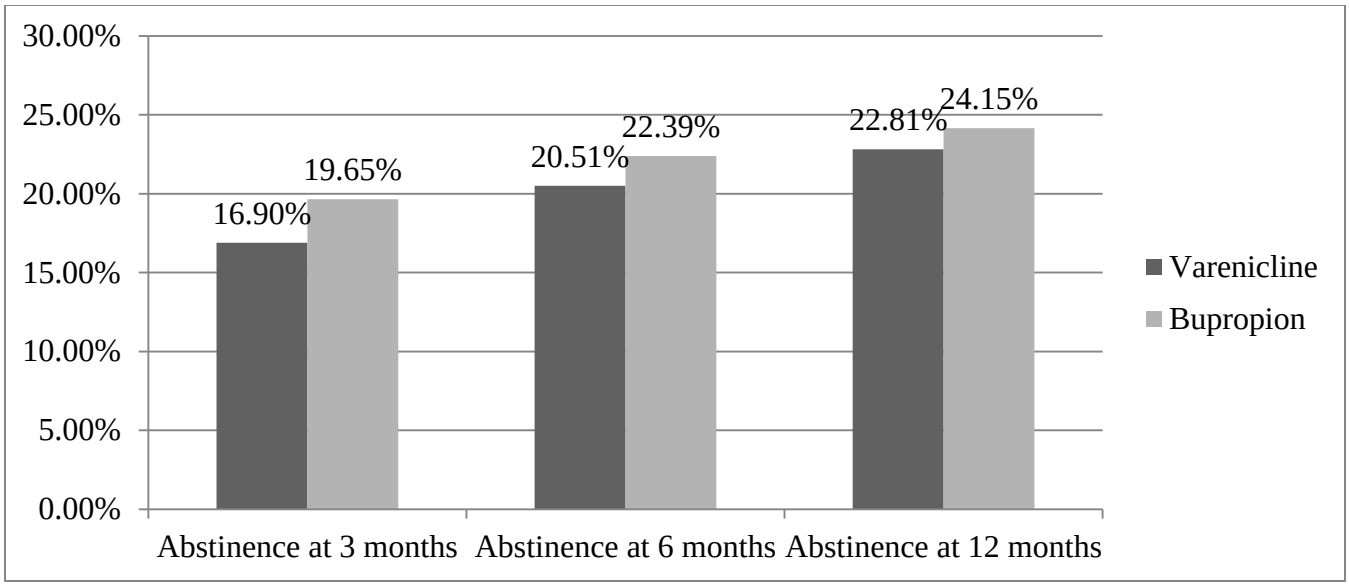

Figure 4

Abstinence Rate of Obese Adult Smokers Who Were Prescribed Varenicline vs. Bupropion At 3-, 6-, and 12-month Follow Up Time Period

Table 1

Baseline Characteristics for Abstinence among Obese Adult Smokers Who Were Prescribed Any Smoking Cessation Medication At 3-, 6-, and 12-month Follow Up Time Period

	Abstinence at 3 months (17.01%, n = 3,106)			Abstinence at 6 months (20.58%, n = 4,714)			Abstinence at 12 months (22.86%, n = 7,021)		
Variables	Varenicline (16.90%, n = 2,958)	Bupropion (19.65%, n = 148)	p-value	Varenicline (20.51%, n = 4,506)	Bupropion (22.39%, n = 208)	p-value	Varenicline (22.86%, n = 6,730)	Bupropion (24.15%, n = 291)	p-value
Age (±SD)	43.50 (11.96)	44.35 (12.88)	0.00**	43.93 (12.10)	44.56 (13.09)	0.00**	44.30 (12.17)	44.89 (13.19)	0.00***
Baseline BMI (±SD)	35.45 (5.41)	35.75 (5.55)	0.37	35.51 (5.48)	35.67 (5.48)	0.98	35.51 (5.52)	35.74 (5.57)	0.73
Weight change (±SD)	1.18 (16.75)	0.23 (25.90)	0.00***	2.14 (18.14)	0.22 (25.32)	0.00***	3.12 (20.89)	1.47 (17.50)	0.00***
Gender			0.00***			0.00***			0.00***
Female	49.67	59.76		50.63	59.10		51.90	59.17	
Male	50.33	40.24		49.37	40.90		48.10	40.83	
Age group			0.04*			0.02*			0.00**
18 – 39	39.16	37.72		37.92	37.57		36.82	36.27	
40 – 64	56.48	56.04		57.22	55.54		58.03	56.18	
≥65	4.35	6.24		4.86	6.89		5.14	7.55	
Race			0.98			0.95			0.62
White	39.92	39.97		40.90	40.80		42.30	41.58	
Non-White	60.08	60.03		59.10	59.20		57.70	58.42	
Region			0.03*			0.04*			0.00**
Midwest	26.38	27.79		25.91	27.69		25.97	29.40	
Northeast	21.51	16.89		22.35	18.32		23.00	18.27	
South	31.69	34.04		31.41	32.87		31.19	32.39	
West	20.41	21.28		20.33	21.12		19.85	19.93	
Payment type			0.40			0.35			0.01**
Commercial	71.54	68.60		70.03	66.95		69.21	63.59	
Medi-care/caid	21.86	23.48		23.40	25.73		24.33	27.66	
Self-paid	6.61	7.92		6.58	7.32		6.46	8.75	
Specialty group			0.25			0.03*			0.17

Primary Care	89.37	87.71		90.45	87.80		91.44	90.03	
Specialty care	10.63	12.29		9.55	12.20		8.56	9.97	
Hypertension			0.16			0.02*			0.10
No	87.16	85.39		87.04	84.50		87.27	85.64	
Yes	12.84	14.61		12.96	15.50		12.73	14.36	
Depression			0.09			0.11			0.05
No	93.81	92.30		93.58	92.25		93.44	92.03	
Yes	6.19	7.70		6.42	7.75		6.56	7.97	
Weight reduction drug			0.14			0.16			0.27
No	92.17	90.70		91.82	90.53		91.44	90.54	
Yes	7.83	9.30		8.18	9.47		8.56	9.46	
Alcohol dependence			0.16			0.11			0.04*
No	51.82	54.45		53.54	56.19		55.52	44.48	
Yes	48.18	45.55		46.46	43.81		58.51	41.49	
Smoking counseling			0.12			0.06			0.02*
No	52.89	55.78		54.00	57.16		55.68	59.00	
Yes	47.11	44.22		46.00	42.84		44.32	41.00	
# of cigarettes smoked per day			0.95			0.68			0.67
No	46.64	46.75		48.72	49.41		51.32	51.95	
Yes	53.36	53.25		51.28	50.59		48.68	48.05	
NRT			0.00***			0.00***			0.00***
No	98.20	92.03		97.48	90.96		96.51	89.05	
Yes	1.80	7.97		2.52	9.04		3.49	10.95	
Abstinence at follow up months			0.05*			0.16			0.28
No	83.10	80.35		79.49	77.61		77.19	75.85	
Yes	16.90	19.65		20.51	22.39		22.81	24.15	

*significance level α is less than 0.05; **significance level α is less than 0.01; *** significance level α is less than 0.001.
Abbreviations: SD – Standard Deviation; BMI – Body Mass Index; NRT = Nicotine Replacement Treatment.

Table 2

Logistic Regression Models for Abstinence among Obese Adult Smokers Who Were Prescribed Any Smoking Cessation Medication At 3-, 6-, and 12-month Follow Up Time Period

	Model 1: Abstinence at 3 months		Model 2: Abstinence at 6 months		Model 3: Abstinence at 12 months	
Variables	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Smoking cessation medication						
Varenicline	1		1		1	
Bupropion	**1.203 (1.001 – 1.446)**		1.118 (0.955 – 1.309)		1.078 (0.942 – 1.233)	
Age group						
18 – 39	**1**	1	1	1	1	1
40 – 64	**1.25 (1.15 – 1.36)**	1.03 (0.91 – 1.17)	**1.26 (1.18 – 1.35)**	**1.10 (1.01 – 1.20)**	**1.27 (1.20 – 1.34)**	**1.16 (1.05 – 1.28)**
≥65	**2.28 (1.93 – 2.69)**	**1.58 (1.21 – 2.06)**	**2.48 (2.17 – 2.84)**	**2.02 (1.70 – 2.39)**	**2.35 (2.11 – 2.63)**	**1.79 (1.46 – 2.20)**
Race						
White	1	1	1	1	1	**1**
Non-white	**0.87 (0.81 – 0. 94)**	**0.86 (0.76 – 0.96)**	**0.87 (0.81 – 0.92)**	**0.88 (0.81 – 0.95)**	**0.87 (0.83 – 0.92)**	**0.86 (0.78 – 0.94)**
Region						
Midwest	1	1	1	1	1	1
Northeast	1.10 (0.98 – 1.24)	**1.21 (1.01 – 1.45)**	**1.26 (1.15 – 1.39)**	**1.37 (1.22 – 1.54)**	**1.23 (1.14 – 1.33)**	**1.30 (1.15 – 1.48)**
South	1.07 (0.97 – 1.19)	1.07 (0.91 – 1.25)	**1.15 (1.05 – 1.26)**	**1.20 (1.07 – 1.33)**	**1.13 (1.05 – 1.21)**	1.11 (0.98 – 1.26)
West	**1.40 (1.25 – 1.56)**	**1.34 (1.12 – 1.60)**	**1.49 (1.35 – 1.63)**	**1.56 (1.39 – 1.75)**	**1.39 (1.28 – 1.50)**	**1.44 (1.24 – 1.66)**
Payment type						
Commercial	1		1		1	1
Medi-care/caid	**1.22 (1.07 – 1.39)**		**1.26 (1.13 – 1.39)**		**1.14 (1.05 – 1.24)**	0.97 (0.86 – 1.08)
Self-paid	0.80 (0.63 – 1.02)		**0.75 (0.62 – 0.92)**		**0.72 (0.61 – 0.85)**	**0.71 (0.58 – 0.86)**
Specialty group						
Primary Care	1	1	1		1	
Specialty care	**1.78 (1.55 – 2.04)**	**1.36 (1.15 – 1.61)**	**1.38 (1.22 – 1.56)**		**1.34 (1.20 – 1.50)**	
Hypertension						
No	1	1	1	1	1	
Yes	**1.14 (1.02 – 1.28)**	**1.25 (1.06 – 1.47)**	**1.12 (1.02 – 1.23)**	**1.14 (1.02 - 1.28)**	1.06 (0.98 – 1.15)	
Alcohol dependence						
No	1	1	1	1	1	1
Yes	**0.57 (0.53 – 0. 62)**	**0.64 (0.57 – 0.72)**	**0.65 (0.61 – 0.69)**	**0.68 (0.63 – 0.74)**	**0.72 (0.68 – 0.76)**	**0.77 (0.70 – 0.85)**
Weight-reduction drug						

No	1	1	1	1	1	1
Yes	**1.50 (1.32 – 1.71)**	**1.51 (1.25 – 1.83)**	**1.33 (1.20 – 1.49)**	**1.36 (1.20 – 1.55)**	**1.20 (1.10 – 1.32)**	**1.50 (1.30 – 1.73)**
Smoking counseling						
No	1	1	1	1	1	1
Yes	**0.43 (0.39 – 0.46)**	**0.50 (0.45 – 0.57)**	**0.48 (0.45 – 0.52)**	**0.52 (0.48 – 0.57)**	**0.55 (0.52 – 0.58)**	**0.59 (0.54 – 0.65)**
# of cigarettes smoked per day						
No	1	1	1	1	1	1
Yes	**0.68 (0.63 – 0.73)**	**0.83 (0.74 – 0.93)**	**0.70 (0.65 – 0.74)**	**0.81 (0.75 – 0.87)**	**0.74 (0.70 – 0.78)**	**0.89 (0.81 – 0.97)**
Base BMI value	**1.02 (1.01 – 1.02)**	**1.02 (1.01 – 1.03)**	**1.02 (1.01 – 1.02)**	**1.02 (1.01 – 1.02)**	**1.01 (1.00 – 1.02)**	**1.02 (1.01 – 1.02)**

Abbreviations: OR = Odds Ratio; 95% CI = 95% Confidence Interval; AMI = Acute Myocardial Infarction; BMI = Body Mass Index.

Table 3

Logistic Regression Models for Abstinence among Morbid Obese Adult Smokers Who Were Prescribed Any Smoking Cessation Medication At 3-, 6-, and 12-month Follow Up Time Period

	Model 1: Abstinence at 3 months		Model 2: Abstinence at 6 months		Model 3: Abstinence at 12 months	
	No confounder	With confounder	No confounder	With confounder	No confounder	With confounder
Variables	OR: (95% CI)	OR: (95% CI)	OR: (95% CI)	OR: (95% CI)	OR: (95% CI)	OR: (95% CI)
Gender						
Female	1	1	1			
Male	**0.69 (0.55 – 0.88)**	**0.69 (0.51 – 0.93)**	**0.78 (0.64 – 0.94)**			
Age group						
18 – 39			1		1	1
40 – 64			1.18 (0.97 – 1.43)		**1.26 (1.01 – 1.58)**	1.21 (0.82 – 1.78)
≥65			**1.96 (1.14 – 3.38)**		**2.09 (1.13 – 3.86)**	**4.11 (1.40 – 12.09)**
Region						
Midwest	1		1	1		
Northeast	1.20 (0.85 – 1.69)		**1.51 (1.14 – 1.99)**	**2.00 (1.37 – 2.91)**		
South	**1.37 (1.01 – 1.85)**		**1.38 (1.07 – 1.79)**	**1.65 (1.15 – 2.36)**		
West	**1.59 (1.15 – 2.20)**		**1.63 (1.23 – 2.15)**	**1.73 (1.17 – 2.56)**		
Payment type						
Commercial					1	
Medi-care/caid					1.16 (0.91 – 1.49)	
Self-paid					**0.61 (0.38 – 0.98)**	
Alcohol dependence						
No	1	1	1			
Yes	**0.51 (0.45 – 0.70)**	**0.72 (0.55 – 0.94)**	**0.68 (0.56 – 0.82)**			
Weight reduction drug						
No	1	1	1	1	1	
Yes	**1.77 (1.32 – 2.36)**	**1.66 (1.24 – 2.17)**	**1.47 (1.14 – 1.90)**	**1.56 (1.12 – 2.19)**	**1.63 (1.23 – 2.15)**	
Weight gain drug						
No			**1**			
Yes			**1.30 (1.03 – 1.64)**			
Smoking counseling						
No	1	1	1	1	1	
Yes	**0.46 (0.37 – 0.58)**	**0.66 (0.50 – 0.87)**	**0.51 (0.42 – 0.62)**	**0.59 (0.45 – 0.76)**	**0.56 (0.45 – 0.70)**	
# of cigarettes						

smoked per day				
No			1	
Yes			**0.79 (0.66 – 0.95)**	
Base BMI value	**1.03 (1.01 – 1.05)**	**1.02 (1.00 – 1.05)**	**1.03 (1.01 – 1.04)**	**1.03 (1.01 – 1.05)**

Abbreviations: OR = Odds Ratio; CI = Confidence Interval; AMI = Acute Myocardial Infarction; BMI = Body Mass Index.

