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Patterns of Tobacco Product Use in the US Population using the Population Assessment of Tobacco and Health Study

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By
Wellington Chukwuma Onyenwe
Doctor of Philosophy

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Division of Environmental Health & Health Promotion and Behavior

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An abstract of
a dissertation submitted to the School of Public Health at Georgia State University
in partial fulfillment of the requirements for the degree of
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Abstract

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The U.S. Centers for Disease Control and Prevention (CDC) reported that, in the United States, tobacco product use is the prominent cause of avoidable disease, disability, and death in the year 2017. While tobacco use has severe public health consequences, it has been difficult to fully understand the behaviors surrounding this preventable public health challenge. Introduced in 2011, the Population Assessment of Tobacco and Health (PATH) Study's purpose is to influence the Food and Drug Administration's regulatory activities via the Family Smoking Prevention and Tobacco Control Act (TCA). The PATH study is a longitudinal cohort study examining tobacco use and behavior in adolescents and adults. The purpose of this dissertation is to examine use and behavior for tobacco products over time and examine both initiation and switching of products. In our analysis, we found that demographically, those who initiated or consistently used smokeless products over time were white and male while those who used traditional combustible products varied more in terms of racial makeup. With smokeless and traditional combustible products, most participants chose to use tobacco products with moderate nicotine levels, regardless of previous exposure in a prior study wave. There was very little evidence of product switching that resulted in increased tar/nicotine content differences among the population we studied. Younger participants were using electronic cigarettes in greater proportions than adults and as opposed to traditional combustible products. We also found that the rate of nicotine metabolism was not related to frequency of e-cigarette use or type of product. These results provide insight into ways in which prevention strategies can be targeted to groups that are more likely to initiate and stay using tobacco products.

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To my cohort, we have certainly been through the wringer and pushed to the limit with this program. Thank you all for the unbreakable bond during the high times and the frustrating ones. You certainly were the foundation, support system and comedic relief simultaneously.

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My culinary community and the Food Network, thank you for your support, creative outlet and encouragement. You showed me that dreams can become reality and that doctors do indeed have time to be chefs.

Lastly, to whomever may read this body of work, please remember, you are and will always be a product of your environment. Only you can determine the quality, influence, and impact of the product.

Dedication

For the Ahaiwe (Ahapuiwe) and Onyenwe families of our respective Eziala and Akpodim communities. For Ezinihitte Mbaise local Government Area in Imo State, Nigeria. “Onyeaghala Nwanne Ya! Igbo Kwenu!”

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List of Abbreviations

Audio Computer-Assisted Self-Interviewing (ACASI)
Balanced Repeated Replication (BRR)
Biomarker Restricted-Use Files (RUF)
Body Mass Index (BMI)
Center for Tobacco Products (CTP)
Chronic Obstructive Pulmonary Disease (COPD)
Civilian, Noninstitutionalized Population (CNP)
Computer-Assisted Personal Interviewing (CAPI)
CYP2A6 Cytochrome P450 Family 2 Subfamily A Member 6 (CYP2A6)
Dataset 1011 (DS1011)
Dataset 1012 (DS1012)
Dataset 1036 (DS1036)
Dataset 1101 (DS1101)
Dataset 1121 (DS1121)
Dataset 1131 (DS1131)
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Dataset 4001 (DS4001)
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Dataset 4212 (DS4212)
Dataset 4322 (DS4322)
Electronic Cigarettes (E-Cigarettes)
Electronic Nicotine Delivery Systems (ENDS)
Family Smoking Prevention and Tobacco Control Act (TCA)
Food and Drug Administration (FDA)
Human Immunodeficiency Virus (HIV)
Inter-university Consortium for Political and Social Research (ICPSR)
Little Cigar, and Cigarillo (LCC)
Monitoring the Future Study (MTF)
National Health Interview Survey (NHIS)
National Institute on Drug Abuse (NIDA)
National Institutes of Health (NIH)
National Longitudinal Study of Adolescent Health (Add Health)
National Survey on Drug Use and Health (NSDUH)
National Youth Tobacco Surveys (NYTS)
Nicotine Exposure Questions (NEQs)
Nicotine Metabolite Ratio (NMR)
Odds Ratio (OR)
Population Assessment of Tobacco and Health (PATH)
Primary Sampling Units (PSUs)
Relative Risk (RR)
Serum Panel - Cotinine and Hydroxycotinine (SCOT)
Sudden Infant Death Syndrome (SIDS)
Trans-3’-Hydroxycotinine (3HC)
U.S. Smokeless Tobacco (USST)
United States (U.S.)
Urine Panel - Urinary Nicotine Metabolites (UNICM)
US Centers for Disease Control and Prevention (CDC)
Virtual Data Enclave (VDE)
Youth Risk Behavior Surveillance System (YRBSS)

Chapter I. Introduction

Background and Statement of Problem

The U.S. Centers for Disease Control and Prevention (CDC) reported that, in the United States, tobacco product use is the prominent cause of avoidable disease, disability, and death in the year 2017.[1, 2] In fact, they also stated, a significant portion of all tobacco use begins during adolescence and early adulthood.[1, 2] Cigarette tobacco use, and other forms of tobacco use, is the leading cause of preventable morbidity and mortality in the United States (U.S.). In the U.S. alone, more than 480,000 lives were lost due to smoking-related diseases in 2020.[3, 4] More importantly, smoking costs the U.S. at least $130 billion in direct healthcare expenditures.[3, 4] Smoking and tobacco use are responsible for more deaths each year than Human Immunodeficiency Virus (HIV), motor vehicle injuries, firearm-related events, illegal drug use, and alcohol use, combined.[5] It was recently found that smoking is responsible for 90% of all lung cancer mortality.[5] Moreover, in comparison to breast cancer, more women die each year from lung cancer.[5] Cigarette smoking and tobacco use is responsible for about 80% of all mortality resulting from chronic obstructive pulmonary disease (COPD); it also increases the risk for mortality from all causes in men and women.[5] In the past five decades, the risk of dying from cigarette smoking has risen in the U.S.[5] Although smoking rates have been declining, as of 2018, it was reported that roughly 34 million US adults still smoked cigarettes.[6] Additionally, CDC found that for every 30 Americans living with a serious smoking-related illness, there is one American who dies as a result of smoking.[6]

Tobacco product use leads to cancers, heart disease, stroke, various lung diseases, type 2 diabetes, and other chronic health conditions.[6] Smoking not only impacts the immediate smoker, but can also raise premature birth and sudden infant death syndrome (SIDS) risk in pregnant women.[6] Tobacco use resulting in secondhand smoke affects 58 million non-smoking Americans.[6] In addition, secondhand smoke has been causatively linked to diseases such as stroke, lung cancer, and coronary heart disease in adults.[6] It was found that children exposed to secondhand smoke had an elevated risk of SIDS.[6] Exposed children also exhibited compromised lung function, increased occurrence of severe asthma attacks, middle ear disease, and acute respiratory infections.[6]

Smokeless tobacco carries a lower risk of adverse health effects than traditional combustible products, yet bears a similar risk to that of electronic cigarettes.[1, 7-9] Although associated with lower risk of health effects, it has been proven no safe level of smokeless tobacco use currently exists.[10-13] These products typically contain over 3000 chemicals including nicotine, making them highly addictive in nature.[9, 12, 14] They contain 28 cancer-causing chemicals, in which the tobacco-specific nitrosamines are the most prominent. Smokeless tobacco use is highly correlated with dental disease, oral, esophageal and pancreatic cancers.[14] Also, smokeless tobacco when pregnant increases the risk for adverse reproductive effects including stillbirth, premature birth and low birth weight.[3, 5, 9, 13-15]

Electronic cigarettes (e-cigarettes) were initially considered safer than conventional traditional combustible products; however, there is growing recognition that the e-cigarette aerosol can contain harmful substances.[16] These may include nicotine, ultrafine particles that can be inhaled deep into the lungs and flavoring such as diacetyl; diacetyl is a chemical linked to a serious lung disease. They may also contain volatile organic compounds cancer-causing chemicals, heavy metals such as nickel, tin, and lead, in addition to nicotine.[16] Though e-cigarette aerosol has fewer harmful chemicals than traditional combustible tobacco product smoke, it is still not proven to be a safe alternative.[16] In addition, e-cigarettes can yield injuries such as having defective batteries which can lead to fires and explosions resulting in serious adverse effects.[16] Both children and adults have been poisoned by ingesting, inhaling or absorbing e-cigarette liquid via the eyes or skin, displaying how acute nicotine exposure can be toxic.[16, 17]

Differentiation of Tobacco Products

Traditionally, smokeless tobacco use involves sniffing, chewing, or putting the tobacco product in-between the gums and cheeks/lips.[18] In the United States, the two main varieties of smokeless tobacco used consist of snuff (dry and finely ground tobacco, moist/bag-like pouches) and chewing tobacco (plug, loose leaf and twist); dissolvable tobacco (lozenges, sticks, strips and orbs) use on the rise.[19, 20] Experimentation with smokeless tobacco by new users may increase especially with the accessibility of low-nicotine containing, flavored, smokeless tobacco products not having harsh attributes as similar products before.[19, 20] Furthermore, dissolvable tobacco products often appeal to youth and younger users because they most times have attractive packaging, the appearance of candy or small mints (slowly dissolve in the mouth), and are easily hidden from view; they also pose an accidental poisoning risk for children.[19-22]

Traditional combustible tobacco products consist of cigarettes, cigars, hookah, little cigars, and cigarillos. As mentioned previously, these products are the highest ranking cause of disease that is preventable worldwide.[20, 23] Cigarettes may vary in size (long vs. short cigarettes) but cigars have much greater variability in size and nicotine delivery. In fact, cigars with smaller sizes are sometimes referred to as cigarillos and small filtered cigars.[20] With their large size, cigars can provide 10-times as much nicotine, deliver 2-times more tar, and deliver more than 5-times more carbon monoxide in comparison to a filtered cigarette.[20] With the exception of menthol cigarettes, flavored cigarettes are illegal currently in the US, though cigarette-resembling products available on the market labeled “little cigars” include flavors that resemble fruit or candy, which is more attractive to adolescents and young adults.[20] In addition to young adults thinking cigars are less addictive and present fewer health risks than cigarettes, they are typically less expensive than cigarettes; these attributes also may appeal to youth.[20] Smokers of both cigars and cigarettes are exposed to nicotine, alongside toxic, carcinogenic chemicals that are produced when the tobacco product is burned.[20]

E-cigarettes are a categorized group of devices that produce an inhalable aerosol produced by heating liquid.[1, 3] These aerosols typically contain nicotine, flavorings, propylene glycol, glycerin and other additives.[1, 3] These products have a variety of designs and appearances as shown in the figure below (Figure 1.1).[1, 3] In fact, the diverse and nonstandard naming and classification conventions for the devices is a major hurdle in monitoring and surveilling these products, and their patterns of use.[1, 3] However, in May 2016, the Food and Drug Administration (FDA) exercised its regulatory authority over e-cigarettes deeming them to be under FDA's tobacco product regulatory authority.[1, 3] Though they now fall under the umbrella of tobacco products, these devices are referred to, by the companies themselves, and by consumers, as "e-cigarettes, e-cigs, cigalikes, e-hookahs, mods, vape pens, vapes, tank systems, and electronic nicotine delivery systems (ENDS)."[1, 3]

Figure 1.1 Diversity of E-Cigarette Products

Source: Photo by Mandie Mills, CDC.

Patterns of Tobacco Product Use in the United States

In 2017, approximately 20% of high school students (2.95 million) and 5% of middle school students (0.67 million) currently used tobacco products.[1-3, 17] These were reported to have been the most commonly used electronic tobacco product among both middle and high school students since 2014.`[1-3, 17] In fact, one in two high school students that reported using a tobacco product and two in five middle school students that reported using a tobacco product, also reported using ≥2 tobacco products.[1-3, 17] One source reported that, "An estimated 4.1% of high school students are current smokeless tobacco users. Smokeless tobacco use is much more common among male than female high school students (6.8% versus 1.3%)."[1, 17] With high school students that reported use of smokeless tobacco, the frequency of use was highest amongst American Indian or Alaska Natives (9.2%), trailed by whites (5.7%), then Native Hawaiian or Pacific Islanders (5.3%), Hispanics (2.2%), Blacks (0.9%), and lastly Asians (0.7%).[7, 17]

3.8% of U.S. adults were current smokeless tobacco users; furthermore, the reported use was much higher among men than women (6.8% vs. 1.0%), in 2017.[7, 17] Furthermore, American Indian/Alaska Natives and whites were reported having the highest use.[7, 17] It was also found that in 2017, an estimated 34.3 million or 14.0% of adults 18 years of age and older, were current cigarette smokers.[7, 17] Furthermore, in the same year, 15.8% of men currently smoked cigarettes daily compared to 12.2% of women.[17, 23] Considering race ethnicity within the same year, American Indians/Alaska Natives (24.6%) had the highest prevalence of current cigarette smoking, followed by non-Hispanic whites (15.3%), non-Hispanic blacks (15.1%), Hispanics (9.9%) and Asian-Americans (7.0%).[17, 23] With adults who stated that they have ever smoked daily, 78% had smoked their first cigarette by the time they were 18 years of age, and 94% had by age 21.[17, 23]

E-cigarettes were the most regularly used tobacco product among high school (11.7%; 1.73 million) and middle school (3.3%; 0.39 million) students, in 2017.[2] Within the same group, smokeless tobacco use was higher among males than among females with e-cigarettes being most commonly used tobacco product among non-Hispanic white (14.2%) and Hispanic (10.1%) high school students.[2] Among middle and high school students, both ever and past-30-day e-cigarette use have more than tripled since 2011.[2] Recent data show that, "The prevalence of past-30-day use of e-cigarettes is similar among high school students (16% in 2015, 13.4% in 2014) and young adults 18–24 years of age (13.6% in 2013–2014) compared to middle school students (5.3% in 2015, 3.9% in 2014) and adults 25 years of age and older (5.7% in 2013–2014)."[2] According to CDC, their growing popularity amongst teenagers and young adults has revealed that "Past-30-day use of e-cigarettes among 8th-, 10th-, and 12th-grade students (6.8%, 10.4%, and 10.4%, respectively) exceeded exclusive, past-30-day use of conventional cigarettes in 2015 (1.4%, 2.2%, and 5.3%, respectively)."[2] Furthermore, e-cigarette use is strongly associated with the use of other tobacco products among youth and young adults, particularly the use of traditional combustible tobacco products.[4] It was found in 2015 that 58.8% of high school students who were current users of traditional combustible tobacco products were also current users of e-cigarettes.[2] It was found by the CDC that youth are more likely to use e-cigarettes than adults.[16] Furthermore, in 2020, 3.6 million U.S. middle and high school students used e-cigarettes in the past 30 days of participating in the study. This included 4.7% of middle school students and 19.6% of high school students, which was an increase from years past.[16]

According to CDC, those who reported being 18–24 years of age, saw e-cigarette tobacco product use more than double from 2013 to 2014; this was after a time frame of very little change between years 2011 to 2013. Though in contrast to their younger counterparts in the same time period, adults' past-30-day use of traditional cigarettes (9.6%) surpassed exclusive, past-30-day use of e-cigarettes (6.1%); though simultaneous use is common amongst both age groups.[2] From the same study, it was found that flavored e-cigarette use among young adult current users (18–24 years of age) exceeds that of older adult current users (25 years of age and older).[2] In 2019, 4.5% of U.S. adults were current e-cigarette users; 36.9% of those users also currently smoked cigarettes, while 39.5% reported being former cigarettes smokers, and 23.6% never reporting ever smoking cigarettes.[16] The percentage of those reporting never smoked cigarettes was the highest among those aged 18–24 years (56.0%), amongst current adult e-cigarette, and lowest in older age groups.[16]

There is clear evidence of a growing trend in increasing various tobacco product use amongst multiple age groups even with successes of tobacco cessation programs decreasing overall number of people using traditional combustible products. Although certain products are utilized more within specific age groups, there is still an increase of new users and continued existence of current users. However, the data from many of these studies are snapshots in time and cross-sectional. Even still they depict a growing trend in a troubling direction that defies public health practice and stewardship. There is also a lack of understanding of the graduation or progression process based on nicotine content in products versus identifying smoker use types.

Understanding Initiation, Product Switching and Nicotine Dependence and Relationship with Progression of Tobacco Use Behavioral Patterns

U.S. Smokeless Tobacco (USST) created a strategy for new users to "graduate" up to tobacco product brands that contain more nicotine over time.[24, 25] USST's "The Graduation Theory", a strategic marketing document, described this theory as "newly attracted users of smokeless tobacco are most likely to begin with products that are milder tasting, more flavored, and/or easier to control in the mouth."[24, 25] Furthermore, the study also found that there is a natural progression of switching between tobacco product brands; that is, users would switch to products that taste more full-bodied, would have less flavor/sweet flavor and also have a higher intensity of tobacco taste than the perceived entry level tobacco product.[25] It has been slowly accepted that flavored tobacco products are widely considered to be starter products. These types of products use flavors to mask the bad taste of tobacco and entice youth to begin use; there have been studies that show that youth "mistakenly believed flavored tobacco products were less harmful than their non-flavored counterparts."[26, 27] It was also found that youth are much more likely to begin experimentation with other tobacco products, once they begin using one tobacco product.[26, 27]

Recent campaign ads highlighting the negative effects of smoking and encouraging smoking cessation have served as the impetus for the tobacco industry to create products and strategies to attract new generations of tobacco users. For example, in 1981, a Philip Morris research report stated "The importance of knowing as much as possible about teenage smoking and attitudes because today's teenager is tomorrow's potential regular customer"; the majority of smokers first begin as teenagers.[28] Furthermore in 1998, the chairman of Liggett and Myers Tobacco Company, Bennett Lebow, stated that "if you are really and truly not going to sell to children, you are going to be out of business in 30 years."[29] Also, another historical point, in 1984 a RJ Reynolds internal document stated that "Younger adult smokers are the only source of replacement smokers and that, should younger adults turn away from smoking, the industry must decline, as a population which does not give birth will eventually dwindle."[30] In fact years later, a former sales representative for RJ Reynolds, Terrence Sullivan, publicly stated that when he asked an RJ Reynolds executive which young people they were targeting, junior high kids or even younger, the executive replied that "If they have lips, the tobacco companies wanted them."[31]

In a 2006 court ruling by a US district court judge, it was found that in order to recruit new, or replacement smokers, cigarette manufacturers intentionally marketed to young teenagers/adults under the age of 21. This action was done to ensure the economic future and longevity of the industry.[23] In 1972, a Brown and Williamson research paper stated that there were pipe tobacco products that had a sweet aromatic taste that teenagers would have gravitated towards.[32] Furthermore, a 1978 Lorillard research report found that the ideal desired product had a pleasant aroma, produced no after breath nor stale smoke on clothing or in the air; they felt this was evidence of a psychologically better, healthier smoke because that which was enjoyed, tasted and smelled good could not be so bad.[33]

In 1979, in a memo between tobacco executives on fruit flavored chewing products, they felt that younger chewers would be attracted to products with less tobacco taste and that the industry investigate the "possibility of borrowing switching study data from the company which produces Life Savers candy" to determine flavors for teens with the largest appeal.[34] Another 2005 report on tobacco marketing strategies, in the journal *Health Affairs*, found evidence that the tobacco industry “developed flavored cigarettes and packaging in order to intentionally appeal to young people”.[35]

At the Harvard School of Public Health newspaper, the Harvard gazette, Gary Carpenter, the author of a report and research analyst for the University, stated that, “Flavored cigarettes can promote youth smoking initiation and help young occasional smokers become daily smokers by reducing or masking the natural harshness and taste of tobacco smoke and increasing the acceptability of the toxic product”.[35] Furthermore Greg Connolly, his colleague at the University, commented that the packaging and imagery of flavored products serve as powerful new sources of promotion.[36] Also, seasonal titles and availability of some of the products further supports evidence that these cigarettes are “designed to be starter cigarettes, rather than those designed and marketed to build brand loyalty”.[36]

Many national surveys have provided data estimating smoking behavior among adolescents and young adults in the United States, typically in cross-sectional surveys. Some of these major data sources include National Youth Tobacco Survey (NYTS), Monitoring the Future Study (MTF), National Longitudinal Study of Adolescent Health (Add Health), National Health Interview Survey (NHIS), National Survey on Drug Use and Health (NSDUH), and Youth Risk Behavior Surveillance System (YRBSS), along with the Surgeon General’s report *Preventing Tobacco Use Among Youth and Young Adults*.[37] These findings uncovered that initiation of tobacco use in almost all cases begins before adulthood and that this pattern has not significantly changed since 1964.[37] In fact, it was found among adults ages 30 to 34 who ever smoked daily, that 89.8 percent tried their first cigarette before age 19, and 99.2 percent by age 26.[37] Furthermore, the 2012 Surgeon General’s report concluded that a relatively high proportion of adult smokers initiate at a relatively early age; in fact, more than one-third of adults, or 36.7%, reported that they tried their first cigarette by age 14.[37]

According to the Substance Abuse and Mental Health Services Administration, the rates of cigarette smoking have been declining, yet there have been recent signs of the slowing of that pattern. Furthermore, evidence clearly shows an increasing trend toward lighter use as among past-30-day cigarette smokers, though the proportion of daily smokers has been decreasing; however, with nondaily smokers, the trend has been increasing.[37] Unfortunately, the same type of information is not as extensive on other or newer tobacco products, specifically for trends in their use. As new tobacco products surface frequently and are constantly modified, it is difficult to assess data for tobacco products other than traditional cigarettes. As alluded to in the data, adolescent and young adult tobacco use has been defined by successive actions categorized by multiple behaviors and feelings, ranging from initiation to cessation. Adolescent tobacco use varies highly amongst adolescents regarding frequency and intensity of use.[38, 39]

However, there is evidence to suggest that recent approaches to marketing may be shifting use trends. A study investigated the initiation, motivation, and decision-making with regards to cigarette, little cigar, and cigarillo (LCCs) tobacco product use. This study was an audio-recorded in-depth interview of 60 individuals, aged 14–28. It concluded that the study participants reported smoking more than or equal to 1 cigarillo per week; half of the study participants reported that they also smoked cigarettes.[38] In fact, with dual users, 60% initiated smoking LCCs before or at the same time as cigarettes.[38] Within the same set of dual users, 40% began smoking cigarettes before LCCs.[38] When asked about reasons for smoking cigarettes in addition to LCCs, the individuals stated that marketing advertisements swayed their brand selection choice and the brands advertised were easily accessible.[38] In addition, cravings were satisfied in less time when smoking the LCC products, as opposed to other products.[38] Also, cigarette smokers reported first smoking LCCs in social settings, sharing LCCs with other smokers. Cigarette smokers also first smoked LCCs as opposed to cigarettes due to being able to afford a single LCC but not a pack of cigarettes.[38] However, there is very limited to no systematic data collected regarding how patterns of tobacco product use vary by product type or by combinations of use, including product switching.

