FLORIDA INTERNATIONAL UNIVERSITY

Miami, Florida

CHARACTERIZING THE DEVELOPMENT AND TRAJECTORIES OF NICOTINE DEPENDENCE AMONG A COHORT OF ADOLESCENT WATERPIPE AND CIGARETTE SMOKERS

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Mohammad Ebrahimi Kalan

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This dissertation, written by Mohammad Ebrahimi Kalan, and entitled Characterizing the Development and Trajectories of Nicotine Dependence Among a Cohort of Adolescent Waterpipe and Cigarette Smokers, having been approved in respect to style and intellectual content, is referred to you for judgment.

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DEDICATION

This dissertation is dedicated to my beloved Mother and Father, my lovely wife Ela, and my beautiful sister Roghi. Without their sacrifice, unconditional support, this work would have not been possible. I also dedicate my dissertation to my amazing siblings, my cute nieces and nephews, and all Ebrahimi's family. You all helped me make my dream comes true.

I love you all.

Ebi

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ABSTRACT OF THE DISSERTATION

CHARACTERIZING THE DEVELOPMENT AND TRAJECTORIES OF NICOTINE DEPENDENCE AMONG A COHORT OF ADOLESCENT WATERPIPE AND CIGARETTE SMOKERS

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Nicotine dependence (ND) is the fundamental reason that people persist in using tobacco products, which kill more than eight million people every year globally. So far, ND research has primarily focused on cigarettes, yet for many youths worldwide, tobacco use, and addiction is maintained by means other than the cigarette including waterpipe (WP) smoking (a.k.a. hookah). It is important to better understand the WP-associated ND trajectories given its unique use features that can influence ND development such as its time-consuming preparation and consumption, intermittent use, and strong sensory and social cues. Hence, using data from 8 waves (2015-2020) of the Waterpipe Dependence in Lebanese Youth (WDLY) study, this pioneer research compared the development of ND symptoms and their predictors among adolescent current (past 30 days) WP (n=283) and cigarette (n=146) smokers. Also, we identified ND trajectories from early to late adolescence in current WP smokers and examine baseline correlates by each identified trajectory. We evaluated the initial ND symptoms using the Hooked on Nicotine Checklist

(HONC) and the full syndrome of ND using the International Classification of Diseases-10th revision (ICD-10 ND).

Our findings indicated that compared with adolescent cigarette smokers, initial ND symptoms and full syndrome of ND can develop sooner after starting to smoke and progress more rapidly among adolescent WP smokers. Among WP smokers, predictors of developing full ND syndrome include being younger, believing that WP smokers have more friends, depression, high levels of impulsivity, and initiating smoking at a younger age. For cigarette smokers, predictors of full ND syndrome were being younger and initiating smoking at a younger age. Finally, A mixture modeling approach yielded a four-class solution that best fitted the data varying in the timing of ND onset during adolescence: no-onset of ND (43.9%), early-adolescence onset (16.2%), mid-adolescence (26.6%), and late-adolescence (13.3%) onset of ND symptoms among WP smokers.

In conclusion, our findings suggest that the developing, implementing, and evaluating intervention programs with adolescent WP smokers should be guided by the WP-specific trajectory of ND.

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ABBREVIATIONS AND ACRONYMS

WDLY	Waterpipe Dependence in Lebanese Youth
WP	Waterpipe
ND	Nicotine Dependence
HONC	Hooked on Nicotine Checklist
ICD-10	International Classification of Diseases, 10th
CDC	version Center for Disease Control and Prevention
WHO	World Health Organization
EMR	Eastern Mediterranean Region
BMI	Body mass index
USA	United States of America
SD	Standard Deviation
OR	Odds ratios
HR	Hazard Ratio
K-M	Kaplan-Meier
CI	Confidence Interval
SAS	Statistical Analysis System
SPSS	Statistical Package for the Social Sciences
FCTC	Framework Convention on Tobacco Control
CPHR	Cox Proportional Hazard Regression

INTRODUCTION

Tobacco smoking is the leading cause of morbidity and mortality, contributing to millions of deaths every year and wreaking havoc on the welfare of families and communities worldwide (WHO, 2017). Most of the health consequences of the tobacco epidemic are borne by developing countries, a trend that is likely to accelerate. About 80% of the world's 1.1 billion smokers live in developing countries (WHO, 2018). Although smokers are usually aware of the health risks of smoking, they find quitting difficult due to the formidable grip of nicotine dependence (ND) (El-Shahawy & Haddad, 2015). According to the 1988 Surgeon General's report, "Nicotine is the drug in tobacco that causes addiction" (HHS, 1988). So far, ND research has primarily focused on cigarettes (Agrawal et al., 2011; Coban et al., 2018; Rojas, et al, 1998), yet for many youths worldwide, tobacco use and addiction are maintained by means other than the cigarette. Over the past decade, waterpipe (WP) smoking (a.k.a. hookah, shisha, narghile) has dramatically increased among youth and young populations worldwide (Maziak et al., 2015). Available evidence suggests that WP smoking is addictive and is associated with smoking-related diseases such as cancer (Aboaziza & Eissenberg, 2015; Bahelah et al., 2016; Waziry et al., 2017).

Following the smoking WP, smokers get a notable increase in their plasma nicotine concentration that may lead to behavioral symptoms of ND (e.g. craving, withdrawal) during short-time abstinence that is relieved by smoking (Auf et al., 2012; Ben Taleb et al., 2018; Macaron, 1997; Maynard, Gage, & Munafò, 2013; Maziak, Eissenberg, & Ward, 2005; Maziak, Jawad, et al., 2015; Maziak et al., 2011). Many WP-related ND symptoms

are seen with cigarette smoking, however, the appearances and developmental trajectories of ND symptoms in WP smokers are likely influenced by its unique features and use patterns (Maziak et al., 2005). For example, WP tobacco smoking is a predominately social activity, take place mostly among peers or family with long smoking sessions (~ 1hour), has limited access and portability with unique sensory cues that can shape a distinctive pattern of ND development (Akl et al., 2013; Akl et al., 2015; Jawad et al., 2013; Maziak et al., 2005; Maziak, Taleb, et al., 2015). Identifying the developmental pattern of ND and how it differs from cigarettes is essential to develop and adapt existing cessation and prevention interventions to curb WP smoking among youth. Therefore, monitoring the natural process of ND development among adolescent WP and cigarette smokers can provide pivotal insights about common and distinctive features that are of importance for interventions to curb WP use.

Several national and international surveillance systems closely monitored WP's worrisome trends and recognized the need to respond to the WP epidemic through interventions, policy, and product regulation(Al-Lawati et al, 2008; Global Youth Tabacco Survey Collaborative Group, 2002; Studies, 2017; Wang et al., 2018; Warren et al., 2009). Unfortunately, this is hindered in part by the lack of knowledge of how ND develops and manifests in WP smokers. Characterizing the natural course of ND and identifying the factors that predict ND in adolescents WP and cigarette smokers will help guide the timing and composition of cessation treatments, and target those at greater risk of relapse by providing additional support. For example, a fast ND trajectory that involves significant withdrawal symptoms in WP smokers can indicate the need for earlier intervention, or the use of medication to assist with quitting. Also, demonstrating ND in WP smokers will help

counter deceptive product labeling, and provide ammunition for advocacy efforts to limit WP promotion and youth access. Furthermore, classifying the ND symptoms levels may enable the tailoring of intervention efforts to specifically target adolescent smokers based on their classes of ND symptoms and their unique characteristics. For example, a previous study suggests the existence of three classes of adolescent cigarette smokers based on symptomology labeled as rapid, slower, and resistant to the onset of ND (DiFranza et al., 2000). However, no previous studies have characterized a similar sub-grouping (classes) based on ND symptoms among adolescent WP smokers. Taken together, this longitudinal study provides a robust examination of the changes in development and sequence of ND symptoms among adolescent WP and cigarette smokers.