MANUSCRIPT 2

Comparative Effectiveness of Smoking Cessation Medications to Attenuate Weight Gain Following Cessation

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Abstract

OBJECTIVE: The objective of this study was to compare the post-cessation weight gain following the use of one of the two Food and Drug Administration (FDA) approved smoking cessation medications during 3-, 6-, and 12-month follow up among obese smokers.

METHODS: A population-based retrospective cohort study was conducted using the General Electric (GE) electronic medical record database (2006 – 2011). The cohort consisted of obese adult smokers newly initiating use of an FDA-approved smoking cessation medication (bupropion vs. varenicline). The outcome variable was weight change at 3, 6, or 12 months following the first prescription. Descriptive analyses and t-tests were conducted to assess the frequency distribution of sample characteristics and their association with the post-cessation weight change. Multivariate linear regression models as well as general linear models (GLMs) were carried out to identify predictors of weight change at 3, 6, and 12 months after assessing the model assumptions, with the use of multiple imputation to account for missing data for covariates.

RESULTS: The mean weight change was 1.14 pounds (±17.26), 2.06 pounds (±18.46), and 3.06 pounds (±20.78) at 3-, 6-, and 12-month, respectively. Obese smokers who were prescribed varenicline had a mean weight gain of 1.18 pounds (±16.75), 2.14 pounds (±18.14), and 3.12 pounds (±20.89) for each follow up, while those who were prescribed bupropion had a mean weight gain of 0.23 pounds (±25.90), 0.22 pounds (±25.32), and 1.47 pounds (±17.50), respectively. Descriptive analysis showed that obese smokers taking bupropion had less weight gain than those taking varenicline at each follow up; however, this association was not statistically significant after accounting for all covariates. Significant predictors of weight change

included: being diagnosed with diabetes, hyperlipidemia, taking weight influencing medications, and smoked at least one cigarette per day.

CONCLUSIONS: There is an overall slight weight change of weight following smoking cessation at 3-, 6-, and 12-month follow up among obese adult smokers who were prescribed bupropion or varenicline. Bupropion can attenuate more weight gain at 3, 6, and 12 months following smoking cessation among obese smokers compared to varenicline. However, type of smoking cessation medication use (varenicline vs. bupropion) and NRT use were not identified as predictors of post-cessation weight change.

Key Words: Comparative effectiveness, Smoking cessation, Obesity, Weight Change, Varenicline, Bupropion

INTRODUCTION

Tobacco use remains the largest preventable cause of mortality and morbidity in the United States (US), with an estimated 443,000 deaths attributable to smoking, as well as considerable annual direct medical costs, and potential life years lost (Centers for Disease Control and Prevention, 2011; Atlanta (GA): Centers for Disease Control and Prevention, 2010). In the US, an estimated 19% of women and 23% of men are current smokers (Audrain-McGovern and Benowitz, 2011). Efforts to promote smoking cessation among smokers should be a routine preventive health care measure as tobacco-related disease is preventable (Corelli and Hudmon, 2002).

There are several challenges to quitting smoking, including withdrawal symptoms, relapse, and weight gain. Weight gain is considered one of the major reasons that can hinder smoking cessation success (Meyers et al., 1997). Borrelli and Mermelstein (1998) noted that weight gain was associated with subsequent relapse (Borreli and Mermelstein, 1998); Swan et al. (1993) found that "weight concerned" female smokers were more likely to relapse than any other group (Swan et al., 1993); Meyers et al. (1997) concluded a lower likelihood of quitting smoking among weight-concerned smokers than any other group (Meyers et al., 1997). Weight gain is one of the major cited reasons for continuity of smoking and relapse after smoking cessation, especially among women (Klesges et al., 1989; Klesges and Shumaker, 1992). In the US, the majority of smokers who quit smoking gain weight (Parsons et al., 2009). Only 25% of former smokers maintain a normal post-cessation weight (Lycett et al., 2011). Consequently, there is a pervasive concern among smokers that quitting smoking is in general accompanied with weight gain; this weight gain can lessen some of the health benefits of quitting smoking (Audrain-McGovern and Benowitz, 2011; Lycett et al., 2011).

Although most health care providers consider the benefits of the cessation to significantly outweigh the health risks associated with post-cessation weight gain (Audrain-McGovern and Benowitz, 2011), post-cessation weight gain may contribute to an increased risk of type 2 diabetes (Yeh et al., 2010), hypertension (Janzon et al., 2004), and may reduce the improvement of lung function (Chinn et al., 2005). Literature reports that the incidence of type 2 diabetes is increased by 50-100% in the first three years following cessation (Davey Smith et al., 2005; Yeh et al., 2010). Also, abstainers have a 30% increased risk of hypertension compared to those that continue smoking (Gerace et al., 1991). In addition, the improvement in lung function of quitters has been reported to decrease by 38% in men and 17% in women, as a consequence of smoking cessation-related weight gain (Chinn et al., 2005).

Weight gain occurs greatest in the first 1-2 months and mostly within the first 5 months, although it can continue to increase for 6 or more months after quitting (Audrain-McGovern and Benowitz, 2011). Smokers who are either underweight or overweight appear to gain more weight after quitting smoking than those who are normal weight (Lycett et al., 2011). Obese smokers gain most weight following quitting smoking, while those who continue smoking are likely to remain stable or lose weight (Lycett et al., 2011). Hence, obese quitters have the greatest need for interventions to ameliorate weight gain (Lycett et al., 2011). Considering that obese individuals already have an increased diabetes risk (Garber, 2011; Lycett et al., 2011), there is an increased concern of developing diabetes as a consequence of post smoking cessation weight gain among obese smokers attempting to quit. While literature reports that smokers who were prescribed bupropion had a lesser post cessation weight gain than those who were prescribed varenicline for short time period, it is not clear which smoking cessation strategy is more effective in terms of reducing weight gain following cessation among obese smokers. A

systematic review study shows that combination of smoking cessation medications (with at least one Food and Drug Administration (FDA) approved drug) had less post-cessation weight gain than individual drugs or placebo (Yang et al., 2012). However, no studies compared weight gain following varenicline versus bupropion for longer-term follow up. To better assess the effectiveness of each smoking cessation strategy, it is essential to understand which FDA approved smoking cessation strategy is more likely to attenuate weight gain among obese smokers. Therefore, the objective of this study was to compare the post-cessation weight gain following the use of one of the two FDA-approved smoking cessation medications during 3, 6-, and 12-month follow up among obese smokers. Knowledge gained from this study will provide additional information on the effectiveness and benefit of smoking cessation medications among obese adult smokers. That will help the policy-makers and clinicians optimize drug regimen to treat obese smokers.

METHODS

Study Design and Data Sources

This study was a population-based retrospective cohort study using General Electric (GE) healthcare clinical data. It is a real-world observational, daily-updated and nationally representative clinical data, rich in information of millions of patients in the ambulatory primary care setting in the US. It had approximately 20 million unique patients as of 2011. It has the results of lab tests (in both numeric and test form), vital signs such as height and weight, calculations such as body mass index (BMI), and other clinical findings associated with patient care like pain scores, smoking status that are not available in other databases.

The uniqueness and the features of the GE healthcare clinical data mentioned above make it the optimal clinical database to be used for conducting this study. GE clinical data set has been widely used in the literature to study obesity and smoking (McAdam-Marx et al., 2010; McAdam-Marx et al., 2011; Brixner et al., 2009; Horton et al., 2010; Pieber et al., 2010). For example, one of the studies was designed to assess effectiveness of different statins among diabetes mellitus patients with one of the covariates of smoking status (Fox et al., 2007).

The G-power 3.1.4 statistical software was used for sample size calculation with a 0.05 α-level, 80% power. A medium effect size for weight change of 0.15, with a normal distribution, two-tails F-test for multivariate linear regression model would need a number of 166 observations. Based upon the preliminary analysis, therefore, difference with a small to medium effect size (0.15) can be detected using GE database.

Measures

The index date was defined as the first day of being prescribed smoking cessation medication. Wash-out period was defined as not receiving any smoking cessation medication during the 6 months before the index date (Chatterjee et al., 2012). New users were defined as taking at least one smoking cessation medication between July 1st 2006 and December 31st 2011, while not taking any smoking cessation medication during wash-out period.

The outcome variable was weight change at 3-, 6-, and 12-month follow up times. *Weight change* was calculated using weight at follow up time subtracted weight at baseline. Weight at baseline was the weight measured on or after (most close to) the index date, while weight at each follow up time was the weight measured on or before (most close to) the follow up time.

The *BMI* is a simple index of weight-for-height that is commonly used to classify underweight, overweight and obesity in adults. It was defined as the weight in kilograms divided by the square of height in meters (kg/m^2) and was rounded to the nearest tenth. Obesity was classified according to BMI by the World Health Organization (WHO).

Smoking status was classified as *never smoked, formerly smoked, not currently smoking,* and *currently smoking*, which are dummy variables of *smoking status* in GE healthcare clinical data. *Abstinence* was defined as being reported as 'not current' or 'former' smoker throughout the follow up period; being reported as 'current' smoker at any point of the follow up period was categorized as non-abstinence.

Study Population

Inclusion criteria

The study cohort was identified using the following inclusion criteria: 1) obese, 2) aged 18 years or older, 3) enrolled in the GE healthcare clinical data in the US between January 2006 and December 2011 (Bupropion was first approved by FDA as the non-nicotine medication for smoking cessation in 1997, while varenicline was first approved in 2006), and 4) received at least one smoking cessation medication (Bupropion HCL or Varenicline Tartrate).

Exclusion criteria

For the primary analyses during 3 years of follow-up, persons who met at least one of the following criteria were excluded: 1) missing data on smoking status at baseline and follow up, 2) receiving any of the smoking cessation medication under study during the 6 months of pre-index period, and 3) missing data on weight measure at baseline and follow up.

Statistical Analyses

The cohort consisted of obese smokers newly initiating use of at least one of the FDA-approved smoking cessation medications (bupropion vs. varenicline). The outcome measure – weight change – was followed up by three different timelines: 3-month (end of active treatment effect), 6-month (sustained effect, short term), and 12-month (sustained effect, long term) after the index date. The reason for taking these three different follow-up time period was that the smoking cessation medications are usually required for a 3-month treatment; thus, monitoring the weight change 3 months after the treatment can help understand weight change by the end of treatment. On the other hand, smoking cessation medication may also have a short-term and long-term effect on weight change. A 6-month and 12-month follow up time period are acceptable for assessing the short-term and long-term effect of smoking cessation medications on weight, respectively (Gilpin et al., 1997).

Mean values of weight at baseline, and changes in weight with standard deviation (SD) were assessed for each patient. The outcome measure was assessed as a continuous variable and accounted by covariates. Descriptive analyses were conducted to assess the frequency distribution of sample demographic characteristics at baseline. Student t-tests were conducted among obese smokers for continuous variables to assess the differences of mean values across the smoking cessation medication strategies. Three multivariate linear regression models as well as general linear models (GLMs) were carried out to assess the association between the outcome variable (mean value of weight change) and independent variables after testing for the linear regression assumptions and interaction assessment. The major independent variable was type of smoking cessation medication prescribed (bupropion and varenicline). Other patient characteristics identified as independent variables and potential confounders for the analysis

included the following: age (categorized as 18 – 40/41 – 64/≥65), sex (female/male), race (White/Non-white), region (Midwest/Northeast/South/West), payment type (commercial /government/self-paid), specialty group (primary care/specialty care), BMI at baseline, comorbidities (smoking attributed diseases including hypertension, hyperlipidemia, lung cancer, stroke, chronic obstructive pulmonary disease (COPD), and acute myocardial infarction (AMI)), Nicotine Replacement Treatment (NRT) use (using NRT between index date and follow up), weight counseling (no/ yes), smoking counseling (no/ yes), weight influencing medications (including medications which may cause weight reduction and weight gain, respectively), number of cigarettes smoked per day (no/yes), alcohol dependence (no/ yes), and alcohol consumption (no/ yes).

Linear regression assumption testing

The major assumptions regarding linear regression included: 1) the dependent variable must be continuous; 2) the data to be modeled meets the 'iid' (identically independently distributed) criterion. That means that the error terms, ε, are independent from one another, and identically distributed; 3) the error term is normally distributed with a mean of zero and a standard deviation of ε^2, N (0, ε^2). The assumptions including linearity, multicollinearity, auto correlation, and the effects of outliers and model fit were tested. Linearity was checked by plotting the data to visually check the linear relationship. Multicollinearity was tested by checking the variance inflation factor (VIF) statistic, with a cut off of less than 10 was considered as no multicollinearity. Auto-correlation was checked by the Durbin-Waston statistic, with a value of 2.0 indicates that the data are independent. The effects of outliers were checked by Cook's D, with a Cook's D greater than the absolute value of 2 were investigated. The model fit was tested

by the Lack of Fit test, with a p-value of greater than 0.05 indicating that the model is a good fit and no additional terms are needed.

Missing values

Considering that missing value might have an impact on the model's fit, missing value analyses by using multiple imputation method were performed after assuming that these values were missing at random (Sterne et al., 2009). Unlike single imputation procedure, which each missing value was replaced by a single value, multiple imputation procedure replaced each missing value with a set of plausible values, so that the uncertainty about the right value to impute can be accounted for (Little and Rubin, 2002). The multiple imputed data were considered as complete data and analyzed by using standard procedures. The results from each imputation were then combined. The imputed models were then compared with the multivariate logistic regression models which missing values were considered as incomplete cases and deleted from the analyses.

