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Internalizing Mental Health Symptoms and Nicotine Use Among Adolescents in Canada, England, and the US from 2020-2022

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Dedication

This work is dedicated to my grandfather, Theodore G. Wells, jr., who passed away from smoking-related lung cancer in 2004.

This work is also dedicated to Bonnie Dye, who passed away from smoking-related breast cancer in 2017.

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Abstract

Background: There is a well-established bi-directional relationship between cigarette smoking and internalizing mental health (IMH) symptoms (e.g., symptoms of depression, symptoms of anxiety). However, it is unclear whether IMH symptoms are associated with using different types of nicotine products among adolescents, as adolescents are using a variety of nicotine products, including combustible products (cigarettes), non-combustible products (e-cigarettes), or combinations of both types of products. This dissertation examines associations between IMH symptoms and current use of various types of nicotine products across three countries from 2020-2022.

Methods: Data come from the 2020-2022 waves of the International Tobacco Control (ITC) Adolescents Tobacco and Vaping Survey, an online repeat cross-sectional survey of adolescents aged 16-19 in Canada, England, and the US (n=67946). In the full sample, current nicotine use was examined in four categories: 1) no use, 2) exclusive non-combustible product, 3) exclusive combustible product use, and 4) use of both product types. Respondents reported current symptoms of depression or anxiety, and we generated a dichotomous IMH symptoms variable (yes vs. no). Respondents also reported their age race, sex, gender identity, and socioeconomic status. We examined the association between IMH symptoms and current nicotine use using multinomial logistic regression models that adjusted for covariates. Among the respondents that reported using cigarettes and/or e-cigarettes (n=15522), we also examined the association between

IMH symptoms and nicotine dependence indicators and cessation variables (quit intention, quit attempt).

Results: IMH symptoms were most strongly associated with use of both product types, followed by exclusive non-combustible use, and then exclusive combustible use. Nicotine use and IMH symptoms varied by gender identity. Among adolescents reporting current e-cigarette use, IMH symptoms were positively associated with nicotine dependence indicators. However, for those reporting cigarette use, this association varied by whether they were dual using e-cigarettes. For both products, IMH symptoms were positively associated with quit attempt and unassociated with quit intention. **Conclusions:** This dissertation provides an up-to-date examination of the relationship between mental health and nicotine use among adolescents. Results indicate that non-combustible product use may have a particularly strong relationship with poor mental health among adolescents. Longitudinal research is needed to better understand directionality. Results also provide an understanding of the relationship between gender identity and nicotine use.

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Chapter 1: Introduction

Introduction

Tobacco use remains the leading cause of preventable disease around the world (1). Over the past century, the types of tobacco products available have grown beyond traditional combustible products, such as cigarettes, cigars, and hookahs, to include non-combustible products that contain nicotine, including electronic cigarettes (e-cigarettes) and nicotine pouches. While policies aiming to curb tobacco use have reduced cigarette use, tobacco use among adolescents remains a public health concern, including concerns about increasing e-cigarette use in recent years. E-cigarette use is a health concern for adolescents not only because of the potential for cardiovascular and respiratory effects from use of other tobacco products (2) , but also because nicotine adversely affects brain development (3). Furthermore, some evidence suggests that e-cigarette users are more likely than those who do not use e-cigarettes to go on to become smokers in adulthood (4). However, this evidence is contradicted by US population-level data showing that smoking prevalence continues to decline and is at historically low levels among young people (5).

Adults with mental health conditions are significantly more likely to use tobacco products (6). Mental health conditions are highly prevalent among adolescents; however, they are rarely diagnosed or treated (7). The many different mental health conditions adolescents have can be classified as either internalizing or externalizing. Internalizing or externalizing factors refer to symptoms associated with psychiatric disorders (8).

Internalizing factors include symptoms of anxiety, social withdrawal, dysthymia, depression, and fear. Externalizing factors include behavioral manifestations of aggression, conduct or delinquency problems, substance or alcohol use disorder, hyperactivity, and difficulties with attention (8). Among children and adolescents, the presence of internalizing and externalizing factors are highly correlated, with some referring to the combination of factors as comorbidities (9). This correlation can be partially attributed to genetic factors (10), factors related to the functioning of the limbic system (11,12), and environmental influences (13).

Adolescents with untreated mental health conditions related to either internalizing or externalizing factors are at risk for a number of adverse outcomes, including substance use disorders and suicide (14), which is the third leading cause of death among US teenagers ages 12-19 (15). Furthermore, suicide rates among young people have been increasing dramatically over the past decade (16). Additionally, mental health conditions persist or intensify over time (17). Individuals suffering from mental health conditions have a significantly shorter life expectancy than the general population, largely attributed to substance use-related conditions (18,19). Adolescence can be a turbulent time and those with mental health conditions require additional support, including treatment through therapy, medication, or a combination of the two (7). By promoting treatment for adolescents struggling with mental health, we can reduce these health disparities and promote greater well-being throughout their lives.

Many of the risk factors for both mental health conditions and tobacco use are related, as shown in the Conceptual Model of the Problem (see Figure 1.1). A systematic review of studies examining the association and directionality of mental health conditions

and substance use among young people found that depression and anxiety were positively associated with alcohol, cannabis, and tobacco use, including both cigarette and e-cigarette use. This review concluded that the relationship between tobacco use and depression was bidirectional (20). Similarly, a 2021 systematic review of 40 recent studies focusing specifically on e-cigarettes among adolescents found that e-cigarette use is associated with more mental health problems than non-use; however, directionality is uncertain (21). Researchers posit that among adolescents, nicotine may be used to self-medicate for psychiatric symptoms, enhance cognitive deficits, and reduce unpleasant side effects of psychiatric medications (22). Alternatively, research also suggests that use of tobacco products among adolescents may lead to the development of mental health conditions, including depressive disorders and anxiety (20). Furthermore, as "dual use" of both e-cigarettes and cigarettes among young people has become more prevalent, some researchers suggest that mental health may help explain the transition from exclusive e-cigarette use to dual use (23). For example, one study found that young people identify social facilitation as a primary reason for e-cigarette use, but many transition to dual use with cigarettes to manage stress (24).

Numerous studies using a variety of study designs have examined the relationships between diverse mental health conditions and symptoms and use of various tobacco products among adolescents. Certain subpopulations of adolescents are at higher risk for both tobacco use and mental health conditions. One such subpopulation is adolescents who identify as sexual and gender minorities. Indeed, the number of children and adolescents who identify as gender minorities has increased in recent years (25), There is growing research on the associations of sex and gender identity with the health

of adolescents. Indeed, sex, which refers to anatomical and physical traits (e.g., male, female, intersex), and gender, which refers to identity, expression, and social and cultural expectations (e.g., cisgender, transgender, non-binary), are related to disparities in health, economic and educational attainment, and social support (26). People who identify as sexual and gender minorities are at higher risk for substance use and mental health conditions, among other adverse health outcomes (27). Research shows that, compared to their cisgender peers, gender minority adolescents are more likely to experience mental health symptoms (28,29) and use substances, including tobacco products, alcohol, and drugs (30,31).

The World Health Organization officially declared the start of the COVID-19 pandemic in March 2020, after widespread infections of SARS-CoV-2 were reported in nearly every country in the world (32). From 2020-2022, young people around the world experienced significant disturbances in their lives due to both the stress of living through a pandemic and social isolation from school and public shutdowns (32). A systematic review of studies of children and adolescents amid both COVID-19 and past pandemics found that the prevalence of depression and anxiety among young people during and after pandemics increases (33). Furthermore, pandemics have more severe long term adverse consequences for young people compared to adults (33). Longitudinal studies show that COVID-19 changed adolescent mental health trajectories and resulted in significant increases in symptoms of depression and anxiety in many different countries (34–37). A systematic review of adolescents substance use before and during the COVID-19 pandemic showed that rates of substance use, including tobacco, declined significantly (38). However, recent data suggests that as of 2022, adolescents tobacco use rates may be

increasing to pre-COVID levels (39). Taken together, this information suggests that the COVID-19 pandemic had effects on both the mental health and tobacco use patterns of adolescents; however, to our knowledge, no studies have explicitly examined this relationship.

The proposed dissertation will examine the relationship between nicotine use and internalizing mental health symptoms among adolescents, including gender minority adolescents, in the US, Canada, and England. This dissertation will fill at least two critical gaps in the literature of adolescents tobacco and mental health by 1) examining the relationship between emerging patterns of nicotine use and mental health symptoms from 2020-2022, 2) examining how this relationship has changed over time, including from before the COVID-19 pandemic began through 2022, and 3) examining whether participant characteristics, including country of residence, are associated with this relationship. Canada, England, and the United States are high income countries with historically similar tobacco use patterns (i.e., types of products used, prevalence of use) (1); however, differences in product availability and, to some extent, regulations have resulted in differences in tobacco use rates across the three countries, particularly among adolescents. The results of this research could be used to enhance the understanding of how tobacco use relates to mental health among adolescents, thereby informing interventions and policies to improve the health of adolescents.

Specific Aims

The proposed research will inform the broader research agenda to understand how the adolescents tobacco epidemic is intertwined with the adolescents mental health epidemic, including through the COVID-19 period. **The purpose of this proposed**

research is to describe the relationship between internalizing mental health (IMH) symptoms and current nicotine use among adolescents, how this relationship has changed from February 2020 to August 2022, and what characteristics may moderate the relationship between IMH symptoms and nicotine use.

The data for this dissertation will come from the International Tobacco Control Policy Evaluation Project (ITC) Adolescents Tobacco and Vaping Survey, a national repeat cross-sectional survey conducted in England, Canada, and the United States. I will analyze 5 waves of data collected from February 2020 to August 2022. The expected outcomes of this study are: 1) increased understanding of the associations between internalizing mental health symptoms and current nicotine use patterns among adolescents in Canada, England, and the USA from 2020-2022; 2) an understanding of how this relationship has changed, if at all, from 2020-2022, 3); 3) identification of adolescent participants' characteristics (e.g., sociodemographic characteristics) that moderate the relationship between mental health and nicotine use, and 4) among adolescents who report current use of nicotine products, identification of how internalizing mental health symptoms are associated with different characteristics of nicotine use (e.g., nicotine dependence, intentions to quit, having a quit attempt).

Aim 1. Full Sample Analysis

Aim 1a: Examine the relationship between internalizing mental health symptoms current nicotine use (no-use vs. exclusive combustible product use vs. exclusive use of non-combustible products vs. use of both combustible and non-combustible products) among adolescents in Canada, England, and the USA from 2020-2022

Hypothesis 1a.1: The presence of internalizing mental health symptoms will be positively associated with all categories of current nicotine use. The strength of association between the presence of internalizing mental health symptoms and current nicotine use will follow a gradient: strongest for use of both combustible and non-combustible products, followed by exclusive use of combustible products, and then exclusive use of non-combustible products.

Hypothesis 1a.2: Due to the impact of the COVID-19 pandemic, we also hypothesize that the association between IMH symptoms and current nicotine use will be moderated by time, with the association weakening over the course of the COVID-19 pandemic.

Hypothesis 1a.3: Finally, given differences in nicotine use and mental health in England, Canada, and the US, we hypothesize that the relationship will be moderated by country.

Aim 1b: Determine whether gender identity (i.e., man, woman, transgender, gender non-conforming (GNC)) moderates the relationship between internalizing mental health symptoms and current nicotine use.

Hypothesis 1b: We hypothesize that use of both combustible and non-combustible nicotine products will be more prevalent among transgender and GNC adolescents, and that IMH symptoms will be more likely among transgender and GNC adolescents. We hypothesize that adolescent men will be more likely to use nicotine products, but less likely to have IMH symptoms, than women. We also hypothesize that gender identity will moderate the relationship between IMH symptoms and nicotine use.

Aim 2. Limited Sample Analysis

Aim 2a. Among participants who used e-cigarettes in the prior 30 days, examine the relationship between internalizing mental health symptoms and nicotine dependence indicators (i.e., frequency of e-cigarette use, , perceived addiction to e-cigarettes, and time to first e-cigarette) and cessation variables (intention to quit and ever having a quit attempt).

Hypothesis 2a.1: Among participants who used e-cigarettes in the prior 30 days, internalizing mental health symptoms will be positively associated with nicotine dependence indicators

Hypothesis 2a.2: Among participants who used e-cigarettes in the prior 30 days, internalizing mental health symptoms will be negatively associated with cessation variables

Hypothesis 2a.3: The association between IMH symptoms and all outcomes will be moderated by dual use of cigarettes, where associations will be stronger for those reporting dual use than exclusive use of e-cigarettes.

Aim 2b. Among participants who used cigarettes in the prior 30 days, examine the relationship between internalizing mental health symptoms and nicotine dependence indicators (i.e., frequency of cigarette use, perceived addiction to cigarettes, and time to first cigarette) and cessation variables (intention to quit and ever having a quit attempt).

Hypothesis 2b.1: Among participants who used cigarettes in the prior 30 days, internalizing mental health symptoms will be positively associated with nicotine dependence indicators

Hypothesis 2b.2: Among participants who used cigarettes in the prior 30 days, internalizing mental health symptoms will be negatively associated with cessation variables

Hypothesis 2b.3: The association between IMH symptoms and all outcomes will be moderated by dual use of e-cigarettes, where associations will be stronger for those reporting dual use than exclusive use of cigarettes.

Overall, this research will enhance our understanding of the relationship between nicotine use and mental health by examining specific characteristics of nicotine use (i.e., combustibility, dual use, frequency of use, perceived addiction, time to first use, intentions to quit, having a quit attempt). As the tobacco market diversifies and patterns of tobacco use change, particularly among adolescents, it is essential to understand which types of tobacco use may be most associated with mental health problems. As adults with internalizing mental health problems have higher rates of cigarette smoking, it is possible that the same will hold true for other types of tobacco use. Overall, this research will identify priority groups for policies and targeted interventions that aim to reduce nicotine use and improve the mental health of adolescents.

Figures

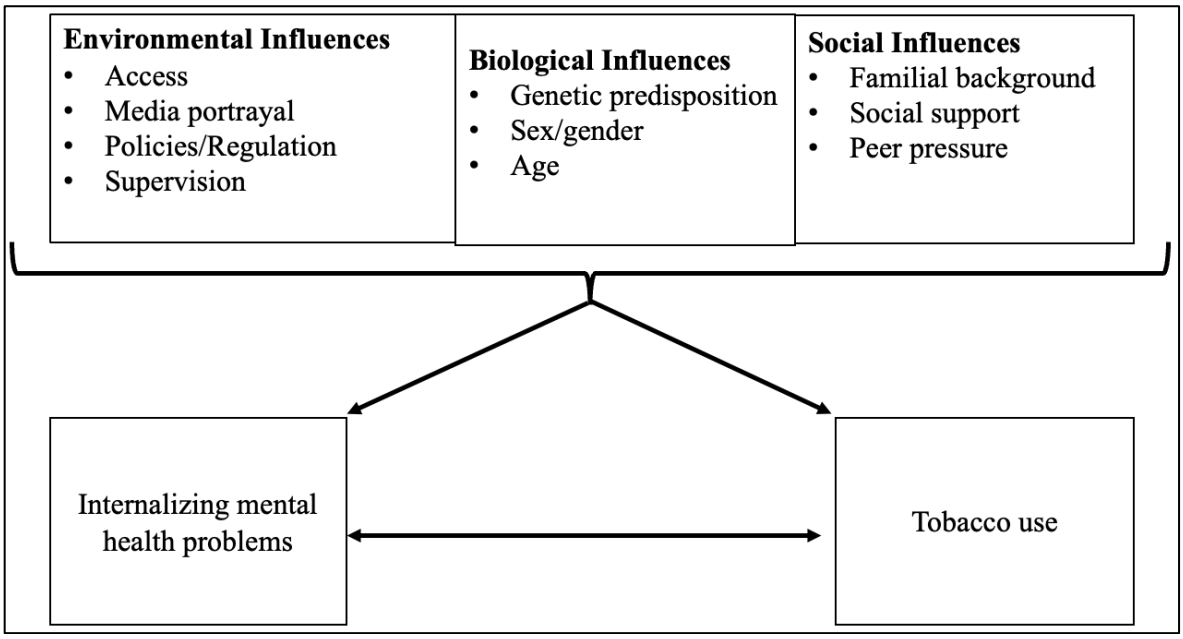

Figure 1.1 Conceptual Model of the Problem

Chapter 2: Background and Significance

Background

This background section will include a review of literature related to the proposed dissertation, setting the foundation for the specific aims, hypotheses, and research questions. The subsections will summarize literature for each aim and sub-aim.

Aim 1a: Internalizing mental health symptoms are associated with cigarette smoking among adolescents.

There is abundance of literature showing a positive association between cigarette use and internalizing mental health symptoms among adolescents. Many of these studies are cross-sectional in design and found significant associations between cigarette smoking and a variety of internalizing factors. For example, the following studies found positive associations between smoking cigarettes and depression. A 2009 cross-sectional study of n=299 urban US adolescents found that past 30-day smoking was significantly associated with depressive symptoms (40). Using cross-sectional data from 2005-2011 in South Korea, one study found that adolescent current or former smokers reported significantly higher prevalence of depression compared to never smokers (41). An analysis of cross-sectional data from the US National Household Survey on Drug Abuse (NHSDA) 1994-1996 (n=13827) showed that adolescent current and former smokers had higher odds of depression compared to nonsmokers (42). A cross-sectional study of Belgian adolescents (n=1037) from 2014-2015 found that cigarette smoking increased the

likelihood of reporting symptoms of depression, anxiety, and stress (43). These studies show that across diverse samples of adolescents, cigarette smoking and depression are positively associated.

Several studies have found differences in the association between cigarette use and depression by gender. A study of n=3621 US middle schoolers published in 2003 found that past 30-day cigarette smoking was associated with depression among girls but not boys (44). A nationally representative study of US 7th-12th graders found that females who reported depressive symptoms were also more likely to report current smoking, but this association was not significant among males (45). These studies suggest that gender may moderate the relationship between cigarette smoking and depression.

Other studies examined internalizing conditions including or in addition to depression. A cross-sectional study of Hungarian adolescents (n=215) found a strong association between symptoms of both depression and anxiety and current cigarette smoking (46). A study of European adolescents (n=12,328) found that internalizing problems (i.e., depression, anxiety, suicidality) were positively associated with current smoking (47). An analysis of National Health and Nutrition Examination Survey (NHANES) data compiled from 1999 to 2004 found that both depression and anxiety were higher among adolescent ever-smokers compared to never smokers (48). A 2005 study of US adolescents ages 14-18 (n=486), a variety of internalizing mental health conditions were found to be associated with current cigarette smoking (49). Among a sample of Canadian students (n=6943), having taken medication for depression or anxiety was significantly associated with current smoking (50). A cross-sectional study of adolescents in Brazil (n=73399) found that psychological distress was positively

associated with cigarette smoking (51). The results of these studies, in addition to the previously mentioned studies in this section, demonstrate that at a single point in time, cigarette smoking may be associated with a variety of internalizing mental health problems. Indeed, only one cross-sectional study reported no association between nicotine use and internalizing factors. Specifically, Hanna et al., 2001 found that using NHANES data, smoking was not associated with depression among adolescents (52).

While cross-sectional studies show there is a positive association between cigarette smoking and internalizing mental health problems, longitudinal studies have been able to provide details about the direction of this association. Several longitudinal studies examined the effect that smoking during adolescence had on the subsequent development of internalizing factors. A cohort study of US adolescents collected data in 1989 and 1994 (n=1731), finding that smoking increased the risk for onset of depressive symptoms (53). Using the 1996-1997 waves from the National Longitudinal Study of Adolescent Health (NLSAH), Goodman & Capitman found that current smoking predicted depressive symptoms one year later (54). The Ontario Child Health Study followed Canadian adolescents from 1983-2001 (n=1282), finding that smoking during adolescence was associated with an increased risk of depression in young adulthood (55). These studies provide evidence that cigarette smoking during adolescence increases the risk of developing depressive symptoms later on.

Two longitudinal studies also examined how adolescent smoking impacts future development of anxiety. A three-wave longitudinal study of US adolescents (n=1709) examined the relationship between daily smoking and anxiety, finding that daily smoking during adolescence (approximately age 16) increased the risk of experiencing panic

attacks and developing a panic disorder in young adulthood (approximately age 24) (56). A longitudinal community study examined the association between cigarette smoking in adolescence and the development of anxiety disorders in young adulthood, finding that heavy smoking during adolescence was associated with a higher risk of generalized anxiety disorder, agoraphobia, and panic disorder as young adults; however, the presence of anxiety disorders in adolescents was not associated with smoking in adulthood (57). These studies suggest that adolescent smoking increases the risk for developing internalizing problems related to anxiety.

While the previously mentioned longitudinal studies found that smoking increases the risk for developing internalizing mental health problems, some longitudinal studies found the opposite. Indeed, the following studies suggest that the presence of internalizing factors during adolescence is associated with subsequent smoking. Longitudinal data from the 1986 and 1993 waves of the teenage attitudes and practices survey showed that adolescents reporting depressive symptoms at baseline were more likely to initiate smoking in the second wave, four years later, than adolescents without baseline depressive symptoms (58). Another examination of NLSAH data found that among never smokers (n=5475), depressed mood increased the risk for smoking initiation (59). A longitudinal study of US adolescents from 1988 to 1998 (n=1205) found that depressive symptoms were predictive of continued smoking at follow up (60). A study of US adolescents (n=2460) conducted in 2013-2014 found that depressive symptoms at baseline increased the risk for onset of cigarette smoking (61).

Among US adolescents who participated in the National Population Health Survey (n=1027), after 10 years, adolescents with depressive symptoms at baseline were

at a higher risk of smoking compared to adolescents without depressive symptoms (62). Among a sample of 1801 Canadian adolescents, depressive symptoms were a risk factor for smoking initiation in early and middle adolescence (63). Using a cohort study of US 6th and 7th graders (n=1699), depressive symptoms at baseline were associated with smoking initiation at follow up, and depressive symptoms at baseline were associated with an increase in frequent smoking among adolescents who reported smoking

Two studies found that this association existed for symptoms and conditions beyond depression. Indeed, in a cohort of Australian adolescents (n-2302), both depressive symptoms and anxiety symptoms were associated with an increased likelihood of smoking initiation (64). Using the National Epidemiologic Survey on Alcohol and Related Conditions, a US cohort study with waves from 2001-2002 and 2004-2005 (n=34,653), researchers found that individuals with internalizing conditions (i.e., depression, dysthymia, general anxiety disorder, social phobia, agoraphobia, and panic disorder) had higher odds of initiating smoking than those without those conditions (65). These studies suggest that the presence of internalizing mental health symptoms, including depression and anxiety, during adolescence increases the risk for initiating cigarette smoking.

Several longitudinal studies also found a bi-directional relationship between tobacco use and internalizing factors. Using a sample of Hong Kong Chinese adolescents (n=1894), current and former smokers had more depressive symptoms compared to never smokers at both waves. Additionally, there was a multidirectional relationship between depressive symptoms and smoking between waves, where smoking at the first wave increased the risk of worsening depressive symptoms in the second wave, and depressive

symptoms at the first wave increased the risk of smoking initiation at the second wave (66). A sample of US adolescents (n=688) showed that smoking during adolescence increases the risk of depressive symptoms in adulthood, and depressive symptoms during adolescence predict smoking in adulthood (67). Brown et al. found in prospective analyses that smoking at baseline increased the risk of developing major depressive disorder. Additionally, they found that prevalence of major depressive disorder was a significant predictor of smoking onset (68). These studies suggest a bidirectional relationship between internalizing mental health symptoms and cigarette smoking.

These studies, when taken together, overwhelmingly suggest that cigarette smoking and internalizing mental health problems are positively associated among a variety of populations of adolescents. However, many of these studies are dated. As cigarette smoking is now at a historical low, and mental health problems appear to be on the rise, there is a need to understand how this relationship is changing using recent data that reflects changes in tobacco use patterns.

Aim 1a: Internalizing mental health symptoms are associated with the use of e-cigarettes and/or other nicotine products among adolescents.

More recent cross-sectional studies have evaluated other tobacco products besides cigarettes, most often e-cigarettes. A recent study using US Adolescents Risk Behavior Survey (YRBS) data from 2015 and 2017 found that e-cigarette users were more likely to report depressive symptoms than non-users (69). Another study of South Korean adolescents (n=5405) found that those who reported past 30 day e-cigarette use were more likely to report symptoms of depression than those who did not (70). These studies

provide evidence from two different populations of adolescents that e-cigarette use is associated with symptoms of depression.

Two studies examined internalizing mental health problems beyond depression. In a study of university students (n=9449), e-cigarette use was significantly associated with symptoms of anxiety (71). A cross-sectional study of US college students (n=631) in 2016 found that e-cigarette use was more prevalent among those with diagnoses of a variety of internalizing mental health conditions, including depression and anxiety (72). Adding to the findings from the previous paragraph, these studies show positive, cross-sectional associations between e-cigarette use and internalizing mental health symptoms.

Multiple studies found that while current e-cigarette use was associated with increased risk of internalizing mental health symptoms compared to non-use, the strength of the association varies by whether adolescents exclusively use e-cigarettes, exclusively use cigarettes, or "dual use" both products. In particular, some studies suggest that internalizing mental health symptoms are more strongly associated with dual use and exclusive cigarette use than with exclusive e-cigarette use. One study found that among US adolescents (n=2488), compared to non-users, those reporting e-cigarette use were more likely to report anxiety symptoms but not depressive symptoms. However, exclusive e-cigarette users were less likely to report symptoms of anxiety and depression compared to exclusive cigarette or dual users (73). Similarly, another study found that among US 9th graders (n=3310), adolescents reporting exclusive e-cigarette use had higher internalizing problems compared to non-users, but fewer internalizing problems compared to exclusive cigarette or dual users (74). The same pattern of results was found among a sample of high schoolers living in Hawaii (n=1941), where e-cigarette users

were more likely to report higher internalizing factors than non-users; however, dual users of e-cigarettes and cigarettes were more likely to report those outcomes than exclusive e-cigarette users (75). These studies suggest that adolescents who use e-cigarettes exclusively may be at lower risk for internalizing mental health problems compared to those who use cigarettes or dual use of cigarettes and e-cigarettes.

Only two cross-sectional studies have explicitly examined the gradient of exclusive e-cigarette, cigarette, and dual use and its association with internalizing mental health. A cross-sectional study of South Korean adolescents (n=62,276) found that exclusive e-cigarette users had a higher prevalence of depressive symptoms and suicidality compared to non-users; furthermore, prevalence of depressive symptoms were highest among dual users, followed by exclusive e-cigarette users, and exclusive cigarette users (76). While this study provides contradicting results with the previously mentioned studies, it does support that there are differences in association between different types of tobacco products and internalizing mental health.

The other cross-sectional study with distinct results found no association between e-cigarette use and internalizing mental health symptoms. Indeed, a 2018 study of Irish adolescents (n=4422) found that after adjusting for family, peer, and community influence, there was no association between cigarette, e-cigarette, or dual use and poor self-reported mental health (77). Of note, this study did find statistically significant associations in univariate models, suggesting that the adjustment variables (e.g., family or peer influence) may account for the association. Taken together, these cross-sectional studies suggest that the relationship between tobacco use involving multiple types of

products is complex, may rely on a number of factors, and needs more research to better elucidate which adolescents are most at risk.