Description of the Population Assessment of Tobacco and Health (PATH) Study and Data Set

A nationally representative longitudinal cohort study, the PATH examines tobacco use and how it affects the health of those that live in the United States.[3] It is the first large longitudinal cohort study on the topic of tobacco product characteristics and use and is led by the National Institutes of Health (NIH) and FDA.[3] The data available provides a pragmatic evidence platform for developing, implementing, and evaluating regulations governing tobacco products. It measures tobacco product use behavior and the resulting health effects. Over time, the goal is to examine the health impact of changes in regulations by surveying tobacco users and nonusers. It gathers data about multiple tobacco products, including cigarettes, e-cigarettes, traditional cigars, cigarillos, filtered cigars, smokeless tobacco, snus pouches, pipe tobacco, hookah, dissolvable tobacco and for youth, bidis and kreteks.[3] Furthermore, biomarkers of exposure and potential harm were measured in the matrices of blood and urine. The biomarker measurements are completed in a subsample of participants and can be analyzed alongside associated data on available tobacco product use.

The sample design in the first Wave (called Wave 1) was a four-stage stratified area probability to select adults (18-24, 25-29 and 30+) and youth ages 12 to 17 from the U.S. civilian, noninstitutionalized population (CNP).[3] In subsequent waves, they added an additional "shadow sample" of youth ages 9 to 11 to be interviewed in subsequent waves.[3] According to ICPSR, "The first stage involved a stratified sample of geographical primary sampling units (PSUs) being selected; a PSU was considered to be a county or group of counties." The second stage involved smaller geographical segments being formed within each PSU; a sample of those segments were then drawn.[3] Residential addresses located in the segments made the third stage sampling frame. Lastly, adults and youth from the sampled households identified at these addresses made up the fourth stage; these data contained varying sampling rates for adults by age, race, and tobacco-use status.[3]

1) The adults were sampled in two phases: “Phase 1 sampling used information provided by one adult household member in the household screener.”[3]

2) “Phase 2 sampling used information that the “sampled adult provided in the Phase 2 screener at the beginning of the adult interview.”[3]

In addition, the parents did not create a separate sample. Yet, the parents who provided permission for their child to complete a youth interview were asked to complete a brief parent interview about their youth selected for the PATH Study.[3] The entirety of the Wave 1 Cohort consisted of all Wave 1 sample participants. In order to construct Wave 4, the Wave 1 Cohort was replenished with a probability sample of adults, youth, and shadow youth ages 10 to 11; these were selected from the CNP at the time of Wave 4. The research plan document also stated that the sample was selected from residential addresses not selected for Wave 1 in the same sampled PSUs and segments using similar within-household sampling procedures.[3] Another distinction made was that this replenishment-like sample was designed to supplement the Wave 1 sample. It was also noted that the sample was not intended to be used for estimation purposes on its own. Instead, the intention was for that sample to be combined for estimation and analysis purposes with Wave 4 adult and youth respondents from the Wave 1 cohort who were in the CNP at the time of Wave 4. As depicted in figure 1.2 below, Wave 4 is composed of respondents that were recorded in both the Wave 1 and the Wave 4 CNP, all Wave 4 replenishment sample respondents and Wave 4 replenishment sample shadow youth. Recruitment Waves are defined as Waves where the PATH Study administered household screeners to sampled adults, youth and shadow youth.

In both Waves 1 and 4, computer-assisted personal interviewing (CAPI) was utilized for the household screener and also for the parent interviews in each Wave; in addition, audio computer-assisted self-interviewing (ACASI) was used for the adult and youth interviews. The report also stated that there were two annual follow-up waves of the Wave 1 Cohort, referred to as Wave 2 and Wave 3. Wave 4 is the third annual follow-up wave for the Wave 1 Cohort, in addition to the first wave of the Wave 4 Cohort. Below,

Figure 2, adapted from the report, illustrates the relationship between the two cohorts, while table 1 provides the data collection dates, sample sizes for the two cohorts and numbers of interviews in each completed wave for which data are available.

Figure 1.2 Depiction of Wave 1 and Wave 4 Cohort Relationship[3]

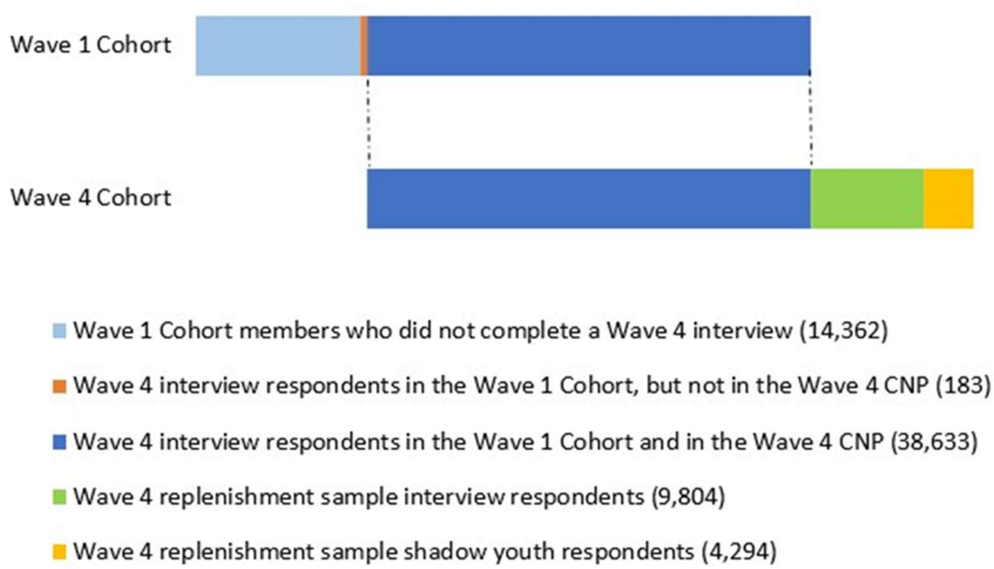

Table 1.1 PATH Study Data Collection Summary, By Wave[3]

WAVE	Data Collection		Interviews Conducted*		
	Start date	End date	Adults	Youth	Parents of youth
1	September 12, 2013	December 14, 2014	32,320	13,651	13,588
2	October 23, 2014	October 30, 2015	28,362	12,172	12,129
3	October 19, 2015	October 23, 2016	28,148	11,814	11,807
4	December 1, 2016	January 3, 2018	33,822	14,798	14,709

*For Wave 4 and subsequent Waves, the number of interviews available for analysis in the Wave 1 and Wave 4 Cohorts will be smaller than these totals.

With regards to the Restricted Use Files in Wave 1, every respondent who completed an adult interview was asked to provide biospecimens. Research participants completing an adult interview for the first time were also asked to provide biospecimens, while participants completing a youth interview in Wave 4 were asked to provide a urine sample; this included newly-sampled adults in Wave 4 and participants after Wave 1 overall. The research plan also noted that three more Waves (5, 6 and 7) of data and biospecimen collection were planned to be biennial. The year 2018 marked the first of the new cohorts with Wave 5, while the multi-Wave design allows for the longitudinal assessment of the participants' patterns of use of tobacco products, tobacco exposures, health, and risks for disease.[3] Other aspects being examined in the PATH Study include participants' "changes in awareness, knowledge, risk perceptions, and attitudes about current and newly emerging tobacco products".[3] Utilizing these self-report measures included demographics, smoking history, and context of nicotine dependence, we seek to create operationalized and measurable outcomes to achieve specific aims for each paper are as follows: Smoking patterns of use of tobacco product use may vary by product or by combinations of products, including product switching. Access to tobacco products may also be impacted by the age at which the participant uses the product as it is much easier to acquire when you are of legal age. Another potential item to investigate would be smoking patterns differentiation in individuals that smoke many low-level nicotine products versus those that smoke minimal high level nicotine products. One could anticipate potential changes in daily use patterns due to this amongst other confounding phenomena.

Statement of Purpose

The aim of this dissertation is to address the progression of tobacco use behavioral patterns based on product switching and nicotine dependence; we will touch on foundational principles of product initiation. More specifically, we plan to examine the graduation theory that users of smokeless tobacco and traditional combustible tobacco products will begin with products that are milder tasting, more flavored, and/or easier to control in the mouth and then transition to products with higher free nicotine content and tar delivery over time.[24] The project seeks to answer three interrelated questions regarding progressive use of various types of tobacco products in the PATH longitudinal cohort using three specific research questions. All papers are descriptive analysis of users and non-users of tobacco products and pertinent demographics from Waves 1-4 (2013-2018).

The analysis of this PATH data will allow us to understand how nicotine dependence translates to different content for individuals in specific age groups. More importantly we will be able to understand different individuals/groups progression of tobacco products use patterns, including how use may vary and product switching. The main research questions for each paper are stated below:

Paper 1: Tobacco Product Use and Product Switching amongst Current Users of Smokeless Tobacco Products using the Population Assessment of Tobacco and Health

This paper will identify and categorize product use of current users in Wave 1 according to free nicotine content (smokeless tobacco). It will also examine the proportion of current users from Wave 1 that have switched to a different product and describe the proportions of those users that switch to a product that has higher nicotine content or tar delivery type.

Using graduation theory as the framework for the analysis we will examine:

- ***What the demographic and behavioral factors associated with products switching (from low free nicotine to higher free nicotine) products are in current users of smokeless tobacco in PATH Wave 1 to Wave 4?***

  H_0: *We hypothesize that there is no association between graduated progression patterns of use and demographic factors (age, gender, race) among longitudinal cohorts of new smokeless tobacco users, adjusting for nicotine content, over time.*

Paper 2: Using Graduation Theory to Examine Traditional Combustible Tobacco Product Use and Switching in the US Population

This paper will identify and categorize product use of current users in Wave 1 according to tar delivery type (traditional tobacco). It will also examine the proportion of current users from Wave 1 that have switched to a different product and describe the proportions of those users that switch to a product that has higher nicotine content or tar delivery type.

(Assuming that some amount of product switching, and progression is occurring) Using graduation theory as the framework for the analysis we will examine:

- ***What the demographic and behavioral factors associated with progression (from low tar delivery to higher tar delivery) products are in current users of combustion/traditional tobacco users in PATH Wave 1 to Wave 4?***

  H_0: We *hypothesize that there is no association between graduated progression patterns of use and demographic factors (age, gender, race) among longitudinal cohorts of new combustion/traditional tobacco users, adjusting for tar/nicotine content, over time.*

Paper 3: Metabolic Phenotype Impacts on E-Cigarette Product Patterns of Use Amongst Wave 1 Longitudinal PATH Data

This paper will explore the relationship between nicotine clearance from e-cigarettes and metabolism in relating genotype and phenotype to smoking behavior and disease risk.

H_0: *We hypothesize that there is no association/statistical dependence between metabolic phenotype and patterns of use among longitudinal cohorts of e-cigarette tobacco users, differentiated by nicotine content, over time*.

CHAPTER II. Paper 1: Tobacco Product Use and Product Switching amongst Current Users of Smokeless Tobacco Products using the Population Assessment of Tobacco and Health

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Abstract

Objective: Using the graduation theory as the framework for the analysis, we examined the demographic and behavioral factors associated with product use and product switching (from low free nicotine to higher free nicotine) in current users of smokeless tobacco in the PATH data set comparing Wave 1 to Wave 4.

Materials and Methods: Wave 1 and Wave 4 respondents were merged to include those who were respondents in both data sets. We examined the risk of smokeless tobacco use in Wave 4 if using smokeless tobacco in Wave 1 for youth, aged-up adults, and adults. We also examined product switching behaviors for adults. We used risk ratios and odds ratios to identify demographic factors that were associated with continued use and initiation between the waves.

Results/Conclusion: We found that more white males reported continued use of smokeless tobacco across all age groups. The most frequently used brands were of medium nicotine content in adults, with very few using low nicotine containing products. Where applicable, those that identify as female and Asian race respectively had lower frequencies of smokeless tobacco use. These results may be indicative that smokeless tobacco product use may be closer tied to brand popularity and moderate nicotine strength.

Introduction/Background

Tobacco use is the leading cause of preventable morbidity and mortality in the United States (U.S.) attributable to more than 480,000 in 2020.[3, 4] While smokeless tobacco carries a lower risk of adverse health effects than traditional combustible tobacco products, it is not risk free.[1, 7-9] These products typically contain over 3000 constituents, including nicotine, making them highly addictive in nature.[9, 12, 14] They are also known to contain 28 cancer-causing chemicals, in which the tobacco-specific nitrosamines are the most prominent.[9, 12, 14] Smokeless tobacco use is highly correlated with several adverse effects, including dental disease and oral, esophageal and pancreatic cancers. Smokeless tobacco use during pregnancy increases the risk for adverse reproductive effects including stillbirth, premature birth, and low birth weight.[3, 5, 9, 13-15]

There is growing evidence that smokeless tobacco products first used are often flavored specifically mint or wintergreen.[40] In another study, a significant number of smokeless tobacco users switched to a flavored brand after already initiating smokeless tobacco use with a regular nonflavored product.[40] While these studies provide some evidence of product switching they focused primarily on adult users and did not describe any demographic characteristics that could assist with targeted prevention strategies.[41] Alpert, et. al. in their study of youth populations, found that brand design, brand proliferation and control of free nicotine likely resulted in the expanded consumption of moist snuff.[42]

With the growing knowledge of adverse health effects, the behavior regarding initiation and consistent use patterns for smokeless tobacco product and brand selection is not fully understood, though some progress has been made.[41] We look to expand our understanding of the relationship between product use over time, product switching and demographic factors using the Population Assessment of Tobacco and Health (PATH) data. The analysis of this PATH data will allow us to understand how nicotine dependence translates to different content for individuals in specific age and demographic groups.

This paper will identify and categorize current users of smokeless tobacco products. These current users are in Wave 1 and Wave 4 of the Population Assessment of Tobacco and Health study. With this information, we will be able to examine product use, product switching and potentially increased exposure as a result of product switching. Specifically, for smokeless products the PATH survey questionnaire data also allows for the categorization of smokeless tobacco loose smokeless tobacco (such as dip, spit, or chewing tobacco) and smokeless tobacco pouches (not including snus). It will also examine the proportion of current users from Wave 1 that have switched to a different product and describe the proportions of those users that switch to a product that has higher nicotine content. Using graduation theory as the framework for the analysis we will examine the demographic, and behavioral factors associated with products switching (from low free nicotine to higher free nicotine) products in current users of smokeless tobacco in PATH Wave 1 to Wave 4.

Methods

Data and Measures

All analysis was completed in SAS 9.46 inside the data enclave for the PATH data set. We selected Wave 1 and Wave 4 for analysis. Wave 1 was intended to select a representative sample of adults and youth ages 12 to 17 from the U.S. civilian, noninstitutionalized population. In subsequent waves, they added an additional "shadow sample" of youth ages 9 to 11. In both Waves 1 and 4, computer-assisted personal interviewing (CAPI) was utilized for the household screener and for the parent interviews in each wave; in addition, audio computer-assisted self-interviewing (ACASI) was used for the adult and youth interviews. We selected to use data from Wave 1 and Wave 4 to examine product use and product switching.

Smokeless User Definition & Background Questionnaire

The following are excerpt descriptions from the ICPSR database data sets and were the basis for the analysis:

ICPSR 36231 Data Files

1. “Dataset 1011 (DS1011) contains the data from the Wave 1 Adult Questionnaire. This data file contains 2,021 variables and 32,320 cases. Each of the cases represents a single, completed interview.”[43]
2. “Dataset 1012 (DS1012) contains the data from the Wave 1 Youth and Parent Questionnaire, which included 1,431 variables and 13,651 cases. The ["Single-Wave"] weight files contain weights for Wave 1 Cohort respondents who completed an interview at Wave 1. The "cross-sectional" weight files contain weights for all respondents in the Wave 1 Cohort.”[43]
3. “Dataset 4001 (DS4001) contains the data from the Wave 4 Adult Questionnaire and contained 2,504 variables and 33,822 cases. Of these, 25,857 are continuing adults having completed a prior Adult questionnaire, 1,900 are "aged-up adults" having previously completed a Youth questionnaire, and 6,065 are ["replenishment sample adults"].”[43] The replenishment sample adults were not used in any analysis for this study.
4. “Dataset 4002 (DS4002) contains the data from the Wave 4 Youth and Parent Questionnaire and included 1,600 variables and 14,798 cases. Among these cases, 9,365 are continuing youth having completed a prior Youth interview, 1,694 cases are "aged-up youth" having previously been sampled as ["shadow youth"], and 3,739 are ["replenishment sample youth"]. No shadow youth or replenishment sample youth were used in the analysis of this study.”[43]
5. “Datasets 4111, 4211, 4321, 4112, 4212, and 4322 (DS4111, DS4211, DS4321, DS4112, DS4212, and DS4322) are data files comprising the weight variables for Wave 4. In Wave 4, the weight variables have been separated into individual data files corresponding to the Wave 1 and Wave 4 Cohorts and different weight types. The ["All-Waves"] weight files contain weights for those Wave 1 Cohort respondents who completed an interview for all waves in which they were old enough or verified their information for waves in which they were not old enough to be

interviewed. The ["Single-Wave"] weight files contain weights for Wave 1 Cohort respondents at Wave 4 who completed an interview at Wave 1, regardless of their participation in previous Waves. The ["cross-sectional"] weight files contain weights for all respondents in the Wave 4 Cohort."[43]

6. "Dataset 1611 (DS1611) contains the Tobacco Universal Product Code (UPC) data from Wave 1. This data file contains 32 variables and 8,601 cases, including UPC values on the packages of tobacco products used or in the possession of adult respondents at the time of Wave 1. The UPC values can be used to identify and validate the specific products used by respondents and augment the analyses of the characteristics of tobacco products used by these respondents at the time of Wave 1."[43]
7. "Dataset 4601 (DS4601) contains the Tobacco Universal Product Code (UPC) data from Wave 4. This data file contains 32 variables and 7,684 cases including UPC values on the packages of tobacco products used or in the possession of adult respondents at the time of Wave 4. The UPC values can be used to identify and validate the specific products used by respondents and augment the analyses of the characteristics of tobacco products used by these respondents at the time of Wave 4. "[43]

Single-Wave weight files were used to weight the data to reflect values that would be representative of the U.S. civilian, noninstitutionalized population. The "Single-Wave" weight files contain weights for Wave 1 Cohort respondents at Wave 4 who completed an interview at Wave 1, regardless of their participation in previous Waves.

Variable Data & Coding

To create the primary outcome of interest, use of smokeless tobacco, and to maintain consistency between the waves, we did the following coding as shown in Table 2.0. For each of the categories, youth, aged-up adults, and adults, we defined users and non-users using the same methodology. Users were defined as those who responded "yes" (coded as '1') in the survey to using smokeless, snus or electronic tobacco products. Non-users were defined as those who responded "no" (coded as '2') in the survey to all questions regarding using smokeless, snus and electronic tobacco products. The remaining that originally answered "don't know", "refused", "missing" or skipped due to skip patterns were recorded as missing (coded as '.')

Table 2.0 Example Coding Used to Combine Product Use for Wave 1 And Wave 4 Any Smokeless Tobacco Product Use

Variables Used in Original PATH Wave 1 Smokeless Coding (Youth)	Variables Used in New Wave 1 Smokeless Coding (Youth)	Variables Used in Original PATH Wave 4 Smokeless Coding (Youth)	Variables Used in New Wave 4 Smokeless Coding (Youth)
R01R_Y_CUR_SMKLS	R01R_Y_CUR_SMKLS	R04R_Y_CUR_SMKLS	R04R_Y_CUR_SMKLS
	R01R_Y_CUR_SNUS		R04R_Y_CUR_SNUS
	R01R_Y_CUR_ECIG		R04R_Y_CUR_EPRODS

In specific analyses, due to low cell counts and frequencies, values had to be aggregated such as demographic categories of race. These groups were strategically aggregated together to ensure that the subgroup size was sufficiently large and to yield enough statistical power for comparison. Preliminary explorative analysis was completed to examine the population demographics and behaviors in Wave 1 and use in Wave 4. Once complete, both waves were sorted by person ID and then merged by person ID. These were the observations used for analysis.

Cross tabulation survey frequency tables were utilized for analysis. To ensure proper weighting, Wave 4 Single-Wave replicate weights from the original data set were included in each procedure that was run. To do so, an additional data set containing the replicate weights was also sorted by person ID and merged to the previously merged Wave 1 and Wave 4 files for youth, aged-up adults, and adults respectively. Those that were missing due to skip patterns, non-response, refused, or did not know, were all classified as missing. These coding procedures were carried out for Wave 1 and Wave 4 youths, aged-up adults, and adults respectively.

In the survey frequency procedure, the variance estimation method used was a balanced repeated replication (BRR) resampling method. Fay's method was used as a modification of the BRR method, and it requires a stratified sample design with two primary sampling units (PSUs) per stratum; the Fay's value used was 0.3. Relative risk, risk difference, and odds ratios were calculated as well; 95% confidence intervals were also included in those calculations. In age-related calculations, the same parameters utilized in the survey frequency procedure were utilized for the survey means procedure; age calculations were stratified by sex.

Survey frequency tables for smokeless tobacco products use by brands were also calculated. These items were also weighted in the same methods as described above. Any brands with a frequency cell count less than three were grouped into the "some other brand" category. The top three brands were examined for patterns of use amongst race and sex stratifications alongside a mean age calculation by brand. Product switching use and loyalty was also examined amongst the top three brands comparing Wave 1 use patterns to Wave 4 use patterns in a cross-tabulation table. A new variable for the top three brands in Wave 1 and Wave 4 was created respectively to each wave, using the current existing smokeless brand variable for each wave. The remaining brands that were used were categorized into "some other brand" for each respective wave in order to not interfere with the analysis data. These analyses were specific to those who were smokeless tobacco product users in Wave 1 and Wave 4. The frequency cell counts represent the raw total population whereas the percentages represent the application of single replicate weights as indicated in the table footnotes.

Results & Overview of Findings

Youth Demographic Characteristics of Continued Smokeless Tobacco Product Use in Waves 1 & Wave 4

In the youth sample, those who remained youth in Wave 1 and Wave 4, there were a total of 5477 observations as seen in table 2.1. Of these, there were 29 survey participants that were smokeless tobacco product users in both Waves 1 and Wave 4. This accounted for < 1% of the total population of youth that responded in both Waves 1 and Wave 4. Of the 29 participants that were users of smokeless tobacco products in both Waves, 9 (or 0.27%) were female, while 20 (0.81%) were male, meaning there were almost three times as many male users of smokeless tobacco products than female (proportional to the size of the population respondents in both genders). A total of 404 participants started using smokeless tobacco products in Wave 4 when they had not been a user of smokeless tobacco products in Wave 1. Most of these were male and identified as white. In addition, as highlighted in the table, a higher proportion of those who were white were more likely than other races to start using smokeless tobacco in Wave 4 (9.5% versus 5.2%). As highlighted in Table 2.2, there was a significant increased risk (relative risk (RR) = 5.47) of using smokeless tobacco products in Wave 4 if the participant had been using in Wave 1. This was slightly greater for males (RR =5.79) than females (RR =4.6). The odds ratio was also calculated and exhibited similar relationships, higher odds of reporting using smokeless tobacco in Wave 4 (OR = 8.55) if using in Wave 1 and higher for males (odds ratio (OR) = 10.1) than females (OR = 6.23). Those that identify as white also had similar risk (RR = 5.61) and odds ratios (OR = 10.2) to males.