In the Middle East countries like Lebanon, the prevalence of WP smoking among adolescents has reached dramatic proportions, where the prevalence of current WP smoking is more than three times (37.2%) that of cigarette smoking (11.2%) among Lebanese youth (Mohammed Jawad et al., 2018; World Health Organization, 2019). Therefore, this Middle Eastern country is in urgent need of WP smoking interventions, and at the same time provides a natural laboratory to study the trajectory of ND development among adolescent WP and cigarette smokers. In a previous report using the baseline data of Waterpipe Dependence in Lebanese Youth (WDLY) study, our team (Bahelah et al., 2016) indicated that the symptoms of ND among adolescent WP smokers can develop at a low level of consumption and frequency of use. However, the longitudinal trajectory of ND development among young WP smokers and how it differs from cigarettes has not been studied yet. This WDLY prospective study was designed to map the natural course of ND development among young WP and cigarette smokers and are used to characterize the

early and most common symptoms of ND and their sequence in adolescent WP and cigarette smokers. Building on such a unique cohort, we also aim to identify and contrast the factors that predict initial ND symptoms and full-blown ND syndrome in adolescents WP and cigarette smokers. Finally, we identified ND trajectories from early to late adolescence in current (past 30 days) WP smokers and examined baseline correlates of each identified trajectory. These findings will be effective for developing WP-specific policies to prevent ND among adolescents and design smoking cessation interventions for those already hooked on nicotine.

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Abstract

Background and objective

Waterpipe (WP) smoking patterns and setting can result in a unique trajectory of nicotine dependence (ND) compared with cigarette smoking. This longitudinal study compared the development of ND symptoms among adolescent WP and cigarette smokers.

Methods

A cohort of 647 eighth and ninth graders in Lebanon were followed over 5 years. This study was based on 283 current exclusive WP and 146 current exclusive cigarette smokers. Kaplan–Meier survival analyses were conducted to evaluate 50% cumulative probability for the development of initial Hooked on Nicotine Checklist symptoms and the International Classification of Diseases, 10th revision (ICD-10) ND.

Results

An initial Hooked on Nicotine Checklist symptom was endorsed by 59% of WP and 50% of cigarette smokers after smoking onset. Among those, 50% of both WP and cigarette smokers did so within 9.7 and 18.5 months, respectively. Approximately 28% of WP smokers and 22% of cigarette smokers developed ICD-10 ND. Among those, 50% of both WP and cigarette smokers did so within 15 and 22 months, respectively. The most

common first to fourth ICD-10 criteria reported by WP smokers were “a strong desire to use tobacco,” “difficulties in controlling tobacco taking behavior,” “neglect of alternative pleasure,” and “use despite harm.” The most common first to fourth ICD-10 criteria reported by cigarette smokers were “a strong desire to use tobacco,” “difficulties in controlling tobacco taking behavior,” “withdrawal,” and “tolerance”.

Conclusions

Compared with adolescent cigarette smokers, initial ND symptoms and ICD-10 ND can develop sooner after starting to smoke and progress more rapidly among adolescent WP smokers. Developing, implementing, and evaluating intervention programs with adolescent WP smokers should be guided by the WP-specific trajectory of ND.

Introduction

Nicotine dependence (ND) is the fundamental reason that people persist in using tobacco products (CDC, 2010), which kill more than 8 million people every year globally (WHO, 2019a). About 80% of the world's 1.1 billion tobacco users live in low- and middle-income countries, where the burden of tobacco-related morbidity and mortality is heaviest (WHO, 2017). Contributing to this burden is waterpipe (WP; a.k.a., shisha, hookah, and narghile), a centuries-old method of smoking tobacco that has increased dramatically around the globe in the last twenty years especially among youth and young adults (Maziak et al., 2015). WP smoking causes ND (Aboaziza & Eissenberg, 2015; Auf et al., 2012; Maziak et al., 2005a) and more than doubles the odds of initiating cigarette smoking (Al Oweini et al., 2020).

According to the Tenth Revision of the International Classification of Diseases and Health Problems (ICD-10), dependence refers to a group of physiological, behavioral, and cognitive phenomena in which the use of a substance (e.g., tobacco products) takes on a much higher importance for a user than other behaviors that once had greater value(WHO, 2020). For example, after using tobacco products (e.g., WP and cigarette), nicotine increases the release of neurotransmitters (e.g., dopamine) that creates the pleasurable sensations which make smoking highly addictive, reinforces continued tobacco use, and makes person dependent on nicotine(CDC, 2010; WHO, 2020).

WP tobacco smokers have a notable increase in plasma nicotine concentration after smoking WP and exhibit behavioral symptoms of ND (e.g. craving, withdrawal) during abstinence that are relieved by smoking (Auf et al., 2012; Ben Taleb et al., 2018; Macaron, Macaron et al., 1997; Maynard et al., 2013; Maziak et al., 2005a; 2011;2015). Although many WP-associated ND symptoms are identical to those seen with cigarette smoking, the development of ND symptoms in WP smokers is likely influenced by its unique features and use patterns (Maziak et al., 2005a). For example, long duration of smoking sessions (averaging an hour), limited access and portability, and unique sensory cues can shape a distinctive pattern of ND development (Akl et al., 2013; 2015; Jawad et al., 2013; Maziak et al., 2005a; 2015). Identifying this pattern and how it differs from cigarettes is essential to develop and adapt existing cessation and prevention interventions to curb WP smoking among youth. Moreover, WP is characterized by intermittent, nondaily smoking that is different from the typical daily smoking for cigarettes which can be associated with unique smoking patterns and ND trajectories for WP smokers compared with cigarette smokers (Aboaziza & Eissenberg, 2015; Maziak et al., 2005a; Akl et al., 2013). Consequently, the

manifestations and sequence of ND symptoms may vary among adolescents WP and cigarette smokers, which is key for identifying and characterizing ND among this population at an early stage. Therefore, monitoring the natural process of ND development among youth WP and cigarette smokers will provide important insights for future interventions aimed at curbing WP use among adolescent smokers.

In Lebanon, WP smoking among youth has reached epidemic proportions, with the prevalence of current WP smoking being more than three times (37.2%) that of cigarette smoking (11.2%) (Jawad et al., 2018; WHO, 2019b). Therefore, this country is in urgent need for WP smoking interventions, and at the same time provides an opportunity to study the trajectory of ND development among adolescent WP and cigarette smokers. In a previous report using baseline data of Waterpipe Dependence in Lebanese Youth (WDLY) study, Bahelah et al (Bahelah et al., 2016a) reported that ND symptoms among adolescent WP smokers can develop at low level of consumption and frequency of use. However, the longitudinal trajectory of ND development among young WP smokers and how it differs from cigarettes has not been studied yet. This WDLY prospective study was designed to map the natural course of ND development among young WP and cigarette smokers and will be used to characterize the early and most common symptoms of ND and their sequence in adolescent WP and cigarette smokers.