All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC) statistical package at a priori significance level of 0.05. GE healthcare clinical data has de-identified patient variables and the protocol was reviewed and approved by the relevant Committee for the Protection of Human Subjects at the University of Houston.

RESULTS

Assumption testing

All the VIF statistic had a value of less than 10, indicating that there was no multicollinearity. Durbin-Watson statistic was between 1.98 and 2.09 (close to 2), indicating that the data were independent and identically distributed. The outliers identified from Cook's D graph were decided to be kept in the model, because the top five highest values and lowest values were

approximately evenly distributed. Lack of Fit test showed a p-value of <0.01 in model 1, indicating that the first model was not a good fit and additional terms were needed, while a p-value of 0.68 in model 2 and 0.89 in model 3, indicating that these two models were good fit and no additional terms were needed. Test of First and Second Moment Specification had a p value of 0.99, indicating that the error terms were independent and identically distributed. However, the normality tests in each model had p values of less than 0.05, which failed to provide evidence that the errors were normally distributed. Therefore, multivariate linear regression models with non-parametric tests were carried out. However, the form of the outcome was not transformed, because it is easier and reasonable to interpret results as a regular form; also, the non-normality might be due to the outliers, which were not excluded from the models.

Baseline characteristic factors

The total sample consisted of 87,065 obese smokers utilizing varenicline or bupropion for smoking cessation between July 2006 and December 2011. **Figure 1** shows the schematic diagram for the cohort. **Table 1** summarizes the cohort social-demographic characteristics at baseline. The mean weight change was 1.14 pounds (±17.26), 2.06 pounds (±18.46), and 3.06 pounds (±20.78) at 3-, 6-, and 12-month, respectively. Obese smokers who were prescribed varenicline had a mean weight gain of 1.18 pounds (±16.75), 2.14 pounds (±18.14), and 3.12 pounds (±20.89) at each follow up, while those who were prescribed bupropion had a mean weight gain of 0.23 pounds (±25.90), 0.22 pounds (±25.32), and 1.47 pounds (±17.50) at 3-, 6-, and 12-month follow up. There were statistically significant differences of weight change for obese smokers who were prescribed varenicline vs. bupropion (p-value was less than <0.01 for each follow up). The mean age was approximately between 44 and 46 years, while the mean baseline weight was approximately between 214 pounds and 221 pounds. There were no

significant differences of age and baseline weight value between obese smokers who were prescribed varenicline vs. bupropion for different follow up.

Multivariate linear regression model

Interaction assessment showed that there was no interaction among the independent variables. Multivariate linear regression models (**Table 2**) show that being diagnosed with diabetes were also significantly negatively associated with weight change (β = -3.55, 95% CI: -6.11 – -0.99, $p < 0.01$ in model 1; β = -5.57, 95% CI: -8.53 – -2.61, $p < 0.01$ in model 2; β = -3.83, 95% CI: -7.40 – -0.26, $p < 0.05$ in model 3). Being diagnosed with hyperlipidemia (β = -2.97, 95% CI: -5.09 – -0.84, $p < 0.01$ in model 3), those who were prescribed weight influencing medications which may cause weight reduction (β = -2.78, 95% CI: -4.72 – -0.83, $p < 0.01$ in model 1) and weight gain (β = 2.14, 95% CI: 0.52 – 3.77, $p < 0.05$ in model 1), respectively, and those who smoked at least one cigarette per day (β = -1.41, 95% CI: -2.71 – -0.12, $p < 0.05$ in model 2) were found to be associated with weight change. However, type of smoking cessation medication being prescribed (varenicline vs. bupropion) and NRT use were not shown to be significant factors associated with weight change at each follow up time.

GLM

The GLM (**Table 3**) shows consistent results compared to multivariate linear regression models. The R-square in both multivariate linear regression models and in GLM procedure were around 0.20. Significant predictors of weight change at different follow ups included being diagnosed with hyperlipidemia, diabetes, and weight influencing medications which may cause weight reduction and weight gain, respectively.

Missing value

When multiple imputation procedure was carried out for handling missing values (**Table 4**), type of smoking cessation medication being prescribed (varenicline vs. bupropion) (β = -3.25, 95% CI: -5.67 – 0.83, p < 0.01 in model 2) and NRT use (β = 2.97, 95% CI: 0.39 – 5.55, p < 0.05 in model 1), being diagnosed with diabetes (β = -2.91, 95% CI: -5.08 - -0.74, p < 0.01 in model 2; β = -2.65, 95% CI: -5.15 - -0.15, p < 0.05 in model 3), COPD (β = 1.88, 95% CI: 0.13 – 3.62, p < 0.05 in model 1), alcohol dependence (β = 1.88, 95% CI: 0.13 – 3.62, p < 0.05 in model 2), depression (β = 2.51, 95% CI: 0.56 – 4.47, p < 0.05 in model 3) and stroke (β = 4.18, 95% CI: 0.01 – 8.36, p < 0.05 in model 1, β = 5.30, 95% CI: 0.32 – 10.28, P < 0.05 in model 3), had alcohol consumption (β = -8.79, 95% CI: -17.25 - -0.33, p < 0.05 in model 2), and smoked at least one cigarette per day (β = -1.29, 95% CI: -17.25 – -0.33, p < 0.01 in model 2) were found significant factors associated with post cessation weight gain.

DISCUSSION

The study showed a slight change of weight following smoking cessation at 3-, 6-, and 12-month follow up among obese adult smokers who were prescribed bupropion or varenicline (ranged from 1.14 pounds to 3.06 pounds). Obese smokers who were prescribed varenicline had a constant weight gain of 1.18 pounds to 3.12 pounds from 3-month to 12-month follow up, whereas those who were prescribed bupropion had a weight gain of 0.23 pounds to 1.47 pounds from 3-month to 12-month follow up. While there was no significant difference of weight at baseline, the weight change was statistically significant among obese smokers who were prescribed varenicline vs. bupropion.

Without any smoking cessation intervention, previous studies indicated that, on average, smokers gain 4-5 kilograms at 12 months after quitting smoking (Aubin et al., 2012). Smokers gain between 7 and 19 pounds within 8 years of their successful initial quitting, whereas those who continue to smoke gain an average of 4 to 5 pounds (Lycett et al., 2011; O'Hara et al., 1998). Williamson et al. (1991) reported that approximately 10% of smokers gained nearly 30 pounds in weight after quitting smoking (Williamson et al., 1991). The weight change assessed in this study is less than that reported from previous studies, this might be related to nicotine dependence level that we were unable to control for, as previous studies indicated that smokers with higher nicotine dependence tend to gain more weight after quitting (Chiolero et al., 2008; Killen et al., 1988); or that our cohort of obese smoker may be concerned more about their post-cessation weight gain than those individual smokers who have regular weight.

Bupropion is an antidepressant drug that has been used for the treatment of major depression since 1989 and was later approved to aid in smoking cessation. Although not approved by FDA for obesity treatment, bupropion was found to be associated with a small degree of weight loss in its depression trials. It was further found that bupropion can help attenuate weight gain following smoking cessation (Hurt et al., 1997; Jorenby et al., 1999; Hays et al., 2001). Bupropion was reported to limit post cessation weight gain at the end of treatment; however, such effect did not persist at 6-, or 12-month follow up (Farley et al., 2012). In addition, in previous literature, bupropion was also shown to reduce weight among overweight and obese individuals (Gadde et al., 2006; Anderson et al., 2002; Jain et al., 2002). Gadde et al. found that overweight and obese women who were prescribed bupropion showed significantly greater weight loss compared to those who were prescribed placebo in a preliminary short-term randomized controlled clinical trial (Gadde et al., 2006). Two other studies reported that bupropion is effective in reducing

weight among obese individuals with and without depressive symptoms, respectively (Anderson et al., 2002; Jain et al., 2002). Although there was evidence that varenicline also significantly reduced post cessation weight gain at end of treatment (Farley et al., 2012), several trials have demonstrated a lesser post cessation weight gain when using bupropion compared to varenicline or placebo (Parsons et al., 2009; Gadde and Xiong, 2007). At the end of treatment, participants taking bupropion were found to gain significantly less weight than those on varenicline (-0.51 pounds (-0.09 to -0.93) (Gonzales et al., 2006; Nides et al., 2006; Jorenby et al., 2006) and placebo (-1.11pounds (-1.47 to -076)) (Parsons et al., 2009). The weight gain was less with bupropion compared to placebo at 1-year (3.8 vs. 5.6pounds) and 2-year follow-up (4.1 vs. 5.4pounds) (Jorenby et al., 1999). All the above findings are consistent with our finding that obese smokers who were prescribed bupropion had less post cessation weight gain than those who were prescribed varenicline.

In our study, factors including being diagnosed with hyperlipidemia and diabetes, had weight influencing medications, and smoked at least one cigarette per day were found to be associated with post-cessation weight change; type of smoking cessation medication being prescribed and NRT use were not significant factors associated with weight change using multivariate linear regression analysis.

Obese smokers who were also diagnosed with hyperlipidemia，diabetes, had lesser weight gain. As patients diagnosed with the above diseases were probably advised to stop smoking and these patients were obese individuals, who are more sensitive about post cessation weight gain; they might have made a conscious effort control weight because they had initial concerns regarding weight gain. Combination interventions of pharmacological smoking cessation interventions

accompanied with weight management interventions should be helpful in stopping smoking and controlling for post-cessation weight gain, however, previous systematic review studies concluded that such effect was limited; nevertheless, personalized weight management support may be effective for stopping smoking and preventing post cessation weight gain (Yang et al., 2012; Farley et al., 2012; Spring et al., 2009).

We found that obese smokers who were prescribed weight influencing medications were more likely to have a weight change than those who did not. To be more specific, those who were prescribed weight influencing medications which may cause weight reduction were more likely to lose weight while those which may cause weight gain were more likely to gain weight. An obese smoker's health is expected to be of high concern to physicians, and patients are usually advised to stop smoking and lose weight. On the other hand, weight-concerned smokers prefer taking weight influencing medications along with quitting smoking. By taking weight control drugs along with cessation, obese smokers might be able to have more control of post cessation weight gain, thus they might be more inclined to continue with cessation, as the increased weight might cause relapse after smoking cessation (Klesges et al., 1989; Klesges and Shumaker, 1992).

Obese smokers who smoked at least one cigarette per day had a lesser change in weight than those who did not. As one of the indicators of nicotine dependence, obese smokers who smoked at least one cigarette per day are more likely to be smokers with high level nicotine dependence, and more prominent post-cessation weight gain is expected to among high-nicotine dependent individuals. There are many other indicators of nicotine dependence like how soon to smoke after waking up, and whether smoke or not when the smoker is very ill that were not available in the dataset and thus might have affected our results (Fagerstrom and Schneider, 1989). In addition, this association was found in 6-month follow up assessment only, not in 3- or 12-month

follow up assessment; therefore, further investigation regarding the association between nicotine dependence with all its indicators and post-cessation weight change is needed.

Obese smokers who were alcohol dependent gained more weight than those who were not, while those who were alcohol consumers gained less weight than those who were not. These findings seem contradictory. However, previous evidence also showed controversial results, including positive, negative, or no relationship, regarding the association between alcohol use/abuse and weight gain (Suter, 2005).

Multiple imputation procedure for exploring the effect of missing value on the outcome showed that type of smoking cessation medication being prescribed, NRT use, being diagnosed with depression, COPD, and stroke, alcohol dependence, and alcohol consumption were significant factors associated with post cessation weight change. The different findings in predicting post cessation weight change between multiple imputed model and baseline model may indicate that missing values could slightly have influenced our results and future research with more complete datasets is needed to confirm the findings of this study.

Strengths and Limitations

Some of the independent variables that have found in previous studies and could be a predictor of the outcome measure are not available in GE database, including: Fagerstrom Tolerance Questionnaire (FTQ) (Fagerstrom and Schneider, 1989), marital status, educational level, others smokers in the household, age started smoking, longest time previously abstinent, readiness to stop, physician visits, number of prior serious attempts, prior NRT use, prior use of hypnotism, and prior use of group therapy sessions; thus, we are unable to control for them in this study.

The limitations in this study are mainly related to using EMR data. Data for smoking and obesity may not be completely recorded and the diagnosis codes in the EMR data may not match those in the administrative claims data. Furthermore, prescription data was identified by physician orders, which does not guarantee that the patient actually filled the prescription. We were unable to control for persistence to smoking cessation medication but abstinence status was controlled for at each follow up. Some confounders such as eating habits, physical activity, and education cannot be controlled for in the analysis as this information is lacking or not feasible to use for analysis. Although these foregoing deficiencies may belie the precision of the finding, the overall research perspective provided by the database, due to its sample size and representativeness of outpatient practice, and availability of BMI and smoking information, serves as an important strength. In addition, multiple imputation procedure was carried to handle the missing values, which helped in exploring and expanding possible results had those values were not missing.

Future study

Smokers with different levels of nicotine dependence may have various results of weight change following smoking cessation. Therefore, future studies should examine the association between smokers with different nicotine dependence and weight change following smoking cessation. In addition, future studies should examine diabetes risk following smoking cessation among obese smokers since such cohort has a high risk of developing type 2 diabetes. It is unknown whether a specific smoking cessation medication strategy could decrease the risk of diabetes; or if weight change is a mediator of development of type 2 diabetes. The ultimate goal is to identify the ideal regimen for the high risk obese smoker population and improve the future health in the American society as a whole.

CONCLUSION

There is an overall slight weight change of weight following smoking cessation at 3-, 6-, and 12-month follow up among obese adult smokers who were prescribed bupropion or varenicline. Bupropion can attenuate more weight gain at 3, 6, and 12 months following smoking cessation among obese smokers compared to varenicline. However, type of smoking cessation medication use (varenicline vs. bupropion) and NRT use were not identified as predictors of post-cessation weight change.

