Eugene Song
MPH Candidate 2014

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"Determining the Effect of Daily Electronic Cigarette Use, Sex, and Cigarettes Smoked at Baseline on the Sum of Average Cigarettes Smoked Per Day Across 3 Measurement Occasions"

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“Determining the Effect of Daily Electronic Cigarette Use, Sex, and Cigarettes Smoked at Baseline on the Sum of Average Cigarettes Smoked Per Day Across 3 Measurement Occasions”

By

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B.A., Integrative Biology
University of California, Berkeley
2011

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Rollins School of Public Health of Emory University
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Abstract

"Determining the Effect of Daily Electronic Cigarette Use, Sex, and Cigarettes Smoked at Baseline on the Sum of Average Cigarettes Smoked Per Day Across 3 Measurement Occasions"
By Eugene Song

Objective: To quantify change in the sum of average cigarettes smoked per day across 3 measurement occasions using gender, daily electronic cigarette use, and the number of cigarettes smoked at baseline as predictors.
Methods: Secondary analysis of the longitudinal Internet survey conducted from 2011 to 2013 by Professor Jean Francois Etter and Professor Christopher Bullen. Secondary analysis was conducted using SAS 9.3 software's PROC GENMOD procedure. Participants were enrolled on websites dedicated to smoking cessation and electronic cigarette use. We assessed change in cigarettes smoked per day from a sample of n=200 participants.
Results: In Model 1, the Poisson regression model predicting the sum of cigarettes smoked over a 12 month period used baseline cigarettes smoked, sex, and daily e-cigarette usage status as predictors (See Table 2). All predictors were significant in Model 1. When exploring interactions in Model 2, for example, the interaction between daily electronic cigarette usage status and cigarettes smoked per day at baseline as well as the interaction between daily electronic cigarette usage and sex, only the latter interaction was found to be significant (See Table 3: OR=0.772; 95%CI:0.683,0.873; p<.0001). All non-interaction terms remained significant (See Table 3: p<.0001). The interaction between daily electronic cigarette usage status and cigarettes smoked per day at baseline can be interpreted as the "treatment effect" of daily electronic use being dependent on the number of cigarettes smoked at baseline. The interpretation of the interaction between daily electronic cigarette use and sex can be interpreted as the "treatment effect" of daily electronic cigarette use being dependent on sex. Overall, daily electronic cigarette users who were male experienced lower rates of cigarettes smoked per day over 3 measurement occasions when compared to women who did not use electronic cigarettes daily.
Conclusions: Demographic characteristics such as sex, cigarette smoking behavior at baseline, and daily electronic cigarette usage play a role in reducing the sum of average cigarettes smoked per day.

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"Determining the Effect of Daily Electronic Cigarette Use, Sex, and Cigarettes Smoked at Baseline on the Sum of Average Cigarettes Smoked Per Day Across 3 Measurement Occasions"

Chapter 1: Introduction

1.1 Introduction and Rationale

Globally, tobacco-related mortality accounts for approximately 6 million deaths with projections reaching more than 8 million by 2030[85]. In the United States, the smoking epidemic poses a significant public health risk with more than 480,000 annual deaths due to cigarette smoking and exposure to second-hand smoke[80]. Smoking contributes to 1 out of 5 deaths in the United States every year[80]. Currently, over 16 million Americans suffer from smoking-related illness, which makes it the leading cause of preventable chronic disease[22].

For the above reasons, smoking cessation has been of great interest. Studies have shown that quitting smoking before the age of 40 reduces the risk of dying from smoking-related disease by approximately 90% and increases life expectancy by 10 years[53, 80]. The independent effect of increased taxes on cigarettes was shown to be successful in decreasing smoking prevalence while smoking bans and mass media campaigns have had moderate impact[96]. There is evidence that the taxation impact on smoking prevalence is stronger among youths, young adults, and persons of low socioeconomic status; however, the impact of taxation was not as effective among heavy and long-term smokers[6].

Nicotine replacement therapies (NRTs) such as chewing gum, skin patches, nose sprays, inhalers, and tablets have made a person's attempt to quit smoking more likely by 1.5 to 2 fold regardless of setting, level of nicotine dependence, and independent of counseling support[82]. However, with fewer than 20% of smokers quitting with NRT and counseling support after one year, long-term cessation rates are dismal[82]. Even the highest-strength NRTs have been shown to deliver lower levels of nicotine at slower speeds than conventional cigarettes[58]. None of the above NRTs adequately satisfy the missing aesthetic and behavioral fixation associated with cigarette smoking, and many users have found traditional NRTs to be cumbersome and unhelpful in the quitting process[14, 90].

Since 2004, the electronic nicotine delivery system (ENDS), more commonly known as the “electronic cigarette”, “e-cigarette”, or “e-cig”, has been marketed as a smoking cessation product by the industry, and it has been hypothesized that e-cigarettes could be more effective than NRTs in smoking cessation due to its resemblance to an actual cigarette and ability to imitate the aesthetic and behavioral cues from conventional cigarette use[12-14]. Interest in the United States has been growing rapidly. In 2011, twenty-one percent of adults who smoked traditional cigarettes had tried the electronic cigarette, up from 10 percent in 2010[71]. Between 2010 and 2011, electronic cigarette use was greater in current smokers compared to both former and never smokers[71]. Online interest in electronic has spiked in the past few years with *Google* searches for ‘electronic cigarettes’ increasing by 5000% between January 2007 and January 2010 and surpassing searches for nicotine medications[33, 97].

Discussion surrounding regulation, toxicity of the chemical used in liquid cartridges, the direct and secondhand effects of e-cigarette vapors, the impact on cessation rates, user perception of ENDS, and its potential as a harm reduction device is limited compared to its NRT counterparts[62]. The availability of studies on user behavior and the long/short-term health impact of electronic cigarettes has been deemed as sparse and lacking[35]. However, a recent longitudinal study of the ‘natural behavior’ of electronic cigarette users indicates that e-cigarettes may help in preventing relapse in former smokers and smoking cessation in current smokers[32].

1.2 Problem Statement

Controversy over Regulation

Much of the controversy in the United States surrounding electronic cigarettes has been centered on regulatory language classifying e-cigarettes as tobacco products rather than medicinal therapies similar to nicotine chewing gum or patches. Based on this classification, a growing list of major American cities, including New York, Boston, and Los Angeles, have banned the use of electronic cigarettes in public places, citing concerns about second-hand vapors and the electronic cigarette's potential as a gateway device to traditional smoking[93]. In December 2010, the United States Court of Appeal ruled that the Food and Drug Administration (FDA) could only regulate e-cigarettes as tobacco products because e-cigarettes were not marketed as therapeutic products; however, it is well-documented that e-cigarette companies and vendors have claimed the potential of e-cigarettes to help smokers in reducing or ceasing tobacco use[9, 27, 33, 51]. The ruling by the U.S Court of Appeal limits the FDA's ability to regulate these products according to the "safe and effective" standard, which applies to medical products only[84]. However, the ruling does allow the FDA to regulate the concentration of nicotine, the level of impurities and contaminants in liquid cartridges, and device specifications (such as battery voltage and cartridge size) of electronic cigarettes, all of which may impact the safety of electronic cigarette users and consequently the general public.

Mixed Laboratory Results and Scarcity of Clinical Trials

Results from laboratory studies of the liquid content of replacement cartridges and vapor emissions have been conflicting and only a few clinical studies on e-cigarette usage have been documented. E-cigarette vapors contain some toxic substances which vary considerably across different brands; however, the levels of toxicants were found to be 9-450 times lower than levels found in cigarette smoke, which suggests that electronic cigarette users may be subject to fewer toxicants[47]. An in vitro (experimentation taking place outside of a living organism) study has shown that while some electronic cigarette vapors are cytotoxic (toxic to living cells), all electronic cigarette vapor extracts included in the study were significantly less cytotoxic compared to cigarette smoke extract[36]. An analysis of 10 of the most popular brands of refill liquids for e-cigarettes showed that detectable impurities were below harmful levels and concluded that when compared to smoking, e-cigarettes are less harmful, even after accounting for the levels of impurities[33]. Although the aforementioned results do not validate the safety of electronic cigarettes, they demonstrate the electronic cigarette's potential as a harm reduction device given that the quality of liquid content and device specifications can be appropriately regulated. However, concerns related to long-term safety of e-cigarette use, lack of data on liquid content and emissions (also with respect to long-term use), and unverified product claims as a quitting aid have been underscored[23, 61, 86, 94], which currently fuel the opposing regulatory environment within the United States.

Harm Reduction and Understanding User Behavior

Tobacco harm reduction (THR) is not an unfamiliar concept; the idea was first introduced by British tobacco addiction research expert Michael A.H. Russell[77]. THR empowers smokers to control the consequences of their nicotine addiction by 1.) decreasing tobacco consumption and 2.) using alternative tobacco products[70]. In recent years, the use of electronic cigarettes as a harm reduction strategy among current cigarette smokers has been pursued as an avenue of study. Several studies have reported e-cigarette use to aid smoking reduction, temporary abstinence, and as a quitting aid[17, 69, 81]. The United Kingdom has proposed harm reduction guidelines that cover the use of licensed nicotine-containing products such as electronic cigarettes; the proposal acknowledges that smokers are harmed by the tar and toxins in tobacco smoke and not necessarily the nicotine they are addicted to. The shift in the regulatory approach suggests that there is awareness that many smokers may not want or have the ability to quit smoking but would like a safer alternative to cigarettes[34]. Additionally, policy makers also recognize that e-cigarettes may better emulate the behavioral and handling cues of cigarette smoking compared to other nicotine delivery devices (inhaler, patch, gum), which produces suppression of craving and withdrawal from nicotine that is not exclusively attributable to nicotine delivery per se[75].

Rather than focusing on regulatory actions that classify electronic cigarettes as tobacco products, the UK's strategy is to regulate and classify e-cigarettes as therapeutic devices based on user needs, which subject the product to quality compliance measures and ensure safety for future users. Thus, it can be seen that the decision to regulate the quality of electronic cigarettes requires consideration of not only the chemical and toxicological qualities of ENDS but also user perception and the "natural behavior" described by Etter et al.[32]. A similar shift in the regulatory approach towards e-cigarettes in the United States would benefit current smokers who are interested in smoking cessation but have failed to do so using currently available NRTs.

1.3 Purpose Statement

Despite limited risk profiling of electronic cigarettes, e-cigarettes have increased in notoriety, awareness, and usage, which indicates that further studies of novel (new to e-cigarettes), daily, and "dual user" (those that use both traditional cigarettes and electronic cigarettes) behavior and demographics are necessary to determine electronic cigarette efficacy in harm reduction. More specifically, the development of an associative model that describes the smoking behavior of dual users requires understanding of user perception and usage patterns of electronic cigarettes over time. The effects of e-cigarettes on health are more evident if the ongoing nature, as opposed to temporary behavior, of electronic cigarette usage is clarified; as of February 2014, the study conducted by Etter and Bullen provides the most detailed information on the behavior of an international cohort of electronic cigarettes users over a 12-month period[32].

Although several studies reviewed user perception and "natural behavior" of electronic cigarette users[2, 32, 89], no studies have longitudinally modeled behavioral data over time with cigarette consumption per day as an outcome of interest. To address this gap in the literature, a current review and a generalized linear model based on the longitudinal Internet survey conducted by Etter et al. from 2011 to 2013 will be presented. Specifically, this model will identify the relationship between daily electronic cigarette use, gender, the number of cigarettes smoked at baseline, and the sum of cigarettes consumed per day across 3 measurement occasions.

1.4 Research Hypothesis

Research Question #1**:** Based on currently available data in the literature, what is the harm reduction potential of electronic cigarettes relative to functionality, chemical content, and toxicological characteristics when compared to conventional cigarettes?

Research Question #2**:** What is the effect of daily electronic cigarette use, gender, and the number of cigarettes smoked at baseline on the sum of average cigarettes smoked per day across 3 measurement occasions?

Hypothesis: Daily electronic cigarette use, being male, and low baseline cigarette count (below the 25th percentile of all observations) reduce the sum of cigarettes smoked per day across 3 measurement occasions.

Null: Daily electronic cigarette use, being male, and baseline cigarette count does not affect the sum of cigarettes consumed per day across 3 measurement occasions.

1.5 Significance Statement

Tobacco smoking continues to be the leading cause of preventable chronic disease and death in the United States[22], and as such, the positive impact on public health that may be achieved by convincing policy makers to reconsider their current misclassification and prohibitory approach towards alternative nicotine products cannot be ignored. There is a need for a licensed nicotine product capable of competing with cigarettes on both a pharmacological and behavioral level while reducing exposure to the harmful toxicants found in conventional cigarettes, which electronic cigarettes have demonstrated thus far based on the currently available data. The use of the electronic cigarette has increased drastically despite limited risk profiling generated through laboratory and clinical settings[34]. This indicates that user perception may play a role in the decision to use e-cigarettes. The United Kingdom's modified regulatory environment indicates a shift in ideology towards a harm reduction strategy, which demonstrates their policy makers' understanding that perception and behavior of electronic cigarette users is equally as important as the biological and toxicological consequences. Further analysis on user perception and behavior is needed so that future regulatory decisions may objectively evaluate the pharmacological, biological, and behavioral impact of using alternative nicotine products such as the electronic cigarette.

The literature review will examine the electronic cigarette's potential to reduce harm to users and compete with conventional cigarettes by investigating the functionality of the electronic cigarette, chemical and toxicological content of electronic cigarette liquid/vapor, chemical and toxicological differences between electronic cigarette liquid and vapor content and traditional cigarette smoke, the health impact of electronic cigarettes, and the awareness, perceptions, and beliefs about e-cigarettes. The current study will also present an associative model that demonstrates the potential association between behavioral and/or demographic characteristics of dual users and cigarettes smoked per day over a 12-month period. Known demographic and behavioral characteristics associated with electronic cigarette use will be identified from the literature review. Based on the final model, implications of significant or non-significant associations will be discussed, which may be meaningful in informing future behavioral studies under clinical settings, and inform policy development on the regulation of emerging nicotine replacement products.