Methods

Sample

For this study, data were obtained from the WDLY, a 5-year prospective study of 647 adolescent WP and cigarette smokers and never-smokers. WDLY data were collected from 38 public and private schools using a list from the Lebanese Ministry of Education

beginning when the students were in 8th or 9th grade. To determine eligibility, a brief in-class, self-administered recruitment survey about students' smoking status was administrated. In order to compare cigarette and WP smokers in terms of ND pattern, students were eligible to participate if they currently (past 30 days) smoked either cigarettes or WP, but not both. We also included non-smokers who were susceptible to smoking initiation in the future. Data were collected in six survey waves between May 2015 and December 2017 at 6-month intervals (Figure 1). A 7th wave was collected in March 2019. A full description of the methodology of WDLY is available elsewhere (Bahelah et al., 2016a). The Institutional Review Boards of Florida International University and the American University of Beirut approved the study protocol.

Figure 1 displays a detailed summary of data collection and a timeline for waves 1 to 7. At baseline (wave 1), a total of (498) 8th-and-9th-graders were enrolled. Of these, 81.5% (n=406) were retained through 7 waves of data collection. Due to the small number of cigarette smokers at baseline (n=32), 104 current cigarette smokers were added to the study during waves 4-6 to provide statistical power to detect differences between WP and cigarette smokers in regard to the timing of ND symptoms. Overall, 149 participants were added to the study during waves 4-6, including cigarette smokers (n=104), WP smokers (n=9), and nonsmokers (n=36), with a retention rate of 78% (n=116) at wave 7.

Between waves 1 and 7, 647 (498 at baseline + 149 added at follow-ups) participants completed at least one wave of the WDLY study. Of the 647 participants, 429 (66.3%) who reported WP-only (n=283) or cigarette-only (n=146) in the past 30-days preceding any interview time were included in the current analyses. Non-smokers (n=87) and participants who switched from WP to cigarettes or vice versa or were both WP and

cigarette users (n=126) and other tobacco product users (n=5; e-cigarettes/e-hookah) were excluded from the analysis.

Measures

The Hooked-on-Nicotine-Checklist (HONC)

The HONC (Bahelah et al., 2016a; DiFranza et al., 2002) was employed to measure loss of autonomy over tobacco use as one of the main outcomes of the present study. The HONC is a validated and widely used instrument that assesses whether any of 10 symptoms of dependence have been experienced (indicated by yes or no responses), including an unsuccessful quit attempt, finding it really hard to quit, and strong cravings to smoke (DiFranza et al., 2002). The HONC's focus on symptoms allows for its use with any nicotine delivery method and is sensitive to detecting initial symptoms of ND among youth (Bahelah et al., 2016a; DiFranza et al., 2002). The Arabic version of HONC used in the WDLY study showed acceptable internal reliability among WP smokers (α=0.74) (Bahelah et al., 2016a).

WHO's International Classification of Diseases, 10th version (ICD-10)

The ICD-10 uses a cluster of behavioral, cognitive and physiological phenomena that develop after repeated use of tobacco products to diagnose ND syndrome (WHO, 1993; DiFranza et al., 2007a). The ICD-10 includes 19 dichotomous (yes, no) items with 6 criteria (Table 2). The ICD-10 diagnosis of ND requires the clustering of 3 or more criterion symptoms of dependence during a 1-year period (DiFranza et al., 2007a). The ICD-10 has been validated among adolescent WP smokers in this cohort using an Arabic version of the 19-item instrument that had acceptable internal reliability (α=0.76) (Bahelah et al., 2016a). We selected the HONC and ICD-10 to assess ND in our study because these two measures

are not tobacco method-specific, making them appropriate for examining ND trajectories irrespective of the type of tobacco product (16,18). See supplementary materials-Appendix I for ICD10 and HONC items.

The dates of first puff on WP/cigarette and onset of each HONC symptom and ICD10 criteria were recorded. The first puff on WP/cigarette was collected with the question "*Have you ever smoked a WP/cigarette even just one puff or two?*" Possible responses were no/yes; if yes, the date of the first puff was recorded as day/month/year. We also recorded the frequency of use (days smoked per month) and quantity (the number of WP/cigarettes smoked per month) at the time of the appearance of each individual HONC items and ICD10 criteria.

Frequency and quantity of use

To maintain consistency with previously published work (Scragg et al., 2008) and simplify the presentation of results, we categorized the quantity of cigarette use per month as 1, 2, 3-4, 5-9, 10-19, 20-99, 100 or more. The quantity of WP use was categorized as smoking ≤1 bowl/head of WP per month, 2, 3-4, 5-9, 10-19, 20-29, or ≥30. The frequency of WP or cigarette smoking per month was adopted from the Global Youth Tobacco Survey (CDC, 2012), which was categorized as smoking a cigarette or WP on 1 or 2 days per month, 3-5, 6-9, 10-19, 20-29, or all 30 days.

To calculate the time intervals (i.e. number of months) between first puff on WP/cigarette and the appearance of each HONC item, ICD10 criteria, and full ICD10 ND syndrome, the date of the first puff was subtracted from the date when the appearance of 1st symptom/criteria or ICD10 ND syndrome took place (Bahelah et al., 2016a).

Statistical analysis

Baseline characteristics were compared between WP and cigarette smokers using frequencies and percentages for categorical variables and mean ± standard deviation (SD) for continuous variables. Categorical variables (proportions) were compared using chi-squared tests, while t-test or Mann-Whitney U/Kruskal-Wallis tests, where applicable, were used to test group differences in continuous variables.

The time-to-event intervals (months) were computed using Kaplan-Meier (K-M) survival analyses stratified by smoking group (WP and cigarette smokers). Because of the positive skew frequently seen with follow-up times, medians are often a better indicator of "average" time-to-event intervals (UCLA, 2019). Therefore, K-M product-limit estimates focused on the time to 50% (median) and corresponding 95% CI of cumulative probability. The log-rank test was used to evaluate differences between WP and cigarette smokers in time (months) until the appearance of initial symptom of HONC, each individual HONC symptom, each ICD10 criteria, and full ND syndrome since first puff.

For this cohort, each participant could endorse 10 HONC items and 6 ICD10 criteria at different time points (i.e., dates) and therefore, produce a sequence of the 1^{st} to 10^{th} HONC symptom and 1^{st} to 6^{th} ICD10 criteria experienced. However, to simplify the presentation of results, we reported the percentage of individuals who endorsed each HONC item and ICD10 criteria only for 1^{st} to 4^{th} symptoms that appeared after the first puff on WP or cigarette. We obtained the quantity and frequency of WP and cigarette use at the time of appearance of initial HONC symptom and full ND syndrome. To control the effect of age, gender, and school type on timing differences between WP and cigarette smokers, we performed a sensitivity analysis using the Cox proportional-hazards model

through the PHREG Procedure in SAS/STATv14.2 (Cox,1972; Savarese& Patetta, 2013). This sensitivity analysis indicated that age differences at onset of smoking and at the time of entry to study, as well as gender and school type, did not affect the observed timing differences between WP and cigarette smokers in experiencing initial HONC symptom or developing the full ICD10 ND during follow up (see supplementary materials-Appendix II). A two-tailed $\alpha = 0.05$ was set *a priori* for all analyses, which were computed using SAS/STATv14.2 (SAS Institute Inc., NC; USA) and SPSS v.22 (IBM Corp., Armonk, NY, USA).