Table 2.1 Wave 1 and Wave 4 Youth Overall & Demographic Stratification Smokeless Tobacco Product Use

Sample	Wave 1 – Wave 4 Yes to Yes Percentage	Wave 1 – Wave 4 Yes to No Percentage	Wave 1 – Wave 4 No to Yes Percentage	Wave 1 – Wave 4 No to No Percentage	Total
Overall Youth	**29 (0.540%)**	**42 (0.760%)**	**404 (8.0%)**	**5002 (91.0%)**	**5477**
Sex Female	9 (0.270%)	20 (0.670%)	178 (7.40%)	2463 (91.7%)	
Sex Male	20 (0.810%)	22 (0.840%)	226 (8.60%)	2520 (89.7%)	
Race White	27 (0.780%)	27 (0.750%)	308 (9.50%)	3149 (89.0%)	
Race Not-White	* (*%)	13 (0.790%)	88 (5.23%)	1560 (93.9%)	

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*
**Race Not-White = All grouped together because of censoring; Black, Asian, and other including multi-racial.*

Table 2.2 Wave 1 and Wave 4 Youth Demographic Risk Calculations

Demographic Characteristics	Relative Risk if Using in Wave 1	Confidence Interval		Odds Ratio	Confidence Interval		Absolute Risk Reduction (ARR) / Risk Difference (RD)	Confidence Interval	
		Lower Limit	Upper Limit		Lower Limit	Upper Limit		Lower Limit	Upper Limit
Overall Youth	**5.47**	**4.07**	**7.34**	**8.55**	**5.27**	**13.9**	**0.330**	**0.450**	**0.220**
Sex Female	4.60	2.63	8.07	6.23	2.79	13.9	0.240	0.410	0.070
Sex Male	5.79	4.11	8.14	10.1	5.45	18.9	0.390	0.550	0.240
Race White	5.61	4.21	7.48	10.2	5.92	17.7	0.410	0.540	0.280
Race Not-White	*	*	*	*	*	*	*	*	*

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*
**Race Not-White = All grouped together because of censoring; Black, Asian, and other including multi-racial.*

Aged-Up Adults Demographic Characteristics of Continued Smokeless Tobacco Product Use in Waves 1 & Wave 4

As indicated in table 2.3, for the sample of youth who had aged up to adults, there were a total of 5055 observations that were included in both Wave 1 and Wave 4. These participants were between 12-17 years of age in Wave 1 but were >17 years of age in Wave 4. Of this group, 3.05% (142 survey participants) were smokeless tobacco product users in both Waves 1 and 4, while 6.55% (304 survey participants) began use by Wave 4 after not using in Wave 1. The majority of these were white males as shown below. White (122 survey participants) and male (116 survey participants) were the demographic characteristics that had the highest proportions of continued use and initiation of smokeless tobacco products between the waves.

Whites were almost four times as likely as non-whites to continue smokeless tobacco product use and almost three times as likely to use smokeless tobacco products in Wave 4 and not in Wave 1. Males were almost twice as likely to use smokeless tobacco products in Wave 4 when not using smokeless tobacco products in Wave 1 compared to females. As highlighted in table 2.4, the relative risk and odds ratios ranged between 5-8 for those who were using smokeless tobacco products in Wave 1 and continued smokeless tobacco product users in Wave 4. These followed the trend of being greater for males (RR = 5.69; OR = 10.33) than females (RR = 5.40; OR = 6.72). Interestingly enough, non-whites had a higher risk and odds ratio (RR = 7.56; OR = 9.72) than whites (RR = 5.52; OR = 7.13). There were also higher amounts of continued smokeless tobacco product use among aged-up youth (3% versus 1% in youth).

Table 2.3 Wave 1 and Wave 4 Aged-Up Adults Smokeless Overall & Demographic Stratification Smokeless Tobacco Product Use

Sample	Wave 1 – Wave 4 Yes to Yes Percentage	Wave 1 – Wave 4 Yes to No Percentage	Wave 1 – Wave 4 No to Yes Percentage	Wave 1 – Wave 4 No to No Percentage	Total
Overall Aged-Up	**142 (3.05%)**	**204 (4.20%)**	**304 (6.55%)**	**4405 (86.20%)**	**5055**
Sex Female	26 (1.17%)	87 (3.67%)	102 (4.41%)	2293 (90.75%)	
Sex Male	116 (4.89%)	117 (4.73%)	202 (8.64%)	2105 (81.73%)	
Race White	122 (4.01%)	143 (4.53%)	247 (8.21%)	2716 (83.24%)	
Race Not-White	20 (1.05%)	61 (3.51%)	57 (3.08%)	1689 (92.35%)	

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*
**Race Not-White =* All grouped together because of censoring; Black, Asian, and other including multi-racial.

Table 2.4 Wave 1 and Wave 4 Aged-Up Adults Demographic Risk Calculations

Demographic Characteristics	Relative Risk if Using in Wave 1	Confidence Interval		Odds Ratio	Confidence Interval		Absolute Risk Reduction (ARR) / Risk Difference (RD)	Confidence Interval	
		Lower Limit	Upper Limit		Lower Limit	Upper Limit		Lower Limit	Upper Limit
Overall Aged-Up	**6.36**	**5.38**	**7.51**	**10.09**	**7.90**	**12.87**	**0.35**	**0.29**	**0.40**
Sex Female	5.40	3.67	7.96	6.72	4.15	10.87	0.19	0.11	0.27
Sex Male	5.69	4.73	6.84	10.33	7.70	13.87	0.41	0.35	0.48
Race White	5.52	4.63	6.59	9.38	7.13	12.34	0.38	0.32	0.44
Race Not White	7.56	4.78	11.96	9.72	5.50	17.18	0.21	0.12	0.31

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*
**Race Not-White =* All grouped together because of censoring; Black, Asian, and other including multi-racial.

Adults Demographic Characteristics of Continued Smokeless Tobacco Product Use in Waves 1 & Wave 4

A total of 22,373 adults were respondents to the survey in Wave 1 and Wave 4. Of these, 1230 (5.5% of the sample) were continued smokeless tobacco product users. As highlighted in table 2.5 below, more males (956 survey respondents) than females (273 survey respondents) who were smokeless tobacco product users in Wave 1 reported using smokeless tobacco in Wave 4. In fact, males were almost 5 times as likely than females to use smokeless tobacco products in both Waves 1 and 4. Due to the higher number of observations, we were able to identify different racial groupings in this sample. Those who identified as other race and were not smokeless tobacco product users in Wave 1 were more likely to start using smokeless tobacco products in Wave 4 than any other race; this also held true for those who identified as "other" and remaining races who were smokeless tobacco product users in both Waves 1 and 4. Those who identified as Asian were least likely to initiate smokeless tobacco use in Wave 4 after not using smokeless tobacco products in Wave 1. Males were almost twice as likely than females to initiate smokeless tobacco product use in Wave 4 after not using smokeless tobacco products in Wave 1. However, within each category and the overall category of adults, the majority of those that were not using smokeless tobacco in Wave 1, did not initiate smokeless tobacco product use in Wave 4.

In comparison to youth, much lower proportions of adults initiated smokeless tobacco use in Wave 4 (4.4% compared to 6% of aged up adults and 8% of youth). However, the relative risk and odds of continuing smokeless tobacco product use if using in Wave 1 were much greater for adults. According to table 2.6, females were at higher risk (RR = 12.31) but lower odds (OR = 21.37) than males of using smokeless tobacco products in Wave 4 after using smokeless tobacco products in Wave 1. This interesting finding may be due to the distribution of smokeless tobacco product usage between waves in relation to behavior. Risk ratios and odds ratio ranged 10-24 and 21-46 times respectively across different groups for those that used smokeless tobacco products in Wave 4, and in Wave 1. In fact, Asians had the highest risk

(RR = 24.79) and odds (OR = 46.74) than any other racial group of using smokeless tobacco products in Wave 4 and in Wave 1. Those who identified as "other" had the least risk (RR = 10.14; OR = 23.30).

Table 2.5 Wave 1 and Wave 4 Adult Overall & Demographic Stratification Smokeless Tobacco Product Use

Sample	Wave 1 – Wave 4 Yes to Yes Percentage	Wave 1 – Wave 4 Yes to No Percentage	Wave 1 – Wave 4 No to Yes Percentage	Wave 1 – Wave 4 No to No Percentage	Total
Overall Adult	**1230 (5.49%)**	**884 (3.95%)**	**944 (4.44%)**	**19315 (92.53%)**	**22373**
Sex Female	273 (1.15%)	341 (1.31%)	397 (1.59%)	10596 (95.94%)	
Sex Male	956 (5.23%)	543 (2.86%)	547 (3.13%)	8700 (88.77%)	
Race White	1039 (3.59%)	711 (2.22%)	741 (2.52%)	13464 (91.67%)	
Race Black	62 (1.18%)	74 (1.30%)	95 (1.64%)	3396 (95.88%)	
Race Asian	12 (0.93%)	13 (1.34%)	11 (0.95%)	557 (96.78%)	
Race Other	108 (3.76%)	75 (2.62%)	84 (3.25%)	1359 (90.38%)	

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*

Table 2.6 Wave 1 and Wave 4 Adult Demographic Risk Calculations

Demographic Characteristics	Relative Risk if Using in Wave 1	Confidence Interval		Odds Ratio	Confidence Interval		Absolute Risk Reduction (ARR) / Risk Difference (RD)	Confidence Interval	
		Lower Limit	Upper Limit		Lower Limit	Upper Limit		Lower Limit	Upper Limit
Overall Adult	**12.49**	**11.62**	**13.42**	**28.47**	**25.55**	**31.73**	**0.54**	**0.51**	**0.56**
Sex Female	12.31	10.80	14.03	21.37	17.70	25.79	0.41	0.37	0.45
Sex Male	10.78	9.86	11.79	28.00	24.44	32.09	0.58	0.55	0.60
Race White	11.38	10.51	12.33	26.55	23.53	29.96	0.54	0.52	0.56
Race Black	16.75	12.78	21.95	29.95	20.19	44.43	0.43	0.34	0.51
Race Asian	24.79	12.14	50.59	46.74	17.44	125.26	0.46	0.26	0.66
Race Other	10.14	7.97	12.89	23.30	16.13	33.66	0.53	0.46	0.60

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*

Adults Brand Characteristics of Continued Smokeless Tobacco Product Use in Waves 1 & Wave 4

Due to the small numbers of observations with the youth and aged-up youth samples, we were only able to compare smokeless tobacco product use and product types within the adult users of smokeless tobacco products. Within the adult population, the brand Copenhagen was the most popular smokeless tobacco brand of choice yielding the highest frequency (239 respondents; ~33%) according to table 2.7. This brand may be considered to have one of the highest amounts of nicotine (based on Goldenson 2017) but not the highest amount of free nicotine. Grizzly, which yielded the highest amount of free nicotine, was also a frequent choice (221 users, 28%) amongst the users of smokeless tobacco products. Skoal was the third most popular smokeless tobacco product reported brand by users (83 users, 13%) with similar concentrations of nicotine (13.4 mg/g), but not free nicotine. Except for the Redman brand, the majority of users responded that they used smokeless tobacco products that were relatively higher in nicotine and free nicotine.

There was little evidence of product switching amongst the top three smokeless brands according to table 2.8. As aforementioned, most smokeless tobacco products users reported using the same brands in both waves. The top three brands, Copenhagen, Grizzly and Skoal, made up 75% of the total products that were used within the adult population. However less than 10% of the total products were considered having low nicotine concentration; the majority were actually of medium concentration.[44] The average user age for Copenhagen, Grizzly and Skoal respectively are 42, 38, and 47. With regards to brand loyalty amongst the top three brands, Copenhagen (178/239 survey respondents between Waves), Grizzly (174/221 survey respondents between Waves) and Skoal (81/83 survey respondents between Waves) were able to retain at least 75% of their users from Wave 1 to Wave 4. Most smokeless tobacco products users reported using the same product in Wave 1 and Wave 4; if smokeless tobacco products users switched, they often selected a brand that was similar in nicotine level indicated in the tables below. The average age within the top three brands ranged from about 38 to 47 years amongst the adults. With the other remaining category, it may have allowed for a wider variety of smokeless tobacco products that would attract adults of different ages.

Table 2.7 Adult Wave 1-4 Top Brands Overall of Smokeless Tobacco Usually/Last Used[45, 46]

	Frequency	Percent	Standard Error of Percent	Nicotine (mg/g)	Free Nicotine (mg/g)
Copenhagen	239	32.6	2.64	13.9	5.40
Grizzly	221	28.6	2.53	11.2	5.90
Skoal	83.0	13.1	1.55	13.4	3.90
Kodiak	27.0	3.96	1.00	11.9	2.30
Red Man	25.0	3.38	0.576	8.60	0.080
Red Seal	20.0	2.93	1.04	13.2	3.10
Longhorn	18.0	2.47	1.00	13.8	5.70
Kayak	14.0	2.01	0.571	11.9	2.30
Levi Garrett	13.0	1.66	0.528	5.30	0.0600
Beechnut	11.0	1.61	0.524	7.10	0.0200
Stoker's	10.0	1.74	0.587	3.80	0.0100
Timber Wolf	5.00	0.827	0.388	14.1	5.20
Husky	4.00	0.395	0.230	12.9	4.80
Hawken	3.00	0.451	0.316	2.90	0.0100
Some Other Brand	31.0	4.25	1.17		
Missing Due to Data Removed Per Respondent Request/ Refused	1.00	**	**		

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*

Table 2.8 Wave 1 and Wave 4 Adult Demographic Stratification Smokeless Tobacco Brands Overall Product Use

Sample	Sex Female	Sex Male	Race White	Race Not-White	Mean Age by Brand
Copenhagen	6.00 (1.04%)	232 (33.0%)	215 (34.0%)	24.0 (20.0%)	Mean: 42.0 95% CL for Mean: [40.1, 43.9]
Grizzly	7.00 (13.0%)	214 (29.0%)	196 (3.02%)	25.0 (26.0%)	Mean: 37.9 95% CL for Mean: [35.6, 40.1]
Skoal	6.00 (14.0%)	77.0 (13.0%)	75.0 (12.0%)	8.0 (15.0%)	Mean: 46.9 95% CL for Mean: [43.4, 50.3]
Somme Other Brand	15.0 (43.0%)	166 (25.0%)	211 (23.0%)	35.0 (39.0%)	Mean: 53.4 Std Dev: 1.39 95% CL for Mean: [50.7, 56.2]
Total	34.0	689	632	92	
Missing	1	N/A	N/A	1	

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*
**Race Not-White =* All grouped together because of censoring; Black, Asian, and other including multi-racial.

Table 2.9 Wave 1 and Wave 4 Adult Top Smokeless Tobacco Brands Overall Product Switching Use

WAVE 4

		Copenhagen	Grizzly	Skoal	Some Other Brand
WAVE 1	**Copenhagen**	178 (25%)	12 (0.82%)	7 (0.72%)	18 (1.9%)
	Grizzly	10 (1.0%)	174 (23%)	8 (0.72%)	9 (1.2%)
	Skoal	6 (0.98%)	11 (0.95%)	81 (8.3%)	** (0.072%)
	Some Other Brand	22 (2.5%)	26 (3.3%)	6 (0.76%)	153 (23%)
	Total	216	223	102	**
	Missing	1			

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*

Discussions, Limitations & Implications for Future Research

In this descriptive analysis, we found that the majority of adult smokeless tobacco users remained loyal to their original brands between Waves 1 and 4. Among the adults, aged-up adults and youth, at least 85% of each respective population were not smokeless tobacco users by Wave 4, when not using in Wave 1. White males were the highest user frequency demographic for each of the three stratified age categories. There was a significantly low frequency of users that used low-nicotine containing smokeless products in both waves, amongst adults. The frequency of use amongst youth and aged-up adults was not possible to draw results with enough statistical power and was also censored due to low numbers of observations. Among racial/ethnic groups, non-Hispanic White adults had the highest prevalence of smokeless tobacco use. Nearly 3 of every 100 (2.9%) non-Hispanic White adults currently used smokeless tobacco.

Those that were aged older were averse to product switching, as we originally hypothesized. If future data permit, it will be interesting to also analyze product switching between product types, rather than switching internally within products. The current limitations of the data set do not yield a high enough frequency of exclusive users in youth, adults, or aged-up adults. The data also do not specify those that have switched between product types, nor the frequency of that action. The data does allow for detailed analysis of dual users, which may be of use for future research. However, we anticipate the dual users of specific products may be low, especially to categorize longitudinally between waves. It also may be difficult to resolve statistically significant differences between the demographic strata and waves amongst dual users, as it was exclusive users. A potential way to achieve this type of analysis would be to increase the sample size overall and introduce new survey questions.

The research did add more breadth to current literature as it confirmed some usage statistics currently available. For example. Copenhagen, Grizzly, and Skoal each hold 25% of the market share, or market percentage; this is defined as the percentage of total sales in the United States. Additionally, about 2 in every 100 (2.1%) adults (or 5.2 million adults) aged 18 or older reported current use of smokeless tobacco products.[47] Furthermore, 4 in every 100 (4.2%) adult men currently, less than 1 in every 100 (0.2%) adult women and less than 1.6% of youth used smokeless tobacco in 2021.[47] These items aligned with our research findings as far as product use, age and sex stratification. The literature also state that people who used only smokeless tobacco were less likely to attempt quitting than people who only smoked cigarettes.[48] Impacts of this research do indeed speak to some of the progress made by the current literature, specifically the Family Smoking Prevention and Tobacco Control Act. Due to this measure, tobacco packages and advertisements since 2009 were required to have larger and more visible labels that warn of health effects.[49] Also every package now must include product warnings for listed ingredients, mouth cancer, gum disease and tooth loss, for not being a safe alternative to cigarettes and being addictive.[49] This research combined with other supporting studies may help smokeless tobacco cessation via targeted marketing strategies targeting white males and other at-risk users from initiation.

Summary and Conclusions

We found no evidence of graduated progression of smokeless tobacco product use; we were unable to assess this with the youth and aged up youth. However, we did document a higher prevalence of use amongst white males across youth, aged-up adults, and adults. The most frequently used brands were of moderate/medium nicotine content in adults, with very few using low nicotine containing products. Where applicable, those that identify as female and Asian race respectively had lower frequencies of smokeless tobacco use. These results may be indicative that smokeless tobacco product use may be closely tied to brand popularity and moderate nicotine strength, especially amongst white males. Impacts from this and previous studies may influence our understanding of demographic patterns of use, and perhaps identify marketing strategies and incidences of adverse health effects in this target population.

CHAPTER III. Paper 2: Using Graduation Theory to Examine Traditional Combustible Tobacco Product Use and Switching in the US Population

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Abstract

Objective: In this paper we identify and categorize the use of traditional combustible tobacco products for current users in Wave 1 and Wave 4 of the Population Assessment of Tobacco and Health. We also examine the proportion of current users from Wave 1 that have switched to a different product and describe the proportions of those users that switch to a product that has higher nicotine content. We examine the demographic factors associated with products switching (from low free nicotine to higher free nicotine) products in current users of traditional combustible tobacco products and their switching choices and relationships to demographic characteristics.

Materials and Methods: SAS 9.46 was used as the primary source of statistical analysis, data management and advanced analytics. We used weights to calculate exploratory and cross-tabulation tables and relative risk and odds to measure relationships between use in Wave 1 and continued used in Wave 4 along demographic variability.

Results/Conclusion: Adults and those youth who aged up during the study were less likely to switch products. There was very little evidence of product switching that exhibited drastic tar/nicotine content differences. Though, younger populations are using electronic cigarettes more both for continued use and for those that initiated use between the waves.

Introduction/Background

Traditional combustible tobacco products traditionally consist of cigarettes, cigars, hookah, little cigars and cigarillos and are the number one cause of preventable disease and death worldwide.[17] In the U.S. alone, more than 480,000 lives are lost due to smoking-related diseases annually and, smoking costs the U.S. at least $130 billion in direct healthcare expenditures.[17] Smoking and tobacco use are responsible for more deaths each year than Human Immunodeficiency Virus (HIV), motor vehicle injuries, firearm-related events, illegal drug use, and alcohol use, combined.[5] It was recently found that smoking causes about 90% of all lung cancer deaths and that more women die from lung cancer each year than from breast cancer.[5] Cigarette smoking has also been found to cause roughly 80% of all deaths from chronic obstructive pulmonary disease (COPD) and increases risk for death from all causes in men and women.[5] Over the last 50 years, the risk of dying from cigarette smoking has increased in the U.S.[5] Although smoking rates have been declining, as of 2018, it was reported that roughly 34 million US adults still smoked cigarettes.[6] On average, 1,600 teenagers try their first cigarette before the age of 18; furthermore, 200 become daily cigarette smokers by age 18.[6] Additionally, CDC found that for every 30 Americans living with a serious smoking-related illness, there is one American who dies as a result of smoking.[6]

Smoking and general tobacco use leads to disease and disability, as it causes damage to most every organ of the body. Tobacco product use leads to cancers, heart disease, stroke, various lung diseases, type 2 diabetes, and other chronic health conditions.[6] Smoking not only impacts the immediate smoker, but can also increase the risk of premature birth and sudden infant death syndrome (SIDS) in pregnant women.[6] Tobacco use resulting in secondhand smoke affects 58 million non-smoking Americans.[6] In addition, Secondhand smoke has been causally linked to diseases such as stroke, lung cancer, and coronary heart disease in adults.[6] It was found that children exposed to secondhand smoke had an elevated risk of SIDS, impaired lung function, acute respiratory infections, middle ear disease, and higher frequency of severe asthma attacks.[6]

Initially, it was believed that electronic cigarettes (e-cigarettes) were safer than conventional traditional combustible products. However, there is growing recognition that the e-cigarette aerosol that users breathe from the device contains harmful substances whose effects are not fully known.[16] These harmful substances may include nicotine and ultrafine particles that can be inhaled deep into the lungs. These harmful substances can also include flavoring like diacetyl (a chemical linked to a serious lung disease), volatile organic compounds, cancer-causing chemicals, heavy metals such as nickel, tin, and lead.[16] Nicotine is not only very addictive and toxic to developing fetuses, it harms adolescent and young adult brain development, from birth to early mid-twenties; it is generally dangerous to pregnant adults and their children. Nicotine is also a health danger for pregnant adults and they're developing babies.[16] Though e-cigarette aerosol has fewer harmful chemicals than traditional combustible tobacco product smoke, it is still not proven to be a safe alternative.[16] In addition, e-cigarettes can yield injuries such as having defective batteries which can lead to fires and explosions resulting in serious adverse effects.[16] Both children and adults have been poisoned by ingesting, inhaling or absorbing e-cigarette liquid through their eyes or skin, displaying how acute nicotine exposure can be toxic.[16, 17]

This paper will identify and categorize product use of current users in Wave 1 according to tar delivery type (traditional combustible tobacco). It will also examine the proportion of current users from Wave 1 that have switched to a different product and describe the proportions of those users that switch to a product that has higher nicotine content or tar delivery type. We look to close the gap using the Population Assessment of Tobacco and Health (PATH) data. The analysis of this PATH data will allow us to understand how nicotine dependence translates to different content/exposure levels for individuals in specific age and demographic groups. More importantly we will be able to understand different individuals/group’s progression of tobacco products use patterns, including how use may vary and product switching. The aim of this paper is to address the progression of tobacco use behavioral patterns based on product switching and nicotine dependence; we will touch on foundational principles of product initiation.

More specifically, we plan to examine the graduation theory that that users of traditional combustible tobacco products will begin with products that are milder tasting, more flavored, and then transition to products with higher free nicotine content/tar delivery over time.[24]

Methods

Data and Measures

All analysis was completed using SAS 9.46. We use descriptive and tabulation statistics to examine demographic patterns for traditional combustible product use in different age groups of the PATH data set. We calculated measures of risk of continued traditional combustible tobacco product use in Wave 4 if reported use in Wave 1. The PATH data has a PATH Master Brand and Product Code List to categorize by brand and tobacco product type. With these categorizations, we can understand who is switching products and the types of products they are switching to.