Longitudinal studies examining the direction of association between e-cigarette, cigarette, and dual use and internalizing mental health problems found a variety of results. Two studies examined waves 1 and 2 (2013-2015) from the Population Assessment of Tobacco and Health (PATH) study, a nationally representative longitudinal study including US adolescents and young adults. The first study, which included a total sample of adolescents ages 12-17 that had never used tobacco products at baseline (n=7702), found that adolescents with high internalizing problems at baseline were at an increased risk of initiating exclusive e-cigarette use at wave 2, but not use of combustible cigarettes or dual use (78). The second study examined only exclusive cigarette use vs. any cigarette use (combining exclusive cigarette and dual use), resulting in a total sample of respondents ages 12-17 (n=8219). This study found that the presence of internalizing factors were associated with a higher likelihood of subsequent cigarette and e-cigarette initiation; however, there was not a significant difference in the strength of association with type of products used (79). These two studies used similar data but slightly different approaches and both found that internalizing problems at baseline increased likelihood of subsequent e-cigarette initiation; however, differences in categorization appear to have resulted in different results for cigarette and dual use results.

Longitudinal studies from other data sources had varying results. Similar to the previously mentioned PATH study focusing on exclusive e-cigarette and any cigarette use, a longitudinal study of US adolescents (n=2460) conducted in 2013-2014 found that

depressive symptoms at baseline increased the risk for onset of exclusive e-cigarette and cigarette use; however, risks for onset of each category were not significantly different from each other (61). Alternatively, a longitudinal study of US adolescents from 2015-2017 (n=2039), there was a bi-directional association between cigarette use and poorer mental health; however, e-cigarette use was not associated with poorer mental health in either direction (80). Finally, in a longitudinal study of US college students (n=3757), baseline symptoms of depression and anxiety were not significantly associated with reporting ever use or current use of cigarettes or e-cigarettes one year later (81). The conflicting results from these studies suggest that more research is needed to understand differences in risk of internalizing mental health problems across different cigarette and e-cigarette use patterns.

Only one study reported examining the relationship between internalizing mental health and a wider variety of tobacco products. Using waves 1 and 2 from the PATH study, and including 12-24 year-olds (n=10533), this study examined tobacco use including cigarettes, e-cigarettes, cigars, cigarillos, pipe, hookah, smokeless tobacco, snus, bidis, kreteks, and dissolvable nicotine. Results showed that those with high severity of internalizing problems at wave 1 were more likely to begin to use any tobacco product (e.g., all products combined). When examining the likelihood of initiating each individual tobacco product, high-severity internalizing problems at baseline were associated with initiation of cigarettes, cigars, cigarillos, hookah, and e-cigarettes, with strength of association in that order from greatest to least. Smokeless tobacco was not associated. Of note, there was not enough statistical power for models involving pipes, kreteks, snus pouches, bidis, and dissolvables, suggesting a need for a bigger sample size

(82). At the present, this is the only study that examine the relationship between nicotine and mental health considering tobacco products beyond cigarette and e-cigarette use. While prevalence of these products is low, there is still a need to understand how adolescents who use different types of tobacco products may be at risk for mental health conditions or vice versa.

These more recent studies provide some evidence that e-cigarette use and internalizing mental health symptoms are positively associated. Studies that include both e-cigarette and cigarette use found differences in association between exclusive use of either product and dual use of cigarettes and e-cigarettes; however, the patterns of strength of association were not consistent across studies. Furthermore, only one study examined nicotine products beyond cigarettes or e-cigarettes. Results from this study suggest a gradient of risk for combustibility, as the combustible products tended to be more strongly associated with internalizing mental health than e-cigarettes; however, given that this is a singular study with small samples sizes of use for other tobacco products and other non-e-cigarette nicotine products were not included, there is a need for a deeper look. The present study will be able to further elucidate the relationship between a wider variety of nicotine products and their associations with internalizing mental health based on combustibility.

Aim 1a: There is limited evidence of how the relationship between internalizing mental health symptoms and nicotine use among adolescents has changed over time.

Very few studies have explicitly examined time trends of smoking and mental health. Indeed, a study that compared two waves of a survey from 1998 to 2008 among Finnish adolescents, found that while smoking rates decreased significantly, there were

few significant changes in internalizing or externalizing symptoms, suggesting the two may not be related, or that the strength of association has changed over time (83). Similarly, a longitudinal study of US adolescents from 2015-2017 (n=2039) found that frequencies of cigarette and e-cigarette use increased over time, whereas frequencies of mental health symptoms did not (80). However, a more recent study, which considers the impact of COVID-19 on this relationship, found that among a sample of adolescents in Iceland (n=59701) with waves from 2016-2020 (before and during the COVID-19 pandemic), depressive symptoms and worsened mental wellbeing increased significantly during the COVID-19 pandemic, whereas cigarette and e-cigarette use decreased (84). Due to the limited number of studies that examine this change over time, specifically considering the COVID-19 pandemic, there is a need for more recent studies across different regulatory contexts.

While there are limited studies examining time trends of tobacco use and mental health over the COVID-19 pandemic, there are more that examine time trends for tobacco independently of mental health and explore the reasons behind these trends. Studies showing decreases in tobacco use among adolescents over the pandemic found that reasons included decreased social interaction and increased concerns about health (23,85,86). These factors may also explain increases in mental health symptoms among adolescents, which have been found in other studies without a focus on tobacco (87,88). While these studies do not explicitly examine the relationship between tobacco use and mental health, they suggest that over time, the pandemic led to a decrease in tobacco use and an increase in internalizing mental health symptoms, both of which may stem from the stress of living through a pandemic, decreased social interactions, and concerns about

health, among other reasons. The present study will be able to confirm whether these suggestions are true and clarify how the relationship between tobacco use and mental health has changed from 2020-2022, including as the impact of COVID-19 has waned.

Aim 1b: The association between internalizing mental health symptoms and current nicotine use will be different across different sociodemographic characteristics.

Nearly all of the previously mentioned studies assessed the effect of sex on the relationship between tobacco use and internalizing mental health symptoms. Many found that the relationship is between tobacco use and internalizing mental health is stronger for females compared to males (42,45,48,49,57,59,65). Two cross-sectional studies found that the relationship between cigarette smoking and internalizing factors was only significant among females. A study of US middle schoolers (n=3261) published in 2003 found that past 30-day cigarette smoking was associated with depression among females but not males (44). A nationally representative study of US 7th-12th graders found that females who reported depressive symptoms were also more likely to report current smoking, but this association was not significant among males (45). These studies suggest that the relationship between tobacco use and internalizing mental health symptoms is stronger among females compared to males.

Alternatively, one study found that the relationship was stronger for males compared to females (89) and two studies found that tobacco use and internalizing mental health were associated among males but not females. Among a cohort of US high schoolers (n=1901), depressive symptoms were significantly associated with subsequent smoking initiation among males, but not among females (89). Another study found that among a sample of Hungarian adolescents (n=215), the positive association between

mental health symptoms and cigarette smoking was significant among males but not females (46). These studies suggest that the relationship between tobacco use and internalizing mental health symptoms is stronger among males compared to females. The remaining studies reported including sex or gender as a moderator in their analyses and found no association, with the relationship between tobacco use and mental health being similar regardless of sex or gender (40,50,63,64,66,68,90,91). Taken altogether, this mixed evidence suggests that sex or gender may moderate the relationship between tobacco use and internalizing factors among adolescents; however, this may depend on a number of factors, including the study population, inclusion of different covariates in adjusted models, and how recently the study was conducted.

At the time of this review, no studies explicitly examine the relationship between tobacco use and mental health among gender minority adolescents. One cross-sectional study of the 2021 NYTS (n=16065) examined this relationship among sexual minority adolescents (e.g., gay, lesbian, bisexual), finding that sexual minority males with internalizing mental health problems were more likely to use e-cigarettes than heterosexual males with internalizing mental health problems (92). Many of the above studies found that gender and/or sex are associated with internalizing mental health symptoms; however, given the growing number of adolescents identifying as gender minorities and their high risk for mental health problems, there is a need for research on the association for gender minority adolescents.

While some sociodemographic characteristics have been studied extensively as moderators of tobacco use and mental health, many gaps remain. For example, while there is abundant evidence related to sex and gender, there are no studies examining

gender minorities. More evidence is needed to solidify age and race as potential moderators of the association between tobacco use and mental health. Finally, there are no studies that examine how this association varies across different countries. The present study aims to fill all of these gaps.

Aim 1a. Among participants who used any nicotine products in the prior 30 days, examine the relationship between internalizing mental health symptoms and characteristics of product use

In examining the association between tobacco use and mental health, there is evidence, albeit limited, that different types of tobacco use are more strongly associated with internalizing mental health symptoms, including poly-tobacco use. As mentioned under Aim 1a, there appears to be a gradient in the strength of association between tobacco use and mental health depending on the product; however, to our knowledge, concurrent use of multiple products has only been examined for dual use of cigarettes and e-cigarettes.

Several studies found that dual use of cigarettes and e-cigarettes was associated with a higher likelihood of internalizing mental health problems than exclusive e-cigarette use. One study found that among US adolescents (n=2488), exclusive e-cigarette users were less likely to report symptoms of anxiety and depression compared to dual users (73). Another study found that among US 9th graders (n=3310), adolescents reporting exclusive e-cigarette use had fewer internalizing problems compared to dual users (74). A similar same pattern of results was found among a sample of high schoolers living in Hawaii (n=1941), where dual users of e-cigarettes and cigarettes were more likely to report those outcomes than exclusive e-cigarette users (75). A cross-sectional

study of South Korean adolescents (n=62276) found that prevalence of depressive symptoms were highest among dual users, followed by exclusive e-cigarette users, and exclusive cigarette users (76). These studies suggest that dual use of cigarettes and e-cigarettes increases the likelihood of experiencing internalizing mental health problems among adolescents.

Two studies found differing results when comparing dual use to exclusive e-cigarette use. A PATH study including adolescents ages 12-17 (n=7702) found that adolescents with high internalizing problems at baseline were at an increased risk of initiating exclusive e-cigarette use at wave 2, but not dual use (78). Another PATH study of US respondents ages 12-17 (n=8219) found that the presence of internalizing factors was not differentially associated between dual use of exclusive e-cigarette use (79). Given that both of these studies are longitudinal, there may be a difference in cross-sectional relationships between dual use and exclusive product use compared to longitudinal relationships. For example, longitudinal analyses of the relationship between substances and mental health may be affected by intervening events between survey waves, such as a change in mental health status over time.

At the present, no studies examine poly-tobacco use compared to single product or dual use and its association with mental health. However, given that dual use of cigarettes and e-cigarettes increases the likelihood of reporting internalizing mental health problems in several studies compared to single use, there could be a further increase with an increased number of products. Furthermore, research shows that multiple tobacco product use among adolescents increases the risk of nicotine dependence and continuation of tobacco use into adulthood (22). This suggests that poly-

tobacco use may be more strongly associated with internalizing mental health symptoms than single product or dual use. The present study will be able to examine multi-product use beyond dual use of cigarettes and e-cigarettes, including more recently popularized nicotine products such as nicotine pouches, which have not yet been examined.

Aim 2a&2b: Among participants reporting current use of cigarettes or e-cigarettes, internalizing mental health symptoms will be associated with nicotine dependence

In examining the association between tobacco use and mental health there is evidence, albeit limited, that different patterns of tobacco use are more strongly associated with internalizing mental health symptoms, including frequency or heaviness of tobacco use, poly-tobacco use, addiction and/or nicotine dependence, intentions to quit, having a quit attempt, and age of product use initiation. The following subsections review studies that present results on samples of participants who have experience with nicotine use or focus results on comparisons of participants of different characteristics of tobacco use.

Nicotine dependence is defined as the physical and psychological factors that make it difficult for a person who uses tobacco products to stop (93). Many measures of nicotine dependence exist. The Faegerstrom test of nicotine dependence focuses on the number of cigarettes smoked per day, how long after waking up an individual smokes their first cigarette, and several other behaviors indicative of addiction to nicotine (94). The Wisconsin Inventory of Smoking Dependence and Motivations (WISDM) focuses on a variety of theory-derived motives that suggest reliance on nicotine (95). The assessment for tobacco dependence using the Diagnostic and Statistical Manual of Mental Disorders (DSM) is comprised of symptoms of withdrawal and tolerance for nicotine (96). Among

adolescents, specific measures of nicotine dependence have been developed to account for the sporadic and irregular pattern of smoking behaviors seen in adolescents, including the Hooked on Nicotine Checklist and the Standard Dependence Index (97). Unfortunately, these measures are lengthy and not ideal for a brief survey. Measures of 'perceived addiction' involve directly asking individuals how addicted they perceive themselves to be to a tobacco product and are positively associated with measures of nicotine dependence (98).

Very few studies examined the association between nicotine dependence/addiction and mental health; however, the results were similar across studies. The following studies all measured nicotine dependence using DSM criteria. A study published in 2011 examined the relationship between tobacco use (cigarette, pipe, and cigar) and subsequent suicidality among Mexican adolescents (ages 12-17) using the Mexican Adolescent Mental Health Survey, finding that nicotine dependence (i.e., according to the DSM-IV) was positively associated with suicidality (99). In 2000, a longitudinal community study of adolescents and young adults (n=3021) investigated associations between social anxiety and nicotine dependence (i.e., according to the DSM-IV), finding that among smokers, symptoms of social anxiety were associated with higher rates of nicotine dependence whether assessed cross-sectionally or longitudinally (100). Finally, a cohort study of adolescent New Zealanders (n=947) found a positive association between baseline depression and subsequent nicotine dependence (i.e., according to the DSM-III) (90).

These studies all suggest that among adolescents who use tobacco products, those who are more nicotine dependent may experience more internalizing mental health

problems than those who are less dependent. However, no studies examine the association between perceived addiction and internalizing mental health. The proposed dissertation will be able to examine how perceived addiction may or may not be related to internalizing mental health among cigarette or e-cigarette users.

Many studies report on the frequency or heaviness of tobacco use as a factor related to intensity of mental health symptoms. A study of European adolescents (n=12,328) found that daily smokers reported higher levels of anxiety and depression than non-daily smokers (44). A study of US adolescents (n=1709) found that experiencing panic attacks was associated with daily smoking but not non-daily smoking (56). Among a sample of Canadian students (n=6943), adolescents who identified as regular smokers had higher likelihood of depression or anxiety than those who identified as irregular smokers (50). A cross-sectional study of adolescents in Brazil (n=73399) found that psychological distress was more likely among adolescents reporting frequent smoking (i.e., smoking at least 7 days in a row) compared to those who did not report frequent smoking (51). A longitudinal community study found that the frequency of cigarette smoking (i.e., occasionally-very often) during adolescence was associated with increased risk of developing anxiety (57).

Only two studies examined the association between frequency of e-cigarette use and mental health. Indeed, a study of US adolescents (n=2460) conducted in 2013-2014 found that among participants using e-cigarettes, frequency of e-cigarette use and depressive symptoms were positively associated; however, this association was not found among cigarette users (61). Alternatively, a study of US adolescents (n=2488) found that among participants reporting exclusive e-cigarette use (n=325), symptoms of anxiety and

depression were not associated with frequency of e-cigarette use (73). The majority of studies have found a positive association between frequency of tobacco use and internalizing mental health problems. However, frequency of tobacco use was measured in many different ways (e.g., daily vs. non-daily, perceived frequency, weekly vs. monthly, etc.). Furthermore, as only two studies examined e-cigarette use, with inconsistent results between the two, more research is needed. The proposed study will be able to examine frequency of cigarette and e-cigarette use in all of the previously mentioned ways and will provide more evidence regarding the relationship for e-cigarette use.

Quit Intention and Quit Attempts

Very few studies have examined how intentions to quit, having a quit attempt were related to internalizing mental health among adolescents. Using a sample of n=1894 Hong Kong Chinese adolescents, among those who reported smoking (n=229), smokers who did not want to quit or had not tried to quit at baseline had higher depressive symptoms 12 months later than smokers who succeeded at quitting (66). Participants in a cohort study in the US who reported current smoking and internalizing mental health conditions at baseline were less likely to quit than smokers without those conditions (65). No studies examined the association between quit intention and internalizing mental health symptoms. While limited, these studies suggest that positive cessation behaviors may be a protective factor for mental health among adolescents. Alternatively, perhaps adolescents without mental health problems are more able to quit or to think about quitting. More research is needed to better understand how intentions to quit, having a quit attempt are related to internalizing mental health problems. Furthermore, no studies

examine intentions to quit, having a quit attempt of e-cigarette users. The proposed study will be able to examine intentions to quit, having a quit attempt of both cigarette and e-cigarette users and how they relate to internalizing mental health symptoms.

Policy Background

According to data from the International Tobacco Control (ITC) Adolescents Vaping survey in 2018, past 30-day e-cigarette use was reported by 9% of adolescents in England, 15% in Canada, and 16% in the US; meanwhile, pat 30-day cigarette smoking was reported by 17% of adolescents in England, 15% in Canada, and 12% in the US (101). Given these differences, it is important to understand the different policy climates in these three countries. Table 2.1 summarizes the major tobacco regulations related to tobacco use among adolescents.

From a global perspective, one of the key differences between Canada, England, and the US is their approach to the World Health Organization Framework Convention on Tobacco Control (FCTC), which recommends a variety of best-practices to reduce tobacco use (e.g., taxes, smoke-free, ad bans, prominent pictorial warning labels). Both Canada and England ratified the FCTC in 2004, as have the majority of countries in the world, whereas the US has not yet ratified it (102). While the US has implemented many of the FCTC components into its own tobacco regulation, failure to ratify the FCTC has caused domestic policy delays and decreased credibility on the global stage (103).

Warning label and product packaging policies also differ across the three countries. In 2001, Canada was the first country to adopt prominent pictorial health warning labels (PHWLs) on the outside and health information messages on the inside of cigarette packages and implemented plain packaging for all tobacco products in early

2020 to add to its policy (104,105). England implemented plain packaging for all cigarette and hand rolling tobacco packaging in 2017 (106). In England, PHWLs have been required on all smoked and smokeless tobacco products since 2010 (107). In the US, there is no proposal for plain packaging. The FDA has approved PHWLs; however, they have so far been successfully challenged by the tobacco industry. Consequentially, the packaging and labeling policies in the US are by far the most relaxed, only requiring small text warning labels on all tobacco products. All three countries only require text warning labels on e-cigarettes with a similar warning focusing on the addictiveness of e-cigarettes (108).

Because Canada and the US are broken up into provinces or states, some regulations vary throughout the country (108). For example, smoke-free policies vary across sub-national jurisdictions. In England, most public places and public transport are 100% smoke free (108). Smoke-free policies in Canada tend to include all tobacco products, whereas smoke-free policies in England and the US tend to include only smoked tobacco products (108). Another factor that differs across countries, but is particularly relevant when studying adolescents, is the legal age of sale of tobacco products, which is 18 in England, 19 in Canada, and 21 in the US (107). However, implementation in Canada and the US varies across provinces/states.

All three countries have different regulations for flavors of tobacco products, and flavors are a key reason that adolescents choose to start using a tobacco product (109). In Canada, all non-menthol flavors have been banned for cigarettes and little cigars since 2010 and menthol flavored cigarettes have been banned since 2016 (108). Health Canada proposed a ban on all e-cigarette flavors in 2021, but it has not been enacted (110). Since

2016, all cigarette flavors have been banned in England; however, they have not banned any flavors for e-cigarettes (108). In the US, all flavors are banned in cigarettes except menthol. E-cigarette flavor bans vary by state and locality (108). Bans on menthol cigarettes in England and Canada led to a substantial decrease in adolescents menthol smoking, whereas such a ban does not exist in the US at the national level, where rates of menthol cigarette smoking are substantially higher than the other two countries (111).

E-cigarettes were not legally on the market in Canada until May 2018 (112), whereas they were readily available in the US and UK for many years before that, with particularly relaxed regulations in the US. In 2019, 18% of US adolescents, 17% of Canadian adolescents, and 12% of English adolescents reported past 30-day vaping (113). When cartridge or pod flavor bans were implemented in the US, disposable e-cigarettes, which were exempt from the ban, became the dominant type of e-cigarette used; whereas this is not the case in Canada (109). However, disposable e-cigarettes are becoming more common in Canada as well (114). Disposable e-cigarettes emerged in the UK in 2022, most commonly in the brand name Elfbar, and have led to an exponential increase in vaping prevalence in England (114,115). In England and Canada, there is a cap on the legal concentration for nicotine in e-cigarettes of 20 mg/ml (107). In the US, no such cap exists. In light of these policy differences, the proposed study aims to examine differences across these countries that could be explained by policy difference.

Significance

As tobacco use remains the leading cause of preventable disease (1) and the evolving nicotine market poses new risks, particularly for young people who are also at risk for mental health problems, there is a need to better understand how nicotine use and

mental health are related among young people. Overall, the proposed dissertation aims to examine the relationship between nicotine use and mental health among adolescents in three different countries, which characteristics mediate and moderate this relationship, and how this relationship has changed over time.

Aim 1 of the proposed dissertation is to examine the relationship between internalizing mental health symptoms and nicotine use. Furthermore, Aim 1 will examine how the relationship changed over time, specifically during the COVID-19 pandemic. Additionally, this aim will examine which participant characteristics are related to internalizing mental health symptoms (i.e., symptoms of depression and symptoms of anxiety). This is important because there is a lack of research examining these relationships in recent years, which have involved both diversification of nicotine products and the COVID-19 pandemic, both of which may have impacted the relationship between adolescents nicotine use and mental health.

Aim 1a will specifically examine changes over time by including data from both before, during, and after the acute phase of the COVID-19 pandemic. Given the salience and novelty of COVID-19, as well as concerns about future pandemics, there is a need to better understand how nicotine use and mental health have changed among adolescents during recent years. Conversations about mental health have become less stigmatized and the awareness of the struggles of adolescents have increased during this time period. Consequentially, improving our understanding of how mental health and nicotine use have changed can be used to develop interventions and policies that can improve the mental health of adolescents and decrease nicotine use as we continue to recover from the acute phase of the COVID-19 pandemic and begin preparing for future pandemics.

Aim 1b will build on this analysis by examining which sociodemographic characteristics affect the relationship between internalizing mental health symptoms and nicotine use, with a focus on gender identity. Studies have already found that the association between nicotine use and internalizing symptoms is stronger for female adolescents compared to male adolescents (42,44,45,48,49); however, this association has not yet been examined beyond binary sex categories. This dissertation will add to that literature using large, national samples from three different countries and including both cisgender and non-cisgender adolescents. It is important to know not only whether the relationship exists and how it has changed over time, but also which characteristics are most strongly related to the relationship. This information can be used to inform targeted interventions for the higher risk subgroups of adolescents defined by gender identity (e.g., targeted campaigns, implementing mental health screening in schools or in primary care settings, cessation programs targeting adolescents with mental health conditions).

Finally, Aim 2 aims to examine the specific characteristics of nicotine use and their relationship with internalizing mental health among adolescents. Studies of nicotine use amongst adolescents usually define tobacco use as either having used a tobacco product in the past 30 days or ever using a tobacco product (116–125). Some studies also consider yearly or weekly use of a tobacco product as current tobacco use (126–128). Other studies have measured susceptibility to use various tobacco products (129–133). Studying tobacco use in this manner is no longer sufficient given the changing landscape of available nicotine products. Indeed, studies increasingly evaluate other characteristics of current tobacco use, including the number of different tobacco products used (116,134–137), grouping products based on whether they are combustible or not

(120,125,138), and frequency of product use (122,139,140). This dissertation will examine nicotine dependence and cessation variables which have not yet been examined as they relate to internalizing mental health. This will greatly expand our understanding of how the diversity of nicotine use patterns and mental health are related among adolescents in recent years, which is currently limited to cigarettes and e-cigarettes. Several studies provide evidence of differences in association for nicotine dependence, having a recent quit attempt, and frequency of use. However, this study would examine all of these characteristics with a national sample from three different countries and with consideration for sociodemographics and changes over time.

Innovation

The proposed dissertation is innovative in several ways. First, it will be the first study of moderators of mental health and nicotine use among adolescents in the context of the COVID-19 pandemic. While past literature has examined the relationship between tobacco use and mental health prior to COVID-19, there are so far no studies that describe how COVID-19 may have impacted the relationship. Given that COVID-19 is ongoing, with future, similar outbreaks forecast, it is essential to provide an up-to-date description of the situation among adolescents to inform intervention and policy development moving forward.

The proposed dissertation will also explicitly analyze participant sociodemographic differences in the relationship between nicotine use and mental health. Specifically, there will be a focus on differences between cis-gender and non-cisgender adolescents, which has not yet been examined. Research on gender minority adolescents is lacking in general, due to data sources with too small sample sizes (measuring sex).

This dissertation will include a data source with a large enough sample that there should be sufficient statistical power to examine gender minority adolescents, and to examine differences across countries. Furthermore, as the number of adolescents identifying as gender minority adolescents has increased in recent years, this dissertation will be able to provide an up-to-date examination of this increase and how it relates to mental health and nicotine use. If the prevalence of adolescents who identify as gender minorities stabilizes or continues to increase, innovative studies like this one can provide an understanding of the risk factors these adolescents face, thereby informing efforts to improve their health.

Another innovative component of the proposed study is the cross-country comparison, which aims to evaluate whether the associations between nicotine use and internalizing mental health symptoms vary across countries. At the present, no studies have examined differences in these associations across different populations, which can provide insight to country-level differences. Consequentially, this study can identify associations that are consistent across different markets and policy environments.

Finally, the proposed dissertation is innovative in that it will examine nicotine use characteristics (i.e., which combinations of product(s) are being used, number of products being used, combustibility of products being used; for cigarette and/or e-cigarette use, frequency of use, having a quit attempt, quit intention, perceived addiction) which have not yet been examined as they relate to mental health among adolescents. As the nicotine market diversifies and adolescents nicotine use characteristics change, innovative studies like these are needed to ensure that we understand how these changes relate to mental health and thereby the overall health of the adolescent population, which in turn informs their health as future adults.