1.6 Definition of Terms

1. **Dual Users**: Individuals that smoke cigarettes daily and use the electronic cigarette daily
2. **Vaporization**: the rapid change of a solid or liquid into steam
3. **Combustion/Pyrolization**: the process of burning tobacco
4. **Harm reduction**: a set of practical strategies and ideas aimed at reducing negative consequences associated with drug use.
5. **Toxicant**: a man-made toxic substance introduced into the environment
6. **Carcinogen:** any substance or agent that is associated with producing cancer cells
7. **Cytotoxic**: a substance that has a toxic effect on living cells
8. **Neurotoxic**: a substance that is poisonous to nerve tissue such as the brain or spinal cord
9. **Haematotoxic**: a substance that causes blood poisoning
10. **Ever-use**: individuals who smoke cigarettes or electronic cigarettes rarely, occasionally or daily.
11. **Completers:** Participants who gave an answer for the outcome of interest at all 3 measurement occasions.
12. **Non-completers:** Participants who had at least one missing value out of the 3 measurement occasions.
13. **Parametric:** a type of analysis that assumes underlying distribution of the data is normal (regression)
14. **Non-Parametric**: a type of analysis that makes no assumptions about data distribution ("connect the dots")

Chapter 2: Literature Review

2.0 Introduction

Electronic cigarette products have been marketed since 2003 as a means of smoking cessation and an alternative to traditional tobacco smoking[9, 27, 33, 51], which has generated great controversy. Few experimental studies in clinical and laboratory settings that measure impact on human health have been conducted in order to verify these claims, mainly due to the fact that is it difficult to determine long-term effects of first-hand and second hand inhalation of e-cigarette vapor[35]; however, when accounting for the information available on chemical content, usage, awareness, perceptions, demographics, and the regulatory environment surrounding electronic cigarettes, the literature available is myriad. The following review will summarize the diverse information available on electronic cigarettes by including: a brief description of electronic cigarette functionality, chemical and toxicological examination of electronic cigarettes, shared chemical and toxicological qualities as well as differences between electronic cigarette liquids and vapors and conventional cigarette smoke, the health impact of electronic cigarettes, and e-cigarette usage patterns and demographics among current smokers.

2.1 Components and Functionality of the Electronic Cigarette

The electronic cigarette consists of a mouthpiece, a microchip circuit, a variable voltage battery (newer models), a red LED simulating a burning cigarette tip, a cartridge containing a liquid composed of propylene glycol (PG) and/or glycerol in water, and a vaporization chamber (also called an atomizer), which produces an aerosol that imitates the smoke of a cigarette[11].

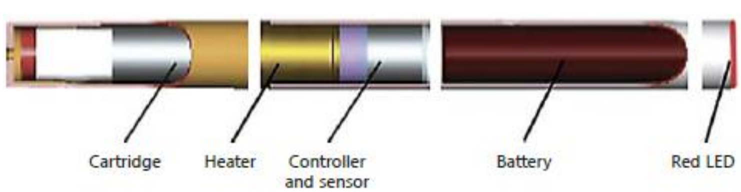

Photo courtesy: Berthelon et al.[9]

2.1.1 Types of electronic cigarettes

Electronic cigarettes vary by battery voltage, different concentrations of nicotine, variations in fluid additives such as propylene glycol and glycerol, and types of impurities and carcinogens

2.1.2 Variation in Battery Voltage

The voltage of the battery has recently been modified in newer models of electronic cigarettes, which affects the temperature in the vaporization chamber. Higher voltages will raise the temperature, produce more vapor, and different flavor[36]. In a study of the cytotoxic impact of electronic cigarette vapors on myocardial tissue, four out of the 20 electronic cigarette vapor samples tested at a regular voltage of 3.7 volts were deemed to be cytotoxic for myocardial function; in contrast, 4 randomly-selected samples tested at high-voltage settings (4.5 volts) reduced some cell viability but results were not deemed to be cytotoxic[36]. Cytotoxicity was defined as having <70% of cells at viable levels. Farsalinos et e. postulates that this statistical non-significance for samples tested at higher voltages can probably be attributed to small sample size[36]. Manufacturing companies have claimed that all batteries, regardless of voltage, will produce temperatures <100°C in order to avoid degradation of the liquid into a toxic substance known as acrolein, which has been identified as a major cigarette-related lung cancer agent[40]; however, there is no reliable data that can substantiate claims that temperatures exceed or remain under a specific temperature[9].

2.1.3 Variation in Liquid Concentration: Chemical Content

Nicotine Concentration

Nicotine concentrations specified on refill liquids vary across different brands, which makes it difficult to compare electronic cigarettes products to conventional cigarettes and assess the quantity of nicotine delivered to the user; however, the content of nicotine in electronic cigarettes was found to closely match levels specified on cartridge labels with reasonable variation[33, 46]. An analysis of 20 models of 10 of the most popular brands of e-cigarette refill liquids using gas and liquid chromatography showed that nicotine levels were between 85-121% of levels described on bottle labels[33]. A second study that assessed nicotine concentration consistency between 5 of the most popular electronic cigarette brands (6 products) showed that variation between batches from the same brand collected at 4-week intervals measured between 1% (95% CI: -5%, 7%) and 20% (95% CI: 14-25%) while variations between different brands within the same batch (samples from 6 products collected in the same week) varied up to 12% relative standard deviation[46]. The study deemed these variations as 'low' and concluded that the risk of nicotine toxicity from the major brands sold in the United Kingdom is minimal. However, the same study noted that nicotine delivery to the user is not necessarily related to nicotine content in liquid cartridges but more so attributable to other variations in electronic cigarette models such as battery strength and cartridge size[46]. Concentrations of nicotine-related impurities may also affect nicotine delivery to the user.

Potential Sources for Nicotine-related Impurities

The study of liquid content conducted by Etter et al. concluded that approximately half of the 20 tested e-cigarette products in the study would be acceptable as medicinal products while the other half of products contained up to 5 times the amount of nicotine-related impurities specified by the European Pharmacopoeia[33]. Variations in nicotine-related impurities were attributable to differences in the manufacturing process of ingredients and liquids, interaction of ingredients with packaging material, and interaction with flavoring, which leads to nicotine oxidization and eventual degradation[33]. Several papers cite the need for quality control measures in order to ensure safety for users[15, 46, 50, 60, 75, 79, 95]. In the United States, electronic cigarettes are not regulated as medicinal products but as tobacco products due to the way the legal system interprets the industry's advertising strategy (e-cigarette companies have successfully argued that their products do not claim to be therapeutic devices)[63]. This legal impasse has made it difficult to regulate quality related to manufacturing and packaging material, liquid content, and other e-cigarette components (battery strength and heater strength), which may subsequently degrade an otherwise uncontaminated raw product[33]. The liquid cartridge contains not only nicotine and nicotine-related impurities but also chemicals used in the food and entertainment industries.

Propylene Glycol(PG) and glycerol

Propylene glycol (propane-1,2-diol/1,2-dihydroxypropane/methyl) is an alcohol that is utilized as a food additive and in cosmetics as a humectant (maintaining moisture), as a solvent in pharmaceuticals for substances that are insoluble in water such as benzodiazepines and phenytoin, and utilized in aerosolized drug delivery devices such as inhalers and nebulizers[9]. Some electronic cigarettes devices use glycerol, which is also nontoxic and used in the food and chemical industries, as a replacement for PG or mix glycerol with PG to lengthen the life of the inhaled/exhaled aerosol[9, 33]. Currently, no occupational limits for PG inhalation have been set in France or the United States (the FDA has classified theatrical mists that use PG as a base chemical as 'generally safe'), but the U.K has marked a threshold for PG vapor and particle inhalation at 474 mg/m^3[(9, 10)]. However, thresholds for PG are not derived from knowledge of toxicity of propylene glycol but based on the fact that there is currently no known toxicity of the chemical in a workplace atmosphere[15]. Although propylene glycol and glycerol are widely regarded as safe by the entertainment and food industries, these chemicals can decompose at high temperatures into carcinogenic compounds associated with lung cancer[36]. Additionally, Diethylene glycol is a known toxic substitute for propylene glycol; Diethylene glycol has been found in electronic cigarettes originating from China and is known to cause mass poisonings and deaths[74]. In addition to Diethylene glycol contamination, there are several other major groups of toxins and carcinogens that have been found in cigarette liquid and vapor.

Toxins and Carcinogens

Performing liquid and gas chromatography analysis of vapors generated by a modified smoking machine from 12 electronic cigarette brands, researchers discovered several carcinogens in e-cigarette liquids and vapors such as carbonyl compounds (formaldehyde, acetaldehyde, acrolein, and o-methylbenzaldehyde), tobacco-specific nitrosamines(NNK and NNN, both carcinogens), polycyclic aromatic hydrocarbons (PAH, carcinogen formed during combustion), volatile organic compounds (toluene and p,m-xylene), and metals (Cadmium, Nickel, and Lead); however, the levels of toxic compounds in e-cigarette vapors were found to be 9-450 times lower than those found in conventional cigarette smoke and in many cases levels were ‘comparable to the trace levels in pharmaceutical preparation’[47]. Polycyclic aromatic hydrocarbons are used to enhance the odorless vapor generated by PG; however, some of these compounds have been deemed as carcinogenic, have the ability to interact with nicotine, and have been shown to be cytotoxic[7, 9, 33, 36]. A recent systematic review of the chemistry of contaminants in electronic cigarettes released in 2014 concluded that although the aforementioned contaminants are present in trace quantities, they have only been detected at levels warranting concern in studies that incorporated unrealistic levels of heating into their study design[15].

Under more realistic conditions, 9 electronic cigarette users were studied during an experiment on indoor air quality, which concluded that levels of polycyclic aromatic hydrocarbons (PAH) increased by 20% from control levels[78]. However, in response to the previous study, Farsalinos et al. cites that significant limitations regarding improper evaluation of control conditions weaken findings related to increased indoor PAH; furthermore, Farsalinos cited another study that demonstrated significant day-to-day environmental variation in PAH levels, which generates further uncertainty about the results from [39][39, 73]. It is evident from the studies above that additional trials in clinical settings, which use more stringent methodologies, are required in order to verify e-cigarette safety under realistic settings.

2.2 Differences Between Electronic Cigarettes and Conventional Cigarettes

Electronic and conventional cigarettes differ in how the industry markets each product, and in mechanistic attributes (combustion in conventional cigarettes compared to aerosolization in e-cigarettes), pricing, chemical content, and aesthetic variations—all of which may affect a person's decision to use an electronic cigarette. However, for purposes of assessing harm reduction potential, this section of the review will compare differences in mechanistic function, chemical content of e-cigarette liquids and vapor with tobacco smoke, and the health impact of electronic cigarette usage based on the currently available data.

2.2.1 Primary Mechanistic Difference: Tobacco Combustion vs. E-Cigarette Vaporization

Both vaporization and combustion utilize heat to release active ingredients such as nicotine and toxins such as acetaldehyde into the bloodstream; however, the major difference is in the temperature used and the resulting by-products formed from each method.

Tobacco Combustion

When smoking tobacco, temperatures can reach up to 200ºC, which leads to pyrolization (burning), and the generation of over 5,000 harmful by-products such as carbon monoxide, benzene, toluene, naphthalene, tars, PAHs, TSNAs, and a lung-cancer agent known as acrolein[18, 76]. Some of these harmful by-products have been found to be produced in electronic cigarette vapors as well, but in lower quantities[47].

Aerosol generation ("vaporization") in E-cigarettes

In contrast, electronic cigarettes deliver vapor without utilizing combustion. The heater ("atomizer/vaporizer") operates at temperatures between 50-60ºC, which is approximately 5-10% of the temperature of a lit cigarette, which suggests that these products as a whole are unlikely to emit the same types (or quantity) that is emitted in cigarette smoke[9, 18].

2.2.2 Chemical Content Comparison

Conventional Cigarettes

According to the American Lung Association, there are approximately 600 ingredients in cigarettes, and when burned, they degrade into more than 7,000 chemicals that are comprised of approximately 70 carcinogens, respiratory toxicants, cardiovascular toxicants, and reproductive or developmental toxicants[3, 4, 72]. Below is a table reproduced from Goniewicz et al., which outlines major toxic compounds identified in tobacco smoke[1, 47, 80, 83]:

Table 1: Toxic Compounds Identified in Tobacco Smoke and Their Effects[1, 47, 80, 83]

Chemical Compounds	Toxic Effects	
	Short-Term	*Long-Term*
Carbonyl compounds Formaldehyde*, acetaldehyde*, acrolein*	Cytotoxic, irritant, dermatitis	Cytotoxic, carcinogenic, pulmonary emphysema, lung cancer
Volatile Organic Compounds (VOCs)* Benzene, toluene, aniline	Irritant	Carcinogenic, liver and kidney damage, neurotoxic (CNS damage), haematotoxic (RBC breakdown)
Tobacco-Specific Nitrosamines (TSNAs)* N'nitrosonomicotine (NNN), 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK), N'-nitrosoethylomethyloamine	Irritant, fatigue, ulcers	Carcinogenic, Heart Disease, Stroke, bone loss
Polycyclic Aromatic Compounds (PAHs)* Benzo(a)pyrene, benzo(a)anthracene, dibenzo(a)anthracene	Irritant	Carcinogenic, kidney and liver damage, haematotoxic
Free Radicals Methyl radical, hydroxyl radical, nitrogen monoxide	Inflammation	Carcinogenic, neurotoxic, stroke, heart disease
Toxic gases Carbon monoxide, hydrogen sulfide, ammonia, sulfur dioxide, hydrogen cyanide	Irritant, headache	Cardiovascular toxicity, carcinogenic

Heavy Metals* Cadmium (Cd), lead (Pb), mercury (Hg)	Muscle pain, headaches, memory loss, fatigue	Carcinogenic, nephrotoxic, neurotoxic, haematotoxic
Other toxicants **Carbon disulfide**	Chest pain, irritant	Neurotoxic, coronary disease, reproductive toxicity
***=compound found in electronic cigarettes also**		

Source: Table adapted from Goniewicz et al.[47]

Electronic Cigarettes

In laboratory studies of electronic cigarette vapor and liquid content, several major toxicants, carcinogens, and other impurities similar to those found in cigarette smoke have been identified[15, 24, 36-38, 47, 50, 78, 87]. However, chemicals identified from liquid analyses and vapor analyses differ because chemical reactions generated by heating liquid refill cartridges yield distinct toxic compounds. Current tests on e-cigarette liquids have shown that liquid refill cartridges may contain no or trace amounts of potentially harmful substances[15, 33, 57]. However, once the liquid is heated, a compound such as acetaldehyde, a major chemical in cigarette smoke, was found in some brands of e-cigarettes but at levels up to 450 times below that which is found in conventional cigarette smoke[47].