Results

Demographic characteristics

Table 1 shows selected characteristics of current (past 30-day) WP and cigarette smokers at the time of study entry. Overall, 174 (61.5%) of WP smokers and 26 (17.8%) of cigarette smokers were females, with a mean age of 13.3 years (SD, 1.9) and 13.8 years (SD, 2.0, $p<.004$), respectively.

Course of symptom development

The proportion of participants reporting each HONC symptom and ICD10 criteria since first puff on WP or cigarette and the number of months after smoking initiation when the cumulative probability of developing each symptom was 50% are shown in **Table 2**.

Course of symptom development (HONC)

There was a marginally significant difference in the proportion of WP and cigarette smokers who experienced an initial HONC symptom (WP=58.7% (n=166) vs cigarette=50.0% (n=73), $p=0.054$).

At least one HONC symptom was reported by 50% of symptomatic WP and cigarette smokers within 9.7 and 18.5 months since smoking initiation, respectively (p<0.001). (**Table 2**). Similarly, the time since smoking initiation to the point at which 50% of participants developed individual HONC symptoms such as "having a strong craving to smoke": (WP: 14.9 vs cigarette: 27.4 months, p=0.010); "feeling addicted": (WP:14.2 vs cigarette: 24.4 months, p<0.001); "having a strong urge to smoke" (WP: 19.2 vs cigarette: 27.6 months, p=0.029), and "hard to refrain from smoking where it is not allowed" (WP: 14.5 vs cigarette: 33.3 months, p<0.010) were significantly shorter among WP smokers compared to cigarette smokers (**Table 2**).

Course of symptom development (ICD10)

ICD10 dependence criteria were met by 27.9 % (n=79) of WP smokers and 21.2% (n=31) of cigarette smokers (*P*=0.082). Among those with ICD10 ND, this milestone was reported by 50% of WP and cigarette smokers within 15.1 and 22.3 months since smoking initiation, respectively (p=0.045) (**Table 2**). The time since smoking initiation to the point at which 50% of participants attained individual criteria of ICD 10 was significantly different between WP and cigarette smokers only for the criteria #1: "A strong desire or sense of compulsion to use tobacco" (WP: 12.1 vs cigarette: 18.5 months, p=0.025) (**Table 2**).

Sequence of ND symptoms

Figure 2 (panel A&B) shows variability in the order of appearance of HONC symptoms based on the percentages of participants who endorsed each HONC item as their 1st to 4th symptoms after smoking initiation. Among 166 symptomatic WP smokers, "having a strong craving to smoke WP" was the first most commonly reported symptom

(by 33.7% of WP smokers), followed by "feeling addicted" (17.5%), "failed quit attempt" (10.2%), and "strong urges to smoke WP" (7.2%). Among 73 symptomatic cigarette smokers, "feeling addicted" was the first most common presenting symptom (39.7%), followed by "having a strong craving to smoke a cigarette" (20.5%), "failed quit attempt" (12.3%), and "feeling irritable" (11%).

Figure 2 (panel C&D) shows variability in the order of developing ICD10 criteria based on the percentages of participants who attained each ICD10 criteria as their 1st to 4th symptoms after smoking initiation. Among 79 WP smokers who met the criteria for ICD10 ND (panel C), "a strong desire or sense of compulsion to use tobacco" was the first most commonly reported symptom (by 51.9% of WP smokers), followed by "difficulties in controlling tobacco-taking behavior in terms of its onset, termination, and levels of use" (41.8%), "neglect of alternative pleasure" (19.0%), and "use despite harm" (11.4%). Among 31 cigarette smokers who developed ICD10 ND (panel D), "a strong desire or sense of compulsion to use tobacco" was the first most common presenting symptom (51.6%), followed by "neglect of alternative pleasure" (35.5%), "a physiological withdrawal state" (25.8%), and "evidence of tolerance" (9.7%).

Frequency and quantity of use

Tables 3 & 4 display the cumulative percentages of quantity and frequency of use at the time of experiencing the initial HONC symptom and attaining ICD10 ND. As shown in **Table 3**, among the 166 symptomatic WP smokers who experienced one or more HONC symptoms, 14.5% presented an initial HONC symptom after smoking ≤1 WP (head/bowl)/month. Only 5.1% of 79 WP smokers who attained ICD10 ND did so after smoking ≤1 WP (head/bowl)/month. Among the 73 symptomatic cigarette smokers who

experienced one or more HONC symptoms, 4.1% experienced the initial HONC symptom after smoking only 1-2 cigarettes/month. Only 0.7% of 31 symptomatic cigarette smokers who met ICD10 ND criteria did so after smoking only 1-2 cigarettes/month.

As shown in **Table 4**, approximately 88% of 166 symptomatic WP smokers experienced an initial HONC symptom before daily smoking, and about 71% of 79 WP smokers who met ICD10 ND criteria did so before daily smoking. While approximately 43% of 73 symptomatic cigarette smokers experienced an initial HONC symptom before daily smoking, about 25.8% of 31 symptomatic cigarette smokers who met ICD10 ND criteria did so before daily smoking.

Discussion

This is the first longitudinal study to compare the trajectories of ND symptoms between adolescent WP and cigarette smokers. Our findings show that adolescent WP smokers experience initial ND symptoms and meet ICD10 dependence criteria earlier and with less frequent use than cigarette smokers. Half of adolescent WP smokers who experienced one or more HONC symptoms did so within 10 months of the first puff on WP, compared to 19 months for cigarette smokers. Similarly, half of adolescent WP smokers who met ICD10 criteria did so within 15.1 months after smoking initiation, compared to 22.3 months for cigarette smokers. In terms of specific symptom appearance, we found that 3 HONC symptoms (i.e., craving, feeling addicted, and urge to smoke) and one ICD10 criterion (i.e., a strong desire or sense of compulsion to use tobacco) develop faster in WP smokers compared to cigarette smokers. We also found that as initial HONC symptoms develop and ICD10 ND criteria are met, adolescent cigarette smokers show more accelerated patterns of increasing use frequency compared to WP smokers.

Interestingly, at a comparable stage of use, more cigarette smokers expressed difficulty in refraining from smoking in places where it is not allowed compared to WP smokers. These findings highlight the potential role of WP-unique features, use patterns, and social setting in ND development, and the need to address early ND symptoms appearance, composition, and contextual factors in WP smoking cessation interventions.

The finding that ND develops more quickly and with a low frequency of use among WP smokers compared to cigarette smokers may be explained by several unique features of WP smoking, including deep inhalation that is required to operate the WP and overcome the device and tubing space (Bahelah et al., 2019; Cobb et al., 2011; Maziak et al., 2019). For example, a smoker can inhale approximately 50-80 L of tobacco smoke during a one-hour WP smoking session compared with 0.5-0.8 L from ~5 min smoking single cigarette (Primack et al., 2019); greater intake of smoke is associated with greater intake of nicotine (Maziak et al., 2019). Other potential contributors include the pleasant and social nature of WP smoking, and its sensory cues (e.g. aromatic smell, bubbling sound, the attractive silhouette of the device), which may provide conditioned cues that enhance the development of ND in adolescent WP smokers (Aboaziza & Eissenberg.,2015; Maziak et al., 2005a; Hammal et al., 2008). These factors should be interpreted in light of the differences in the dose of nicotine delivered and other differences between these two smoking methods.