Tables and Figures

Table 2.1 Examples of Policy Differences Between Canada, England, and the USA as of February 2020

		Canada[1]	England	USA[2]
Regulatory Frameworks	WHO FCTC	Ratified in 2004	Ratified in 2004	Not ratified
Labeling and Packaging	Plain packaging	Implemented for all tobacco products in Feb 2020	Implemented for all cigarette and hand rolling tobacco packaging in May 2017	Not implemented
	Warning Labels	**Cigarettes & Little Cigars:** Pictorial health warning labels (PHWLs) cover 75% of front and back of pack Contain health information messages inside packs **Roll your own tobacco, kreteks, leaf tobacco:** PHWLs cover 50% of the display area on both sides Contain health information messages outside or inside of packaging **Other Combustible Products:** Text-warnings cover 50% of display area on both sides **Smokeless Tobacco Products:** Text warnings cover 50% of display area on both sides	**All smoked tobacco products:** PHWLs cover 65% of the pack **Smokeless Tobacco Products:** PHWLs cover 40% of the pack required for all tobacco products **E-cigarettes:** Text-warnings required	Text warnings required for all tobacco products

[1] With some differences in provincial level regulation
[2] With some differences in state level regulation

		E-cigarettes: Text-warnings required, sizes vary		
	Unit Packaging for Cigarettes	Minimum of 20	Minimum of 20	Minimum of 20
Public Regulations	Smoke-free Policies in Public Places	Varies by province	Only for smoked tobacco products Most public places and transport are 100% smoke free	Varies by state
Flavors		**Cigarettes & Little Cigars:** All flavors banned **E-cigarettes:** No flavors banned	**Cigarettes;** All flavors banned **E-cigarettes:** No flavors banned	**Cigarettes:** All flavors except menthol banned **E-cigarettes:** Varies by state and locality, some states/localities have enacted bans on all flavors
Nicotine concentration cap		**E-cigarettes:** 20 mg/ml	**E-cigarettes:** 20 mg/ml	**E-cigarettes:** None
Age of Sale	All tobacco products	18-19 (varies by province)	18	18 or 21 (varies by state)
Available products	E-cigarettes	Legally available in 2018	2007	2007
	Nicotine pouches	Not legally available	2019	2019

Chapter 3: Research Design and Methods

Overview

The overall goal of the proposed dissertation is to describe how nicotine use and internalizing mental health symptoms are related among adolescents in the US, England, and Canada, moderators of this relationship, and how this relationship has changed over the past two years. The data for this dissertation will come from the International Tobacco Control Policy Evaluation Project (ITC) Adolescents Tobacco and Vaping Survey. This national repeat cross-sectional survey is conducted in England, Canada, and the United States. These are three high-income countries with different regulatory frameworks for tobacco, which allow for rigorous examination of tobacco use patterns. Participants in the study answer questions about their experience with and beliefs about tobacco products, sociodemographic characteristics, and their experience with mental health symptoms.

Study design

This study will use five waves of the ITC Adolescents Tobacco and Vaping Survey conducted between 2020-2022. The surveys were conducted twice in 2020 (February 6 to March 2; August 7-31), twice in 2021 (February; August), and once in 2022 (August). The survey took approximately 20 minutes and was available in English in all countries, plus French in Canada. Survey items included sociodemographic measures and questions about tobacco use. An attention check was presented to respondents during the survey to ensure data integrity. Participants who failed the

attention check (i.e., selected the wrong month when asked what the current month is) were excluded from the analytic sample.

Sample and recruitment

Participants were recruited from the Nielsen Consumer Insights Global Panel, which recruits participants using both probability and non-probability samples. For each survey, Nielsen selected random samples from panels in each country, with a final sample of 4,500 participants was targeted for each country at each survey.

A non-probability based random selection of panelists, parents of panelists (for participants under 18), or panelists with children ages 16-19 received email invitations with a unique survey link to screen for eligibility. Eligible participants were between the ages of 16 and 19 living in each of the three target countries. After reviewing information about the study and consenting to participate, eligible participants completed the survey. Participants received renumeration in accordance with the panel incentive structure, which included point-based rewards, monetary rewards, and/or chances to win monthly prizes.

Measures

All original measures are shown in Table 3.1. Succinct descriptions of the measures and plans for categorization of sociodemographic variables and measures related to each aim are provided below.

Sociodemographic characteristics

Participants were asked which country they live in: Canada, the USA, or England, which will be used as an indicator of location. For each data collection wave, a wave indicator was generated which will be used to differentiate between waves.

Participants indicated their age: 16, 17, 18, or 19. Sex will be categorized as 'male' and 'female.' Participants were asked, "What is your current gender identity?" with response options 'Man', 'Woman', 'Trans male/ trans man', 'Trans female / trans woman', 'Gender queer / Gender non-conforming', or 'Different identity,' where an open response was provided. Where possible, open responses will be coded as 'man', 'woman', 'transman,' 'transwoman,' and 'GNC', aligning with recent recommendations for categorizing gender identity (26). Gender identity will be analyzed as both a two-category variable: 'gender minority' and 'non-gender minority', and as a four-category variable: 'man,' 'woman,' 'transman,' 'transwoman,' and 'GNC.'

Due to the varying types of racial and ethnic groups between the three countries, pooled analyses will involve a binary race variable of 'white only' vs. 'other races or mixed race'; however, participants provided more specific race/ethnicity information in the survey (See Table 3.1). Socioeconomic status was collected using a measure of perceived income adequacy, where participants were asked, "How would you describe your family's financial situation?" with response options 'not meeting basic expenses', 'just meeting basic expenses,' 'meeting needs with a little left over,' 'living comfortably', and 'don't know/refuse' (141).

Aim 1 measures

Current Use of Nicotine Products

Current nicotine use measures were adapted from the Population Assessment of Tobacco and Health (PATH) study surveys (142). Participants reported the number of days (#0-31) in the past month that they had used cigarettes and, separately, e-cigarettes. Any past month use was considered current use (yes vs. no). Current use of little cigars or

cigarillos (LCCs), cigars, bidis, smokeless tobacco, hookah, and nicotine pouches were measured with a checklist for past 30-day use of each product. Using these variables, we will derive the following product use categories: no past 30-day use of any products; exclusive use of combusted products (i.e., cigarettes, little cigars or cigarillos, cigars, bidis, hookah); exclusive use of non-combusted products (i.e., e-cigarette, smokeless tobacco, nicotine pouches); or use of both combusted and non-combusted use (at least one combusted and one non-combusted product).

Mental health symptoms

Mental health symptoms were measured using two items from the Screening Tool for Psychological Distress (STOP-D), which has been validated among adults (143). Symptoms of depression were measured by asking participants, "In the last month, how much have you been bothered by feeling sad, down, or uninterested in life?" Symptoms of anxiety were measured by asking participants, "In the last month, how much have you been bothered by feeling anxious or nervous?" For both items, response options ranged from 0 to 9, with anchors at 0 (not at all), 3 (a little), 6 (moderately), and 9 (severely). We will separately examine 1) each continuous item, 2) each binary versions of these variables (i.e., validated cut-points of 4 for depression symptoms and 5 for anxiety symptoms (143)), 3) a combined continuous version (averaging scores together), and 4) a binary IMH symptoms variable indicating if respondents reported above the cut point for either depression or anxiety symptoms (1) or neither (0) and determine which variable will be used based on the consistency of results. If the results are consistent across the different variables, we will use the binary IMH symptoms variable for ease of interpretation.

Aim 2 measures

Characteristics of Nicotine Use

Current tobacco/nicotine use measures were adapted from the PATH study surveys (142), with questions about cigarette use and e-cigarette use asked separately but otherwise using the same wording. Participants reported the number of days of use in the past month, which was used to examine frequency of use as a continuous variable. Responses of 'don't know' or 'refused' were recoded as missing and were excluded from analyses (n=1110 for cigarettes, n=2144 for e-cigarettes). Time to first use was measured by asking participants, "How soon after waking do you (smoke/vape)?" with response options 'within 5 minutes,' '6-30 minutes,' '31-60 minutes,' and '60+ minutes'. Perceived addiction was measured by asking respondents, "Do you believe you are addicted to (smoking cigarettes / e-cigarettes/vaping?" with response options 'Yes, very much,' 'Yes, a little,' or 'Not at all' (113).

Quit Intentions and Quit Attempt

For intention to quit, participants were asked, "Are you planning on quitting (smoking/vaping)…" with response options 'within the next month,' 'between 1-6 months from now,' recoded as 'intending to quit' and response options 'sometime in the future, beyond 6 months,' 'not planning to quit,' 'I don't currently smoke/vape,' and 'I don't know' coded as 'not intending to quit.' Responses of 'refused' were recoded as missing and were excluded from analyses (n=27 for cigarettes, n=61 for e-cigarettes).

For ever having a quit attempt, participants were asked, "Have you ever tried quitting (smoking/vaping)?" with response options 'yes' and 'no.' Responses of 'don't know' or 'refused' were recoded as missing and were excluded from analyses (n=57 for

cigarettes, n=455 for e-cigarettes). For this outcome for cigarettes in the February 2020 wave, measurement differed from subsequent waves; therefore, respondents from that wave reporting current cigarette use have been dropped from models for this outcome (n=2173).

Data analysis

All analyses for this proposed dissertation will be conducted using Stata version 16. Analytic weights will be used in all analyses. Post-stratification sample weights for all waves were constructed based on population estimates for sociodemographic variables as follows: smoking in the last 30 days National Adolescents Tobacco Survey (NYTS) in the US and the Canadian Student Tobacco, Alcohol and Drugs Survey (CSTADS) in Canada. Respondents were classified into sex-by-age-by-region groups in Canada and England, and sex-by-age-by-region-by-race groups in the US, where sex was male or female, age was 16-17 or 18-19, race/ethnicity was white/Caucasian only or other (in the US only), and geographic region was specific to each country. In the US and Canada, nationally representative estimates from the NYTS and CSTADS were used to calibrate to the trend over time for past 30-day smoking. The data from England were not calibrated to an external trend as there was no benchmark survey available for England in the relevant age range.

All eligible participants who passed the attention check will be included in the analytic sample for Aim 1. For Aim 2a, the limited sample is any participants from the analytic sample for Aim 1 who reported current use of e-cigarettes. Finally, for Aim 2b, the sample is limited to any participants who reported current use of cigarettes.

Sample Characteristics

The full analytic sample (n=67946) was 23% age 16, 26% age 17, 31% age 18, and 21% age 19. The sample was 49% female and 51% male, with 4% of the sample identifying as non-cisgender. For race/ethnicity, 67% of respondents reported being white. When pooled across waves, 60% of the sample reported either symptoms of only depression (12%), only anxiety (7%), or both (41%). In terms of reporting IMH symptoms, 58% of the sample reported IMH symptoms in February 2020, 57% in August 2020, 64% in February 2021, 62% in August 2021, and 58% in August 2022. Most (77%) of the sample reported no past 30-day use of any nicotine product, 9% reported exclusive non-combustible product use, 6% reported exclusive combustible product use, and 8% reported past 30-day use of both combustible and non-combustible products. The two subsamples for Aim 2 were comprised of 8,309 adolescents reporting cigarette use (exclusive=45%, dual=55%) and 11921 adolescents reporting e-cigarette use (exclusive=65%, dual=35%).

Analyses

Aim 1a Analyses

Figure 3.1 includes a conceptual model that illustrates the relationship that will be assessed in the analyses for Aim 1 of the proposed dissertation. Aim 1 involves analysis of the full sample. The primary outcome is past 30-day use of any of the following nicotine products: cigarettes, e-cigarettes, cigars, little cigars/cigarillos, bidis, waterpipe, smokeless tobacco, and nicotine pouches. The dependent variable will have four levels: no current use, exclusive use of combustible products, exclusive use of non-combustible products, and use of both combustible and non-combustible products. The primary

independent variables for Aim 1a are the presence of internalizing mental health symptoms. For this sub-aim, all waves will be combined into one single multinomial regression model. All models will adjust for wave, gender identity, sex, race, age, SES, and country of residence.

An interaction term of wave and IMH symptoms will be included to determine whether there is an interaction between mental health and time as it relates to current nicotine use. I will group waves as follows: February 2020, August 2020, February 2021, August 2021, and August 2022. Because this variable is categorical with five categories, I will globally test the interaction by performing an f-test.

Aim 1b Analyses

Figure 3.1 includes a conceptual model that illustrates the relationship that will be assessed in the analyses for Aim 1b of the proposed dissertation. For Aim 1b, I will examine the association between gender identity (man, woman, transgender, GNC) and nicotine use. All waves will be combined into one single multinomial regression model. All models will adjust for wave, race, age, SES, and country of residence. Next, I will examine the association between gender identity and IMH symptoms. All waves will be combined into one single multinomial regression model. All models will adjust for wave, race, age, SES, and country of residence. Next, I will examine the interaction of gender identity and IMH symptom. I will examine the component interaction coefficients to determine whether the interaction is significant. The final models will include the interaction term if it is deemed significant.

Aim 2.

Aim 2 Analyses

Figures 3.2 and 3.3 include conceptual models that illustrates the relationship that will be assessed in the analyses for Aim 2 of the proposed dissertation. The primary independent variable for Aim 2 is the presence of internalizing mental health symptoms. The outcomes (frequency of use, time to first use, perceived addiction, intention to quit, and ever having a quit attempt) will be modeled separately for e-cigarettes and cigarettes, with only participants who reported using the product in each model. All models will adjust for wave, gender identity, sex, race, age, and country of residence.

For Aim 2, I will run Poisson regression models with frequency of use as the outcome (#1-30 days). I will run multinomial regression models with time to first use as the outcome (within 5 minutes, 6-30 minutes, 31-60 minutes, and hour + (reference)). I will run multinomial regression models with perceived addiction as the outcome (no (ref) vs. yes, a little, yes, a lot). I will run logistic regression models with intention to quit as the outcome (not in the next 6 months vs. yes in the next 6 months). I will run logistic regression models with ever having a quit attempt as the outcome (no (ref) vs. yes).

Dissemination

To disseminate the results of this proposed dissertation, I will prepare presentations for national and international conferences (e.g., Society for Research on Nicotine and Tobacco, Society for Research on Nicotine and Tobacco Europe) and 3 manuscripts to health behavioral journals (Nicotine and Tobacco Research, Addiction, and LGTB Health).

Tables and Figures

Table 3.1 ITC Adolescents Survey Measures

Sociodemographic Measures		
Country	Survey indicator	1. Canada 2. USA 3. England
Wave	Survey indicator	1. Feb 2020 2. Aug 2020 3. Feb 2021 4. Aug 2021 5. Aug 2022
Age	How old are you?	#16-19
Gender	What is your current gender identity?	1. Man 2. Woman 3. Trans male/trans man 4. Trans female/transwoman 5. Gender queer/gender non-conforming 6. Different identity 8. Don't know
Sex	What sex were you assigned at birth, meaning on your original birth certificate?	1. Male 2. Female 8. Don't know
Race (Canada only)	People living in Canada come from many different cultural and racial backgrounds. Are you… (select all that apply)	1. White or European (e.g. British, French, Italian, Portuguese, Ukrainian, Russian) 2. Chinese 3. South Asian (e.g., East Indian, Pakistani, Sri Lankan) 4. Black (African, Caribbean, North American) 5. First Nations (North American Indian, including Status and Non-Status Indians), Métis, or Inuk (Inuit) 6. Filipino 7. Latin American, Central American, South American (e.g., Mexican, Brazilian, Chilean, Guatemalan, Venezuelan, Colombian, Argentinian, Salvadorian,

		Costa Rican) 8. Southeast Asian (e.g., Vietnamese, Cambodian, Indonesian, Laotian) 9. West Asian or Arab (e.g., Egyptian, Saudi Arabian, Syrian, Iranian, Iraqi, Lebanese, Afghani, Palestinian) 10. Korean 11. Japanese 12. Other (please specify) 88. Don't know
Race (England only)	Which of the following best describes your ethnic or racial background?	WHITE 1. English / Welsh / Scottish / Northern Irish / British 2. Irish 3. Gypsy or Irish Traveller 4. Any other White background (please specify) MIXED / MULTIPLE ETHNIC GROUPS 5. White and Black Caribbean 6. White and Black African 7. White and Asian 8. Any other Mixed / Multiple ethnic background (please specify) ASIAN / ASIAN BRITISH 9. Indian 10. Pakistani NOT APPLICABLE - NO FRENCH SURVEY IN UK 94 11. Bangladeshi 12. Chinese 13. Any other Asian background (please specify) BLACK / AFRICAN / CARIBBEAN / BLACK BRITISH 14. African 15. Caribbean 16. Any other Black / African / Caribbean background (please specify) OTHER ETHNIC GROUP 17. Arab

		18. Any other ethnic group (please specify) 88. Don't know
Race (USA only)	People living in the United States come from many different cultural and racial backgrounds. Are you… (select all that apply)	1. White 2. Black or African-American 3. Hispanic or Latino 4. Asian 5. Native Hawaiian or Pacific Islander 6. Native American Indian or Alaska Native 7. Other (please specify) 88. Don't know
Aim 1 Measures		
Current cigarette use	In the past 30 days, on how many days did you smoke cigarettes?	#0-30
Current e-cigarette use	In the past 30 days, on how many days did you use e-cigarettes/vape?	#0-30
Current other product use	In the past 30 DAYS, have you used any of the following? (check box) • Little cigars or cigarillos (plain or flavored) • Cigars (not including little cigars or cigarillos, plain or flavored) • Bidis (little cigarettes hand-rolled in leaves) • Smokeless tobacco (chewing tobacco, pinch, snuff, or snus) • A waterpipe to smoke shisha (herbal or tobacco) Nicotine pouches without tobacco	1. Yes 2. No 8. Don't know
Symptoms of depression	In the last month, how much have you been bothered by feeling sad, down, or uninterested in life?	0- Not at all 1 2 3- A little 4 5 6- Moderately 7 8

		9- Severely
Symptoms of anxiety	In the last month, how much have you been bothered by feeling anxious or nervous?	0- Not at all 1 2 3- A little 4 5 6- Moderately 7 8 9- Severely
Aim 2 Measures		
Cigarette use frequency	In the past 30 days, on how many days did you smoke cigarettes?	#0-30
E-cigarette use frequency	In the past 30 days, on how many days did you use e-cigarettes/vape?	#0-30
Time to first cigarette	How soon after waking do you smoke your first cigarette?	1. Within 5 minutes 2. 6-30 minutes 3. 31-60 minutes 4. 1-4 hours 5. 5-8 hours More than 8 hours
Time to first e-cigarette use	How soon after waking do you first use an e-cigarette/vape?	1. Within 5 minutes 2. 6-30 minutes 3. 31-60 minutes 4. 1-4 hours 5. 5-8 hours More than 8 hours
Perceived addiction to cigarettes	Do you consider yourself addicted to cigarettes?	1. Not at all 2. Yes, a little addicted 3. Yes, very addicted 8. Don't know
Perceived addiction to e-cigarettes	Do you consider yourself addicted to e-cigarettes/vaping?	1. Not at all 2. Yes, a little addicted 3. Yes, very addicted 8. Don't know
Cigarette quit intention	Are you planning to quit smoking…	1. Within the next month

		2. Between 1-6 months from now 3. Sometime in the future, beyond 6 months 4. Not planning to quit 5. I don't currently smoke 8. Don't know
E-cigarette quit intention	Are you planning to quit using e-cigarettes/vaping	1. Within the next month 2. Between 1-6 months from now 3. Sometime in the future, beyond 6 months 4. Not planning to quit 5. I don't currently use e-cigarettes 8. Don't know
Cigarette quit attempt	Have you ever tried to completely stop smoking cigarettes?	1. Yes 2. No 8. Don't know
E-cigarette quit attempt	Have you ever tried to completely stop s using e-cigarettes/vaping?	1. Yes 2. No 8. Don't know

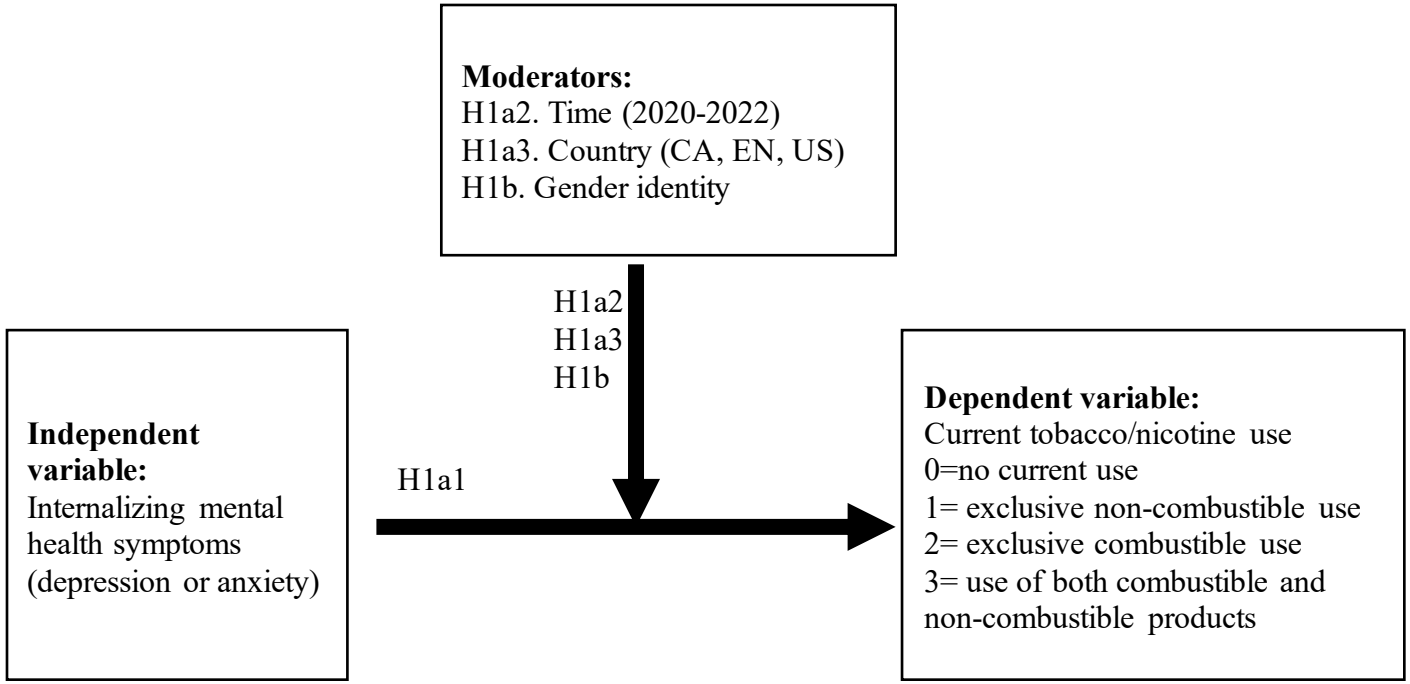

Figure 3.1 Aim 1 Conceptual Model

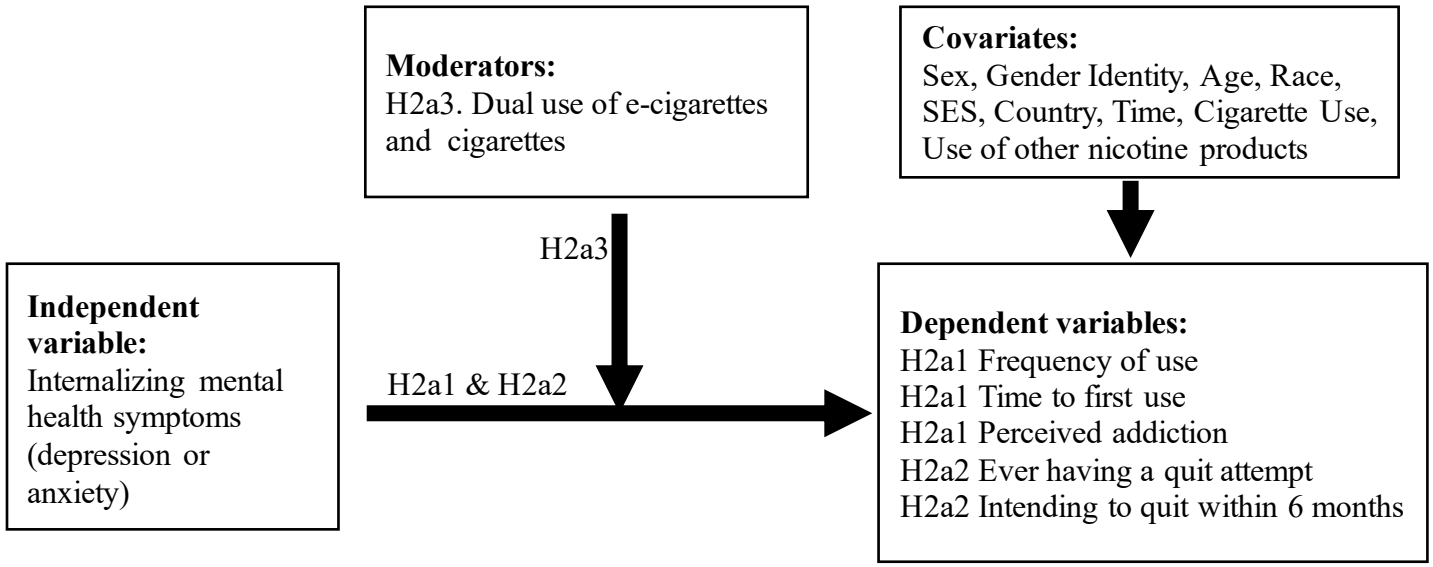

Figure 3.2. Aim 2a Conceptual Model

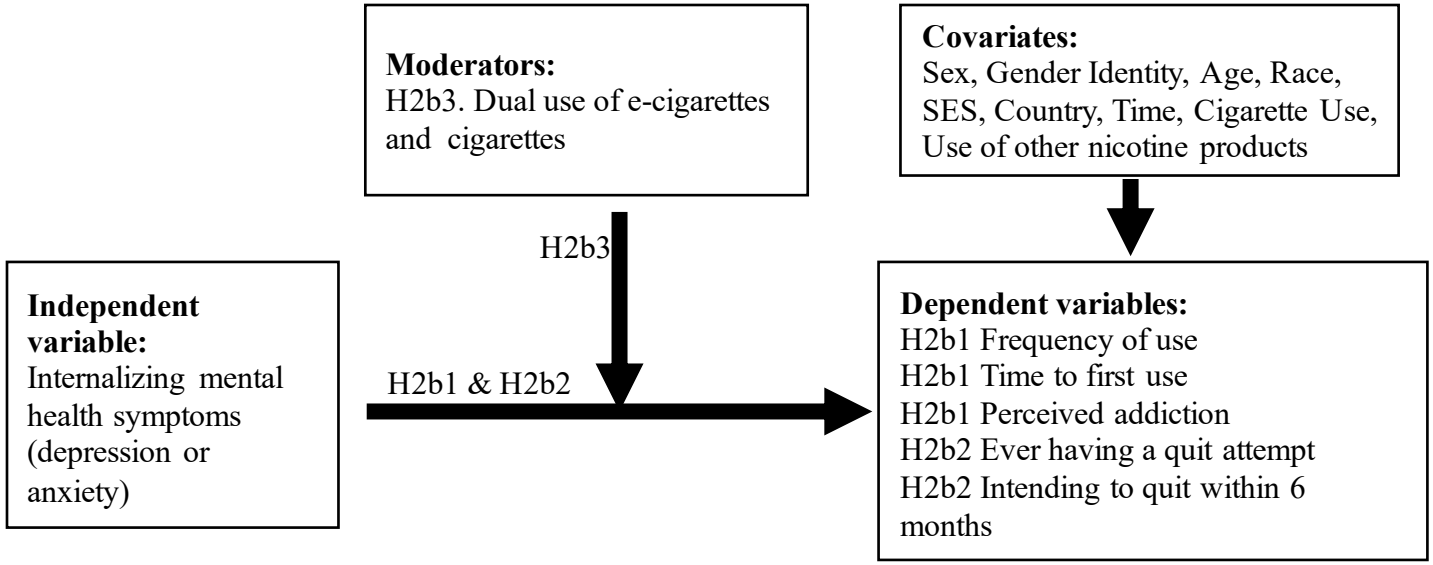

Figure 3.3 Aim 2b Conceptual Model

Chapter 4: Manuscript 1

Trends in Mental Health Symptoms, Nicotine Product Use, and their Association Over Time Among Adolescents in Canada, England, and the US: Findings from the ITC Adolescents Tobacco and Vaping Survey, 2020-2022[3]

Introduction

Internalizing mental health (IMH) problems include symptoms of anxiety and depression (8), and are highly prevalent among adolescents, but rarely diagnosed or treated until adulthood (7). Adolescents with untreated IMH symptoms are at risk for several adverse outcomes, including substance use disorders and suicide (14), which is the third leading cause of death among US teenagers ages 12-19 (15). Individuals suffering from IMH symptoms have a significantly shorter life expectancy than the general population, largely attributable to substance use (18,19). Smoking and IMH symptoms are related cross-sectionally (40–51) and longitudinally: some longitudinal studies finding that smoking causes IMH symptom onset (53–57), some finding that the presence of IMH symptoms leads to smoking initiation (58–65,91), and others finding a bidirectional relationship (66–68,80). This research suggests that adolescent smoking may contribute to IMH symptoms, or that adolescents with IMH symptoms may use nicotine to self-medicate for psychiatric symptoms, enhance cognitive deficits, or reduce npleasant side effects of

[3]Hackworth, E.E., Vidana, D., Hammond, D., Kim, M., Fillo, J., Thrasher, J.F. To be submitted to *Nicotine and Tobacco Research.*

psychiatric medications (22). These findings among adolescents are in line with abundant evidence of a connection between smoking and IMH symptoms in adulthood (144).