Contrarily, a study of the impact of electronic cigarette vapors on indoor air quality showed that levels of polycyclic aromatic compounds (PAHs), another type of carcinogenic compound potentially generated by heating refill liquids, increased by 20%[78]; however, as Farsalinos et al. indicates, uncertainty about this finding exists due to weaknesses in control design and variations in daily environmental PAH concentration, which challenges the implication that indoor PAH concentration increased due to e-cigarette usage[39]. Additionally, cited weaknesses in other study designs have included unrealistic heating conditions, which have generated the problematic levels of toxins warranting concern in many studies[15], and the results from one such study, which utilized a mechanical smoking machine to conduct an analysis of vapors from 12 e-cigarette models, are summarized below:

Table 2: Comparison of toxins in conventional cigarette smoke and electronic cigarette vapor[47]

Toxic Compound	Conventional Cigarette (µg in mainstream smoke)	Electronic Cigarette (µg per 15 puffs)	Ratio (conventional compared to e-cigarette)
Formaldehyde	1.6-5.2	0.20-5.61	9
Acetaldehyde	52-140	0.11-1.36	450
Acrolein	2.4-62	0.07-4.19	15
Toluene	8.3-70	0.02-0.63	120
NNN	0.0005-0.19	0.00008-0.00043	380
NNK	0.012-0.11	0.00011-0.00283	40

Source: Table reproduced from Goniewicz et al.[47]

The table above corroborates the theory that replacing conventional cigarettes with electronic cigarettes may reduce exposure to tobacco-specific toxicants, with levels of toxicants 9-450 times below that which is found in conventional cigarette smoke; however, these results also show that electronic cigarettes are not completely free of harmful substances as claimed by the industry[47]. Though unrealistic heating conditions may be cited as a potential weakness in this study, quality control issues related to battery strength (recall that higher battery voltages generate higher heating temperatures, which may lead to generation of carcinogenic compounds such as Acrolein and lower battery voltages may generate lower heating temperatures), cartridge size, and heater strength weaken the "unrealistic heating" assumption because variations in product quality as well as lack of disclosure of battery strength make it difficult to verify whether this testing environment is in fact unrealistic[33, 36].

2.3 Health impact of electronic cigarettes

Short-Term Effects

Nicotine

Short-term effects of nicotine exposure have been well-documented and show that there are generally no adverse outcomes from short-term exposure to low to moderate levels of nicotine[16, 18, 30, 37, 38, 46, 70, 82]. However, an average bottle of refill liquid for electronic cigarettes contains up to 720mg of nicotine, which is several times the lethal dosage for children and adults[33]. In traditional cigarettes, by-products of tobacco combustion, and not the addictive nicotine, cause adverse health consequences, and as such, using electronic instead of traditional cigarettes may yield a potential short or long-term health benefit[46]. Moreover, based on studies on acute plasma nicotine concentration after electronic cigarette use, researcher hypothesized that e-cigarettes deliver less nicotine than conventional cigarettes[9], and Goniewicz et al. found that all tested e-cig brands delivered less nicotine per puff than conventional cigarettes[46].

Propylene Glycol(PG)

As previously described, propylene glycol is a compound primarily used in the food industry as a humectant and in the entertainment industry for generating theatrical mists (fog machines). PG is absorbed into the small intestine and is transformed into compounds such as pyruvic and lactic acid via glycolysis; however, propylene glycol can also generate toxic compounds such as acetic acid and propionic aldehyde. The half-life of propylene glycol is 2 hours in the blood and 4 hours in the body while the acute lethal dosage (LD50) is ~20g/kg[92].

Pulmonary Function, Plasma Concentrations, and Blood Count

Most of the available literature on acute biological effects of electronic cigarette use discuss pulmonary function, plasma concentrations of nicotine and nicotine-related metabolites, and blood cell counts[25, 41, 42, 52]. A study of acute electronic cigarette use revealed a significant increase in plasma nicotine levels 10 minutes after taking 10 puffs of one specific brand[25]. Vardarvis et al. concluded immediate adverse effects on pulmonary function from e-cigarette smoking[88]; however, a similar study by Flouris et al. on lung function concluded that lung function was not significantly undermined in both active and passive e-cigarette smoking[41].

Flouris et al. cited numerous limitations in the study performed by Vardarvis et al. including: lack of a proper control group and subject randomization, lack of comparisons of the effect of e-cigarette smoking against that of tobacco cigarette smoking, and absence of adjustment of influence of recent smoking[41]. Additionally, in a study that compared active and passive electronic cigarette smoking to active and passive tobacco smoking, complete blood cell counts (i.e. white blood cell, lymphocyte, and granulocyte counts) did not increase in e-cigarette users (current and never smokers) while complete blood cell counts increased for at least one hour in tobacco smokers (both current and never smokers), suggesting the inflammatory response is greater in tobacco smoke than in electronic cigarette vapors[42].

Long-Term Effects

It is premature to conclude that electronic cigarettes are safe to use or effective as a quitting aid because long-term toxicity of electronic cigarette use has not been determined and may be impossible to determine as of now.[13, 35] There have been a few short-term (6 months or less) clinical studies on e-cigarettes with regards to safety and efficacy of exposure to nicotine as well as acceptability; however, studies measuring "hard" outcomes such as smoking-related cancer, cardiovascular events, neurologic events, and chronic obstructive pulmonary disease(COPD), have not been pursued[60].

Manzoli et al. is currently in the process of finalizing a 5-year multi-centric prospective cohort study designed to measure adherence to e-cigarette smoking, efficacy of e-cigarettes in reducing and/or quitting traditional cigarette smoking, and the health effects of electronic cigarettes compared to traditional and mixed smoking habits[60]. Although nicotine can be potentially toxic and fatal in large amounts (lethal dosage in children is 40-60mg and 0.8-1.0mg/kg of body weight in adults[33]), long-term nicotine exposure in appropriate dosages appears to be well-tolerated over months of nicotine therapy[68]. Lastly, long-term toxicity of PG by inhalation or ingestion has not been observed in the rat, which shows that there currently no evidence indicating carcinogenicity or genotoxicity.

2.4 Awareness, Perception, and Use of Electronic Cigarettes

In the United States, electronic cigarettes are used more frequently by current smokers[55, 74], and the popularity of electronic cigarettes continues to increase despite limited risk profiling[34]. According to the CDC, among current U.S adult cigarette smokers, 68.8% report that they want to quit completely, and most smokers stop smoking without using evidence-based treatments[72]. Since 2007, sales of electronic cigarettes have tripled every year and a portion of the recent decrease in conventional cigarette sales in the United States are due to smokers purchasing e-cigarettes[54, 56]. The conclusion of this review will examine potential factors contributing to the rising use of electronic cigarettes including awareness, perception, and usage patterns among e-cigarette users.

2.4.1 Awareness

Tracking E-cigarette Popularity via Internet Search Data

Awareness of electronic cigarettes is generally high and increasing[65]. Tracking the rise in popularity of electronic cigarettes across four countries, a real-time surveillance method based on internet search query data from Google showed that searches for e-cigarettes increased in all nations from July 2008 to February 2010; more specifically, searches for electronic cigarettes were several hundred times greater than search for smoking alternatives in the United Kingdom and the United States[5]. The study concluded that increased tobacco control measures such as clean indoor air laws, tobacco taxes, and anti-smoking communities may be associated with higher levels of electronic cigarette searches online; however, the main limitation cited in this study is the validity of internet search data in projecting future electronic cigarette popularity[5]. Yet, search queries have been used to project health-related outcomes such as influenza in 2009[44] and predict film revenues as well as video game sales[45], which implies that internet searches may also be strong indicators of product popularity, especially because many popular brands are not available in store and must be purchased at online retailers[5].

Demographics

Age: Awareness of electronic cigarettes is significantly higher among young adults (aged 18-35 years) compared to older adults aged ≥65 years of age[2, 55]. In an online survey of 2,649 adults, age was inversely related to awareness (adjusted OR=0.99; 95% CI=0.98,0.99)[64]. A study of electronic cigarette awareness in 10,587 adults in 2009 and 10,328 adults in 2010 concluded that young adults are more aware of e-cigarettes than older adults[74]. A study of 561 healthcare providers in Minnesota showed that although 92% of providers had heard of electronic cigarettes, older providers were less likely than younger providers to be aware of e-cigarettes[67]. Studies have theorized that more awareness in young adults may be attributed to the fact that electronic cigarettes are mostly marketed through electronic and social media outlets, which are traditionally utilized by younger adults[97].

Sex: Studies that explain differences in awareness between sexes either show no difference or higher awareness among males. In a 2010-2011 mail and web survey of over 6,500 participants, King et al. concluded that there males and females did not differ in awareness[55]; however, a study of 2,624 young Midwestern adults showed that men were more likely than women to be aware of electronic cigarettes[21]. Additionally, a mail survey completed by 10,587 adults (≥18 years old) in 2009 and 10,328 adults in 2010, concluded that awareness of ENDS doubled from 16.4% in 2009 to 32.3% in 2010 and that men were more aware of electronic cigarettes[74]. Similarly, 2 surveys conducted in 2010 (online survey: n=2649 and LLSC: n=3658) both concluded that the odds of awareness for electronic cigarettes was more than 50% higher for men ((online survey: 1.57; 95% CI= 1.26, 1.96; LLSC: 1.64; 95% CI= 1.35, 2.00) than women[64].

***Race, Education, and Income Level**:* Race, education, and income level have been shown to have varying associations with awareness of electronic cigarettes[55, 64, 74]. Some studies suggest that awareness of electronic cigarettes is significantly lower in non-Hispanic blacks compared to non-Hispanic Whites[2, 55, 64]. An international 4-country survey of 5,939 participants concluded that non-minority heavy smokers with higher income were more aware of ENDS[2]. Additionally, awareness of electronic cigarettes was found to be lower in those with less than a high-school education[55, 74]; however, there were no consistent differences in awareness observed by income level[55].

***Current Smoking Status**:* Many studies have shown that higher levels of awareness are significantly associated with smoking status[21, 55, 64, 74]. In an international 4-country study of 5,939 current and former smokers in Canada (n=1581), the United States (n=1520), the United Kingdom (n=1325), and Australia (n=1,513), 46.6% of those surveyed were aware of electronic cigarettes (U.S: 73%, UK: 54%, Canada: 40%, Australia: 20%)[2]. The data suggest that smoking status may play a role in awareness. A study of 2,624 young U.S Midwestern adults between 20-28 years of age concluded that current and former smokers were more likely to be aware of electronic cigarettes than never smokers[21]. Similarly, King et al. concluded that when compared to former and never smokers, awareness of electronic cigarettes was significantly higher among current smokers[55]. Furthermore, a mail survey completed by 10,587 adult participants in 2009 and 10,328 adult participants in 2010 found that groups reporting the largest awareness of electronic cigarettes were current smokers (20.7% in 2009 and 49.6% in 2010)[74]. Additionally, a nation1ally representative online study conducted in 2010 on 2,649 never, former, and current smokers concluded that 40.2% (95%CI:37.3,43.1) had heard of e-cigarettes, with the highest level of awareness in current smokers ((57.1%; 95%CI = 53.3, 60.7) when compared to former and never smokers[64].

2.4.2 Perception

How Health-Care Providers Perceive Electronic Cigarettes

In the first study to examine healthcare providers' awareness and attitudes towards electronic cigarettes, a statewide convenience sample of 561 Minnesota healthcare providers conducted in 2013 showed that 92% of providers were aware of electronic cigarettes. From the same study, 75.1% of providers agreed that e-cigarettes could serve as a gateway to other tobacco use; however, providers were mostly obtaining information on e-cigarettes from patient accounts, news stories, and advertisements rather than professional sources such as medical journals[67]. The study cites that a cross-sectional design and low response rate may lead to nonresponse bias; however, the use of a large statewide sample and diversity of respondents add to the validity of this study[67].

User Beliefs about Electronic Cigarettes

Health: Perceived harm reduction

Most studies have found that users perceive electronic cigarettes to be less harmful or healthier than electronic cigarettes and help in tobacco cessation or reduction[2, 21, 31, 48, 64, 65]. In two cross-sectional surveys conducted in 2010 (online: n=2649 and LLSC: n=3658), Pearson et al. cites that smoking status and demographic factors may contribute to users perceiving e-cigarettes as less harmful[64]. Additionally, in a convenience sample answered by 3,587 participants (70% former tobacco smokers), 96% of electronic cigarette users believe that electronic cigarettes help them to quit smoking, 92% believed it helped them to reduce smoking, 84% perceived that e-cigarettes were less toxic than tobacco, 79% said that e-cigarettes help deal with tobacco cravings, and 67% said they help with tobacco withdrawal symptoms[31]. In the same study, 79% of former smokers were afraid of relapsing to smoking if they stopped using the electronic cigarette[31]. In a Polish study of 179 daily e-cigarette users, among respondents who were smoking at the time of starting e-cigarettes, 90% used e-cigarettes to stop smoking or to reduce the harm associated with smoking; 85% felt that e-cigarettes were not completely safe, but were less dangerous than conventional cigarettes, and 93% believed that e-cigarettes were addictive but less so than conventional cigarettes.

Surveys that included smokers who did not use electronic cigarettes generally indicate less confidence in e-cigarettes as a healthier product[65]. In a few probability sample surveys, 15-25% of those who were aware of electronic cigarettes believed they were not less harmful than conventional cigarettes[2, 64]. 21% of respondents to a non-probability survey of current smokers in the United Kingdom felt that electronic cigarettes might not be safe enough while only a third of smokers surveyed in New Zealand perceived e-cigarettes to be less harmful than conventional cigarettes[28, 59].

Cost

Perceptions of cost savings are inconsistent across multiple studies[65]. In several convenience sample surveys conducted internationally and in the United States, a small percent of users said they used electronic cigarettes to save money[26, 29, 48, 89]. However, 53% of conventional cigarette smokers in the United Kingdom felt that e-cigarettes might be too expensive[28].

Satisfaction and Similarity to Conventional Cigarettes

Some studies have found that users enjoy that e-cigarettes resemble traditional cigarettes while others have shown they may be detrimental to cessation or reducing tobacco consumption[8, 26, 29, 63]. Others have reported that the ‘social experience’ of smoking a conventional cigarette cannot be replicated when using an electronic cigarette[20]. In a qualitative study with 11 participants, one of the major themes that emerged related to electronic cigarette satisfaction was bio-behavioral satisfaction (e-cigarette use mimicked smoking a real cigarette and satisfied the oral fixation desire, inhalation experience, 'feeling the smoke hit the back of the throat', and 'seeing the vapor cloud when exhaling')[8].

Other Beliefs

Other themes that have emerged from the literature include concerns about appearance (i.e. preventing teeth yellowing and odor), a sense of 'camaraderie' that electronic cigarette users feel with other users, and overall social acceptability (pride or embarrassment in using electronic cigarettes)[8, 28, 29, 31, 48, 69].

2.4.3 Use

Analysts predict that within a decade, sales of electronic cigarettes will surpass that of tobacco cigarettes[91]. Currently, use of electronic cigarettes is shown to be minimal but rapidly increasing[65]. In 2009, only 1% of adults in the United States had tried electronic cigarettes; however, in 2010, prevalence rates increased to 3%[55, 64, 74]. Rates of use in the United States continued to increase in 2011 (6% prevalence)[55]. In all studies discussing prevalence, current smokers were more likely to have tried electronic cigarettes than former or never smokers[2, 55, 64, 74, 98].