Traditional Combustible User Definition & Background Questionnaire

The following are excerpt descriptions from the ICPSR database data sets and were the basis for the analysis:

ICPSR 36231 Data Files

1. "Dataset 1011 (DS1011) contains the data from the Wave 1 Adult Questionnaire. This data file contains 2,021 variables and 32,320 cases. Each of the cases represents a single, completed interview."[43]
2. "Dataset 1012 (DS1012) contains the data from the Wave 1 Youth and Parent Questionnaire, which included 1,431 variables and 13,651 cases. The ["Single-Wave"] weight files contain weights for Wave 1 Cohort respondents who completed an interview at Wave 1. The ["cross-sectional"] weight files contain weights for all respondents in the Wave 1 Cohort."[43]

3. “Dataset 4001 (DS4001) contains the data from the Wave 4 Adult Questionnaire and contained 2,504 variables and 33,822 cases. Of these, 25,857 are continuing adults having completed a prior Adult questionnaire, 1,900 are ["aged-up adults"] having previously completed a Youth questionnaire, and 6,065 are ["replenishment sample adults"].”[43] The replenishment sample adults were not used in any analysis for this study.
4. “Dataset 4002 (DS4002) contains the data from the Wave 4 Youth and Parent Questionnaire and included 1,600 variables and 14,798 cases. Among these cases, 9,365 are continuing youth having completed a prior Youth interview, 1,694 cases are "aged-up youth" having previously been sampled as ["shadow youth"] and 3,739 are ["replenishment sample youth"]. No shadow youth or replenishment sample youth were used in the analysis of this study.”[43]
5. “Datasets 4111, 4211, 4321, 4112, 4212, and 4322 (DS4111, DS4211, DS4321, DS4112, DS4212, and DS4322) are data files comprising the weight variables for Wave 4. In Wave 4, the weight variables have been separated into individual data files corresponding to the Wave 1 and Wave 4 Cohorts and different weight types. The ["All-Waves"] weight files contain weights for those Wave 1 Cohort respondents who completed an interview for all Waves in which they were old enough or verified their information for Waves in which they were not old enough to be interviewed. The ["Single-Wave"] weight files contain weights for Wave 1 Cohort respondents at Wave 4 who completed an interview at Wave 1, regardless of their participation in previous Waves. The ["cross-sectional"] weight files contain weights for all respondents in the Wave 4 Cohort.”[43]
6. “Dataset 1611 (DS1611) contains the Tobacco Universal Product Code (UPC) data from Wave 1. This data file contains 32 variables and 8,601 cases, including UPC values on the packages of tobacco products used or in the possession of adult respondents at the time of Wave 1. The UPC values can be used to identify and validate the specific products used by respondents and

augment the analyses of the characteristics of tobacco products used by these respondents at the time of Wave 1."[43]

7. "Dataset 4601 (DS4601) contains the Tobacco Universal Product Code (UPC) data from Wave 4. This data file contains 32 variables and 7,684 cases including UPC values on the packages of tobacco products used or in the possession of adult respondents at the time of Wave 4. The UPC values can be used to identify and validate the specific products used by respondents and augment the analyses of the characteristics of tobacco products used by these respondents at the time of Wave 4. "[43]

Single-Wave weight files were used to weight the data to reflect values that would be representative of the U.S. civilian, noninstitutionalized population. The "Single-Wave" weight files contain weights for Wave 1 Cohort respondents at Wave 4 who completed an interview at Wave 1, regardless of their participation in previous waves.

Variable Data & Coding

The traditional combustible variable in the dataset was recoded to have consistency in measurement from Wave 1 to Wave 4. The new traditional combustible variable included those that used all traditional combustible products. To create the primary outcome of interest, use of traditional tobacco products and to maintain consistency between the waves, we did the following coding as shown in Table 3.0. For each of the categories, youth, aged-up adults, and adults, we defined users and non-users using the same methodology. Users were defined as those who responded "yes" (coded as '1') in the survey to using cigarettes, traditional cigars, cigarillos, filtered cigars, pipe tobacco and hookah tobacco products. Non-users were defined as those who responded "no" (coded as '2') in the survey to using cigarettes, traditional cigars, cigarillos, filtered cigars, pipe tobacco and hookah tobacco products. The remaining that originally answered "don't know", "refused", "missing" or skipped dues to skip patterns were recorded as missing (coded as '.'). In addition, since bidis and kreteks did not carry over/were analyzed between waves and age categories (no available data for adults), they were omitted from traditional combustible tobacco product coding.

Table 3.0 Example Coding Used to Combine Product Use for Wave 1 and Wave 4 Any Traditional Combustible Tobacco Product Use

Variables Used in Original PATH Wave 1 Traditional Combustible Coding (Aged-Up Adults)	Variables Used in New Wave 1 Traditional Combustible Coding (Aged-Up Adults)	Variables Used in Original PATH Wave 4 Traditional Combustible Coding (Aged-Up Adults)	Variables Used in New Wave 4 Traditional Combustible Coding (Aged-Up Adults)
R01R_Y_CUR_CIGS	R01R_Y_CUR_CIGS	N/A	R04R_A_CUR_ESTD_CIGS
R01R_Y_CUR_GTRAD	R01R_Y_CUR_GTRAD		R04R_A_CUR_ESTD_GTRAD
R01R_Y_CUR_GRILLO	R01R_Y_CUR_GRILLO		R04R_A_CUR_ESTD_GRILLO
R01R_Y_CUR_GFILTR	R01R_Y_CUR_GFILTR		R04R_A_CUR_ESTD_GFILTR
R01R_Y_CUR_PIPE	R01R_Y_CUR_PIPE		R04R_A_CUR_ESTD_PIPE
R01R_Y_CUR_HOOK	R01R_Y_CUR_HOOK		R04R_A_CUR_ESTD_HOOK

Due to low cell counts and frequencies, in certain circumstances, and reduced statistical power, the demographic variable of race values had to be combined and recoded to create a new category of race. These groups were strategically aggregated together to ensure that the subgroup size was sufficiently large to yield enough statistical power. This is indicated in the tables below. Preliminary explorative analysis was completed to examine the study population in Wave 1 and subsequently the study population in Wave 4. Once complete, both waves were sorted by person ID and then merged by person ID. Rather than deleting those who were not present in both waves, a separate variable for those who were in both ways were included in the analysis; this variable was used as a class statement within each operation that was run to ensure that only our target population was analyzed, but the integrity of the data was maintained as best as possible. Aged-Up adults' categorization was a person ID merge of those who were youths in Wave 1 and adults in Wave 4.

Cross tabulation survey frequency was utilized in SAS to create weighted proportions for all values. To ensure proper weighting, Wave 4 Single-Wave replicate weights from the original data set were included in each procedure. To do so, an additional data set containing the replicate weights was also sorted by person ID and merged to the previously merged Wave 1 and Wave 4 files for youth, aged-up adults, and adults respectively. Those that were missing due to skip patterns, non-response, refused, or did not know, were all classified as missing. These coding procedures were carried out for Waves 1 and 4 youths, aged-up adults, and adults respectively.

In the survey frequency procedure, the variance estimation method used was a balanced repeated replication (BRR) resampling method. Fay's method was used as a modification of the BRR method, and it requires a stratified sample design with two primary sampling units (PSUs) per stratum; the Fay's value used was 0.3. Relative risk, risk difference, and odds ratios were calculated as well; 95% confidence intervals were also included in those calculations. In age-related calculations, the same parameters utilized in the survey frequency procedure were utilized for the survey means procedure; age calculations were stratified by sex.

Survey frequency tables for traditional combustible tobacco product use by brands were also calculated. These items were also weighted in the same methods as described above. Any brands with a frequency cell count less than three were grouped into the “some other brand” category. The top three brands were examined for patterns of use amongst race and sex stratifications alongside a mean age calculation by brand. Product switching use and loyalty was also examined amongst the top three brands comparing Wave 1 use patterns to Wave 4 use patterns in a cross-tabulation table. A new variable for the top three brands in Wave 1 and Wave 4 was created respectively to each wave, using the current existing traditional combustible brand variable for each Wave. The remaining brands that were used, were categorized into “some other brand” for each respective wave in order to not interfere with the analysis data. These analyses were specific to those who were traditional combustible tobacco product users in Wave 1 and Wave 4. The frequency cell counts represent the raw total population whereas the percentages represent the application of single replicate weights as indicated in the table footnotes.

Youth, aged-up adults, and adult datasets were constructed using the following information and datasets above. Parameters were narrowed for each respective dataset with regards to strictly being in Waves 1 and 4 for youth/adults and being a youth in Wave 1 and adult in Wave 4. The traditional combustible variable in the dataset was recoded to have consistency in measurement from Wave 1 to Wave 4. The new traditional combustible variable included those that used all traditional combustible products, including cigarettes, traditional cigars, cigarillos, filtered cigars, pipe tobacco, and hookah. Though electronics are viewed as an alternative to traditional combustible products, they are not considered traditional combustible themselves. Our justification for classifying e-cigarettes as non-combustible products was that they produce a vapor and heat liquids to specific temperatures.[50] In fact, they are sometimes referred to as Electronic Nicotine Delivery Systems (ENDS) and this term also includes devices such as vapes, e-hookahs, e-pipes and e-cigars. These devices work by heating a liquid so that it turns into a waterless steam-resembling vapor for the user to inhale, or 'vape'.[50]

Results & Overview of Findings

Youth Demographic Characteristics of Continued Traditional Combustible Tobacco Product Use in Waves 1 & Wave 4

There were a total of 5341 observations for survey respondents that reported being youth in both Wave 1 and Wave 4, as seen in table 3.1. Less than 1% of the overall youth population reported using traditional combustible tobacco products in Wave 4 after using traditional combustible products in Wave 1. The overall youth population was three times as likely to use traditional combustible products in both Waves 1 and 4, than electronic cigarettes in both Waves 1 and 4. Amongst female and male youth, the behavioral patterns and proportions of traditional combustible tobacco product use were almost identical. Almost 1.5 times as many white youth were likely to use traditional combustible tobacco products in Waves 1 and 4 than those who identify as black. Those who identify as white had the highest likelihood overall of traditional combustible tobacco product use, as opposed to their racial counterparts. Within the female youth population, only 1% reported using traditional combustible tobacco products in both Waves 1 and 4. However, about 92% of the female population reported not using traditional combustible products in Wave 1 norm Wave 4. This pattern was identical for each respective race and males as the table indicates about 1% of each sub-population reported use of traditional combustible tobacco products in Waves 1 and 4; about 90-93% of each sub-population reported not using traditional combustible tobacco products in both Waves 1 and 4. The majority of the youth population were not users of traditional combustible tobacco products in both waves. However, the overall youth population was almost seven times as likely to use e-cigarettes than traditional combustible products in Wave 4 after not using their respective products in Wave 1.

According to table 3.2 the general youth population had a relative risk of 10.59 of using traditional combustible tobacco products in Wave 4 after having used traditional combustible tobacco products in Wave 1, with an odds ratio of 12.1. A youth survey respondent had almost twice the risk and odds, respectively, of using traditional combustible tobacco products than using an e-cigarette in Wave 4, after using their respective products in Wave 1. This may indicate that youth who do not use traditional combustible products in Wave 1, have more chance of using electronic products in Wave 4, while those who use traditional combustible products may be more loyal to their product type from Waves 1 to 4. Males (RR = 7.07; OR = 12.68) and females (RR = 7.06; OR = 11.77) had similar risks and odds of using traditional combustible products in Wave 4 after using traditional combustible products in Wave 1. Those who identified as black had the highest risk ratio (RR = 9.78) and odds ratio (OR = 17.6) of using traditional combustible tobacco products in Wave 4 after using traditional combustible tobacco in Wave 1. Those who identified as Asian and other contrarily had the lowest risk (RR = 6.97) and odds (OR = 12.0). These findings may also be influenced by their respective population sizes.

Table 3.1 Wave 1 and Wave 4 Youth Overall & Demographic Stratification of Traditional Combustible Tobacco Product Use (Overall E-Cigarette Tobacco Product Use Comparison)

Sample	Wave 1 – Wave 4 Yes to Yes Percentage	Wave 1 – Wave 4 Yes to No Percentage	Wave 1 – Wave 4 No to Yes Percentage	Wave 1 – Wave 4 No to No Percentage	Total
Overall Youth Traditional Combustible	**53 (0.910%)**	**340 (6.65%)**	**63 (1.14%)**	**4885 (91.4%)**	**5341**
Overall Youth E-Cigarette	**16 (0.270%)**	**39 (0.660%)**	**355 (7.00%)**	**5152 (92.1%)**	**5562**
Sex Female	28 (0.950%)	36 (1.25%)	158 (6.20%)	2390 (91.6%)	
Sex Male	25 (0.870%)	27 (1.03%)	181 (6.87%)	2479 (91.2%)	
Race White	32 (0.840%)	40 (1.20%)	234 (7.09%)	3112 (90.9%)	
Race Black	8 (1.04%)	9 (0.900%)	40 (4.78%)	791 (93.3%)	
Race Asian/Other Race Including Multi-Racial	11 (1.18%)	13 (1.32%)	50 (5.90%)	710 (91.6%)	

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*

Table 3.2 Wave 1 and Wave 4 Youth Demographic Risk Calculations

Demographic Characteristics	Relative Risk If Using in Wave 1	Confidence Interval		Odds Ratio	Confidence Interval		Absolute Risk Reduction (ARR) / Risk Difference (RD)	Confidence Interval	
		Lower Limit	Upper Limit		Lower Limit	Upper Limit		Lower Limit	Upper Limit
Overall Youth Traditional Combustible	**10.59**	**7.46**	**15.0**	**12.1**	**8.25**	**17.7**	**0.12**	**0.0900**	**0.160**
Overall Youth E-Cigarette	**4.51**	**2.95**	**6.90**	**5.95**	**3.29**	**10.8**	**0.230**	**0.110**	**0.350**
Sex Female	7.06	5.14	9.68	11.77	7.00	19.78	0.38	0.25	0.50
Sex Male	7.07	5.15	9.69	12.68	7.21	22.30	0.410	0.280	0.550
Race White	7.06	5.14	9.68	11.77	7.00	19.78	0.380	0.250	0.500
Race Black	9.78	5.43	17.6	17.6	6.44	47.97	0.420	0.180	0.660
Race Asian/Other Race Including Multi-Racial	6.97	4.18	11.6	12.0	5.12	28.2	0.390	0.190	0.590

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*

Aged-Up Adults Demographic Characteristics of Continued Traditional Combustible Tobacco Product Use in Waves 1 & Wave 4

Amongst the aged-up adult population (4993 respondents), those who used traditional combustible products in Wave 1 and Wave 4 were almost four times as likely to continue using traditional combustible products as opposed to electronic cigarettes in Wave 4. Amongst the total aged-up adult population, 6% continued to be traditional combustible product users, using in both Wave 1 and in Wave 4. Those who were not traditional combustible tobacco users in Wave 1 but traditional combustible tobacco users in Wave 4, were twice as likely to use traditional combustible products as opposed to electronic cigarettes in Wave 4. The male and female traditional combustible product use were identical in Wave 4, regardless of use of traditional combustible products in Wave 1. Those who identify as white were 3.5 times as likely than Asians to use traditional combustible tobacco products in Wave 4, after using traditional combustible tobacco products in Wave 1. Those who identify as white were twice as likely as Asians to use traditional combustible tobacco products and Wave 4, after not using traditional combustible tobacco products in Wave 1. Those who identified as “other” race were three times as likely to use traditional combustible products in Wave 4 after using traditional combustible tobacco products in Wave 1. The Asian race was least likely to use traditional combustible products in both Waves 1 and 4, in comparison to other racial groups. Asians were also least likely to use traditional combustible tobacco in Wave 4 after not using traditional combustible tobacco in Wave 1. Those who identify as black were twice as likely than Asians to not use traditional combustible cigarettes in Wave 4 after not using traditional combustible tobacco in Wave 1. Out of all races, those who identified as “other” race or “multiracial” had the highest likelihood of using traditional combustible products in Wave 4 after not using traditional combustible tobacco in Wave 1; though the majority of the aged-up adults’ population were comprised of those who identified as white.

As shown in table 3.4, aged-up adults had similar risk ratios and odds ratios of using traditional combustible products (RR = 4.08; OR = 7.47) versus electronic tobacco products (RR = 4.94; OR = 6.44) in Wave 4 after using traditional combustible tobacco in Wave 1. Aged-Up female adults had a higher risk and odds of using traditional combustible tobacco products in Wave 4 after using traditional combustible tobacco in Wave 1. Those who identify as Asian had the highest risk and odds (RR = 14.8; OR = 25.8) amongst their racial counterparts of using traditional combustible tobacco products in Wave 4 after using traditional combustible tobacco in Wave 1; the values of the white black and other race were similar in nature with the exception of the black odds as indicated in table 3.4.

Table 3.3 Wave 1 and Wave 4 Aged-Up Overall & Demographic Stratification of Traditional Combustible Tobacco Product Use (Overall E-Cigarette Tobacco Product Use Comparison)

SAMPLE	Wave 1 – Wave 4 Yes to Yes Percentage	Wave 1 – Wave 4 Yes to No Percentage	Wave 1 – Wave 4 No to Yes Percentage	Wave 1 – Wave 4 No to No Percentage	Total
Overall Aged-Up Adult Traditional Combustible	**293** **6.10%**	**266** **5.37%**	**642** **12.9%**	**4351** **87.1%**	**4993**
Overall Aged-Up Adult E-Cigarette	**73** **1.42%**	**192** **3.74%**	**270** **5.86%**	**4571** **88.7%**	**5109**
Sex Female	137 5.78%	139 5.72%	142 5.84%	2056 82.7%	
Sex Male	156 6.42%	127 5.06%	207 8.48%	2022 80.0%	
Race White	218 7.05%	169 5.32%	247 7.84%	2564 79.8%	
Race Black	28 4.09%	53 7.21%	41 5.66%	642 83.0%	
Race Asian	4 1.95%	5 2.64%	4 2.80%	129 92.6%	
Other Race Including Multi-Racial	38 6.14%	26 4.40%	49 8.57%	493 80.9%	

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*

Table 3.4 Wave 1 and Wave 4 Aged-Up Demographic Risk Calculations

Demographic Characteristics	Relative Risk If Using in Wave 1	Confidence Interval		Odds Ratio	Confidence Interval		Absolute Risk Reduction (ARR) / Risk Difference (RD)	Confidence Interval	
		Lower Limit	Upper Limit		Lower Limit	Upper Limit		Lower Limit	Upper Limit
Overall Aged-Up Adult Traditional Combustible	**4.08**	**3.66**	**4.54**	**7.47**	**6.20**	**8.99**	**0.40**	**0.35**	**0.44**
Overall Aged-Up Adult E-Cigarette	**4.94**	**3.94**	**6.20**	**6.44**	**4.79**	**8.66**	**0.220**	**0.170**	**0.270**
Sex Female	7.68	6.30	9.37	14.27	10.7	19.1	0.430	0.370	0.490
Sex Male	5.94	5.02	7.01	12.0	9.12	15.8	0.460	0.400	0.520
Race White	6.41	5.53	7.43	13.4	10.5	17.0	0.480	0.420	0.530
Race Black	5.76	3.78	8.78	8.27	4.74	14.4	0.290	0.180	0.390
Race Asian	14.8	4.40	49.6	25.80	4.96	134	0.410	0.090	0.740
Race Other Race Including Multi-Racial	6.57	4.70	9.18	14.70	8.24	26.2	0.500	0.380	0.630

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*

Adults Demographic Characteristics of Continued Traditional Combustible Tobacco Product Use in Waves 1 & Wave 4

The overall adult population (22061 survey respondents) was almost 17 times as likely to use traditional combustible products than electronic products in Wave 4, after using their respective tobacco product in Wave 1. The same population was twice as likely to use traditional combustible products than electronic cigarettes in Wave 4, after not using their respective product in Wave 1. Nearly half of the population continued to not use traditional combustible products in Wave 4 after not using traditional combustible tobacco in Wave 1. However, 17% of the total adult population used traditional combustible products in Wave 4 after using traditional combustible tobacco in Wave 1. Males were more likely than females to use traditional combustible tobacco by Wave 4 after using traditional combustible tobacco in Wave 1. Males were less likely to use traditional combustible products in Wave 4 than females after using traditional combustible tobacco in Wave 1. More females did not use traditional combustible products than males in Wave 4 after not using traditional combustible tobacco in Wave 1. The Asian race was three times less likely than any other race to initiate traditional combustible tobacco use in Wave 4 after using traditional combustible tobacco in Wave 1. Those who identify as black or other were almost three times as likely than Asians to continue traditional combustible product use in Wave 4 after using traditional combustible tobacco in Wave 1; whites were nearly twice as likely than Asians to do so as well. Those who identify as white were least likely to not use traditional combustible products in Wave 4 after not being using traditional combustible tobacco in Wave 1.

According to table 3.6, the general adult population that used electronic tobacco products had a risk of 7.84 of continued use in Wave 4 after using electronic tobacco products in Wave 1. Within the same adult population, the risk of using electronic tobacco products was higher than those that used traditional combustible tobacco products (RR = 10.36) in Wave 1 and Wave 4. However, overall adults who used traditional combustible products in Wave 1 had much higher odds (OR = 36.1), almost twice the odds of electronic tobacco products (OR = 17.0), of using traditional combustible tobacco in Wave 4. Women had a higher risk of continued traditional combustible tobacco product use in Wave 4 after using traditional combustible tobacco in Wave 1 than males. In fact, the odds for female use of traditional combustible tobacco in both Waves 1 and 4 were nearly 1.5 to twice that of a male that used traditional combustible tobacco in both Waves 1 and 4. Asians were at the highest risk (RR = 11.8) of using traditional combustible tobacco products in Wave 4 after using traditional combustible tobacco in Wave 1. Their odds (OR = 37.0) of using traditional combustible tobacco products in Wave 4 after using traditional combustible tobacco in Wave 1, were similar to that of their white counterparts. The black and other racial groups had similar risks and odds of using traditional combustible tobacco products in Wave 4 after using traditional combustible tobacco in Wave 1.