Over the past decade, the types of nicotine products have grown beyond traditional combustible (e.g., cigarettes, cigars, hookahs) and non-combustible tobacco products (e.g., smokeless tobacco) to include products such as electronic cigarettes (e-cigarettes) and nicotine pouches. Non-combustible products are less harmful than combustible products (145), since most carcinogens and other toxicants responsible for the health burden from tobacco use result from combustion (146–148). Nevertheless, non-combustible products can still be harmful, including cardiovascular and respiratory effects, as well as the risk of nicotine addiction (3). Beyond physical health, mental health effects of nicotine use may also be a concern among adolescents; however, more research is needed to better understand how mental health and nicotine use are related in this population.

While the link between smoking and IMH problems in adolescence is well-established, there is less evidence surrounding the potential relationship between IMH and use of newer nicotine products. Several recent, cross-sectional studies have found positive associations between IMH symptoms and e-cigarette use (69–72), and two longitudinal studies found that IMH symptoms predicted subsequent e-cigarette use (78,79). A few cross-sectional studies found a gradient of association, where IMH problems were highest in those reporting dual use, lower in those reporting exclusive cigarette use, and lowest in those reporting exclusive e-cigarette use (73–75). Only one study has examined the relationship between IMH problems and nicotine products beyond cigarettes and e-cigarettes, finding that adolescents with IMH problems were

more likely than their counterparts to subsequentially use any tobacco product when grouping all products together compared to use of no products (82). While this study suggests that a wide variety of tobacco products beyond cigarettes and e-cigarettes may be related to IMH problems among adolescents, it remains unclear which types of products or combinations of products may pose the highest risk.

The recent COVID-19 pandemic has impacted both mental health and nicotine use rates. From 2020-2022, young people around the world experienced significant disturbances in their lives due to both the stress of living through a pandemic and social isolation from school and public shutdowns (32). Longitudinal studies show that COVID-19 changed adolescent mental health trajectories and resulted in significant increases in symptoms of depression and anxiety in many different countries (34–37). By contrast, rates of substance use, including tobacco, declined during COVID-19 (38), likely due to reduced opportunities to access and share products during lock downs. However, as of 2022, adolescents' tobacco use rates may be returning to pre-COVID levels or increasing (39,149,150). This information suggests that the COVID-19 pandemic had effects on both the mental health and tobacco use patterns of adolescents.

Many countries have implemented policies to reduce combustible tobacco use (e.g., taxes, smoke-free policies, sales and marketing restrictions) (107). By contrast, a few countries have adopted harm reduction policies, such as in the UK (151), that promote switching to e-cigarettes as a lower risk alternative for adults who smoke and want to quit. Consequentially, e-cigarette use among adolescents has recently increased in England, whereas it has remained relatively stable in countries without such policies (i.e., Canada and USA) (150). Given the differences in regulatory frameworks, there is a

need to examine whether countries with different policies in place have differences in nicotine use rates and the strength of association with IMH symptoms.

The purpose of this study is to fill the gap in research related to adolescents IMH symptoms and use of a wide variety of nicotine products. We hypothesize that the presence of IMH symptoms will be positively associated with all categories of current nicotine use: exclusive combustible product use, exclusive non-combustible product use, and use of both product types. In line with prior research, the strength of association between the presence of IMH symptoms and current nicotine use will follow a gradient similar with that found in studies of e-cigarette, cigarette, and dual use: weakest for exclusive use of non-combustible products, followed by exclusive use of combustible products, and strongest for use of both combustible and non-combustible products. Due to the impact of the COVID-19 pandemic, we also hypothesize that the association between IMH symptoms and current nicotine use will be moderated by time, with the association weakening over the course of the COVID-19 pandemic. Finally, given differences in nicotine use and mental health in England, Canada, and the US, we hypothesize that the relationship will be moderated by country.

Methods

Data Source

The data for this study comes from the International Tobacco Control (ITC) Policy Evaluation Project Adolescents Tobacco and Vaping Survey, a repeat cross-sectional survey of national samples of adolescents in England, Canada, and the United States (US) (141). This study uses five waves of the ITC Adolescents Tobacco and Vaping Survey conducted between 2020-2022: two surveys in 2020 (February to March;

August); two in 2021 (February; August); and one in 2022 (August). Eligible participants were between the ages of 16 and 19 living in each of the three target countries. Participants were recruited from the Nielsen Consumer Insights Global Panel, with a final sample target of 4,500 participants for each country at each survey. For each survey, Nielsen selected random samples from both probability and non-probability panels in each country.

A random selection of panelists, parents of panelists (for participants under 18), or panelists with children ages 16-19 received email invitations with a unique survey link to screen for eligibility. After reviewing information about the study and consenting to participate, eligible participants completed the survey. The survey took approximately 20 minutes to answer and was available in English in all countries, plus French in Canada. Participants received renumeration in accordance with the panel incentive structure, which included point-based rewards, monetary rewards, and/or chances to win monthly prizes.

Measures

Dependent Variable: Current Use of Nicotine Products

Current nicotine use measures were adapted from the Population Assessment of Tobacco and Health (PATH) study surveys (142). Participants reported the number of days (0-31) in the past month that they had used cigarettes and, separately, e-cigarettes. Any past month use was considered current use (yes vs. no). Current use of little cigars or cigarillos (LCCs), cigars, bidis, smokeless tobacco, hookah, and nicotine pouches were measured with a checklist for past 30-day use of each product. Using these variables, we derived the following product use categories: no past 30-day use of any products;

exclusive use of combusted products (i.e., cigarettes, little cigars or cigarillos, cigars, bidis, hookah); exclusive use of non-combusted products (i.e., e-cigarette, smokeless tobacco, nicotine pouches); or use of both combusted and non-combusted use (at least one combusted and one non-combusted product).

Independent Variable: Internalizing Mental Health Symptoms

Mental health symptoms were measured using two items from the Screening Tool for Psychological Distress (STOP-D), which has been validated among adults (143). Symptoms of depression were measured by asking participants, "In the last month, how much have you been bothered by feeling sad, down, or uninterested in life?" Symptoms of anxiety were measured by asking participants, "In the last month, how much have you been bothered by feeling anxious or nervous?" For both items, response options ranged from 0 to 9, with anchors at 0 (not at all), 3 (a little), 6 (moderately), and 9 (severely). Respondents who selected 'don't know' or 'refused' were excluded from the analytic sample (n=1,031).

For the present study, we examined 1) each continuous item, 2) each binary versions of these variables (i.e., validated cut-points of 4 for depression symptoms and 5 for anxiety symptoms (143)), 3) a combined continuous version (averaging scores together), and 4) a binary IMH symptoms variable indicating if respondents reported above the cut point for either depression or anxiety symptoms (1) or neither (0).

Covariates

Participants indicated their age (16, 17, 18, or 19) and sex at birth: (male, female). Participants were asked, "What is your current gender identity?" with response options 'Man', 'Woman', 'Trans male/ trans man', 'Trans female / trans woman', 'Gender queer

/ Gender non-conforming', or 'Different identity,' where an open response was provided. Where possible, open responses (n=8392) were coded as man, woman, transgender, and GNC, aligning with recent recommendations for categorizing gender identity (26). These categories were recoded to 'cisgender' (i.e., man, woman) or non-cisgender (i.e., trans male, trans female, gender queer/gender non-conforming, different identity). Invalid responses, responses of 'Don't know', and 'Refused' were coded as missing and were excluded from analyses (n=465).

Participants provided country-specific race/ethnicity information in the survey; however, pooled analyses involved a binary race variable of 'white only' vs. 'other races or mixed race'. Socioeconomic status was collected using a measure of perceived income adequacy, where participants were asked, "How would you describe your family's financial situation?" with response options 'not meeting basic expenses', 'just meeting basic expenses,' 'meeting needs with a little left over,' 'living comfortably', and 'don't know/refuse.' Participants were asked which country they live in: Canada, the USA, or England, which was used as an indicator of location. For each data collection wave, a wave indicator was generated.

Analyses

In our assessment of the indictors of IMH symptoms, we found that symptoms of anxiety and symptoms of depression were strongly correlated (continuous measure $r=0.76$, binary measure $r=0.61$, $p<0.001$). Sensitivity analyses of primary analyses with the measures as separate indicators and as a combined binary IMH symptoms variable produced very similar results (see Table 4.1); therefore, we used the binary IMH symptoms variable for ease of interpretation.

Trends in nicotine use and IMH symptoms over time were examined using simple prevalence rates and chi-square tests, adjusting for post-stratification weights. Adjusted multinomial regression models were estimated with a four-level product use dependent variable: no current use (reference group); exclusive use of combustible products; exclusive use of non-combustible products; and use of both combustible and non-combustible products. The primary independent variable was IMH symptoms.

Interactions of IMH symptoms with wave and country were examined by creating an interaction term of *IMH symptoms x Wave* and *IMH symptoms x country* and including them in separate multinomial regression models. A global interaction test was conducted to determine whether the interaction terms were significant. Variables moderating the relationship between IMH symptoms and nicotine use were then examined by stratifying the main analyses by that variable (i.e., stratifying the model estimating the association between IMH symptoms and nicotine use by wave). We calculated predicted probabilities of IMH symptoms for each nicotine use status over time, adjusting for the covariates and interaction in the model.

All analyses adjusted for wave, gender identity, sex, race, age, SES, and country of residence. In addition, sample weights were constructed based on population estimates for sociodemographic variables (age, sex, region in all countries; race in US only) and past 30 day smoking (based on national estimates in US and Canada; unavailable in England) (141). All analyses were conducted using Stata version 16.

Results

Sample Characteristics

The sample characteristics by wave are provided in Table 4.2. The full analytic sample (n=67,946) was 23% age 16, 26% age 17, 31% age 18, and 21% age 19. The sample was 49% female and 51% male, with 4% of the sample identifying as non-cisgender. For race/ethnicity, 67% of respondents reported being white.

Nicotine Use

Prevalence of products by wave are shown in Table 4.2. Most (77%) of the sample reported no past 30-day use of any nicotine product, 9% reported exclusive non-combustible product use, 6% reported exclusive combustible product use, and 8% reported past 30-day use of both combustible and non-combustible products.

Internalizing Mental Health Symptoms

When pooled across waves, 60% of the sample reported either symptoms of only depression (12%), only anxiety (7%), or both (41%). In terms of reporting IMH symptoms, 58% of the sample reported IMH symptoms in February 2020, 57% in August 2020, 64% in February 2021, 62% in August 2021, and 58% in August 2022. Trends in IMH symptom prevalence by current nicotine use status is shown in Figure 4.1.

Associations Between IMH Symptoms and Current Nicotine Use

In both unadjusted and adjusted multinomial models (see Tables 4.3 and 4.4), IMH symptoms were positively associated with all categories of current nicotine use compared to non-current use. Risk ratios appear in a gradient, with the lowest risk for exclusive combustible use (Adjusted relative risk ratio [ARRR]: 1.27, 95% Confidence Interval [CI]=1.19-1.36), followed by exclusive non-combustible use (ARRR: 1.69, 95%

CI=1.59-1.80), and the highest risk for both combustible and non-combustible use (ARRR: 1.85, 95% CI=1.73-1.97).

Interactions

Next, we added interaction terms to the adjusted multinomial models for nicotine product use to examine the moderating role of country and wave. The interaction between IMH symptoms and country was not statistically significant (global F-test p=0.260), but the interaction between IMH symptoms and wave was statistically significant (global F-test p<0.001).

In order to better understand the interaction between IMH symptoms and wave, we stratified our primary analyses by wave (see Table 4.5 and Table 4.6) and calculated predicted probabilities (see Figure 4.2). In all individual waves except for August 2022, we see the same patterns of statistically significant ARRRs for IMH symptoms and the current nicotine use categories: strongest for those who use both types of nicotine products, followed by exclusive non-combustible use, and then exclusive combustible use. However, in August 2022, IMH symptoms were not associated with exclusive combustible use, but were associated with exclusive non-combustible use (ARRR: 1.80, 95% C.I.=1.58-2.04) and use of both product types (ARRR: 1.81, 95% C.I.=1.56-2.10). These findings are depicted in Figure 4.2, where patterns are similar for non-combustible use and use of both product types, but the relationship between IMH symptoms and exclusive combustible use changes at the last wave.

Discussion

This study found that the presence of IMH symptoms is associated with current nicotine use among adolescents, adding to the robust literature of the strong association

between IMH problems and cigarette smoking (40–51,53–68,80,91) and more recently developing literature finding a link between IMH problems and e-cigarette use (69–75,78,79). This finding also aligns with the study of IMH problems and multiple tobacco products (82).

When examining the relationship between IMH symptoms and nicotine use categorized by combustibility, this study provides evidence of a gradient where IMH symptoms are most likely among adolescents using both combustible and non-combustible products, second most likely among those using exclusively non-combustible products, and least likely among those using exclusively combustible products. However, all groups were more likely to report IMH symptoms compared to adolescents not currently using any nicotine product. This differs from previous studies and our hypothesis that dual use and exclusive cigarette use would be associated with a higher risk for IMH problems compared exclusive e-cigarette use (73–75). These studies were conducted prior to 2020, so perhaps the relationship between e-cigarette use and IMH symptoms has changed. Indeed, our results suggest that non-combustible product use, largely driven by e-cigarette use, may increase the risk of IMH problems beyond that of combustible product use. Another possible explanation is that adolescents using non-combustible products may be more nicotine dependent than combustible products, given that these products are easier to conceal (152). More research is needed to replicate and better understand this finding.

We found that country did not moderate the relationship between IMH symptoms and nicotine use, suggesting that the association between IMH symptoms and nicotine use was similar between countries, which aligns with our hypothesis. We found a

significant interaction between IMH symptoms and wave on nicotine use, as hypothesized; however, the direction of this interaction differed from our prediction. When examining the analyses stratified by wave, we found that the strength of association between IMH symptoms and all types of nicotine use was positive for all waves except for exclusive combustible use in August 2022. Indeed, there was no association between IMH symptoms and exclusive combustible use in August of 2022. Given that the patterns are as expected for all earlier waves and all other types of use, this suggests that the August 2022 finding could be an anomaly, or that there may be a recent change in the relationship between IMH symptoms and exclusive combustible product use. For example, perhaps adolescents who have IMH symptoms are shifting towards non-combustible products because they are better able to satisfy their nicotine cravings, or they are easier to use discretely. Research is needed to understand the relationship between IMH symptoms and nicotine dependence of e-cigarette and dual use. Longitudinal research may be needed to understand whether people with IMH symptoms are more likely to escalate use or whether people who use start to express IMH symptoms, perhaps because they are becoming dependent and experience withdrawal symptoms. Future studies should also examine if the relationship between IMH symptoms and nicotine use is moderated by other characteristics, such as sociodemographic characteristics that we found were correlated of nicotine use, including gender identity, race, and SES.

This study has several strengths, including using a large, national data set from three separate countries, over multiple survey waves. The consistent results between the countries suggest that the relationship between nicotine use and IMH symptoms is

consistent across geography, culture, and policy contexts. There are also some limitations to this study. First, as this is cross-sectional data, causation cannot be concluded from these results. Future studies of these relationships may use longitudinal data to confirm directionality. Regardless of the directionality of the association, the strong relationship between nicotine use and IMH symptoms found in this study is cause for concern. It is apparent that use of nicotine resulting in IMH symptoms is a problem. However, it is also concerning in the other direction (i.e., IMH symptoms resulting in nicotine use). Some research indicates that people with mental health problems may use nicotine to manage IMH symptoms (22); however, in our cross-sectional study, our measure of current IMH symptoms, as opposed to IMH diagnosis, being associated with current nicotine use suggests that if this is the case, the management of symptoms using nicotine may not be effective. Furthermore, the standard of care of IMH conditions among adolescents is well-established and involves cognitive-behavioral therapy or interpersonal therapy, pharmacological treatment of selective serotonin reuptake inhibitors, or a combination of both (153).

Another limitation of this study is that the IMH measure has only been validated in adults at the present. However, the prevalence rates of symptoms of depression and anxiety found by these measures are similar to population-level prevalence rates found using other measures (154). Furthermore, given that diagnoses of IMH conditions does not occur until adulthood for most people (7), measuring self-reported experiences with common IMH symptoms (i.e., feeling depressed, feeling worried) appears to be a reasonable way to measure IMH symptoms in adolescents.

Overall, this study describes the relationship between IMH symptoms and nicotine use among adolescents in three countries before, during, and after the acute phase of the COVID-19 pandemic. Findings suggest that nicotine use remains a risk factor for IMH problems among this population. Indeed, the likelihood of IMH problems was highest for e-cigarettes, which have replaced combusted cigarettes as the most popular nicotine product among adolescents in Canada, the US, and England. This study highlights a need to address both the high nicotine use rates among adolescents in all three countries, and the widespread mental health challenges confronting adolescents.

Tables and Figures

Table 4.1 Sensitivity Analysis: IMH Measurement Options and Association with Nicotine Use Categories

		Exclusive Combustible Use		**Exclusive Non-Combustible Use**		**Both**	
		RRR(95% CI)[1]	*ARRR (95%CI)[2]*	*RRR(95% CI) [1]*	*ARRR (95% CI)[2]*	*RRR(95% CI) [1]*	*ARRR (95% CI)[2]*
Model 1 Depression (continuous)		ref	ref	ref	ref	ref	ref
	(0-9)	**1.06 (1.05-1.07)*** **	**1.06 (1.04-1.07)*** **	**1.11 (1.10-1.12)*** **	**1.10 (1.09-1.11)*** **	**1.13 (1.12-1.14)*** **	**1.13 (1.12-1.14)*** **
Model 2 Depression (binary)	No	ref	ref	ref	ref	ref	ref
	Yes	**1.34 (1.26-1.43)*** **	**1.33 (1.24-1.42)*** **	**1.69 (1.60-1.79)*** **	**1.62 (1.53-1.72)*** **	**1.82 (1.72-1.93)*** **	**1.84 (1.73-1.95)*** **
Model 3 Anxiety (continuous)		ref	ref	ref	ref	ref	ref
	(0-9)	**1.02 (1.01-1.03)*** **	**1.03 (1.02-1.04)*** **	**1.11 (1.10-1.12)*** **	**1.09 (1.08-1.10)*** **	**1.10 (1.09-1.11)*** **	**1.11 (1.10-1.12)*** **
Model 4 Anxiety (binary)	No	ref	ref	ref	ref	ref	ref
	Yes	**1.14 (1.07-1.21)*** **	**1.16 (1.09-1.24)*** **	**1.67 (1.58-1.76)*** **	**1.52 (1.43-1.60)*** **	**1.57 (1.48-1.66)*** **	**1.59 (1.50-1.69)*** **
Model 5 IMH combined (continuous)		ref	ref	ref	ref	ref	ref
	(0-9)	**1.04 (1.03-1.06)*** **	**1.05 (1.03-1.06)*** **	**1.12 (1.11-1.14)*** **	**1.11 (1.10-1.12)*** **	**1.13 (1.12-1.14)*** **	**1.14 (1.13-1.15)*** **
Final Model IMH combined (binary)	No	ref	ref	ref	ref	ref	ref
	Yes	**1.26 (1.18-1.34)*** **	**1.27 (1.19-1.36)*** **	**1.81 (1.70-1.92)*** **	**1.69 (1.59-1.80)*** **	**1.81 (1.70-1.92)*** **	**1.85 (1.73-1.97)*** **

RRR – relative risk ratio; ARRR- adjusted relative risk ratio; CI – confidence interval; IMH- internalizing mental health

[1]RRRs were estimated in multinomial regression model with current nicotine use (ref=no use) as the outcome.

[2]Model adjusted for IMH symptoms, wave, country, age, sex, gender identity, race, and SES.

Bold indicates statistical significance. p<.05: *, p<.01: **, p<001: *** All models are weighted.

Table 4.2 Sample Characteristics by Wave

Characteristics	Categories	Feb 2020 n=13461	Aug 2020 n=14353	Feb 2021 n=13957	Aug 2021 n=13579	Aug 2022 n=12596	Total n=67946
				n (weighted %)			
Country	Canada	4167 (30.9%)	4221 (29.4%)	4543 (32.5%)	4537 (33.4%)	4329 (34.3%)	21797 (32.0%)
	England	4215 (31.3%)	4215 (29.5%)	4241 (30.4%)	4251 (31.2%)	4197 (33.3%)	21131 (31.1%)
	USA	5079 (37.8%)	5079 (41.2%)	5173 (37.1%)	4791 (35.4%)	4070 (32.4%)	25018 (36.9%)
Age	16	2877 (23.7%)	3195 (23.0%)	3159 (22.2%)	2633 (22.8%)	2217 (21.7%)	14081 (22.7%)
	17	3108 (24.9%)	3611 (25.7)	3951 (26.3%)	3229 (26.8%)	2915 (28.0%)	16814 (26.3%)
	18	4208 (30.0%)	4503 (30.9%)	4243 (31.9%)	4481 (29.7%)	4355 (30.2%)	21790 (30.6%)
	19	3268 (21.4%)	3044 (20.5%)	2604 (19.6%)	3236 (20.7%)	3109 (20.2%)	15261 (20.5%)
Sex	Female	8604 (48.8%)	9392 (48.9%)	9695 (48.9%)	9357 (48.9%)	8410 (48.9%)	45458 (48.9%)
Gender Identity	Gender minority	307 (2.0%)	432 (2.6%)	533 (3.2%)	796 (5.0%)	774 (5.4%)	2842 (3.6%)
Race	White	8660 (69.2%)	8429 (67.7%)	8315 (65.7%)	7513 (64.0%)	7769 (66.8%)	40686 (66.7%)
SES	Not meeting needs	765 (4.6%)	483 (3.0%)	506 (3.4%)	471 (3.1%)	687 (4.3%)	2912 (3.7%)
	Just meeting needs	3545 (24.4%)	3302 (21.1%)	3254 (21.1%)	3195 (20.8%)	3512 (26.4%)	16808 (22.7%)
	Meeting needs	4329 (32.8%)	4963 (34.9%)	4532 (32.9%)	4762 (35.9%)	4147 (32.8%)	22733 (33.9%)
	Living comfortably	4262 (34.3%)	4890 (36.2%)	4931 (38.1%)	4508 (35.7%)	3688 (32.4%)	22279 (35.4%)
	No response	560 (4.0%)	715 (4.7%)	734 (4.6%)	643 (4.5%)	562 (4.1%)	3214 (4.4%)
Depression symptoms	Yes	7508 (50.3%)	7725 (49.9%)	8591 (56.9%)	7999 (53.6%)	6959 (49.8%)	38782 (52.1%)
Anxiety symptoms	Yes	7085 (47.3%)	7005 (44.8%)	7829 (51.8%)	7505 (50.2%)	6566 (46.4%)	35990 (48.1%)
IMH symptoms [1]	Yes	8542 (57.8%)	8838 (57.1%)	9561 (63.8%)	9111 (61.6%)	8046 (57.7%)	44098 (59.6%)
Current nicotine use [2]	None	9346 (74.4%)	11214 (79.3%)	10726 (78.2%)	10170 (78.1%)	8722 (73.9%)	50178 (76.9%)
	Exclusive combustible	1322 (9.5%)	997 (7.0%)	1216 (8.1%)	1226 (8.8%)	1572 (10.9%)	6333 (8.8%)
	Exclusive non-combustibl	1216 (7.1%)	1071 (6.9%)	913 (6.3%)	910 (5.4%)	840 (6.5%)	4950 (6.4%)
	Both types	1577 (9.0%)	1071 (6.8%)	1102 (7.3%)	1273 (7.7%)	1462 (8.7%)	6485 (7.9%)

IMH- internalizing mental health.

[1] IMH symptoms includes reporting either symptoms of depression or anxiety.

[2] Current nicotine use includes reporting use of a nicotine product in the past 30 days. Exclusive combustible products include cigarettes, cigars, little cigars or cigarillos, bidis, and hookah. Exclusive non-combustible products include e-cigarettes, nicotine pouches, and smokeless tobacco. Both types include at least one combustible and non-combustible product.

Prevalence rates are weighted.

