2023

Evaluating the Acute Effect of Vaping on Food Intake

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EVALUATING THE ACUTE EFFECT OF VAPING ON FOOD INTAKE

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science at Virginia Commonwealth University.

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July 2023

Acknowledgements

I would like to express my gratitude for the support that I have received from the CSTP & BHRL. I am especially appreciative of the guidance and support that my mentor, Dr. Caroline Cobb, has provided me through this journey and additionally that of my committee members, Drs. Barnes, Moreno, and Mazzeo. Additionally, I would like to thank the lab of Dr. Corby Martin, with particular recognition to Dr. Christoph Höchsmann, at the Ingestive Behavior, Weight Management, & Health Promotion Laboratory at Pennington Biomedical Research Center for their significant contribution to the design of this project. I also would like to convey a special thank you to our wonderful Research Assistants (Akansha Anbil, Rabia Imran, and Madison Combs) and our lab manager (Nicoleta Gaitin) who have provided essential support in prepping for this study. I am very thankful and honored to be a part of this excellent team which conveys a passion towards enhancing scientific knowledge.

I am grateful to my wonderful family to include my parents Dr. Alphonse Sirica and Annette Sirica who has always displayed support, kindness, and patience and who continuously gave me the strength to keep reaching for the stars. Also, a specific acknowledgement, to my daughter Autumn, who is my light and motivation. Secondly, to my brother Nick and sister-in-law Sarah, for all of their love and support through this entire process. This acknowledgement is especially for Marisa Maldonado, who recently passed. Thank you, Marisa, for always teaching me to be the best version of myself.

This research was supported by the National Institute on Drug Abuse of the National Institutes of Health under Award Number U54DA036105 and the Center for Tobacco Products of the U.S. Food and Drug Administration. The content is solely the responsibility of the authors

and does not necessarily represent the official views of the National Institutes of Health or the Food and Drug Administration.

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List of Abbreviations

Ad lib	Ad libitum
ANOVA	Analysis of variance
BP	Blood pressure
CDC	Centers for Disease Control and Prevention
CO	Carbon monoxide
CTP	Center for Tobacco Products
CSTP	Center for the Study of Tobacco Products
ENDS	Electronic Nicotine Delivery System
FCQ-State	Food Craving Questionnaire -State
FDA	U.S. Food and Drug Administration
FTC	Federal Trade Commission
g	Gram
HR	Heart rate
ITP	Investigational Tobacco Product
IRB	Institutional Review Board
kcal	Kilocalories
mg	Milligram
MNWS	Minnesota Nicotine Withdrawal Scale
nAChR	Nicotinic acetylcholine receptors
NCI	National Cancer Institute
NCCDPHP	National Center for Chronic Disease Prevention and Health Promotion
ng	Nanogram

NIDA	National Institute on Drug Abuse
mL	Milliliter
PG	Propylene glycol
Adapted “SWEET” test	Adapted Smoking-related Weight and Episodes Test
TFAH	Trust for America’s Health
POMC	Proopiomelanocortin cells
VAS	Visual Analog Scale
VG	Vegetable glycerin

Abstract

Weight control is a common motive for initiation and continued cigarette smoking, and fear of post-cessation weight gain has been cited as an important barrier to smoking cessation. Empirical evidence supports the idea that nicotine alone or delivered via cigarettes reduces appetite and ultimately body weight by acting upon brain and hormonal mechanisms. Electronic nicotine delivery systems (ENDS) represent a new class of tobacco products that have been marketed for weight control and are increasingly being used for this purpose among users. For ENDS users who engage in quitting ENDS, it is possible that they may experience similar weight-related challenges as is observed for cigarette smokers, but there have been no acute controlled clinical examinations of the effects of ENDS on appetite which are inclusive of food intake and related subjective effects around hunger, craving, and satiety. The goal of the current study was to address this pertinent research gap.

Thirty-four current ENDS users (18-65) years of age completed two randomly ordered clinical lab sessions (within-subject design) following overnight abstinence from any tobacco/nicotine product and food and drinks other than water. Sessions differed by product administration, which included an active ENDS condition (5% nicotine Virginia Tobacco Flavored JUUL) and a control (uncharged JUUL and empty pod). During the active condition, participants were directed to take a total of 20 puffs within 20 minutes; whereas the control condition, participants were given the option to utilize the JUUL product but were not required to take puffs. Forty-five minutes following condition administration, participants were escorted to a different lab room for an *ad lib* meal consisting of 21 easy to access food items that ranged from salty (peanuts), fatty (cheese), savory (chicken), and sweet (candy). Participants were given up to 30 minutes for the *ad lib* meal, but they were not required to utilize the full time period.

Subjective ratings of nicotine-related side effects/abstinence symptoms, hunger, and satiety were given at four time points during the session, and food craving (Food Craving Questionnaire-State) was assessed once during the session. Repeated measures analysis of variance and Bonferroni-corrected pairwise comparisons were used to compare condition differences in energy intake and subjective effects.

Of the 34 completers, the mean age was ~25 years, 38.3% female, ~60 % non-white. There was no significant difference in energy intake (kcal) between the active (1011.9±98.8) and control (939.4±88.4) conditions as well as no significant differences in macronutrient intake. Regarding subjective effects, significant condition by time effects were observed for hunger and satiety; specifically following active condition administration, satiety significantly increased and hunger significantly decreased relative to baseline. Following control condition administration, satiety ratings remained relatively constant and hunger significantly increased relative to baseline.

Taken together, our results indicate that acute ENDS use suppressed feelings of hunger and increased satiety, but these subjective effects did not translate to reduced energy intake measured objectively during an *ad lib* buffet meal. These data help clarify the role of acute ENDS use on energy intake and provide a novel contribution to the existing literature on the acute effects of nicotine administration on appetite. Future ENDS cessation efforts should consider the inclusion of information addressing the perceived effectiveness of ENDS for appetite control and/or weight management.

Introduction

Overview

Weight control is a common motive for initiation and continued smoking, and fear of post-cessation weight gain is cited as an important barrier to smoking cessation and/or relapse (Beebe & Bush, 2015; Pinto et al., 1999; White, 2012). The relations among smoking, appetite, and body weight are complex and incompletely understood, but evidence supports the idea that nicotine delivered alone or via cigarettes reduces appetite, and ultimately body weight, by acting upon brain and hormonal mechanisms (Audrain-McGovern & Benowitz, 2011). Whether these effects extend to other tobacco products such as electronic nicotine delivery systems (ENDS) is unknown. Nonetheless, marketing for ENDS has included weight control messages (Lyu et al., 2022) and are being used for this purpose among cigarette smokers and ENDS users (Jackson et al., 2019; Pineiro et al., 2016; Strong et al., 2015). Better understanding of the effects of ENDS on appetite and weight-related factors could inform future cessation efforts and considerations for ENDS users and for cigarette smokers that use ENDS as a harm reduction or cessation aid (Hartmann-Boyce et al., 2021; NASEM, 2018).

Public Health Impact of Cigarette Smoking, ENDS, and Obesity in the U.S.

Tobacco use and obesity have large public health impacts in the United States (U.S.). Although cigarette smoking declined from 20.9% in 2005 to 12.5% in 2020 for adults, over 16 million individuals in the U.S. live with a smoking-related disease (CDC, 2021). At the same time, use of alternative forms of tobacco, like ENDS, is increasing. For instance, from 2017 to 2018, ENDS usage increased dramatically from 11.7% to 20.8% in adolescents (CDC, 2021). Among adults in 2018, ENDS usage was highest among those ages 18-24 years (7.6%), non-Hispanic white (3.7%), and male (4.3%) (CDC, 2020). Another important health marker, obesity,

is also increasing across multiple age groups. The incidence of obesity has increased by 26% since 2008, reaching above 40% of the U.S. adult population in 2019, with non-Hispanic Black adults experiencing the highest incidence at 50% (CDC, 2022; TFAH, 2020). Critically, tobacco use and obesity pose similar health risks including cardiovascular disease, endocrine and metabolic disorders, and respiratory disorders (Audrain-McGovern & Benowitz, 2011; Bush et al., 2016). Tobacco smoking and obesity are leading causes of premature morbidity and mortality in the U.S., and obesity is a strong contributor to worsening conditions caused by smoking (Roos et al., 2017).

In addition to tobacco-related health behaviors and weight-related conditions serving as health risk factors, the use of nicotine-containing products and subsequent cessation attempts are related to weight control, weight gain, and obesity. Perceptions that cigarette smoking and ENDS use prevent weight gain are common in adolescents, and are associated with initiation (Mantey et al., 2020; Potter et al., 2004). These perceptions might perpetuate cigarette smoking (Wee et al., 2001), but evidence related to ENDS use and fear of cessation-related weight gain is sparse (Jackson et al., 2019). Associative studies provide mixed evidence on the impact of smoking on obesity (Dare et al., 2015; Tuovinen et al., 2016), but likely these effects depend on age and intensity of smoking, and/or time since quitting (Dare et al., 2015). For example, it is not uncommon for smokers who recently quit to experience weight gain within the first few months post-cessation (Klesges et al., 1997; O'Hara et al., 1998; Russo et al., 2016). Weight gain after smoking cessation can increase risk for the onset of new health conditions or exacerbating current conditions (Audrain-McGovern & Benowitz, 2011; Bush et al., 2016; Yeh et al., 2010), but the benefits of smoking cessation on mortality risk outweigh these concerns (Doll et al., 2004; Prospective Studies et al., 2009). Whether weight gain and associated health benefit/harm

occurs following ENDS cessation is unclear as few studies have focused on this specific outcome (Russo et al., 2018; Wawryk-Gawda et al., 2019).

With recent increases in ENDS use among older populations, including those with previous smoking history (Cornelius et al., 2020), interventions for ENDS users need to be cognizant of potential weight-related concerns. Of note, results from a recent Cochrane review noted that there were no programs or treatments with a moderate certainty to reduce long-term cigarette smoking cessation related-weight gain (Hartmann-Boyce et al., 2021). Evidence from this review highlighted that personalized weight-management treatment and nicotine replacement therapy had some evidence of effectiveness for this purpose. Whether ENDS, an emerging tool for harm reduction and smoking cessation (Hartmann-Boyce et al., 2021; NASEM, 2018), might complement existing strategies to address weight gain and concerns among smokers is also unknown (Hod et al., 2022). To best address the burdens of cigarette smoking, ENDS use, and obesity in the U.S., innovative approaches are needed to inform cessation efforts for ENDS users and cigarette smokers. Critical to the development of these efforts is understanding the role of nicotine in influencing patterns of tobacco use, appetite, and body weight.

Nicotine: Pharmacology and Effects on Appetite and Body Weight

Nicotine is a well-known stimulant that is derived from the tobacco plant (a nightshade plant in which nicotine is the naturally produced alkaloid; Holloway, 2014). Synthetic versions of nicotine (i.e. tobacco-free nicotine) can also be produced in the laboratory environment (Jordt, 2021). When nicotine is consumed by inhalation (i.e., smoke from a cigarette), it rapidly diffuses to the brain in about 10-20 seconds (Goriounova & Mansvelder, 2012), where it binds to and activates nicotinic acetylcholine receptors (nAChRs) (Benowitz, 2009; Dani, 2015; Wittenberg et al., 2020). Once bound, nicotine enhances the release and metabolism of acetylcholine,

stimulates the dopaminergic system, and increases the concentration of dopamine in the mesocortico-limbic system involving the ventral tegmental area, nucleus accumbens, and forebrain (Addicott et al., 2019; Benowitz, 2009; Wittenberg et al., 2020). Similar to other drugs of abuse, with repeated exposure to nicotine, tolerance or neuroadaptation occurs, and in turn, additional nAChR sites develop in the brain, eliciting the need for more nicotine use for these receptor systems to be stimulated (Benowitz, 2009). These changes are considered critical mediators of the development of nicotine dependence (Wittenberg et al., 2020). In addition, nicotine's pharmacological effects are associated with increases in psychomotor activity, attention, and cognitive function as well as anxiety reduction and mood stabilization (Benowitz et al., 2021; Valentine & Sofuoglu, 2018).

Nicotine also directly impacts areas of the central nervous system associated with appetite control and metabolic rate (Audrain-McGovern & Benowitz, 2011; Benowitz et al., 2021). Although these mechanisms are incompletely understood, there is evidence that nicotine might augment the effects of leptin, a satiety signaling hormone (Jo et al., 2002), and act similarly to some drugs used to treat obesity by increasing norepinephrine, dopamine, and/or serotonin levels (Ioannides-Demos et al., 2011). Another hypothesis is that nicotine likely triggers a response in the proopiomelanocortin (POMC) cells in the hypothalamus, which are responsible primarily for food inhibition and increasing energy expenditure (Picciotto & Mineur, 2013). POMC cells are also the major targets of appetite suppression hormones such as leptin and insulin (Picciotto & Mineur, 2013; Varela & Horvath, 2012). In addition to these potential mechanisms, nicotine delivered from cigarette smoking can increase the body's resting metabolic rate by about 10%, which in the absence of increased caloric intake can result in substantive weight loss over time (Hofstetter et al., 1986). Taken together, this information highlights the

complexity of nicotine's pharmacological effects on appetite and body weight. Although a wealth of preclinical and clinical investigations using various methods have tried to disentangle these effects, acute clinical designs represent one means to better understand how nicotine use in various forms immediately impacts appetite (which is inclusive of food intake) and associated factors.

Acute Clinical Studies of Nicotine's Effects on Appetite

Studies spanning over several decades have aimed to understand why smoking is associated with reduced body weight which was assumed to be from acute suppression of appetite (e.g., Grunberg, 1982). More recent work in this area has also explored whether effects differ when nicotine is delivered via nasal spray (versus a cigarette; e.g., Perkins et al., 1991), and if changes in appetite-related hormonal markers relate to effects observed (Yannakoulia et al., 2018). However, across these studies, there is considerable variation in the methodology used, and findings observed in regards to nicotine and acute appetite suppression.

One of the earliest controlled studies tested whether cigarette smoking reduced sweet, salty, and bland food intake in an experimental setting (Grunberg, 1982). Forty-three participants represented three groups: non-smokers, smokers who smoked two cigarettes immediately prior to the meal, or smokers who were deprived of cigarettes for about 12 hours prior to the session. All smokers in this study had used at least 15 cigarettes per day for at least 2 years. Participants arrived around lunchtime but were asked not to eat lunch prior to the session. They were asked to eat and rate nine foods categorized by sweet, salty, or bland category (researcher-defined). They chose three of the foods to eat again and the amount eaten at this point was compared by group. Total food consumption groups did not differ significantly across groups, although non-smokers ate slightly more food than both smoking groups. When compared by food category, non-

deprived smokers during the session ate less sweet food than both deprived smokers and non-smokers, but this difference was not significant. Food preference following the initial testing showed that non-smokers had a significantly higher preference for sweet food than did non-deprived smokers. The author concluded that cigarette smoking decreases, and abstinence increases, consumption of sweet foods, which might relate to effects on body weight (Grunberg, 1982).