Table 3.5 Wave 1 and Wave 4 Adult Overall & Demographic Stratification of Traditional Combustible Tobacco Product Use (Overall E-Cigarette Tobacco Product Use Comparison)

Sample	Wave 1 – Wave 4 Yes to Yes Percentage	Wave 1 – Wave 4 Yes to No Percentage	Wave 1 – Wave 4 No to Yes Percentage	Wave 1 – Wave 4 No to No Percentage	Total
Overall Adult Traditional Combustible	**7154 (16.9%)**	**1732 (4.13%)**	**1353 (3.82%)**	**11822 (53.6%)**	**22061**
Overall Adult E-Cigarette	**453 (1.05%)**	**644 (1.42%)**	**856 (1.99%)**	**20629 (95.5%)**	**22617**
Sex Female	3518 (14.3%)	776 (3.17%)	634 (3.27%)	6448 (79.3%)	
Sex Male	3634 (19.7%)	956 (5.19%)	718 (4.42%)	5359 (70.7%)	
Race White	5171 (16.8%)	1253 (4.09%)	856 (5.43%)	8479 (3.47%)	
Race Black	1194 (21.0%)	263 (4.36%)	309 (6.00%)	1796 (68.7%)	
Race Asian	77 (7.14%)	33 (3.20%)	28 (2.01%)	444 (87.7%)	
Race Other	593 (21.7%)	136 (5.12%)	120 (5.27%)	754 (67.9%)	

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*

Table 3.6 Wave 1 and Wave 4 Adult Demographic Risk Calculations

Demographic Characteristics	Relative Risk If Using in Wave 1	Confidence Interval		Odds Ratio	Confidence Interval		Absolute Risk Reduction (ARR) / Risk Difference (RD)	Confidence Interval	
		Lower Limit	Upper Limit		Lower Limit	Upper Limit		Lower Limit	Upper Limit
Overall Adult Traditional Combustible	**7.84**	**7.45**	**8.25**	**36.1**	**33.4**	**39.0**	**0.700**	**0.690**	**0.710**
Overall Adult E-Cigarette	**10.36**	**9.41**	**11.41**	**17.0**	**14.0**	**19.5**	**0.370**	**0.340**	**0.400**
Sex Female	9.15	8.49	9.87	46.0	41.2	51.6	0.730	0.720	0.740
Sex Male	6.70	6.25	7.19	28.4	25.5	31.5	0.670	0.660	0.690
Race White	8.78	8.23	9.37	40.9	37.2	44.9	0.710	0.700	0.720
Race Black	5.58	5.02	6.21	26.4	22.0	31.6	0.670	0.650	0.700
Race Asian	11.8	8.07	17.3	37.0	21.2	64.7	0.640	0.550	0.730
Other Race Including Multi-Racial	5.92	5.00	7.02	27.4	21.0	35.8	0.680	0.640	0.710

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*

Adults Brand Characteristics of Continued Traditional Combustible Tobacco Product Use in Waves 1 & Wave 4

The three most common brands of traditional combustible tobacco products used between Waves 1 and Wave 4 were Marlboro (35% of total brands used), Newport (17% of total brands used) and Camel (10% of total brands used). There was little evidence of product switching amongst the top three traditional combustible brands across the demographic groups. Most users reported using the same brands in both waves. In fact, Marlboro brand had the highest proportion of users who reported using the brand in both waves with 86% (1707/1995) users continued reporting use, as depicted in tables 3.7 and 3.8A. It was slightly less for Newport where close to 80% reported using Newport in both waves and much lower for Camel (~60%). More people who used Camel were likely to switch to a different brand between Waves 1 and Wave 4. Users of Newport and Camel in Wave 1 that switched to another brand and Wave 4 were more likely to switch to Marlboro.

Table 3.7 Adult Wave 1-4 Top 3 Brands Overall of Traditional Combustible Cigarette Tobacco Usually/Last Used

	Frequency	Percent	Standard Error of Percent
Marlboro	1995	35.2	0.856
Newport	1080	16.8	0.801
Camel	632.0	10.3	0.523
Some Other Brand	2124	37.7	0.943
Total	5831	100	
Missing	18		

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*

Table 3.8A Wave 1 and Wave 4 Adult Top Traditional Combustible Cigarettes Tobacco Brands Overall Product Switching Use

WAVE 4

		Marlboro	Newport	Camel	Some Other Brand
WAVE 1	Marlboro	1707 Percent: 30.6% Std. Err.: 0.821	74.0 Percent: 1.14% Std. Err.: 0.1584	133.0 Percent: 2.21% Std. Err.: 0.225	311.0 Percent: 5.315% Std. Err.: 0.290
	Newport	56.0 Percent: 0.849% Std. Err.: 0.135	892 Percent: 14.0% Std. Err.: 0.707	14.0 Percent: 0.196% Std. Err.: 0.0554	111 Percent: 1.63% Std. Err.: 0.191
	Camel	81.0 Percent: 1.16% Std. Err.: 0.125	10.0 Percent: 0.117% Std. Err.: 0.0430	426 Percent: 6.95% Std. Err.: 0.447	82.0 Percent: 1.36% Std. Err.: 0.161
	Some Other Brand	147 Percent: 2.60% Std. Err.: 0.236	103 Percent: 1.59% Std. Err.: 0.186	58.0 Percent: 0.991% Std. Err.: 0.154	1614 Percent: 29.4% Std. Err.: 0.896
	Total	1991	1079	631.0	2118
	Missing	30			

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*

Table 3.8B shows the majority of those that identified as white used Marlboro between Waves 1 and 4, with 75% (1486/1995) users reporting continued use. Table 3.8C shows that the majority of those that identified as not white used Marlboro between Waves 1 and 4, with 58% (622/1080) users reporting continued use. There was high brand loyalty amongst each respective category of race. The same behavior was exhibited amongst the sexes. For males (Table 3.8D), Marlboro was the preferred brand having 835 continued users, with Newport falling just short of half of the Marlboro user population having 423 continued users and subsequently Camel being nearly half of the continued Newport population having 220 continued users. For females (Table 3.8E), a very similar trend followed. Marlboro was the preferred brand having 871 continued users, with Newport falling just short of half of the Marlboro user population having 468 continued users and subsequently Camel being nearly half of the continued Newport population having 206 continued users. Both females and males preferred Marlboro as their top brand, followed by Newport and then Camel in subsequent order when reporting using traditional combustible tobacco products in Wave 4 after using traditional combustible tobacco in Wave 1. Women were more likely to switch from some other brand in Wave 1 to Marlboro in Wave 4 than men.

Table 3.8B Wave 1 and Wave 4 Adult Top Traditional Combustible Cigarette Tobacco Brands Overall Product Switching Use (White, Non-Hispanic)

		WAVE 4			
		Marlboro	Newport	Camel	Some Other Brand
WAVE 1	Marlboro	1486 Percent: 35.7% Std. Err.: 0.981	54.0 Percent: 1.15% Std. Err.: 0.182	111 Percent: 2.48% Std. Err.: 0.270	258 Percent: 5.97% Std. Err.: 0.325
	Newport	38.0 Percent: 0.818% Std. Err.: 0.148	270 Percent: 6.13% Std. Err.: 0.533	4.00 Percent: 0.0975% Std. Err.: 0.0571	48.0 Percent: 1.045% Std. Err.: 0.183
	Camel	63.0 Percent: 1.23% Std. Err.: 0.140	6.00 Percent: 0.101% Std. Err.: 0.0480	361 Percent: 7.95% Std. Err.: 0.520	65.0 Percent: 1.46% Std. Err.: 0.179
	Some Other Brand	122.0 Percent: 2.95% Std. Err.: 0.287	41.0 Percent: 0.835% Std. Err.: 0.124	46.0 Percent: 1.06% Std. Err.: 0.188	1239 Percent: 31.0% Std. Err.: 1.01
	Total	1709	371	522	1610
	Missing	20			

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*

Table 3.8C Wave 1 and Wave 4 Adult Top Traditional Combustible Cigarette Tobacco Brands Overall Product Switching Use (Not-White)

		WAVE 4			
		Marlboro	Newport	Camel	Some Other Brand
WAVE 1	Marlboro	221 Percent: 14.17% Std. Err.: 1.13	20.0 Percent: 1.08% Std. Err.: 0.257	22.0 Percent: 1.35% Std. Err.: 0.349	53.0 Percent: 3.24% Std. Err.: 0.486
	Newport	18.0 Percent: 0.947% Std. Err.: 0.239	622 Percent: 39.0% Std. Err.: 39.0	10.0 Percent: 0.510% Std. Err.: 0.149	63.0 Percent: 3.50% Std. Err.: 0.516
	Camel	18.0 Percent: 0.955% Std. Err.: 0.263	4.00 Percent: 0.170% Std. Err.: 0.0932	65.0 Percent: 3.78% Std. Err.: 0.5941	17.0 Percent: 1.03% Std. Err.: 0.324
	Some Other Brand	25.0 Percent: 1.47% Std. Err.: 0.374	62.0 Percent: 3.99% Std. Err.: 0.612	12.0 Percent: 0.786% Std. Err.: 0.209	375 Percent: 24.0% Std. Err.: 1.70
	Total	282	708	109	508
	Missing	10			

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*
**Race Not-White = All grouped together because of censoring; Black, Asian, and other including multi-racial.*

Table 3.8D Wave 1 and Wave 4 Adult Top Traditional Combustible Cigarette Tobacco Brands Overall Product Switching Use (Sex = Male)

WAVE 4

WAVE 1		Marlboro	Newport	Camel	Some Other Brand
	Marlboro	835 Percent: 23.0% Std. Err.: 0.698	42.0 Percent: 1.16% Std. Err.: 0.177	80 Percent: 2.20% Std. Err.: 0.243	97.0 Percent: 2.67% Std. Err.: 0.267
	Newport	26.0 Percent 0.720% Std. Err: 0.140	423 Percent 11.6% Std. Err: 0.532	10.0 Percent 0.280% Std. Err: 0.0869	19.0 Percent 0.52% Std. Err: 0.120
	Camel	37.0 Percent 1.02% Std. Err: 0.167	3.00 Percent 0.0800% Std. Err: 0.0476	220 Percent 6.05% Std. Err: 0.396	23.0 Percent 0.630% Std. Err: 0.132
	Some Other Brand	56.0 Percent 1.54% Std. Err: 0.204	49.0 Percent 1.35% Std. Err: 0.191	30.0 Percent 0.830% Std. Err: 0.150	76.0 Percent 2.09% Std. Err: 0.237
	Total	954	517	340	215
	Missing	18			

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*

Within the top 10 sub-brand traditional combustible tobacco products, Newport on average had the highest nicotine, tar and carbon monoxide concentrations; the highest used sub brand product was Newport Full Flavor Menthol 100s. According to table A1 (appendix), there was no significant evidence of switching from products containing high tar, nicotine, or carbon monoxide levels to lighter products. With the exception of Marlboro Gold Non-Menthol 100s, Camel Blue Non-Menthol Kings and Marlboro Gold Non-Menthol Kings, most traditional combustible sub brand products that were used in Wave 4 were either full flavor, menthol or a combination thereof, containing nearly identical nicotine, tar and carbon monoxide concentrations according to table 3.9.

Table 3.8E Wave 1 and Wave 4 Adult Top Traditional Combustible Cigarette Tobacco Brands Overall Product Switching Use (Sex = Female)

WAVE 4

		Marlboro	Newport	Camel	Some Other Brand
WAVE 1	**Marlboro**	871 Percent: 29.9% Std Err: 1.20	32.0 Percent: 0.982% Std Err: 0.183	53.0 Percent: 1.49% Std Err: 0.210	145 Percent: 4.73% Std Err: 0.433
	Newport	30.0 Percent: 0.899% Std Err: 0.205	468 Percent: 13.59% Std Err: 0.829	4.00 Percent: 0.0962% Std Err: 0.0517	57.0 Percent: 1.55% Std Err: 0.236
	Camel	44.0 Percent: 1.13% Std Err: 0.151	7.00 Percent: 0.166% Std Err: 0.0726	206 Percent: 6.47% Std Err: 0.580	35.0 Percent:1.00% Std Err: 0.192
	Some Other Brand	93.0 Percent: 3.27% Std Err: 0.325	54.0 Percent: 1.462% Std Err: 0.213	28.0 Percent: 0.865% Std Err: 0.178	917 Percent: 32.4% Std Err: 1.09
	Total	1038	561	291	1154
	Missing	18			

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*

When assessing whether or not product switching could be attributed to changes in tar and nicotine levels, due to the limited product switching, there was not much evidence of traditional combustible tobacco product switching based on the table categories indicated between Waves. The top three sub brands used in Wave 4 by those who used traditional combustible products in Wave 1 were as follows: Newport Full Flavor Menthol Kings (344/3044 users; 11.3% of Wave 4 traditional combustible tobacco user population), Marlboro Red Non-Menthol Kings (273/3044 users; 9.0% of Wave 4 traditional combustible tobacco user population), Newport Full Flavor Menthol 100s (261/3044 users; 8.6% of Wave 4 traditional combustible tobacco user population).

Table 3.9 Wave 1 and Wave 4 Adult Top 10 Traditional Combustible Cigarette Tobacco Sub-Brands Overall Product Switching Use[51-53]

Top 10 Sub-Brands Wave 1-4	International Organization for Standardization (ISO) Smoke Analysis (mg/cig)		
	Tar	Nicotine	CO
Camel Blue Non-Menthol Kings	9.84	0.837	10.9
Camel Crush Non-Menthol and Menthol Kings	13.5	1.07	12.5
Camel Filters Non-Menthol Kings	15.1	1.21	14.1
Marlboro Gold Non-Menthol Kings	8.97	0.670	10.2
Marlboro Gold Non-Menthol 100s	8.72	0.679	10.8
Marlboro Full Flavor Menthol Kings	14.4	0.980	13.5
Marlboro Red Non-Menthol Kings	14.0	0.956	13.3
Marlboro Red Non-Menthol 100s	15.3	1.09	15.4
Newport Full Flavor Menthol Kings	15.4	1.08	15.1
Newport Full Flavor Menthol 100s	18.2	1.50	15.5

Discussions, Limitations & Implications for Future Research

Overall, there was a low percentage of both traditional combustible tobacco products and e-cigarette use in the youth population. Though it is concerning that regardless of the tobacco product type, there were new users by Wave 4 that did not use in Wave 1. This may in fact be due to societal pressures and strategic marketing. Our findings do show that electronic cigarettes are more popular than traditional combustible cigarettes amongst those youth who did not use tobacco products in previous Wave 1. In both adult categories, white males have the highest frequency of use. Though, in all cases population size to determine statistical differences was a concern especially after stratification across different subcategories. The stratification did not fully allow for a thorough analysis in subgroups. As a result, racial categories had to be combined, which does not allow us to understand the full scope of patterns of use. We also have to take into account unmeasured confounding that is uncorrelated with variables/covariates, which is a limitation of any observational study. Though, a strength of the PATH study is that it is a large representative sample of the US population and conducts annual in-household follow-up self-assessments.

The populations of youth and aged-up adults did not provide enough data that were statistically large enough to identify categories of brand use. An increase in survey respondents over time would allow for more robust statistical analyses with more definitive findings. This information can inform new public health policies aimed at smoking cessation within targeted age groups. For those that we were able to analyze brand use, this information regarding brand loyalty aligned with current literature. In fact, 2017 sales data indicate Marlboro was the most popular cigarette brand in the United States, with sales greater than the next seven leading competitors combined.[54] Our research findings were also in line with the Surgeon General's Report of the three most heavily advertised brands, Marlboro, Newport, and Camel, being the preferred brands of cigarettes smoked by young people and adults.[55] Future implications and the impact of this research could focus smoking cessation efforts in marketing and media to target mentholated items surrounding these top brands. For example prior to 2010, manufacturers labeled cigarettes as "light" or "ultra-light" if the product delivered <15 mg of tar when measured by an automated smoking machine.[56] To combat misleading tobacco products, the 2009 Family Smoking Prevention and Tobacco Control Act, prohibited the use of terms like "light," "low," and "mild" on tobacco product labels.[49] This potentially reduced the appearance of these products as safe alternatives to smoking cessation and may have impacted the graduation theory as nicotine/tar level measurements may not be as significantly dispersed as originally thought. It is also indicative of why our results yielded extremely low frequencies of these types of products. This paper contributes another layer of understanding as far as the interconnectedness of marketing, brand loyalty and traditional combustible tobacco product use behavior. Future research could explore further variables and apply correlation/regression models to examine relationships, such as African Americans using menthol vs. non menthol products in relation to other races and sexes.

Summary and Conclusions

With the results of the PATH data analysis, we did not have sufficient data to confirm the "graduation theory" for traditional combustible products, with regards to patterns of use. Most adult participants chose to use traditional combustible tobacco products with moderate nicotine levels, regardless of previous use in a prior wave. There was very little evidence of product switching that exhibited drastic tar/nicotine content differences. Younger populations are using electronic cigarettes more and more.

CHAPTER IV. Paper 3: Metabolic Phenotype and association with E-Cigarette Product Patterns of Use Amongst Wave 1 Longitudinal PATH Data

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Abstract

Objective: We analyzed nicotine metabolism by examining nicotine metabolite ratios (hydroxycotinine vs. cotinine). These biomarkers of tobacco exposure are essential in characterizing actual human exposure to harmful or potentially harmful chemicals resulting from tobacco use.

Materials and Methods: This study used the serum and urinary concentrations of biomarkers specifically by examining nicotine metabolite ratios (hydroxycotinine vs. cotinine) to assess exposure. We used data collected from PATH Wave 1 data. We also looked at associations between e-cigarette types and the metabolic phenotypes as it relates to age, sex, and race-ethnicity within PATH study data.

Results/Conclusion: In our analysis we found that a small percentage (~7%) of the available biomarker results were linked to the adult population that reported using e-cigarettes the day of the survey or within 72 hours. The highest frequency of use was reported within the past hour of the survey. Of those that reported e-cigarette use, 29% were fast metabolizers and 71% were slow metabolizers according to reported serum trans-3-hydroxycotinine to cotinine metabolite ratio.

Within the Wave 1 Cohort there were more slow metabolizers than fast metabolizers that used e-cigarettes every day or some days. Most of these individuals were white females. Slow metabolizers reported using products more frequently in the past hour than fast metabolizers on the day results were recorded suggesting that metabolism may impact frequency of use of e-cigarettes.

Introduction/Background

The US Department of Health and Human Services identified tobacco use as the leading cause of preventable disease and death in the United States, with nearly all tobacco use beginning during youth and young adulthood.[2, 3] These products typically contain over 3000 constituents, including nicotine, making it highly addictive in nature.[12-14] Nicotine is a chiral alkaloid found in tobacco that is widely used recreationally as a stimulant and anxiolytic. It is also used as a pharmaceutical drug for smoking cessation to relieve withdrawal symptoms.[57] Through decades of studies, it has been proven that nicotine is highly addictive, though there are questions about how addiction varies in different age groups and race/ethnicities.[58-60] Electronic cigarettes (e-cigarettes) are commonly used by those who are seeking to reduce or quit cigarette smoking, though efficacy studies are ongoing. Some organizations, advocacy groups and policymakers have not accepted e-cigarettes as efficacious for smoking cessation, citing lack of evidence of efficacy and safety.[61, 62] The addictive qualities of nicotine, e-cigarette use and its relationship to metabolism produce a gap in literature that is still developing.

Recent studies have found that the rate of nicotine metabolism to cotinine is determined primarily by CYP2A6 activity and influences tobacco dependence and smoking-induced disease risk.[58] However, it has also been found that the prevalence of CYP2A6 gene variants can differ by race, with greater numbers of gene variants in African Americans compared to Caucasians.[58] One study that investigated nicotine disposition kinetics and metabolism by CYP2A6 genotype and enzymatic activity, as measured by nicotine metabolite ratio (NMR), found that CYP2A6 genotype, NMR and nicotine pharmacokinetic data may inform studies of individual differences in smoking behavior and biomarkers of nicotine exposure.[58] Nicotine Metabolite Ratio (NMR) is the ratio of trans-3’-hydroxycotinine (3HC) to cotinine, which can be measured in blood, saliva, or urine.[63] Studies have also shown that large racial/ethnic differences exist in the rate and pathways of nicotine and cotinine metabolism, and also within the frequency of CYP2A6 gene variants.[40, 58, 64-66]

As has been recognized, there are different kinds of e-cigarettes (some deliver little nicotine, while others deliver much more; this may potentially influence outcomes) and there are people who have different metabolic phenotypes (fast metabolizers vs. slow metabolizers) that use these products.[3, 59] It has also been recorded that some people metabolize nicotine rapidly and constantly look for their next dosage, and others metabolize nicotine very slowly, smoke more infrequently and typically do not feel a strong addiction to nicotine/cigarettes.[66, 67] Because e-cigarettes are still fairly new as aforementioned, scientists are still learning about their long-term health effects and the addictiveness of these products. Knowing the toxic and addictive properties of nicotine, it was proposed more than 20 years ago that individuals who metabolize nicotine poorly would smoke less.[68] This translated to smoking fewer cigarettes per day, or smoking each cigarette less intensely, when juxtaposed to smokers that metabolize nicotine more effectively.[68] Slow metabolizers as a consequence, would have lower incidence of lung cancer, resulting from lower exposure to carcinogens and harmful chemicals delivered with each inhalation of smoke.[68] Numerous studies have reported that smokers who carry reduced activity or null CYP2A6 alleles do smoke less; our goal is to see if this holds true for e-cigarettes using the PATH survey data.[68] The goal of this research paper is to explore the relationship between nicotine clearance related to the use of e-cigarettes and metabolism in relating genotype and phenotype to smoking behavior and disease risk.

Methods

Data and Measures

SAS 9.46 was used as the primary source of statistical analysis, data management and advanced analytics. Cross-tabulation was utilized to examine PATH data. For this paper, we examined the biomarker measurements in Wave 1. These are completed in a subsample of participants and can be analyzed alongside associated data on available tobacco product use.

The sample design in the first wave (called Wave 1) was a four-stage stratified area probability to select adults (18-24, 25-29 and 30+) and youth ages 12 to 17 from the U.S. civilian, noninstitutionalized population (CNP). In subsequent waves, they added an additional "shadow sample" of youth ages 9 to 11 to be interviewed. Only the first wave will be used in this analysis. The first stage involved a stratified sample of geographical primary sampling units (PSUs) being selected; a PSU was considered to be a county or group of counties. In the second the second stage, smaller geographical segments were formed within each PSU, with a sample of those segments then being drawn. The third stage sampling frame was comprised of the residential addresses located in these segments. Lastly, adults and youth from the sampled households identified at these addresses made up the fourth stage; these data contained varying sampling rates for adults by age, race, and tobacco-use status.

1. The adults were sampled in two phases: "Phase 1 sampling used information provided by one adult household member in the household screener."[3]
2. "Phase 2 sampling used information that the "sampled adult provided in the Phase 2 screener at the beginning of the adult interview."[3]

In addition, the parents did not create a separate sample. Yet, the parents who provided permission for their child to complete a youth interview were asked to complete a brief parent interview about their youth selected for the PATH Study.[3] The entirety of the Wave 1 Cohort consisted of all Wave 1 sample participants.

With regards to the Restricted Use Files in Wave 1, every respondent who completed an adult interview was asked to provide biospecimens. Research participants completing an adult interview for the first time were also asked to provide biospecimens.[3] Other aspects being examined in the PATH Study include participants' "changes in awareness, knowledge, risk perceptions, and attitudes about current and newly emerging tobacco products".[3] In this paper we examined, within the e-cigarette user population, if slow metabolizers are more likely to use the products that are more like cigarettes, while conversely, fast metabolizers are more likely to use 2nd, and 3rd generation devices.