Although there are differences in the timing and order of appearance of ND symptoms in WP vs. cigarette smokers, the earliest appearing symptoms are generally the same. Three of the four most common ones are identical for WP and cigarette smokers (i.e., strong craving, feeling addicted, and failed quit attempts) suggesting largely similar processes but

distinct timing, with ND onset being much more rapid in WP smokers. Additionally, where differences in appearance of ICD10 criteria exist (difficulty controlling use and use despite harm, appear as 1st-4th for WP, whereas physiological withdrawal and tolerance appear for cigarette smokers), it suggests that conditioned responses to the social, cognitive, and sensory cues may be more important determinants of early manifestation of ND symptoms in WP whereas physiological changes are more important early on for cigarette smokers. These WP-specific patterns highlight the importance of targeting social cues (e.g., laws prohibiting WP in restaurants) and sensory cues (e.g., banning WP tobacco flavors, just as flavored cigarettes are banned in the US) for WP cessation interventions.

One interesting finding is that although the number of participants endorsing different HONC symptoms was similar between the two products, difficulty in refraining from tobacco was reported by a higher proportion of cigarette smokers than WP despite taking longer time to endorse this symptom. Our earlier results of predictors of progression of WP smoking showed difficulty refraining from smoking WP while in a restaurant strongly predicted progression in ND symptoms in adolescent WP smokers, underling the role of smoking cues in WP-serving venues and the important role of these venues in promoting ND (Bahelah et al., 2019). These findings reflect a new nuance in the difference in addiction patterns between cigarettes and WP smokers. They can also mean that although WP smokers develop ND symptoms faster, they have less difficulty refraining from smoking than cigarette smokers in tobacco-free settings. This notion has important implications for WP smoking cessation as it means that earlier intervention (because WP smokers develop ND symptoms faster) potentially may lead to higher rates of cessation given that WP smokers also have less difficulty refraining from smoking WP than cigarette

smokers. Also, as discussed above, among ICD10 criteria, “use despite harm” was reported in higher proportion and earlier for WP smokers than cigarettes. This emphasizes that even for a tobacco use method that is considered by many as safer than cigarettes (WHO, 2020; Hammal et al., 2008; Salloum et al., 2019; Ozouni et al., 2017), the more nicotine dependent smokers continue their WP smoking despite full awareness of its harms.

This study has some limitations. First tobacco use data were collected by self-report and may be intentionally distorted by social desirability response bias. However, self-reported smoking behavior has been shown to be a reliable and valid method in adolescent survey studies (Stein wt al., 2002; Binnie et al., 2004). Second, the longitudinal nature of the study makes possible errors in recalling the dates of events which happened remotely. We minimized the likelihood of this error by means of methods that improve recall of events (e.g., personal landmarks, bounded recall, decomposition, and a visual aid) (DiFranza et al.,2000;2002;2007b). Finally, most of the cigarette smokers that we recruited during waves 4, 5, and 6 of the study were 11th or 12th graders that raised the age of cigarette smokers compared to WP smokers at the time of entry to study. Also, the age of smoking initiation was slightly higher for cigarettes compared to WP smokers. However, our sensitivity analyses revealed that after adjusting for age of smoking initiation and age at the time of entry to study, differences in time-to-event (initial HONC symptom or full ICD10 ND) between WP and cigarette smokers remained significant.

Conclusions

This longitudinal study, for the first time, provides a robust examination of the development of ND and sequence of symptom presentation among adolescents who smoke WP compared to cigarettes. It shows that early development of symptoms of dependence

and the full syndrome of ND that are important in relapse and cessation appear earlier with low frequency and quantity of use in adolescent WP smokers compared to cigarette smokers.

We also documented that early HONC symptoms and ICD10 criteria develop in almost similar sequences for WP and cigarette smokers, with faster appearance of ND symptoms among WP smokers compared with cigarette smokers. Accordingly, WP smokers who manifest early ND symptoms should be identified and offered cessation treatment as early as possible to avoid further development of ND syndrome and to increase the likelihood of successful quitting. Failed quit attempts manifests as an early symptom of ND among WP smokers which may warrant intervention efforts to boost quitting self-efficacy, which at least among cigarette smokers is an important determinant of success (Bektas et al., 2010; Perkins et al., 2012) and predicts adherence to WP cessation treatment (Asfar et al., 2014).

Our results also suggest that cessation efforts with adolescents early in their WP use may benefit from targeting the extinction of social and sensory cues that are associated with ND rather than physiological symptoms which tend to manifest somewhat later. It is also important to educate youths who smoke to recognize their early symptoms of ND which in turn will prompt earlier and more-effective cessation efforts. To achieve higher effectiveness, WP-tailored interventions need to consider the unique trajectories of appearance of ND symptoms.

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Tables and Figures

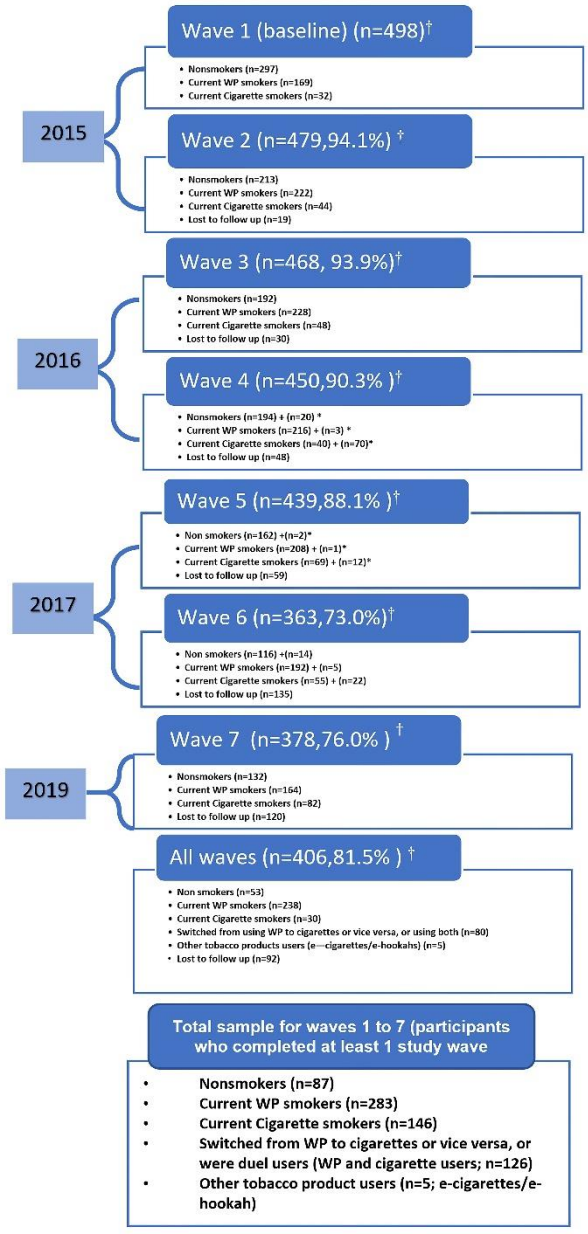

Figure 1. Data collection process for the Waterpipe Dependence in Lebanese Youth (WDLY) study, 2015-2019.† the numbers and percentages represent participants who took part in the interview for the same wave. *Note: 149 participants were added to the study during waves 4, 5, and 6; including WP smokers (n=9), cigarette smokers (n=104) as well as susceptible nonsmokers (n=36) with the retention rate of 78% (n=116) at wave 7. Note: This study characterizes the natural course of ND symptoms among exclusive WP and exclusive cigarette users, therefore, nonsmokers and subjects who smoked both WP and cigarettes or other tobacco products at various times were excluded from the analysis.