Subsequent studies conducted by Perkins and colleagues (1991; 1992; 1994) focused on nicotine's acute effects on appetite in smokers versus non-smokers (Perkins et al., 1991) as well as the effects of nicotine and hunger among male and female smokers (Perkins et al., 1992; Perkins et al., 1994). In one study, 20 male participants were recruited (10 smokers; 10 non-smokers) to participate in four laboratory sessions, preceded by overnight food/smoking abstinence. Sessions differed by breakfast availability (a caloric-containing liquid [simulating breakfast] or water) that was followed by nasal spray (15 ug/kg nicotine or placebo; Perkins et al., 1991). The nasal spray was administered every 20 minutes for 2 hours following breakfast manipulation. After each nasal spray administration, participants completed subjective measures of hunger and satiety. On days in which water was consumed, the session ended after the final 20-minute rest period and the completion of the subjective questions; on days in which participants consumed the caloric liquid, they were then presented with a final nicotine spray administration followed by a 20-minute *ad lib* buffet style meal. Subjective effects revealed that nicotine administration was associated with decreased ratings of hunger, relative to placebo, but only if participants consumed the caloric liquid first. Nicotine administration significantly reduced food consumption relative to the placebo during the meal), and when examined by macronutrient category, nicotine administration significantly reduced consumption of

carbohydrates. Together, findings suggested nicotine-related suppression of hunger and food consumption but only when participants had not abstained from the prior meal (Perkins et al., 1991).

This team performed a similarly designed study to Perkins et al. (1991) with a sample of 10 male and 10 female smokers (Perkins et al., 1992). Following overnight abstinence from food and smoking, participants took part in four laboratory sessions in which they received either nicotine-containing nasal spray (7.5, 15, 30 ug/kg) or a placebo every 30 minutes for 2 hours prior to an *ad lib* buffet meal; subjective measures assessed hunger, satiety, and cigarette cravings before each dose administration (Perkins et al., 1992). Hunger ratings did not differ significantly by nicotine dose or sex, but cigarette cravings significantly decreased with nicotine administration. However, nicotine administration was associated with greater calories consumed from food, although no significant dose-related effects were observed (kcals ranged from ~650-700 across conditions) and with no significant interaction for sex. When examined by macronutrient category, carbohydrate intake was significantly increased relative to placebo for 7.5 and 15 nicotine ug/kg. The authors concluded that results did not support the idea that nicotine acutely suppressed hunger or food intake in smokers who have abstained from nicotine/food (Perkins et al., 1992).

Another study conducted by Perkins and colleagues (1994) examined the effects of cigarette smoking and nicotine on appetite among 10 male and 10 female smokers who completed three 2-hour sessions preceded by overnight abstinence from tobacco/food differing in cigarette access/exposure: own brand cigarette (0.75 mg nicotine), a low nicotine cigarette (0.1 mg), or a sham (unlit) cigarette. Computerized instructions regarding when to smoke and how long to inhale were presented to participants via a video monitor; puffing was signaled once

every 20 sec for 2 to 5 minutes for 8 puffs in total. This process was performed 4 times (4 cigarettes). Plasma nicotine and expired carbon monoxide (CO) were used to measure the amount of nicotine and smoke exposure between conditions. Similar to previous studies (Perkins et al. 1991; 1992), feelings of hunger and cigarette cravings were recorded throughout. At the end of each session, participants were provided access to an *ad lib* meal containing 15 items. There were no significant condition-related effects for subjective hunger over time although, the first own brand cigarette administration did initially decrease hunger for men and women. These effects contrasted with those for cigarette craving, which decreased markedly for both active cigarette conditions. Although males tended to eat more during the meal, the cigarette condition had no significant effects in mean (±standard error) caloric intake by condition (own brand cigarette 334±36 kcal, low nicotine cigarette 363±39 kcal, sham 346±39 kcal) or in macronutrient or taste selection regardless of sex (Perkins et al., 1994). Taken together, these findings suggest that the ability of nicotine to acutely suppress hunger and eating behavior after overnight abstinence might be minimal/non-existent (Perkins et al., 1992; 1994) unless a meal is consumed prior (Perkins et al., 1991).

A study performed by Bulik and colleagues (1991) contributes to the contradictory nature in findings regarding the influence of nicotine on appetite. In this study, five women with a bulimia nervosa diagnosis who were also current smokers participated in four sessions on four consecutive days which involved an initial habituation day, followed by three randomly ordered conditions with overnight abstinence from food/smoking: regular own brand, low nicotine (0.2 mg), and a nonsmoking condition. Participants were instructed on smoking days to smoke every 30 minutes for 4 hours (8 cigarettes in total); on nonsmoking days, participants drew a line during the same time intervals. Participants were provided access to vending machines with food

and cigarettes and were instructed to eat *ad lib*. The fact that participants had access to a vending machine with food as opposed to a single test meal is important to note because participants had access to food throughout the entirety of their session. Study findings indicated that mean (±standard deviation) energy consumed in the nonsmoking condition (832±495 kcal) was significantly greater compared with consumption in the low nicotine (509±206 kcal) and regular cigarette (477±295 kcal) conditions (Bulik et al., 1991).

A more recent study of the effects of nicotine on appetite suppression focused on the effects of appetite-related hormones in addition to food intake (Yannakoulia et al., 2018). Here 14 healthy male smokers participated in two lab sessions (cigarette versus sham) after overnight abstinence from food/drink (except water) and smoking. In the cigarette condition, participants smoked two own brand cigarettes within 15 minutes and the control condition (sham) involved participants holding an unlit cigarette. After 45 minutes, participants were presented with an *ad lib* meal consisting of 7 food items. Blood samples were taken from participants at three time points during the session (fasting, before meal, and 1 hour after meal) and were analyzed for obestatin, ghrelin, glucagon-like-peptide-1, cholecystokinin, and insulin. Subjective feelings of hunger, satiety, desire to eat, and cigarette craving were assessed at the same time points as the blood draws. Findings revealed a significant decrease in mean (±standard deviation) energy intake for the cigarette condition (673±245 kcal), as opposed to the sham (825±310 kcal), but no significant differences observed between conditions for appetite-related feelings or related hormones. Interestingly, there was a negative correlation between years of smoking and the difference in caloric intake between conditions ($r=-0.707$, $p=0.007$; Yannakoulia et al., 2018). These data suggest that the acute appetite suppressing effects of nicotine might be less pronounced among smokers with a longer history of use.

Based upon this prior research, there is some evidence of an acute decrease in caloric intake after the administration of a conventional tobacco cigarette following food/tobacco abstinence in small and selective sample sizes (Yannakoulia et al., 2018; Bulik et al., 1991). However, clinical research in this area has been limited in scope, sample composition (smoking and non-smoking populations), and nicotine-containing products tested (cigarette and nicotine nasal spray). Furthermore, most other research conducted on the use of nicotine for weight management, or in relationship to weight gain, focuses on cigarettes as the primary product (Audrain-McGovern & Benowitz, 2011). The role of other novel forms of nicotine delivery, such as ENDS, for weight management, and the impact of their use on subsequent weight gain during cessation, is largely unexplored. Reported use of ENDS for weight management purposes has been steadily increasing, particularly among adolescents (Sanchez et al., 2021) and young adults (Pokhrel et al., 2021). Therefore, it is of the utmost importance to enhance understanding of how ENDS products work, how they are marketed (including for weight control), and common perceptions around ENDS products for these purposes. The following sections will discuss each of these points in greater detail.

Overview of Electronic Nicotine Delivery Systems (ENDS)

ENDS, also known as “e-cigs”, “vapes”, and “mods”, come in all shapes, sizes, and forms, but the basic elements include a battery, heating element or atomizer which includes a coil and wick, reservoir for holding ENDS liquid (which is generally nicotine-containing), and a mouthpiece (NIDA, 2020; Breland et al.,2017). Current ENDS were introduced to the Chinese market by 2004, and to the U.S. market by the mid-2000’s (Fadus et al., 2019). According to a report from the U.S. Federal Trade Commission (FTC), ENDS sales increased from around 300 million in 2015, to around 2 billion in 2018, with sales in flavored cartridges increasing seven-

fold among youth during that time (FTC, 2022). In 2020, the U.S. market for ENDS products obtained a value around 6 billion and is expected to continue growing with a compound annual growth rate of 27.3% by 2028 (U.S. e-cigarette & vape market size, share report 2021-2028, n.d). Within the past few years, ENDS products have continued to evolve in terms of nicotine delivery and product design which has impacted use behavior (Breland et al., 2017). Having a better understanding of how ENDS product features influence use behavior is important in understanding their role in public health.

In general, ENDS work by activating a battery source that is connected to a heating element or atomizer/coil that heats a nicotine-containing liquid into an aerosol which is then inhaled by the user (Breland et al, 2017). ENDS devices and other product features vary considerably in terms of the battery size/capacity, ability to be user modified/replaced, and the characteristics of the heating element (Breland et al., 2017). In terms of liquid characteristics, propylene glycol (PG) and vegetable glycerin (VG), at varying ratios, are typically utilized as a means to generate vapor and as a carrier system for nicotine and other constituents (Woodall et al., 2020). The nicotine found in ENDS liquid also varies in concentration from 0 mg/ml to upwards of 36 mg/mL and the form of nicotine (protonated; salt form/NicH (+)) vs. non-protonated, free-base/Nic). ENDS aerosol containing protonated nicotine is believed to be less aversive, easier to inhale, and more appealing than free-base products (Gholap et al., 2020; Talih et al., 2020). The increased harshness in free-base nicotine is due to the higher level of alkalinity compared to the protonated form; neutralizing the pH of the liquid is used to create the protonated form (Duell et al., 2019; Leventhal et al., 2021). These properties might be why ENDS products like JUUL which contain protonated nicotine at higher concentrations (e.g., 5% or ~59 mg/ml) have become increasingly popular (Fadus et al., 2019; Talih et al., 2019).

Like other tobacco products, ENDS are currently overseen by the Center for Tobacco Products (CTP) under the Food and Drug Administration (FDA), although there are specific differences in terms of which policies apply to this product class. Current regulations around ENDS products include limiting sales to those who are 21 years or older, requiring a warning label related to nicotine content, restriction on use of health claims (unless FDA-authorized) and a requirement to submit products for FDA authorization prior to marketing (FDA, 2016). In early 2020, the FDA finalized a policy to reduce flavor availability in cartridge-based ENDS products, meaning that the only available flavors included tobacco and menthol (FDA, 2020). The updated policy around flavors specifically applied to JUUL and other products with replaceable cartridges (a.k.a., pods) but not to disposable ENDS (containing no modifiable components) or ENDS liquids (for use in liquid tanks/reservoirs that are sold separately; see Figure 1 for examples). Of note, this FDA flavor restriction policy for cartridge-based ENDS was in response to the rising levels of ENDS usage among youth (FDA, 2020).

Figure 1. Example ENDS liquid (Vape Pink Cookie Butter), cartridge-based ENDS (JUUL battery and JUUL pod), and disposable ENDS (Puff Bar).

National estimates from 2011-2018 indicate that 68% of high school students who use ENDS use flavored products (Cullen et al., 2018). The use of flavors to attract youth and young adults is well-established as a means to mask the harshness and flavor of traditional tobacco products (Kostygina & Ling, 2016; Mead et al., 2019). The use of flavors in ENDS has been a continued concern for public health as the availability of such flavors have previously been associated with facilitating nicotine addiction among youth (NCCDPHP, 2016). Furthermore, with flavors contributing to increased usage, the risks of exposure to potentially harmful toxicants present within ENDS products has also become a substantial concern (NCCDPHP, 2016). With the growing popularity of pod-based ENDS brands like JUUL and others, it is

important to enhance understanding of how these products deliver the primary dependence-inducing constituent – nicotine (Voos et al., 2019).

ENDS Nicotine Delivery Characteristics

Many factors influence the nicotine delivery capability of ENDS including the device and liquid features described above, as well as user behavior (i.e., puff topography), and user experience (i.e., experienced or naive to ENDS). Several studies and reviews on this topic highlight how nicotine delivery within this tobacco product class has evolved over time (Breland et al., 2017; Voos et al., 2019; Yingst et al., 2019) with reference to specific "generations" of products. Early generation ENDS appeared to be less effective in terms of nicotine delivery, compared with a conventional tobacco cigarette with 10 puffs resulting in less than 2 ng/ml plasma nicotine in one report of two ENDS products as compared to a ~16 ng/ml plasma nicotine increase from a cigarette among naive ENDS users (Vansickel et al., 2010). Other evidence has quickly mounted from groups varying in ENDS experience and various device-liquid combinations that indicate ENDS can deliver nicotine to a similar, if not higher, degree than a cigarette (Hiler et al., 2017; Vansickel & Eissenberg, 2013; Wagener et al., 2017).

Of note, several acute studies have explored the nicotine delivery characteristics from newer generation ENDS products including pod-based products. For instance, one clinical lab study explored the effectiveness of nicotine absorption among first generation (same size as cigarette/no activation button) and newer/advanced generation (larger than cigarette w/ activation button) ENDS products and combustible cigarettes among 14 ENDS users and 10 cigarette smokers (Yingst et al., 2019). Results indicated that newer generation/advanced ENDS products delivered significantly more nicotine than first generation ENDS (maximum serum nicotine concentration of 11.5 ng/mL vs. 2.8 ng/mL), but overall ENDS were less effective at delivering

nicotine than combustible cigarettes (maximum serum nicotine concentration of 25.9 ng/mL in cigarettes vs. 9.0 ng/mL in ENDS overall; Yingst et al., 2019). Critically, despite these differences in nicotine delivery between ENDS device generations, there were no significant differences in the ability of these products to suppress subjective effects of withdrawal and craving (Yingst et al., 2019).

Another pharmacokinetic examination of multiple generations of ENDS products and cigarettes explored more specifically how the liquid nicotine concentration of JUUL influences nicotine delivery among 18 current ENDS users who also smoked cigarettes (Phillips-Waller et al., 2021). Here the European (EU) version of JUUL (limited to 20 mg/mL nicotine) was compared to U.S. version of JUUL with ~59 mg/mL of nicotine, own brand cigarettes, and other tobacco conditions using a cross over design involving 5 minutes *ad lib* use following overnight smoking abstinence. Study findings demonstrated that EU JUUL delivered significantly less nicotine than US JUUL, own brand cigarettes, and other ENDS products tested (Phillips-Waller et al., 2021). When comparing median maximum plasma nicotine level (C_{max}), US JUUL was more than 5 times higher than EU JUUL, and 1.6 times higher than that achieved by cigarette smoking (US JUUL = 21.1 ng/mL, EU JUUL = 3.8 ng/mL, cigarette = 12.9 ng/ml; Phillips-Waller et al., 2021). Subjectively, ratings of withdrawal relief and urges to smoke were lower when using US JUUL compared to EU JUUL, but the difference was not statistically significant (Phillips-Waller et al., 2021). Regarding subjective ratings between EU JUUL and other cig-a-like refillable ENDS products, there were no significant differences in responses on any of the measures (Phillips-Waller et al., 2021). These data highlight the ability of JUUL products to deliver nicotine at levels higher than those observed with cigarette smoking among experienced users.