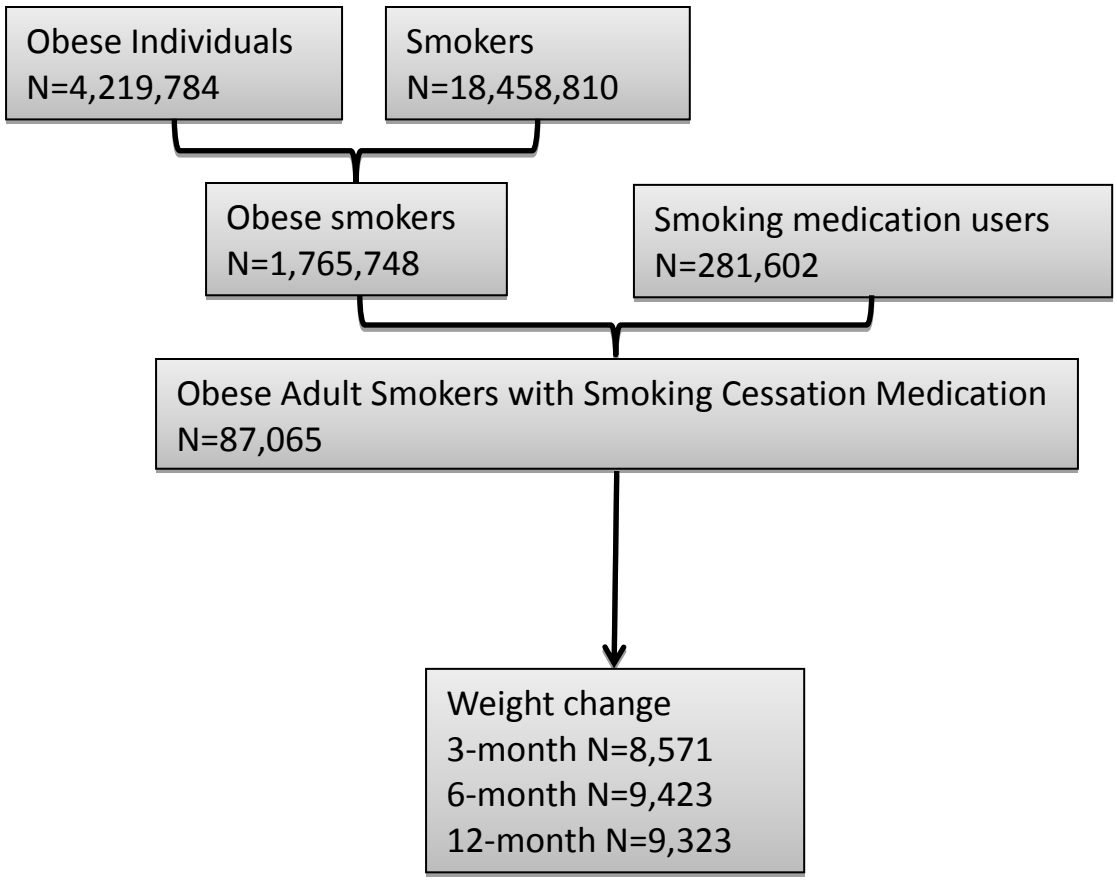

Figure 1

Schematic Diagram for the Cohort

Table 1.

Baseline Characteristics of Obese Smokers Who Used FDA-approved Smoking Cessation Medication and Weight Change at 3-, 6-, and 12-month Follow up Time Period

	Model 1: weight change at 3 months (1.14 ± 17.26)			Model 2: weight change at 6 months (2.06 ± 18.46)			Model 3: weight change at 12 months (3.06 ± 20.78)		
Variables	Varenicline (1.18 ± 16.75)	Bupropion (0.23 ± 25.90)	p-value .00***	Varenicline (2.14 ± 18.14)	Bupropion (0.22 ± 25.32)	p-value .00***	Varenicline (3.12 ± 20.89)	Bupropion (1.47 ± 17.50)	p-value .00***
Age (±SD)	43.96 (12.08)	44.70 (12.59)	0.25	45.14 (12.39)	45.14 (12.39)	0.14	45.65 (12.42)	45.57 (12.93)	0.28
Baseline weight (±SD)	220.4 (44.63)	218.7 (42.23)	0.62	216.9 (44.55)	215.8 (48.69)	0.82	213.9 (43.41)	215.5 (46.54)	0.06
Gender			0.01**			0.06			0.03*
Female	53.20	59.95		54.33	59.44		54.48	60.34	
Male	46.80	40..05		45.67	40.56		45.52	39.66	
Age group			0.87			0.74			0.58
18 – 39	37.43	36.13		34.28	36.11		32.67	32.76	
40 – 64	57.60	58.90		59.26	57.22		60.68	59.20	
≥65	4.97	4.97		6.45	6.67		6.65	8.05	
Race			0.47			0.46			0.05*
White	43.50	41.62		44.74	42.78		47.60	42.24	
Non-white	56.50	58.38		55.26	57.22		52.40	57.76	
Region			0.21			0.89			0.00**
Midwest	25.56	27.23		24.38	26.11		24.22	32.47	
Northeast	20.35	16.49		22.52	21.94		22.45	17.82	
South	32.33	35.60		33.23	33.06		34.31	33.33	
West	21.77	20.68		19.87	18.89		19.02	16.38	
Payment type			0.83			0.87			0.02
Commercial	67.40	65.45		65.13	64.58		66.69	59.14	
Medi-care/caid	25.26	27.23		28.52	28.13		27.83	31.18	

Self-paid	7.34	7.33		6.34	7.29		5.47	9.68	
Specialty group			0.35			0.08			0.04
Primary Care	91.40	89.66		93.30	90.42		93.40	96.68	
Specialty care	8.60	10.34		6.70	9.58		6.60	3.32	
Hypertension			0.62			0.09			0.87
No	84.44	83.51		85.19	81.94		85.95	85.63	
Yes	15.56	16.49		14.81	18.06		14.05	14.37	
Hyperlipidemia			0.84			0.99			0.91
No	86.81	87.17		86.09	86.11		86.27	86.49	
Yes	13.19	12.83		13.91	13.89		13.73	13.51	
Lung Cancer			0.75§			0.40			0.22
No	99.11	98.95		99.05	98.61		99.30	99.14	
Yes	0.89	1.05		0.95	1.39		0.70	0.86	
Stroke			0.85§			0.57§			0.10§
No	99.05	98.95		99.17	99.44		98.95	99.71	
Yes	0.95	1.05		0.83	0.56		1.05	0.29	
COPD			0.40			0.68			0.73
No	93.50	92.41		92.75	93.33		93.50	93.97	
Yes	6.50	7.59		7.25	6.67		6.50	6.03	
Diabetes			0.22			0.96			0.21
No	94.18	92.67		93.68	93.61		94.41	95.98	
Yes	5.82	7.33		6.32	6.39		5.59	4.02	
Depression			0.13			0.66			0.41
No	92.43	90.31		92.56	91.94		92.49	93.68	
Yes	7.57	9.69		7.44	8.06		7.51	6.32	
Weight reduction drugs			0.08			0.63*			0.76
No	90.66	87.96		90.74	90.00		90.91	91.38	
Yes	9.34	12.04		9.26	10.00		9.09	8.62	
Weight gain drugs			0.52			0.74			0.57
No	85.47	84.29		83.99	83.33		84.20	85.34	
Yes	14.53	15.71		16.01	16.67		15.80	14.66	
Alcohol Dependent			0.24			0.95			0.38
No	50.87	53.93		54.83	55.00		56.53	58.91	

Yes	49.13	46.07		45.17	45.00		43.47	41.09	
Smoking counseling			0.56			0.23			0.73
No	54.51	56.02		55.40	58.61		59.71	60.63	
Yes	45.49	43.98		44.60	41.39		40.29	39.37	
Weight counseling			0.82			0.07[§]			0.64[§]
No	98.28	98.43		98.83	99.72		99.54	99.71	
Yes	1.72	1.57		1.17	0.28		0.46	0.29	
# of cigarettes per day			0.97			0.11			0.43
No	47.27	47.38		52.07	56.39		57.05	59.20	
Yes	52.73	52.62		47.93	43.61		42.95	40.80	
Alcohol consumption			0.19[§]			0.25[§]			0.28[§]
No	99.15	98.95		99.26	99.44		99.40	99.43	
Yes	0.85	1.05		0.74	0.56		0.60	0.57	
NRT			.00***			.01***			.00***
No	97.53	91.88		96.34	91.11		95.26	87.07	
Yes	2.47	8.12		3.66	8.89		4.74	12.93	
Abstinence			0.15			0.82			0.99
No	76.37	79.58		72.50	73.06		70.16	70.11	
Yes	23.63	20.42		27.50	26.94		29.84	29.89	

[§]Fisher's Exact Test was used.

*significance level α is less than 0.05, **significance level α is less than 0.01, ***significance level α is less than 0.0001.

Abbreviations: SD – Standard Deviation; COPD - Chronic Obstructive Pulmonary Disease; NRT = Nicotine Replacement Treatment

Table 2.

Multivariate Linear Regression Models for Weight Change among Obese Adult Smokers Who Were Prescribed Any Smoking Cessation Medication at 3-, 6-, and 12-month Follow up Time

	Model 1: weight change at 3 months		Model 2: weight change at 6 months		Model 3: weight change at 12 months	
Variables	beta coefficient (95% CI)	p-value	beta coefficient (95% CI)	p-value	beta coefficient (95% CI)	p-value
Smoking cessation medication	-1.16 (-3.84 – 1.53)	0.40	-3.16 (-6.54 – 0.21)	0.07	-0.18 (-3.92 – 3.55)	0.92
NRT	0.77 (-2.54 – 4.08)	0.65	2.73 (-0.52 – 5.98)	0.10	-0.79 (-4.14 – 2.56)	0.64
Hyperlipidemia					-2.97 (-5.09 – -0.84)	0.01**
Diabetes	-3.55 (-6.11 – -0.99)	0.01**	-5.57 (-8.53 – -2.61)	0.00**	-3.83 (-7.40 – -0.26)	0.04*
Weight reduction drugs	-2.78 (-4.72 – -0.83)	0.00**				
Weight gain drugs	2.14 (0.52 – 3.77)	0.01*				
# of cigarettes smoked per day			-1.41 (-2.71 – -0.12)	0.03*		

Abbreviations: CI – Confidence Interval; NRT – Nicotine Replacement Therapy.
*significance α level is less than 0.05, **significance α level is less than 0.01, ***significance α level is less than 0.0001.

Table 3.

General Linear Model (GLM) for Weight Change at 3-, 6-, and 12-month Follow up Times

	Model 1: weight change at 3 months		Model 2: weight change at 6 months		Model 3: weight change at 12 months	
Variables	beta coefficient	p-value	Beta coefficient	p-value	Beta coefficient	p-value
Smoking cessation medication						
No	1		1		1	
Yes	-1.05 (1.37)	0.44	-3.10 (1.71)	0.07	.00 (1.90)	0.99
NRT						
No	1		1		1	
Yes	0.83 (1.69)	0.62	2.81 (1.65)	0.09	-0.64 (1.70)	0.71
Hyperlipidemia						
No					1	0.01**
Yes					-2.90 (1.08)	
Diabetes						
No	1	0.01*	1	0.00**	1	0.04*
Yes	-3.43 (1.30)		-5.35 (1.50)		-3.77 (1.81)	
Weight reduction drugs						
No	1					
Yes	-2.89 (0.99)	0.00**				
Weight gain drugs						
No	1					
Yes	2.09 (0.83)	0.01*				

Abbreviations: GLM NRT – Nicotine Replacement Therapy.

*significant α level is less than 0.05, **significant α level is less than 0.01, ***significant α level is less than 0.001.

Table 4.

Multivariate Linear Regression Models for Weight Change at 3-, 6-, and 12-month Follow up Times with Multiple Imputation for Missing Values

	Model 1: weight change at 3 months		Model 2: weight change at 6 months		Model 3: weight change at 12 months	
Variables	beta coefficient (95% CI)	p-value	beta coefficient (95% CI)	p-value	beta coefficient (95% CI)	p-value
Smoking cessation medication			-3.25 (-5.67 - -0.83)-	0.01**		
NRT	2.97 (0.39 – 5.55)	0.02*				
Depression					2.51 (0.56 – 4.47)	0.01*
Diabetes			-2.91 (-5.08 - -0.74)	0.01**	-2.65 (-5.15 - -0.15)	0.03*
COPD	1.88 (0.13 – 3.62)	0.03*				
Alcohol dependence			1.18 (0.23 – 2.13)	0.01*		
Stroke	4.18 (0.01 – 8.36)	0.04*			5.30 (0.32 – 10.28)	0.04*
Alcohol consumption			-8.79 (-17.25 - -0.33)	0.04*		
# of cigarettes smoked per day			-1.29 (-17.25 - -0.33)	0.01**		

Abbreviations: COPD - Chronic Obstructive Pulmonary Disease; CI – Confidence Interval; NRT – Nicotine Replacement Therapy
*significant α level is less than 0.05; **significant α level is less than 0.01; ***significant α level is less than 0.001.

MANUSCRIPT 3

Comparison of Diabetes Risk following Smoking Cessation Using Varenicline vs. Bupropion among Obese Smokers

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Abstract

OBJECTIVE: Recent literature suggests an initial increased risk of diabetes following smoking cessation. Our objective was to compare the risk of developing diabetes among obese smokers using bupropion vs. varenicline as well as other predictors during the first year post-cessation. **METHODS:** A population-based retrospective cohort study was conducted using the General Electric (GE) electronic medical record database (2006 – 2011). The cohort consisted of obese adult smokers without a diabetes diagnosis at baseline and newly initiating use of either bupropion or varenicline. This cohort was then followed for 1 year to observe the risk of developing diabetes. The relative risk of bupropion vs. varenicline on developing diabetes was assessed using Cox Proportional Hazards regression model after controlling for covariates. Main covariates included gender, race, age group, specialty group, payment type, hypertension, hyperlipidemia, weight influencing medications (including medications which may cause weight reduction and weight gain), weight counseling, baseline body mass index (BMI) value, and number of cigarettes smoked per day. Sensitivity analyses were conducted for follow up time from 2-year to 5-year follow ups. **RESULTS:** The sample comprised of 78,002 obese smokers of which 1,937 (2.36%) obese smokers developed diabetes during the 1 year follow-up. Diabetes incidence rate was relatively comparable among obese adult smokers who used varenicline and bupropion (23.50 vs. 25.80 per 1,000 person-years) for smoking cessation at 1 year follow up time. Obese smokers who were prescribed bupropion had a statistically significant higher risk of developing diabetes during 1 year following smoking cessation than those who were prescribed varenicline. (Hazard Ratio [HR]: 1.58, 95% Confidence Interval [CI]: 1.09 - 2.27) in the multivariate model. Main covariates that were found to be significant included: demographic factors (gender, race, age group, specialty group, payment type, number of cigarettes smoked per

day, baseline BMI value), morbidity (hypertension), and medication and health service use (weight influencing medications). Sensitivity analyses indicated that our model was robust from 3-year to 5-year follow up, but not robust for 2-year follow up. **CONCLUSIONS:** Obese smokers who were prescribed bupropion had a higher risk of developing diabetes during 1 year follow up assessment compared to those who were prescribed varenicline. Obese smokers who were prescribed bupropion had a higher risk of developing diabetes during 1 year follow up assessment than those who were prescribed varenicline. The clinical significance of the finding that bupropion had a higher risk of developing diabetes may need further investigation.