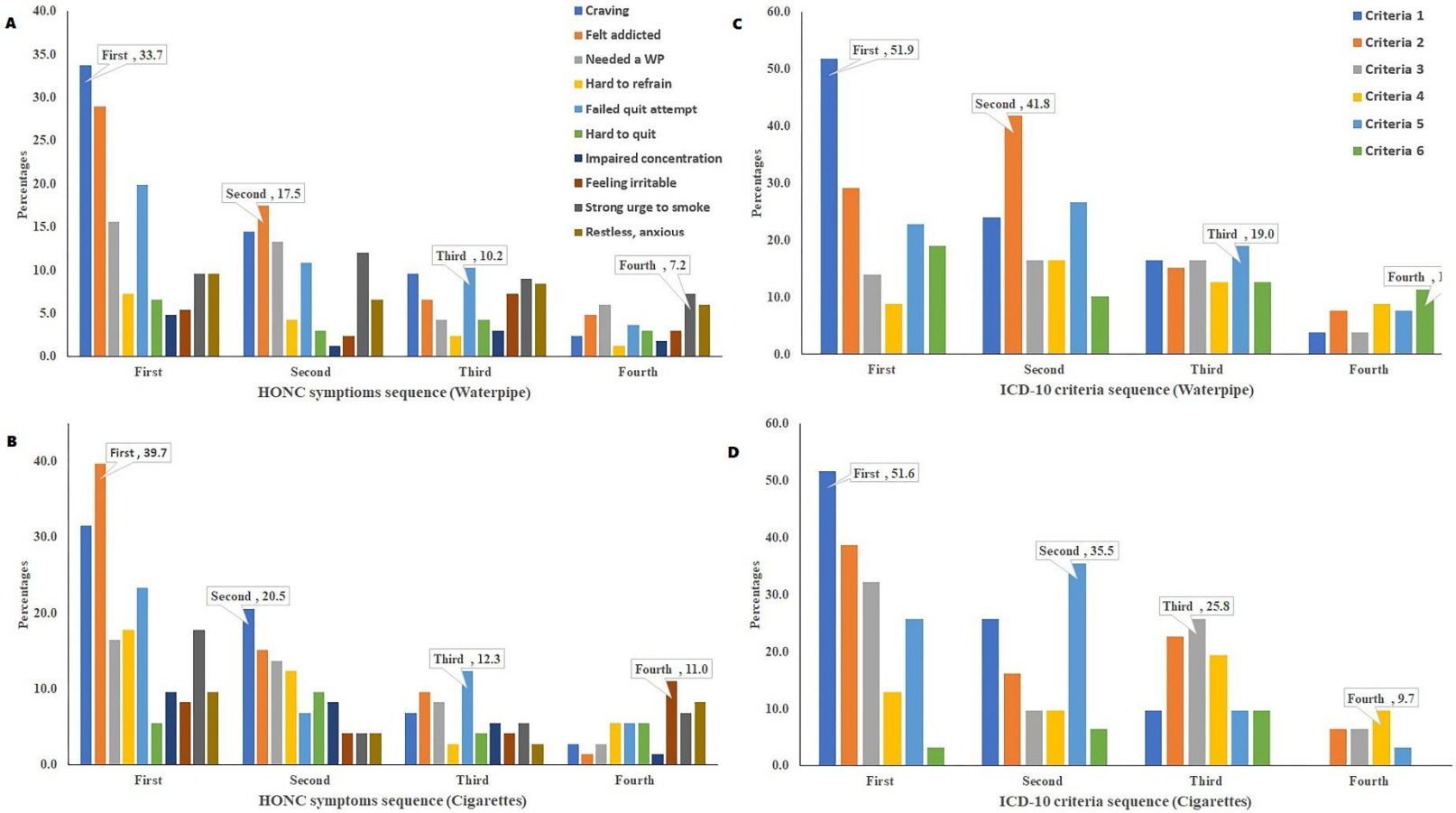

Figure 2. Order of appearance of 10 HONC symptoms and 6 ICD10 criteria. The bars display percentages of 166 WP (panel A) and 73 cigarettes (panel B) smokers who endorsed HONC symptoms as their first, second, third, and fourth symptoms based on temporality sequence since smoking initiation. The bars also display percentages of 79 WP (panel C) and 31 cigarettes (panel D) smokers who attained each ICD10 criteria as their first, second, third, and fourth ND symptoms based on temporality sequence since smoking initiation. Six criteria of ICD-10 includes criteria 1: "a strong desire or sense of compulsion to use tobacco"; criteria 2: "difficulties in controlling tobacco-taking behavior in terms of its onset, termination, and levels of use"; criteria 3: "a physiological withdrawal state"; criteria 4: "evidence of tolerance"; criteria 5: "neglect of alternative pleasure"; and criteria 6: "use despite harm".

Table 1. Selected characteristics of adolescent WP and cigarette smokers at entry into the WDLY study*

	Total (n=429)	**Waterpipe (n=283)**	**Cigarette (n=146)**	***p-value***
Age, years, mean (SD)	14.7 (1.6)	14.1 (1.3)	15.8 (1.5)	<0.001
Sex, n (%)				<0.001
Male	229 (53.4)	109 (38.5)	120 (82.2)	
Female	200 (46.6)	174 (61.5)	26 (17.8)	
School type, n (%)				0.003
Public	224 (52.2)	134 (47.3)	90 (61.6)	
Private	205(47.8)	149 (52.7)	56 (38.4)	
School grades, n (%)				<0.001
8th	164 (38.4)	141 (49.8)	29(17.4)	
9th	154 (36.1)	131 (46.3)	29(17.4)	
10th	24 (5.6)	2(0.7)	28(16.8)	
11th	59 (13.8)	5 (1.8)	59(35.3)	
12th	26 (6.1)	4 (1.4)	22(13.2)	
BMI, mean (SD)	21.7 (4.2)	21.3 (4.0)	23.1 (4.4)	0.015
Age first smoked tobacco, mean (SD)	–	13.3 (1.9)	13.8(2.0)	0.004
Age first HONC item was experienced mean (SD) [a]	–	14.0(1.6)	15.6 (1.6)	<0.001
Age of attaining ICD-10 ND	–	14.5 (1.4)	15.6 (1.7)	0.002

HONC, Hooked on Nicotine Checklist; ICD-10 ND, International Classification of Diseases, Nicotine Dependence (≥3 criteria), * 274 WP smokers and 42 Cigarette smokers entered the study in Wave 1, 9 WP smokers were added to the study during waves four (n=3), five (n=1), and six (n=5). 104 cigarette smokers were added to the study during waves four (n=70), five (n=12), and six (n=22). [a] Age first HONC item was experienced and age of attaining ICD-10 ND were among 166 WP and 73 cigarette smokers who experienced initial HONC symptom and attained ICD10 ND.