Many studies have included only current and former smokers in their samples[65]. In the Legacy Longitudinal Smoker Cohort survey assessed by Pearson et al., current smokers were more likely to have tried electronic cigarettes than former smokers (6% vs. 3%, respectively)[64]. A study of 2,624 young U.S Midwestern adults between 20-28 years of age concluded that current and former smokers were more likely to be aware of electronic cigarettes than never smokers[21]. In the four-countries surveyed by the International Tobacco Control, 8% of current and former smokers had ever tried electronic cigarettes[2]. The study showed that prevalence was highest among daily heavy smokers and lowest among long-term quitters. Users of electronic cigarettes were not more likely to have quit smoking than non-users.

Other surveys have used probability samples to discuss use of electronic cigarettes among young adults, which varies according to the location and year of the survey. A study of male adolescents in 2011 and Korean adolescents in 2008 showed a 1% prevalence while a study on polish high school students and university students from 2010-2011 showed 21% prevalence[19, 49, 66].

In general, population-based surveys showed that current smokers were not current electronic cigarette users (current=within past 30 days)[65]. Of those who were current users of more than one tobacco product (i.e, cigarettes, hookah, cigars, and snuff), greater than 11% had used e-cigarettes in the past month[74]. In a second study, among Polish youth and young adult who were current smokers, 11% were currently using electronic cigarettes[49]. In 2010, two probability samples of United States adults showed that between 4% and 6% of current smokers had used electronic cigarettes in the past 30 days[64, 74]. In the United Kingdom, a large survey based on s survey panel methodology concluded that 3% of daily smokers in 2010 and 7% of daily smokers in 2012 were using electronic cigarettes[28].

In convenience samples, dual use of e-cigarettes with conventional cigarettes was fairly common. In studies that included only daily electronic cigarette users, between 12%–34% of electronic cigarette users were current smokers[26, 31, 43, 48]. In a study of 179 Polish electronic cigarette users, 6% used hookah, snuff or some other tobacco product (other than a conventional cigarette)[49]. However, among a sample of people who had bought an e-cigarette six months prior to the study, 35% of current electronic cigarette users did not smoke cigarettes, which suggests up to 65% dual use prevalence[81].

Chapter 3: Methods and Materials

3.1 Introduction

Criteria for inclusion in the literature review were as follows: 1) chemical/toxicological assessment of electronic cigarette liquids and vapors as well conventional cigarette smoke were conducted in a laboratory setting or in a clinical trial and 2.) Behavioral data on electronic cigarette use were presented separately for current, former, and never smokers, and 3.) The majority of behavioral data on awareness and perception are based on either probability sampling methods or methods that are representative of the population.

We searched the electronic literature database PubMed for relevant journal articles published through March 2014 using multiple combinations of keywords such as electronic nicotine delivery systems, ENDS, electronic cigarette, e-cigarette, e-cig, vaper, and smoking. Following electronic search, references listed in each study were examined and additional relevant articles were obtained using the same inclusion criteria.

The data for the secondary analysis comes from an international longitudinal Internet survey originally conducted by Professor Jean-François Etter at the University of Geneva, Switzerland from 2010-2013. An electronic version of the questionnaire can be found at http://www.stop-tabac.ch/fr_hon/ECIG_EN/version2010.html. The survey involved a 51-item questionnaire covering 1.) Demographics, 2.) Electronic cigarette use history, 3.) Tobacco use history, and 4.) Beliefs about electronic cigarettes.

3.2 Population and Sample Description

The survey relied on self-reports on electronic cigarette and tobacco use from former and current smokers. Using a convenience sampling method, baseline data was collected starting in 2010 and follow-up data collected at one month and 12 months was collected from August 2011-January 2013. Dual users were required to recall how many cigarettes per day, on average, they smoked at baseline (month 0), one month, and 12 months. In the original study conducted by Etter et al., data collected at one month and one year was analyzed. In the present study, we present descriptive and analytic data collected from baseline, one month, and one year.

There were n=1329 respondents at baseline and n=773 (58%) agreed to participate in a follow-up questionnaire. At one month, out of the n=773 that agreed to participate, n=477 ([477/773]*100=**62%**) responded, and at 12 months, n=367 ([367/773]*100=**47%**) responded. All but 52 participants had missing data (a total of n=556 chose not to participate in follow-up, and a total of n=721 were either missing outcome data at 1 month or 12 months). N=200 were selected for modeling purposes. N=200 includes all participants who are missing a maximum of one measurement occasion (in other words, n=200 has at least two measurement occasions recorded). An offset was generated to account for the missing observation, which is explained below. Additionally, justification for deleting observations that were missing more than one measurement occasion is discussed below as well.

3.3 Justification

Electronic cigarettes are primarily purchased on the Internet, and as such online recruitment of participants was deemed the most appropriate method of data collection[32]. Etter et al. posted a questionnaire in English and French on the smoking cessation website “Stop-Tabac.ch”, and also requested that websites that sold electronic cigarette products or forums that discussed these products publish the link to the online questionnaire.

For modeling purposes, a convenience sample of n=200 was collected based on completeness of data, visual assessment of average change trajectory plots of completers and non-completers, and robustness of the analysis method. Visual assessment of non-parametric and parametric average change trajectories revealed that the rate of change between completers (all 3 measurement occasions recorded) and non-completers (missing at least one measurement occasion) shared similar trajectory paths, which implies that the missing data may be ignorable. SAS 9.3 software's PROC GENMOD method accounts for missing data by inserting a logarithmic offset (a weight) to each response by taking the log of the total number of responses across all measurement occasion minus the number of missing observations (log[n-nmiss]). To clarify the use of an offset, each subject in the sample was followed for 3 measurement occasions (baseline, 1 month, 1 year). If this was not the case, (i.e., some participants failed to follow-up at one month or some at one year) and these missing data were ignored in the model, the Poisson regression estimates would be biased, since the model assumes that all participants were observed over 3 measurement occasions. The offset value corresponds to the logged version of the variable specifying length of time an individual was followed (either 2 or 3 measurement occasions) minus the number of missing measurement occasions (restricted to a maximum of 1 missing occasion during data cleaning). Many observations were missing responses for at least two measurement occasions, which would lead to an undefined weighting value when calculating the offset (i.e. if n=1 and nmiss=2, then log[1-2]=undefined). As such, analysis was restricted to observations that had a recorded outcome value at baseline and only one missing response in the two subsequent measurement occasions in order to calculate an offset value that was not undefined. Additionally, observations that were missing a recorded value at baseline but had a recorded value in each of the two subsequent follow-up occasions were included in the analysis as well.

3.4 Research Design

The longitudinal study originally conducted by Etter et al. is both quantitative and qualitative in nature. The Internet questionnaire assessed changes in the 'natural behavior' of electronic cigarette users over a 12-month period, collecting both demographic information as well as data on usage patterns. The study did not aim to establish causal links between electronic cigarette use and smoking behavior but aim to describe behavior change over time.

Similar to the nature of the original study, the secondary analysis presented in this paper seeks to describe the effect of daily e-cigarette usage, baseline number of cigarettes smoked, and gender on overall smoking behavior over 3 measurement occasions. The variables sex, daily e-cigarette usage status (dailyeciguser), and baseline cigarettes smoked, were identified as potential predictors of interest during the review of the literature. The final model will allow us to describe how smoking behavior is conditional not only on daily electronic cigarette use and gender but also on the starting number of cigarettes smoked at baseline.

3.5 Procedures and Data Analysis

The high prevalence of missing data led to consideration of multiple model construction schemes. A generalized linear model using SAS 9.3 software's PROC GENMOD was produced based on the Poisson distribution. Demographic characteristics such as income level, and education status were not included in the model based on findings from the literature. Gender status and daily electronic cigarette use were identified as variables of interest based on the literature, which generally agreed that awareness and use of electronic cigarettes was highest among current smokers who are male.

To complete the study, both analytic and descriptive methods were utilized. A discussion surrounding the analytic method will be discussed first. To review, statistical models are mathematical representations of population behavior. When a particular statistical model is used to explain a particular set of data, we are implying that the particular model generated gave rise to data that was collected. To clarify, the statistical model presented is not a statement about the sample behavior—it is a statement about the population process that generated the data. The statistical model is presented using parameters (intercepts, slopes, standard errors, etc.) that describe specific characteristics about a population and odds ratios (OR) that quantify the effect of daily electronic cigarette used and baseline cigarettes smoked per day.

For this study, a generalized linear model was created using the GENMOD procedure in SAS 9.3 software (Cary, N.C). Generalized linear models are advantageous in the analysis of count data collected during repeated measurement occasions. Other models using PROC GLM or LOGISTIC cannot fit complex data collected over repeated measures. GENMOD can fit data from several types of distributions. If a distribution is not available as an option, the user may specify a custom option. The particular distribution used in this analysis is the Poisson distribution, which is generally used for count data. Other distributions include Gamma, Inverse Gaussian, and Negative Binomial.

Correlated data can occur as a result of clustered data (i.e. taking repeated measurements on subjects or as a result of subjects belonging to the same cluster). Failing to account for correlated measurements can result in underestimating variance, which may lead to low p-values. In cases where there is potential for correlated data, the presence of missing data, and non-normality in outcome/predictor distribution, GENMOD is the preferred method over previously mentioned options.

In this particular study, each participant answered a question, “How many cigarettes do you smoke per day?” at baseline, 1 month, and 12 months, which resulted in discrete count responses. A discrete frequency distribution of an event spread throughout a fixed time period (in this study, 12 months) is known as the Poisson distribution. The goal of this study was to observe the Poisson distribution and to estimate the probability of increased cigarette smoking based on how the treatment (in this study, the “treatment” is being a daily electronic cigarette user) affects this probability. A base model assessing the significance of daily electronic use on reduced smoking is presented first. Second, a model that quantifies the effect of daily e-cigarette use conditional on the number of cigarettes (the interaction between daily e-cigarette usage status and baseline cigarettes smoked per day) smoked at baseline is presented. In order to assess the interaction between the "treatment" (being a daily electronic cigarette user) and cigarettes smoked per day at baseline, three quartiles were calculated (5, 15, 25) and compared against each other in estimate statements in the final model to assess differences between daily electronic cigarette users and non-daily users. In both models, the sum of total cigarettes smoked over 3 measurement occasions is calculated due to non-normality of responses at each respective measurement occasion. Once sums were calculated for each observation, normality in the outcome variable was achieved (as specified by the Poisson distribution), and analysis was conducted.

The convenience sample of n=200 was created by sorting the original data set into two separate data sets. The first data set included all participants that had recorded outcomes at all measurement occasions (i.e. there was a value for average cigarettes smoked per day at baseline, 1 month, and 1 year). Additionally, if an observation had a present value at baseline but was missing only one other observation (either at 1 month or 12 months), then that observation was included in the first data set as well. The first data set totaled to n=179 observations that fit this criteria. The second data set was created by including only observations that had a missing baseline but had recorded values at both 1 month and 12 month follow-up. The second data set totaled to n=21 observations. N=200 observations was obtained after combing results from both data sets.

Descriptive assessments of categorical variables were conducted using frequency statements and univariate procedures were used to examine the outcome of interest, cigarettes per day. Histograms were created to assess normality of the outcome variable of interest at baseline, 1 month, and 12 months. Due to non-normality of the response variable at 1 month and 12 months, a "sum" variable was created to account for non-normality. The sum variable combined responses from each measurement occasion (baseline, 1 month, and 12 months) to calculate total cigarettes smoked per day across 12 months. Parametric (smoothed) and non-parametric average change trajectory plots were created to assess change trajectories of completers (n=52) and non-completers (n=1277). Paneled parametric and non-parametric average change trajectories were also generated by daily e-cigarette usage status. Both parametric and non-parametric individual subject profile plots were created to visually assess trends in completers. Subject profile plots for non-completers were not created. Upon arrival at the final model, parametric prototypical change trajectories of predicted sum values for cigarettes smoked per day were generated in order to visualize differences in projected cigarettes smoked per day between daily e-cigarette users and non-daily users.

3.6 Ethical Considerations

After careful review of the dataset for protected health information, this analysis was determined to be IRB-exempt because it is an analysis of secondary data and all data were de-identified prior to analysis. The survey was administered online through January 2013 and created by trained staff employed by the University of Geneva, Switzerland.

Chapter 4: Results

Introduction

In Model 1, the Poisson regression model predicting the sum of cigarettes smoked over a 12 month period used baseline cigarettes smoked, sex, and daily e-cigarette usage status as predictors (**See Table 2)**. All predictors were significant in Model 1. When exploring interactions in Model 2, for example, the interaction between daily electronic cigarette usage status and cigarettes smoked per day at baseline as well as the interaction between daily electronic cigarette usage and sex, only the latter interaction was found to be significant (**See Table 3:** OR=0.772; 95%CI:0.683,0.873; $p<.0001$). All non-interaction terms remained significant (**See Table 3:** $p<.0001$). The interaction between daily electronic cigarette usage status and cigarettes smoked per day at baseline can be interpreted as the "treatment effect" of daily electronic use being dependent on the number of cigarettes smoked at baseline. The interpretation of the interaction between daily electronic cigarette use and sex can be interpreted as the "treatment effect" of daily electronic cigarette use being dependent on sex. Overall, daily electronic cigarette users who were male experienced lower rates of cigarettes smoked per day over 3 measurement occasions when compared to women who did not use electronic cigarettes daily.

Findings: Descriptive Statistics

Table 1: Distribution of Cigarettes Smoked per Day and Gender at all measurement occasions by daily electronic cigarette usage status (n=200)

	Daily E-Cig User Mean (SD) or N	Non-Daily E-Cig User Mean (SD) or N	P-Value
N_Male*	79	45	n/a
N_Female*	25	42	n/a
N_baseline**	105	65	n/a
N_1month***	92	57	n/a
N_12months****	79	33	n/a
CPD_baseline	14.11 (14.74)	17.85 (10.10)	0.07
CPD_1month	3.00(7.87)	14.38(10.19)	<.0001
CPD_12months	4.99(9.23)	12.15 (8.52)	<0.001

*N_Male and N_Female=9 missing
**N_baseline=30 missing
***N_1month=51 missing
****N_12months=88 missing

Table 1 summarizes the demographic characteristics of the sample. Notice the different number of responses for each measurement period (N_baseline, N_1month, and N_12months). Mean cigarettes smoked per day at baseline (CPD_baseline) was significantly lower among daily electronic users compared to non-daily electronic users (p=0.07). Mean cigarettes smoked per day at 1 month is also significantly lower among daily electronic cigarette users when compared to non-daily e-cigarette users (p<.0001). At 12 months, mean cigarettes smoked per day is significantly lower than the mean cigarettes per day by non-daily electronic cigarette users (p<.001). Additionally, among daily electronic cigarette users, mean cigarettes smoked per day increased between the 1 month follow-up and the 1 year follow-up (3.00 to 4.99), which does not agree with the trend typically observed from baseline to 12 months for both daily e-cigarette users and non-daily users; however, this change was not statistically significant (p=0.13).