Table 4.3 Correlates of Current Nicotine Use on Sample Characteristics

		Non-use (n=50178)	**Exclusive Combustible (n=4950)**		**Exclusive Non-Combustible (n=6333)**		**Both (n=6485)**	
	Category	**%**	**%**	***ARRR(95% CI)[1]***	**%**	***ARRR(95% CI)[1]***	**%**	***ARRR(95% CI)[1]***
IMH Symptoms	No	43.0%	37.4%	ref	29.4%	ref	29.4%	ref
	Yes	57.0%	62.6%	**1.27 (1.19-1.36)*** **	70.6	**1.69 (1.59-1.80)*** **	70.6%	**1.85 (1.73-1.97)*** **
Wave	Feb 20	19.2%	21.9%	ref	21.4%	ref	22.5%	ref
	Aug 20	21.8%	22.5%	0.95 (0.87-1.05)	16.8%	**0.70 (0.64-0.77)*** **	18.3%	**0.76 (0.69-0.83)*** **
	Feb 21	20.9%	20.2%	**0.86 (0.78-0.95)** **	18.9%	**0.81 (0.74-0.88)*** **	19.1%	**0.79 (0.72-0.86)*** **
	Aug 21	20.3%	16.7%	**0.73 (0.66-0.81)*** **	20.0%	**0.91 (0.84-0.99)***	19.6%	**0.84 (0.77-0.92)*** **
	Aug 22	17.8%	18.7%	**0.88 (0.80-0.98)***	22.9%	**1.18 (1.09-1.28)*** **	20.5%	0.96 (0.88-1.05)
Country	Canada	32.5%	26.4%	ref	34.7%	ref	29.2%	ref
	England	29.4%	50.2%	**2.06 (1.91-2.22)*** **	22.4%	**0.65 (0.60-0.70)*** **	42.0%	**1.50 (1.40-1.61)*** **
	USA	38.1%	23.4%	**0.72 (0.66-0.78)*** **	42.9%	0.99 (0.93-1.28)	28.8%	**0.79 (0.73-0.85)*** **
Age	16	24.4%	16.5%	ref	16.9%	ref	17.5%	ref
	17	27.2%	25.2%	**1.40 (1.27-1.54)*** **	22.7%	**1.16 (1.07-1.27)** **	22.2%	**1.15 (1.05-1.25)** **
	18	29.5%	32.7%	**1.59 (1.44-1.74)*** **	35.8%	**1.67 (1.55-1.81)*** **	33.3%	**1.48 (1.36-1.61)*** **
	19	18.9%	25.6%	**2.01 (1.82-2.22)*** **	24.6%	**1.74 (1.59-1.89)*** **	27.0%	**1.88 (1.72-2.05)*** **
Sex	Female	49.4%	41.2%	ref	56.0%	ref	42.3%	ref
	Male	50.6%	58.8%	**1.53 (1.44-1.64)*** **	44.0%	**0.87 (0.83-0.92)*** **	57.7%	**1.59 (1.50-1.69)*** **
Gender Identity	Non-gender minority	96.0%	95.9%	ref	95.8%	ref	94.9%	ref
	Gender minority	3.5%	3.5%	1.09 (0.92-1.29)	3.7%	**0.80 (0.69-0.92)** **	4.4%	**1.20 (1.04-1.38)***
Race	White	64.9%	68.8%	ref	75.1%	ref	72.5%	ref
	Other	33.9%	29.8%	**0.85 (0.79-0.91)*** **	24.1%	**0.55 (0.52-0.59)*** **	26.5%	**0.67 (0.62-0.71)*** **
SES	Not meeting needs	2.8%	6.8%	ref	4.6%	ref	8.2%	ref
	Just meeting needs	21.1%	28.5%	**0.54 (0.47-0.62)*** **	26.1%	**0.81 (0.70-0.93)** **	29.0%	**0.47 (0.42-0.53)*** **
	Meeting needs	34.7%	30.4%	**0.35 (0.30-0.40)*** **	32.5%	**0.64 (0.55-0.73)*** **	30.0%	**0.31 (0.27-0.34)*** **
	Living comfortably	36.6%	30.5%	**0.34 (0.30-0.39)*** **	36.6%	**0.63 (0.55-0.73)*** **	30.6%	**0.30 (0.27-0.34)*** **
	No response	4.7%	3.8%	**0.33 (0.27-0.41)*** **	4.7%	**0.56 (0.46-0.68)*** **	2.2%	**0.18 (0.14-0.22)*** **

ARRR- adjusted relative risk ratio; CI – confidence interval; IMH- internalizing mental health; SES – socioeconomic status

[1]ARRRs were estimated in multinomial regression model with current nicotine use (ref=no use) as the outcome. Model adjusted for IMH symptoms, wave, country, age, sex, gender identity, race, and SES.

Bold indicates statistical significance. p<.05: *, p<.01: **, p<001: *** All models and prevalence rates are weighted.

Table 4.4 Sensitivity Analysis: Correlates of Current Nicotine Use on Sample Characteristics Crude Models

		Non-use (n=50178)	**Exclusive Combustible (n=4950)**		**Exclusive Non-Combustible (n=6333)**		**Both (n=6485)**	
	Category	**%**	**%**	***RRR(95% CI)[1]***	**%**	***RRR(95% CI)[1]***	**%**	***RRR(95% CI)[1]***
IMH Symptoms	No	43.0%	37.4%	ref	29.4%	ref	29.4%	ref
	Yes	57.0%	62.6%	**1.26 (1.18-1.34)*** **	70.6	**1.81 (1.70-1.92)*** **	70.6%	**1.81 (1.70-1.92)*** **
Wave	Feb 20	19.2%	21.9%	ref	21.4%	ref	22.5%	ref
	Aug 20	21.8%	22.5%	**0.90 (0.82-0.99)***	16.8%	**0.69 (0.64-0.76)*** **	18.3%	**0.72 (0.66-0.78)*** **
	Feb 21	20.9%	20.2%	**0.85 (0.77-0.93)** **	18.9%	**0.81 (0.75-0.88)*** **	19.1%	**0.78 (0.71-0.85)*** **
	Aug 21	20.3%	16.7%	**0.72 (0.65-0.79)*** **	20.0%	**0.88 (0.81-0.96)** **	19.6%	**0.82 (0.75-0.90)*** **
	Aug 22	17.8%	18.7%	0.92 (0.83-1.01)	22.9%	**1.15 (1.06-1.25)** **	20.5%	0.98 (0.90-1.07)
Country	Canada	32.5%	26.4%	ref	34.7%	ref	29.2%	ref
	England	29.4%	50.2%	**2.10 (1.95-2.26)*** **	22.4%	**0.72 (0.67-0.77)*** **	42.0%	**1.59 (1.49-1.70)*** **
	USA	38.1%	23.4%	**0.75 (0.69-0.82)*** **	42.9%	1.05 (0.99-1.12)	28.8%	**0.84 (0.78-0.90)*** **
Age	16	24.4%	16.5%	ref	16.9%	ref	17.5%	ref
	17	27.2%	25.2%	**1.36 (1.24-1.50)*** **	22.7%	**1.20 (1.10-1.31)*** **	22.2%	**1.13 (1.04-1.24)** **
	18	29.5%	32.7%	**1.63 (1.49-1.79)*** **	35.8%	**1.75 (1.62-1.89)*** **	33.3%	**1.57 (1.45-1.71)*** **
	19	18.9%	25.6%	**2.00 (1.82-2.21)*** **	24.6%	**1.88 (1.73-2.05)*** **	27.0%	**1.99 (1.82-2.17)*** **
Sex	Female	49.4%	41.2%	ref	56.0%	ref	42.3%	ref
	Male	50.6%	58.8%	**1.39 (1.31-1.48)*** **	44.0%	**0.77 (0.73-0.81)*** **	57.7%	**1.33 (1.26-1.41)*** **
Gender Identity	Non-gender minority	96.0%	95.9%	ref	95.8%	ref	94.9%	ref
	Gender minority	3.5%	3.5%	1.00 (0.85-1.18)	3.7%	1.05 (0.91-1.21)	4.4%	**1.27 (1.10-1.45)** **
Race	White	64.9%	68.8%	ref	75.1%	ref	72.5%	ref
	Other	33.9%	29.8%	**0.83 (0.78-0.89)*** **	24.1%	**0.61 (0.58-0.65)*** **	26.5%	**0.70 (0.66-0.75)*** **
SES	Not meeting needs	2.8%	6.8%	ref	4.6%	ref	8.2%	ref
	Just meeting needs	21.1%	28.5%	**0.56 (0.49-0.64)*** **	26.1%	**0.77 (0.67-0.88)*** **	29.0%	**0.47 (0.42-0.53)*** **
	Meeting needs	34.7%	30.4%	**0.36 (0.32-0.42)*** **	32.5%	**0.58 (0.50-0.66)*** **	30.0%	**0.30 (0.26-0.34)*** **
	Living comfortably	36.6%	30.5%	**0.35 (0.30-0.40)*** **	36.6%	**0.56 (0.49-0.65)*** **	30.6%	**0.29 (0.26-0.32)*** **
	No response	4.7%	3.8%	**0.33 (0.27-0.41)*** **	4.7%	**0.46 (0.38-0.56)*** **	2.2%	**0.16 (0.13-0.20)*** **

RRR – relative risk ratio; CI – confidence interval; IMH- internalizing mental health; SES – socioeconomic status

[1]RRRs were estimated in multinomial regression models with current nicotine use (ref=no use) as the outcome.

Bold indicates statistical significance. p<.05: *, p<.01: **, p<001: *** All models and prevalence rates are weighted.

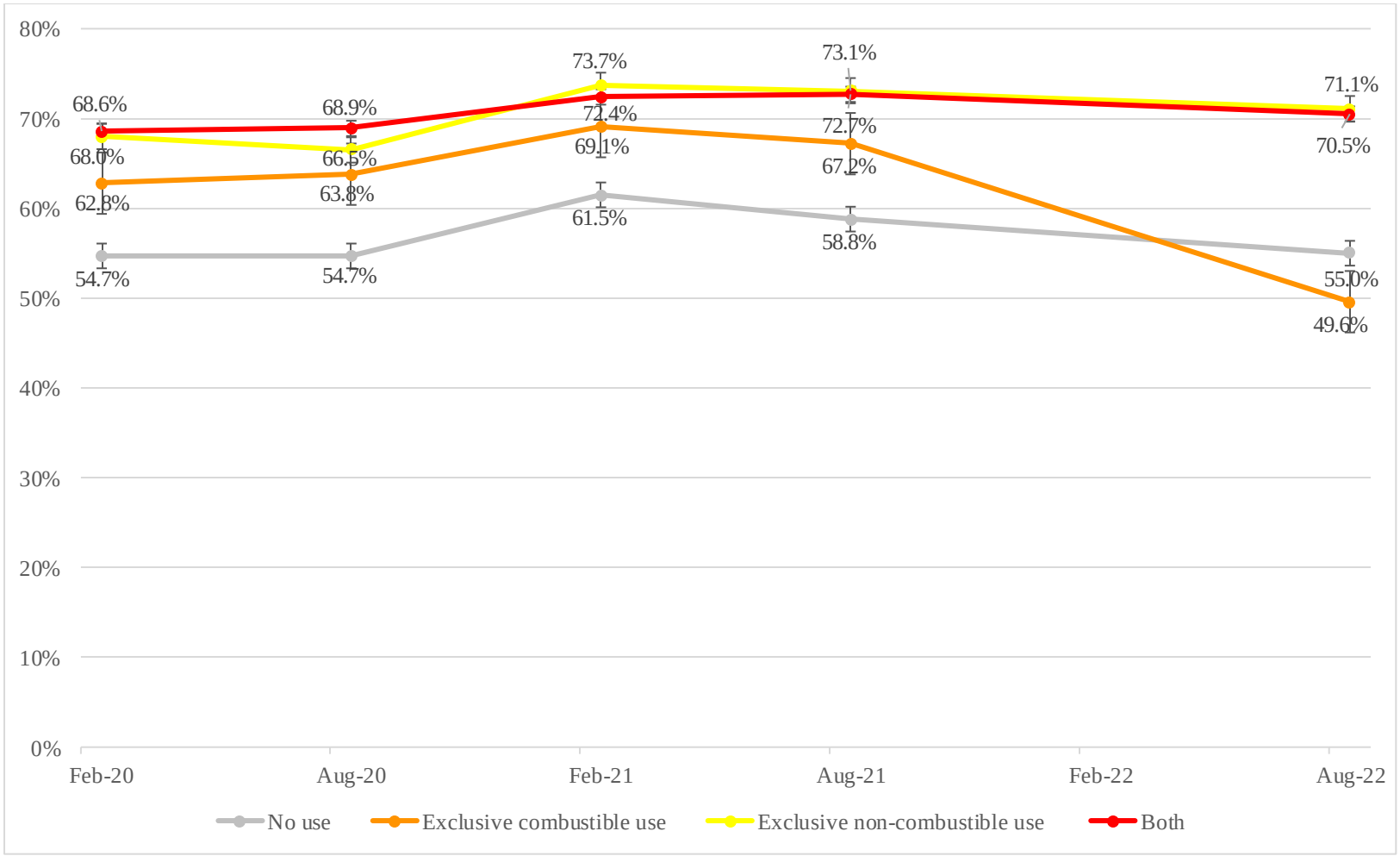

Figure 4.1. Trends in Internalizing Mental Health Symptom Prevalence by Current Nicotine Use
Figure illustrates prevalence of internalizing mental health symptoms by nicotine use type from 2020-2022. All prevalence rates are weighted.

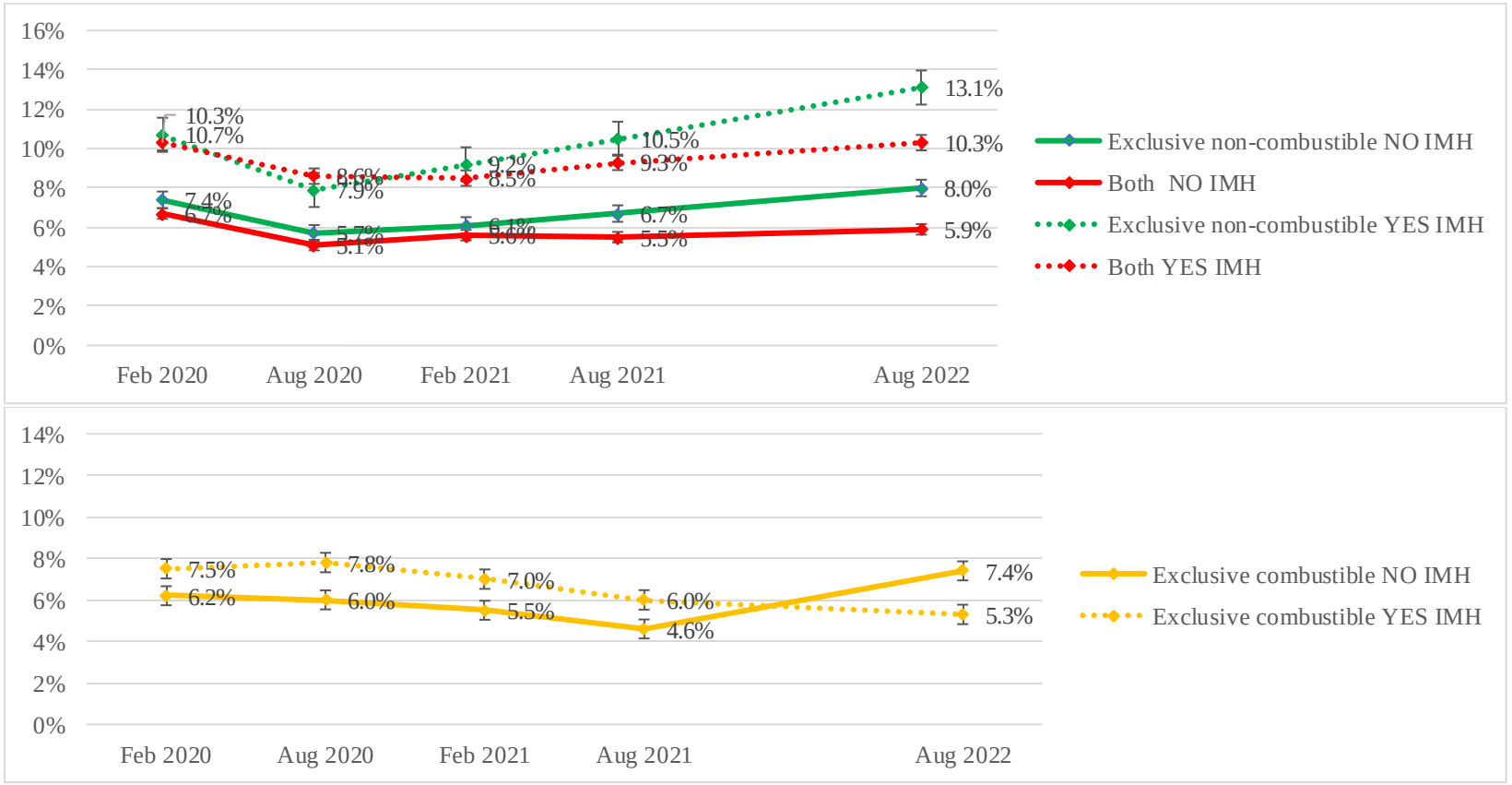

Figure 4.2. Predicted Probabilities of Nicotine Use by Internalizing Mental Health Symptoms Over Time Stratified by Use Type
Top graph includes prevalence of exclusive non-combustible and both product use by internalizing mental health (IMH) symptoms over time. Bottom graph shows prevalence of exclusive combustible use by IMH status over time. All prevalence rates are weighted and adjust for wave, country, age, sex, gender identity, race, and socioeconomic status.

Table 4.5 Association Between Internalizing Mental Health Symptoms and Current Nicotine Use Stratified by Wave

Strata		Exclusive Combustible Use *ARRR(95% CI)*[1]	Exclusive Non-Combustible Use *ARRR(95% CI)*[1]	Both *ARRR(95% CI)*[1]
February 2020 (n=13461)	No	ref	ref	ref
IMH Symptoms	Yes	**1.22 (1.05-1.41)****	**1.67 (1.46-1.90)*****	**1.89 (1.65-2.17)*****
August 2020 (n=14353)	No	ref	ref	ref
IMH Symptoms	Yes	**1.45 (1.25-1.67)*****	**1.60 (1.39-1.85)*****	**1.98 (1.71-2.29)*****
February 2021 (n=13957)	No	ref	ref	ref
IMH Symptoms	Yes	**1.39 (1.19-1.63)*****	**1.59 (1.38-1.84)*****	**1.63 (1.40-1.89)*****
August 2021 (n=13579)	No	ref	ref	ref
IMH Symptoms	Yes	**1.47 (1.24-1.73)*****	**1.82 (1.58-2.09)*****	**2.00 (1.73-2.32)*****
August 2022 (n=12596)	No	ref	ref	ref
IMH Symptoms	Yes	0.95 (0.81-1.11)	**1.80 (1.58-2.05)*****	**1.82 (1.57-2.10)*****

ARRR – adjusted relative risk ratio; CI – confidence interval; IMH – internalizing mental health

[1]ARRRs were estimated in multinomial regression model with current nicotine use (ref=no use) as the outcome. Model adjusted for IMH symptoms, wave, country, age, sex, gender identity, race, and socioeconomic status.

Bold indicates statistical significance. p<.05: *, p<.01: **, p<001: *** All models are weighted.

Table 4.6 Sensitivity Analysis: Crude Association Between IMH Symptoms and Current Nicotine Use Stratified by Wave

Strata		**Exclusive Combustible Use** *RRR(95% CI)*[1]	**Exclusive Non-Combustible Use** *RRR(95% CI)*[1]	**Both** *RRR(95% CI)*[1]
February 2020 (n=13461)	No	ref	ref	ref
IMH Symptoms	Yes	**1.40 (1.22-1.61)*** **	**1.76 (1.56-1.99)*** **	**1.81 (1.59-2.06)*** **
August 2020 (n=14353)	No	ref	ref	ref
IMH Symptoms	Yes	**1.46 (1.28-1.67)*** **	**1.65 (1.44-1.89)*** **	**1.84 (1.60-2.11)*** **
February 2021 (n=13957)	No	ref	ref	ref
IMH Symptoms	Yes	**1.40 (1.21-1.62)*** **	**1.75 (1.53-2.01)*** **	**1.63 (1.42-1.89)*** **
August 2021 (n=13579)	No	ref	ref	ref
IMH Symptoms	Yes	**1.44 (1.22-1.68)*** **	**1.90 (1.66-2.17)*** **	**1.87 (1.62-2.15)*** **
August 2022 (n=12596)	No	ref	ref	ref
IMH Symptoms	Yes	**0.81 (0.70-0.93)** **	**2.02 (1.78-2.28)*** **	**1.95 (1.71-2.24)*** **

RRR – adjusted relative risk ratio; CI – confidence interval; IMH – internalizing mental health
[1]RRRs were estimated in multinomial regression models with current nicotine use (ref=no use) as the outcome.
Bold indicates statistical significance. p<.05: *, p<.01: **, p<001: *** All models are weighted.

Chapter 5: Manuscript 2

The Association Between Internalizing Mental Health Symptoms and Characteristics of Cigarette and E-cigarette Use Among Adolescents in Canada, England, and the US[4]

Introduction

While cigarette use among adolescents has declined in recent years, tobacco use remains a public health concern, especially due to increasing e-cigarette use in recent years. E-cigarette use is associated with adverse cardiovascular and respiratory effects (2), with additional evidence that nicotine adversely affects brain development (3) and that mental health can be worsened by both e-cigarette use (21) and combustible cigarette use (144). There is limited evidence that different patterns of use (e.g., indicators of nicotine dependence, cessation behaviors) are more strongly associated with mental health symptoms (44,50,65,66,90,99,100). However, this limited evidence focuses largely on cigarette use and data from the period before e-cigarette use became popular among adolescents (e.g., 2017). Consequentially, these studies do not evaluate dual use of both products, which is increasingly common among adolescents (155) and has been found to be more strongly associated with poor mental health than exclusive use of either product (73–75). Furthermore, the COVID-19 pandemic impacted both adolescent mental health

[4] Hackworth, E.E., Vidana, D., Hammond, D., Kim, M., Fillo, J., Thrasher, J.F. To be submitted to *Addiction*.

(33–37) and tobacco/nicotine use (38,39). This study aimed to better understand how mental health is related to characteristics of cigarette, e-cigarette, and dual use among adolescents. Adolescents with untreated IMH conditions (e.g., depression, anxiety) are at risk for a number of adverse outcomes, including substance use disorders and suicide (14). Individuals suffering from untreated IMH conditions have a significantly shorter life expectancy than the general population (18,19). Several studies have found that nicotine dependence, defined as encompassing the physical and psychological factors that make it difficult for a person who uses tobacco products to stop (93), is positively associated with IMH problems among adolescents (90,99,100). However, these studies use a variety of measures of nicotine dependence that focus only on cigarette use.

Frequency of use, another indicator of nicotine dependence, is also associated with IMH symptoms and conditions among adolescents (44,50,51,56,57). Studies of cigarette smoking have found consistent, positive associations with IMH and smoking frequency. The few studies to examine IMH and e-cigarette use have found that IMH symptoms were positively associated with frequency of e-cigarette use (61), while another found no association (73). No studies have considered dual use of cigarettes and e-cigarettes to our knowledge.

IMH symptoms are also associated with quit intentions and quit attempts. While evidence among adults suggests that a lack of quit attempt or intention to quit are positively associated with IMH problems (e.g., (156,157)), only two studies have examined this among adolescents and both focus only on cigarette smoking. One study found that adolescents who smoked and did not want to quit or had not tried to quit had more IMH symptoms at follow up than adolescents who reported smoking at baseline but

successfully quit at follow up (66). Similarly, the other study found that adolescents with IMH conditions at baseline were less likely to quit at follow up than those without IMH conditions (65). While limited, these studies suggest that making a quit attempt or intending to quit may be related to better mental health among adolescents. More research is needed to better understand how quit attempts and quit intention are related to IMH symptoms, particularly for e-cigarette use, for which there is no evidence to date.

The purpose of this study is to examine IMH symptoms and indicators of dependence, quit intentions, and quit attempts among adolescents who use cigarettes and/or e-cigarettes. We hypothesized that the presence of IMH symptoms would be positively associated with dependence and negatively associated with quit attempt and quit intention, for both cigarette and e-cigarette use. We also hypothesized that dual use would moderate this relationship for all outcomes, where associations would be stronger for dual use compared to exclusive use.

Methods

Data Source

The data for this study come from the International Tobacco Control (ITC) Adolescents Tobacco and Vaping Survey. This national repeat cross-sectional survey is conducted in England, Canada, and the United States (USA). Participants answer questions about their experience with and beliefs about tobacco products, sociodemographic characteristics, and their mental health symptoms (150). The current study uses five waves of the ITC Adolescents Tobacco and Vaping Survey conducted between 2020-2022, including two surveys in 2020 (February-March; August), two in 2021 (February; August), and one in 2022 (August).

Participants were recruited from the Nielsen Consumer Insights Global Panel, which is a non-probability based sample. A random selection of panelists, parents of panelists (for participants under 18), or panelists with children ages 16-19 received email invitations with a unique survey link to screen for eligibility. Eligible participants were between the ages of 16 and 19 living in each of the three target countries. Participants received renumeration in accordance with the panel incentive structure, which included point-based rewards, monetary rewards, and/or chances to win monthly prizes.

The two analytic samples for this study were comprised of those who reported current cigarette use (n=8405) and current e-cigarette use (n=12049). Participants reporting dual use of both products were included in both samples. Participants indicating no current use of either product were excluded (n=53279). Participants who responded 'don't know' or 'refused' for mental health variables were excluded (n=176), resulting in a total analytic sample of 15522.

Measures

Dependent Variables: Indicators of Dependence

Current tobacco/nicotine use measures were adapted from the PATH study surveys (142), with questions about cigarette use and e-cigarette use asked separately but otherwise using the same wording.

Participants reported the number of days of use in the past month, which was used to examine frequency of use as a continuous variable. Responses of 'don't know' or 'refused' were recoded as missing and were excluded from analyses (n=1110 for cigarettes, n=2144 for e-cigarettes). Time to first use was measured by asking participants, "How soon after waking do you (smoke/vape)?" with response options

'within 5 minutes,' '6-30 minutes,' '31-60 minutes,' and '60+ minutes'. Responses of 'don't know' or 'refused' were recoded as missing and were excluded from analyses (n=776 for cigarettes, n=1095 for e-cigarettes).

Perceived addiction was measured by asking respondents, "Do you believe you are addicted to (smoking cigarettes / e-cigarettes/vaping?" with response options 'Yes, very much,' 'Yes, a little,' or 'Not at all' (113). Responses of 'don't know' or 'refused' were recoded as missing and were excluded from analyses (n=132 for cigarettes, n=466 for e-cigarettes).

Dependent Variables: Quit Intentions and Quit Attempt

For intention to quit, participants were asked, "Are you planning on quitting (smoking/vaping)…" with response options 'within the next month,' 'between 1-6 months from now,' recoded as 'intending to quit' and response options 'sometime in the future, beyond 6 months,' 'not planning to quit,' 'I don't currently smoke/vape,' and 'I don't know' coded as 'not intending to quit.' Responses of 'refused' were recoded as missing and were excluded from analyses (n=27 for cigarettes, n=61 for e-cigarettes).

For ever having a quit attempt, participants were asked, "Have you ever tried quitting (smoking/vaping)?" with response options 'yes' and 'no.' Responses of 'don't know' or 'refused' were recoded as missing and were excluded from analyses (n=57 for cigarettes, n=455 for e-cigarettes). For this outcome for cigarettes in the February 2020 wave, measurement differed from subsequent waves; therefore, respondents from that wave reporting current cigarette use have been dropped from models for this outcome (n=2173).

Mental health symptoms

Mental health symptoms were measured using two items from the Screening Tool for Psychological Distress (STOP-D), which has been validated among adults (143). Symptoms of depression were measured by asking participants, "In the last month, how much have you been bothered by feeling sad, down, or uninterested in life?" Symptoms of anxiety were measured by asking participants, "In the last month, how much have you been bothered by feeling anxious or nervous?" For both items, response options ranged from 0-9 (0='not at all,' 3='a little', 6='moderately', and 9='severely'). We assessed these as both continuous and binary variables (i.e., validated cut-points of 4 for depression symptoms and 5 for anxiety symptoms (143), and as both separate indicators and combined (i.e., average of continuous variables; either reporting symptoms of depression and/or anxiety vs not). Items were combined to create a dichotomous IMH symptoms variable.

Covariates

Participants were asked if they used any of the following tobacco products in the past 30 days: little cigars or cigarillos (LCCs), cigars, bidis, smokeless tobacco, hookah, and nicotine pouches. A variable 'other tobacco product use' was generated, with participants indicating using any of those products in the past month being coded as 'yes' and those who did not being coded as 'no.' A dual use variable was also generated, where participants who reported use of both cigarettes and e-cigarettes in the past month were coded as 'yes' and those who did not being coded as 'no.'