Table 2. Time (months) to 50% (median) cumulative probability of endorsement of HONC symptoms since first puff on WP/cigarette

	Proportion reporting symptoms %[†]			Time to 50% cumulative probability, Estimate (95% CI), months		
HONC Symptoms [a]	Waterpipe smokers (n=283)	Cigarette smokers (n=146)	Chi-Square p-value	Waterpipe smokers	Cigarette smokers	Log-Rank p-value
				First puff on WP	First puff on cigarette	
Diminished autonomy [b]	58.7	50.0	0.054	9.7 (7.5-11.8)	18.5 (14.7-26.3)	**<0.001**
Craving	38.5	33.6	0.313	14.9 (11.9-20.2)	27.4 (18.4-30.5)	**0.010**
Felt addicted	36.7	34.9	0.710	14.1 (11.5-17.9)	24.4 (16.7-35.5)	**<0.001**
Failed quit attempt	29.0	26.7	0.622	17.1 (13.8-21.1)	20.6 (12.1-31.6)	0.179
Strong urge to smoke	28.6	19.9	**0.049**	19.2 (13.9-23.0)	27.6 (16.7-36.5)	**0.029**
Restless, anxious, or nervous	21.6	18.5	0.457	17.8 (14.2-23.0)	25.7 (17.9-33.7)	0.261
Needed a WP/cigarette	17.7	21.2	0.423	21.0 (11.9-27.5)	24.6 (16.7-32.1)	0.643
Hard to quit	17.3	17.1	0.960	21.6 (14.5-29.4)	28.8 (18.6-40.7)	0.749
Feeling irritable	16.6	16.4	0.964	17.0 (12.4-26.6)	24.1 (16.7-36.5)	0.213
Hard to refrain	11.7	21.9 *	0.005	14.5 (11.1-22.4)	33.3 (21.2-39.1)	**0.010**
Impaired concentration	9.9	15.8	0.076	28.4 (18.1-37.5)	32.7 (18.6-40.7)	0.298
ICD10 criteria 1: A strong desire or sense of compulsion to use tobacco	30.7	25.3	0.242	12.1 (9.6-15.1)	18.5 (15.6-32.8)	**0.025**
ICD10 criteria 2: Difficulties in controlling tobacco-taking behavior in terms of its onset, termination, and levels of use	29.3	24.0	0.239	16.1 (13.1-18.6)	28.6 (18.4-31.6)	0.068
ICD10 criteria 3: A physiological withdrawal state	18.0	16.4	0.683	18.6 (13.2-28.7)	24.0 (14.1-31.9)	0.479
ICD10 criteria 4: Evidence of tolerance	15.5	11.6	0.273	15.8 (11.1-23.0)	19.4 (12.3-33.3)	0.104
ICD10 criteria 5: Neglect of alternative pleasure	25.1	17.1	0.061	14.8 (11.06-19.5)	21.7 (12.3-35.4)	0.083
ICD10 criteria 6: Use despite harm	16.6	8.2 *	0.017	17.5 (12.1-22.1)	27.8 (3.0-46.7)	0.273
Full ICD10 ND syndrome	27.9	21.2	0.133	15.1 (13.1-18.2)	22.3 (15.6-31.7)	**0.045**

[†]Proportion of the cohort reporting each symptom. * Chi-square tests indicate the significant differences between proportion of each HONC item/or each ICD10 Criteria for WP and cigarettes. [a] Participants reported HONC symptoms by responding yes/no to the questions: Craving; "Have you ever had strong cravings to smoke WP/cigarette?" Felt addicted; "Have you ever felt like you are addicted to smoking WP/cigarette?" Failed quit attempt; "Have you ever tried to quit smoking but could not do it?" Strong urge to smoke; "Did you feel a strong need or urge to smoke WP/cigarette?" Restless, anxious, nervous; "Did you feel restless, anxious, or nervous because you could not smoke?" Needed a WP/cigarette; "Have you ever felt like you really needed a WP/cigarette?" Hard to quit; "Do you smoke now because it is really hard to quit?" Feeling irritable; "Did you feel more irritable because you could not smoke WP/cigarette?" Hard to refrain; "Is it hard to keep from smoking in places where you are not supposed to, like school?" Impaired concentration; "Did you find it hard to concentrate because you could not smoke WP/cigarette?"
[b] Endorsing ≥ one HONC symptoms.

Table 3. Cumulative percentages of quantity of use at the time of experiencing initial HONC symptom and attaining ICD10 ND among adolescent waterpipe and cigarette smokers

	WP smokers			Cigarette smokers	
Quantity [a]	HONC (n=166) [b]	ICD10 (79) [c]	**Quantity** [a]	HONC (n=73) [d]	ICD10 (n=31) [e]
≤1	14.5	5.1	**1**	1.4	0.7
2	28.3	12.7	**2**	4.1	0.7
3 to 4	51.8	25.3	**3-4**	9.6	0.7
5 to 9	67.5	45.6	**5-9**	13.7	19.9
10 to 19	83.7	63.3	**10-19**	20.5	19.9
20 to 29	89.8	69.6	**20-99**	35.6	41.1
≥30	10.2	29.4	**≥100**	64.4	58.9

[a] Quantity of use (the number of WP/cigarettes smoked in the past month) at the time of the appearance of initial HONC symptom and attaining ICD10 ND. [b]166 symptomatic WP smokers who endorsed at least one HONC symptom. [c] 79 symptomatic WP smokers who attained ICD10 ND, [d] 73 symptomatic cigarette smokers who endorsed at least one HONC symptom. [e] 31 symptomatic WP smokers who attained ICD10 ND.
Note: Percentages are based on cumulative order.

Table 4. Cumulative percentages of frequency of use at the time of experiencing initial HONC symptom and attaining ICD10 ND among adolescent waterpipe and cigarette smokers

	HONC comparing WP to cigarettes		ICD10 ND comparing WP to cigarettes	
Frequency [a]	WP (n=166) [b]	Cigarettes (n=73) [c]	WP (79)[d]	Cigarettes (n=31) [e]
1-2 days	25.9	5.5	15.2	3.2
3-5	55.4	20.5	30.4	3.2
6-9	66.9	21.9	44.3	6.5
10-19	80.7	34.2	64.6	12.9
20-29	87.3	42.5	70.9	25.8
30 days*	12.7	57.5	29.1	74.2

[a] Frequency of use (days smoked per month) at the time of the appearance of initial HONC symptom and attaining ICD10 ND. [b]166 symptomatic WP smokers who endorsed at least one HONC symptom. [c] 73 symptomatic cigarette smokers who endorsed at least one HONC symptom. [d]79 symptomatic WP smokers who attained ICD10 ND. [e] 31 symptomatic WP smokers who attained ICD10 ND.
Note: Percentages are based on cumulative order.

Supplementary materials

Appendix I-Questionnaires

Nineteen-item survey represents the 6 criteria of nicotine dependence based on the International Classification of Diseases-10th revision (ICD10) and includes the 10 items of Hooked on Nicotine Checklist (HONC; **BOLD** items) . Attainment of any 1 item in a criterion (any 2 items in criterion 3) represents an endorsement of that criterion and attaining ≥3 criteria over a 12-month period is needed for the diagnosis of nicotine dependence. Endorsement of any HONC item indicates that a smoker presents initial dependence symptom.