In contrast, another clinical lab study compared the nicotine delivery and other acute effects between JUUL (59 mg/ml), a novel heated tobacco product (IQOS; heats pressed tobacco rods to produce an aerosol) and own-brand cigarette smoking among 18 current smokers who were naive to JUUL and IQOS use (Maloney et al., 2020). Using a within-subjects design, for each condition participants abstained overnight from tobacco/nicotine and then completed a controlled 10-puff bout (30 second interpuff interval) followed by 90 minutes *ad lib* product use. Mean (SD) plasma nicotine levels following 10 puffs of use were highest for cigarette smoking (20.4 [11.4] ng/ml) followed by JUUL (9.8 [4.9] ng/ml) and IQOS (12.7 [6.1] ng/ml). Nicotine delivery during *ad lib* use followed a similar pattern. All products were effective in reducing some nicotine abstinence symptoms (Maloney et al., 2020). This work highlights how user experience and likely puff topography (e.g., the number of seconds of inhalation), in addition to ENDS characteristics, contribute to nicotine delivery and associated effects.

An important complement to these clinical laboratory examinations of ENDS nicotine delivery are analytical chemistry-based approaches to investigating differences in ENDS emissions. An examination of sixteen popular ENDS products across the Polish, U.K., and U.S. markets tested aerosol generated via a smoking machine to simulate real life usage (Goniewicz et al., 2013). In this study, total nicotine levels after one series of 15 puffs approximated a yield of 0.025 mg to 0.77 mg across ENDS, which is less than that of a traditional cigarette (1.54 to 2.60 mg; Djordjevic et al., 2000; Goniewicz et al., 2013). Another examination of nicotine yield from second and third generation ENDS products revealed a range of 1.01 mg to 10.61 mg per 20 ENDS puffs which is comparable to, if not far exceeding, that of the cigarettes examined (1.76 mg to 2.20 mg; Farsalinos et al., 2016). However, it is important to note that device generation, battery power, liquid nicotine concentration, other liquid characteristics, and use behavior are all

factors contributing to the variability among nicotine yield/delivery between products (Farsalinos et al., 2016; Voos et al., 2019; Yingst et al., 2019).

Taken together with previous work indicating that acute nicotine delivery (via cigarettes and nicotine nasal spray) impacts appetite including food intake and subjective effects, it is likely that later generation ENDS such as JUUL that deliver cigarette-levels of nicotine might impact these same outcomes under acute use conditions. Importantly, ENDS have been marketed with weight control messaging by the industry, and there are increasing reports of their use for this purpose among cigarette smokers and ENDS users. The following section highlights this evidence.

ENDS Marketing, Use for Weight Control/Concerns, and Influence on Eating Behavior

Marketing for ENDS products varies in the media source, messaging, and target population, but many reports have highlighted the use of claims regarding ENDS as a harm reduction and/or cessation aid for cigarette smoking (Collins et al., 2019; Lyu et al., 2022). These health marketing claims have included the mention of ENDS for use of weight control (Lyu et al., 2022) which is an often-reported reason for smoking initiation (Morean & Wedel, 2017; Sanchez et al., 2021) and an important barrier to smoking cessation (Beebe & Bush, 2015; Jackson et al., 2019). In support of these marketing messages, there is other evidence that ENDS manufacturers, and those in related industries, have patented ENDS products with weight control or weight loss as a primary intent (Singh et al., 2018). An international search performed in 2016 identified 23 different unique patents for ENDS products with weight control and/or weight loss features; most of these patents were sponsored by the tobacco industry (Singh et al., 2018). Consistent with these marketing messages and product development, emerging research has documented reports of ENDS as a form of weight control, and highlighted a relationship among

ENDS use, weight concerns, and/or disordered eating behavior in adolescent and adult populations.

Evidence among adolescent populations supports the idea that ENDS use is associated with intentions to lose weight (Sanchez et al., 2021; Mantley et al., 2020). For instance, one study utilized data from the 2015 Youth Risk Behavior Surveillance survey (n=12,647; ages ranged from 9^{th} -12^{th} grade students) to evaluate associations between ENDS use and weight control among adolescents (Mantey et al., 2020). Regression models across sex indicated ENDS use was associated with increased likelihood of intentions to lose weight even after controlling for covariates such as perceived body weight and past 30-day tobacco use. Not surprisingly, when stratified by sex, this same pattern of association was present for girls. In contrast, among boys, ENDS use was positively associated with intentions to gain weight (Mantey et al., 2020). Relatedly, in another school-based sample of adolescent ENDS users (Texas School Physical Activity and Nutrition Study; n=9,056), ENDS dependence was positively associated with ratings from three out of four subscales of the Minnesota Eating Behavior Survey (a measure assessing a range of behaviors and attitudes related to eating disorders) including weight preoccupation, binge eating, and compensatory behavior, but not body mass index (Naveed et al., 2021). Whether ENDS use contributes to the development of disordered eating behavior or predicts future weight-related problems is unclear but is deserving of future study.

Similar patterns of associations among ENDS use, weight concerns, and disordered eating behavior have been observed within young adult populations. Cross-sectional data from 470 students across several colleges located at Oahu, Hawaii were used to evaluate whether weight concerns were associated with ENDS use (Bennett & Pokhrel, 2018). Results indicated that weight-related concerns (i.e., worry over weight and body shape) were significantly

associated with lifetime and current cigarette usage, but not with ENDS use. Interestingly, when analyses examined associations by tobacco use frequency (e.g., daily, less than daily but at least once a week), higher weight concerns were associated with greater ENDS use frequency, suggesting that ENDS users concerned about weight gain might use at a higher intensity (Bennett & Pokhrel, 2018). Another convenience sample of college students (n=230) varying in cigarette smoking and ENDS use status was assessed for perceptions of ENDS utility for weight/appetite control and patterns of tobacco-related weight concerns and eating pathology (Napolitano et al., 2020). Beliefs regarding ENDS' ability to control appetite and help smokers from gaining weight when they quit varied by smoking and ENDS use status, with cigarette smokers and dual users holding more similar beliefs (13-17% endorsed these statements). Correlations indicated that greater endorsement of ENDS for weight/appetite control was associated with more eating pathology and body dissatisfaction (Napolitano et al., 2020). Another study utilizing cross-sectional data from the 2018-2019 Healthy Minds Survey further explored associations with ENDS use and self-reported eating disorder diagnosis and risk among a large population of college students (Ganson & Nagata, 2021). Among the analytic sample of 10,761, 19% of the sample reported using ENDS in the past 30 days, 3.7% reported an eating disorder diagnosis, and 25% were at elevated risk for eating disorder development. Regression models revealed significant associations between ENDS use and lifetime eating disorder diagnosis and eating disorder risk (Ganson & Nagata, 2021). As noted with adolescent populations, the temporal nature of these relationships between ENDS use and disordered eating behavior has yet to be elucidated.

The idea that ENDS can prevent weight gain after quitting smoking, and their use for other weight control purposes, has been endorsed by adult tobacco users (Jackson et al., 2019),

and there is a subset of ENDS users who already use these products for weight management (Morean & Wedel, 2017). In a cross-sectional population study in England, views and practices around ENDS and weight control were explored among current smokers (n=1240), past year smokers (n=1320), and current ENDS users (n=394) in 2018 (Jackson et al., 2019). Relevant findings were that 1 in 16 past year smokers endorsed the idea that ENDS use (i.e., vaping) would prevent smoking cessation-related weight gain, and 1 in 22 ENDS users reported using ENDS for this purpose. Relatedly, but less prevalent, was the use of ENDS as a meal replacement tool, a practice endorsed by 1 in 50 ENDS users (Jackson et al., 2019). An online survey of adult ENDS users who reported wanting to lose or maintain their weight revealed a host of factors associated with the use of ENDS for weight management (Morean & Wedel, 2017). Participants that reported ENDS use for weight loss/control (13.5% of the sample) were more likely to vape more frequently, be overweight, restrict calories, have poor impulse control, and prefer ENDS liquid flavors such as coffee or vanilla (Morean & Wedel, 2017). Taken together, results highlight the perceived utility of ENDS for weight control among smokers and ENDS users, and although estimates of use for this purpose are relatively low, these use patterns could change and/or be influenced by targeted ENDS marketing or emerging reports from scientific or other sources.

In addition to these observational studies, one medical-record-based study examined the effects of ENDS on post-cessation weight gain among smokers (Russo et al., 2018). In this investigation, current smokers were categorized into three groups based on their tobacco use behavior at subsequent 6- and 12-month clinic visits: regular daily ENDS use at both visits (ENDS user group), cigarette smoking with no ENDS use (smoker group), and successful smoking abstinence following a cessation program (quitters). These groups were then compared

in terms of body weight. Results identified little evidence of post-cessation weight gain at 12 months in individuals who reduced cigarette consumption by switching to ENDS; moreover, there was only a modest post-cessation increase in weight among exclusive ENDS users, compared with quitters who did not use ENDS (Russo et al., 2018). This study appears to be the only empirical evidence supporting the idea that ENDS can be used to counteract weight gain associated with smoking cessation, or that ENDS use can impact body weight using a retrospective longitudinal design.

Gaps in the literature related to ENDS use, weight control/concerns, and eating behavior also include a lack of information from diverse groups from historically minoritized communities, such as those who identify as Black/African American (AA), Hispanic/Latinx, and sexual and gender minorities (i.e., lesbian, gay, bisexual, trans, queer, intersex, asexual individuals; LGBTQIA+). Increased focus is needed among these groups due to their increased risk for tobacco-related health consequences, post-cessation weight/weight gain concerns, and disordered eating behavior (Beebe & Bush, 2015; NCI, 2017; Parker and Harriger, 2020). For example, one study that explored post-cessation weight gain concerns among Oklahoma Tobacco Helpline callers by race/ethnicity demonstrated that weight concerns were more prevalent among women who identified as overweight, and post-cessation weight gain was a particularly strong concern among Black/AA and Hispanic women interested in quitting smoking (Beebe & Bush, 2015). A community-based survey sample collected in a southeastern state indicated that Black/AA smokers were more likely to report using ENDS for cessation and to report intentions for continued ENDS use compared to White and Hispanic participants (Webb Hooper & Kolar, 2016). Additionally, the LGBTQIA+ community might be more likely to engage in ENDS use for weight control, as studies demonstrate that eating disorder prevalence is higher among gay

men, those who identify as bisexual, and transgender adults and adolescents, as compared to those that identify as heterosexual (Feldman & Meyer, 2007; Parker & Harriger, 2020). Indeed, reports of ENDS use indicated that it was almost twice as frequent in the LGBTQIA+ community (13%) as compared to those who identified as heterosexual/cis-gender (4.8%) (Al Rifai et al., 2020; Parker & Harriger, 2020). Perceived minority stress brought on by stigma, discrimination, environmental stress, and prejudice, all of which contribute to higher mental health disorders among the LGBTQIA+ community might contribute to both ENDS usage and eating disorder symptomatology within this community (Meyer, 2003). These data and others highlight the need to understand ENDS use in the context of weight control/concerns to help mitigate the potential harms for minoritized communities.

Due to a combination of factors, including the similarity of perceived utility of ENDS for weight control, consistent with that observed for among cigarette smoking, (French & Jeffery, 1995), and effective ENDS industry marketing and product development (Lyu et al., 2022; Singh et al., 2018), emerging data across multiple populations indicates ENDS use is associated with the belief in it effectiveness as a weight control agent, as well as with weight concerns and disordered eating behavior. Missing from this literature are more controlled clinical trial designs of the effects of ENDS on these weight-related outcomes as well as the influence of minoritized group status.

Statement of the Problem

Tobacco use and obesity continue to have large public health impacts and the interplay of weight control and the perceived utility of smoking continues to be associated with increased likelihood for initiation and less successful cessation (Beebe & Bush, 2015; Pinto et al., 1999). Evidence supports the premise that nicotine impacts areas of the central nervous system

associated with appetite and metabolic rate via complex pathways (Audrain-McGovern & Benowitz, 2011). Some acute clinical lab examinations of cigarette-delivered nicotine suggest one mechanism may be the acute suppression of appetite (i.e., food intake and related effects) following tobacco product use (Bulik et al., 1991; Yannakoulia et al., 2018). Whether novel tobacco products such as ENDS have similar effects in this regard are unknown. Many newer generation ENDS, such as higher nicotine content JUUL, are as effective as cigarette smoking in terms of nicotine delivery depending on user experience (Phillips-Waller et al., 2021; Maloney et al., 2020), and emerging data indicate that a subset of cigarette and ENDS users report ENDS usage for weight control purposes (Ganson & Nagata, 2021; Morean et al., 2020; Morean & Wedel, 2017). To inform future cessation efforts and considerations for ENDS users, and for cigarette smokers that use ENDS as a harm reduction or cessation aid (Hartmann-Boyce et al., 2021; NASEM, 2018), research is needed to understand how acute ENDS use impacts appetite and related outcomes.

The Present Study

Therefore, the present clinical lab study utilized a cross-over design to examine whether the acute use of a newer generation ENDS capable of cigarette-like nicotine delivery prior the administration of an *ad lib* buffet meal impacted food intake as compared to a control condition involving no nicotine delivery. The main outcome was energy intake during the buffet (indexed by kilocalories) between active and control conditions. We hypothesized that the active condition would result in significantly less energy intake compared to the control. Secondary outcomes included dietary fat, carbohydrate, and protein intake, and we hypothesized that we would also observe a decrease in these parameters after the administration of the active condition. Other

secondary hypotheses were that after administration of the active condition, subjective feelings of hunger/craving would be decreased and that satiety would be increased.

Method

Study Design and Power

This study employed a two-condition randomized cross-over design with an active condition (20 puffs of 5% nicotine Virginia Tobacco Flavored JUUL pod) and control condition (access to an empty JUUL compatible pod and uncharged JUUL battery for up to 20 puffs).

The target sample size was determined via a power analysis using data from Yannakoulia et al. (2018) in which a mean±SD difference of 152±190 kcal lower food intake was observed following an acute active smoking condition (cigarette) versus sham (unlit cigarette) 45 minutes after the 15 minute smoking/sham condition. Assuming a more conservative mean difference in food intake between the active and control conditions in our study of 100±200 kcal (effect size of 0.50), following similar procedures (20-minute active condition followed by a 45-minute wait period before the buffet meal), the sample size needed to detect a significant difference between the two conditions with a power of 80% and an alpha-level of 0.05 (two-sided) was 34.