The following are excerpt descriptions from the ICPSR database data sets and were the basis for the analysis:

ICPSR 36840 Data Files

1. "Dataset 1036 (DS1036) is a Biomarker Restricted-Use Files (RUF) and contains the data from the Wave 1 Adult Questionnaire; Urine Panel - Urinary Nicotine Metabolites (Cotinine and Hydroxycotinine or UNICM) ."[43]
2. "Dataset 1101 (DS1101) is a Biomarker Restricted-Use Files (RUF) and contains the data from the Wave 1 Adult Questionnaire; Blood Collection and NEQ Data."[43]
3. "Dataset 1121 (DS1121) is a Biomarker Restricted-Use Files (RUF) and contains the data from the Wave 1 Adult Questionnaire; Blood Biomarker Weights."[43]
4. "Dataset 1131 (DS1131) is a Biomarker Restricted-Use Files (RUF) and contains the data from the Wave 1 Adult Questionnaire; Serum Panel - Cotinine and Hydroxycotinine (SCOT) ."[43]

ICPSR 36231 Data Files

1. "Dataset 1011 (DS1011) contains the data from the Wave 1 Adult Questionnaire. This data file contains 2,021 variables and 32,320 cases. Each of the cases represents a single, completed interview."[43]

2. “Dataset 1012 (DS1012) contains the data from the Wave 1 Youth and Parent Questionnaire, which included 1,431 variables and 13,651 cases. The ["Single-Wave"] weight files contain weights for Wave 1 Cohort respondents who completed an interview at Wave 1. The ["cross-sectional"] weight files contain weights for all respondents in the Wave 1 Cohort.”[43]

Single-Wave weight files were used to weight the data to reflect values that would be representative of the U.S. civilian, noninstitutionalized population. The "Single-Wave" weight files contain weights for Wave 1 Cohort respondents who completed an interview at Wave 1.

Variable Data & Coding

Due to low cell counts and frequencies, in certain circumstances, race values had to be combined and recoded to create a new aggregate category of race. These groups were aggregate to ensure that the subgroup size is sufficiently large to yield enough statistical power. This is indicated in the tables below. Age and sex were not recoded for any purposes of analysis. Preliminary explorative analysis was completed to examine the study population in Wave 1. To procure the table values, cross tabulation survey frequency tables were utilized. To ensure proper weighting, Wave 1 Single-Wave replicate weights from the original data set were included in each procedure that was run. To do so, an additional data set containing the replicate weights was also sorted by person ID and merged with Wave 1 adults. Those that were missing due to skip patterns, non-response, refused, or did not know, were all classified as missing. These coding procedures were carried out for Wave 1 adults.

In the survey frequency procedure, the variance estimation method used was a balanced repeated replication (BRR) resampling method. Fay’s method was used as a modification of the BRR method, and it requires a stratified sample design with two primary sampling units (PSUs) per stratum; the Fay’s value used was 0.3. In age-related calculations, the same parameters utilized in the survey frequency procedure were utilized for the survey means procedure; age calculations were stratified by sex. NMR and number of puff variables were respectively recoded to become categorical variables as indicated below. The NMR cut point of 0.31 was determined by current literature standards to determine those that were Fast Metabolizer (<0.31) vs. Slow Metabolizer (>=0.31).[58, 65, 67, 69] A continuous variable for number of puffs taken from an e-cigarette within 72 hours was also recoded. The original variable converted to a categorical variable that was set at points determined after thorough review of histograms and natural break-points in the data. These groups were aggregated to ensure that the subgroup size is sufficiently large and yield enough statistical power. The result can be seen in table 4.0.

Table 4.0 Wave 1 Number of Puffs Taken from an E-Cigarette Today/Yesterday/Day Before Yesterday

Variables Used in Original Path Wave 1 Electronic Cigarette Coding (Adults)	Variables Used in New Wave 1 Electronic Cigarette Coding (Adults)
Continuous Variable	10 or Less Puffs
	11 - 39 Puffs
	40 or More Puffs

Results & Overview of Findings

About 7% of the Biomarker Restricted-Use File merged adult population reported using e-cigarettes the day of the survey or within 72 hours as seen in table 4.1 and 4.2. Amongst those that used e-cigarettes within the past 72 hours, the highest frequency of use was reported doing so within the past hour of the survey. The most frequent part of the day survey respondents used e-cigarettes was in the morning according to table 4.3. In table 4.4, almost 62% of respondents reported using 10 or less puffs of electronic cigarettes the day of the survey, the day before or within 72 hours. A total of 25% reported using 11 to 39 puffs within that same time span. Furthermore 74% reported not using e-cigarettes every day or some days.

Table 4.1 Wave 1 Last Time Used an E-Cigarette

	Frequency	Percent	Standard Error of Percent
In the Past Hour	209	40.5%	2.43
Sometime Today	79.0	15.1%	1.97
Yesterday	137	23.7%	1.93
Day Before Yesterday	33.0	5.19%	0.93
Three or More Days Ago	90.0	15.6%	1.74
Total	548	100.00%	
Missing	8.00		

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*

Table 4.2 Wave 1 Used E-Cigarettes Today, Yesterday or the Day Before Yesterday

	Frequency	Percent	Standard Error of Percent
Yes	542	7.13%	0.350
No	4932	92.9%	0.350
Total	5474	100.00%	
Missing	13.0		

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*

Table 4.3 Wave 1 Part of Day When Last Used an E-Cigarette

	Frequency	Percent	Standard Error of Percent
Morning	96.0	37.92	4.17
Afternoon	82.0	32.4%	3.56
Evening	71.0	29.6%	3.10
Total	249	100%	

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*

Table 4.4 Wave 1 Number of Puffs Taken from an E-Cigarette Today/Yesterday/Day Before Yesterday

	Frequency	Percent	Standard Error of Percent
10 or Less Puffs	289	61.7%	2.38
11 - 39 Puffs	107	25.0%	2.03
40 or More Puffs	34.0	13.3%	1.85
Total	453	100.00%	
Missing - Not Ascertained/Don't Know	5.00		

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*

Of those that reported e-cigarette use, 29% were fast metabolizers and 71% were slow metabolizers according to reported NMR as reported in table 4.5. Within the Wave 1 Cohort, there were more slow metabolizers (3585 survey respondents) present than fast metabolizers (1949 survey respondents) overall that used e-cigarettes every day or some days according to table 4.5.

Table 4.5 Wave 1 Nicotine Metabolite Ratio Comparison: Fast Metabolizer (<0.31) vs. Slow Metabolizer (>=0.31)

	Frequency	Percent	Standard Error of Percent
Fast Metabolizer	1949	29.2%	0.8756
Slow Metabolizer	3585	70.8%	0.8756
Total	5534	100.00%	

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*

Upon taking a closer look at the population, more women than men reported using e-cigarettes every day or some days in table 4.6 below. In addition, more individuals that identify as white use e-cigarettes every day or somedays than those who do not identify as white. Most of these individuals were white females. In fact, females were almost three times as likely than males to be slow metabolizers and use e-cigarettes every day or some days.

Table 4.6 Wave 1 Nicotine Metabolite Ratio (Slow/Fast Metabolizers) vs. Uses E-Cigarettes Every Day or Some Days

	Slow Metabolizer		Fast Metabolizer	
Sample	**Yes**	**No**	**Yes**	**No**
Wave 1 Cohort	10.0 18.9%	25.0 54.8%	4.00 7.87%	8.00 19.3%
Sex Female	7.00 24.6%	15.0 59.3%	* * %	3.00 16.1%
Sex Male	3.00 8.85%	10.0 48.3%	4.00 19.0%	5.00 23.9%
Race White	8.00 22.2%	18.0 54.6%	* * %	5.00 17.9%
Race Not-White	* * %	7.00 55.1%	* * %	3.00 23.0%

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*
**Race Not-White = All grouped together because of censoring; Black, Asian, and other including multi-racial.*

Amongst Wave 1 users of electronic tobacco products that took 10 or less puffs, slow metabolizers were almost 1.5 times more likely to have taken 10 or less puffs than fast metabolizers within 72 hours of the survey response. Those who identified as not white were almost twice as likely to be fast metabolizers and use 10 or less puffs of e-cigarettes within 72 hours of the survey response. Within each demographic category, there was a higher likelihood of using e-cigarettes within the past hour of responding to the survey as opposed to 48 hours before. In fact, both slow and fast metabolizers used the product more recently, within the past hour of the survey, as opposed to days past. These results are indicated below in tables 4.7 and 4.8.

Table 4.7 Wave 1 Nicotine Metabolite Ratio (Slow/Fast Metabolizers) vs. Last Time Used an E-Cigarette

	Slow Metabolizer					Fast Metabolizer				
	In The Past Hour	Sometime Today	Yesterday	Day Before Yesterday	Three Or More Days Ago	In The Past Hour	Sometime Today	Yesterday	Day Before Yesterday	Three Or More Days Ago
Wave 1 Cohort	134 26.3%	50.0 9.70%	82 14.6%	19.0 2.81%	53.0 8.46%	75.0 14.2%	29.0 5.39%	55.0 9.15%	14.0 2.38%	37.0 7.09%
Sex Female	83.0 29.2%	23.0 8.00%	50.0 16.3%	12.0 3.12%	32.0 10.1%	35.0 11.0%	17.0 6.15%	27.0 8.27%	6.0 2.11%	18.0 5.86%
Sex Male	51 23.1%	27.0 11.6%	32.0 12.7%	7.00 2.47	21.0 6.70%	40.0 17.7%	12.0 4.56%	28.0 10.1%	8.00 2.66%	19.0 8.44%
Race White	115 28.8%	33.0 7.07%	68.0 15.8%	12.0 2.39%	45.0 11.3%	59.0 14.1%	19.0 4.70%	38.0 8.51%	12.0 2.52%	22.0 4.84%
Race Not-White	19.0 15.4%	5.00 2.97%	14.0 9.42%	7.00 4.58%	20.0 14.3%	16.0 14.8%	7.00 7.72%	17.0 11.9%	* *%	18.0 17.2%

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*
**Race Not-White = All grouped together because of censoring; Black, Asian, and other including multi-racial.*

Table 4.8 Wave 1 Nicotine Metabolite Ratio (Slow/Fast Metabolizers) vs. Number of Puffs Taken from an E-Cigarette Today/Yesterday/Day Before Yesterday

	Slow Metabolizer			Fast Metabolizer		
Sample	**10 or Less Puffs**	**11 - 39 Puffs**	**40 or More Puffs**	**10 or Less Puffs**	**11 - 39 Puffs**	**40 or More Puffs**
Wave 1 Cohort	247 43.7%	63.0 11.8%	34.0 6.54%	145 24.9%	44.0 8.66%	23.0 4.40%
Sex Female	146 46.9%	36.0 12.8%	22.0 7.29%	75.0 23.2%	21.0 7.27%	8.00 2.52%
Sex Male	101 40.1%	27.0 40.1%	12.0 5.71%	70.0 26.8%	23.0 10.2%	15.0 6.45%
Race White	190 44.4%	56.0 13.6%	30.0 7.22%	96.0 21.3%	38.0 9.33%	18.0 4.11%
Race Not-White	57.0 40.9%	7.00 4.26%	4.00 3.75%	49.0 39.6%	6.00 5.90%	5.00 5.59%

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*
**Race Not-White = All grouped together because of censoring; Black, Asian, and other including multi-racial.*

Discussions, Limitations & Implications for Future Research

Overall, the data set had more slow metabolizers than fast metabolizers; almost 1.5 times more to be exact. This may be a partial explanation for the resulting outcomes as the population was not split evenly regarding this aspect. As indicated in the above tables, those who were slow metabolizers were more likely to use electronic tobacco products more frequently than fast metabolizers. This is a bit counterintuitive to what was originally expected and the current literature.

We used a dichotomous measure for metabolism compared to a quartile measure. The quartile division method of NMR for the classification of slow (<0.14), moderate (0.14–0.23) and fast metabolizers (>0.23) was the method used in another study that analyzed nicotine metabolism.[70] With regards to biological factors, previous studies showed that NMR is higher in females.[71, 72] Other studies have shown that that females are faster metabolizers than males; also age and body mass index (BMI) have been negatively associated with NMR.[70-73] Results from past studies indicate that non-nicotine users are slow to moderate metabolizers, and nicotine containing tobacco/ e-cigarette smokers, both users and dual users, are fast metabolizers.[70] Evidence has shown higher nicotine dependence of fast metabolizers, and faster metabolizers taking a higher nicotine dose in order to alleviate withdrawal symptoms; however our results can not 100% support this based on the study population.[74] These results may be indicative of limitations within the data set, or new potential trends amongst sub-populations. It would be interesting to analyze a nationally representative data set that is a bit more catered toward these variables and parameters. That way, we would be able to truly understand the behavior and patterns of electronic tobacco product use based on nicotine metabolite ratios.

Future research could also expand to investigate regression models and correlative analysis. This future research may help us understand smoking cessation and also how to create marketing strategies geared at those who practice the behavior more. From a historical perspective, that marketing strategy would potentially focus heavily on young women as they have a higher likelihood of using electronic cigarettes that contain nicotine. It would also be interesting to investigate dual tobacco product users versus exclusive electronic tobacco product users to see if there is a difference in nicotine metabolic ratios within this population. This information intertwined with current marketing strategies, physiological and biological differences alongside smoking status/frequency would allow us to better understand smoking behaviors.

Summary and Conclusions

Overall, our results did not match our original hypothesis. It was anticipated that those who potentially carried inactive CYP2A6 alleles (slow metabolizers) would not use e-cigarette products as frequently as those who potentially carried active CYP2A6 alleles (fast metabolizers). A possible explanation for this was that there may be a new trend of social users of e-cigarettes, which may rely on societal pressures to use products more frequently as opposed to usage that is dependent upon metabolism. As aforementioned, there are different kinds of e-cigarettes; some deliver little nicotine, while others deliver much more. This in combination with electronic tobacco users who have different metabolic phenotypes (fast metabolizers vs. slow metabolizers), may have also potentially influenced the outcomes in this paper.[3, 59]This may also potentially help explain frequency of use in proximity to the survey participation. It would be interesting to examine exclusive e-cigarette users and stratified age groups alongside other demographics. Further, respondents were asked to report their use of all nicotine-containing products during the 3-day period prior to the time of any biospecimen collection to facilitate interpretation of biomarker results; these were referred to Nicotine Exposure Questions or NEQs.[3] It would also be interesting to examine both blood and urine NEQs across different waves to see if there were differing patterns of use amongst these subpopulations. However, due to the limitations of the data set and final population size once data are refined, this may not be possible at this time; if the PATH dataset were more robust in the future waves, there may be more possibilities.

CHAPTER V. Dissertation Summary and Future Directions in Research

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Dissertation Summary, Practical Implications for Future Directions in Research & Final Thoughts

The purpose of this dissertation was to address the progression of tobacco use behavioral patterns based on product switching and nicotine dependence. The manuscripts were intended to inform the current literature as it pertains to a carefully specified nationally representative sample and behavior surrounding smokeless, traditional combustible and electronic tobacco products. The set of papers also touched on product initiation, or highlighting statistical changes of those who were not using tobacco products in Wave 1 but were reporting using tobacco products by Wave 4. Lastly, the set of papers explored the graduation theory to examine if users of smokeless tobacco and traditional combustible tobacco products begin with products that are milder tasting, more flavored, and/or easier to control in the mouth and then transition to products with higher free nicotine content and tar delivery over time.[24] This was accomplished using the PATH data which allowed us to understand how nicotine dependence translated to different content/exposure levels for individuals in specific demographic groups.

Manuscript 1

The first manuscript completed a descriptive and exploratory analysis of tobacco behavioral patterns of use and product switching among current users of smokeless tobacco products. Utilizing descriptive statistics, we identified and categorized smokeless tobacco product use of current users in Wave 1 according to free nicotine content. We also examined the proportion of current users from Wave 1 that switched to a different product and described the proportions of those users that switched to a product that had differing nicotine content type. Overall, we found that the majority of smokeless tobacco users remained loyal to their original brands between Waves 1 and 4. When contrasting continued product use over different age groups, we found that older respondents were averse to product switching, most likely having been long-time chronic users of the same product, since the beginning of the study. There was no evidence of graduated progression in the adult respondents in our sample. We documented a higher prevalence of use amongst white males across all age groups including youth, aged-up adults, and adults. With regard to nicotine potency, we also saw that the most frequently used brands were of moderate/medium nicotine content in adults, with very few of the population using low nicotine containing products. These results may be indicative that smokeless tobacco product use may be closer tied to brand popularity and moderate nicotine strength, particularly in adult continuing users.

We documented relatively high proportions of users that remained loyal to their original brands between Waves 1 and 4. Those that were aged older were averse to product switching, as we originally hypothesized. If future data permits, it will be interesting to also analyze product switching between product types, rather than switching internally within products. The current limitations of the data set do not yield a high enough frequency of exclusive users in youth, adults, or aged-up adults to be able to complete these analyses as intended. The data also do not specify those that have switched between product types, nor the frequency of that action. The data does allow for detailed analysis of dual users, which may be of use for future research. However, we anticipate the exclusive use of specific products may be low, especially longitudinally between waves. It also may be difficult to resolve statistically significant differences between the demographic strata and waves amongst dual users, as it was focused on exclusive users. A potential way to achieve this type of analysis would be to increase the sample size overall and introduce new survey questions to more specifically understand the commitment to brand and usage

Important findings from our work were the confirmation of the major brands that were frequently used by smokeless tobacco product users. For example. Copenhagen, Grizzly, and Skoal each hold 25% of the market share, or market percentage; this is defined as the percentage of total sales in the United States. We found those three product brands to be the most frequently reported in our study. Our work also confirmed that while smokeless tobacco product use is generally a small percentage of the population as shown in other studies [47] there are specific groups that are more likely to use these products and to continue to use them over time. We also identified a high relative risk of continued smokeless tobacco product use, especially for adults, for those that were already using smokeless tobacco products in Wave 1. As suggested in other literature, people who used only smokeless tobacco were less likely to attempt quitting than people who only smoked cigarettes.[48]

In future research, assessing the impact of tobacco packages and advertisements have been required to have larger and more visible labels that warn of health effects.[49] Our work suggests that smokeless tobacco cessation materials targeting white males and other at-risk users from initiation might be an important strategy.

Though there was no evidence, nor correlation of graduated progression as shown in our cross-tabulation data, there was a higher prevalence of use amongst white males across youth, aged-up adults, and adults. The most frequently used brands were of moderate/medium nicotine content in adults, with very few of the population using low nicotine containing products. Where applicable, those that identify as female and Asian race respectively had lower frequencies of smokeless tobacco use. These results may be indicative that smokeless tobacco product use may be closer tied to brand popularity and moderate nicotine strength, especially amongst white males. Impacts from this and previous studies may influence patterns of use, marketing strategies and incidences of adverse health effects.

Manuscript 2

The second manuscript set out to accomplish a similar study as the first, differing only by the examination of traditional combustible tobacco products, as opposed to smokeless. We were able to successfully categorize product use of current users in Wave 1 according to tar delivery type (traditional tobacco). We also were able to determine the implications of current users from Wave 1 that have switched to a different traditional combustible product based on nicotine/tar delivery type.

Overall, there was a low percentage of both traditional combustible tobacco products and electronic cigarette use in the youth population. Though it is concerning that regardless of the tobacco product type, there were new users by Wave 4 that did not use in Wave 1. This may in fact be due to societal pressures and strategic marketing. Our findings do show that e-cigarettes are more popular than traditional combustible cigarettes amongst those youth who did not use tobacco products in previous Wave 1. However, this trend was reversed amongst aged-up adults and adults. In both adult categories, white males have the highest frequency of use. Though, in all cases population size was a concern especially after stratification across different subcategories. The stratification did not fully allow for a thorough analysis in subgroups. As a result, racial categories for instance had to be combined, which does not allow us to understand the full scope of patterns of use. We also must take into account unmeasured confounding that is uncorrelated with variables/covariates, which is a limitation of any observational study.

Our analysis of traditional combustible products found brand loyalty was common with Marlboro being the most selected brand among adult users. In fact, 2017 sales data indicate Marlboro was the most popular cigarette brand in the United States, with sales greater than the next seven leading competitors combined.[54] Our research findings were also in line with the Surgeon General's Report of the three most heavily advertised brands, Marlboro, Newport, and Camel, being the preferred brands of cigarettes smoked by young people and adults.[55] Future implications and the impact of this research could focus smoking cessation efforts in marketing and media to target mentholated items surrounding these top brands. There have been efforts to target marketing, For example prior to 2010, manufacturers labeled cigarettes as "light" or "ultra-light" if the product delivered <15 mg of tar when measured by an automated smoking machine.[56] To combat misleading tobacco products, the 2009 Family Smoking Prevention and Tobacco Control Act, prohibited the use of terms like "light," "low," and "mild" on tobacco product labels.[49] This potentially reduced the appearance of these products as safe alternatives to smoking cessation and may have impacted the graduation theory as nicotine/tar level measurements may not be as significantly dispersed as originally thought. It also is indicative of why our results yielded extremely low frequencies of these types of products. This paper contributes another layer of understanding as far as the interconnectedness of marketing, brand loyalty and traditional combustible tobacco product use behavior. Future research could explore further variables and apply correlation/regression models to examine relationships, such as African Americans using menthol vs. non menthol products in relation to other races and sexes.

With the results of the PATH data analysis, we were unable to confirm the "graduation theory" for traditional combustible products in adults with respect to patterns of use. Most adult participants chose to use traditional combustible tobacco products with moderate nicotine levels, regardless of previous exposure in a prior Wave. There was very little evidence of product switching that exhibited drastic tar/nicotine content differences. Though, younger populations are using electronic cigarettes more and more.

Manuscript 3

In our third manuscript accomplished examining the role that metabolic phenotype plays regarding tobacco product patterns of use (daily/current users)/switching among the PATH Wave 1 longitudinal cohort of e-cigarette tobacco users. We were able to identify differences in metabolizers and e-cigarette use. Overall, we found that there were more respondents classified as slow metabolizers than fast metabolizers; almost 1.5 times more to be exact. Those who were slow metabolizers were more likely to use electronic tobacco products more frequently than fast metabolizers. This is a bit counterintuitive to what was originally expected and the current literature. One study used a quartile method similar to our categorization of metabolism with the exception of splitting slow metabolizers further into slow and moderate as opposed to just slow.

Results from past studies indicate that non-nicotine users are slow to moderate metabolizers, and nicotine containing tobacco/ e-cigarette smokers, both users and dual users, are fast metabolizers.[70] Evidence has shown higher nicotine dependence of fast metabolizers and faster metabolizers taking a higher nicotine dose in order to alleviate withdrawal symptoms; however our results cannot support this based on the study population.[74] These results may possibly be indicative of limitations within the data set, or new potential trends amongst sub-populations. Future research could also expand to investigate regression models and correlative analysis. This future research may help us understand smoking cessation and how to create health promotion strategies geared at those who practice the behavior more. From a historical perspective, that marketing strategy would potentially focus heavily on young women as they have a higher likelihood of using electronic cigarettes that contain nicotine. It would also be interesting to investigate dual tobacco product users versus exclusive electronic tobacco product users to see if there is a difference in nicotine metabolic ratios within this population. This information intertwined with current marketing strategies, physiological and biological differences, alongside smoking status / frequency would allow us to better understand smoking behaviors.

Overall, our results did not match our original hypothesis based on the merged dataset that was analyzed. It was anticipated that those who potentially carried inactive CYP2A6 alleles (slow metabolizers) would not use e-cigarette products as frequently as those who potentially carried active CYP2A6 alleles (fast metabolizers). A possible explanation for this was that there may be a new trend of social users of e-cigarettes, which may rely on pure and societal pressures to use products more frequently as opposed to usage that is dependent upon metabolism. This may also potentially help explain frequency of use in proximity to the survey participation. It would be interesting to examine exclusive electronic cigarette users and stratified age groups alongside other demographics. It would also be interesting to examine both blood and urine NEQs across different waves to see if there were differing patterns of use amongst these subpopulations. However, due to the limitations of the data set and final population size once data are refined, this may not be possible at this time; if the PATH dataset were more robust in the future waves, there may be more possibilities.