INTRODUCTION

Both cigarette smoking and obesity are the highest ranked preventable causes of morbidity and mortality with a significant economic burden in the United States (US) (Corelli and Hudmon, 2002, Mokdad et al., 2004). Both smoking and obesity are associated with an increased risk of type 2 diabetes (Ezzati et al., 2006; Kawakami et al. 1997; Nakanishi et al. 2000; Wannamethee et al. 2001; Willi et al. 2007); therefore, smoking cessation should help decrease the risk of diabetes among smokers. However, Yeh et al. (2010) reported that although cigarette smoking leads to higher risk of development of type 2 diabetes, quitting smoking may initially increase this risk (Yeh et al., 2010).

Smokers with chronic diseases stated a high motivation to stop smoking compared to those who are healthy. However, the rates of smoking among patients diagnosed with diabetes do not appear to reduce (Tonstad, 2009). Published literature shows evidence that there is an association of cigarette smoking with the development of type 2 diabetes (Tonstad, 2009; Will et al., 2001; Hur et al., 2007). Will et al. (2001) indicated that compared with non-smokers, smokers who take 2 packs of cigarettes a day or more at baseline had a significantly higher rate of developing diabetes, while smoking cessation equaled these rates after 5-10 years. A previous study found a significantly higher risk of developing diabetes among current male smokers (odds ratio (OR): 1.49, 95% confidence interval (CI): 1.13-1.96) compared to non-smokers (Beziaud et al., 2004). However, several studies have reported an increased risk of diabetes following smoking cessation. Hur et al., (2007) found that both continuing smokers and former smokers had a higher adjusted risk ratio (OR: 1.60, 95% CI: 1.29-1.97 for continuing smokers; OR: 1.22, 95% CI: 0.96-1.55 for former smokers) of developing diabetes compared to non-smokers over an 8-year period, while an equal adjusted risk ratio over a 20-year period. Wannamethee et al. (2001)

found that men who quit smoking in the first 5 years of follow-up had a significant mean weight gain and subsequently higher risk of developing diabetes (adjusted relative risk: 2.03, 95% CI: 1.22 – 3.37) than non-smokers. Yeh et al. (2010) found that in the first 3 years of follow-up, compared with non-smokers, the hazard ratios of diabetes among former smokers, new quitters (defined as smokers who stopped smoking at 3-year follow up), and continuing smokers were 1.22 (95% CI: 0.99 – 1.50), 1.73 (95% CI: 1.19 – 2.53), and 1.31 (95% CI: 1.04 – 1.65), respectively, which means smoking cessation leads to higher short-term risk. Therefore, quitting smoking leading to a high risk of developing diabetes is a concern for smokers, especially for obese smokers, who have the potential to gain most weight following quitting smoking (Lycett et al., 2011), and are at a higher risk of developing diabetes prior to quitting.

The US Public Health Service Clinical Practice Guidelines suggest that smoking cessation interventions should include at least one Food and Drug Administration (FDA-approved medication in combination with tobacco dependence counseling if feasible and not medically contraindicated, to increase the likelihood of smoking cessation success (Fiore, 2000). Several smoking cessation pharmacotherapies have been evaluated to be effective and are available for preventing post-cessation weight gain for smokers. First-line smoking cessation medications, which are approved by the FDA, include nicotine agonists (also known as nicotine replacement therapies (NRTs)), nicotine antagonists (sustained-release bupropion hydrochloride <amfebutamone>), and nicotine partial agonists (varenicline <Chantix>). NRTs include nicotine gum, nicotine transdermal patches, nicotine nasal spray, and nicotine inhaler. The use of approved smoking cessation medications doubled the likelihood of quitting smoking (Fiore, 2000). Moreover, previous evidence showed that there is a lesser post cessation weight gain when using bupropion compared to varenicline (Parsons et al., 2009; Gadde and Xiong, 2007,

Yang et al., 2012). At the end of treatment, participants taking bupropion were found to gain significantly less weight than those on varenicline (-0.51 pounds (-0.09 to -0.93) (Gonzales et al., 2006; Nides et al., 2006; Jorenby et al., 2006). Obese adult smokers who were prescribed bupropion significantly lessen post-cessation weight gain compared to those who were prescribed varenicline from 3-month to 12-month follow up (Yang et al., to be submitted). To date, no study has examined the risk of developing diabetes after cessation with different cessation medications among obese smokers. It is not clear if one smoking cessation strategy is more effective in reducing the risk of developing diabetes following cessation among obese smokers. Therefore, the objective of this study was to compare the risk of developing diabetes among obese smokers using bupropion vs. varenicline as well as other predictors during the first year post-cessation. Knowledge gained from this study will provide additional information on the effectiveness and benefit of smoking cessation medications among obese adult smokers. That will help the policy-makers and clinicians optimize drug regimen to treat obese smokers.

METHODS

Data Sources

This study was a population-based retrospective cohort study and used General Electric (GE) healthcare clinical data. GE healthcare clinical data is a real-world observational, daily-updated and nationally representative clinical data, rich in information of millions of patients in the ambulatory primary care setting in the US. It had approximately 20 million unique patients as of 2011. The data includes results of lab tests (in both numeric and test form), vital signs such as height and weight, calculations such as body mass index (BMI), and other clinical findings associated with patient care like pain scores, smoking status that are not available in other databases.

The uniqueness and the features of the GE healthcare clinical data mentioned above make it the optimal clinical database to be used for conducting this study. GE clinical data-set has been widely used in the literature to study obesity and smoking (McAdam-Marx et al., 2011; McAdam-Marx et al., 2010; Brixner et al., 2009; Horton et al., 2010; Pieber et al., 2010). For example, one of the studies was designed to assess effectiveness of different statins among diabetes mellitus patients with one of the covariates of smoking status (Fox et al., 2007).

Measures

The outcome variable was time to develop diabetes within a 1-year follow up time.

The *BMI* is a simple index of weight-for-height that is commonly used to classify underweight, overweight and obesity in adults. It was defined as the weight in kilograms divided by the square of height in meters (kg/m2) and was rounded to the nearest tenth. *Obesity* was classified according to BMI by the World Health Organization (WHO). Individuals whose BMI was greater than 30 were classified as obese, while those whose BMI was greater than 40 were classified as morbid obese (Seidell, 2007).

Smoking status was classified as *never smoked, formerly smoked, not currently smoking, and currently smoking*, which are dummy variables of smoking status in GE healthcare clinical data. *Never smoker* was defined as an individual who has not smoked 100 or more cigarettes during his/her lifetime; *former smoker* or *not current smoker* was defined as an individual who has smoked at least 100 cigarettes during his/her lifetime, but not currently smoke; *current smoker* was defined as an individual who has smoked at least 100 cigarettes during his/her lifetime and still regularly smokes every day or periodically.

Abstinence was defined as being reported as 'not current' or 'former' smoker throughout the follow up period; being reported as 'current' smoker at any point of the follow up period was categorized as non-abstinence.

Diagnosis of type 2 diabetes was identified by using International Classification of Diseases, 9th version, Clinical Modification (ICD-9-CM): '250'.

Study Population

Inclusion criteria

The study cohort was identified using the following inclusion criteria: 1) obese, 2) aged 18 years or older, 3) enrolled in the GE healthcare clinical data in the US between January 2006 and December 2011 (Bupropion was first approved by the Food and Drug Administration (FDA) as the non-nicotine medication for smoking cessation in 1997, while varenicline was first approved in 2006), and 4) received at least one smoking cessation medication (Bupropion HCL or Varenicline Tartrate).

The index date was defined as the first day of being prescribed smoking cessation medication. Wash-out period was defined as not receiving any smoking cessation medications 6 months before the index date (Chatterjee et al., 2012). New users were defined as taking at least one smoking cessation medication between July 1st 2006 and December 31 2011, while not taking any smoking cessation medication during wash-out period.

Exclusion criteria

For the primary analyses during 1 year of follow-up, persons who met at least one of the following criteria were excluded: 1) missing data on smoking status at baseline and follow up, 2)

2) being diagnosed with diabetes before index date, and 3) no follow-up or incomplete incident diabetes information.

Study Design

A population-based retrospective cohort study was conducted using the GE electronic medical record database between 2006 and 2011. The cohort consisted of obese adult smokers newly initiating use of at least one of the FDA-approved smoking cessation medications (bupropion vs. varenicline) without a diabetes diagnosis at baseline. The outcome variable was time to developing diabetes following first smoking cessation prescription with a 1-year follow up after the index date.

Statistical Analyses

Descriptive analyses were conducted on the study population to assess the frequency distribution of sample demographic characteristics, covariates such as clinical conditions, and medication use, and outcomes (development of diabetes). Chi-square test was conducted among obese smokers for categorical variables to assess the frequencies and associations of the development of diabetes and other covariates across smoking cessation medications (bupropion and varenicline).

Univariate survival analyses were conducted by using Kaplan-Meier survival curves for the unadjusted association of time to develop diabetes between dummy variables. Statistically significant differences were assessed by using log-rank test. Cox Proportional Hazards (PH) regression model was carried out to examine the diabetes risk adjusting for potential confounders. The major independent variable was type of smoking cessation medication prescribed (bupropion and varenicline). The following patient characteristics identified as independent variables and potential confounders for the analysis were included: age (categorized as 18–

40/41–64/≥65), sex (female/male), race (white/non-white), region (Midwest/Northeast/South/West), payment type (commercial/government/self-paid), specialty group (primary care/specialty care), BMI at baseline, comorbidities (smoking attributed diseases including hypertension, hyperlipidemia, lung cancer, stroke, chronic obstructive pulmonary disease (COPD), and acute myocardial infarction (AMI)), NRT use (using NRT between index date and follow up), weight counseling (no/yes), smoking counseling (no/yes), weight influencing medications (including medications which may cause weight reduction and weight gain, respectively), number of cigarettes smoked per day (no/yes), alcohol dependent (no/yes), and alcohol consumption (no/yes).

The primary independent variable of interest was checked for PH assumption by using Schoenfeld test. The independent variable was considered as a time-variant variable that confounded with time if the PH assumption was violated. Time-dependent variable was created as an interaction term to adjust for time variant variable. Hazard ratio (HR) and its 95% CI were used to present the results for Cox PH regression model. Sensitivity analyses were conducted for follow up time from 2-year to 5-year follow ups to check the model robustness.

To further compare the risk factors of being diagnosed with diabetes at 1 year follow up time from smoking among morbid obese smokers who were prescribed bupropion vs. varenicline, Cox PH regression models were carried out among morbid obese smokers.

Considering weight change and abstinence at 1 year follow up might be causal determinant variables of development of type 2 diabetes, and, smoking cessation medication use (varenicline or bupropion) might be a causal determinant variable of weight change and abstinence; in other words, weight change and abstinence are predictors hypothesized to lie on the causal pathway

between smoking cessation medication use and type 2 diabetes, and thus to confound the effects of smoking cessation medication on development of type 2 diabetes, analyses which controlled for weight change and abstinence were carried out to assess the direct effect of weight change and abstinence on smoking cessation medication and development of type 2 diabetes. Kaplan-Meier curves with log-rank tests were carried out to identify whether weight change or abstinence is a confounder, followed by Cox PH regression models to assess the percentage changes of coefficients of smoking cessation medications. A change of 10% or more in coefficients was considered as confounding effects. Figure 1 shows the directed acyclic graph (DAG) of which representing the effects of smoking cessation medication use and weight change/abstinence on development of type 2 diabetes.

All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC) statistical package at a priori significance level of 0.05. GE healthcare clinical data has de-identified patient variables and the protocol was reviewed and approved by the relevant Committee for the Protection of Human Subjects at the University of Houston.

RESULTS

Patients Baseline Characteristics

All individuals who were diagnosed with diabetes at baseline (N = 9,063) were excluded from the sample for this analysis. Thus, the study sample was comprised of 78,002 obese adult smokers who were prescribed varenicline or bupropion without being diagnosed with diabetes at baseline. Figure 2 shows the schematic diagram for the cohort selection. A final 1,937 (2.36%) individuals were diagnosed with diabetes within the 1 year follow up time. The smoking cessation medication adjusted diabetes incidence rates were 23.50 and 25.80 per 1,000 person-

years for varenicline vs. bupropion users. Age adjusted diabetes incidence rates were 10.70, 29.50, and 39.10 per 1,000 person-years for aged between 18 and 39, between 40 and 64, and aged 65 years and older, respectively. The diabetes incidence rate was 10.70 and 29.50 per 1,000 person-years for new quitters and continuing smokers, respectively. The mean months of developing diabetes for study participants who were prescribed varenicline were 5.52 months (n = 5,473), with a median value of 5.39 months, while the mean months of developing diabetes for study participants who were prescribed bupropion were 5.04 months (n = 176), with a median value of 4.87 months. The *t*-test showed that there was no statistically significant difference of mean months of developing diabetes ($p = 0.84$). Obese smokers who were diagnosed with diabetes (BMI value at baseline: 25.26 (±18.22)) during the 1-year follow up period had significantly higher BMI at baseline than those who were not (BMI value at baseline: 22.12 (±17.54), $p<0.05$); There also was no statistically significant difference of BMI value at baseline between varenicline (Mean: 22.15 ± SD: 17.56) and bupropion (Mean: 23.50 ± 17.45) users ($p = 0.65$). The frequency distribution of patients' baseline characteristics are presented in **Table 1**.