Participant Selection

The study involved participants who were relatively healthy adult ENDS users aged 18-65 years. This age range aligned with the target age group from national estimates of tobacco use, which indicates the highest proportion of individuals who engage in ENDS use are adults aged 25-64 years (CDC, 2022). Individuals aged 18-20 years were included as Virginia law (enacted July 1, 2020) permits individuals under age 21 to have access to nicotine products only when they are a part of a scientific study (law 18.2-371.2;Virginia, 2020).

Inclusion criteria included being aged 18-65 years which was verified by an identification card and reporting either everyday ENDS use with a liquid concentration of at least 0.3% (3

mg/mL) nicotine or reporting ENDS use of at least 3 times a week at a liquid concentration of at least 3% (30 mg/mL) nicotine for the past 30 days. This criterion was developed with several considerations in mind, including to ensure that participants who enrolled were frequent ENDS users and were not subjected to any adverse effects with the ENDS product/liquid used during the study.

Exclusion criteria included any self-reported current, diagnosed medical conditions that involved the heart, respiratory system, immune system, kidneys, liver, or seizure disorders. Participants who had an observed systolic blood pressure of >140 or a diastolic blood pressure >90 during screening were excluded for safety reasons. Participants who self-reported current, diagnosed psychiatric conditions, current psychiatric treatment, or psychotropic medication use were also excluded. Other self-reported or diagnosed medical conditions (e.g., diabetes, food allergies, thyroid disease, Lyme disease) were considered for exclusion after consultation with the Principal Investigator (PI) and medical monitor (Thokozeni Lipato, MD). Participants who were pregnant or breast feeding were excluded; pregnancy status was confirmed by urinalysis at screening. Participants who used progestin intrauterine devices (IUDs), birth control injections (Depo-Provera, etc.), or had received a hysterectomy and still had ovaries were not eligible to participate. This exclusion criterion was established by the Pennington Biomedical Research Center (protocol 1611; *Food Intake Testing and the Menstrual Cycle*) which focuses on recruitment during the luteal phase of the cycle (days 16-28 for an average cycle) in which progesterone levels are increasing and estrogen levels are decreasing. Use of progestin IUDs and hormone injections were exclusionary because hormonal levels are not similar to those seen in the luteal phase, and these hormone levels impact food intake (Yu et al., 2011). Regarding substance use, participants who reported alcohol use >25 days out of 30 and cannabis use >20

days out of 30 were excluded due to the potential impact of frequent use of these substances with food intake which may hinder data quality (Christiansen et al., 2016; Tarragon & Moreno, 2019). These values were established using previous guidelines at the Virginia Commonwealth University (VCU) Center for the Study of Tobacco Products (CSTP). Individuals who reported illicit drug use were also excluded from the study as this behavior raises risks to participants and may impact data quality. Other exclusion criteria guidelines included participants who reported wanting to quit tobacco products within the next 30 days, were unwilling to take 20 puffs of the ENDS product, were unwilling to consume the food items provided for the buffet meal due to dietary limitations or preferences, and reported food allergies. Most of these exclusion criteria were established for participant safety purposes, as tobacco product use or abstinence could exacerbate physical and mental health conditions, is dangerous for fetal growth during pregnancy, and poses a risk to fetal health during breast feeding.

Recruitment

Recruitment occurred within the Greater Richmond Area of Virginia. College campus locations, vape stores, convenience stories, libraries, university-online telegram announcements, and craigslist.org were the primary places of recruitment. IRB-approved flyers and advertisements were posted in such places. All flyers and advertisements linked participants directly to the CSTP phone number and CSTP studies webpage which linked participants to the CSTP screening survey/registry (HM20002567). All in-person participant interactions took place within the CSTP laboratory located on VCU's Monroe Park campus.

Informed Consent and Screening

All participants completed a two-part screening process which involved an initial screen for eligibility through the CSTP registry. Potentially eligible participants were notified via phone

or email by the research assistant (RA) to schedule a time for an in-person screen for the study. During the in-person screen, the informed consent document was first reviewed by the RA and then participants had the opportunity to sign. Consent was an on-going process and assumed when a participant made and completed follow-up appointments. Prior to participant signing, the RA reviewed any questions with the participant regarding the consent process and ensured that the participant fully understood the study prior to signing and was competent enough to voluntarily decide to participate in the study. Participants were allowed to discontinue study procedures at any point in which they chose to do so. After informed consent was obtained, participants completed additional screening questionnaires on demographics, health status, tobacco product use, and eating behavior to confirm eligibility. Biological female participants were asked to provide a urine sample to rule out pregnancy prior to enrollment.

Participant Safety

The methods and procedures used in this study involved minimal risk to participants. Similar methods and procedures have been used previously numerous times at the CSTP for over the course of 20 years. During this study we asked participants to refrain from smoking, eating, and drinking (except water) for 12 hours prior to each session. During this abstinence period, participants were informed that they might experience some mild discomfort, but this discomfort was not medically dangerous. The participants who enrolled in this study were regular ENDS users which minimized adverse events from the ENDS product/liquid used during this study. All CSTP staff-maintained training on good clinical practices, including the protection of participants' safety and rights.

Blood pressure (BP) and heart rate (HR) were obtained during screening and at the beginning and end of each session. If a participant's BP during screening was above 140 systolic

and/or 90 diastolic, the participant was not enrolled in the study, per study exclusion criteria. If elevated blood pressure readings (>150 or >100 diastolic) occurred during a session, staff notified the research nurse for evaluation of the participant. Participants were withdrawn from the study if the PI/medical monitor/research nurse had any safety concerns. Participants were not identified by name or initials; only by alphanumeric code. All data were stored in a locked cabinet available to CSTP staff only. The use of REDCap and Qualtrics were both used as data monitoring tools during this study; both are secure applications for monitoring and managing data. During the study, participants were asked questions that were potentially sensitive in nature (substance use history, etc.); all participants were given the right to refuse to answer any study-related question that they felt uncomfortable doing so.

Due to special circumstances involving the COVID-19 pandemic, we enforced measures to increase participant safety in this regard. Such measures included screening for COVID-19 symptoms and exposure upon arrival to the in-person sessions. All participants along with laboratory staff were required to wear a mask (except for study-specific exceptions) and practice safe social distancing. To limit potential exposure, Zoom was used as an intercom system as needed.

In June 2022, the FDA denied the marketing application for JUUL, which was the ENDS utilized in this study. Denial of JUUL products was put into effect after the FDA determined that not enough evidence was provided regarding the toxicological makeup of JUUL's device, but this denial was subsequently ordered an administrative stay which means that the state agency review board does not provide legal authorization to market, sell, or ship any form of JUUL items (FDA, 2022). However, to date, the FDA has not received clinical information to suggest an immediate hazard associated with JUUL and pods (FDA, 2022). This updated information

was provided to participants during the consent process and those who were currently enrolled were re-consented with the new information. An Investigational Tobacco Product (ITP) application was submitted to the FDA in July 2022 and upon submission of the ITP application and updated consent, the current study obtained IRB approval to continue.

Materials

ENDS Materials and Estimates/Rationale. Participants were provided a standard JUUL battery (www.JUUL.com). The JUUL battery was either charged (active condition) using a USB JUUL device charger or an uncharged (control condition). The active condition utilized a 5% Virginia Tobacco flavored JUUL pod inserted into the battery; the control condition utilized a blank (empty JUUL-compatible refillable) pod inserted into the battery. ENDS devices and nicotine-containing pods were purchased at JUUL.com and via local tobacco retailers in 2021. Empty pods (Gem Pod, Uptown Tech) were purchased from online suppliers (e.g., gemvaping.com) in 2021-2022. JUUL pod liquid nicotine concentration was verified prior to usage by the Bioanalytical Analysis Core Laboratory at VCU to ensure equivocal and appropriate nicotine concentrations. Across six random pods tested, nicotine concentrations ranged from 56-57 mg/mL and exhibited relative consistency across pod lot numbers analyzed (KC13SA20A, KB26SA01A).

For the active condition, 20 puffs of a JUUL pod containing 5% nicotine was anticipated to deliver 1.6 mg of nicotine (yield derived from Goniewicz et al., 2019), which is equal to approximately 1.5 cigarettes (yield derived from ISO standard test methods 10315:200012; Digard et al., 2013). This amount of nicotine exposure was selected to increase the likelihood of nicotine-related effects on primary outcomes. Of note, these yield estimates are based on machine smoking/ENDS use and thus are an imperfect measure of actual exposure.

For the control condition, the use of an uncharged JUUL containing an empty pod was selected to more closely match the sham condition used in Yannakoulia et al. (2018) by exposing participants to some ENDS-related stimuli (versus no tobacco-related paraphernalia).

Other Devices. The use of an expired air carbon monoxide (CO), blood pressure (BP), and heart rate (HR) monitors were used to collect physiological data during the screening and experimental sessions. In particular, CO was assessed with the BreathCO monitor (Vitalograph, Lenaxa, KS), and BP/HR was measured using equipment that sounds an alarm if safety parameters are exceeded (Model 506, Criticare Systems). The CO monitor was used as a tool to measure tobacco/nicotine abstinence at the beginning of each session and the Criticare monitor was used to measure BP in the beginning and end of each session for safety purposes.

The use of Ohaus and Accuris portable scales were used for the measurement of food weights before and after the *ad lib* buffet meal. Due to unforeseen complications regarding the Ohaus scale (Model CT1200), the primary scale used within this study was the Accuris scale (Model W3200-1200). Both scales were calibrated prior to session utilizing a 10 gram (g) weight and zeroed out prior to usage. Both the Accuris instrument scale and Ohaus portable scale have a readability of 0.01 g. To obtain participant weight during the screening session, the use of a Seca digital scale (Model 876-1321004) was employed.

Food Items. For the *ad lib* buffet items, a total of 21 food items were offered at each experimental session. Each food item and portion were identical across sessions and participants in order to maintain consistency. Items were set up the same way for each session, utilizing standard size paper bowls (~15.6-16.2 g), and paper dinner plates (10.5”; 23-26.2 g). The food items consisted of commercially available and ready to eat items which included a mix of salty (corn chips, popcorn, etc.), sweet (raisins, M&M’s, etc.), fatty (cheddar and gouda cheese;

cheese dip), and savory (chicken tenders, etc.). Items chosen were high in fat and sugar to promote consumption which were sized appropriately (0.5-1.5 cups) in order to allow for repeated servings and so that participants did not remember that exact consumption amount that they consumed between sessions.

Procedures

Participants completed a total of three laboratory visits including an in-person screen and two experimental sessions which differed by condition (active vs. control; randomized). The independent variable was condition (active vs. control) and the primary dependent variable was energy intake (indexed via the kcal of food consumed). Although the participants completed both the conditions, which condition was performed first was randomly ordered and assigned. Recruitment for the study ended when all participants (n=34) successfully completed both conditions.

Once participants were deemed eligible following the initial screening visit, they were scheduled for two sessions, preferably one week apart in which they experienced either the active or control condition, completed session measures, and have had an *ad lib* buffet meal. For persons participating in hormonal therapy with estrogen/progesterone and/or premenopausal women, sessions were scheduled when the individual is taking progesterone or in the luteal phase of the menstruation cycle as not to interfere with eating behavior (Butera et al., 2010). Prior to each session, participants were asked to refrain from beverages (other than water), food, nicotine/tobacco products, and cannabis (if applicable) for at least 12 hours. Upon arrival to their session, participants signed a verification form confirming their abstinence and CO was measured in order to verify abstinence from combustible nicotine products. To continue in the session, participant CO was required to be ½ of what the baseline measurement was (i.e. if 8

ppm at baseline, must be 4 ppm at session). The ~12-hour abstinence period was put in to place as a way to minimize any effects of prior meals and previous tobacco use and induce hunger/abstinence-related effects (Yannakoulia et al., 2018). Participants arrived to their experimental session in the morning before 11:00 AM to help control for time of day. This time also was chosen to minimize discomfort that may be experienced through extended periods of food/tobacco/nicotine abstinence. Upon arrival participants had baseline vitals checked (BP/HR) and took a pre-session questionnaire to measure any changes in health since the previous in-person visit. After completing the pre-session questionnaire, participants then were asked to sit in the session room for 1 hour. Participants were instructed that they may sleep during this time, read a book from the list of PI-approved reading material, or complete puzzles. Participants were not allowed to use any electronic devices as the information on such cannot be controlled and advertisements or information could influence how the participant felt towards food/hunger. The 1-hour waiting period was instilled as an additional precaution. If participants did not comply with the 12-hour tobacco/nicotine abstinence, the 1-hour period ensured that the participants have at least abstained from nicotine for this time.

After the 1hour rest period was completed, participants were then asked to complete the first set of subjective questions which included measuring specific appetite feelings, nicotine cravings, and other tobacco abstinence-related symptoms. After completing the first set of subjective questions, participants were then asked to engage in the control condition or the active condition. Participants were instructed to take a total of 20 puffs in 20 minutes during the active condition of a 5% Virginia Tobacco Flavored JUUL or sit with an uncharged JUUL loaded with an empty pod for 20 minutes during the control condition in which they were given the option to take puffs from the empty JUUL pod and uncharged JUUL, read, or complete puzzles. After

participating in the experimental condition (either active or control), participants were instructed to take the subjective measurements for the second time. After completion of the second set of subjective measures, participants began their 45-minute break prior to the *ad lib* buffet meal. During this break period, the same rules applied that were previously set during the 1-hour rest period. At the 30-minute time point during the 45-minute break, participants were instructed to complete the Food Craving Questionnaire-State (FCQ-State); after completion of this measure, participants waited until instructed to take the subjective measures for the third time. After this 45-minute time frame, participants were escorted to another laboratory room where they had access to an *ad lib* buffet meal for up to 30 minutes. The meal included a total of 21 food items as described above. Caloric intake (kcal/gram per food) was measured by the difference obtained from pre/post weights of food items.

Previous validation of buffet meal designs was conducted by Allirot et al. (2012) in which the study concluded that offering buffet style meals in a normal eating environment is a valid tool for assessing intervention effects (Allirot et al., 2012). Our buffet setting was modified for the clinical lab to emulate a natural eating environment as closely as possible. We utilized the Pennington Biomedical Research Center Ingestive Behavior, Weight Management, and Health Promotion Laboratory buffet design as a model for setting up the items. After the participant indicated their meal was complete or 30 minutes elapsed, they were instructed to complete a final set of subjective measures and the RA obtained the participant's BP/HR to ensure participant safety prior to session end. At the end of the session, the participant was paid and the next session was scheduled if applicable. Across all sessions, participants were paid a total of $198.00.

It should be noted that unobtrusive video surveillance via Zoom was used to ensure that the participant did not take any more than 20 puffs during the active condition and as a means to ensure that participants do not take any of the food items with them during the *ad lib* buffet meal. These video data were not be stored. The estimated time line for each experimental session was around 3 hours from start to finish, with most ending around 2.5 hours.