Distribution plots of long format data showed that the outcome variable was non-normally distributed at 1 month and 12 months (**Figure 2 and 3**); however, distribution was normal at baseline (**Figure 1**). Long format data sets were created to give each participant three observations, and assess response variable distribution over all measurement occasions for all participants. For example, participant 1 would have one observation for baseline, one at 1 month, and one at 12 months. Therefore, every normal plot was based on 600 observations (200 participants multiplied by 3 measurement occasions). Skewness and kurtosis for cigarettes smoked per day at baseline was calculated to be 0.853 and 0.549, respectively, which indicates normality. Skewness and kurtosis for cigarettes smoked per day at 1 month was 1.858 and 4.347, respectively, which indicates non-normality. Skewness and kurtosis for cigarettes smoked per day at 12 months was calculated to be 1.363 and 1.193, respectively, which also indicates non-normal distribution.

Figure 1: Distribution of Cigarettes Smoked Per Day at Baseline (long form sample, n=600 observations)

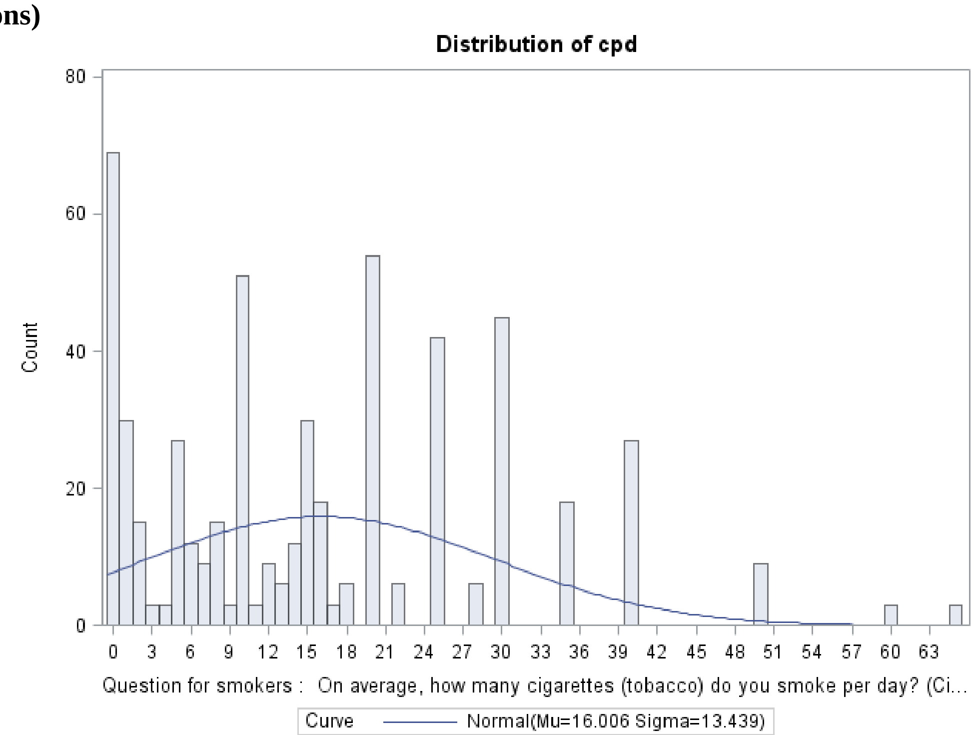

Figure 2: Distribution of Cigarettes Smoked Per Day at 1 Month (long form sample, n=600 observations)

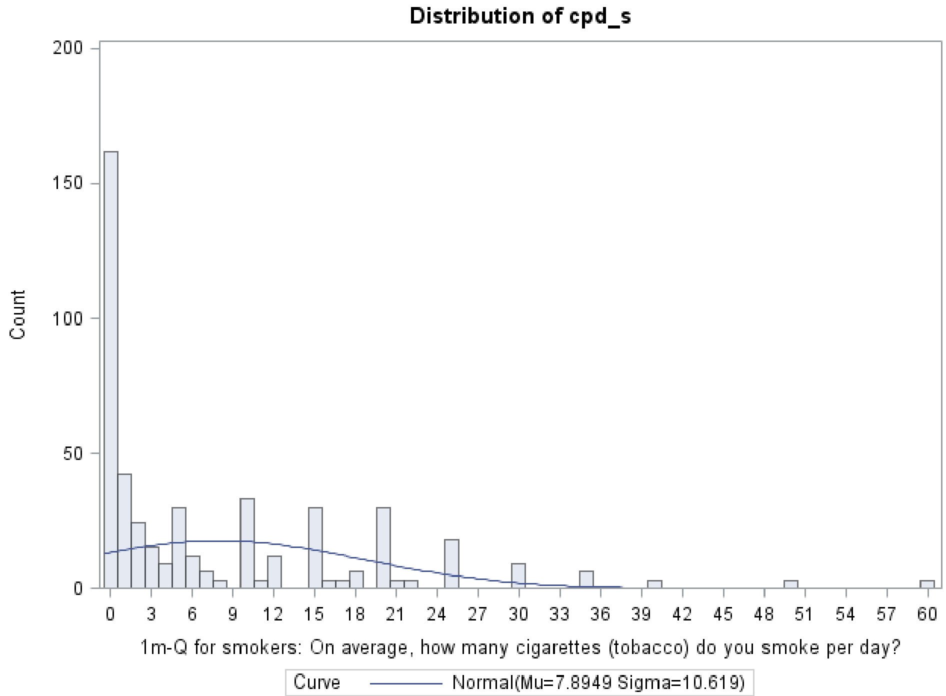

Figure 3: Distribution of Cigarettes Smoked Per Day at 12 Months (long form sample, n=600 observations)

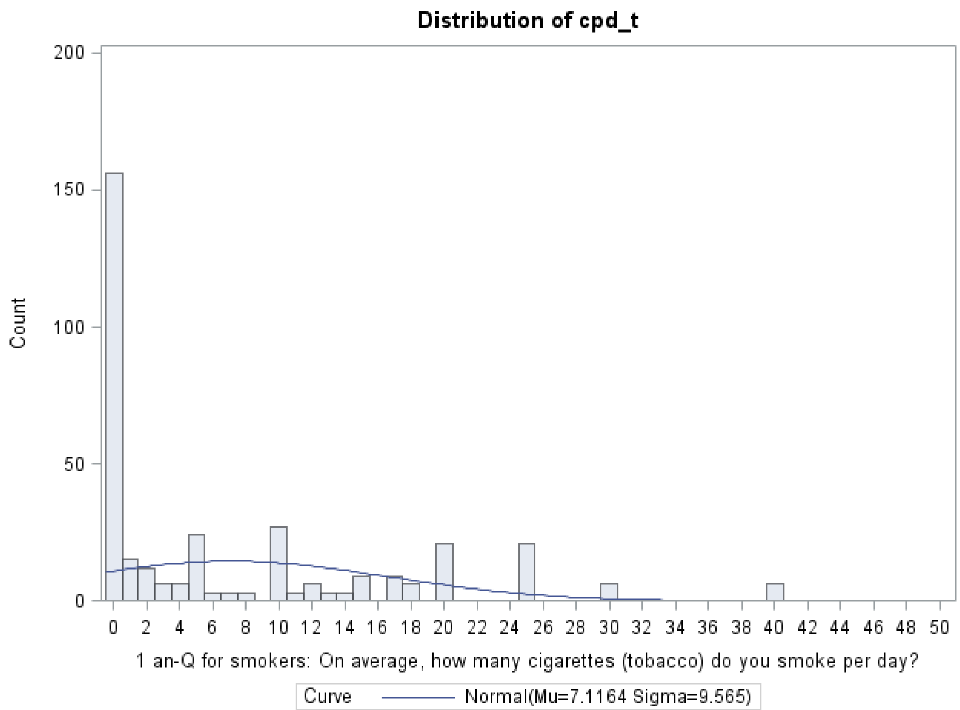

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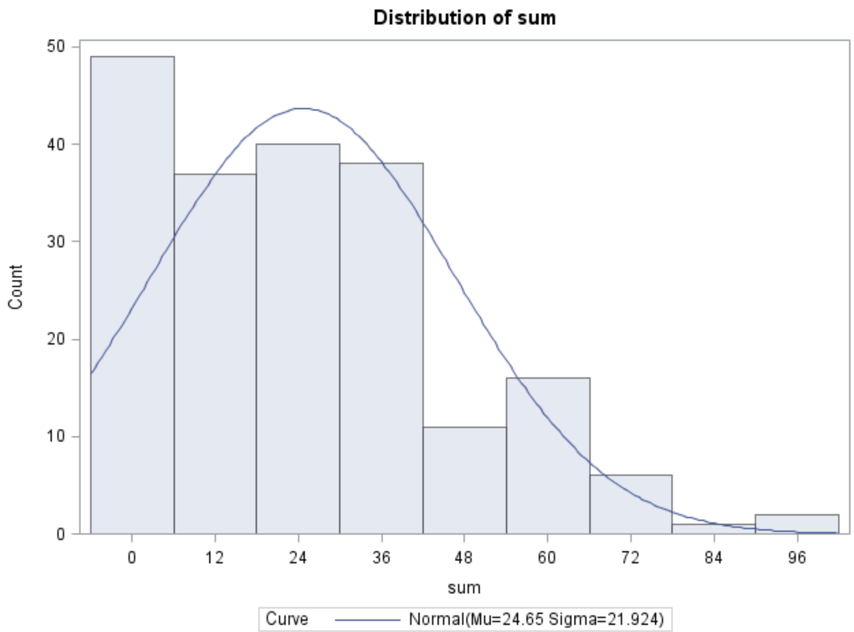
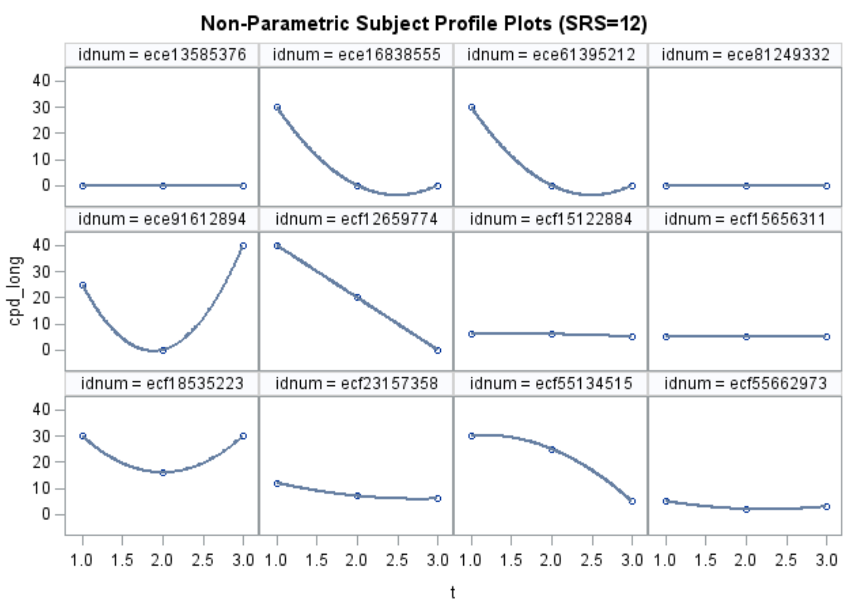
Figure 4: Distribution of the Sum of Cigarettes Smoked Per Day Across 3 Measurement Occasions (long form converted to short form where n=200)



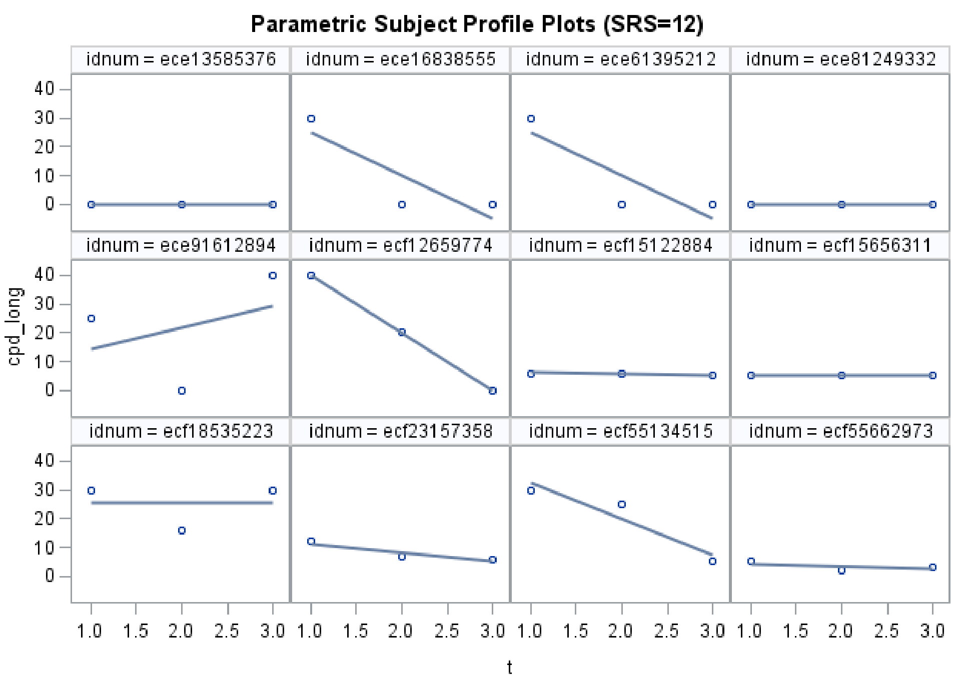
In order to account for non-normal distribution of outcome variables at 1 month and 12 months, average cigarettes smoked per day were summed from all three measurement occasions. The variable "sum" was used as the response variable in both models presented in this paper. Figure 4 shows a fairly normal distribution of the new outcome variable "sum". Skewness and kurtosis of "sum" is 0.907 and 0.478, respectively.

Figure 5: Non-Parametric Subject Profile Plots of 12 Randomly Selected Completers



12 parametric and non-parametric subject profile plots were generated by simple random sampling from the sample of n=52 completers to examine possible trends. Both non-parametric and parametric analysis (**Figure 5 and Figure 6**) show that there is a general change in cigarettes smoked per day (represented by the variable "cpd_long") at baseline (t=1.0), 1 month (t=2.0), and 12 months (t=3.0). In Figure 6 (parametric), we see that as time (t) increases from 1.0 to 3.0, there seems to be a downward linear trend. In Figure 5 (non-parametric), we still observe a general decrease in cpd_long over a 12 month period. Results from both trend analyses suggest that average cigarettes smoked per day at baseline is an outcome that changes over time due to predictors such as sex and usage patterns.