Participants indicated their age: 16, 17, 18, or 19 and their sex at birth: 'male' or 'female.' Participants were asked, "What is your current gender identity?" with response

options ‘Man’, ‘Woman’, ‘Trans male/ trans man’, ‘Trans female / trans woman’, ‘Gender queer / Gender non-conforming’, or ‘Different identity,’ where an open response was provided. Where possible, open responses were coded as man, woman, transgender, and GNC, aligning with recent recommendations for categorizing gender identity (26). These categories were recoded to ‘cisgender’ (i.e., man, woman) or non-cisgender (i.e., trans male, trans female, gender queer/gender non-conforming, different identity). Invalid responses were coded as missing but remained in analyses. Due to the varying types of racial and ethnic groups between the three countries, we derived a binary race variable (white only vs. other races or mixed race). Socioeconomic status (SES) was collected using a measure of perceived income adequacy, where participants were asked, “How would you describe your family’s financial situation?” with response options ‘not meeting basic expenses’, ‘just meeting basic expenses,’ ‘meeting needs with a little left over,’ ‘living comfortably’, and ‘don’t know/refuse’ (141). Participants were asked in which country they live: Canada, the USA, or England, which was used as an indicator of location. For each data collection wave, a wave indicator was generated.

Analyses

For each outcome (i.e., frequency of cigarette use/e-cigarette use; time to first cigarette/e-cigarette; perceived addiction to cigarettes/e-cigarettes; quit attempt of cigarettes/e-cigarettes; intention to quit smoking/e-cigarette use), a model was estimated using all respondents reporting use of the product (cigarettes or e-cigarettes). The primary independent variable for all models was the presence of IMH symptoms (symptoms of depression or anxiety vs. none). For a sensitivity analysis to ensure the dichotomous

version of the IMH symptom was consistent with the continuous version of that variable, we re-ran all models with the continuous variable.

Associations between IMH symptoms and frequency of use were examined using a Poisson regression model with frequency of use as the outcome (#1-30 days). Multinomial regression models were estimated for the outcomes of time to first use (1 hour+ (ref), 31-60 min, 6-30 min, and within 5 min) and perceived addiction (no (ref) vs. yes, a little, yes, a lot). For time to first use models, frequency of use was included as a covariate. Finally, logistic regression models were estimated for binary outcomes of ever having a quit attempt (no=reference) and quit intentions in the next 6 months (no=reference).

In order to examine the potential moderating effect of dual use, we assessed the interaction between IMH symptoms and dual use of cigarettes and e-cigarettes by creating an interaction term and adding it into the adjusted models for each outcome. When the interaction term was significant, we then stratified the main analyses by dual use or exclusive use and evaluated the coefficient associated with IMH.

All analyses include post-stratification sample weights, which were constructed based on population estimates for sociodemographic variables (age, sex, region in all countries; race in US only) and past 30 day smoking (based on national estimates in US and Canada; unavailable in England) (141). All models adjusted for dual use, use of other tobacco products, wave, sex, gender identity, race, age, SES, and country of residence. All analyses were conducted using Stata version 16

Results

Sample Characteristics

The sample characteristics are provided in Table 5.1. The analytic sample (n=15522) included 8,309 adolescents reporting cigarette use (exclusive=45%, dual=55%) and 11921 adolescents reporting e-cigarette use (exclusive=65%, dual=35%).

Nicotine Dependence Indicators

The association between IMH symptoms and nicotine dependence outcomes are shown in Table 5.2. Sensitivity analyses with the continuous IMH symptoms variable are shown in Table 5.3 and are consistent with the dichotomous results. IMH symptoms were associated with frequency of cigarette use in unadjusted models, but the association was no longer significant after adjusting for covariates. IMH symptoms were positively associated with frequency of e-cigarette use (adjusted coefficient.=0.07, SE=0.02).

IMH symptoms were positively associated with earlier time to first cigarette (i.e., $ARRR_{\text{within 31-60 minutes vs > 1 hour}}$=1.23, 95%CI=1.04-1.46; $ARRR_{\text{6-30 minutes vs >1 hour}}$=1.24, 95%CI=1.06-1.46), though not for first use within 5 minutes. IMH symptoms were positively associated with time to first use of e-cigarettes within 6-30 minutes (ARRR=1.32, 95% CI=1.16-1.52), and within 5 minutes (ARRR=1.64, 95% CI=1.41-1.92), but not within 31-60 minutes.

IMH symptoms were negatively associated with perceiving oneself to be a little addicted to cigarettes (ARRR: 0.89, 95% CI=0.79-0.99) but positively associated with perceiving oneself to be very addicted to cigarettes (ARRR= 1.41, 95%CI= 1.22-1.64). IMH symptoms were positively associated with perceiving oneself to be both a little

addicted to e-cigarettes (ARRR=1.21, 95% CI=1.10-1.33) and very addicted to e-cigarettes (ARRR=1.76, 1.55-1.99).

Cessation Variables

The association between IMH symptoms and cessation variables (i.e., quit intention and quit attempts) are shown in Table 5.4 and sensitivity analyses with the continuous IMH symptoms variable are shown in Table 5.5. IMH symptoms were not associated with intention to quit cigarettes or e-cigarettes.

IMH symptoms were positively associated with higher odds of ever having tried to quit cigarettes (AOR=1.60, 95% CI=1.38-1.85). IMH symptoms were positively associated with higher odds of ever having tried to quit e-cigarettes (AOR=1.47, 95% CI=1.31-1.65). Sensitivity analyses were consistent.

Interaction of IMH Symptoms and Dual Use

The interaction of IMH symptoms and dual use was statistically significant in the models for time to first cigarette and perceived addiction to cigarettes. Results for these outcomes stratified by dual use are shown in Table 5.6 and sensitivity analyses with the continuous IMH symptoms variable are shown in Table 5.7.

Among adolescents reporting exclusive cigarette use, IMH symptoms were associated with cigarette use within 5 minutes compared to using 1 hour or more after waking (ARRR=0.65, 95% CI=0.49-08.88), but not with other categories. Alternatively, among adolescents reporting dual use, IMH symptoms were positively associated with earlier time to first use, where the strongest association was within 5 minutes (ARRR=1.52, 95% CI=1.16-1.99), followed by 6-30 minutes (ARRR=1.32, 95% CI=1.07-1.63), and then 31-60 minutes (ARRR=1.30, 95% CI=1.03-1.65).

Among adolescents reporting exclusive cigarette use, IMH symptoms were negatively associated with perceiving oneself to be a little addicted to cigarettes (ARRR=0.80, 95% CI=0.68-0.93) and positively associated with perceiving oneself to be very addicted to cigarettes, but only in the unadjusted model. Among adolescents reporting dual use, IMH symptoms were positively associated with perceiving oneself to be very addicted to cigarettes (ARRR=1.76, 95% CI=1.42-2.18), but unassociated with perceiving oneself to be a little addicted to cigarettes. Sensitivity analyses were consistent.

Discussion

This study found that adolescents with IMH symptoms have different patterns of cigarette and/or e-cigarette use than those who do not have IMH symptoms. In particular, we found that IMH symptoms were positively associated with a number of indicators of e-cigarette dependence, with inconsistent results for indicators of cigarette dependence. We also found that IMH symptoms were positively associated with ever having a quit attempt for both cigarettes and e-cigarettes, but there was no association for quit intention after adjusting for covariates.

Our findings that IMH symptoms were positively associated with e-cigarette use frequency but not with cigarette use frequency are consistent with another study that evaluated depressive symptoms among adolescents (61). Previous studies focusing on the association between mental health and cigarette smoking frequency found a positive association (44,50,51,56,57), though all analyzed data collected prior to 2017, when e-cigarette use became more popular among adolescents. Our study, with more recent data, suggests that this association has shifted away from smoking behaviors and toward e-

cigarette use. Adolescents with IMH symptoms may be more likely to use e-cigarettes frequently due to the fact that e-cigarettes are easier to hide and use discretely than cigarettes (158). Alternatively, they may be using e-cigarettes to self-medicate IMH symptoms. Longitudinal research is needed to explore this relationship.

IMH symptoms were positively associated with earlier time to first use of e-cigarettes. While no prior studies have examined the association between IMH symptoms and time to first use among adolescents, this finding aligns with our finding for frequency of use, where there was a positive association with e-cigarette use but not cigarette use. However, after considering dual use, there was a positive association between IMH symptoms and earlier time to first cigarette among adolescents reporting dual use but not exclusive cigarette use. It is possible that adolescents more prone to IMH symptoms may be more likely to use e-cigarettes; however, longitudinal research is needed to better understand directionality.

For perceived addiction, we found that IMH symptoms were positively associated with perceiving oneself to be a little or very addicted to e-cigarettes. The association between IMH symptoms and perceived addiction to cigarettes was moderated by dual use. Among those reporting dual use, IMH symptoms were positively associated with perceived addiction; however, among those reporting exclusive cigarette use, IMH symptoms were negatively associated with perceived addiction. To our knowledge, the association between IMH symptoms and perceived addiction have not been examined yet. Studies have found that IMH symptoms are positively associated with various measures of nicotine dependence among adolescents (90,99,100,159); however, these studies all focus on adolescent use of cigarettes from 1977-2005, before e-cigarettes were

on the market. Furthermore, it is possible that adolescents with particularly high risk for mental health problems are more likely to engage in dual use. Longitudinal studies are needed to better understand the directionality of these relationships.

IMH symptoms were not significantly associated with intentions to quit either cigarettes or e-cigarettes. This contradicted our hypotheses, which were based on studies of adults that have generally found that quit intention is predictive of successful cessation (156,157). However, there is evidence that among adults who have not successfully quit, people who smoke with mental health conditions are just as motivated to quit smoking as those without mental health conditions (160) and that among psychiatric populations, quit intention is not associated with current mental health symptoms (161). Our results suggest that similar patterns of association also apply to adolescents.

We found that IMH symptoms were positively associated with having attempted to quit both cigarettes and e-cigarettes, whether intention to quit was examined continuously or categorically. This finding may be due to the nicotine withdrawal symptoms during quit attempts. For example, nicotine withdrawal results in worsened mental health symptoms which are then alleviated by continuing to use nicotine in the short term (162). Indeed, adolescents with poor mental health may be more likely to relapse when they try to quit, as found in one prior study (159). Furthermore, a recent study found that adults with depression who smoke cigarettes were more likely to attempt to quit than those without depression (163), though, to our knowledge, no such studies have been conducted among adolescents. More research is needed to better understand cessation behaviors and beliefs among adolescents to better understand these findings,

including longitudinal studies that evaluate subsequent quit attempts, as this cross-sectional study focused only on ever having tried to quit.

This study has several strengths, including using large, national data sets from three countries, with the data weighted to draw population-level inferences. The measures were the same for both cigarettes and e-cigarettes, facilitating comparisons around the strength of associations across products. However, there are several limitations to this study. First, causation cannot be concluded from these cross-sectional data, and future studies with longitudinal data will be required to confirm directionality. Another limitation is that the IMH measures have only been validated in adults at the present. However, the prevalence rates of any symptoms of depression and anxiety found by these measures are similar to population-level prevalence rates found using other measures (154), suggesting that our measurements are appropriate for the adolescent population. Furthermore, our sensitivity analyses indicate consistent results between the continuous and dichotomous version of the IMH variable.

While some interpretations of our findings warrant further research, our results suggest that IMH problems are prevalent and comorbid with more frequent use and dependence of nicotine products, particularly e-cigarettes, in adolescents. Other studies show that smoking cessation interventions for adolescents should include coping and stress management skills, as well as mental health referral protocols (164). Furthermore, stress reduction techniques that include physical activity have been found to increase smoking cessation success rates among teenagers (165) and may also work for e-cigarette cessation, as well. Similarly, tobacco/nicotine use prevention campaigns targeting adolescents may wish to include testimonials from individuals with IMH problems who

struggle with cessation, as this type of campaign has been shown to be more effective at increasing smoking cessation for adults who smoke with IMH problems (166). Recent campaigns from public health organizations including the Truth Initiative have begun incorporating concerns about mental health among adolescents who use nicotine products (167), and our results support this approach.

Tables and Figures

Table 5.1 Sample Characteristics

Characteristics	**Categories**	**Cigarette Use (n=8309) n (weighted %)[1]**	**E-Cigarette Use (n=11921) n (weighted %)[1]**
Wave	Feb 2020	2173 (23.3%)	2751 (22.5%)
	Aug 2020	1535 (20.6%)	1889 (17.4%)
	Feb 2021	1407 (19.2%)	2112 (18.5%)
	Aug 2021	1533 (17.1%)	2285 (19.4%)
	Aug 2022	1661 (19.7%)	2884 (22.2%)
Country	Canada	2139 (27.1%)	3964 (32.7%)
	England	3909 (54.1%)	3654 (31.4%)
	USA	2261 (18.8%)	4303 (35.9%)
Age	16	1373 (18.1%)	1843 (17.2%)
	17	1972 (26.1%)	2515 (22.6%)
	18	2686 (31.0%)	4258 (34.8%)
	19	2278 (24.8%)	3305 (25.4%)
Sex	Male	3246 (57.3%)	3780 (49.1%)
Gender Identity	Cisgender	7875 (95.9%)	11305 (95.7%)
Race	White	6104 (77.8%)	8355 (75.5%)
SES	Not meeting needs	701 (7.2%)	819 (6.2%)
	Just meeting needs	2545 (28.2%)	3512 (27.5%)
	Meeting needs	2501 (31.0%)	3757 (31.7%)
	Living comfortably	2289 (30.6%)	3430 (31.7%)
	No response	273 (2.9%)	403 (3.0%)
IMH Symptoms	Yes	5930 (66.7%)	8958 (70.9%)
Dual Use	Yes	4708 (45.6%)	4708 (34.8%)
Use of other nicotine products	Yes	2819 (33.4%)	3194 (26.6%)
Frequency of use [2]	Mean (SE)	13.6 (0.14)	15.07 (0.12)
Time to first use [2]	Within 5 minutes	845 (10.7%)	2221 (18.8%)
	6-30 minutes	1530 (19.8%)	2219 (20.3%)
	31-60 minutes	1071 (14.3%)	1326 (12.4%)
	1 hour+	4087 (55.3%)	5060 (48.5%)

Perceived addiction [2]	Not at all	2973 (36.0%)	4663 (42.1%)
	A little	3695 (46.5%)	4448 (39.1%)
	Very	1509 (17.5%)	2344 (18.8%)
Intend to quit within 6 months [2]	Yes	2348 (33.0%)	3313 (32.1%)
Ever had a quit attempt [2]	Yes	3312 (50.1%)	5367 (46.6%)

Table 5.2 Internalizing Mental Health Symptoms and Nicotine Dependence Outcomes for using Cigarettes and E-cigarettes

Frequency of Use[1]							
		#1-30 days					
		b (SE)	Adj. b(SE)				
Cigarettes (n=7199)							
IMH	No	ref	ref				
Symptoms	Yes	**-0.07 (0.03)****	-0.04 (0.03)				
E-cigarettes (n=9777)							
IMH	No	ref	ref				
Symptoms	Yes	**0.09 (0.02)*****	**0.05 (0.02)***				
Time to First Use (ref >60 minutes)[2]							
		31-60 min		6-30 min		Within 5 min	
		RRR (95% CI)	*ARRR (95% CI)*	*RRR (95% CI)*	*ARRR (95% CI)*	*RRR (95% CI)*	*ARRR (95% CI)*
Cigarettes (n=7553)							
IMH	No	ref	ref	ref	ref	ref	ref
Symptoms	Yes	**1.19 (1.03-1.37)***	**1.31 (1.07-1.61)****	**1.19 (1.04-1.34)****	**1.29 (1.07-1.56)****	1.04 (0.89-1.22)	0.87 (0.70-1.08)
E-cigarettes (n=10826)							
IMH	No	ref	ref	ref	ref	ref	ref
Symptoms	Yes	1.05 (0.93-1.20)	1.19 (0.92-1.32)	**1.33 (1.19-1.49)*****	**1.41 (1.21-1.66)*****	**1.80 (1.59-2.03)*****	**1.57 (1.31-1.87)*****
Perceived Addiction (ref "not at all")[3]							
		A little		Very			
		RRR (95% CI)	*ARRR (95% CI)*	*RRR (95% CI)*	*ARRR (95% CI)*		
Cigarettes (n=81777)							
IMH	No	ref	ref	ref	ref		
Symptoms	Yes	**0.89 (0.78-0.95)****	0.99 (0.87-1.12)	**1.43 (1.25-1.65)*****	**1.44 (1.21-1.71)*****		
E-cigarettes (n=11455)							
IMH	No	ref	ref	ref	ref		
Symptoms	Yes	**1.13 (1.03-1.23)****	**1.13 (1.02-1.26)***	**1.74 (1.54-1.96)*****	**1.62 (1.40-1.87)*****		

RRR: relative risk ratio, ARRR: adjusted relative risk ratio, IMH: Internalizing mental health symptoms; CI – confidence interval

Adjusted models include dual use, other tobacco product use, age, sex, race, socioeconomic status, wave, and country.

[1] Poisson regression models. DV: frequency of use in the prior month (range=1-30 days)

[2] Multinomial logistic regression models. DV: Time to first use (>60 min=reference). Also adjusts for frequency of use.

[3] Multinomial logistic regression models. DV: Perceived addiction (not at all=reference).

All models are weighted. Bold indicates statistical significance; *:p<0.05, **:p<0.01, ***:p<0.001.

Table 5.3 Sensitivity Analysis: Continuous Internalizing Mental Health Symptoms and Nicotine Dependence Outcomes

Frequency of Use[1]						
	#1-30 days					
	b (SE)	*Adj. b(SE)*				
Cigarettes (n=7199)						
IMH	ref	ref				
Symptoms	-0.01 (0.004)	-0.001 (0.005)				
E-cigarettes (n=9777)						
IMH	Ref	ref				
Symptoms	**0.02 (0.004)*** **	**0.02 (0.004)*** **				
Time to First Use (ref >60 minutes)[2]						
	31-60 min		6-30 min		Within 5 min	
	RRR (95% CI)	*ARRR (95% CI)*	*RRR (95% CI)*	*ARRR (95% CI)*	*RRR (95% CI)*	*ARRR (95% CI)*
Cigarettes (n=7553)						
IMH	ref	ref	ref	ref	ref	ref
Symptoms	**1.03 (1.01-1.06)***	**1.03 (1.00-1.07)***	**1.02 (1.00-1.04)***	1.02 (0.99-1.05)	1.01 (0.98-1.04)	0.99 (0.96-1.03)
E-cigarettes (n=10826)						
IMH	ref	ref	ref	ref	ref	ref
Symptoms	1.01 (0.98-1.03)	1.02 (0.99-1.05)	**1.06 (1.04-1.08)*** **	**1.06 (1.03-1.08)*** **	**1.13 (1.11-1.15)*** **	**1.11 (1.08-1.14)*** **
Perceived Addiction (ref "not at all")[3]						
	A little		Very			
	RRR (95% CI)	*ARRR (95% CI)*	*RRR (95% CI)*	*ARRR (95% CI)*		
Cigarettes (n=81777)						
IMH	ref	ref	ref	ref		
Symptoms	**0.98 (0.96-0.99)** **	0.98 (0.97-1.00)	**1.10 (1.07-1.12)*** **	**1.10 (1.07-1.13)*** **		
E-cigarettes (n=11455)						
IMH	ref	ref	ref	ref		
Symptoms	**1.03 (1.01-1.04)** **	**1.04 (1.03-1.06)*** **	**1.15 (1.13-1.17)*** **	**1.17 (1.14-1.19)*** **		

RRR: relative risk ratio, ARRR: adjusted relative risk ratio, IMH: Internalizing mental health symptoms; CI – confidence interval

Adjusted models include dual use, other tobacco product use, age, sex, race, socioeconomic status, wave, and country. IMH symptoms variable includes a 9-point scale (0=no symptoms, 9=severe symptoms)

[1] Poisson regression models. DV: frequency of use in the prior month (range=1-30 days)

[2] Multinomial logistic regression models. DV: Time to first use (>60 min=reference). Also adjusts for frequency of use.

[3] Multinomial logistic regression models. DV: Perceived addiction (not at all=reference).

All models are weighted. Bold indicates statistical significance; *:p<0.05, **:p<0.01, ***:p<0.001.

Table 5.4 Internalizing Mental Health Symptoms and Cigarette and E-cigarette Cessation Variables

		Intention to Quit Within 6 Months[1] *OR (95% CI)*	*AOR (95% CI)*
Cigarettes (n=7100)			
IMH Symptoms	No	ref	ref
	Yes	**1.19 (1.04-1.36)***	1.01 (0.86-1.18)
E-cigarettes (n=10386)			
IMH Symptoms	No	ref	ref
	Yes	**1.12 (1.00-1.26)***	1.16 (0.98-1.34)

		Ever Had a Quit Attempt[2] *OR (95% CI)*	*AOR (95% CI)*
Cigarettes (n=6079)			
IMH Symptoms	No	ref	ref
	Yes	**1.97 (1.72-2.25)*****	**1.59 (1.38-1.84)*****
E-cigarettes (n=9073)			
IMH Symptoms	No	ref	ref
	Yes	**1.51 (1.34-1.70)*****	**1.51 (1.33-1.71)*****

OR: relative risk ratio, AOR: adjusted odds ratio, IMH: Internalizing mental health symptoms; CI – confidence interval
Adjusted models include dual use, other tobacco product use, age, sex, race, socioeconomic status, wave, and country.
[1] Logistic regression models. DV: Intention to quit in next 6 months (no=reference)
[2] Logistic regression models. DV: Ever having quit attempt (no=reference). Excludes February 2020 wave due to administration differences.
All models are weighted. Bold indicates statistical significance; *:p<0.05, **:p<0.01, ***:p<0.001

Table 5.5 Sensitivity Analysis: Continuous Internalizing Mental Health Symptoms and Cigarette and E-cigarette Cessation Variables

		Intention to Quit Within 6 Months[1] *OR (95% CI)*	*AOR (95% CI)*
Cigarettes (n=7100)			
IMH Symptoms	(0-9)	ref 1.03 (0.98-1.05)	ref 1.02 0.99-1.05)
E-cigarettes (n=10386)			
IMH Symptoms	(0-9)	ref 1.00 (0.99-1.03)	ref 1.01 (0.99-1.03)

		Ever Had a Quit Attempt[2] *OR (95% CI)*	*AOR (95% CI)*
Cigarettes (n=6079)			
IMH Symptoms	(0-9)	ref **1.13 (1.10-1.16)*** **	ref **1.09 (1.06-1.12)*** **
E-cigarettes (n=9073)			
IMH Symptoms	(0-9)	ref **1.08 (1.06-1.10)*** **	ref **1.08 (1.06-1.10)*** **

OR: odds ratio, AOR: adjusted odds ratio, IMH: Internalizing mental health symptoms
Adjusted models include dual use, other tobacco product use, age, sex, race, socioeconomic status, wave, and country. IMH symptoms variable includes a 9-point scale (0=no symptoms, 9=severe symptoms)
[1] Logistic regression models. DV: Intention to quit in next 6 months (no=reference)
[2] Logistic regression models. DV: Ever having quit attempt (no=reference). Excludes February 2020 wave due to administration differences.
All models are weighted. Bold indicates statistical significance; *:p<0.05, **:p<0.01, ***:p<0.001

Table 5.6 Association of IMH Symptoms and Time to First Cigarette and Perceived Addiction to Cigarettes Stratified by Dual Use

		Time to First Cigarette[1]					
		31-60 min		**6-30 min**		**Within 5 min**	
		RRR (95% CI)	*ARRR (95% CI)*	*RRR (95% CI)*	*ARRR (95% CI)*	*RRR (95% CI)*	*ARRR (95% CI)*
Exclusive cigarette (n=3279)							
IMH Symptoms	**No**	ref	ref	ref	ref	ref	ref
	Yes	1.08 (0.88-1.32)	1.22 (0.94-1.57)	1.19 (0.99-1.43)	1.21 (0.95-1.55)	**0.70 (0.56-0.89)****	**0.67 (0.50-0.91)****
Dual use (n=4254)							
IMH Symptoms	**No**	ref	ref	ref	ref	ref	ref
	Yes	**1.37 (1.11-1.68)****	**1.31 (1.04-1.66)***	**1.19 (1.00-1.41)***	**1.33 (1.07-1.64)****	**1.54 (1.22-1.94)*****	**1.52 (1.16-1.99)****
		Perceived Addiction to Cigarettes[2]					
		A little addicted		**Very addicted**			
		RRR (95% CI)	*ARRR (95% CI)*	*RRR (95% CI)*	*ARRR (95% CI)*		
Exclusive cigarette (n=3959)							
IMH Symptoms	**No**	ref	ref	ref	ref		
	Yes	**0.76 (0.66-0.87)*****	**0.81 (0.69-0.94)****	**1.27 (1.05-1.54)***	1.17 (0.95-1.45)		
Dual use (n=4756)							
IMH Symptoms	**No**	ref	ref	ref	ref		
	Yes	0.94 (0.81-1.08)	1.02 (0.88-1.19)	**1.60 (1.30-1.96)*****	**1.77 (1.42-2.19)*****		

RRR: relative risk ratio, ARRR: adjusted relative risk ratio; CI – confidence interval; IMH: Internalizing mental health symptoms
Models adjust for IMH symptoms, other tobacco product use, age, sex, race, socioeconomic status, wave, and country.
[1] Multinomial logistic regression models. DV: Time to first use (>60 min, 31-60 min, 6-30 min, within 5 min). Also adjusts for frequency of use. [2] Multinomial logistic regression models. DV: Perceived addiction (not at all vs. a little, very).
All models are weighted. Bold indicates statistical significance; *:p<0.05, **:p<0.01, ***:p<0.001

Table 5.7 Sensitivity Analysis: Association of Continuous IMH Symptoms and Time to First Cigarette and Perceived Addiction to Cigarettes Stratified by Dual Use Status

	Time to First Cigarette[1]					
	31-60 min		**6-30 min**		**Within 5 min**	
	RRR (95% CI)	*ARRR (95% CI)*	*RRR (95% CI)*	*ARRR (95% CI)*	*RRR (95% CI)*	*ARRR (95% CI)*
Exclusive cigarette (n=3279)						
IMH Symptoms	ref	ref	ref	ref	ref	ref
	1.02 (0.98-1.06)	1.03 (0.98-1.08)	1.02 (0.99-1.05)	1.01 (0.97-1.06)	**0.94 (0.90-0.98)****	**0.91 (0.86-0.96)*****
Dual use (n=4254)						
IMH Symptoms	ref	ref	ref	ref	ref	ref
	1.05 (1.02-1.09)**	1.04 (0.99-1.08)	1.02 (0.99-1.05)	1.03 (0.99-1.07)	**1.09 (1.04-1.13)*****	**1.09 (1.04-1.14)*****
	Perceived Addiction to Cigarettes[2]					
	A little addicted		**Very addicted**			
	RRR (95% CI)	*ARRR (95% CI)*	*RRR (95% CI)*	*ARRR (95% CI)*		
Exclusive cigarette (n=3959)						
IMH Symptoms	ref	ref	ref	ref		
	0.96 (0.94-0.98)**	**0.97 (0.95-0.99)***	**1.07 (1.04-1.11)*****	1.06 (0.99-1.10)		
Dual use (n=4756)						
IMH Symptoms	ref	ref	ref	ref		
	0.98 (0.96-1.00)	1.00 (0.98-1.03)	**1.12 (1.08-1.16)*****	**1.15 (1.11-1.19)*****		

RRR: relative risk ratio, ARRR: adjusted relative risk ratio; CI – confidence interval; IMH: Internalizing mental health symptoms
Models adjust for IMH symptoms (0-9), other tobacco product use, age, sex, race, socioeconomic status, wave, and country.
[1] Multinomial logistic regression models. DV: Time to first use (>60 min, 31-60 min, 6-30 min, within 5 min). Also adjusts for frequency of use. [2] Multinomial logistic regression models. DV: Perceived addiction (not at all vs. a little, very).
All models are weighted. Bold indicates statistical significance; *:p<0.05, **:p<0.01, ***:p<0.001

Chapter 6: Manuscript 3

The Relationship Between Gender Identity, Nicotine Use, and Mental Health Among Adolescents in Canada, England, and the US from 2020-2022[5]

Introduction

Use of nicotine products among adolescents remains a public health concern, especially in light of the high prevalence of adolescent e-cigarette use, the growing array of nicotine-containing products available, and adolescents' tendency to underestimate the potential harm (39). While all adolescents are at risk for nicotine use, some groups are more at risk than others. For example, adolescent males consistently have higher rates of nicotine use than adolescent females (168,169). Adolescents with sexual minority identities- that is, those who identify as gay, lesbian, or bisexual, or who are attracted to people of the same gender (170)- have higher rates of nicotine use than non-sexual minority adolescents (171). However, there is a dearth of research examining nicotine use among gender minority adolescents- that is, those whose gender identity (man, woman, non-binary) is different from their sex assigned at birth (male, female) and include identities of transgender and gender non-conforming (GNC) (170). Due to low prevalence rates of these groups in the population, researchers often group sexual and gender minorities (SGM) together as one high-risk group (172–174); however, given that

[5] Hackworth, E.E., Vidana, D., Hammond, D., Kim, M., Fillo, J., Thrasher, J.F. To be submitted to *LGBT Health*..

sexual identity and gender identity are distinct constructs, there is a need to disentangle these risk factors.