Baseline Measures

All potentially eligible participants completed self-report items related to sociodemographic information which included information on gender, sex assigned at birth, race and ethnicity, current health and psychiatric conditions (including health symptoms commonly associated with ENDS use such as respiratory and gastrointestinal issues), drug and alcohol use, history and patterns of tobacco use, nicotine dependence, perceived risk and harm of tobacco products, and discounting behavior. Baseline measures included items from the Population Assessment of Tobacco or Health (https://pathstudyinfo.nih.gov/) and the PhenX toolkit, which consisted of highly-prioritized and validated measurement tools for inclusion in research studies (www.phenXtoolkit.org). We also measured current physical activity utilizing the International Physical Activity Questionnaire (Craig et al., 2003). A hypothetical purchase task was administered utilizing various amounts of money to further assess demand for one's own brand ENDS (Cassidy et al., 2020; Cassidy et al., 2017; Jacobs & Bickel, 1999). The psychological impact towards existing in a food abundant environment and feelings towards appetite was assessed at baseline utilizing the Power of Food Scale (Lowe et al., 2009) and eating behavior measured by the Eating Inventory (administered on paper; Stunkard & Messick, 1985). Smoking in response to body image concerns and a way as a way to control appetite was measured by an

adapted version of the Smoking-related Weight and Eating Episode Test (SWEET; Adams et al., 2011).

Outcome Measures

Subjective Measures. Subjective measures were administered at four time points during each session: after the initial rest period was complete (approximately five minutes before condition administration), immediately following condition administration (20 minutes post the beginning of condition administration) immediately prior to the buffet administration (approximately, 60 minutes post condition administration), and following the completion of the buffet administration (varied by participants; maximum of 95 minutes post condition administration).

Subjective measures included three sets of visual analog scale (VAS) items at multiple timepoints: *Adapted Minnesota Nicotine Withdrawal Scale* (Hughes & Hatsukami, 1986), *Direct Effects of Nicotine Scale* (Perkins et al., 1993), and *Pennington VAS items (*Pennington Biomedical Research Center). One subjective measure, *Food Craving Questionnaire-State (FCQ-State),* was administered only after the active/control condition and 15 minutes before the *ad lib* meal. Two of the three scales administered (Adapted Minnesota Nicotine Withdrawal Scale and Direct Effects of Nicotine Scale) focused on the participant's current feelings towards nicotine craving and abstinence-related symptoms. The Pennington scale items measured feelings around hunger and food craving. Each VAS item contains a single word, phrase, or sentence prompt that was paired with a horizontal line that was used for responding. For the majority (but not all items) VAS items, the phrase "Not at all" was on the left of the line, and the phrase "Extremely" was on the right of the line. Each scale went from 0-100 and participants could click on any point on the line with the mouse/cursor to reflect how they are currently

feeling in response to the questions being asked; a numerical value was displayed which aligned to the value selected on the horizontal scale. Further information regarding each individual scale is listed below; scale *alpha* levels are cited when available.

The *Adapted Minnesota Nicotine Withdrawal Scale (MNWS)* was used to measure the severity of abstinence-related symptoms from nicotine (Hughes & Hatsukami, 1986). VAS items include: "URGES to use an e-cigarette", "Irritability/frustration/anger", "Difficulty Concentrating", "Restlessness", "Impatient", CRAVING an e-cigarette", "Drowsiness", "URGES to smoke a cigarette", and "CRAVING a cigarette". Previous clinical lab studies have used this scale and have found it to be an appropriate measurement of nicotine abstinence-related symptoms. For example, in one clinical laboratory study analyzing the risk of tobacco dependence and disease associated with waterpipe tobacco smoking for intermittent and daily waterpipe smokers found some evidence of higher baseline scores for nicotine abstinence symptomology and during the placebo condition (Cobb et al., 2015). A confirmatory factor analyses of the MNWS conducted by Toll et al (2007) which used clinical research samples (n=723) of current smokers trying to quit found that increases in subjective measures of withdrawal were associated with poorer smoking outcomes for two of the clinical studies analyzed (Toll et al., 2007).

The *Direct Effects of Nicotine Scale* was used to assess the positive and aversive effects of nicotine (Perkins et al., 1993). This scale consists of a total of 10 items which inquired about participant's feelings at the current moment. VAS items consist of the following: "Nauseous", "Dizzy"," Lightheaded", "Nervous", "Sweaty", "Headache", "Excessive salivation", "Heart pounding", "Confused", and "Weak".

The *Pennington Visual Analog Scale* was used to assess feelings around the physical and emotional sensations of feeling hungry *(*Pennington Biomedical Research Center; Ingestive Behavior, Weight Management, & Health Promotion Laboratory, 2021). This assessment consists of 11 items which asked participants to reflect about their feelings about the "current moment" such as: " How sad do you feel at the moment?", " How happy do you feel at the moment?", "How anxious do you feel at the moment?", "How hungry do you feel at the moment?", "How full do you feel at the moment?", "How satisfied do you feel at the moment?", " How much do you think you can eat right now?", "Would you like to eat something sweet?", "Would you like to eat something salty?", "Would you like to eat something savory?", and "Would you like to eat something fatty?". This scale was adapted from previous scales that assessed specific appetite feelings around hunger, desire to eat, and fullness; such scales have been previously tested for reliability and validity (Flint et al., 2000; Parker et al., 2004; Stubbs et al., 2000). Due to researcher error, the last four questions were not administered to four participants at the start of the study.

The *FCQ-state* measured the intensity of a total of 9 state dimensions around food. Using a 5-point Likert-type scale ranging from 1 *(strongly disagree)* to 5 *(strongly agree)*, participants were asked to measure the extent to how they feel at the very moment. The scale consists of 15 multiple choice questions which include questions that assess current feelings around hunger at the current moment in which some example questions include the following: "I am craving one or more specific foods", "I have an intense desire to eat one or more specific foods", "I would feel more alert if I could satisfy my cravings", "My desire to eat one or more specific foods seems overpowering". This scale was chosen for this research study because it provided a good demonstration of cravings being associated with certain food types and that the ingestion of those

cravings fulfills subjective feelings of satisfaction associated with food consumption (Moreno et al., 2008).

Scoring of the FCQ-State involved utilizing the five-factor technique which is outlined by Capeda-Benito et al. (2000) which involved breaking down the 15 items to those that looked at an intense desire to eat (1,2,3); anticipation of positive reinforcement that may result from eating (4,5,6); anticipation of relief from negative states and feelings as a result of eating (items 7,8,9); lack of control over eating (items 10,11,12), and craving as a physiological state (items, 13, 14,15) ; (Capeda-Benito et al., 2000; Meule, 2020). For a total score, all 15 items were summed together and higher scores indicate a higher intensity or craving to eat (Meule, 2020). The range for total scores is around 15-75; intense desire to eat, anticipation of positive reinforcement that may result from eating; anticipation of relief from negative states and feelings as a result of eating, lack of control over eating, and craving as a physiological state all have ranges from 3-15 (Capeda-Benito et al., 2000).

Energy and macronutrient intake. Energy (kcal) and macronutrient intake (total fat, saturated fat, trans fat, cholesterol, sodium, total carbohydrates, dietary fiber, total sugar, added sugar, protein, vitamin D, iron, calcium, and potassium) was measured by directly weighing food provision and waste for each item; food intake is calculated by difference of pre and post plate weights. Macronutrient details per gram for each food item were abstracted from food packaging and/or publicly available nutritional information found online.

Data Analysis Plan

First, all data werre reviewed for data entry errors and missing data. We characterized the sample descriptively using the baseline measures assessed. Then relevant coding and/or scale-specific calculations were performed. Statistical assumptions were reviewed and tested with

appropriate transformations as needed. There were no missing data for energy intake. Missing data across subjective items ranged from 0 to 2.9% and on average was 1.5%. Due to the low proportion of missing data, we used mean replacement to correct relevant items to ensure their inclusion in subsequent statistical analyses. We initially performed a mixed ANOVA to examine the effect of condition order (active then control, control then active; between-subjects) and condition (active, control; within-subjects) on energy intake. The main effect of condition order and the interaction of condition order and condition were not statistically significant for energy intake: condition order, df (1,32) =0.795, p=0.373; condition x condition order, df (1,32)=0.411, p=0.526); subsequent analyses excluded condition order as a between-subjects factor for parsimony and power-related reasons.

For energy and macronutrient intake indices and the FCQ-state, a one-way repeated measures ANOVA was used to detect differences by condition (active, control). For all other subjective measures, a two-way repeated measures ANOVA was used to test differences by condition (active, control) and time (1, 2, 3, 4). For all ANOVAs, adjustments for sphericity violations were assessed, and Huynh-Feldt correction values were reported. Post-hoc testing with a Bonferroni corrected repeated measures t-test was used to evaluate significant model results (McHugh, 2011).

Exploratory analyses tested the influence of sex assigned at birth, past 30-day cigarette smoking status, and ENDS use history on energy intake based on previous literature performed among cigarette smokers (Perkins et al., 1992; Yannakoulia et al., 2018). Two mixed ANOVAs were performed by sex (male, female) and past 30-day cigarette smoking status (yes, no) as a between-subjects factor and condition (active, control) as a within-subjects factor. To explore the impact of ENDS use history, we utilized a similar approach to Yannakoulia et al. (2018) and

examined the correlation between the length of ENDS use (in years) and the difference in energy intake between active and control.

Results

Participant Characteristics

Table 1 demonstrates participant demographic and psychosocial characteristics. A total of 52 participants provided informed consent, and of those, 34 completed the study. The remaining 18 were determined ineligible for study participation due to failure to meet specific study criteria (i.e. food allergies, hormonal therapy/birth control that would interfere with food intake, or failure to meet study specific medical criteria), or self-withdrew, due to scheduling conflicts (n=6).

As displayed in Table 1, among study completers, in terms of sex assigned at birth, 58.8% were male and 41.2% were female. Gender identity distribution was similar in proportion to sex assigned at birth with some exceptions with one individual identifying as non-binary and two individuals who were sex assigned female at birth but identified as male at screening. The average age of the sample was 25.7 years (standard deviation [SD]=8.4). The sample was relatively diverse in race/ethnicity with 14.7% identifying as Asian, an additional 14.7% identifying as Black or African American, 11.8% identifying Middle Eastern, 44.1 % identifying as White, 8.8% identifying as more than one race, and 5.9% of participants who preferred to self-describe. Additionally, 14.7% of participants identified as Hispanic/Latino/a/ Spanish origin, with most identifying with ancestral ties to Cuba, Mexico, or Central America. The majority of the sample (61.8%) reported a yearly household income of equal to or greater than $50,000, reported some college or higher (82.4%) and were either currently employed (38.2%) or a student (44.1%).

Table 1. Sample Demographics

Characteristic	Sample Size n=34
Age (years), M (SD)	25.7 (8.4)
Gender Identity, n (%)	
Female/woman/she/her	11.0 (32.4)
Male/man/he/him	21 (61.7)
Non-binary	1 (2.9)
Missing	1 (2.9)
Sex assigned at birth, n (%)	
Male	20 (58.8)
Female	14 (41.2)
Race, n (%)	
Asian	5 (14.7)
Black or African American	5 (14.7)
Middle Eastern	4 (11.8)
More than one race	3 (8.8)
White	15 (44.1)
Preferred to self-describe	2 (5.9)
Hispanic/Latino/of Spanish origin, n (%)	
No	29 (85.3)
Yes	5 (14.7)
Ancestry n (%) n=5	
Cuban/Cuban American	2 (40.0)
Mexican/Mexican American	1 (20.0)
Central/South American	2 (40.0)
Annual Income, n (%)	
Below $50,000	9 (26.5)
$50,000 or greater	22 (61.8)
Don’t know	3 (11.8)
Education, n (%)	
High school graduate/GED	6 (17.6)
Some college or higher	28 (82.4)
Employment status, n (%)	
Working now	13 (38.2)
Not working	6 (17.6)
Student	15 (44.1)

Note: For employment status, working (includes full-time, part-time, and military), not working (includes only temporarily laid off/sick leave, non-working disabled permanent or temporary, looking for work/unemployed, keeping house, retired, and non-working student, full time student is an additional category).

As displayed in Table 2, in terms of alcohol and cannabis use, among ever users, on average, participants reported drinking 5 days and using cannabis on 4 days in the past 30. The majority of participants reported using ENDS products every day (79.4%) with an average nicotine concentration of 5.7% (SD=7.9). The relatively high SD for nicotine concentration has to do with the variability of products among participants and whether prefilled or refillable cartridges were used as described in more detail in Table 2. JUUL was preferred by a little more than 1/3rd of participants (35.3%), and non-tobacco flavors were the most common (91.2%). Among participants who reported past 30-day cigarette use (n=12), 41.7% reported everyday use and 50% reported someday use. Participants who reported past 30-day cigarette use reported smoking about 3 cigarettes a day (SD=1.6). Participants who smoked cigarettes reported smoking at this frequency for ~10 years (SD=12.8). Regarding other tobacco products used in the past 30 days (other than cigarettes and ENDS), low frequencies were observed across all types examined with the exception of hookah/shisha. The PROMIS-E for assessing nicotine dependence in individuals who report using ENDS use indicated low to moderate dependence (mean [M]=2.2, SD=0.9); similar findings were observed for the PROMIS measure for cigarette smoking dependence with a mean of 2.7 (SD=0.9; n=12).

Table 2. Alcohol, Cannabis, and Tobacco Use Characteristics

Characteristic	Sample Size n=34
Past 30-day use of alcohol in days, M (SD) (n=34)	4.6 (3.9)
Past 30-day use of cannabis in days, M (SD) (n=28)	3.7 (5.8)
Do you now use e-cigarettes every day, some days, or not at all?	
Every day	27 (79.4)
Some days	7 (20.6)
How many days in a typical week do you use an e-cigarette? M (SD)	4.7 (0.8)
How many cartridges or pods or amount of e-liquid do you use per day? (number of cartridges or pods or ml) M (SD)	
Cartridges or pods (n=25)	3.9 (9.1)
e-liquid in mL (n=7)	13.6 (17.1)
Missing	2
For how long have you used e-cigarettes at this frequency? M (SD)	2.3 (0.9)
What brand of e-cigarette do you prefer? n (%)	
JUUL	12 (35.3)
VUSE	6 (17.6)
Hyde	7(20.6)
Other	9 (26.5)
E-cigarette cartridge/% nicotine M (SD)	5.7 (7.9)
E-cigarette flavor, n (%)	
Tobacco flavor	3 (8.8)
Non-tobacco flavor (fruit, menthol,sweet)	31 (91.2)
Ever cigarette use, n (%)	
Yes	30 (88.2)
No	4 (11.8)
Past 30-day cigarette use, n (%)	
Yes	12 (40.0)
No	18 (60.0)
Missing	4
Do you now smoke cigarettes, every day, some days, or not at all? n=12; n	
Every day	5 (41.7)
Some days	6 (50)
Not at all	1 (2.9)
Cigarettes smoked per day, M (SD)	2.5 (1.6)
Years smoking this number, M (SD)	10.2 (12.8)
During the last 30 days, on how many days have you used any additional tobacco products? n (%)	
Hookah/shisha	7 (20.6)
Cigarillos, filtered cigars/little cigars	5 (14.7)
Traditional Cigars	3 (8.8)
Chewing tobacco or dip/snuff	1 (2.9)
Nicotine replacement therapy	1 (2.9)
Pipe (w/ tobacco)	0
PROMIS-E, M (SD)	2.2 (0.9)
PROMIS, M (SD)	2.7 (0.9)

Note: E-cigarette is synonymous with ENDS; actual items used the term “e-cigarette”.