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Appendices, Tables and Figures

Manuscript 1

N/A

Manuscript 2

Table A1 Wave 1 and Wave 4 Adult Regular Brand of Cigarette Selection Based on Nicotine/Tar Levels

SAMPLE	ADULT
WAVE 1 – WAVE 4 YES TO YES PERCENTAGE	600 Percent: 11.6% Std. Err.: 0.521
WAVE 1 – WAVE 4 YES TO NO PERCENTAGE	752 Percent: 14.5 % Std. Err.: 0.504
WAVE 1 – WAVE 4 NO TO YES PERCENTAGE	630 Percent: 12.4 % Std. Err.: 0.456
WAVE 1 – WAVE 4 NO TO NO PERCENTAGE	3187 Percent: 61.5% Std. Err.: 0.709
MISSING	84.0
TOTAL	5169

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*
**R01_AC9011: In choosing regular brand of cigarettes, part of your decision was based on the following: The tar and nicotine levels*

Table A2 Wave 1 and Wave 4 Adult Top 10 Traditional Combustible Cigarette Tobacco Sub-Brands Overall Product Switching Use

Top 10 Sub-Brands Wave 4 (columns); Top 10 Sub-Brands Wave 1 (rows)

	Camel Blue Non-Menthol Kings	Camel Crush Non-Menthol And Menthol Kings	Camel Filters Non-Menthol Kings	Marlboro Gold Non-Menthol Kings	Marlboro Gold Non-Menthol 100s	Marlboro Full Flavor Menthol Kings	Marlboro Red Non-Menthol Kings	Marlboro Red Non-Menthol 100s	Newport Full Flavor Menthol Kings	Newport Full Flavor Menthol 100s	Other Full Flavor Menthol Product	Other Full Flavor Non-Menthol Product	Other Light Menthol Product	Other Light Non-Menthol Product	Some Other Product
Camel Blue Non-Menthol Kings	78 Percent: 1.60% Std. Err.: 0.206	** Percent: **% Std. Err.: **	3 Percent: 0.01% Std. Err.: 0.0077	5 Percent: 0.085% Std. Err.: 0.0389	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	6 Percent: 0.140% Std. Err.: 0.0738	11 Percent: 0.189% Std. Err.: 0.0488	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	81 Percent: 0.360% Std. Err.: 0.0397
Camel Crush Non-Menthol and Menthol Kings	4 Percent: 0.0953% Std. Err.: 0.0533	36 Percent: 0.6554% Std. Err.: 0.124	6 Percent: 0.0300% Std. Err.: 0108	3 Percent: 0.0422% Std. Err.: 0.0244	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	3 Percent: 0.0407% Std. Err.: 0.0265	-** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	40 Percent: 0.687% Std. Err.: 0.147	10 Percent: 0.143% Std. Err.: 0.0491	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	116 Percent: 0.51% Std. Err.: 0.0475
Camel Filters Non-Menthol Kings	Percent: 0.0760% Std. Err.: 0.0373	** Percent: **% Std. Err.: **	58 Percent: 0.991% Std. Err.: 067	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	7 Percent: 0.0895% Std. Err.: 0.0305	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	4 Percent: 0.0636% Std. Err.: 0.0215	28 Percent: 0.434% Std. Err.: 0.0864	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **
Marlboro Gold Non-Menthol Kings	4 Percent: 0.0794% Std. Err.: 0.0446	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	234 Percent: 4.955% Std. Err.: 0.381	4 Percent: 0.0859% Std. Err.: 0.0475	** Percent: **% Std. Err.: **	14 Percent: 0.233% Std. Err.: 0.0682	** Percent: **% Std. Err.: **	5 Percent: 0.137% Std. Err.: 0.062	** Percent: **% Std. Err.: **	19 Percent: 0.459% Std. Err.: 0.107	88 Percent: 1.71% Std. Err.: 0.195	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	7 Percent: 0.124% Std. Err.: 0.0488
Marlboro Gold Non-Menthol 100s	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	72 Percent: 1.471% Std. Err.: 0.227	15 Percent: 0.270% Std. Err.: 0.0656	** Percent: **% Std. Err.: **	6 Percent: 0.0964% Std. Err.: 0.0407	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	4 Percent: 0.0780% Std. Err.: 0.0393	31 Percent: 0.522% Std. Err.: 0.0838	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	4 Percent: 0.102% Std. Err.: 0.0557
Marlboro Full Flavor Menthol Kings	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	55 Percent: 0.9123% Std. Err.: 0.123	7 Percent: 0.0921% Std. Err.: 0.0349	** Percent: **% Std. Err.: **	7 Percent: 0.111% Std. Err.: 0.0486	** Percent: **% Std. Err.: **	46 Percent: 0.729% Std. Err.: 0.119	6 Percent: 0.112 % Std. Err.: 0.0503	4 Percent: 0.0743% Std. Err.: 0.0383	** Percent: **% Std. Err.: **	3 Percent: 0.0385% Std. Err.: 0.0244
Marlboro Red Non-Menthol Kings	4 Percent: 0.0620% Std. Err.: 0.0333	** Percent: **% Std. Err.: **	13 Percent: 0.226% Std. Err.: 0.0696	17 Percent: 0.483% Std. Err.: 0.122	** Percent: **% Std. Err.: **	3 Percent: 0.0429% Std. Err.: 0.0266	273 Percent: 5.444% Std. Err.: 0.3444	4 Percent: 0.0619% Std. Err.: 0.0333	7 Percent: 0.122% Std. Err.: 0.0489	** Percent: **% Std. Err.: **	19 Percent: 0.355% Std. Err.: 0.0989	129 Percent: 2.18% Std. Err.: 0.2049	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	10 Percent: 0.204% Std. Err.: 0.0739

Marlboro Red Non-Menthol 100s	3 Percent: 0.0509% Std. Err.: 0.0305	** Percent: **% Std. Err.: **	22 Percent: 0.365% Std. Err.: 0.0825	7 Percent: 0.115% Std. Err.: 0.0514	** Percent: **% Std. Err.: **	3 Percent: 0.0582% Std. Err.: 0.0427	117 Percent: 2.101% Std. Err.: 0.245	32 Percent: 0.511% Std. Err.: 0.109	4 Percent: 0.0581% Std. Err.: 0.029	** Percent: **% Std. Err.: **	8 Percent: 0.178% Std. Err.: 0.0551	91 Percent: 1.494% Std. Err.: 0.169	** Percent: **% Std. Err.: *	** Percent: **% Std. Err.: *	** Percent: **% Std. Err.: **
Newport Full Flavor Menthol Kings	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	7 Percent: 0.106% Std. Err.: 0.041	4 Percent: 0.0481% Std. Err.: 0.0256	** Percent: **% Std. Err.: **	344 Percent: 5.862% Std. Err.: 0.383	106 Percent: 1.76% Std. Err.: 0.224	64 Percent: 1.06% Std. Err.: 0.153	25 Percent: 0.371% Std. Err.: 0.0861	** Percent: **% Std. Err.: **	3 Percent: 0.0366% Std. Err.: 0.0254	4 Percent: 0.0652% Std. Err.: 0.0381
Newport Full Flavor Menthol 100s	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	7 Percent: 0.116% Std. Err.: 0.0513	** Percent: **% Std. Err.: **	261 Percent: 4.274% Std. Err.: 0.326	81 Percent: 1.28% Std. Err.: 0.144	106 Percent: 1.76% Std. Err.: 0.224	33 Percent: 0.556% Std. Err.: 0.113	5 Percent: 0.0803% Std. Err.: 0.0435	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **
Other Full Flavor Menthol Product	3 Percent: 0.0486% Std. Err.: 0.0286	3 Percent: 0.0242% Std. Err.: 0.0138	2 Percent: 0.0348% Std. Err.: 0.0267	10 Percent: 0.245% Std. Err.: 0.0934	** Percent: **% Std. Err.: **	51 Percent: 0.796% Std. Err.: 0.125	11 Percent: 0.153% Std. Err.: 0.0451	** Percent: **% Std. Err.: **	51 Percent: 0.800% Std. Err.: 0.122	37 Percent: 0.594% Std. Err.: 0.0958	878 Percent: 15.7% Std. Err.: 0.648	54 Percent: 0.919% Std. Err.: 0.144	5 Percent: 0.0596% Std. Err.: 0.0313	6 Percent: 0.109% Std. Err.: 0.0608	11 Percent: 0.188% Std. Err.: 0.0712
Other Full Flavor Non-Menthol Product	16 Percent: 0.317% Std. Err.: 0.094	11 Percent: 0.173% Std. Err: 0.0558	24 Percent: 0.3856% Std. Err.: 0.101	57 Percent: 1.19% Std. Err.: 0.171	5 Percent: 0.120% Std. Err.: 0.0612	8 Percent: 0.103% Std. Err.: 0.0395	68 Percent: 1.20% Std. Err.: 0.137	5 Percent: 0.0894% Std. Err.: 0.0438	12 Percent: 0.234% Std. Err.: 0.0796	5 Percent: 0.057% Std. Err.: 0.0294	94 Percent: 1.502% Std. Err.: 0.164	1186 Percent: 23.4% Std. Err.: 0.776	6 Percent: 0.0869% Std. Err.: 0.040	** Percent: **% Std. Err.: **	35 Percent: 0.698% Std. Err.: 0.126
Other Light Menthol Product	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	5 Percent: 0.0833% Std. Err.: 0.0416	** Percent: **% Std. Err.: **	27 Percent: 0.4394% Std. Err.: 0.0914	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **
Other Light Non-Menthol Product	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	4 Percent: 0.0657% Std. Err.: 0.0383	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	3 Percent: 0.0325% Std. Err.: 0.0186	** Percent: **% Std. Err.: **
Some Other Product	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	10 Percent: 0.196% Std. Err.: 0.0659	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	10 Percent: 0.194% Std. Err.: 0.077	** Percent: **% Std. Err.: **	4 Percent: 0.0749% Std. Err.: 0.0402	** Percent: **% Std. Err.: **	13 Percent: 0.236% Std. Err.: 0.0725	25 Percent: 0.533% Std. Err.: 0.123	** Percent: **% Std. Err.: **	** Percent: **% Std. Err.: **	9 Percent: 0.181% Std. Err.: 0.0635

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*

Table A3 Wave 1 Nicotine Metabolite Ratio (Slow/Fast Metabolizers) vs. Last Time Used an E-Cigarette (Age * Sex)

	Sample	Mean Age	
		Sex Female	**Sex Male**
Slow Metabolizer	**In The Past Hour**	Overall Mean: 45.88 Std. Err. of Mean: 1.66 95% CI for Mean: [42.60, 49.17]	Overall Mean: 42.34 Std. Err. of Mean: 2.41 95% CI for Mean: [37.55, 47.12]
	Yesterday	Overall Mean: 42.27 Std. Err. of Mean: 1.85 95% CI for Mean: [38.61, 45.93]	Overall Mean: 35.39 Std. Err. of Mean: 3.76 95% CI for Mean: [27.94, 42.85]
	Three or More Days Ago	Overall Mean: 41.68 Std. Err. of Mean: 2.84 95% CI for Mean: [36.05, 47.32]	Overall Mean: 42.5 Std. Err. of Mean: 3.56 95% CI for Mean: [35.4, 49.5]
	Sometime Today	Overall Mean: 45.2 Std. Err. of Mean: 2.96 95% CI for Mean: [39.4, 51.1]	Overall Mean: 36.4 Std. Err. of Mean: 3.34 95% CI for Mean: [29.8, 43.0]
	Day Before Yesterday	Overall Mean: 36.2 Std. Err. of Mean: 4.28 95% CI for Mean: [27.7, 44.7]	Overall Mean: 41.3 Std. Err. of Mean: 8.31 95% CI for Mean: [24.8, 57.8]
Fast Metabolizer	**In The Past Hour**	Overall Mean:42.0 Std. Err. of Mean: 2.96 95% CI for Mean: [36.1, 47.8]	Overall Mean: 42.3 Std. Err. of Mean: 2.41 95% CI for Mean: [37.6, 47.1]
	Yesterday	Overall Mean: 34.3 Std. Err. of Mean: 2.84 95% CI for Mean: [28.69, 39.9]	Overall Mean: 35.4 Std. Err. of Mean: 3.76 95% CI for Mean: [2.94, 42.8]
	Three or More Days Ago	Overall Mean: 35.3 Std. Err. of Mean: 2.79 95% CI for Mean: [29.8, 40.8]	Overall Mean: 42.5 Std. Err. of Mean: 3.56 95% CI for Mean: [35.4, 49.5]
	Sometime Today	Overall Mean: 40.5 Std. Err. of Mean: 4.06 95% CI for Mean: [32.5, 48.6]	Overall Mean: 36.4 Std. Err. of Mean: 3.34 95% CI for Mean: [29.8, 43.0]
	Day Before Yesterday	Overall Mean: 38.7 Std. Err. of Mean: 6.44 95% CI for Mean: [26.0, 51.5]	Overall Mean: 41.3 Std. Err. of Mean: 8.31 95% CI for Mean: [24.8, 57.8]

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*

Table A4 Wave 1 Nicotine Metabolite Ratio (Slow/Fast Metabolizers) vs Number of Puffs Taken from an E-Cigarette Today/Yesterday/Day Before Yesterday (Age * Sex)

Sample		Mean Age: Sex Female	Mean Age: Sex Male
Slow Metabolizer	10 or Less Puffs	Overall Mean: 44.1 Std. Err. of Mean: 1.17 95% CL for Mean: [41.8, 46.4]	Overall Mean: 41.5 Std. Err. of Mean: 1.74 95% CL for Mean: [38.1, 45.0]
	11 - 39 Puffs	Overall Mean: 43.7 Std. Err. of Mean: 2.2 95% CL for Mean: [39.3, 48.2]	Overall Mean: 33.6 Std. Err. of Mean: 2.9 95% CL for Mean: [27.9, 39.4]
	40 or More Puffs	Overall Mean: 45.3 Std. Err. of Mean: 3.10 95% CL for Mean: [39.2, 51.5]	Overall Mean: 38.56 Std. Err. of Mean: 6.36 95% CL for Mean: [25.9, 51.2]
Fast Metabolizer	10 or Less Puffs	Overall Mean: 40.1 Std. Err. of Mean: 0.842 95% CL for Mean: [38.4, 41.7]	Overall Mean: 34.3 Std. Err. of Mean:1.79 95% CL for Mean: [30.8, 37.8]
	11 - 39 Puffs	Overall Mean: 43.0 Std. Err. of Mean: 3.50 95% CL for Mean: [36.1, 50.0]	Overall Mean: 36.3 Std. Err. of Mean: 3.33 95% CL for Mean: [29.6, 42.9]
	40 or More Puffs	Overall Mean: 46.3 Std. Err. of Mean: 8.36 95% CL for Mean: [29.7, 62.9]	Overall Mean: 38.4 Std. Err. of Mean: 4.33 95% CL for Mean: [29.8, 47.0]

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*

Table A5 Wave 1 Nicotine Metabolite Ratio (Slow/Fast Metabolizers) vs. Uses E-Cigarettes Every Day or Some Days (Age * Sex)

	Sample	Mean Age	
		Sex Female	Sex Male
Slow Metabolizer	Yes	Overall Mean: 35.3 Std. Err. of Mean: 5.44 95% CL for Mean: [24.5, 46.1]	Overall Mean: 46.5 Std. Err. of Mean:11.3 95% CL for Mean: [24.1, 68.9]
	No	Overall Mean: * Std. Err. of Mean: * 95% CL for Mean: *	Overall Mean: 41.5 Std. Err. of Mean: 6.39 95% CL for Mean: [28.8, 54.1]
Fast Metabolizer	Yes	Overall Mean: 47.6 Std. Err. of Mean: 5.95 95% CL for Mean: [35.8, 59.4]	Overall Mean: 44.9 Std. Err. of Mean: 7.08 95% CL for Mean: [30.9, 58.9]
	No	Overall Mean: 46.6 Std. Err. of Mean: 0.957 95% CL for Mean: [44.7, 48.5]	Overall Mean: 41.4 Std. Err. of Mean: 7.72 95% CL for Mean: [26.0, 56.7]

**Percent = Represents Percent of the Non-Institutionalized US Population. The standard error and percentages represent weighted values, though frequencies reported reflect PATH study sample size.*

Additional Background & Dissertation Justification

Paper 1: Tobacco Product Use and Product Switching amongst Current Users of Smokeless Tobacco Products using the Population Assessment of Tobacco and Health

Smokeless tobacco carries a lower risk of adverse health effects than traditional combustible products, yet its risk of health effects are similar to those associated with use of electronic cigarettes.[7-9] Smokeless tobacco products typically contain over 3000 constituents, including nicotine, making it highly addictive in nature.[12-14] They are known to contain 28 cancer-causing chemicals, in which tobacco-specific nitrosamines are the most prominent.[12-14] Use of smokeless tobacco is highly correlated with several adverse health effects including dental disease, and oral, esophageal and pancreatic cancers.[14] Use during pregnancy increases the risk for adverse reproductive effects including stillbirth, premature birth and low birth weight.[3, 13-15] While health effects from use of smokeless tobacco are clear, there is less known about contemporary use of these products as the products and approaches to marketing them have changed.[75]

As new smokeless tobacco products are introduced into the market and constantly modified to attract users, it is more difficult to assess data on these new tobacco products. The analysis of the data provided in the Population Assessment of Tobacco and Health can assist in understanding continued use and, product switching for those who use smokeless tobacco products. This can allow us to understand different progression patterns of tobacco products use patterns among various age groups, including how use may vary by product or by combinations of products, including product switching. The project seeks to answer questions regarding the novel and progressive use of smokeless tobacco products in the PATH longitudinal cohort using specific research questions. Longitudinal data analysis of smokeless tobacco use and product choice is key to understanding use patterns and progression of use of products. This knowledge can help to identify important strategies to reduce use and mitigate the health effects of the preventable illness associated with smokeless tobacco product use.

There have been few and limited studies that examine patterns of smokeless tobacco product use and variability by product type including product switching over time in use. Most studies have to use cross-sectional data, limited to adults and do not include other economic demographics that could strengthen our understanding of the patterns and which groups are most at risk for continued or increased exposures.[4, 38, 39]

The aim of this paper is to help in understanding patterns of smokeless tobacco use behavior alongside nicotine dependence in the progression of tobacco use. It will investigate progression over time using the PATH data set. It has been well documented that tobacco companies purposely market smokeless tobacco products that have low levels of free nicotine. The result is that it may result in initiation of tobacco product usage by youth and adolescents.[4] Because users may need more nicotine over time as they develop tolerance, low levels of free nicotine may no longer satisfy.[25, 35] This encourages the user to move up the nicotine intensity scale by using products with more free nicotine, until they reached products with very high concentration of nicotine.[25, 35] While this theory has been examined in some settings, it has not yet been examined using cohort data, specifically the data available in the PATH study. This investigation will differ from other studies as it provides an understanding using longitudinal cohort based on a nationally representative sample of smokeless tobacco user and non-user cohorts.

Significance

Initiation of tobacco use in almost all cases begins before adulthood and this pattern has not significantly changed since 1964.[9] However, many of these research projects focused on cross-sectional data within a finite age group demographic and do not account for market expansion in terms of product variety and availability since 1964.[76-78] While the rates of cigarette smoking have been declining, there is evidence of increasing trends toward lighter tobacco product use as among those who smoked cigarettes in the past 30 days, the proportion of those who smoke every day has been decreasing; however, with nondaily smokers, the trend has been increasing.[38] Unfortunately, the same type of data is not as extensive on smokeless tobacco products, specifically for trends in their use. As new tobacco products surface frequently and are constantly modified, it is difficult to assess data on these new tobacco products. Adolescent and young adult tobacco use has been defined as by successions of actions categorized multiple behaviors and feelings, ranging from initiation to cessation. Adolescent tobacco use varies highly amongst adolescents regarding frequency and intensity of use.[38, 39] In fact, in three separate studies, it was noted that the pattern of experimentation with tobacco products has changed considerably over the past decade, with adolescents and young adults now commonly experimenting with multiple tobacco products.[76-78] Because it takes a number of years for most people to become fully nicotine dependent, longitudinal studies are needed to identify the association between products tried and later daily cigarette smoking.[2]

The analysis of this longitudinal PATH data will allow us to understand how nicotine dependence using smokeless tobacco translates to different content/exposure levels for individuals in specific age groups. More importantly, we will be able to understand different progression patterns of tobacco products use patterns among various age groups, including how use may vary by product or by combinations of products, including product switching. The project seeks to answer questions regarding the novel and progressive use of smokeless tobacco products in the PATH longitudinal cohort using specific research questions.

Research Questions/Aim & Approach:

The research proposes the following questions:

1. What is the prevalence of use smokeless tobacco products comparing participants in Wave 1 and Wave 4.

2. What is risk/prevalence of switching/considering switching from smokeless tobacco products to other products amongst each age group between Wave 1 and Wave 4?
    - Low-Level Users
    - High-Level Users
3. We will also explore how these are affected by demographic covariant factors, specifically stratifying participants by age, gender and race.

As noted above, the risk difference will be calculated for both those that go from low users to high users. We will also explore how those switches are affected by potential covariant factors. The 95% confidence interval and all calculations will take into account the appropriate statistical weighting techniques as highlighted in the Pierce et al., 2021 paper.[4] As described above, the adjusted risk differences (aRDs) would be computed from multivariable logistic regression as demonstrated in Pierce et al., 2021.[4] Briefly, each model could be adjusted for the following: age, age at first experimentation, sex, race/ethnicity, exposure to smokers.

Another potential analysis methodology to avoid duplication of Pierce et al., work would be to use latent transition analysis.[4, 21] Latent transition is the movement from one latent subgroup to another over time and the analysis enables researchers to estimate how membership in the subgroups change over time using longitudinal data.[22, 79] This was performed in a cohort of adolescent and young adults to examine dating and sexual risk behavior.[22, 79] The overall goal of the study was to explore dating and sexual risk behavior longitudinally in this population, while exploring whether substance use behaviors like cigarette use, drunkenness and marijuana use, were predictive of dating and sexual risk behavior. [23-24] The study also examined gender differences in dating and sexual risk behavior, alongside gender differences in the effects of substance use on this behavior.[22, 79] This concept would be another possible approach to consider for this PATH study. However, to examine associations with progression to daily use and also product switching of tobacco products at Wave 4, we would have to ascertain the subsample who were ever users of tobacco at Wave 1 and who did use at least 1 tobacco product by Wave 3.[4] We would also follow similar methodologies found in a paper by Richter, et. Al.[80] In that study, the purpose was to provide consumers, researchers, and public health officials with information on pH, levels of total nicotine, un-ionized nicotine, moisture and TSNAs in popular smokeless tobacco brands. In either approach, we will utilize their measurements of total nicotine in smokeless products in our assessments of tobacco product switching amongst PATH study participants.[80] We will utilize the categorization and groupings outlined in the first research product, categorizing by brand and tobacco product type. With these categorizations, the PATH data will also allow us to use that data to stratify participants by age, gender, race. Using this information, we can understand who is switching products and the types of products they are switching to. More background research on products will afford us the opportunity to identify significant groupings related to PATH data specific tobacco products, including nicotine and tar content.