Figure 6: Parametric Individual Subject Project Plots of 12 Randomly Selected Completers



Figures 7-10 show average trend differences in cigarette smoked per day over 12 months between completers and non-completers. All four average change trajectory plots indicate a downward trend in the outcome of interest over time, regardless of completion status. However, visual inspection of the average change trajectory of non-completers in Figure 10 reveals a steeper decline in trajectory than the average change trajectory of completers in Figure 8, which suggests that the rate of change in cigarettes smoked per day over 12 months among completers was lower than the rate of change in non-completers. The trend difference observed between the two groups implies that the sample should incorporate participants from both pools in order to remain as true to the original data distribution as possible. All four trajectories demonstrate a convincing linear change between average cigarette smoked per day (cpd_long) and time.

Figure 7: Non-Parametric Average Change Trajectories for Completers (n=52)

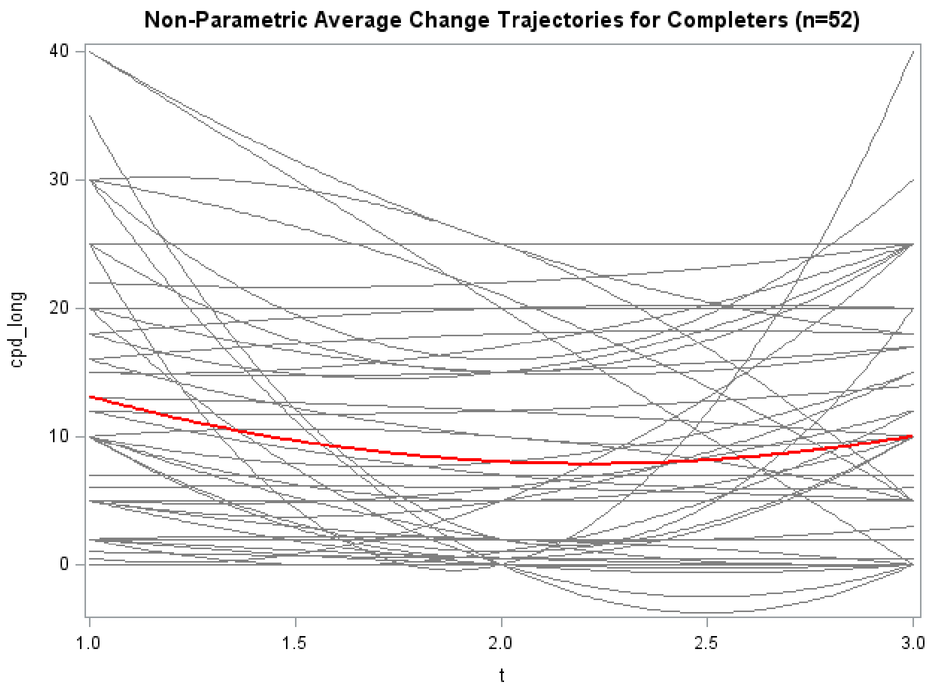


Figure 8: Parametric Average Change Trajectories for Completers (n=52)

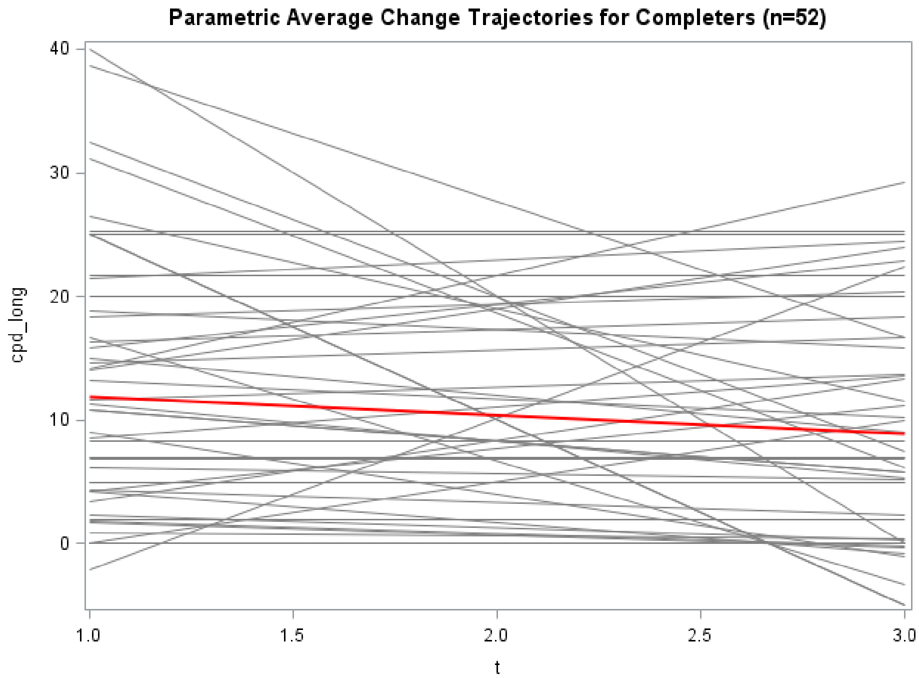


Figure 9: Non-Parametric Average Change Trajectories for Non-Completers (n=1277)

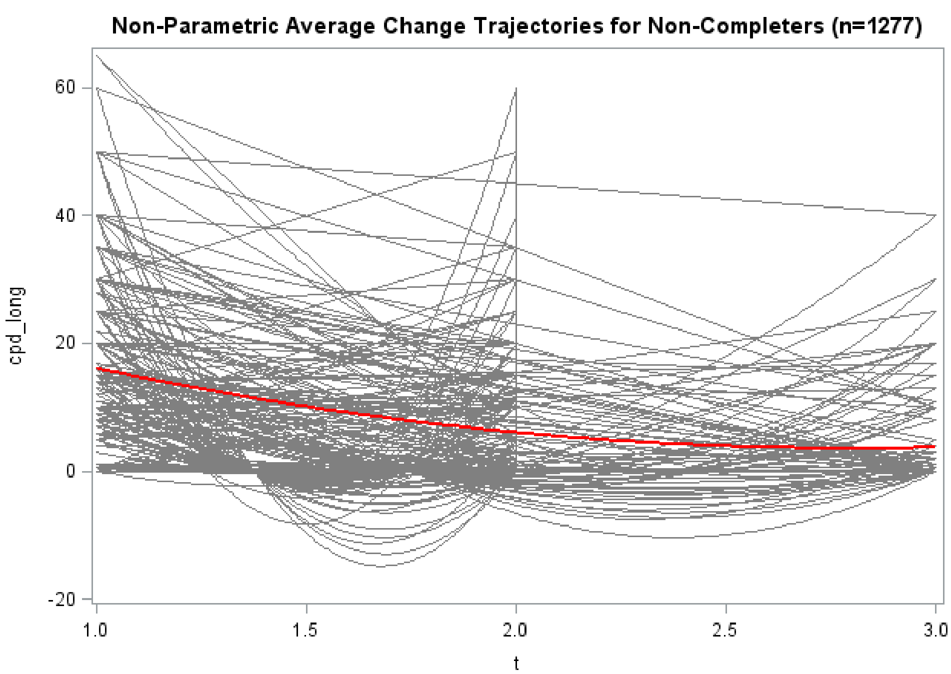
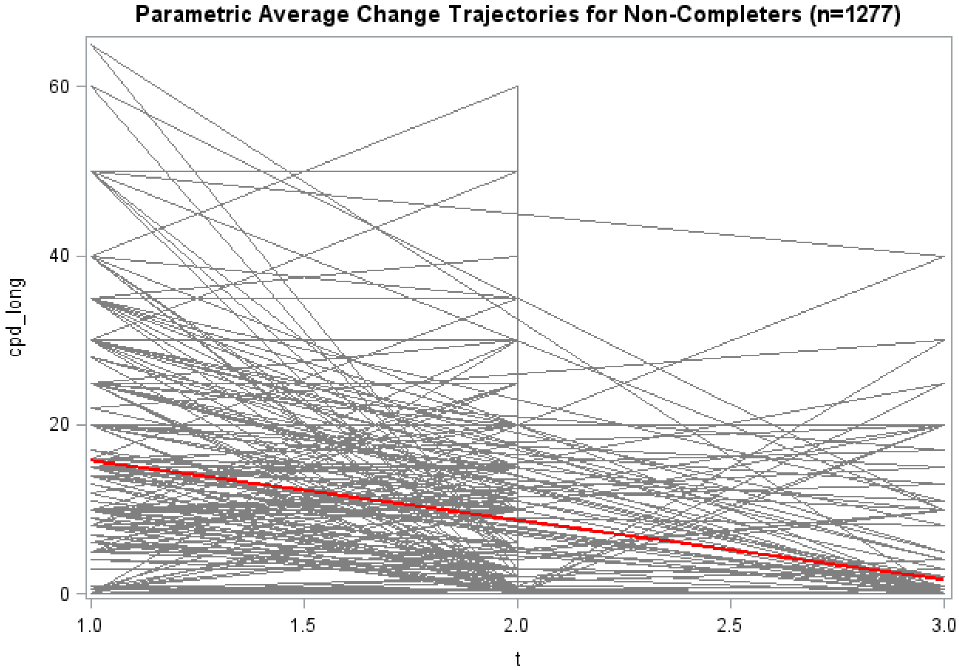


Figure 10: Parametric Average Change Trajectories for Non-Completers (n=1277)



Figures 11 and 12 show non-parametric and parametric average change trajectories paneled by daily electronic cigarette usage status for the sample (n=200). Visual inspection of the non-parametric analysis in Figure 11 shows that the average change trajectory dips slightly in daily electronic cigarette users when compared to non-daily users; however, the difference is not pronounced or extremely apparent. The initial number of cigarettes smoked at baseline (t=1.0) also does not appear to be different between the two groups. In non-parametric analysis, the difference in slope is more apparent than the difference in initial cigarettes smoked at baseline. Visual inspection of the parametric analysis in Figure 12 shows that average change trajectory is also slightly steeper in daily electronic cigarette users; however, this difference is also no obvious from a visual inspection. The difference in baseline cigarettes smoked (t=1.0) is clearly lower in daily electronic cigarette users compared to non-daily users.

Figure 11: Non-Parametric Average Change Trajectories By Daily Electronic Cigarette Usage Status for Sample (n=200)

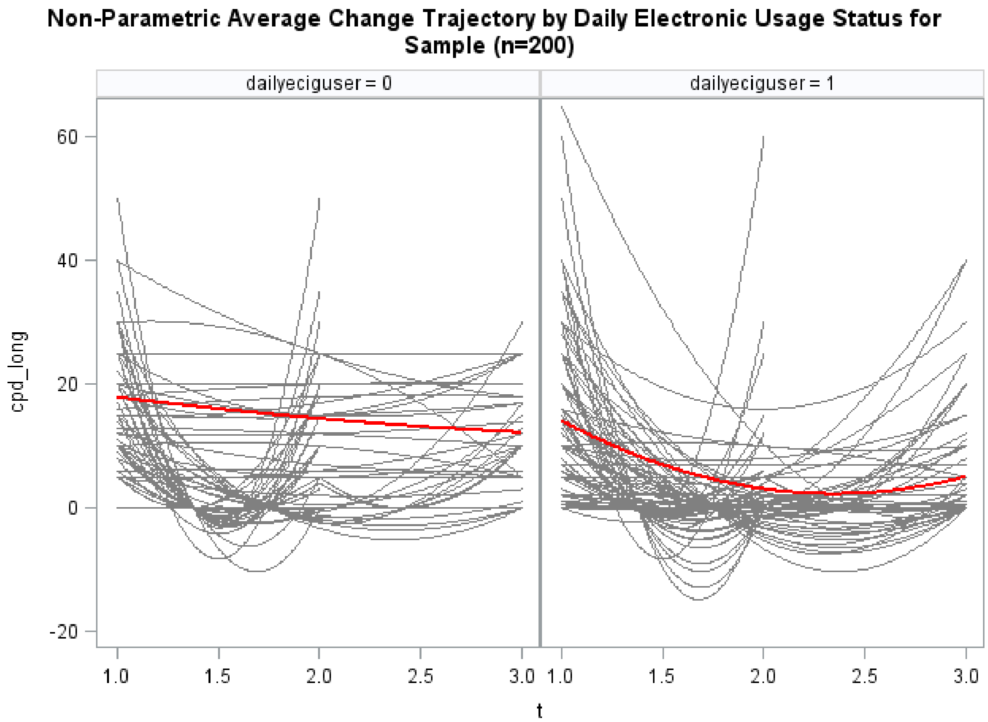
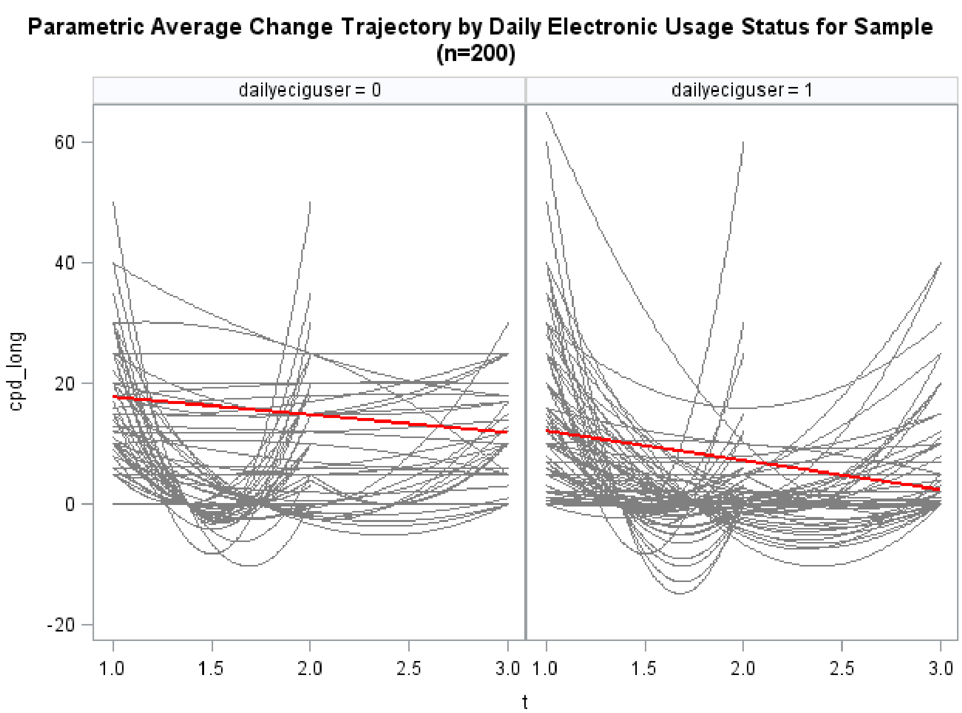


Figure 12: Parametric Average Change Trajectories By Daily Electronic Cigarette Usage Status for Sample (n=200)



In Figures 13 and 14, non-parametric and parametric average change trajectories are paneled by sex for the sample (n=200). In Figure 13, the average change trajectories are virtually identical between males and females (sex=1 is male); however, the baseline number of cigarettes smoked at t=1.0 (baseline) is visibly higher in males than in females. In the parametric analysis in Figure 14, the baseline number of cigarettes smoked at baseline is also higher for males. Additionally, the average change trajectory is slightly steeper in males than the trajectory for females; but once again, differences between slope and initial starting point are not obvious, which indicates that further exploration by non-visual means is necessary.