In reference to eating behavior and weight gain concerns around vaping cessation, the use of the Pennington Vaping Questionnaire indicated that the majority of the participants (67.6%) were not concerned about weight gain if they were to stop using ENDS. Of those that did endorse a concern around weight gain (n=11), (63.6%) reported that weight gain concerns influenced on their decision to quit ENDS. Findings from the power of food scale indicated that there was only a minimal to moderate effect of the influence of food on influencing appetite despite living in a food abundant environment (M=2.7, SD=0.8). The adapted version of the "SWEET" scale indicated that, on average, most experienced no to minimal concerns around vaping for weight control purposes (M=1.1, SD=0.8). The Pearson Eating Inventory measured eating behavior around cognitive restraint, disinhibition, and hunger. The results indicated that on average, participants scored within the low to average range on each construct: Cognitive restraint M=7.1 (SD=5.4); disinhibition M=7.3 (SD=3.7); and hunger M=5.8 (SD=2.8). However, it is important to note that across all constructs measured in the Pearson Eating Inventory, the range of responses were highly variable with some responses (i.e., participant scores of 18 on cognitive restraint) reaching up to the clinical range, in which higher scores may be linked to participants who are more likely to utilize ENDS for weight management.

The mean height of participants was around 5'7"; mean body weight was 171.6 pounds (SD=44.3). From these measurements, body mass index (BMI) was calculated by dividing the participant weight by squared height in inches and multiplying by a conversion factor 703 in order to convert pounds and inches squared to kilograms and meters squared (CDC, 2022). The average participant BMI was 26.2 which according to CDC guidelines, is slightly over the "normal" weight range of 18.5-24.9 (CDC, 2022). These calculations should be interpreted with caution because such numbers are not always truly representative of an individual's muscle to fat

ratio, particularly among racially diverse individuals (Caleyachetty et al., 2021; Heymsfield et al., 2016). Table 3 presents results for instruments used to analyze ENDS influence on appetite and eating behavior.

Table 3. ENDS-related Eating Behavior and Physical Characteristics

Characteristic	Sample Size n=34
Adapted items from the SWEET test, M (SD)	1.1 (0.8)
Are you generally worried that you might gain weight if you stop using e-cigarettes? n (%)	
Yes	11 (32.4)
No	23 (67.6)
Does that influence your decision not to stop? (if yes to worry above) n (%) (n=11)	
Yes	7 (63.6)
No	4 (36.4)
Power of Food Scale, M (SD)	2.7 (0.8)
Eating Inventory, M (SD) and participant response range	
Cognitive Restraint of Eating	7.1 (5.4) Range: 0-18
Disinhibition	7.3 (3.7) Range: 1-14
Hunger	5.8 (2.8) Range: 1-11
Height in inches, M (SD)	67.8 (3.7)
Weight in lbs, M (SD)	171.6 (44.3)
BMI based on Height (in)^2 and Weight *703, M (SD)	26.2 (6.4)

Note: SWEET stands for Smoking-related Weight and Episodes Test

Energy Intake

A one-way repeated measures ANOVA of energy intake (kcal) by condition (active vs. control) revealed no significant main effect of condition (p=0.108; see Table 3). Descriptive examination by condition indicated slightly higher mean (±standard error of the mean [SEM]) energy intake during the active condition (1011.9±98.8 kcal) compared to the control condition (939.94±88.4 kcal).

Table 4. Statistical Analysis Results for Energy Intake

	Condition		
Outcome	*F*	*p*	ηp^2
Kilocalories	2.7	0.108	0.076
Total Fat	1.4	0.251	0.040
Saturated Fat	1.3	0.260	0.038
Cholesterol	0.2	0.632	0.007
Sodium	1.9	0.180	0.054
Carbohydrate	1.3	0.259	0.038
Fiber	0.5	0.506	0.014
Sugars	2.4	0.134	0.067
Added Sugar	2.7	0.107	0.077
Protein	3.5	0.070	0.096
Vitamin D	<0.1	0.950	<0.001
Iron	0.4	0.556	0.011
Calcium	<0.1	0.858	0.001
Potassium	<0.1	0.998	<0.001

Note: df (1,33). Used Huynh-Feldt Correction.

Across all macronutrients assessed, similar to energy intake, no significant main effects were observed for condition (see Table 4 for more detail). However, there were slightly higher *F*-values for among sugar, added sugar, and protein intake (*F*s>2.3). For macronutrients with *F* values that were <0.1 condition means were almost identical. As similarly observed for kcals, slightly more consumption was observed during the active condition as compared to control for sugar (active=42.7±6.2 g vs. control=38.8±5.3 g), added sugar (active=34.1±4.9 g vs control=30.9±3.8 g), and protein (active=136.1±54.8 g vs. control=133.8±5.3 g).

Exploratory analyses evaluated the influence of sex assigned at birth (male, n=20 or female, n=14) and past 30-day cigarette use (yes, n=12, no, n=22) on kcal as between-subject factors. There were no significant main effects or interactions involving either factor (all *F*s<1.0, *p*s>0.13). Interestingly, males did eat slightly more than females in both conditions (males=1130.2±126.7 kcal vs. females=843.02±151.4 kcal) as compared to the control condition

(males=1046.4±113.4 kcal, vs females=787.6±135.5 kcal). Those who smoked cigarettes in the past 30 days consumed slightly less kcals in both the active condition (cigarette smoking=866.6±165.8 kcal vs. no cigarette smoking=1091.2±122.4 kcal) and control condition (cigarette smoking=724.9±143.6 kcal vs. no cigarette smoking=1057.0±106.1 kcal).

Another exploratory analysis examined the association between ENDS use in years and the difference in kcals between conditions. The correlation between these two variables was not significant (*r=-0.103*, *p*=0.561, n=34). Figure 2 displays a scatterplot of this correlation.

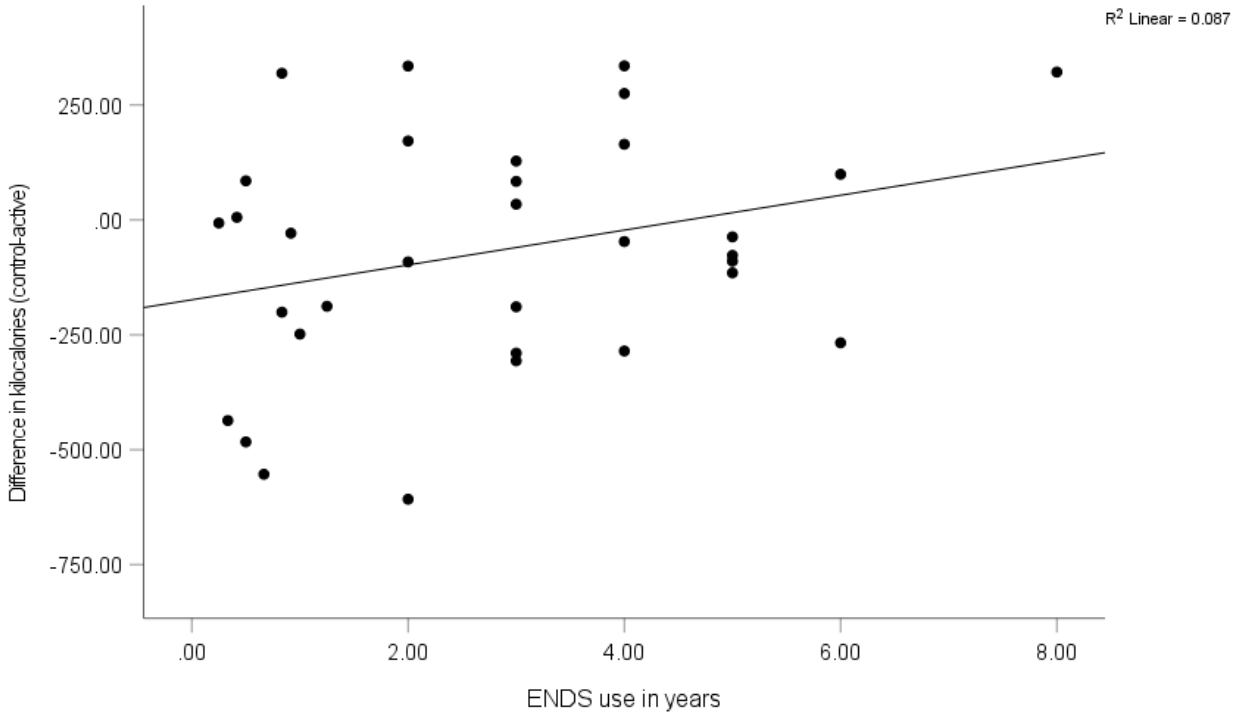

Figure 2: Scatterplot of ENDS use in years and difference in kilocalories consumed between conditions (*p*=0.561, n=34)

Subjective Measures

Tobacco/Nicotine Abstinence Symptoms and Nicotine-Related Effects. Across the adapted MNWS and Direct Effects Scale there were 11 items that had a significant condition by

time interaction (Fs>2.9, ps<0.049): urges to use an e-cigarette, irritability/frustration/anger, difficulty concentrating, restlessness, impatient, craving an e-cigarette, urges to smoke a cigarette, craving a cigarette, nauseous, dizzy, lightheaded, and heart pounding (see Table 5). All of these items were examined between conditions at each time point and by time within condition (changes relative to time 0 or baseline) using paired samples t-tests with a Bonferroni correction (10 total comparisons: p<0.005). Urges to use an e-cigarette was the item with the largest F value for the interaction (F=30.9). Relative to baseline (65.2±4.8), mean urges decreased significantly following condition administration (29.4±4.0; <0.001) and remained significantly decreased for the remainder of the session (ps<0.001). No significant changes relative to baseline were observed for the control condition. Between conditions, urges to use an e-cigarette were significantly lower for active compared to control immediately following condition administration (29.4±4.0 vs. 73.3±4.0; p<0.001) and for the remainder of the session. Similar patterns to urges to use an e-cigarette were observed for the craving an e-cigarette item. Figure 3 below displays findings in more detail.

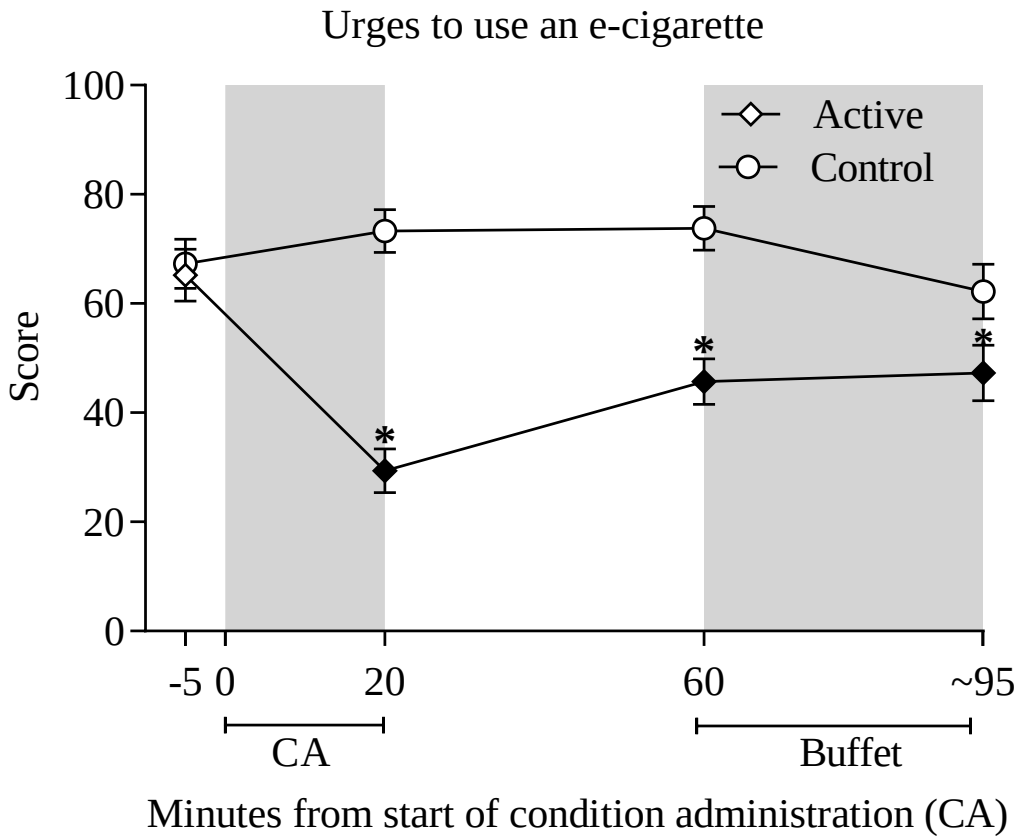

Figure 3. Mean±SEM for urges to use an e-cigarette item (n=34). Filled symbols represent a significant difference relative to -5 minutes, and asterisks represent a significant difference between conditions at that time point (all *p*s<0.005).