While SGM research has continued to grow, research specifically focusing on gender minority adolescents remains limited (172–174). The number of adolescents who identify as a gender minority has increased in recent years (25), but very little is known about their nicotine use behaviors compared to non-gender minority adolescents. Studies of adults find a positive association between gender minority identity and nicotine use (175–178). Studies of SGM samples find elevated rates of smoking among gender minority adolescents compared to sexual minority adolescents (179,180). However, without a comparison to non-gender minority adolescents, it is difficult to disentangle the impact of sexual identity vs. gender identity. While sexual and gender minority identities may overlap among some adolescents, grouping them together prevents a nuanced assessment of gender minority adolescents and the unique health challenges they may face (25). For example, gender minority adolescents may experience more discrimination based on physical appearance, particularly early in transition; whereas sexual minority adolescents may be perceived as heterosexual (181). Health discrimination is reported by both groups; however, sexual minority adolescents may face challenges regarding assumptions of heteronormativity, whereas gender minority adolescents may face barriers regarding gender affirming care (172). Additionally, a lack of familial support is widespread among transgender and GNC individuals and greatly impacts their health (182). As these types of discrimination can all impact health, it is important for research to distinguish between sexual minorities and gender minorities.

In addition to differentiating between SGM identities, there is a need to better understand specific gender identities, as unique experiences may contribute to nicotine product use and health (25). For example, transgender and GNC individuals may face different types of discrimination (183) and may have different experiences with gender dysphoria (25). Among the public, there is a lack of understanding of what encompasses a GNC identity, while transgender identities have more established definition (25). As such, protective factors like social communities and peer support may be stronger for transgender adolescents compared to GNC adolescents (25). One study of adults found similar smoking rates among transgender and GNC adults (184), whereas another found lower smoking prevalence among GNC adults compared to transgender adults (185). To our knowledge, only one study has examined the relationship between nicotine use and gender identity including gender minority identities among adolescents: compared to non-transgender adolescents, transgender adolescents reported higher prevalence of nicotine product use; however, this study did not differentiate between transgender and GNC identities (186). Currently, no studies have examined differences in patterns of nicotine use for transgender or GNC adolescents, and how these patterns may differ from non-gender minority adolescents. Therefore, more research is needed on these important and growing groups of gender minority adolescents.

The growing array of nicotine-containing products beyond cigarettes have complicated the study of nicotine product use. Indeed, non-combustible products (e.g., e-cigarettes, nicotine pouches) appear less harmful than combustible products (e.g., cigarettes, cigars) (145), since most carcinogens to which people are exposed when they use combustible tobacco products result from combustion (146–148). Nevertheless,

adolescents use of any nicotine product is a concern due to the harms of combustion and the potential harms of nicotine use, as nicotine can adversely affect brain development (3). Given the potential differences in risk based on combustion, there is a need to further understand the diversity of nicotine product use between gender identities.

Across the spectrum of adolescents gender identities, another public health concern is mental health. Specifically, Internalizing mental health (IMH) symptoms (i.e., symptoms of anxiety and depression (8)) are highly prevalent among adolescents, rarely diagnosed or treated (7), and increasing (187). Adolescents with untreated IMH symptoms are at risk for a number of adverse outcomes, including substance use disorders and suicide (14). Individuals suffering from mental health conditions have a significantly shorter life expectancy than the general population, largely attributed to substance use-related conditions, including nicotine use (18,19). Gender minority adolescents are exposed to a variety of social stressors, including stigma, discrimination, and bias events that can contribute to mental health problems (28,29,188), and exhibit higher rates of IMH problems, self-harm, and suicidality (189).

There is abundant evidence that nicotine use and IMH symptoms are positively associated (20). Furthermore, many studies have found evidence that the relationship between nicotine use and internalizing mental health is stronger for females compared to males (42,44,45,48,49,57,59,65), though a few studies have found the inverse (46,89) or no differences (40,50,63,64,66,68,90,91). To our knowledge, no studies have explicitly examined the relationship between nicotine use and mental health among gender minority adolescents. Given disproportionate health risks in these populations, this is important research gap to fill.

The purpose of this study is to examine associations between gender identity, nicotine use, and IMH symptoms. We hypothesize that use of both combustible and non-combustible nicotine products will be more prevalent among transgender and GNC adolescents, and that IMH symptoms will be more likely among transgender and GNC adolescents. We hypothesize that adolescent men will be more likely to use nicotine products, but less likely to have IMH symptoms, than women. We also hypothesize that gender identity will moderate the relationship between IMH symptoms and nicotine use. Our previous work has shown that adolescents who report IMH symptoms are also more likely to report use of combustible and non-combustible nicotine products; however, it is unclear whether gender identity may moderate this relationship.

Methods

Data Source

The data for this study come from the International Tobacco Control (ITC) Policy Evaluation Project Adolescents Tobacco and Vaping Survey, a repeat cross-sectional survey of national samples of adolescents in England, Canada, and the United States (USA). This study uses five waves of the ITC Adolescents Tobacco and Vaping Survey conducted between 2020-2022: two surveys in 2020 (February to March; August); two in 2021 (February; August); and one in 2022 (August). Participants were recruited from the Nielsen Consumer Insights Global Panel, with a final sample target of 4,500 participants for each country at each survey. For each survey, Nielsen selected random samples from both probability and non-probability panels in each country.

A non-probability random selection of panelists, parents of panelists (for participants under 18), or panelists with children ages 16-19 received email invitations

with a unique survey link to screen for eligibility. Eligible participants were between the ages of 16 and 19 living in each of the three target countries. After reviewing information about the study and consenting to participate, eligible participants completed the survey. Participants received renumeration in accordance with the panel incentive structure, which included point-based rewards, monetary rewards, and/or chances to win monthly prizes. All participants from the full sample were included in this analytic sample, with the exception of participants who had an invalid response for the gender identity variable (n=492).

Measures

Tobacco/Nicotine Product Use

Current nicotine use measures were adapted from national surveys to monitor tobacco use in the US (142). The number of days of cigarette and e-cigarette use in the past month were used to derive dichotomous 'current use' variables for each product (i.e., 1=1-30 days; 0= no days). Current (i.e. past 30 day) use of little cigars or cigarillos (LCCs), cigars, bidis, smokeless tobacco, hookah, and nicotine pouches were measured with a checklist (responses: 'yes' or 'no'). Patterns of product use was derived using these current use variables: no past 30-day use of any products; exclusive use of combusted products (cigarettes, little cigars or cigarillos, cigars, bidis, hookah); exclusive use of non-combusted products (e-cigarette, smokeless tobacco, and nicotine pouches); or use of both combusted and non-combusted use (at least one combusted and one non-combusted product).

Gender Identity Measure

Participants were asked, "What is your current gender identity?" with response options 'Man', 'Woman', 'Trans male/ trans man', 'Trans female / trans woman', 'Gender queer / Gender non-conforming', or 'Different identity,' where an open response was provided. Where possible, open responses (n=804) were coded as man, woman, transman, transwoman, and GNC, aligning with recent recommendations for categorizing gender identity (26). Responses that did not fit into any of these categories (n=492) were excluded from the analytic sample. Primary analyses were stratified by whether participants had selected the 'Gender queer / GNC' closed-ended response or had been categorized as 'GNC' through their open-ended response.

Mental health symptoms

Mental health symptoms were measured using two items from the Screening Tool for Psychological Distress (STOP-D), which has been validated among adults (143). Symptoms of depression were measured by asking participants, "In the last month, how much have you been bothered by feeling sad, down, or uninterested in life?" Symptoms of anxiety were measured by asking participants, "In the last month, how much have you been bothered by feeling anxious or nervous?" For both items, response options ranged from 0-9, where 0='not at all,' 3='a little', 6='moderately', and 9='severely'. We assessed these as both continuous and binary variables (i.e., validated cut-points of 4 for depression symptoms and 5 for anxiety symptoms (143), and as both separate indicators and combined (i.e., average of continuous variables; either reporting symptoms of depression and/or anxiety vs not) for all analyses.

Covariates

Participants indicated their age: 16, 17, 18, or 19. Due to the varying types of racial and ethnic groups between the three countries, we derived a binary race variable (white only vs. other races or mixed race). Socioeconomic status (SES) was collected using a measure of perceived income adequacy, where participants were asked, "How would you describe your family's financial situation?" with response options 'not meeting basic expenses', 'just meeting basic expenses,' 'meeting needs with a little left over,' 'living comfortably', and 'don't know/refuse' (141). Participants were asked in which country they live (Canada, the USA, or England), with indicators for location derived. For each data collection wave, a wave indicator was generated to differentiate survey timing.

Analyses

Prevalence rates of various nicotine products were examined using post-stratification weights. For nicotine use as an outcome, bivariate and adjusted multinomial regression models were estimated with a four-level product use dependent variable: no current use (reference group); exclusive use of combustible products; exclusive use of non-combustible products; and use of both combustible and non-combustible products. All models include IMH symptoms and gender identity, adjusting for wave, race, age, SES, and country of residence.

For IMH symptoms as an outcome, bivariate and adjusted logistic regression models were estimated with a binary IMH symptoms variable as the outcome (reference=no IMH symptoms). All models included gender identity, with adjusted models also including race, age, SES, wave, country of residence, and nicotine use.

Interactions of the dichotomous IMH symptoms measure and gender identity were examined by creating an interaction term for the binary *IMH symptoms x Gender identity (4-levels, reference= IMH symptoms, woman)* and adding the interaction term into the adjusted model, with each component interaction evaluated separately. Significant models were then re-estimated after stratifying the models by gender identity.

All analyses included post-stratification sample weights, which were constructed based on population estimates for sociodemographic variables (age, sex, region in all countries; race in US only) and past 30 day smoking (based on national estimates in US and Canada; unavailable in England) (141). All analyses were conducted using Stata version 16.

Results

Sample Characteristics

The full sample characteristics are shown in Table 6.1. After weighting, the total sample (n=67537) included 50.0% of respondents identifying as a man, 46.4% identifying as a woman, 2.3% identifying as GNC, and 0.9% identifying as a transman, and 0.4% identifying as a transwoman.

Nicotine Use

Figure 6.1 illustrates the prevalence of any past 30-day nicotine use and the prevalence rates of the most popular nicotine products by gender identity. The prevalence of any current nicotine product use was 35.6% among transmen, 34.2% among transwomen, 23.7% among men, 22.4% among women, and 18.8% among GNC participants. Within each gender identity group, e-cigarettes were the most prevalent product used: 21.9% of transmen, 17.6% of transwomen,16.1% of women, 14.7% of

men, and 14.3% of GNC participants. Cigarette use was the second most prevalent product for all gender identities, with 16.2% of transmen, 11.1% of men, 10.5% of transwomen, 8.6% of women, and 8.0% of GNC participants reporting current cigarette use.

The models examining associations between gender identity and current nicotine use are shown in Table 6.2 (adjusted model) and Table 6.3 (crude models). Compared to men, women were less likely to report exclusive combustible use (ARRR=0.66, 95% CI=0.62-0.71), as were GNC participants (ARRR= 0.44, 95% CI=0.33-0.58, respectively). Transmen were more likely to report exclusive combustible use (ARRR=1.51, 95% CI=1.15-1.97), as were transwomen (ARRR=1.80, 95% CI=1.24-2.61).

In terms of exclusive non-combustible use, women were more likely to report use than men (ARRR=1.17 95% CI=1.11-1.24) and GNC adolescents were less likely (ARRR=0.73, 95% CI=0.60-0.88). Transgender identities were not associated with exclusive non-combustible use. For use of both product types, women were less likely to report use (ARRR=0.64, 95% CI=0.60-0.68), as were GNC participants (ARRR= 0.61, 95% CI=0.50-0.75, respectively). Transmen were more likely to report both product use (ARRR=1.41, 95% CI=1.11-1.80), but there was no association for transwomen.

Other correlates of current nicotine use are shown in Table 6.2. Of note, IMH symptoms and age were positively associated with all types of nicotine use. Non-white race and SES were negatively associated with all types of nicotine use. Nicotine use also differed by country. In a sensitivity analysis, we found that responses between closed-

ended GNC participants and open-ended GNC participants were consistent (See Table 6.4).

Internalizing Mental Health Symptoms

The models examining the association between gender identity and current IMH symptoms are shown in Table 6.5. Overall, 47.4% of men, 70.8% of women, 77.3% of transwomen, 82.6% of transmen, and 88.5% of GNC participants reported past 30-day IMH symptoms. In adjusted models, all gender identities had significantly higher odds of reporting current IMH symptoms compared to men, with a gradient of the strongest association for GNC participants (AOR: 9.27, 95% CI=7.59-11.32), followed by transmen (AOR: 5.06, 3.99-6.43), transwomen, (AOR: 3.46, 2.39-5.01), and women (AOR: 2.75, 95% CI=2.65-2.87). Results are consistent in crude models. A sensitivity analysis with the continuous IMH measure is shown in Table 6.6. Results are consistent with the dichotomous IMH measure. In an additional sensitivity analysis, we found that responses between closed-ended GNC participants and open-ended GNC participants were consistent (See Table 6.7).

Interactions

We found significant interactions between IMH symptoms and all gender identity categories (See Table 6.8). Stratified analyses (Table 6.9) showed clear differences in the strength of association between IMH symptoms and nicotine product use across gender identity groups. Among men, having IMH symptoms was associated with greater likelihood of exclusively using combustible products (ARRR=1.44, 95% CI=1.29-1.59), exclusively using non-combustible products (ARRR=1.53, 95% CI=1.38-1.70), and using

both product types (ARRR=2.04, 95% CI=1.85-2.25) compared to those without IMH symptoms.

Among women, there was no association between IMH symptoms and exclusive combustible use; however, those with IMH symptoms were more likely to exclusively use non-combustible products (ARRR=1.98, 95% CI= 1.83-2.15) and to use both product types (ARRR=1.64, 95% CI=1.49-1.81) than those without IMH symptoms.

For both transgender identity groups, we found an inverse association between IMH symptoms and nicotine use. Among transwomen, those with IMH symptoms were less likely to report exclusive combustible use (ARRR= 0.19, 95% CI=0.07-0.53) and use of both types (ARRR= 0.14, 95% CI=0.05-0.36), but there was no association with exclusive non-combustible use. Among transmen, those with IMH symptoms were less likely to report exclusive combustible use (ARRR=0.44, 95% CI=0.25-0.79) and exclusive non-combustible use (ARRR=0.52, 95% CI=0.29-0.93), but there was no association with use of both types. Among GNC participants, there was no statistically significant association between IMH symptoms and using any of the categories of nicotine products. A sensitivity analysis with the continuous IMH measure is shown in Table 6.10. Results are consistent.

Discussion

This study describes relationships between gender identity and nicotine use among adolescents, including how IMH appears to play a role in this relationship. E-cigarettes and cigarettes were the most commonly used nicotine products regardless of gender identity. The prevalence of current nicotine use was highest among transmen, followed by transwomen, men, women, and then GNC participants, who had the lowest

current use. This aligns with a study that found an increased likelihood in nicotine use among gender minority adolescents compared to non-gender minority adolescents (186). Surveillance data from 2022 in Canada reported differences in current nicotine use between adolescent men, women, and gender minority adolescents (i.e., those identifying as transgender, gender diverse, and/or questioning), finding that gender minority adolescents had the highest rates of any nicotine product use, followed by men, and women had the lowest (190). While our findings align with these in that gender minority adolescents may have higher nicotine rates than non-gender minority adolescents, our study is the first to our knowledge to examine nicotine use between specific gender minority identities, finding that transgender identities appear to be at higher risk and GNC identities appear to be at lower risk than non-gender minority identities.

While very few studies have examined health differences between transgender and GNC adolescents, two studies have found worse health outcomes for transgender adolescents compared to GNC adolescents (191,192). While explanations for these differences are unclear, it is possible GNC adolescents may have more protective factors in place to prevent nicotine use, such as parental and peer support. Transgender individuals in early stages of transitioning may be particularly vulnerable as they lack the benefits that being a member of the transgender community may provide (193). Another possible explanation is that GNC youth may find nicotine use less appealing in general. Future research should examine potential explanations and continue to examine differences between transgender and GNC adolescents, as they appear to have distinct health risks.

We found differences in the types of products used between gender identities as well. Specifically, we found that men were more likely to use combustible nicotine products, including use of both product types, compared to women. Alternatively, women were more likely to engage in non-combustible product use compared to men. This differs slightly from recent data from Canada (190), England (194), and the US (195), which showed similar rates of cigarette use between adolescent men and women, but higher rates of e-cigarette use among adolescent women compared to men.

In our study, GNC adolescents were lowest risk for all types of nicotine use, but there were differences in product type risk between the transgender identities. Indeed, both transmen and transwomen were most likely to report exclusive combustible use. Transmen were also more likely to report use of both product types. However, there was no significant difference in exclusive non-combustible use. To our knowledge, only one study has examined differences between transgender and GNC adolescent nicotine use, focusing only on cigarette smoking among SGM youth and finding higher smoking prevalence among transgender adolescents and lower smoking prevalence among nonbinary adolescents compared to sexual minority men (180). Our study adds to this literature, suggesting distinctions between GNC adolescents, transmen, and transwomen may be important.

In terms of mental health, we found that the prevalence of experiencing IMH symptoms was highest among GNC participants, followed by transmen, transwomen, women, and then men, who had the lowest prevalence of IMH symptoms. It is well established that women report IMH symptoms more than men (196), and our results support that. Our finding regarding higher IMH symptom burden among transgender and

GNC adolescents aligns with evidence that SGM adolescents have worse mental health than non-SGM adolescents (28,29). A study of adults found worse mental health among GNC individuals compared to transgender individuals (184), but, to our knowledge, no such study has been conducted among adolescents.

Gender identity moderated the relationship between IMH symptoms and nicotine use, with different patterns of association across identity groups. Among men, IMH symptoms were associated with all types of use. Among women, IMH symptoms were associated with use of non-combustibles and of both product types. Among both transgender categories, IMH symptoms were associated with decreased use of nicotine use. Among GNC participants, IMH symptoms were not associated with nicotine use. Many studies focusing on the relationship between IMH symptoms and cigarette smoking suggest that sex moderates this relationship, with most finding stronger associations for females (42,44,45,48,49,57,59,65), and two finding a stronger association for males (46,89). This study builds on these findings, by providing evidence that the moderation of gender identity on IMH symptoms and nicotine use goes beyond the gender binary. It was unexpected that transgender adolescents with IMH symptoms were less likely to use nicotine products compared to those without IMH symptoms, while there is no association between IMH symptoms and nicotine use among GNC adolescents. This is likely because there were relatively higher rates of IMH symptoms among GNC adolescents and relatively lower rates of nicotine use among GNC adolescents compared to transgender adolescents. To our knowledge, this is the first study that has examined the potential moderation of gender identity beyond just cigarettes, and with gender identities beyond the gender binary. Future studies should continue examining the nuances of

adolescents' gender identity and how it relates to nicotine use among a diverse array of products.

This study has several strengths, including use of a large, national data set from three separate countries. This allowed us to examine gender identities that have relatively low prevalence. Our convenience sample may have resulted in selection bias; however, as the data were weighted, population-level inferences can be drawn. There are several limitations to this study as well. First, as data were cross-sectional, causation cannot be concluded from these results. This is potentially problematic when evaluating the association between IMH and nicotine product use because this relationship is likely bi-directional (20). Future studies should use longitudinal data to evaluate directionality; however, this is likely less of a concern when assessing associations between gender identity and nicotine product use, as use is unlikely to cause adolescents to change their identities. Given country-level differences in nicotine use and differencing contexts for gender identity, it may be beneficial to examine country-specific relationships. Another limitation of this study is that the IMH measure has, to date, only been validated among adults. However, the prevalence rates of symptoms of depression and anxiety found by these measures are similar to population-level prevalence rates found using other measures (154).

While our measure of gender identity appears to have successfully differentiated between transgender and GNC identities, it is important to note that gender identity is fluid and that some identities that fit under the GNC category may have specific characteristics that require further evaluation. Additionally, some adolescents may feel their gender identity fits under both the transgender and GNC categories (25). However,

there is evidence that transgender identities and GNC identities are generally distinct (197,198), and recognizing such differences is essential to fostering the well-being of adolescents with these identities (25) and may be important to consider when developing interventions that are targeted toward gender minorities. Finally, this study did not measure sexual orientation. While it is beneficial to distinguish between SGM identities, there may be important nuances of including sexual orientation in analyses of gender identity, which merits future research.

Overall, this study describes the relationship between gender identity, nicotine use, and mental health among adolescents in three countries. In addition to confirming elevated risk of combustible use among adolescent men and non-combustible use among adolescent women, these results highlight a need to address the high nicotine use rates among transgender adolescents and the mental health of gender minority adolescents. A guide of best practices for ethical research of SGM adolescents exists (199), and our findings support that research on adolescents incorporate these best practices in order to safely and accurately research this at-risk population.

Tables and Figures

Table 6.1 Sample Characteristics by Gender Identity

		Man n=21954	Woman n=42741	Transmen n=785	Transwomen n=246	GNC n=1811	Total n=67537
					N (Weighted %)		
Country	Canada	7766 (32.1%)	13031 (32.1%)	247 (31.4%)	74 (26.2%)	521 (29.1%)	21639 (32.0%)
	England	7324 (31.3%)	12998 (31.4%)	218 (28.8%)	73 (24.3%)	424 (23.8%)	21037 (31.1%)
	USA	6864 (36.6%)	16712 (36.5%)	320 (39.8%)	99 (49.6%)	866 (47.2%)	24861 (36.9%)
Wave	Feb 20	4769 (20.0%)	8320 (20.4%)	126 (15.9%)	33 (10.6%)	148 (8.7%)	13396 (19.8%)
	Aug 20	4885 (21.3%)	8967 (21.4%)	159 (19.5%)	40 (16.1%)	233 (13.7%)	14284 (21.1%)
	Feb 21	4152 (20.5%)	9184 (20.8%)	152 (19.4%)	50 (19.6%)	331 (17.6%)	13869 (20.5%)
	Aug 21	4085 (19.8%)	8597 (19.5%)	162 (22.1%)	61 (25.5%)	573 (30.3%)	13478 (20.0%)
	Aug 22	4063 (18.4%)	7673 (18.0%)	186 (23.3%)	62 (28.2%)	526 (29.8%)	12510 (18.5%)
Age	16	5593 (23.9%)	7899 (21.6%)	135 (20.4%)	54 (19.1%)	327 (21.0%)	14008 (22.7%)
	17	5957 (25.3%)	10068 (27.4%)	186 (26.1%)	44 (18.1%)	460 (28.8%)	16715 (26.3%)
	18	6263 (31.0%)	14408 (29.9%)	276 (31.7%)	86 (37.6%)	609 (30.7%)	21642 (30.5%)
	19	4141 (19.8%)	10366 (21.2%)	188 (21.8%)	62 (25.2%)	415 (19.5%)	15172 (20.5%)
Race	White	14019 (66.9%)	24751 (66.4%)	530 (74.7%)	126 (64.9%)	1095 (70.6%)	40521 (66.8%)
	Other races	7642 (32.0%)	17464 (32.6%)	242 (23.9%)	111 (31.6%)	689 (28.2%)	26148 (32.1%)
	No response	293 (1.1%)	526 (1.0%)	13 (1.4%)	9 (3.6%)	27 (1.2%)	868 (1.1%)
Perceived Income Adequacy	Not meeting needs	868 (3.5%)	1878 (3.8%)	48 (5.9%)	11 (3.2%)	81 (4.0%)	2886 (3.7%)
	Just meeting needs	4879 (21.1%)	10986 (23.9%)	261 (32.0%)	76 (34.4%)	513 (26.2%)	16715 (22.7%)
	Meeting needs	7532 (34.1%)	14129 (33.8%)	273 (34.7%)	81 (31.5%)	628 (34.0%)	22643 (33.9%)
	Living comfortably	7672 (37.0%)	13759 (34.3%)	178 (24.5%)	63 (26.4%)	507 (31.8%)	22179 (35.5%)
	No response	1003 (4.3%)	1989 (4.3%)	25 (2.9%)	15 (4.5%)	82 (4.1%)	3114 (4.3%)
IMH Symptoms	Yes	10529 (47.4%)	30839 (70.8%)	648 (82.6%)	175 (77.3%)	1622 (88.5%)	43813 (59.6%)
Nicotine use	None	16000 (76.3%)	31872 (77.6%)	474 (64.5%)	139 (65.8%)	1391 (81.2%)	49876 (76.9%)
	Exclusive non-combustible	1633 (7.5%)	4394 (10.2%)	86 (11.0%)	25 (9.9%)	157 (8.0%)	6295 (8.8%)
	Exclusive combustible	1906 (7.4%)	2782 (5.5%)	94 (10.7%)	42 (11.8%)	95 (3.5%)	4919 (6.4%)
	Both	2415 (8.8%)	3693 (6.7%)	131 (13.9%)	40 (12.5%)	168 (7.4%)	6447 (7.9%)

GNC- gender non-conforming, IMH- internalizing mental health.
All prevalence rates are weighted.