Anticipated Outcomes, Public Health Implications and Limitations:

A recent pediatrics paper found that trying e-cigarettes and multiple other tobacco products before age 18 years is strongly associated with later daily cigarette smoking.[76-78] The recent large increase in e-cigarette and smokeless use will likely reverse the decline in traditional/combustible smoking among US young adults.[76-78] The introduction of other demographic variables will offer a wider scope of the subject matter as it is unclear how older participants will respond. Based on current existing data, we hypothesize that those that are aged older will be averse to product switching, having been long-time chronic user of the same product. However, those that are aged younger, will be more open to product switching when it comes to user characteristics. It may also provide more data for analysis in a future paper to analyze product switching between product types, rather than switching internally within products. However, there may be limitations that may be outside the scope of what the project is able to uncover. We do not know if the subset of smokeless tobacco users will be large or small within the PATH data set especially considering those who are switching. It also may be difficult to resolve statistically significant differences between the demographic strata and Waves. We lastly must consider that unmeasured confounding that is uncorrelated with the covariates available is a limitation of any observational study.[2, 21] However, this should not detract from the strengths of the PATH study. It is a large representative sample of the US population and annual in-household follow-up self-assessments.[2, 21] Though it is noted that there was attrition between surveys, all survey weights are available to minimize effects on study estimates.[2, 21]. The analysis above will help uncover potential patterns of smokeless tobacco product use and help us understand how various groups product switching tendencies. This information can inform new public health policies aimed at smokeless tobacco cessation within targeted age groups.

Paper 2: Using Graduation Theory to Examine Combustible Tobacco Product Use and Switching in the US Population

The leading cause of preventable morbidity and mortality in the United States (U.S.) is tobacco use, mostly in the form of cigarette smoking. In just the U.S. alone, more than 480,000 lives were lost due to smoking-related diseases, in the year 2014.[2] More importantly, smoking costs the U.S. at least $130 billion in direct healthcare expenditures.[3] Smoking and tobacco use is responsible for more deaths each year than Human Immunodeficiency Virus (HIV), motor vehicle injuries, firearm-related events, illegal drug use, and alcohol use, combined.[5] It was recently found that smoking causes about 90% of all lung cancer deaths and that more women die from lung cancer each year than from breast cancer.[5] Cigarette smoking has also been found to cause roughly 80% of all deaths from chronic obstructive pulmonary disease (COPD) and increases risk for death from all causes in men and women.[5] In total, the proportional risk of dying from cigarette smoking has increased over the last 50 years in the U.S even if smoking rates have declined.[5]

To begin to understand and potentially mitigate this continued public health burden of concern, longitudinal data analysis is key. Currently, most research investigations examine cross-sectional data.[4, 38, 39] The select research examples cite using limited age groups (adolescents to young adults) and do not include other economic demographics that would provide a more well-rounded scope of the subject matter.[4, 38, 39] This research paper aims to evaluate and examine the patterns of traditional combusted tobacco use and behavior alongside the progression of tobacco use.

This paper will provide a descriptive and analytical approach to understand ever users of traditional/combustible tobacco. It will investigate progression over time using the PATH data set, specifically data from Waves 1 and 4. It has been well documented that tobacco companies purposely market traditional/combustible tobacco products that have low levels of tar. The result is that it may result in initiation of tobacco product usage by youth and adolescents.[4] As a result of the low levels of tar/nicotine, the products are no longer satisfying.[25, 35] This encourages the user to move up the tar/nicotine intensity scale by using products with more tar/nicotine delivery, until they reached products very high concentrations and delivery of tar/nicotine.[25, 35] While this process of progression to different products has been examined in some settings, it has not been extensively examined using the cohort data, specifically the data available in the PATH study. This investigation will differ from other studies as it provides an understanding using longitudinal cohort based on a nationally representative sample of tobacco ever users and daily user cohorts; specifically, it will look at all age groups and traditional/combustible tobacco products, as opposed to finite age parameters found in other research publications. Rather than analyzing free nicotine in this project, we will be examining tar delivery in full flavored and light cigarettes amongst longitudinal cohorts in the PATH Waves 1 and 4. We will be testing if the graduation theory holds true and if we can draw connections similar to those found in the 2001 paper by Shiffman, "Smokers' Beliefs about "Light" and "Ultra-Light" cigarettes."[58] Specifically, as outlined in the previous research product, we will utilize the categorization and groupings outlined in the first research product, categorizing by brand and tobacco product type. With these categorizations, the PATH data will also allow us to use that data to stratify participants by demographics to include age, gender and race. Using this information, we can understand who is switching products and the types of products they are switching to. More background research on products will afford us the opportunity to identify significant groupings related to PATH data specific tobacco products, including nicotine and tar content.

Significance

The rationale in this research proposal product is similar in nature to the research product focusing on smokeless tobacco. As aforementioned, since 1964, many national surveys have shown that initiation of tobacco use in almost all cases begins before adulthood; these were focused on cross-sectional data within a finite age group demographic and do not account for market.[9, 38, 76-78] With increasing trends showing lighter use as among those who smoked cigarettes in the past 30 days, nondaily smokers trends have conversely been increasing.[38] Studies found that patterns of experimentation with tobacco products have changed considerably over the past decade, with adolescents and young adults now commonly experimenting with multiple tobacco products.[76-78] The analysis of this longitudinal PATH data will allow us to understand how nicotine dependence developed using traditional/combustible tobacco translates to different tar content/exposure levels for individuals in specific age groups. More importantly, we will be able to understand different individuals/groups progression of tobacco products use patterns, including how use may vary within individuals/groups by product or by combinations of products, including product switching. The project seeks to answer questions regarding the novel and progressive use of traditional/combustible tobacco products in the PATH longitudinal cohort using specific research questions. One study has come close to exploring this type of analysis, however they identified predictors of becoming a daily cigarette smoker over the course of 4 years only amongst 12- to 24-year-olds at Wave 1 of the PATH study.[4] They were however able to determine ever use, age at first use, and daily use through Wave 4 for 12 tobacco products.[4] Our research product will not only focus on the same time period, but it will differ as it will include more age groups and dynamics that will add to the analysis and literature. Another similar study aimed to determine the association between e-cigarette use and subsequent smoking cessation in a nationally representative cohort of US smokers followed for 2 years (PATH Waves 1-3).[81] They were able to find that US adult cigarette smokers, daily e-cigarette use, compared to no e-cigarette use, was associated with a 77% increased odds of prolonged cigarette smoking abstinence over the subsequent 2 years.[81] Another study with adults found that any use of e-cigarettes, hookah, noncigarette combustible tobacco, or smokeless tobacco was independently associated with cigarette smoking 1 year later.[82] Furthermore, use of more than 1 product increased the odds of progressing to cigarette use.[82] Though these definitely add to the field of study, we previously established that most initiation of tobacco product use begins with teenagers, which is missing in these research products. Our research product would hopefully help close that gap.

Research Question/Aim & Approach:

As stated in the first research product, the purpose of the research is to use PATH data to examine whether the “graduation theory” holds for traditional/combustible, smokeless and e-cigarette products, with regards to patterns of use. U.S. Smokeless Tobacco (USST) developed a strategy for new users to “graduate” up to higher brands over time. The overarching research question/aim for this project is to what is the association between the outcome of graduated progression patterns of tobacco product use among longitudinal cohorts of new traditional/combustible tobacco users? Unlike other studies that limit ages from 12-24, this study will include all ages in the PATH study in order to try and understand the theory and research question from a larger perspective. We will be using responses from the PATH survey questionnaire as noted in chapter one to establish risk and calculate risk difference. We will analyze study covariates to identify how to differentiate this research study product from previous publications.

Much like the previous chapter, this analysis approach will utilize PATH survey questions in order to calculate risk, risk difference and 95% confidence interval for the risk difference. These calculations will allow us to investigate risk between Waves 1 and 4, in hopes of understanding risks of product use, product switching and the consideration of product switching. We will also explore how switching to different categories are affected by potential covariant factors. The methodology of proposed paper 2A would be applicable here, however it will be modified in terms of categorization of tobacco products. We will be examining tar delivery and how that is associated with full/light flavor combustible tobacco products. We would still take into account the appropriate statistical weighting techniques in calculating the 95% confidence interval and all calculations as highlighted in the Pierce et al., 2021 paper. However, we will not use latent transition analysis in this research product as described in chapter 2. We feel that we will have to use distinct and specific variables related to product type and nicotine delivery system in an attempt to distinguish the work from Pierce et al.[4] As described above, the adjusted risk differences (aRDs) would be computed from multivariable logistic regression as demonstrated in Pierce et al., 2021, however with the adjustment for additional variables such as age, age at first experimentation, sex, race/ethnicity, exposure to smokers, etc. we would achieve a research product that varies in methodology and structure, although slightly, to those that have been previously published.

Anticipated Outcomes, Public Health Implications and Limitations:

A recent pediatrics paper found that trying e-cigarettes and multiple other tobacco products before age 18 years is strongly associated with later daily cigarette smoking.[76-78] The recent large increase in e-cigarette and smokeless use will likely reverse the decline in cigarette and traditional/combustible smoking among US young adults.[76-78] We hypothesize that the same associations will hold true for traditional/combustible tobacco patterns of use. The introduction of other demographic variables will offer a wider scope of the subject matter as it is unclear how older participants will respond. However, judging from past literature, the emergence of these tobacco items becoming more common place and widely accepted, we feel as though more initiation will occur outside of adolescent groups, especially with more appealing, flavored tobacco products with less nicotine content. However, this begs limitations that may be outside the scope of what the project is able to uncover. We do not know if the subset of traditional/combustible tobacco users will be large or small. It also may be difficult to resolve statistically significant differences between the demographic strata and Waves. We lastly must consider that unmeasured confounding that is uncorrelated with the covariates is a limitation of any observational study.[2, 4] However, this should not detract from the strengths of the PATH study. It is a large representative sample of the US population and annual in-household follow-up self-assessments.[2, 4] Though it is noted that there was attrition between surveys, all survey weights are available to minimize effects on study estimates.[2, 4] The analysis above will help uncover potential patterns of traditional/combustible tobacco product switching tendencies. This information can inform new public health policies aimed at smoking cessation within targeted age groups.

Paper 3: Metabolic Phenotype Impacts on E-Cigarette Product Patterns of Use Amongst Wave 1 Longitudinal PATH Data

Nicotine is a chiral alkaloid found in tobacco that is widely used recreationally as a stimulant and anxiolytic. Furthermore, it is also used as a pharmaceutical drug for smoking cessation to relieve withdrawal symptoms.[57] Through decades of studies, it has been proven that nicotine is highly addictive, though there is question about how addiction varies different age groups and race/ethnicities.[58-60] It has been found that the rate of nicotine metabolism to cotinine is determined primarily by CYP2A6 activity and influences tobacco dependence and smoking-induced disease risk.[58] However, it has also been found that the prevalence of CYP2A6 gene variants can differ by race, with greater numbers in African American compared to Caucasians.[58] One study that investigated nicotine disposition kinetics and metabolism by CYP2A6 genotype and enzymatic activity, as measured by nicotine metabolite ratio, found that CYP2A6 genotype, NMR and nicotine pharmacokinetic data may inform studies of individual differences in smoking behavior and biomarkers of nicotine exposure.[58] Studies have also shown that large racial/ethnic differences exist in the rate and pathways of nicotine and cotinine metabolism, and also within the frequency of CYP2A6 gene variants.[40, 58, 64-66] The goal of this research paper is to explore the relationship between nicotine clearance from e-cigarettes and metabolism in relating genotype and phenotype to smoking behavior and disease risk.

As outlined in the literature, there are different kinds of e-cigarettes (some deliver little nicotine, while others deliver much more) and there are people who have different metabolic phenotypes (fast metabolizers vs. slow metabolizers) that use these products.[3, 59] It has also been recorded that some people metabolize nicotine rapidly and constantly look for their next dosage, and others metabolize nicotine very slowly, smoke more infrequently and typically do not feel a strong addiction to nicotine/cigarettes. This was evident as Zhu et al reported that cotinine levels were disproportionately high for the same nicotine intake in people with reduced CYP2A6 enzymatic activity, as cotinine clearance was reduced to a greater extent than cotinine formation from nicotine; this was also observed among those with slower activity in the study.[67] Another study reported that smokers who are fully null of metabolic activity have markedly reduced cotinine levels as they simply do not make much cotinine.[58] This study concluded that relative changes in cotinine formation versus clearance vary substantially according to the particular genetic variant; this is also possibly due to variability in activity of competing metabolic pathways.[58] Paper three will examine e-cigarette types and their association with user metabolic phenotypes as it relates to age, sex, and race-ethnicity within PATH study data.

Significance

In previous chapters, we established that in 2017, the US Department of Health and Human Services identified tobacco use as the leading cause of preventable disease and death in the United States, with nearly all tobacco use beginning during youth and young adulthood.[1, 2] These products typically contain over 3000 constituents, including nicotine, making it highly addictive in nature.[12-14]

Though the initial thought that electronic cigarettes were safe than conventional combustible products, the e-cigarette aerosol that users breathe from the device and exhale can contain harmful and potentially harmful substances.[16] These harmful substances may include nicotine and ultrafine particles that can be inhaled deep into the lungs. These harmful substances can also include flavoring like diacetyl (a chemical linked to a serious lung disease), volatile organic compounds, cancer-causing chemicals, heavy metals such as nickel, tin, and lead.[16] Though e-cigarettes are still fairly new as aforementioned, scientists are still learning about their long-term health effects and it's relation to addiction. As of now scientists have concluded similar facts based on what are known as health effects. Nicotine is highly addictive and toxic to developing fetuses, and it can harm adolescent and young adult brain development, proven to continue into the early mid-twenties. Though e-cigarette aerosol generally contains less harmful chemicals than smoke burned from tobacco products, it is still not proven to be a safe alternative.

Despite looming presence of negative health effects mentioned above, addiction or compulsive drug-seeking and use is still prevalent and is the underlying impetus behind this research product.[83] Though many try to quit smoking and end nicotine addiction, only about 6 percent of smokers are able to quit in a given year.[83] In fact it was reported that a temporary surge of endorphins within the reward circuits of the brain cause a short-term euphoria when nicotine is administered.[68] This surge or “high” is much shorter lived than other drugs. In addition, nicotine increases levels of the neurotransmitter dopamine in these reward circuits, which then reinforces the behavior of taking the drug, acting very similar to other drugs of abuse.[83] After multiple and repeated exposures, it has been shown that brain circuit sensitivity to dopamine is altered, leading to changes in other brain circuits involved in learning, stress, and self-control.[83] In fact, for the majority of tobacco users, the long-term brain changes induced by continued nicotine exposure result in addiction.[83] This in turn, involves withdrawal symptoms when not smoking, and difficulty adhering to the resolution to quit.[83]

Knowing the toxic and addictive properties of nicotine, it was proposed more than 20 years ago that individuals who metabolize nicotine poorly would smoke less, either fewer cigarettes per day or less intensely per cigarette, compared to smokers who metabolize nicotine more efficiently.[68] These slow metabolizers would then be less likely to develop lung cancer due to their lower exposure to the many carcinogens delivered with nicotine in each puff of smoke.[68] Numerous studies have reported that smokers who carry reduced activity or null CYP2A6 alleles do smoke less; our goal is to see if this holds true for e-cigarettes using the PATH survey data.[68]

Research Question/Aim & Approach:

Each adult respondent, who completed the interview at Wave 1, was asked to provide at least two biospecimens. Providing biospecimens was voluntary and was not a condition of participation. Respondents were asked to report their use of all nicotine-containing products during the 3-day period prior to the time of any biospecimen collection to facilitate interpretation of biomarker results; these were referred to Nicotine Exposure Questions or NEQs.[3] Of the 32,320 respondents who completed the adult interview at Wave 1, 21,801 (67.4%) provided a urine specimen and 14,520 (44.9%) provided a blood specimen.[3] A sample of 11,522 adults who provided sufficient urine for the planned analyses were selected from a diverse mix of six tobacco product use groups representing never, current, and recent former (within 12 months) users of tobacco products.[3] This group constitutes the Wave 1 Biomarker Core. Of the 11,522 adults, 7,159 also provided a blood specimen. All urine and blood specimens provided by the Wave 1 Biomarker Core were sent for laboratory analysis.[3] References to the collection of biospecimens will be specified by the collected specimen, i.e., urine and (whole) blood. However, references to biomarker analyses and analytes will be specified by the type of matrix (serum, plasma, or urine) used for the analysis.

We propose to analyze nicotine metabolism by examining nicotine metabolite ratios (hydroxycotinine vs. cotinine). These biomarkers of tobacco exposure are essential in characterizing actual human exposure to harmful or potentially harmful chemicals resulting from tobacco use. This study will use the serum and urinary concentrations of biomarkers of exposure information, collected from PATH Wave 1 data, to examine e-cigarette types and their association with user metabolic phenotypes as it relates to age, sex, and race-ethnicity within PATH study data. In order to achieve this, a master linkage data file is included with each respondent’s unique identifier and variables that indicate which biomarker data files contain data pertaining to that respondent within a Wave, and across Waves.

The biomarker restricted use data consist of the following files that will be included for each Wave; this information is also highlighted in figure A1 below, according to the user guide.[3]

A set of data files containing biomarker assay results. Laboratory data for each biomarker assay is included in the panel data file. Separate data files (referred to as "collection data files") containing metadata about the blood and urine specimen collection processes, including questionnaire responses to the NEQs. Separate biomarker weight files containing the full sample weight and the replicate weight variables. There are separate files for analysis of blood specimens, urine specimens, and oxidative stress data (F2PG2a; starting in Wave 2)

Figure A1 "Table 2" Adapted from PATH Biomarker Restricted-Use Files Guide[3]

Table 2. Biomarker data files for the Wave 1 Biomarker Core, by wave

Biomarker Panel Assay Data Files	Abbreviation	Matrix	BOE or BOPH	Wave(s)*
enzymatic creatinine	CREAU	urine	N/A	1- 4
speciated arsenic panel	AsSpec	urine	BOE	1, 2
metals	Metals	urine	BOE	1- 4
hydroxy polycyclic aromatic hydrocarbons	PAH	urine	BOE	1- 4
tobacco-specific nitrosamines	TSNA	urine	BOE	1- 4
urinary nicotine metabolites (cotinine, hydroxycotinine, etc.)	UNICM	urine	BOE	1- 4
volatile organic compound metabolites	VOCM	urine	BOE	1- 4
oxidative stress biomarker (8-isoprostane)	F2PG2a	urine	BOPH	1, 2
high-sensitivity C-reactive protein	hsCRP	serum	BOPH	1
serum cotinine and hydroxycotinine	SCOT	serum	BOE	1
interleukin 6	IL6	serum	BOPH	1
intracellular adhesion molecule	sICAM	serum	BOPH	1
fibrinogen activity (Clauss)	fibro	plasma	BOPH	1
Collection Data Files	**Abbreviation**	**Matrix**	**BOE or BOPH**	**Wave (s)***
blood (collection & NEQ data)	BLOOD	N/A	N/A	1
urine (collection & NEQ data)	URINE	N/A	N/A	1- 4
Biomarker Weight File **	**Abbreviation**	**Matrix**	**BOE or BOPH**	**Wave(s)***
blood		N/A	N/A	1
urine		N/A	N/A	1- 4

Notes. BOE = Biomarker of exposure; BOPH = Biomarker of potential harm; NEQ = Nicotine Exposure Questions.

*Panels are added to the data files on an on-going basis. Please see the Laboratory File Inventory for which panels are currently available in the data files. Also, see each panel's Laboratory Panel Documentation for details on which analytes were measured at each wave and other wave-specific data considerations. Blood was analyzed from the Wave 1 Biomarker Core at Wave 1, and corresponding serum and plasma BOPH and BOE data are available only for Wave 1.

**Biomarker Weight files, for a given specimen, are created for the Wave 1 Biomarker Core at each wave.

In this paper we will more specifically investigate, within the e-cigarette user population, if slow metabolizers are more likely to use cigalikes, while conversely, fast metabolizers are more likely to use 2nd, and 3rd generation devices. We also want to understand if slow metabolizers are more likely to use less e-liquid each day than fast metabolizers due to genetic variation as covered above and below. We intend to evaluate this by defining “success” as complete switching and “failure” as long-term dual use. Ultimately, we aim to uncover if smokers that are defined as slow metabolizers, due to genetic variation, are better able to switch completely to e-cigarettes if they use cigalikes and use less e-liquid each day compared to fast metabolizers. However, we will also examine if the opposite holds true as far as smokers who are fast metabolizers. For example, would they be more likely to be successful at complete switching if they use a 2nd, and 3rd generation device and use more e-liquid each day?

Anticipated Outcomes, Public Health Implications and Limitations:

The analysis above will help uncover potential patterns of e-cigarette use based on metabolic phenotypes and genotypes amongst various age groups, race/ethnicities and sex. Metabolic genotypes essentially comprise all chemical reactions an organism catalyzes by way of enzymes encoded in its genome.[84] However, metabolic phenotype is the sum of an organism’s observable characteristics.[62] The fundamental difference between phenotype and genotype is that, where genotype is inherited from an organism’s parents, the phenotype is influenced by the genotype and can be influenced by epigenetic modifications, environmental and lifestyle factors.[62]

Based on literature reviews and 20+ years of research, we feel that individuals who metabolize nicotine poorly would vape less, either fewer e-cigarettes per day or less intensely per e-cigarette, and be more likely to use e-cigarettes, like cigalikes, that deliver lower levels of nicotine compared to smokers who metabolize nicotine more efficiently.[68] This again would depend upon choice of e-cigarette product. In fact, a study published that about 50% of the initiation of tobacco dependence is genetically influenced.[85] The same study found that the maintenance of dependent smoking behavior and amount smoked have approximately 70% genetic contribution.[85] Due to this genetically polymorphic phenomenon, individuals that carry inactive CYP2A6 alleles have decreased nicotine metabolism.[85] They are also far less likely to become smokers, however those that do, smoke fewer cigarettes per day.[85]

Decrease in smoking behavior is scientifically confirmable by measuring carbon monoxide levels, which is a measure of smoke inhalation, along with plasma and urine nicotine and cotinine levels.[85]

On the other hand, if a duplication variant in the CYP2A6 gene locus has been identified, this may increase nicotine inactivation and, in turn, smoking.[85] Regarding public health implications, we feel that those who metabolize nicotine poorly would then be less likely to become smokers. We could also decipher which e-cigarette product will help smokers with different NMR to quit smoking completely, though this would rely heavily upon whether these are exclusive ENDS users or dual users of other tobacco products.

It has been recorded in numerous studies that smokers who carry reduced activity or null CYP2A6 alleles do smoke less.[16, 68, 85] Yet, variation in metabolism pathways, other than those catalyzed by P450 2A6, can impact biomarkers of both nicotine metabolism and dose.[68] It is imperative to also understand this information regarding smokers with low levels of UGT2B10-catalyzed nicotine and cotinine glucuronidation, due to the UGT2B10 genotype influences plasma cotinine levels.[68] Murphy uncovered that cotinine is not glucuronidated in 15% of African American smokers (compared to 1% of Whites) due to the prevalence of a UGT2B10 splice variant.[68] This specific variant can result in higher plasma cotinine levels per e-cigarette in this group, which in turn may also influence the accuracy of the 3HCOT to cotinine ratio as a measure of P450 2A6 activity.[68] The challenge is to see if the PATH data can accomplish this level of measurement and accuracy given the biomarkers provided.