Table 5. Statistical Analysis Results for Subjective Measures

	Condition (C)			Time (T)			C X T		
Outcome	*F*	*p*	*ηp 2*	*F*	*p*	*ηp 2*	*F*	*p*	*ηp 2*
Adapted Minnesota Nicotine Withdrawal Scale[a]									
Urges to use an e-cigarette	63.6	**<0.001**	0.658	8.6	**<0.001**	0.206	30.9	**<0.001**	0.483
Irritability/frustration/anger	21.7	**<0.001**	0.397	10.5	**<0.001**	0.241	7.5	**<0.001**	0.185
Difficulty Concentrating	4.9	**0.034**	0.129	21.0	**<0.001**	0.389	5.3	**0.002**	0.138
Restlessness	3.2	0.085	0.087	12.4	**<0.001**	0.273	3.1	**0.036**	0.086
Impatient	13.1	**<0.001**	0.285	14.4	**<0.001**	0.304	5.6	**0.002**	0.145
Craving an e-cigarette	71.3	**<0.001**	0.684	8.5	**<0.001**	0.204	29.3	**<0.001**	0.470
Drowsiness	1.6	0.212	0.047	25.1	**<0.001**	0.432	2.5	0.077	0.071
Urges to smoke a cigarette	11.7	**0.002**	0.261	6.9	**<0.001**	0.172	3.3	**0.036**	0.090
Craving a cigarette	11.4	**0.002**	0.257	10.2	**<0.001**	0.237	4.6	**0.011**	0.122
The Direct Effects of Nicotine Scale[a]									
Nauseous	0.2	0.630	0.007	4.3	**0.008**	0.114	3.0	**0.045**	0.084
Dizzy	2.4	0.133	0.067	11.6	**<0.001**	0.261	6.3	**0.002**	0.160
Lightheaded	0.0	0.885	0.001	14.6	**<0.001**	0.307	4.2	**0.008**	0.113
Nervous	1.7	0.196	0.050	2.7	0.076	0.075	0.2	0.871	0.007
Sweaty	2.2	0.145	0.063	3.2	0.055	0.087	2.1	0.119	0.060
Headache	4.1	0.051	0.110	10.9	**<0.001**	0.248	2.4	0.086	0.067
Excessive salvation	1.0	0.317	0.030	0.8	0.449	0.023	1.8	0.151	0.053
Heart pounding	0.1	0.810	0.002	5.5	**0.003**	0.143	4.8	**0.004**	0.126
Confused	0.1	0.743	0.003	0.9	0.418	0.027	0.7	0.500	0.021
Weak	0.3	0.575	0.010	15.2	**<0.001**	0.315	0.2	0.792	0.007
Pennington Visual Analog Scale									
How sad do you feel at the moment?[a]	1.1	0.293	0.034	7.4	**<0.001**	0.184	1.0	0.374	0.030
How happy do you feel at the moment?[a]	2.9	0.099	0.080	14.6	**<0.001**	0.307	0.4	0.698	0.013
How anxious do you feel at the moment?[a]	0.0	0.975	<0.001	12.7	**<0.001**	0.278	5.6	**0.001**	0.145
How hungry do you feel at moment? [a]	3.8	0.060	0.103	125.7	**<0.001**	0.792	7.4	**<0.001**	0.184
How full do you feel at the moment? [a]	2.0	0.170	0.056	162.2	**<0.001**	0.831	0.8	0.482	0.024
How satisfied do you feel at the moment? [a]	25.6	**<0.001**	0.437	90.5	**<0.001**	0.733	4.3	**0.011**	0.115
How much do you think you can eat right now? [a]	2.8	0.106	0.077	95.2	**<0.001**	0.743	2.4	0.081	0.067
Would you like to eat something sweet? [a]	2.9	0.097	0.081	36.6	**<0.001**	0.526	1.3	0.277	0.038
Would you like to eat something salty? (n=30)[b]	1.2	0.279	0.040	59.8	**<0.001**	0.674	2.8	**0.045**	0.088
Would you like to eat something savory? (n=30)[b]	1.0	0.333	0.032	76.1	**<0.001**	0.724	1.4	0.264	0.045
Would you like to eat something fatty? (n=30)[b]	0.9	0.352	0.030	45.3	**<0.001**	0.610	1.5	0.238	0.048

Note: [a]Condition (T) df (1,33), Time (T) df (3, 31), C X T df (3, 31); [b]C df (1,29), T df (3, 27), C X T df (3, 27); Used Huynh-Feldt Correction. **Bold** indicates $p<0.05$.

For irritability/frustration/anger, relative to baseline (25.9±4.2), mean scores decreased significantly following the administration of the active condition (11.0±2.3; $p<0.001$), and there was also a significant decrease noted after the buffet meal administration in the active condition (9.4±3.4; $p<0.001$). No significant changes relative to baseline were observed in the control condition. At every time point following condition administration, scores for the active condition were significantly higher than control (all ps<0.001) with the largest difference at 20 minutes (active 35.0±5.3 vs. control 11.0±2.3).

For difficulty concentrating, relative to baseline, there was a significant decrease in the active condition at 35 minutes post-condition administration (40.5±4.7 to 21.4±3.7; $p=0.002$) and after the buffet meal administration from initial baseline (40.5±4.7 vs. 6.4±1.6; $p<0.001$). Regarding the control condition, relative to baseline, the only significant change was following the buffet meal administration (36.3±5.0 to 19.5±4.1; $p<0.001$). Between conditions, the active condition had a significantly lower mean score compared to control at the time point following buffet administration (6.2 vs 1.6± vs19.5±4.1; $p<0.001$). Restlessness and impatient demonstrated similar patterns to this latter item. Figure 4 below displays results for difficulty concentrating.

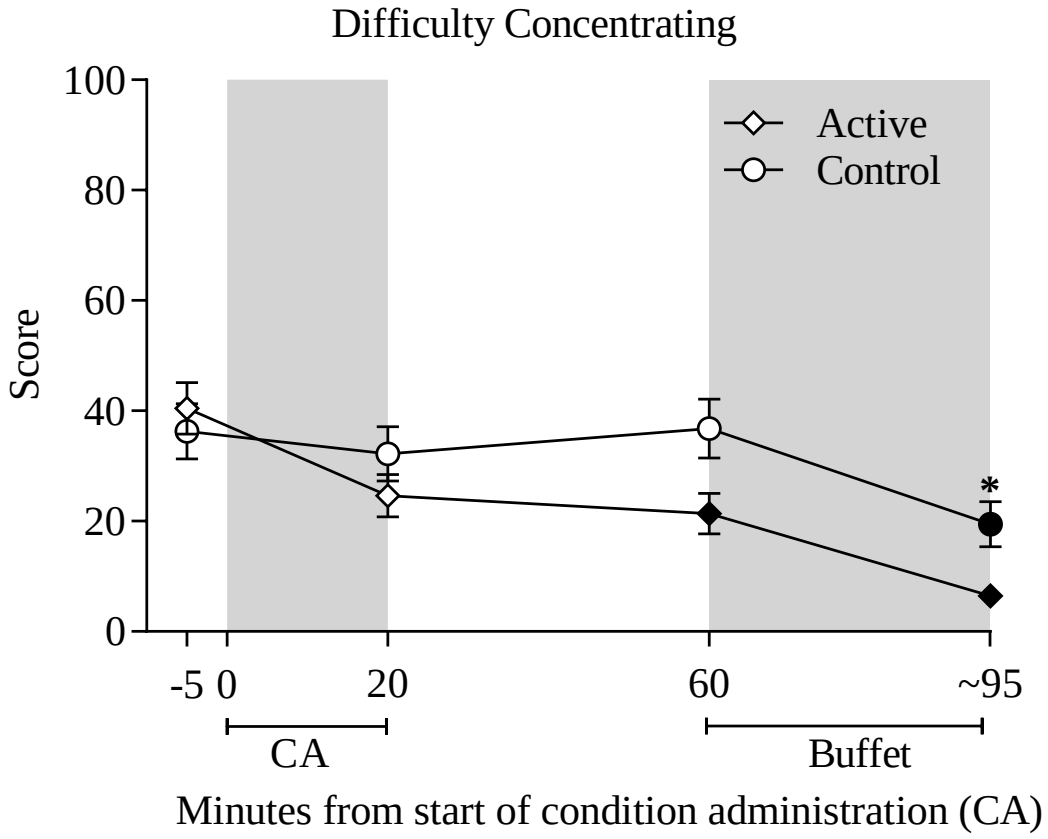

Figure 4. Mean±SEM for the difficulty concentrating item (n=34). Filled symbols represent a significant difference relative to -5 minutes, and asterisks represent a significant difference between conditions at that time point (all *p*s<0.005).

Relative to baseline, cravings to use a cigarette dropped significantly directly following the administration of the active condition (31.3±6.4 to 11.0±3.3; $p<0.001$) and remained low for the remainder of the session (*p*s<0.003). Relative to the baseline, no significant changes were observed in cravings to use a cigarette for the control condition. Between conditions, significant differences were observed following condition administration with mean cravings being higher in the control condition than the active (32.2±6.1 vs. 11.0±3.2; $p<0.001$) and also higher cravings observed in the control condition directly before buffet meal administration (36.6±6.7 vs.

19.7±5.2; *p*=0.003). There were no significant differences between conditions relative to baseline observed in urges to use a cigarette.

Dizziness had the largest *F*-value for the interaction (*F*=6.3) among the Direct Effects of Nicotine Scale items, and the only significant difference observed was directly following the condition administration, with the active condition displaying higher mean values than the control (20.5±4.0 vs. 8.0±2.0; *p*=0.002) and no significant differences between conditions. A relatively similar pattern was observed for nausea, lightheadedness, and heart pounding.

Pennington Visual Analog Scale (PVAS). Of the 11 PVAS items, only four items had a significant condition by time interaction: “How anxious do you feel at the moment?”, “How hungry do you feel at the moment?”, “How satisfied do you feel at the moment?”, and “Would you like to eat something salty?”. The item assessing hunger (How hungry do you feel at the moment?) had the largest *F*-value for the interaction (*F*=7.4; see Figure 5). Regarding feelings of hunger, in the control condition, feelings of hunger significantly increased relative to baseline (56.87 ± 4.3) following the condition administration (64.84 ± 4.3), and remained high before the buffet meal (71.00 ±3.8; all *ps* <0.001); there was little change in the active condition during this same time period. Hunger ratings for both conditions significantly decreased relative to baseline following the buffet meal (*ps*<0.001), and there were no significant between condition differences at any time point, Figure 5 below depicts findings towards feelings of hunger in more detail.

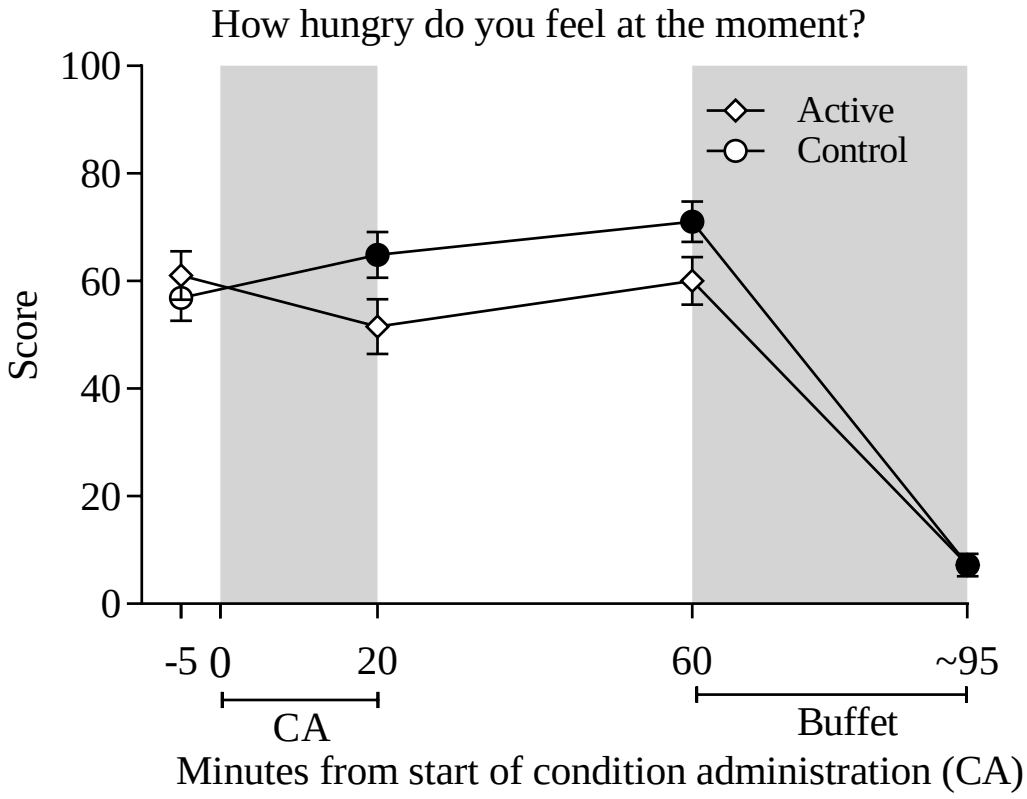

Figure 5. Mean±SEM for the hunger item (n=34). Filled symbols represent a significant difference relative to -5 minutes, and asterisks represent a significant difference between conditions at that time point (all *p*s<0.005)

For feelings of satiety (How satisfied do you feel at the moment?), relative to baseline, there was a significant increase in satiety directly after active condition administration (26.0±3.4 to 39.3±3.4; $p<0.001$) but not during the control condition. After administration of the buffet meal, there was a significant increase in satiety relative to baseline for both conditions to a similar extent (*p*s<0.001). Between conditions, the active condition resulted in significantly higher satiety ratings than the control, immediately following condition administration (39.3±3.4 vs 21.2±3.4; $p<0.001$) and directly before the buffet meal (34.0±3.6 vs 19.5±4.0, $p<0.001$).

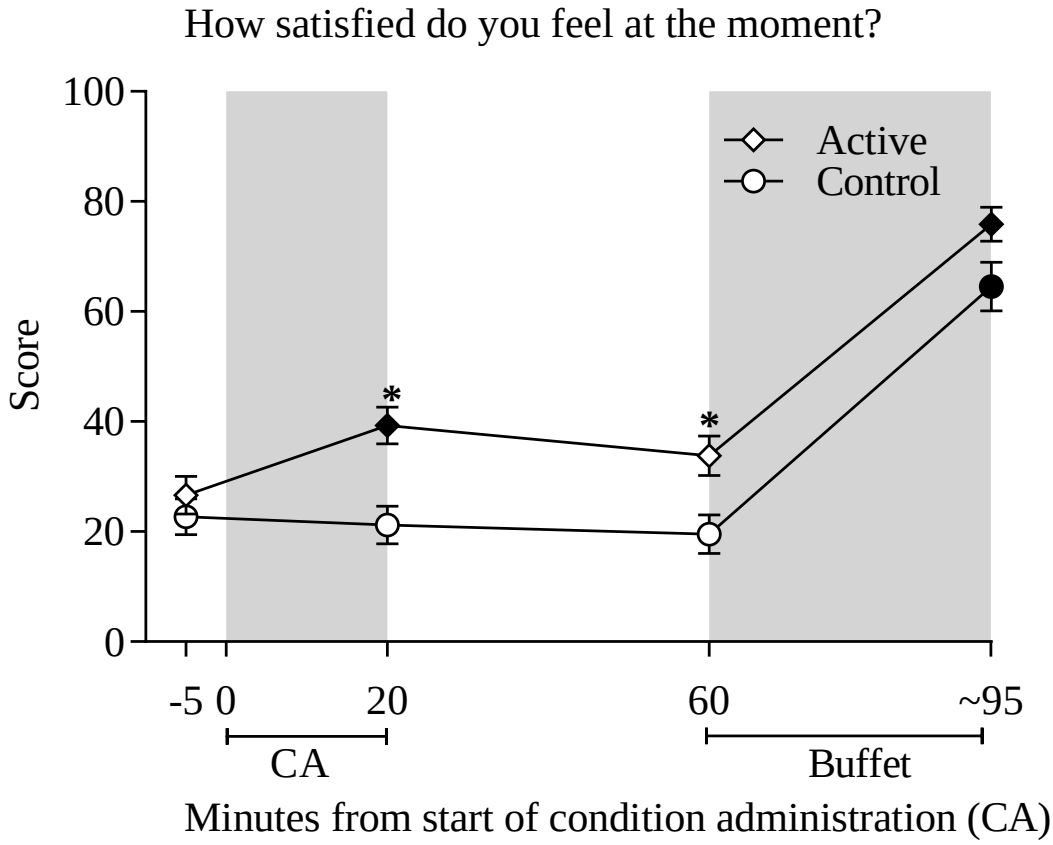

Figure 6. Mean±SEM for the satiety item (n=34). Filled symbols represent a significant difference relative to -5 minutes, and asterisks represent a significant difference between conditions at that time point (all *p*s<0.005).