Figure 13: Non-Parametric Average Change Trajectories By Sex for Sample (n=200)

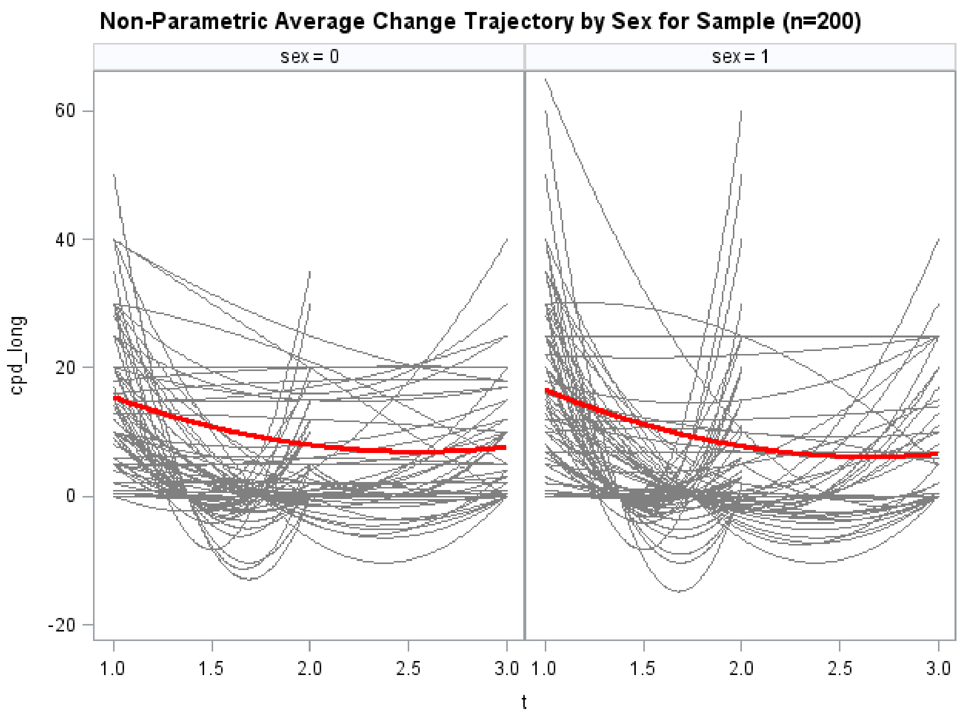
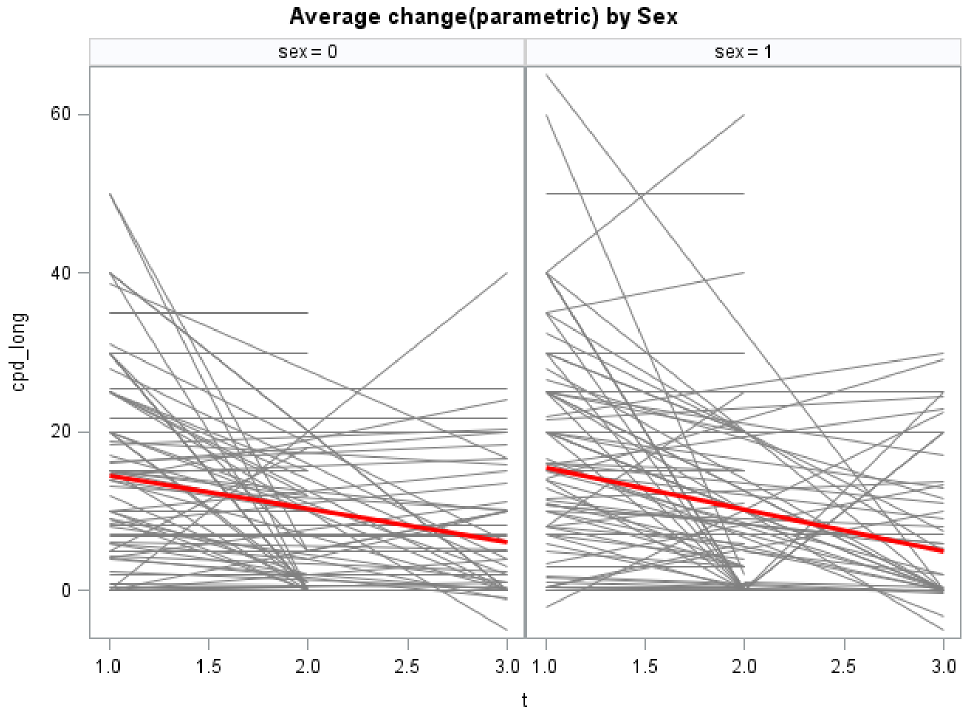


Figure 14: Parametric Average Change Trajectories By Sex for Sample (n=200)



Main Findings: Models 1 and 2

Graphical representations of trends and distribution generated through descriptive data analysis concluded that differences between sex and daily electronic cigarette use were present but further analysis was needed in order to explore differences in daily electronic cigarette use and sex. Below are results from running 2 Poisson regression models with the sum of average cigarettes smoked per day across 3 measurement occasions (the "sum" variable) as the outcome and cigarettes smoked per day at baseline (cpd_baseline), daily electronic cigarette usage status (dailyeciguser), and sex as predictors of interest.

Model 1 Results

Table 2: Odds Ratio Estimates from Model 1 (no interaction terms), n=200.

Effect	OR	95% CI		Chi-Square	P-Value
Cpd_baseline	1.051	1.049	1.053	2484.87	<.0001
Dailyeciguser	0.615	0.579	0.654	247.42	<.0001
Sex	1.066	1.002	1.134	4.14	.042

Interpretation:

We obtain a highly significant reduction in the average number of cigarettes smoked per day across 3 measurement occasions in daily electronic cigarette users (OR: 0.615; 95%CI: 0.579, 0.654), in comparison to the non-daily electronic cigarette users (dailyeciguser=0). In this model, daily electronic cigarette users experience a 38.5% reduction in the average number of cigarettes smoked per day over 3 measurement occasions when controlling for sex and cigarettes smoked at baseline (cpd_baseline).

The number of cigarettes smoked at baseline (cpd_baseline) is also highly significant (OR:1.051; 95%CI:1.049,1.053); every 1 unit increase in cigarettes smoked at baseline is equivalent to a 5.1% increase in the average number of cigarettes smoked per day across all 3 measurement occasions when controlling for daily e-cigarette usage status and sex. Sex is also highly significant in this model (OR=1.066; 95%CI: 1.002, 1.134) . Compared to females, males (sex=1) experience a 6.6% increase in the average number of cigarettes smoked per day across 3 measurement occasions when controlling for daily electronic cigarette usage status and cigarettes smoked at baseline.

Model 2 Results:

Table 3: Odds Ratio Estimates from Model 2 (with interaction terms), n=200.

Effect	OR	95% CI		Chi-Square	P-Value
Cpd_baseline	1.048	1.044	1.052	639.71	<.0001
Dailyeciguser	0.649	0.573	0.735	46.47	<.0001
Sex	1.205	1.108	1.310	19.01	<.0001
Cpd_baseline*dailyeciguser	1.004	0.999	1.008	2.74	.098
Sex*dailyeciguser	0.772	0.683	0.873	17.07	<.0001

Interpretation:

Again, we obtain a highly significant reduction in the average number of cigarettes smoked per day across 3 measurement occasions in daily electronic cigarette users (OR: 0.649; 95%CI: 0.573, 0.735), in comparison to the non-daily electronic cigarette users (dailyeciguser=0). In this model, daily electronic cigarette users experience a 35.1% reduction in the average number of cigarettes smoked per day over 3 measurement occasions when controlling for sex and cigarettes smoked at baseline (cpd_baseline).

The number of cigarettes smoked at baseline (cpd_baseline) is also highly significant (OR:1.048; 95%CI:1.044,1.052); every 1 unit increase in cigarettes smoked at baseline is equivalent to a 4.8% increase in the average number of cigarettes smoked per day across all 3 measurement occasions when controlling for daily e-cigarette usage status and sex. Sex is also highly significant in this model (OR=1.205; 95%CI: 1.108, 1.310). When compared to females, males (sex=1) experience a 20.5% increase in the average number of cigarettes smoked per day across 3 measurement occasions when controlling for daily electronic cigarette usage status and cigarettes smoked at baseline.

The interaction between cigarettes smoked at baseline and daily electronic cigarette usage status (cpd_baseline*dailyeciguser) is not significant (OR=1.004; 95%CI:0.999,1.008); p=.098), which indicates that the effect of daily electronic cigarette use is not significantly associated with the number of cigarettes smoked at baseline; however, the interaction between sex and daily electronic cigarette usage status (sex*dailyeciguser) is highly significant (OR=0.772; 95%CI:0.683,0.873; p<.0001). When compared to females who are not daily electronic cigarette users, males who are daily electronic cigarette smokers experienced a 22.8% reduction in the average number of cigarettes smoked per day across 3 measurement occasions when controlling for all other predictors. We explored both significant and non-significant interaction terms. For the non-significant interaction term, we explored differences between quartiles of cigarettes smoked at baseline (the 25^{th}, 50^{th}, and 75^{th} percentile of cigarettes smoked at baseline is 5, 15, and 25, respectively). For the significant interaction term (sex*dailyeciguser), we explored changes in gender while keeping daily e-cigarette usage status and baseline cigarettes smoked constant.

Quartile and Gender Comparison Results:

Table 4: Exploring the Sex*Dailyeciguser interaction term, keeping cpd_baseline and dailyeciguser constant between Gender changes, n=200.

Effect	OR	95% CI		Chi-Square	P-Value
Male, DailyEcigUser=1, cpd_baseline=5	0.615	0.551	0.686	76.10	<.0001
Female, DailyEcigUser=1, cpd_baseline=5	0.660	0.5914	0.737	54.35	<.0001
Male, DailyEcigUser=1, cpd_baseline=15	0.637	0.585	0.694	106.26	<.0001
Female, DailyEcigUser=1, cpd_baseline=15	0.685	0.625	0.750	66.51	<.0001
Male, DailyEcigUser=1, cpd_baseline=25	0.661	0.610	0.716	102.64	<.0001
Female, DailyEcigUser=1, cpd_baseline=25	0.710	0.649	0.777	55.55	<.0001
Male, DailyEcigUser=0, cpd_baseline=5	1.227	1.121	1.344	19.52	<.0001
Female, DailyEcigUser=0, cpd_baseline=5	1.018	0.997	1.041	2.74	.098
Male, DailyEcigUser=0, cpd_baseline=15	1.273	1.133	1.429	16.58	<.0001
Female, DailyEcigUser=0, cpd_baseline=15	1.056	0.990	1.127	2.74	.098
Male, DailyEcigUser=0, cpd_baseline=25	1.320	1.136	1.533	13.20	<.001
Female, DailyEcigUser=0, cpd_baseline=25	1.095	0.983	1.220	2.74	.098

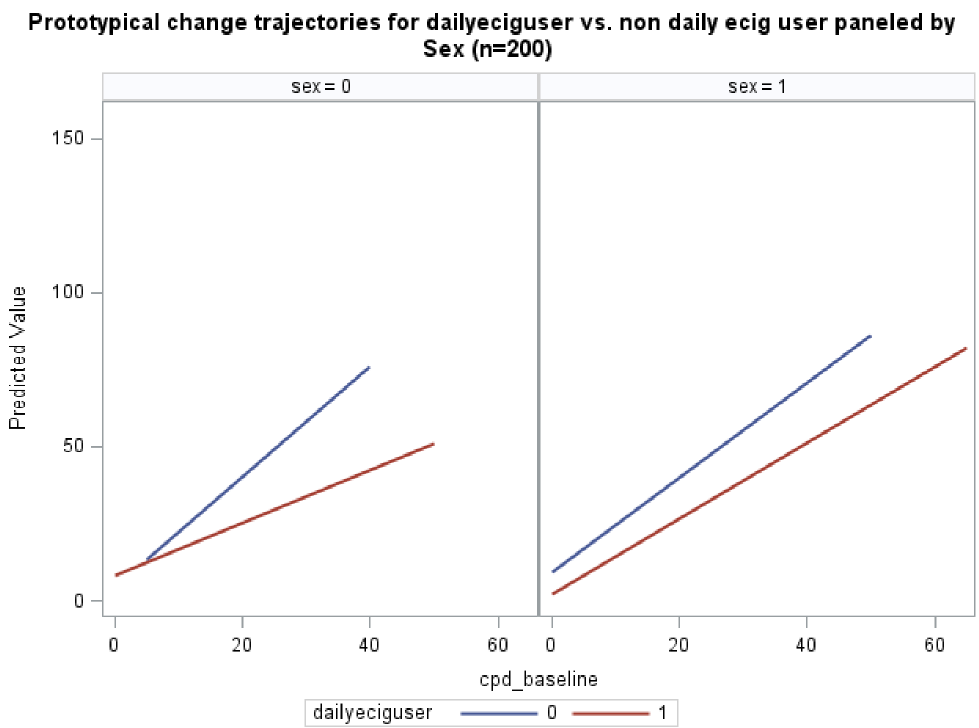
From Table 3, we see that the interaction between sex and daily electronic cigarette usage status (sex*dailyeciguser) was significant and the interaction between cigarettes smoked at baseline and daily electronic cigarette usage status (cpd_baseline*dailyeciguser) was not significant. We explore the both the significant and non-significant interactions by comparing quartile values for cigarettes smoked at baseline (we have to include quartile values for the non-significant interaction because it is still a predictor included in the model) and differentiating gender.

Overall, males experience greater reductions in the sum of cigarettes smoked per day over 3 measurement occasions than females when keeping cigarettes smoked per day at baseline constant. A similar pattern of reduction is observed at 15 and 25 cigarettes smoked per day at baseline (the 50th and 75th percentiles). For example, for male and female daily electronic cigarette users who smoke 5 cigarettes at baseline, males experience a 38.5% reduction in the average number of cigarettes smoked per day over 3 measurement occasions while females experience a 34% reduction (**see Table 4**).

When keeping sex and daily electronic cigarette use constant and modifying baseline cigarettes smoked per day (i.e. male, daily electronic cigarette users at cpd_baseline=5, 15, and 25), we see a reduced number of cigarettes smoked per day over 3 measurement occasions at lower baseline cigarette values. As baseline cigarettes smoked increases to the 50th and 75th percentiles, the number of average cigarettes smoked per day over 3 measurement occasions still decreases; however, less so than the reduction seen at the 25th percentile (38.5% reduction when baseline cigarettes smoked per day is 5, 36.3% reduction when baseline cigarettes smoked per day is 15, and 33.9% reduction when baseline cigarettes smoked per day is 25). A similar pattern is observed in females who are daily electronic cigarette users at 5, 15, and 25 cigarettes smoked per day at baseline. Males who are not daily electronic cigarette users experience an increase of 22.7% 27.3%, and 32% in the average number of cigarettes smoked per day over 3 measurement occasions at cpd_baseline levels of 5, 15, and 25 respectively.