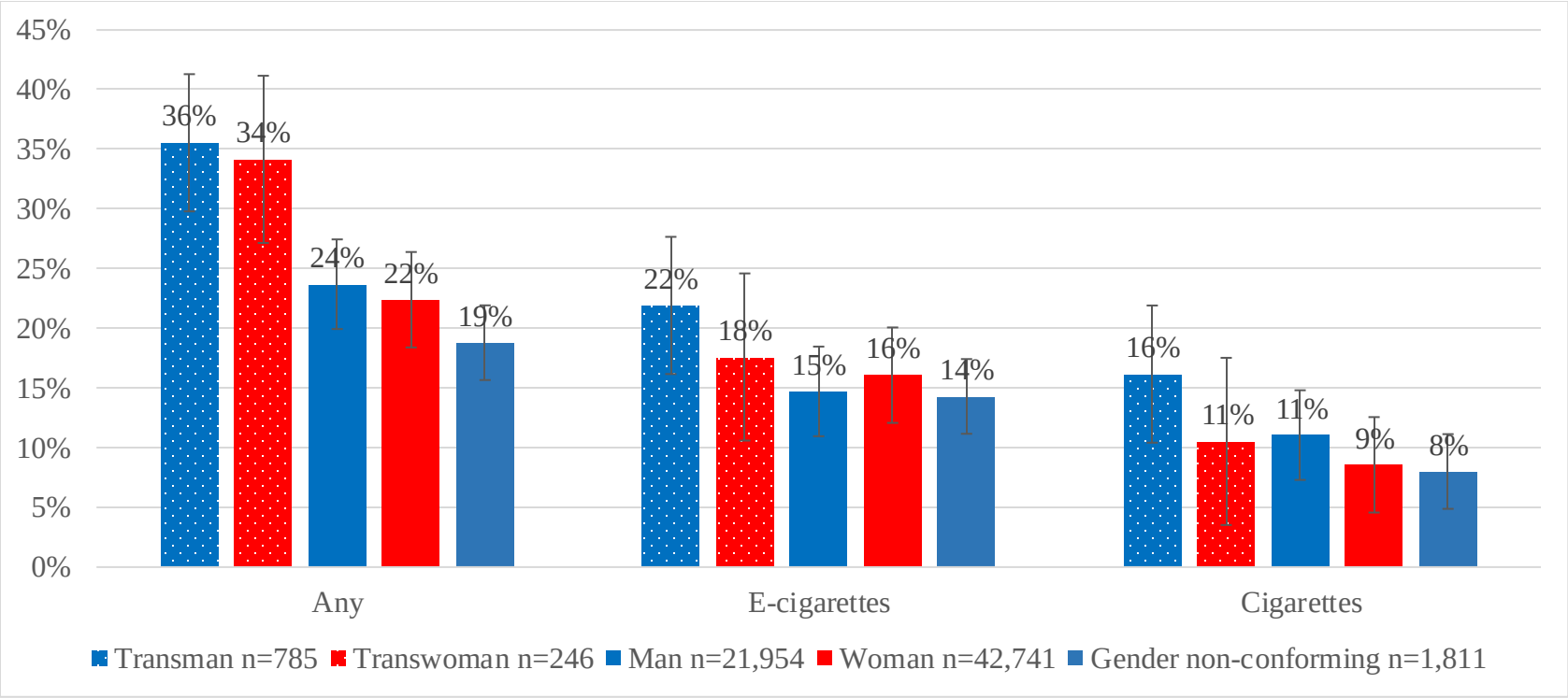

Figure 6.1. Current use of cigarettes, e-cigarettes, and any nicotine product by Gender Identity Among Adolescents from Canada, England and the US, 2020-2022

Sample includes 21954 identifying as a man, 42741 identifying as a woman, 785 identifying as a transman, 246 identifying as a transwoman, and 1811 with gender non-conforming (GNC) identities. All prevalence rates are weighted. Any nicotine product use includes any past 30-day use of cigarettes, e-cigarettes, little cigars or cigarillos, cigars, bidis, hookah, smokeless tobacco, and nicotine pouches.

Table 6.2 Adjusted Correlates of Current Nicotine Use

		Exclusive combustible use	Exclusive non-combustible use	Both
		ARRR (95% CI)	ARRR (95% CI)	ARRR (95% CI)
Gender Identity	Man	ref	ref	ref
	Woman	**0.66 (0.62-0.71)*** **	**1.17 (1.11-1.24)*** **	**0.64 (0.60-0.68)*** **
	Transman	**1.51 (1.15-1.97)** **	1.31 (1.00-1.70)	**1.41 (1.11-1.80)** **
	Transwoman	**1.80 (1.24-2.61)** **	1.13 (0.76-1.69)	1.37 (0.96-1.97)
	GNC	**0.43 (0.32-0.56)*** **	**0.73 (0.60-0.88)** **	**0.61 (0.50-0.75)*** **
IMH symptoms	No	ref	ref	ref
	Yes	**1.27 (1.18-1.35)*** **	**1.69 (1.59-1.80)*** **	**1.85 (1.74-1.98)*** **
Country	Canada	ref	ref	ref
	England	**2.06 (1.91-2.23)*** **	**0.64 (0.60-0.69)*** **	**1.50 (1.40-1.61)*** **
	US	**0.72 (0.66-0.78)*** **	0.98 (0.92-1.05)	**0.78 (0.73-0.85)*** **
Age	16	ref	ref	ref
	17	**1.40 (1.27-1.54)*** **	**1.16 (1.06-1.26)** **	**1.14 (1.04-1.24)*** **
	18	**1.59 (1.45-1.75)*** **	**1.67 (1.54-1.81)*** **	**1.48 (1.36-1.61)*** **
	19	**2.01 (1.82-2.22)*** **	**1.73 (1.59-1.89)*** **	**1.88 (1.73-2.06)*** **
Race	White	ref	ref	ref
	Other races	**0.85 (0.79-0.91)*** **	**0.55 (0.52-0.59)*** **	**0.67 (0.62-0.71)*** **
SES	1	ref	ref	ref
	2	**0.53 (0.46-0.61)*** **	**0.82 (0.71-0.95)** **	**0.46 (0.41-0.52)*** **
	3	**0.35 (0.30-0.40)*** **	**0.65 (0.56-0.74)*** **	**0.30 (0.27-0.34)*** **
	4	**0.34 (0.29-0.39)*** **	**0.64 (0.56-0.74)*** **	**0.30 (0.27-0.34)*** **
	5	**0.33 (0.27-0.40)*** **	**0.56 (0.46-0.68)*** **	**0.17 (0.14-0.22)*** **
Wave	Feb 20	ref	ref	ref
	Aug 20	0.95 (0.87-1.05)	**0.70 (0.64-0.77)*** **	**0.76 (0.69-0.83)*** **
	Feb 21	**0.87 (0.79-0.96)** **	**0.81 (0.74-0.88)*** **	**0.78 (0.72-0.86)*** **
	Aug 21	**0.73 (0.66-0.81)*** **	**0.91 (0.84-0.99)**	**0.84 (0.77-0.92)*** **
	Aug 22	**0.89 (0.80-0.98)**	**1.19 (1.10-1.29)*** **	0.97 (0.88-1.06)

ARRR – adjusted relative risk ratio; CI – confidence interval.
ARRRs were estimated in multinomial logistic regression model with current nicotine use as the outcome (ref=no use) and adjusted for all covariates. Bold indicates statistical significance; *:p<0.05, **:p<0.01, ***:p<0.001. All models are weighted.

Table 6.3 Sensitivity Analysis: Crude Correlates of Current Nicotine Use

		Exclusive combustible use	Exclusive non-combustible use	Both
		RRR (95% CI)	RRR (95% CI)	RRR (95% CI)
Gender Identity	Man	ref	ref	ref
	Woman	**0.73 (0.68-0.78)*** **	**1.34 (1.26-1.41)*** **	**0.75 (0.71-0.80)*** **
	Transman	**1.71 (1.32-2.23)*** **	**1.73 (1.34-2.25)*** **	**1.87 (1.48-2.37)*** **
	Transwoman	**1.85 (1.29-2.67)*** **	**1.52 (1.03-2.25)***	**1.65 (1.16-2.35)****
	GNC	**0.44 (0.33-0.58)*** **	1.00 (0.83-1.21)	**0.79 (0.65-0.96)***
IMH symptoms	No	ref	ref	ref
	Yes	**1.26 (1.18-1.34)*** **	**1.82 (1.71-1.92)*** **	**1.82 (1.71-1.93)*** **
Country	Canada	ref	ref	ref
	England	**2.11 (1.96 -2.27)*** **	**0.71 (0.66-0.77)*** **	**1.59 (1.48-1.70)*** **
	US	**0.75 (0.69-0.82)*** **	1.05 (0.99-1.12)	**0.84 (0.78-0.90)*** **
Age	16	ref	ref	ref
	17	**1.36 (1.24-1.50)*** **	**1.20 (1.10-1.30)*** **	**1.13 (1.03-1.23)****
	18	**1.64 (1.50-1.80)*** **	**1.75 (1.62-1.90)*** **	**1.57 (1.45-1.71)*** **
	19	**2.00 (1.82-2.21)*** **	**1.88 (1.73-2.05)*** **	**2.00 (1.83-2.18)**
Race	White	ref	ref	ref
	Other races	**0.83 (0.77-0.88)*** **	**0.61 (0.57-0.65)*** **	**0.70 (0.65-0.74)*** **
SES	1	ref	ref	ref
	2	**0.55 (0.48-0.64)*** **	**0.78 (0.67-0.89)*** **	**0.47 (0.41-0.52)*** **
	3	**0.36 (0.31-0.41)*** **	**0.59 (0.51-0.67)*** **	**0.30 (0.26-0.33)*** **
	4	**0.34 (0.30-0.39)*** **	**0.57 (0.50-0.65)*** **	**0.29 (0.25-0.32)*** **
	5	**0.33 (0.27-0.40)*** **	**0.46 (0.38-0.56)*** **	**0.16 (0.13-0.19)*** **
Wave	Feb 20	ref	ref	ref
	Aug 20	**0.90 (0.82-0.99)***	**0.69 (0.64-0.76)*** **	**0.72 (0.66-0.78)*** **
	Feb 21	**0.85 (0.77-0.93)****	**0.81 (0.75-0.89)*** **	**0.77 (0.71-0.85)*** **
	Aug 21	**0.71 (0.65-0.79)*** **	**0.88 (0.81-0.96)****	**0.82 (0.75-0.89)*** **
	Aug 22	0.92 (0.83-1.01)	**1.15 (1.06-1.25)****	0.98 (0.90-1.07)

RRR – relative risk ratio; CI – confidence interval.
RRRs were estimated in multinomial logistic regression models with current nicotine use as the outcome (ref=no use).
Bold indicates statistical significance; *:p<0.05, **:p<0.01, ***:p<0.001. All models are weighted.

Table 6.4 Sensitivity Analysis: Association Between GNC Response Coding and Nicotine Use

		Exclusive combustible use		Exclusive non-combustible use		Both	
		RRR (95% CI)[1]	ARRR (95% CI)[2]	RRR (95% CI)[1]	ARRR (95% CI)[2]	RRR (95% CI)[1]	ARRR (95% CI)[2]
GNC	Closed-ended (n=1500)	ref	ref	ref	ref	ref	ref
	Open-ended (n=311)	0.36 (0.14-1.21)	0.31 (0.05-1.91)	0.88 (0.56-1.39)	0.57 (0.23-1.43)	0.62 (0.36-1.05)	0.58 (0.23-1.49)

RRR – relative risk ratio; ARRR – adjusted relative risk ratio; CI – confidence interval.
[1]RRRs were estimated in multinomial logistic regression models with current nicotine use as the outcome (ref=no use). The primary independent variable was whether GNC participants selected the closed-ended response option (i.e., 'gender queer, gender non-conforming') or selected 'different identity' and had open-ended responses coded.
[2]Adjusted models adjust for internalizing mental health symptoms, country, wave, age, race, and socioeconomic status.
Bold indicates statistical significance; *:p<0.05, **:p<0.01, ***:p<0.001. All models are weighted.

Table 6.5 Association Between Gender Identity and Current Internalizing Mental Health Symptoms

		Internalizing Mental Health Symptoms (n=67537)	
	%	OR (95% CI)	AOR (95% CI)[1]
Man	47.4%	ref	ref
Woman	70.8%	**2.69 (2.59-2.80)*** **	**2.75 (2.65-2.87)*** **
Transwoman	77.3%	**3.79 (2.67-5.38)*** **	**3.46 (2.39-5.01)*** **
Transman	82.6%	**5.26 (4.20-6.59)*** **	**5.06 (3.99-6.43)*** **
Gender non-conforming	88.5%	**8.57 (7.04-10.42)*** **	**9.27 (7.59-11.32)*** **

OR – odds ratio; AOR – adjusted odds ratio; CI – confidence interval

[1]ORs were estimated in logistic regression models with current internalizing mental health symptoms (ref=no) as the outcome.

[2]Adjusted models adjust for gender identity, nicotine use, country, wave, age, race, and socioeconomic status.

Bold indicates statistical significance; *:p<0.05, **:p<0.01, ***:p<0.001. All models are weighted.

Table 6.6 Sensitivity Analysis: Association Between Gender Identity and Continuous Internalizing Mental Health Symptoms

	Internalizing Mental Health Symptoms (0-9) (n=67537)	
	Coeff (SE)[1]	Adjusted Coeff (SE)
Man	ref	ref
Woman	**1.52 (0.02)*** **	**1.49 (0.02)*** **
Transwoman	**1.83 (0.18)*** **	**1.65 (0.19)*** **
Transman	**2.39 (0.10)*** **	**2.23 (0.10)*** **
Gender non-conforming	**2.88 (0.07)*** **	**2.89 (0.07)*** **

[1]Coefficients (coeff) and standard errors (SE) were estimated in linear regression models with current internalizing mental health symptoms (0-9) as the outcome.
[2]Adjusted models adjust for gender identity, nicotine use, country, wave, age, race, and SES.
Bold indicates statistical significance; *:p<0.05, **:p<0.01, ***:p<0.001. All models are weighted.

Table 6.7 Sensitivity Analysis: Association Between Gender Non-Conforming Open-Ended Response Coding and Internalizing Mental Health Symptoms

		IMH symptoms (yes vs. no)	
		OR (95% CI)	AOR (95% CI)[1]
GNC	Closed-ended (n=1500)	ref	ref
	Open-ended (n=311)	1.23 (0.71-2.16)	1.21 (0.69-2.11)

IMH – internalizing mental health; OR – odds ratio; AOR – adjusted odds ratio; CI – confidence interval.
[1]ORs were estimated in logistic regression models with IMH symptoms as the outcome (ref=no). The primary independent variable was whether GNC participants selected the closed-ended response option (i.e., 'gender queer, gender non-conforming') or selected 'different identity' and had open-ended responses coded.
[2]Adjusted model adjusts for internalizing mental health symptoms, country, wave, age, race, and socioeconomic status.
Bold indicates statistical significance; *:p<0.05, **:p<0.01, ***:p<0.001. All models are weighted.

Table 6.8 Component Interaction of IMH Symptoms x Gender Identity on Nicotine Use

	Exclusive combustible use (n=4919)	Exclusive non-combustible use (n=6295)	Use of both types (n=6447)
		ARRR (95% CI)[1]	
IMH symptoms x gender identity			
IMH symptoms x woman	ref	ref	ref
IMH symptoms x man	**1.25 (1.09-1.44)****	**0.77 (0.68-0.87)*****	**1.20 (1.05-1.38)*****
IMH symptoms x transwoman	**0.20 (0.09-0.45)*****	**0.26 (0.10-0.68)*****	**0.11 (0.05-0.24)*****
IMH symptoms x transwoman	**0.41 (0.22-0.76)****	**0.27 (0.14-0.50)*****	**0.50 (0.26-0.96)***
IMH symptoms x GNC	0.60 (0.27-1.35)	0.87 (0.42-1.81)	**0.53 (0.28-0.98)***

IMH – internalizing mental health; ARRR – adjusted relative risk ratio; CI – confidence interval

[1]ARRRs found in multinomial regression model with current tobacco/nicotine use (ref=no current use) as the outcome and include the interaction of IMH symptoms and gender identity. All models adjust for age, race, country, wave, and socioeconomic status.

Table 6.9 Association Between Internalizing Mental Health Symptoms and Nicotine Use Stratified by Gender Identity

Strata	IMH Symptoms	Exclusive combustible use		Exclusive non-combustible use		Use of both types	
		RRR (95% CI)[1]	ARRR (95% CI)[2]	RRR (95% CI)[1]	ARRR (95% CI)[2]	RRR (95% CI)[1]	ARRR (95% CI)[2]
Man	No	ref	ref	ref	ref	ref	ref
(n=21954)	Yes	**1.52 (1.37-1.68)*** **	**1.44 (1.29-1.59)*** **	**1.56 (1.41-1.72)*** **	**1.53 (1.38-1.70)*** **	**2.16 (1.96-2.39)*** **	**2.04 (1.85-2.25)*** **
Woman	No	ref	ref	ref	ref	ref	ref
(n=42741)	Yes	**1.25 (1.14-1.38)*** **	1.08 (0.98-1.20)	**2.09 (1.93-2.27)*** **	**1.98 (1.83-2.15)*** **	**1.86 (1.70-2.05)*** **	**1.64 (1.49-1.81)*** **
Transwoman	No	ref	ref	ref	ref	ref	ref
(n=246)	Yes	**0.26 (0.11-0.61)** **	**0.19 (0.07-0.53)** **	0.62 (0.22-1.76)	0.46 (0.15-1.43)	**0.23 (0.10-0.52)*** **	**0.14 (0.05-0.36)*** **
Transman	No	ref	ref	ref	ref	ref	ref
(n=785)	Yes	**0.43 (0.25-0.74)** **	**0.44 (0.25-0.79)** **	**0.54 (0.31-0.95)* **	**0.52 (0.29-0.93)* **	0.81 (0.47-1.41)	0.89 (0.49-1.61)
GNC	No	ref	ref	ref	ref	ref	ref
(n=1811)	Yes	0.83 (0.40-1.71)	0.76 (0.36-1.61)	1.81 (0.93-3.50)	1.75 (0.90-3.43)	1.03 (0.59-1.80)	0.83 (0.47-1.48)

IMH – internalizing mental health; RRR – relative risk ratio; ARRR – adjusted relative risk ratio; CI – confidence interval
[1]RRRs found in separate multinomial regression models stratified by gender identity with current nicotine use (ref=no current use) as the outcome and IMH symptoms as the independent variable. [2]Adjusted models adjust for country, wave, age, race, and socioeconomic status.
Bold indicates statistical significance; *:p<0.05, **:p<0.01, ***:p<0.001. All models are weighted.

Table 6.10 Sensitivity Analysis: Association Between Continuous Internalizing Mental Health Symptoms and Nicotine Use Stratified by Gender Identity

Strata	Exclusive combustible use		Exclusive non-combustible use		Use of both types	
	RRR (95% CI)[1]	ARRR (95% CI)[2]	RRR (95% CI)[1]	ARRR (95% CI)[2]	RRR (95% CI)[1]	ARRR (95% CI)[2]
Man	ref	ref	ref	ref	ref	ref
(n=21954)	**1.08 (1.06-1.10)*** **	**1.07 (1.05-1.09)*** **	**1.09 (1.07-1.11)*** **	**1.08 (1.06-1.10)*** **	**1.18 (1.16-1.20)*** **	**1.16 (1.14-1.18)*** **
Woman	ref	ref	ref	ref	ref	ref
(n=42741)	**1.06 (1.05-1.08)*** **	1.03 (0.99-1.05)	**1.16 (1.14-1.18)**	**1.15 (1.13-1.16)*** **	**1.15 (1.14-1.17)*** **	**1.12 (1.11-1.14)*** **
Transwoman	ref	ref	ref	ref	ref	ref
(n=246)	**0.77 (0.65-0.91)** **	**0.76 (0.62-0.92)** **	**0.83 (0.69-0.99)***	0.80 (0.65-1.00)	**0.77 (0.65-0.91)** **	**0.72 (0.60-0.88)** **
Transman	ref	ref	ref	ref	ref	ref
(n=785)	**0.83 (0.75-0.92)*** **	**0.83 (0.75-0.92)*** **	0.99 (0.89-1.10)	0.97 (0.87-1.09)	0.92 (0.84-1.01)	0.92 (0.83-1.00)
GNC	ref	ref	ref	ref	ref	ref
(n=1811)	1.00 (0.89-1.13)	0.98 (0.87-1.11)	**1.10 (1.01-1.21)***	1.11 (0.99-1.23)	1.04 (0.95-1.14)	1.00 (0.92-1.10)

IMH – internalizing mental health; RRR – relative risk ratio; ARRR – adjusted relative risk ratio; CI – confidence interval
[1]RRRs found in separate multinomial regression models stratified by gender identity with current nicotine use (ref=no current use) as the outcome and IMH symptoms (0-9) as the independent variable. [2]Adjusted models adjust for country, wave, age, race, and socioeconomic status.
Bold indicates statistical significance; *:p<0.05, **:p<0.01, ***:p<0.001. All models are weighted.

Chapter 7: Conclusions and Implications

When cigarettes were the primary method of nicotine product use among adolescents, it was clear that there was a positive association between IMH symptoms and smoking cross-sectionally (40–51), longitudinally with smoking predicting IMH symptoms (53–57) or with IMH symptoms predicting smoking (58–65,91), and bidirectionally (66–68,80). However, in recent years, the array of nicotine products available have expanded and the prevalence of adolescents with IMH symptoms has grown; in this context, it is unclear how the relationship between nicotine product use and mental health may have changed.

The goal of this dissertation was to examine how IMH symptoms are related to different patterns and types of nicotine use from 2020 to 2022, using 4 annual cross-sectional surveys of adolescents in Canada, England, and the US from the ITC Adolescents Tobacco Survey. Specifically, this dissertation addressed 3 research questions: 1) Are IMH symptoms positively associated with any current nicotine product use among adolescents; does the strength of these associations depend on the type of nicotine product used; and are the associations between IMH and nicotine product use different over time or across countries? 2) Among a sample of adolescents who currently use e-cigarettes and, separately cigarettes, are IMH symptoms associated with indicators of nicotine dependence (i.e., number of days used; time to first use) and cessation-related variables (i.e., prior quit attempts; quit intentions) for each specific product; and do these relationships vary by whether adolescents use both e-cigarettes and cigarettes (i.e., “dual

use") compared to exclusive product use? 3) Does the association between IMH symptoms and current nicotine product use (i.e., exclusive combustible use, exclusive non-combustible product use, use of both product types) vary by gender identity (i.e., man, woman, transgender, GNC)?

In **Manuscript 1,** I examined the relationship between IMH symptoms and nicotine use among adolescents in three countries from 2020-2022; that is, before, during, and after the acute phase of the COVID-19 pandemic. I found that IMH symptoms were positively associated with all categories of nicotine use. However, the results provided evidence of a gradient, where IMH symptoms were most strongly associated with using both combustible and non-combustible products, followed by exclusive non-combustible products, and, finally, exclusive use of combustible products. While e-cigarettes have replaced combusted cigarettes as the most popular nicotine product among adolescents in Canada, England, and the US, the findings from this dissertation indicate that IMH symptoms are most strongly associated with concurrent use of both combustible and non-combustible products. Furthermore, the association is stronger for non-combustible products compared to combustible products. Given that these categories of use are largely driven by e-cigarettes and cigarettes, these findings signal that there may be a concern for mental health and e-cigarette use among adolescents.

In terms of moderation results, this study found that country in which adolescents lived did not moderate this association, suggesting that this pattern of association is relatively consistent across Canada, England and the US; however, there was evidence of changes in the association over time. This finding may indicate that as the types of

products adolescents are using is changing, it is possible that their association with mental health may also vary.

In **Manuscript 2,** I analyzed a subsample of adolescents who reported current e-cigarette or cigarette use, to examine the association between IMH symptoms and indicators of nicotine dependence and cessation, specifically quit intentions and prior quit attempts. I found that adolescents with IMH symptoms have different patterns of cigarette and/or e-cigarette use than those without IMH symptoms. Specifically, we found positive associations between IMH symptoms and indicators of nicotine dependence among adolescents who reported current e-cigarette use. For adolescents who reported current cigarette use, the associations between IMH symptoms and indicators of nicotine dependence were moderated by whether they also used e-cigarettes (i.e., dual use). Indeed, mental health symptoms were more strongly associated with nicotine dependence indicators for adolescents reporting dual use than exclusive cigarette use, suggesting that adolescents reporting mental health symptoms may be at particular risk for heavier dual use. Among adolescents who used either product, IMH symptoms were not associated with intention to quit, but positively associated with reporting ever having a quit attempt. This finding suggests that cessation may be particularly difficult for adolescents with IMH symptoms, or that adolescents who have attempted to quit may develop IMH symptoms.

Among adolescents using e-cigarettes and cigarettes, there appears to be a strong association between poor mental health and nicotine dependence of e-cigarettes, and nicotine dependence of cigarettes among those reporting dual use. These findings indicate that while e-cigarettes may be a less harmful product than cigarettes, there may be unique

implications on adolescents mental health that warrant further research. As non-combustible nicotine products become more established as the primary types of nicotine delivery devices among adolescents, longitudinal research is needed to better understand the directionality of this relationship and how concurrent combustible product use may play a role.

In **Manuscript 3**, I investigated the association between gender identity and nicotine use, IMH symptoms, and the interaction of gender identity and IMH symptoms on nicotine use. Individuals with gender minority identities are at high risk for a variety of poor health outcomes; however, very little is known about how these outcomes exist among adolescents, and if there are specific differences between types of gender identities (i.e., transgender compared to GNC identities). In the present research, I found that adolescents who repored transgender identities were most likely to use all types of nicotine products, whereas adolescents who reported GNC identities were least likely to use these products, with those who identified as male or female women falling in the middle. Adolescents who reported GNC identities were also the most likely to report IMH symptoms, followed by transmen, transwomen, women, and then men. Gender identity moderated the association between IMH symptoms and nicotine use. Men and women with IMH symptoms were more likely to use nicotine products compared to their counterparts without IMH symptoms, whereas transgender adolescents with IMH symptoms were less likely to use nicotine products. There was no association for GNC adolescents.

When examining differences in gender identity, this dissertation identifies adolescents with transgender identities as particularly at-risk for both poor mental health

and nicotine use, while those with GNC identities are at risk for poor mental health but not nicotine use. More research is needed to better understand the health behaviors of these distinct vulnerable groups, and to intervene to reduce health disparities between gender minority adolescents and their non-minority counterparts.

These three studies provide an in-depth examination of how IMH symptoms and nicotine use are associated among adolescents from 2020-2022, encompassing the COVID-19 pandemic, adolescents mental health crisis, and diversification of nicotine products. In conclusion, this dissertation provides evidence that adolescents around the globe continue to struggle with nicotine use, and that mental health – an increasingly salient health concern among adolescents - appears to play an important role; however, future research in this area will need to consider the different types of products adolescents use. We identify several vulnerable groups of adolescents at-risk for using nicotine products, including those with mental health problems and transgender adolescents. Longitudinal research is needed to understand the directionality of these findings, and consequentially, determine how to best intervene. Studies are needed to continue examining the differences between gender minority adolescents, including how to best measure their identities. Interventions aiming to reduce nicotine use among adolescents may wish to include testimonials from individuals with IMH problems who struggle with cessation, and it may be necessary to specifically target transgender adolescents.

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