Kaplan Meier Curve

Kaplan Meier curves of time to developing diabetes stratified by smoking cessation medications and age categories are presented in **Figure 3** and **Figure 4**, respectively. Log-rank test stratified by smoking cessation medication ($p<0.05$), and age category ($p<0.01$) indicated that there were statistically significant differences of time to developing diabetes between type of smoking cessation medication use and among age categories.

Cox PH Regression Model

Type of smoking cessation medication use was not detected as a time varying variable by Schoenfeld test ($p = 0.43$); however, weight change as a categorical variable (categorized as positive weight change and negative weight change) was detected as a time varying variable ($p<0.01$). The final Cox PH regression model showed obese smokers who were prescribed bupropion were more likely to develop diabetes than those who were prescribed varenicline at 1-year follow up (HR: 1.58, 95% CI: 1.09 – 2.27). The adjusted predictors of risks of developing diabetes during 1 year follow up time among obese smokes using Cox PH regression model is shown in Table 2.

The risk of developing diabetes among male patients was 31% higher than females (HR: 1.31, 95% CI: 1.14 – 1.51). Non-white patients were 16% less likely to develop diabetes than white (HR: 0.84, 95% CI: 0.73 – 0.98). Patients aged between 40 and 65 (HR: 2.03, 95% CI: 1.65 – 2.50) and aged above 65 (HR: 2.24, 95% CI: 1.66 – 3.02) were more likely to develop diabetes than those aged between 18 and 39. Patients who went for specialty care were less likely to develop diabetes than those who went for primary care (HR: 0.64, 95% CI: 0.46 – 0.89). Patients who had Medicare/Medicaid were more likely to develop diabetes than those who had commercial insurance (HR: 1.38, 95% CI: 1.17 – 1.62). Patients who were diagnosed with hypertension (HR: 1.59, 95% CI: 1.31 – 1.93) were more likely to develop diabetes than those who were not. Patients who were prescribed weight influencing medications (HR: 1.90, 95% CI: 1.56 – 2.33 for weight reduction; HR: 1.37, 95% CI: 1.15 – 1.63 for weight gain) were more likely to develop diabetes than those who did not. The risk of developing diabetes among patients who smoked at least one cigarette per day were 16% less than those who did not (HR: 0.84, 95% CI: 0.72 – 0.98). The risk of developing diabetes increased 1% with the increase of each unit of BMI value

at baseline. Confounding analysis showed that abstinence was not a confounder. However, when weight change was considered as a confounder, there was no statistically significant difference of developing type 2 diabetes between bupropion vs. varenicline users (Table 3).

Sensitivity Analyses

Sensitivity analyses showed that bupropion had a higher risk of developing diabetes than varenicline from 3-year follow up (HR: 1.50, 95% CI: 1.14 – 1.96), 4-year follow up (HR: 1.70, 95% CI: 1.30 – 2.22), and 5-year follow up (HR: 1.59, 95% CI: 1.23 – 2.07). However, this significant finding was not sustained when the follow up time was 2-year (HR: 1.28, 95% CI: 0.95 – 1.72).

Morbid Obese Smokers

By excluding a number of 1,374 morbid obese individuals who were diagnosed with diabetes at baseline, the sample comprises of 6,674 morbid obese adult smokers who were prescribed varenicline or bupropion without being diagnosed with diabetes at baseline. A total number of 256 (3.87%) morbid obese individuals were diagnosed with diabetes within the 1 year follow up period. The smoking cessation medication adjusted diabetes incidence rates were 39.20 and 24.00 per 1,000 person-years for varenicline vs. bupropion users. Age adjusted diabetes incidence rates were 19.20, 51.70, and 57.80 per 1,000 person-years for aged between 18 and 39, between 40 and 64, and aged 65 years and older, respectively. The diabetes incidence rate was 34.00 and 58.00 per 1,000 person-years for new quitters and continuing smokers, respectively. The mean months of developing diabetes for the individuals who were prescribed varenicline were 5.32 (±3.50) months (n = 546), while the mean months of developing diabetes in individuals who were prescribed bupropion were 5.10 (±2.95) months (n = 19). The *t*-test

showed that there were no statistically significant differences of mean months of developing diabetes (p = 0.40), nor BMI value at baseline (p=0.93) among morbid obese smokers.

Kaplan Meier curves of time to developing diabetes stratified by type of smoking cessation medication use and age categories are presented in **Figure 5** and **Figure 6**, respectively. Log-rank test stratified by smoking cessation medication (p = 0.37) and age category (p = 0.03) indicated that there were no statistically significant differences of time to developing diabetes between type of smoking cessation medication use or among age categories.

The final Cox PH regression model showed that there was no statistically significant difference among morbid obese smokers who were prescribed varenicline vs. bupropion of developing diabetes within 1 year follow up (HR: 0.60, 95% CI: 0.08 – 4.41). Patients who were prescribed weight influencing medications were more likely to develop diabetes than those who did not (HR: 1.84, 95% CI: 1.11 – 3.04 for weight reduction medications). Patients who had alcohol consumption were more likely to develop diabetes than those who did not (HR: 1.81, 95% CI: 1.21 – 2.69).

DISCUSSION

Diabetes incidence rate was found to be 23.60 per 1,000 person-years among obese adult smokers who used varenicline and bupropion for smoking cessation at 1 year follow up. This finding is much higher than the finding from a 5-year longitudinal study, which found an incidence rate of 14.40 per 1,000 person-years during 5 years follow up (Rodbard et al., 2012). This finding is also higher than the finding from Yeh et al., which found that the unadjusted diabetes incidence rates among middle-aged adults were 10.1 (8.9 – 11.6), 13.2 (11.6 – 15.3), 17.8 (12.2 – 25.2), and 13.3 (10.9 – 15.7) for never-smokers, former smokers, new quitters, and

continuing smokers, respectively at 3-year follow-up (Yeh, et al., 2010). Unlike Yeh's study, which categorized smoking status as never-smokers, former smoker at baseline, new quitter (that the smoker was currently smoking at baseline but quitted smoking at follow up), and continuing smokers (that the smoker did not quit smoking at baseline nor follow up) among adults without diabetes at baseline, our study included only smokers who were obese and were prescribed varenicline or bupropion, thus the observed rates are not in comparison to nonsmokers. This explains differences in observed rates from Yeh et al. where our study documented a diabetes incidence rate of 23.50 and 25.80 per 1,000 person-years for new quitters and continuing smokers, and Yeh et al. found the incidence rate of 17.8 and 13.3 for new quitters (persons who smoked at baseline but quitted smoking in 3 years) and continuing smokers who were not abstinent (Yeh et al., 2010). This finding is slightly higher than the finding from Nakanishi et al. among a Japanese population, which found that diabetes incidence rate increased from 9.0 to 21.3 for current smokers with increased nicotine dependence levels for 5 years follow up (Nakanishi et al., 2000). Our finding is higher than that of study conducted by Hur et al., (2007) among a Korea population, which found the crude diabetes rate of 6.1 and 4.5 for continuing smokers and new quitters (quitting within the first 2 years of follow up) (Hur et al., 2007). These studies also compared the diabetes risk to nonsmokers/never smokers of all weight levels while our study included only obese smokers.

Our finding that age adjusted incidence rates were 10.70, 29.50, and 39.10 per 1,000 person-years for aged between 18 and 39, between 40 and 64, and aged 65 years and older is also higher than the study that conducted by Kawakami et al., (1997) among a Japanese population, which found that the crude diabetes incidence rate of 2.2 per 1,000 person-years, with age-adjusted incidence rates of 1.1, 2.5 and 3.6 per 1,000 person-years for the 18-34, 35-44, and 45-53 age

groups, respectively for an 8 years follow up (Kawakami et al., 1997). Overall, our finding of crude diabetes incidence rate of 23.60 per 1,000 person-years is slightly different from that of other studies, possibly due to different study sample population, and/or different period of follow up.

We also found that the crude diabetes incidence rate was 38.70 per 1,000 person-years among morbid obese adult smokers who used varenicline or bupropion for smoking cessation. This crude incidence rate was almost 50% more than the rate among obese smokers. This finding is not surprising given that obesity is a major risk factor for developing Type 2 diabetes, especially among individuals with morbid obesity. Being morbidly obese is known to considerably increase the risk for illness including diabetes (Chiu et al., 2013). Post cessation weight gain among such population at risk may result in even worse health conditions.

Predictors of risks of developing diabetes during 1 year follow up among obese smokers using Cox PH regression model found in this study included: type of smoking cessation medication use, gender, race, age group, specialty group, payment type, diagnosis with hypertension, using weight influencing medications (including medications that can cause weight reduction and weight gain, respectively), number of cigarettes smoked per day, and base BMI value. Among morbid obese smokers, factors including weight influencing medications (medications that can cause weight reduction) and alcohol consumption remained significant predictors of risk of developing diabetes during 1 year follow up assessment.

The association between smoking and developing of diabetes is well documented in the literature (Tonstad, 2009; Will et al., 2001; Hur et al., 2007). A higher diabetes risk after quitting smoking has also been reported compared to the risk in non-smokers. The risk of developing diabetes

peaked at 3 years after quitting and attenuated to 9 years follow up after quitting smoking (Yeh et al., 2010). In addition, continuing smokers were found to be more likely to develop diabetes than new quitters or ex-smokers, while heavy smokers (smokers who smoke 20 cigarettes or more per day) were more likely to develop diabetes than those who smoke less than 20 cigarettes per day (Kawakami et al., 1997; Nakanishi et al., 2000; Hur et al., 2007; Yeh et al., 2010). Bupropion has been reported to cause lesser post cessation weight gain compared to varenicline (Parsons et al., 2009; Gadde and Xiong, 2007, Yang et al., to be submitted). At the end of treatment, participants taking bupropion were found to gain significantly less weight than those on varenicline (-0.51 pounds (-0.09 to -0.93) (Parsons et al., 2009). Obese smokers who were prescribed varenicline had a mean weight gain of 1.18 pounds (±16.75), 2.14 pounds (±18.14), and 3.12 pounds (±20.89) at 3-, 6-, and 12-month follow up, while those who were prescribed bupropion had a mean weight gain of 0.23 pounds (±25.90), 0.22 pounds (±25.32), and 1.47 pounds (±17.50) at each follow up (p-value <0.01 at each follow up) (Yang et al., to be submitted). However, while there was no statistically significant difference of BMI value at baseline, we found that the risk of developing diabetes within a 1-year follow up period was higher among obese adult smokers taking bupropion compared to those taking varenicline. While post cessation weight change may affect diabetes risk (Yeh et al., 2010; Wannamethee et al., 2001), there seems to be other mechanisms that may cause increased diabetes risk following cessation as this study shows a higher risk of developing diabetes among bupropion users compared to varenicline users despite gaining less weight. It might be due to factors such as lack of physical activity, and diet (such as unbalanced energy intake). It was reported that the increase in energy intake and the decrease in the resulting metabolic rate may occur following smoking cessation (Moffatt and Owens, 1991; Stamford et al., 1986), which may affect the beneficial

effect of smoking cessation. It might also be due to insulin resistance caused by smoking cessation, although previously studies did not find such association between the increased level of insulin resistance and smoking cessation among former smokers comparing to current smokers (Rönnemaa et al., 1996; Daniel and Cargo, 2004; Pyorala et al., 1985). Another explanation could be related to the adverse effects of cigarettes smoking on β-cell function, which may result in pancreatic dysfunction (Daniel and Cargo, 2004; Oba et al., 2012). Future research is needed to investigate the causes of this increased risk. In addition, sensitivity analyses indicated that our model was robust from 3-year to 5-year follow up, but not robust for 2-year follow up; however, this might be due to the presence of unequal proportions of censored data. Given the close diabetes incidence rates, the large sample size, and results from sensitivity analysis which could possibly due to unequal proportion of censored data, the clinical significance of the finding that bupropion had a higher risk of developing diabetes may need further investigation.

Some demographic factors including gender, race, age group, specialty group, payment type, and baseline BMI value were found to be factors associated with risks of developing diabetes during 1 year follow up among obese smokers using Cox PH regression model. The findings of these demographic factors were also found to be significant in previous studies (Schmidt et al., 2005). Based on the results of the unadjusted Kaplan Meier curves and log-rank tests, it was found that there was statistically significant difference of risk of developing diabetes across different age groups among this cohort. It was also found that male obese smokers were more likely to develop diabetes than females during 1 year follow up following smoking cessation. These findings are not surprising. One recent study conducted by Holden et al. (2013) found that diagnosis of diabetes was associated with age categories and gender. The study reported that the

incidence of type 2 diabetes increased with different age categories; moreover, the incidence of diabetes was higher for males after the age of 40 while higher for females aged less than 40 (Holden et al., 2013). In addition, diabetes diagnosis was also associated with other factors such as BMI (Hillier and Pedula, 2001; Holden et al., 2013). Non-white patients were found to be less likely to have the risk of developing diabetes than white. This finding although is not consistent with quite a few published studies (Schmidt et al., 2005; Lipton et al., 1993; Brancati et al., 2000), which indicated that Africa American race (or black) is more likely to develop diabetes than white, our study categorized the race variable as white and non-white, which included black, Hispanic, Asian, Indian (American), and multiple races which might explain these differences in findings. In addition, patients who had specialty care were less likely to develop diabetes, possibly due to the specialty care offered by the specialists. Patients who had Medicare/Medicaid insurance were more likely to develop diabetes than those who had commercial insurance. Medicare/Medicaid patients tend to be older, sicker, or poorer compared to those who have commercial insurance based on the eligibility criteria, which could in turn influence the risk of developing diabetes during 1 year follow up.

Obese smokers who were diagnosed with hypertension were more likely to develop diabetes during 1 year follow up. Being diagnosed with hypertension is highly associated with being diagnosed with type 2 diabetes. These findings are consistent with the findings from previous literature (Hippisley-Cox et al., 2009).