In Figure 15 (below), a predicted prototypical change trajectory was generated to show differences in predicted sums of cigarettes smoked (y-axis= “predicted value”) between the sexes at varying baseline cigarette levels. When comparing the red line on the right panel (male, dailyeciguser=1) to the blue line on the left panel (female, dailyeciguser=0), we see a marked difference in predicted rate changes in the sum of cigarettes smoked across 3 measurement occasions. This corresponds to the OR value of 0.772 obtained during analysis of the interaction term “sex*dailyeciguser” in Model 2. Additionally, when we compare daily electronic cigarette users to non-daily electronic cigarette users within the same panel, we see that daily electronic cigarette users have a lower rate of increase in the sum of average cigarettes smoked per day across 3 measurement occasions when compared to non-daily electronic cigarette users.

Figure 15: Parametric Predicted Prototypical Change Trajectories for Daily E-Cigarette Users vs. Non-Daily E-cigarette Users Paneled By Sex (n=200)



Chapter 5: Discussion

5.1 Statement of Principal Findings

Literature Review: Research Question 1

There are consistent findings across the literature, which indicate the toxicity of electronic cigarettes; however, in general, findings of toxicity have been under experimental conditions where 1.) Unrealistic levels of heating or usage were incorporated, 2.) Inappropriate control designs were implemented and 3.) Levels of toxicity found in electronic cigarettes were found to be lower than levels of toxicity in conventional cigarettes. The few experiments conducted on health impact (specifically pulmonary function, cytotoxicity on myocardial cells, and blood cell counts) have shown immediate short-term adverse effects, some of which are comparable to smoking; however, health effects have yet to be studied in the long-term let alone compared to the long-term health effects of smoking conventional cigarettes. The study on myocardial cell viability showed that cigarette smoke extract detrimentally impacted myocardial cell function while electronic cigarette vapor extract reduced some viability but the myocardial cell remained intact[36].

Regarding awareness, perceptions, and usage, the literature consistently indicates that current and former smokers were more likely to be aware of and use electronic nicotine delivery systems than never smokers, which agrees with the findings of Pepper et al.[65]. In general, surveys on perception indicate that most users felt electronic cigarettes were less harmful or healthier than conventional cigarettes. In terms of demographics, findings on awareness levels between males and females either show no difference or higher awareness in males. With regard to age, younger adults (between 18-45 years old) are more likely to be aware of electronic cigarettes than adults greater than 65 years of age. In general, income, education, and race were not shown to be significant predictors of awareness of electronic cigarettes.

Secondary Analysis: Research Question 2

Model 1:

Model 1 verifies the hypothesis posed in this paper. In Model 1, daily electronic cigarette users experienced a 38.5% reduction in the average number of cigarettes smoked per day over 3 measurement occasions when controlling for sex and cigarettes smoked at baseline (Table 2). Males experienced a 6.6% increase in the average number of cigarettes smoked per day across 3 measurement occasions when controlling for daily electronic cigarette usage status and cigarettes smoked at baseline (Table 2). The number of cigarettes smoked at baseline is also highly significant; every 1 unit increase in cigarettes smoked at baseline is equivalent to a 5.1% increase in the average number of cigarettes smoked per day across all 3 measurement occasions when controlling for daily e-cigarette usage status and sex

Model 2:

When including interaction terms (sex*dailyeciguser and cpd_baseline*dailyeciguser), daily electronic cigarette users experienced a 35.1% reduction in the average number of cigarettes smoked per day over 3 measurement occasions when controlling for sex and cigarettes smoked at baseline (Table 3). Males experienced a 20.5% increase in the average number of cigarettes smoked per day across 3 measurement occasions when controlling for daily electronic cigarette usage status and cigarettes smoked at baseline (Table 3).

Although the hypothesis was verified by Model 2, the interaction between cigarettes smoked at baseline and daily electronic cigarette usage status was not significant (Table 3: p=.098), which indicates that the effect of daily electronic cigarette use is not significantly associated with the number of cigarettes smoked at baseline; however, the interaction between sex and daily electronic cigarette usage status was significant (Table 3: p<.0001). When compared to females who are not daily electronic cigarette users, males who are daily electronic cigarette smokers experienced a 22.8% reduction in the average number of cigarettes smoked per day across 3 measurement occasions when controlling for all other predictors (Table 3).

Quartile Analysis:

We explored both significant and non-significant interaction terms during the quartile analysis, which was dichotomized by sex. For the non-significant interaction term, we explored differences between quartiles of cigarettes smoked at baseline (the 25th, 50th, and 75th percentile of cigarettes smoked at baseline is 5, 15, and 25, respectively). For the significant interaction term (sex*dailyeciguser), we explored changes in gender while keeping daily e-cigarette usage status and baseline cigarettes smoked constant.

Overall, males experience greater reductions in the sum of cigarettes smoked per day over 3 measurement occasions than females when keeping daily electronic cigarette use and cigarettes smoked per day at baseline constant (Table 4). A similar reduction pattern was observed at 15 and 25 cigarettes smoked per day at baseline (the 50th and 75th percentiles). For example, for male and female daily electronic cigarette users who smoke 5 cigarettes at baseline, males experienced a 38.5% reduction in the average number of cigarettes smoked per day over 3 measurement occasions while females experienced a 34% reduction (see Table 4). Additionally, irrespective of gender, the sum of cigarettes smoked per day across 3 measurement occasions decreased as the number of cigarettes smoked at baseline decreased.

Predicted Prototypical Change Trajectory

The predicted prototypical change trajectory showed differences in predicted sums of cigarettes smoked across 3 measurement occasions between males and females. There were noticeable differences between male daily electronic cigarette users and female non-daily electronic cigarette users. Additionally, when we compare daily electronic cigarette users to non-daily electronic cigarette users within the same panel, we observed that daily electronic cigarette users had a lower rate of increase in the sum of average cigarettes smoked per day across 3 measurement occasions when compared to non-daily electronic cigarette users.

5.2 Strengths and Limitations of the study

Strengths

The main strength of this study relates to the methodology for secondary analysis, which balances the non-normal data obtained from primary data collection. In general, ignoring missingness in the modeling process is not an acceptable approach because of the large presence of nonresponse bias introduced into the sample; however, with the introduction of a logarithmic offset, we were not only able to include observations with missing data points (at baseline, or 1 month, or 12 months), but also able to sum the outcome of interest (average cigarettes smoked per day) in order to generate a normalized dependent variable appropriate for Poisson regression.

Second, findings that daily electronic cigarette use may reduce the sum of average cigarettes smoked over a set period of time corroborate conclusions from the original analysis conducted by Etter et al.[32]. Additionally, the significance of being a male electronic cigarette user also corroborates findings from the literature, which generally agree that males have higher awareness and usage of electronic cigarettes than females[21, 64, 74]. Furthermore, with regard to the review of the literature, few studies to date have provided comprehensive reviews with respect to both biological and behavioral aspects of electronic cigarette use, which adds to the strength of the literature review.

Limitations

There are several limitations with regards to the sampling methodology of the original study conducted by Etter et al. as well as the secondary analysis. The original study relied on self-reports of the use of electronic cigarettes and tobacco, which may over/underestimate the number of cigarettes smoked per day. Additionally, the convenience sample from the original study was drawn from a smoking cessation website, which weakens the finding that electronic cigarette users were more likely to seek smoking cessation than non-users. Furthermore, daily electronic cigarette users who actively participate on web forums and product websites have more positive opinions about electronic cigarettes than daily electronic cigarette users who are not active forum participants. For example, people who purchase electronic cigarettes in retail stores rather than online distributors may have a different opinion about e-cigarettes. Having a more positive opinion about a product may introduce bias because users may be compelled to believe a product is working due to their favorable perspective. Lastly, the original study oversampled daily electronic cigarette users, former smokers, older individuals (all at follow-up), and experienced considerable incomplete participation at follow-up, which limits the generalizability of the results. However, the results from the present study may still be applicable to current smokers who are daily electronic cigarette users.

The aforementioned limitations apply to the current secondary analysis as well. In addition to these limitations, the current study was also faced with the task of adapting the analysis for missing data. Originally, n=52 participants (the total number of participants who had complete information at baseline, 1 month, and 12 months) were included in the final model, which inevitably introduces bias due to non-inclusion of non-ignorable missing data; however, after introducing new criterion to create a logarithmic offset, we were able to increase this sample size to 200 participants by allowing for one missing measurement occasion (out of 3) for each observation.

Lastly, in Model 1, the number of cigarettes smoked at baseline was highly significant (OR:1.051; 95%CI:1.049,1.053); however, the odds ratio obtained is not a very convincing one. Additionally, in model 2, the number of cigarettes smoked at baseline was also highly significant (OR:1.048; 95%CI:1.044,1.052); however, as in Model 1, the odds ratio was not very convincing in terms of practical significance.

5.3 Implications and Recommendations

Although statistical significance was obtained in both models, practical significance is difficult to ascertain due to large blocks of missing data and the method of primary data collection. Regardless of the method used to address missing data, either through logarithmic offsets or through imputation, nonresponse bias will always be present. The trajectories of non-responders and responders may be similar or different for varying reasons that are difficult to pinpoint. As such, efforts should be made to limit missingness in order to generate a model that is as true to the data as possible. The convenience sampling methodology used in the primary analysis also contributes to doubts about generalizability to the rest of the smoking population. As stated before, Etter et al. collected survey data from a smoking cessation website[32], where most electronic cigarette users were smokers who were already in the process of quitting or reducing their cigarette consumption. Previous studies have shown that most electronic cigarette users are current smokers, which means that results from both the primary and secondary analysis are confounded by the “former smoker” makeup of the population sample. Meaning, estimates showing reduction of cigarette smoking may actually be overestimates generated by the “intent-to-quit” characteristic of the sampled population, and the reductions that we see among current daily electronic cigarette users may be amplified by the fact that they have been planning to quit or reduce their tobacco consumption.

Although the interaction between cigarettes smoked at baseline and daily electronic cigarette use was not significant in a statistically meaningful way, it may still be practically significant. One would logically conclude that using electronic cigarettes daily (assuming there is a "treatment" affect that alleviates nicotine cravings) would be affected by the number of reported cigarettes smoked at baseline. However, even though the interaction term was not significant (p=0.098), we are mainly concerned about identifying the overall trend observed from increasing baseline cigarette consumption while accounting for electronic cigarette usage status and sex. The trend indicated that in general, the effect of daily electronic cigarette use experienced diminishing returns as the number of baseline cigarettes increases. Hence, practical significance of the impact observed from daily electronic cigarette usage (which may be affected by baseline cigarettes smoked) may still be worth investigating.

Additionally, on average, there are fewer cigarettes smoked among daily electronic cigarette users when there are fewer cigarettes smoked at baseline across both genders. Among those that smoke a higher number of cigarettes at baseline (at least at the 75^{th} percentile), there is still a reduction in the number of cigarettes smoked over 3 measurement occasions albeit less so when compared to those that smoke cigarettes at the 25^{th} percentile. This suggests that electronic cigarette use may be useful in reducing the number of cigarettes smoked among all types of smokers, and harm reduction—the reduction in total number of cigarettes smoked across multiple measurement occasions—is present in all genders.

Third, the interaction term between sex and daily electronic cigarette use was found to be statistically meaningful; however, this may be due to the fact that males are more aware of electronic cigarettes than females, hence, males' usage of electronic cigarettes is higher than female usage, which may affect estimates. A sampling methodology that is representative of the entire population may allow us to make future deductions about how sex impacts the effect of daily electronic cigarette use; however, due to the original sampling method, we can only generalize results to former and current smokers.

Fourth, the results from the literature review and secondary analysis aim to provide an objective analysis of the benefits and harms of electronic cigarettes. Findings from both the literature review and secondary analysis suggest that the electronic cigarette may have potential use in harm reduction. The literature in general suggests that although toxins are present in electronic cigarettes, they are present in amounts comparable to environmental levels of toxins, such as environmental PAH (polycyclic aromatic hydrocarbons). Studies that have found toxin levels above environmental levels have been based on unsound research design and unrealistic heating conditions (such as using a smoking machine compared to studying an actual human user)[15], which implies that resulting concentrations of toxic compounds in vapor may be overestimates, and consequently, ratios comparing e-cigarette toxins to conventional cigarette toxins may be underestimates; variations in e-cigarette components such as battery strength or cartridge size may also bias levels of toxins. Higher battery strengths lead to higher vaporization temperatures, which may lead to by-products like Acrolein or increased levels of PAHs. On the other hand, lower battery voltages may lead to lower vaporization temperatures, which may produce entirely different levels and types of toxins and make it difficult to ascertain long-term health benefits and/or disadvantages. Standardized quality management must be enforced for e-cigarette manufacturing in order to systematically test and regulate these products.

The conclusion of the secondary analysis presented a predicted prototypical change trajectory (figure 15). Although the predicted change trajectory showed an overall upward trend (implying that higher cigarettes smoked at baseline means higher sums of cigarettes smoked across 3 measurement occasions), the initial status and overall rate of the sum of cigarettes smoked at baseline, 1 month, and 12 months was lower for daily electronic cigarette users than non-daily users. The same pattern was observed across both genders and remained consistent across quartiles of cigarettes smoked at baseline. This suggests that demographic characteristics may not play a major role in harm reduction, and electronic cigarettes can potentially reduce cigarette consumption in males and females.

5.4 Future research and direction

Future research in the electronic cigarette domain needs to address four areas of interest. First, missingness and attrition must be addressed in observational studies aiming to assess true "natural behavior" of a cohort of electronic cigarette users. Without complete data, results from observational studies are difficult to generalize to a larger smoking cohort. Second, associations of age, income, sex, and intent with reduced cigarette consumption (among current daily e-electronic cigarette users) need to be studied further in order to clarify the mixed results presented in the current review. Third, in order for public health officials to accurately assess the harm reduction or harm potential of electronic cigarettes on a biological level, standardized manufacturing quality must be monitored and regulated by independent parties. Without quality regulation, differences in health outcomes are difficult to attribute to a specific causative agent (hardware component, liquid degradation, etc.). Finally, despite the lower concentration of harmful chemicals and lack of reliable evidence verifying significance of toxic emission levels from electronic cigarettes, the safety of electronic cigarettes has yet to be proven through clinical studies on health impact[35]. Additional clinical studies that employ sound research design need to be pursued in order to validate or deny the safety of electronic cigarettes.

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