For feelings of anxiety at the current moment, relative to baseline, scores in the active condition dropped significantly before (31.1±4.6 vs 19.3±3.7; $p<0.001$) and directly after the buffet meal administration (31.1±4.6 vs 15.5±3.4). In the control condition, relative to baseline a significant decrease was only observed after the buffet meal administration (25.1±4.2 vs 7.2±1.7; $p<0.001$). There were no significant between condition differences at any time point.

Relative to baseline, there was a significant decrease in cravings of something salty (n=30) in the active (58.3±5.0 to 15.6±3.2) and control (56.0±5.6 vs 15.5±3.6) conditions

directly after the buffet meal administration (*ps*<0.001). There were no other significant differences relative to baseline or significant between condition differences at any time point.

Food Craving Questionnaire-State. A one-way repeated measures ANOVA was used to evaluate the influence of condition on overall craving of food as well as the 5 additional factors which are depicted in more detail in Table 6. While no significant main effects were observed, anticipation of relief from negative states and feelings as a result of eating factor had the highest *F*-value (2.6). Descriptive examination revealed slightly but not significantly lower scores in the active condition vs. control (10.2±0.4 vs. 11.0±0.5) for this factor as well as two others, but the opposite pattern was observed for two other factors in which slightly higher scores were observed for the active condition compared to control.

Table 6. Food Craving Questionnaire-State

Food Craving Questionnaire (FCQ)-State	Condition *F*	*p*	ηp^2	Active M±SEM	Control M±SEM
FCQ-State Total Score	<0.1	0.861	0.001	49.0±1.6	49.4±2.17
An intense desire to eat	1.1	0.308	0.032	10.4±0.49	9.6±0.6
Anticipation of positive reinforcement that may result from eating	0.5	0.472	0.016	10.6±0.42	10.2±0.5
Anticipation of relief from negative states and feelings as a result of eating	2.6	0.113	0.074	10.2±0.4	11.0±0.5
Lack of control over eating	0.8	0.369	0.024	6.9±0.5	7.2±0.4
Craving as a physiological state	1.4	0.239	0.042	10.9±0.4	11.4±0.4

Note: df (1,33)

Discussion

Overview

This study examined the acute effect of a newer generation ENDS capable of cigarette-like levels of nicotine when used by experienced ENDS users (Phillips-Waller et al., 2021) on energy intake during an *ad lib* buffet meal and associated subjective effects using a cross-over design. To our knowledge, this is the first clinical lab study examining this effect with acute

ENDS use; and there are mixed findings from similar work using cigarettes and nicotine nasal spray. Therefore, this work was innovative and addresses important gaps in the literature regarding nicotine's ability to acutely suppress appetite.

Energy Intake

We hypothesized that relative to the control condition, the active nicotine-containing ENDS condition would result in a significant decrease in energy and macronutrient intake during the *ad lib* meal. This hypothesis was not supported. There was not a significant difference in energy or macronutrient intake between conditions which is consistent with results from some previous literature performed with cigarettes and nicotine nasal spray under various conditions (Perkins et al., 1992; Perkins et al., 1994; Grunberg, 1982). However, these findings were inconsistent with smoking-related energy intake suppression observed within two previous studies examining the acute effects of smoking 2 own brand cigarettes in 15 minutes (Yannakoulia et al., 2018) and smoking 8 own brand cigarettes over a 4-hour period (Bulik et al., 1991). Critically, for one of these studies, the sample size included only 5 participants who had previously reported eating disorder pathology (Bulik et al., 1991). Compared to the more recent report (Yannakoulia et al., 2018), we observed slightly higher levels of energy intake (900-1000 kcal vs. 700-900 kcal) and more variability (as indexed by SD; 500-600 kcal vs. 200-300 kcal) between participants. Of note, we utilized many similar design features as this latter study including the use of a sham condition, controlling bout length (20 ENDS puffs in 20 minutes vs. 2 cigarettes in 15 minutes), enforcing 12-hour abstinence from tobacco products, alcohol, food

and drink prior to each session, and the inclusion of a 45-minute interval prior to the buffet meal administration.

There also were several critical differences in the sample composition and study design that might account for the discrepancy between current findings and those of Yannakoulia et al. (2018). We were powered to detect a difference of 100 kcal±200 SD, with an effect size of 0.5 which was generated from estimates from Yannakoulia et al. (2018). Of importance, we were not powered to detect equivalence between conditions. Our sample was 2.4 times larger and more diverse in race/ethnicity and sex (e.g., 38% non-male vs. 0% non-male) which likely increased variability between participants. The tobacco product of interest also differed: 5% nicotine containing JUUL ENDS vs. own brand cigarettes. Although JUUL was among the most highly preferred ENDS brands among our participants, more than 60% preferred other ENDS brands, and more than 90% preferred ENDS flavors other than tobacco. Condition instructions attempted to ensure equivalent ENDS use and associated nicotine delivery between participants, but it is possible that participants altered their puff topography (as in Hiler et al., 2017) and/or found the active condition aversive compared to their own brand ENDS. These effects also could have reduced the impact of the active condition on energy intake. Future work should consider the use of own brand ENDS as a comparator condition. Relatedly, participants in Yannakoulia et al. (2018) also were required to take puffs of the sham cigarette condition. In contrast, in the present study participants were provided a sham ENDS for optional use. Forced sham puffs might have increased subjective effects of discomfort and craving in the absence of nicotine and other associated cues and could have ultimately resulted in higher energy intake. Even considering these limitations, results of the current study suggest acute nicotine-containing ENDS use suppress energy intake relative to no ENDS use, and these effects may not be comparable to that

observed with cigarette smoking under similar conditions. Descriptive findings that indicated slightly higher energy intake following ENDS use were unexpected. While speculative, this behavior could support the premise that "nicotine potentiates the reinforcing properties of other rewards" (Rupprecht et al.,2015) such as food, but the potential impact of conditioning/associative learning and/or pharmacological interactions cannot be ignored.

We also performed exploratory analyses to test whether sex, past 30-day cigarette use, and length of ENDS use influenced condition-related differences in energy intake. There were no significant differences in energy intake by condition between males and females, but males did consume slightly more during each condition on average than females (~1000-1100 kcal vs. ~800 kcals). These findings are consistent with previous literature which examined differences in sex on energy intake utilizing various nicotine administration methods including cigarettes and nicotine nasal spray (Perkins et al., 1992; 1994). Also, of note, our findings are not surprising that men ate slightly more given the gender differences in metabolic needs and given social pressure for women to eat less (Grzymislawska et al.,2020). Past 30-day cigarette use also did not significantly interact with condition-related effects, but interestingly, participants who reported past 30-day cigarette use had slightly lower energy intake in both conditions compared to those without recent smoking history (~700-900 kcal vs. ~1000-1100 kcal).

The analysis regarding length of time using an ENDS and condition-related effects was performed in lieu of previous evidence demonstrating that the shorter amount of time an individual has smoked, the more cigarette-associated energy intake suppression was observed (Yannakoulia et al., 2018). Interestingly, while not statistically significant, our data highlight a potential opposite effect, that the longer and individual has used an ENDS, the more likely they were to consume fewer calories during the active condition compared to the control condition.

Critically, most participants in our sample reported ENDS use of around 2 years; in Yannakoulia et al. (2018) average time spent smoking was around 10 years. Participant age may confound these findings.

Subjective Measures

We hypothesized that the active nicotine-containing ENDS condition would suppress feelings of hunger and food craving and increase satiety relative to the control condition. Consistent with this hypothesis, a significant increase in feelings of hunger was observed following the control condition administration but not the active condition, and a significant increase in satiety was observed following the active condition administration but not the control. In contrast to feelings of hunger, food-related cravings (indexed by the FCQ-state) measured immediately prior to the buffet meal indicated no significant differences between conditions across multiple factors. The FCQ-state focuses specifically on the intensity of food craving especially around certain food deprivations, cues to certain foods, and food intake (Meule, 2020). Higher scores on the FCQ-state have been correlated with increased caloric consumption (Ng & Davis, 2013), but this measure also has been shown to be influenced by environmental factors that contribute to cravings of certain foods, such as deprivation of a particular food item (i.e., sweet or savory item; Meule et al., 2014). Some consider specific food cravings (i.e., feelings directed towards a certain food item, flavor, or texture) to be differentiated from physiological feelings of hunger encompassing stomach growling, irritability, and dizziness associated with not eating (Meule, 2020). This idea may help explain the discrepancy between subjective ratings of hunger and food-related cravings in this study.

Compared to six prior studies that tested the acute effect of nicotine-containing products as relative to control on subjective measures (Perkins et al., 1991, Perkins et al., 1992, Perkins et

al., 1994; Bulik et al., 1991; Grunberg, 1982; Yannakoulia et al. 2018), our assessments are among the most comprehensive to date with the inclusion of eating-related items as well as nicotine abstinence symptomology and nicotine-related side effects. Interestingly, among the four studies that included a subjective measure of hunger, only one observed nicotine-related suppression (Perkins et al., 1991) as in the present study. Among the two studies that measured desire to eat/binge, neither showed condition-related differences for this subjective measure although food intake was significantly lower for the active nicotine-containing condition relative to control for both (Bulik et al., 1991; Yannakoulia et al., 2018). In the three previous studies that measured condition-related effects on subjective satiety, there were no condition-related differences, unlike the present study. Taken together, this work highlights a dearth of prior evidence indicating nicotine administration suppresses subjective feelings of hunger and food craving and increases satiety. The present study provides contrasting information for some of these measures.

Other findings that were more consistent with prior work in this area indicated that the active condition was effective in reducing nicotine abstinence-related symptoms including e-cigarette urges and craving, irritability, and difficulty concentrating. The scope of this suppression is consistent with studies evaluating the acute effects of JUUL and other ENDS following acute administration (Maloney et al., 2020; Hiler et al., 2017). Similar findings in cigarette-related craving relief has been observed in four previous acute studies following the administration of nicotine-containing products (Yannakoulia et al., 2018; Perkins et al., 1994; Perkins et al., 1992; Bulik et al., 1991). Likely due to 40% of participants reporting past 30-day cigarette smoking, significant decreases in urges to smoke cigarettes and cigarette craving also were observed following the active nicotine-containing ENDS condition. Of note, in the present

study, baseline ratings of craving a cigarette (~30/100) were about half of that observed for baseline ratings of craving an e-cigarette (~60/100) which is consistent with the sample composition of primary ENDS users.

Consistent with a previous acute evaluation of nicotine delivered via nasal spray (Perkins et al., 1993) but not two prior acute ENDS evaluations (Hiler et al., 2017; Yingst et al., 2019), small increases in subjective ratings for several nicotine-related side effects were observed following the active condition administration in this study including nauseous, dizzy, lightheaded, and heart pounding. These effects are likely due to the stimulant properties associated with nicotine (Benowitz, 2009) and might have been enhanced due to overnight abstinence not only from tobacco/nicotine, but also food and drink other than water.

In summary, the active condition suppressed subjective feelings of hunger and nicotine abstinence symptoms, and increased satiety and nicotine-associated side effects. It is important to note that these subjective effects did not correspond to a significant decrease in energy intake during the active condition compared to the control. Subjective effects may not be directly driving eating behavior, but these effects may belie other self-reports of ENDS use for weight control purposes (Ganson & Nagata, 2021; Morean et al., 2020; Morean & Wedel, 2017). These findings could lead to actionable approaches towards enhancing ENDS cessation efforts, with a particular focus on addressing perceptions of ENDS-related appetite control and/or weight

management. Further research is needed to identify what drives these perceptions and how to best implement strategies to counteract them.

Limitations

It is important to note that our study has some limitations that might impact generalizability. We recruited a convenience sample of individuals who currently use ENDS from the Greater Richmond Area; thus, our findings may not generalize to different populations and regions. Also, similar to Yannakoulia et al. (2018) and Perkins et al. (1994), participants were asked to maintain overnight (at least 12 hours) abstinence from food and drinks other than water and nicotine-containing products which was confirmed by imperfect measures including expired air CO and participant attestation via a form signature. As ENDS use does not involve CO exposure, and there is no acute method to determine food-related abstinence, it is possible that participants may not have adhered to protocol instructions. A study that involves an in-person and/or monitored abstinence period may be a more effective way to deal with this concern. By using a 1 hour waiting period prior to the start of the study, the current study attempted to provide some control in terms of ensuring that participants maintained abstinent from food and nicotine-containing products for at least a 1-hour period.

Another limitation in our study was the study product tested. Although ~35% of participants in our study preferred JUUL, the remainder preferred another ENDS brand and might not have used a JUUL previously. Additionally, participants in our sample were limited to a tobacco-flavored ENDS, which likely differed from their preferred ENDS flavor (menthol, blue razz, etc). These product characteristics may have influenced participant use behavior and the

amount of nicotine that was absorbed. Given that we did not collect puff topography or blood nicotine levels, the extent of this limitation is difficult to conclude.

Another limitation common to controlled eating paradigms was that participants received the buffet meal in a lab environment while being observed by the researcher. While we took every step to minimize this effect (i.e., unobtrusive monitoring to try and create a more natural buffet environment), the disclosure of monitoring and the lab setting may have had some influence on participants' eating behavior. Future work could consider assessing participant perceptions of the buffet environment and the influence of the setting on their responding and associated behavior.

Conclusions

This clinical lab study examined the acute effects of nicotine-containing ENDS use on energy intake and associated subjective effects. Findings indicate that acute ENDS use following overnight abstinence did not significantly impact energy intake relative to a control condition, but there was an ENDS-associated decrease in feelings of hunger and increase in feelings of satiety. Other subjective effects suggested ENDS use was effective in reducing nicotine abstinence symptoms and produced mild nicotine-related side effects.

Building from this work, future research is needed to explore perceptions of and reasons for ENDS use as an appetite control method as well as examine other features of ENDS including liquid nicotine concentration and flavor and their impact on appetite and hunger. Considering recent increases in ENDS use among younger populations, lack of tailored ENDS cessation programs, and rapidly changing regulatory environment, this information can help guide tobacco prevention/intervention efforts and tobacco policy aimed to decrease negative health

consequences associated with ENDS use. A focus on populations underrepresented in clinical research and at high risk for tobacco use and related consequences is required to reduce tobacco-related disparities and advance health equity Due to there being higher risk factors and perceived stress among underrepresented communities, ENDS use for weight control may be more prominent. Future work among underrepresent populations can play an integral role in targeting prevention/intervention efforts.

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