We also found that the risk of developing diabetes among patients who were prescribed a drug that affects weight (which can cause weight reduction and weight gain) was more than those who did not. The risk of diabetes is greatly increased by weight gain (Wannamethee and Shaper, 1999). As each kilogram of weight gain over 10 years increases the risk by 4.5%, maintaining a

healthy body weight is critical for the prevention and treatment of type 2 diabetes (Eyre et al., 2004). Therefore, it might be beneficial for obese individuals, particularly obese smokers who are attempting to quit smoking, to take weight influencing medications to obtain optimal weight management intervention at the beginning of smoking cessation, when weight gain could be a big concern for all smokers. However, our finding regarding using weight influencing medications which may limit the weight gain increases the risk of developing diabetes are contrary to what we expected. A possible explanation of such finding could be that obese smokers who were prescribed weight influencing medications had worse health conditions to begin with, such as more severe obesity, heavier smokers; thus, they had higher risk of developing diabetes during the 1 year follow up. The risk of diabetes following cessation may have been induced by other mechanisms than weight gain only and these mechanisms should be identified and addressed in future studies.

Obese smokers who smoked at least one cigarette per day had a higher risk of developing diabetes compared to those who did not. A potential explanation could be related to nicotine dependence as the group of obese smokers who smoked at least one cigarette per day are more likely to be smokers with high level nicotine dependence, thus they might have a higher chance of developing diabetes. This finding is consistent with previous studies which found that smoking and developing of diabetes are highly associated (Tonstad, 2009; Will et al., 2001; Hur et al., 2007).

Strengths and Limitations

There are certain limitations in this study. This observational cohort study limits us from drawing a causal relationship of time to develop diabetes at 1-year follow up. Another major limitation of

this study was missing value issue. With missing values, it is difficult to generalize our results. However, GE data is rich in clinical information with proper smoking status and smoking cessation medications, it was considered an appropriate database for the research questions. Other limitations in this are mainly the broad-based issues related to using EMR data. Data for smoking and obesity may not be completely recorded and the diagnosis codes in the EMR data may not match those in the administrative claims data. Some of the independent variables found significant in previous studies and could be a predictor of the outcome measure are not available in GE database, including: Fagerstrom Tolerance Questionnaire (FTQ) (Fagerstrom and Schneider, 1989), marital status, educational level, others smokers in the household, age started smoking, longest time previously abstinent, readiness to stop, physician visits, number of prior serious attempts, prior NRT use, prior use of hypnotism, and prior use of group therapy sessions; thus, it is one of the limitations in this study. In addition, selection bias, including self-selection bias by physicians' and patients' choices may exist. Furthermore, prescription data were identified by physician orders, which do not guarantee that the patients actually filled the prescription. Persistence of smoking cessation medication use was not measured in our study; however, abstinence until follow up time was controlled for. Some confounders such as eating habits and education cannot be controlled for in the analysis as this information is lacking. Although these foregoing deficiencies may belie the precision of the finding, the overall research perspective provided by the database, due to its sample size and representativeness of outpatient practice, and availability of BMI and smoking information, serves as an important strength.

Future Study

It is unknown whether behavioral interventions including diet, physical activities would decrease the risk of diabetes among obese smokers attempting to quit; yet, if any, it is unknown which

strategy is more effective. For example, single diet intervention, physical activity intervention, pharmacological intervention, or (any) combination(s) of these interventions. Future studies should examine diabetes risks of pharmacological interventions and behavioral interventions following smoking cessation among obese smokers and investigate the potential mechanisms that lead to the increased diabetes risk. In addition, it was reported that Chantix was found to be effective in aiding patients diagnosed with cardiovascular disease (CVD) and COPD. However, it is unknown whether this fact can be consistent if retrospective data analysis with large sample size is applied. Future studies regarding the effectiveness of type of smoking cessation medication can be researched among patients with CVD and/or COPD. Further, it is also unknown whether personalized pharmacological and behavioral interventions would have positive effect in decreasing the risk of developing of diabetes. If any, what kind of guidelines and criteria can be offered to develop personalized pharmacological and behavioral interventions.

CONCLUSIONS

The crude diabetes incidence rate was found to be comparable among obese adult smokers who used varenicline and bupropion for smoking cessation at 1 year follow up. After controlling for potential confounders, obese smokers who were prescribed bupropion showed a higher risk of developing diabetes during 1 year follow up assessment than those who were prescribed varenicline. Given the close diabetes incidence rates, the large sample size, and results from sensitivity analysis which could possibly due to unequal censoring, the clinical significance of the finding that bupropion had a higher risk of developing diabetes may need further investigation. Healthcare professionals should always monitor potential risks associated with quitting especially among a high risk population of obese smokers and evaluate potential interventions that can decrease these risks including the potential benefits of smoking cessation

medication (i.e.: varenicline vs. bupropion) when deciding which pharmacological cessation intervention to use for the smokers among this high risk population.

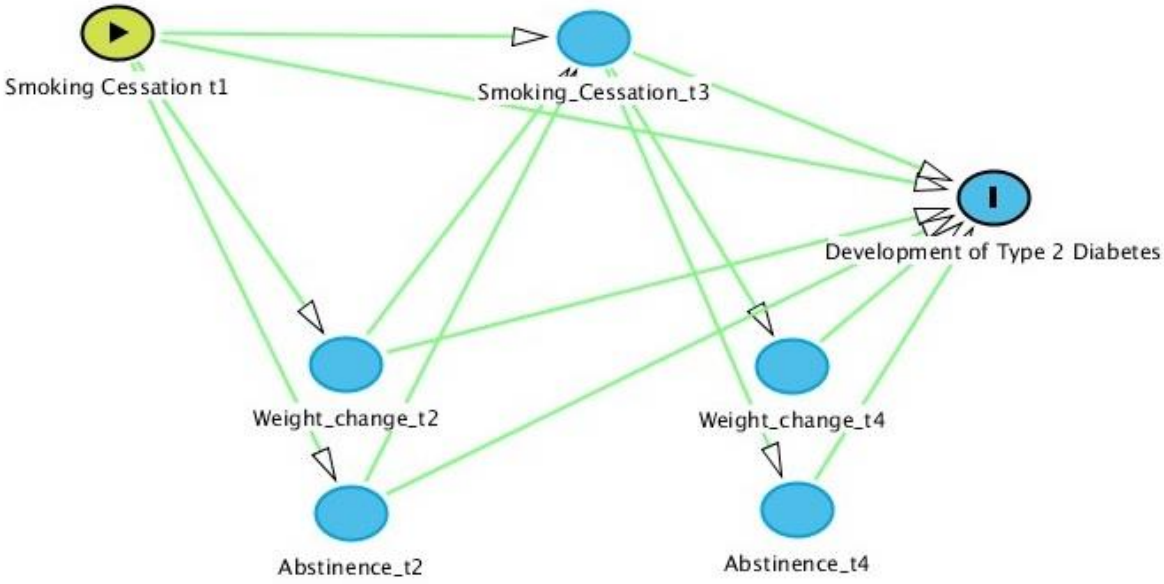

Figure 1

Directed Acyclic Graph (DAG) of Effect of Smoking Cessation, Weight Change, and Abstinence on Development of Type 2 Diabetes at 1 Year Follow up Time

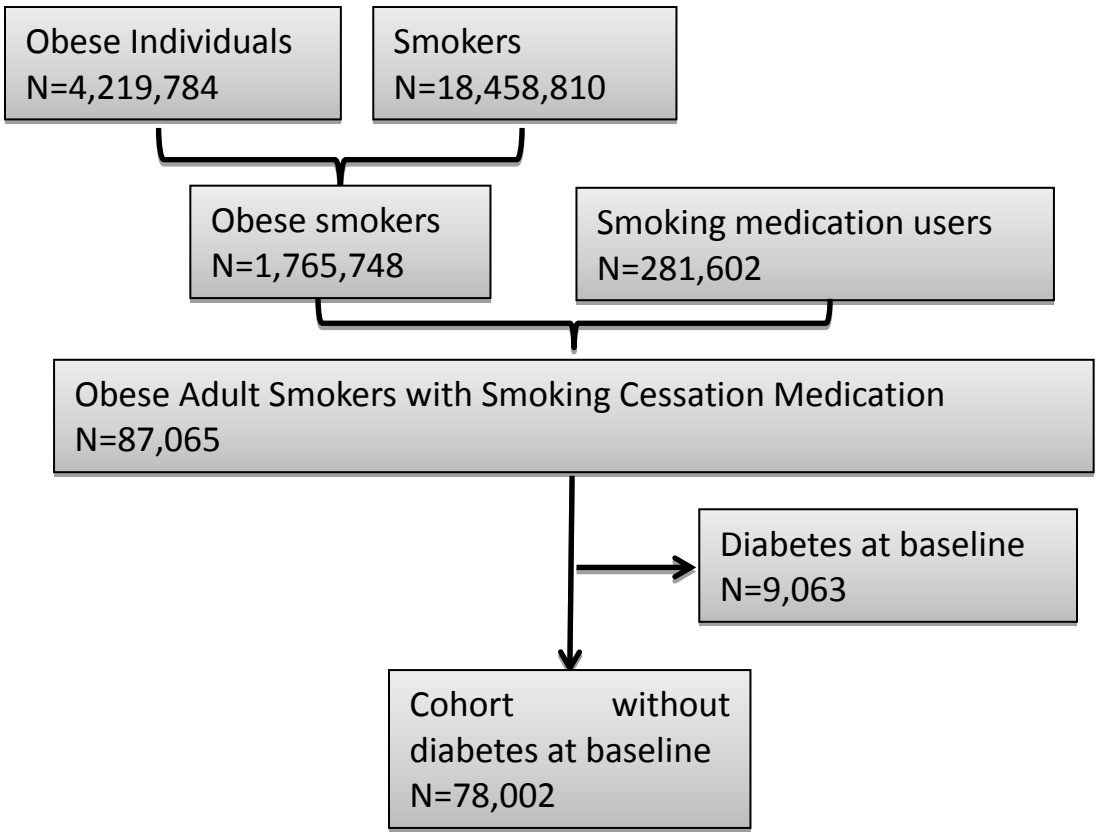

Figure 2

Schematic Diagram for Study Cohort

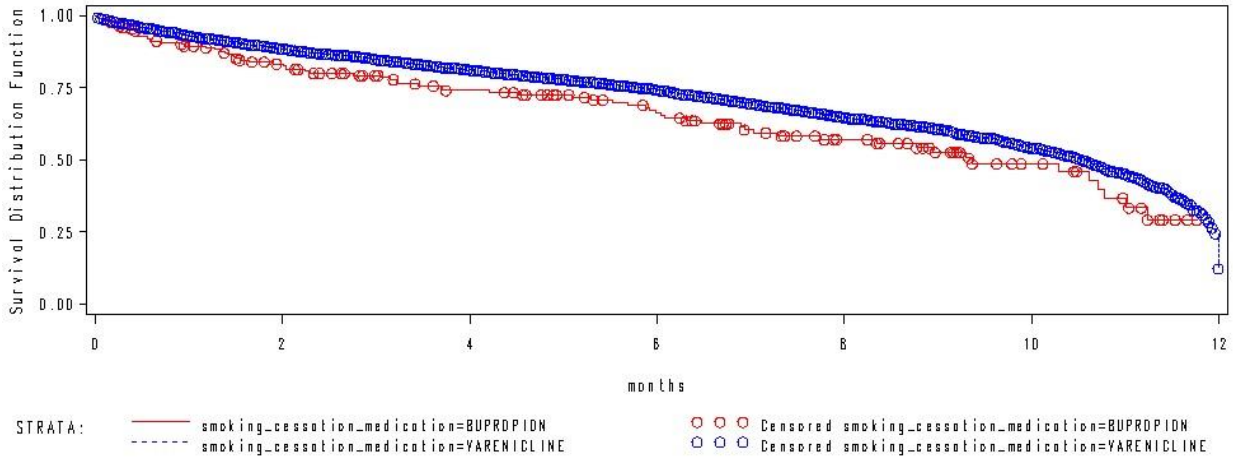

Figure 3.

Kaplan Meier Curves of Risks of Developing Diabetes during 1 Year Follow Up Stratified by Type of Smoking Cessation Medication Use among Obese Smokers Prescribed a Smoking Cessation Medication

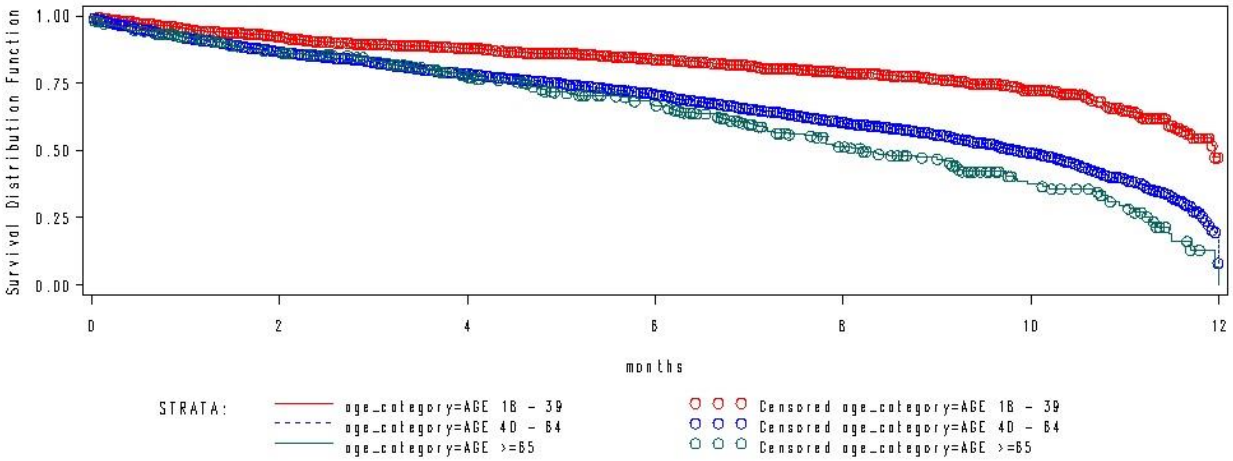

Figure 4.

Kaplan Meier Curves of Risks of Developing Diabetes during 1 Year Follow Up Stratified by Age among Obese Smokers Prescribed a Smoking Cessation Medication

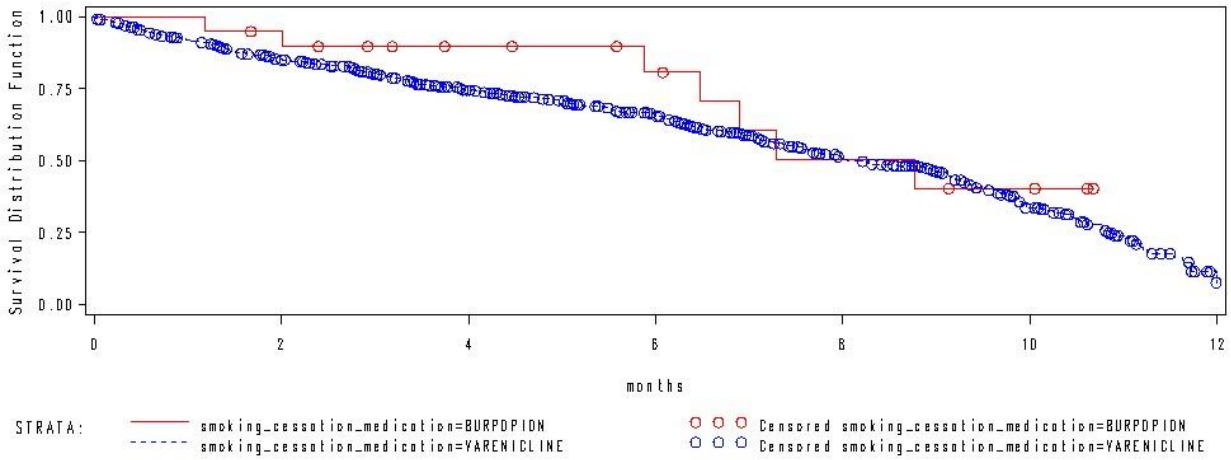

Figure 5.

Kaplan Meier Curves of Risks of Developing Diabetes during 1 Year Follow Up Stratified by Type of Smoking Cessation Medication Use among Morbid Obese Smokers Prescribed a Smoking Cessation Medication

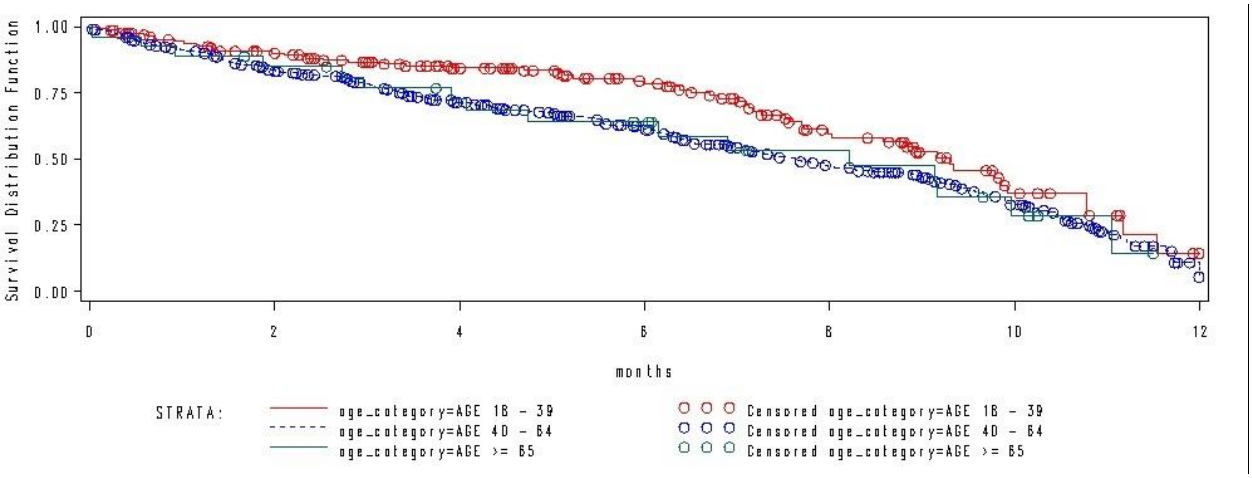

Figure 6.

Kaplan Meier Curves of Risks of Developing Diabetes during 1 Year Follow Up Stratified by Age among Morbid Obese Smokers Prescribed a Smoking Cessation Medication

Table 1.

Baseline Characteristics of Risks of Developing Diabetes during 1 Year Follow Up Time Period among Obese Smokers

Variables	Varenicline % (N)	Bupropion % (N)	p value
NRT			0.60
No	90.47 (1689)	88.57 (62)	
Yes	9.53 (178)	11.43 (8)	
Gender			0.20
Male	47.94 (895)	55.71(39)	
Female	52.06 (972)	44.29 (31)	
Race			0.77
White	49.65 (927)	51.43 (36)	
Non-white	50.35 (940)	48.57 (34)	
Region			0.88
Midwest	23.99 (447)	22.86 (16)	
Northeast	23.30 (434)	20.00 (14)	
South	33.28 (620)	37.14 (26)	
West	19.43 (362)	20.00 (14)	
Payment type			0.25[§]
Commercial	54.02 (565)	60.98 (25)	
Medi-care/caid	40.44 (423)	29.27 (12)	
Self-paid	5.54 (58)	9.76 (4)	
Age group			0.56
18 – 39	15.32 (286)	18.57 (13)	
40 – 64	75.63 (1412)	70.00 (49)	
≥65	9.05 (169)	11.43 (8)	
Specialty group			0.25[§]
Primary care	94.85 (1307)	96.15 (50)	
Specialty care	5.15 (71)	3.85 (2)	
Hypertension			0.12
No	79.16 (1478)	71.43 (50)	
Yes	20.84 (389)	28.57 (20)	
Hyperlipidemia			0.78
No	81.52 (1522)	82.86 (58)	
Yes	18.48 (345)	17.14 (12)	
COPD			0.99
No	90.04 (1681)	90.00 (63)	
Yes	9.96 (186)	10.00 (7)	
Depression			0.18[§]
No	92.29 (1723)	92.86 (65)	
Yes	7.71 (144)	7.14 (5)	
Alcohol dependent			0.84
No	60.26 (1125)	61.43 (43)	

Yes	39.74 (742)	38.57 (27)	
Weight reduction drug			0.21
No	84.20 (1572)	78.57 (55)	
Yes	15.80 (295)	21.43 (15)	
Weight gain drug			0.36
No	73.49 (1372)	68.57 (48)	
Yes	26.51 (495)	31.43 (22)	
Smoking counseling			0.67
No	65.35 (1220)	62.86 (44)	
Yes	34.65 (647)	37.14 (26)	
# of cigarettes smoked per day			0.36
No	59.72 (1115)	54.29 (38)	
Yes	40.28 (752)	45.71 (32)	
Abstinence to follow up			0.53
No	73.75 (1377)	77.14 (54)	
Yes	26.25 (490)	22.86 (16)	

Abbreviations: COPD – Chronic Obstructive Pulmonary Disease, NRT – Nicotine Replacement Therapy

[§] Fisher's exact test was applied.

[*]Indicate statistical significance at an alpha level of 0.05.

[**]Indicate statistical significance at an alpha level of 0.01.

[***]Indicate statistical significance at an alpha level of 0.001.

Table 2.

Predictors of Risks of Developing Diabetes during 1 Year Follow Up Time among Obese Smokes Using Cox Proportional Hazard Regression Model

Variables	Hazard Ratio	95% Confidence Interval	p-value
Smoking cessation medication			
Varenicline	Reference		
Bupropion	1.58	1.09 - 2.27	0.01*
Gender			
Female	Reference		
Male	1.31	1.14 – 1.51	0.01**
Race			
White	Reference		
Non-white	0.84	(0.73 – 0.98)	0.02*
Age group			
18-39	Reference		
40-64	2.03	1.65 – 2.50	0.01***
≥65	2.24	1.66 – 3.02	0.01***
Specialty group			
Primary care	Reference		
Specialty care	0.64	0.46 – 0.89	0.01**
Payment type			
Commercial	Reference		
Medi-care/caid	1.38	1.17 – 1.62	0.01***
Self-paid	1.34	0.97 – 1.86	0.08
Hypertension			
No	Reference		
Yes	1.59	1.31 – 1.93	0.01***
Weight reduction drug			
No	Reference		
Yes	1.90	1.56 – 2.33	0.01***
Weight gain drug			
No	Reference		
Yes	1.37	1.15 – 1.63	0.01**
# of cigarettes smoked per day			
No	Reference		
Yes	0.84	0.72 – 0.98	0.02*
Base BMI value	1.01	1.01 – 1.02	0.01***

*Indicate statistical significance at an alpha level of 0.05.
**Indicate statistical significance at an alpha level of 0.01.
***Indicate statistical significance at an alpha level of 0.001.

Table 3.

Predictors of Risks of Developing Diabetes during 1 Year Follow Up Time among Obese Smokes Using Cox Proportional Hazard Regression Model with Weight Change and Abstinence as a Confounder

Variables	Hazard Ratio	95% Confidence Interval	p-value
Smoking cessation medication			
Varenicline	Reference		
Bupropion	1.51	0.98 - 2.34	0.06
Gender			
Female	Reference		
Male	1.34	1.13 – 1.58	0.01**
Race			
White	Reference		
Non-white	0.80	(0.68 – 0.96)	0.01**
Age group			
18-39	Reference		
40-64	1.71	1.35 – 2.16	0.01***
≥65	1.76	1.25 – 2.48	0.01***
Payment type			
Commercial	Reference		
Medi-care/caid	1.32	1.09 – 1.60	0.01**
Self-paid	1.11	0.76 – 1.62	0.60
Hypertension			
No	Reference		
Yes	1.77	1.42 – 2.20	0.01***
Weight reduction drug			
No	Reference		
Yes	1.85	1.46 – 2.34	0.01***
Weight gain drug			
No	Reference		
Yes	1.28	1.05 – 1.57	0.01**
Base BMI value	1.01	1.01 – 1.02	0.01***
# of cigarettes smoked per day			
No	Reference		
Yes	0.88	0.78 – 0.99	0.03*
Weight change			
Negative	Reference		
Positive	1.86	1.40 – 2.47	0.01***
Months * weight change	0.92	0.88 – 0.97	0.01**

*Indicate statistical significance at an alpha level of 0.05.
**Indicate statistical significance at an alpha level of 0.01.
***Indicate statistical significance at an alpha level of 0.001.

Table 4.

Predictors of Risks of Developing Diabetes during 1 Year Follow Up Time among Morbid Obese Smokes Using Cox Proportional Hazard Regression Model

Variables	Hazard Ratio	95% Confidence Interval	p-value
Smoking cessation medication			
Varenicline	Reference		
Bupropion	0.60	0.08 – 4.41	0.61
Alcohol consumption			
No	Reference		
Yes	1.81	1.21 – 2.69	0.01**
Weight reduction drug			
No	Reference		
Yes	1.84	1.11 – 3.04	0.02*

*Indicate statistical significance at an alpha level of 0.05.

** Indicate statistical significance at an alpha level of 0.01.

*** Indicate statistical significance at an alpha level of 0.0001.

SUMMARY OF FINDINGS

Summary of Findings	
Objective 1	
1	An overall abstinence rate between approximately 18% and 23% from 3- to 12-month follow up.
2	No treatment differences were found between varenicline and bupropion use in terms of abstinence after adjusting for covariates.
3	Results from missing value analyses and mediation analyses showed consistent results compared to the baseline models.
4	The mediation analyses among obese adult smokers and morbid obese smokers indicated that weight change had a substantial effect on smoking cessation medication use in predicting abstinence.
5	The risk factors of abstinence found in this study included: *Demographics*: age, race, region, payment type, and specialty group, and baseline BMI value *Comorbidities*: being diagnosed with hypertension *Medication and Health Utilization*: alcohol dependence, weight influencing medications, smoking counseling, and number of cigarettes smoked per day
Objective 2	
1	A slight change of weight (ranged from 1.14pounds to 3.06pounds) following smoking cessation at 3-, 6-, and 12-month follow up among obese adult smokers.
2	There was no statistically significant difference of weight gain between bupropion use vs. varenicline use after controlling for covariates at baseline.
3	Mediation analysis indicated that abstinence had a substantial effect on smoking cessation medication use in predicting weight gain.
4	Factors associated with post-cessation weight gain: *Comorbidities*: being diagnosed with hyperlipidemia and diabetes *Medication and Health Service Utilization*: weight influencing drugs, and number of cigarettes smoked per day
Objective 3	
1	The diabetes incidence rates stratified by varenicline and bupropion were relatively comparable (23.50 vs. 25.80 per 1,000 person-years for varenicline vs. bupropion).
2	Mediation analysis with weight change as a mediator showed consistent results.
3	Predictors of risks of developing diabetes during 3 years follow up included: *Major independent variable:* type of smoking cessation medication use *Demographics:* gender, race, age group, specialty group, payment type *Comorbidities:* diagnosis with hypertension *Medication and Health Service Utilization:* using weight influencing medications, number of cigarettes smoked per day, base BMI value
4	Sensitivity analysis: 3-year to 5-year follow up assessment: be consistent with the baseline model 2year follow up assessment: not be consistent with the baseline model (might be due to unequal proportions of censored data)

CONCLUSIONS

Abstinence rates were higher among obese smokers who were taking bupropion vs. those who were taking varenicline at 3, 6, and 12-month follow up. While many studies reported better abstinence with varenicline compared to bupropion, we found no such difference among obese smokers after adjusted for other covariates.

Bupropion can attenuate more weight gain at 3, 6, and 12 months following smoking cessation among obese smokers compared to varenicline. However, bupropion was not identified as a predictor of lesser post-cessation weight gain compared to varenicline after controlled for other covariates.

Crude comparable diabetes incidence rate was found among obese adult smokers who used varenicline and bupropion for smoking cessation at 1 year follow up. Obese smokers who were prescribed bupropion had a higher risk of developing diabetes during 1 year follow up assessment than those who were prescribed varenicline. Given the close diabetes incidence rates, the large sample size, and results from sensitivity analysis which could be possibly due to unequal censoring, the clinical significance of the finding that bupropion had a higher risk of developing diabetes may need further investigation.

Predictors identified in this study should be considered when designing smoking cessation interventions among the high risk population of obese smokers. Healthcare professionals should always consider potential risks of quitting when deciding to stop patients from smoking as well as the potential benefits of type of smoking cessation medication (i.e.: varenicline vs. bupropion) against its potential risk when deciding which pharmacological cessation intervention to use for the smokers among this high risk population.

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