1. A strong desire or sense of compulsion to use tobacco (4 items)	
a.	**Have you ever had strong cravings to smoke waterpipe? yes/no**
b.	**Have you ever felt like you were addicted to waterpipe?**
c.	**Have you ever felt like you really needed a waterpipe?**
d.	**Is it hard to keep from smoking waterpipe in places where you are not supposed to, like school?**
2.Difficulties in controlling tobacco-taking behavior in terms of its onset, termination, or levels of use	
a.	**Have you ever tried to quit waterpipe smoking but could not do it?**
b.	**Do you smoke waterpipe now because it is really hard to quit?**
c.	Are you smoking waterpipe more now than you planned to when you started?
3.A physiological withdrawal state (5 items)	
When you have tried to stop smoking or when you have not been able to smoke…	
a.	**Did you find it hard to concentrate because you could not smoke waterpipe?**
b.	**Did you feel more irritable because you could not smoke waterpipe?**
c.	**Did you feel a strong need or urge to smoke waterpipe?**
d.	**Did you feel nervous, restless, or anxious because you could not smoke waterpipe?**
e.	Do you smoke waterpipe to avoid withdrawal symptoms?
4.Evidence of tolerance (2 items)	
a.	Do you find that you need to smoke waterpipe more often than you used to?
b.	Do you have to smoke waterpipe more often now to feel relaxed than you used to?
5.Neglect of alternative pleasures	
a.	Do you find that you are spending more of your free time trying to get waterpipe?
b.	Have you cut down on your physical activities or sports because you smoke waterpipe?
c.	Do you ever give up going places or doing things because waterpipe smoking is not allowed?
d.	Have you stopped hanging out with certain friends because you smoke waterpipe?
6.Use despite harm (1 item)	
a.	Has a doctor or nurse told you that you should quit smoking waterpipe because it was damaging your health?

Appendix II- Cox Proportional Hazards Model on timing differences between WP and cigarette smokers for presenting HONC symptoms and attaining ICD 10 ND criteria.

Table A. Cox Proportional Hazards Model on timing differences between WP and cigarette smokers for presenting HONC symptoms

	DF	Parameter estimates	Standard Errors	Chi-Square	Pr > ChiSq	Hazard ratio	95% Hazard Ratio Confidence	
Smoking method (WP & Cigarettes)	1	0.64119	0.16656	14.8197	0.0001	**1.899**	**1.37**	**2.632**
Gender of the student	1	-0.08315	0.1505	0.3053	0.5806	0.92	0.685	1.236
Type of the school	1	-0.26236	0.14065	3.4795	0.0621	0.769	0.584	1.013
Age at the entry to the study	1	-0.23657	0.06724	12.3786	0.0004	0.789	0.692	0.901
Age of smoking Initiation	1	0.31453	0.04043	60.5218	<.0001	1.37	1.265	1.483

Table B. Cox Proportional Hazards Model on timing differences between WP and cigarette smokers for attaining ICD10 ND

	DF	Parameter estimates	Standard Errors	Chi-Square	Pr > ChiSq	Hazard ratio	95% Hazard Ratio Confidence	
Smoking method (WP & Cigarettes)	1	1.07537	0.26733	16.1818	<.0001	**2.931**	**1.736**	**4.95**
Gender of the student	1	-0.28423	0.21498	1.748	0.1861	0.753	0.494	1.147
Type of the school	1	0.06739	0.2306	0.0854	0.7701	1.07	0.681	1.681
Age at the entry to the study	1	-0.67695	0.10691	40.0971	<.0001	0.508	0.412	0.627
Age of smoking Initiation	1	0.80681	0.08756	84.9082	<.0001	2.241	1.887	2.66

MANUSCRIPT 2

Ebrahimi Kalan, M., Bahelah, R., Bursac, Z., Ben Taleb, Z., DiFranza, J.R., Tleis, M., Nakkash, R., Jebai, R., Alam, M.M., Cano, M.Á., Sutherland, M.T., Fenni, K., Asfar, T., Eissenberg, T., Ward, K.D., Maziak, W., 2020. Predictors of nicotine dependence among adolescent waterpipe and cigarette smokers: A 6-year longitudinal analysis. *Drug and Alcohol Depend*, 217, 108346.

Abstract

Background and objective

Identifying the factors associated with nicotine dependence (ND) is essential to prevent initiation and continued use, and to promote cessation among youth. This study aims to document the predictors of the appearance of initial ND symptoms and full ND syndrome among adolescent waterpipe (WP) and cigarette smokers.

Methods

A 6-year longitudinal study was conducted among 8th and 9th graders from 38 schools in Lebanon. The analysis sample included exclusive-WP (n=228) and exclusive-cigarette smokers (n=139). Weighted Cox proportional hazards models were used to characterizing predictors of initial ND symptoms and full ND syndrome.

Results

Predictors of experiencing initial ND symptoms among WP smokers included low maternal educational level, having a sibling who smoked WP, low physical activity, high body mass index (BMI), smoking initiation at a younger age. For cigarette smokers these

were being male, younger, having lower BMI, having a sibling who smoked cigarettes, living in a crowded household, and smoking daily. Among WP smokers, predictors of developing full ND syndrome include being younger, believing that WP smokers have more friends, depression, high levels of impulsivity, and initiating smoking at a younger age. For cigarette smokers, predictors of full ND syndrome were being younger and initiating smoking at a younger age.

Conclusions

Smoking cessation and prevention interventions targeting youth should address modifiable, and tobacco use-specific factors that influence the development of ND among young WP and cigarette smokers. They also need to start at a younger age to target those most vulnerable to developing life-long addiction to tobacco products.

Introduction

Every year, an estimated 8 million people die of tobacco-caused diseases worldwide (WHO, 2019). Initiating tobacco use during adolescence doubles the rate of premature death (Thomson et al., 2020). Waterpipe (WP; hookah, shisha, narghile)–a centuries-old tobacco use method– exposes users to nicotine (Aboaziza and Eissenberg, 2014) and other toxicants similar to those present in cigarettes (Primack et al., 2016). WP tobacco smoking is becoming widespread globally especially in the Eastern Mediterranean Region (EMR) (Jawad et al., 2018; WHO, 2015) where approximately 10.3% of adolescents report past-month (current) WP use (Jawad et al., 2018).

Nicotine is a highly addictive psychomotor stimulant associated with continued use and dependence on tobacco products, and understanding factors influencing nicotine dependence (ND) in tobacco users is critical to design effective prevention and cessation

interventions. Yet, studies addressing ND have just begun investigating the diversity of tobacco products used by youth and the importance of understanding product-specific features and contextual factors leading to ND (DiFranza et al., 2000, 2002a; Hu et al., 2008; Sharapova et al., 2020; Ward, K. D. et al., 2015). For example, WP users are exposed to significant amounts of nicotine during the typically long smoking sessions (average 1 hour) and experience ND symptoms (e.g., abstinence-induced withdrawal and craving that are relieved by subsequent smoking). Moreover, WP social aspects, commonly reinforced by WP cafés can provide important cues for ND in WP smokers (Bahelah et al., 2018)). Identifying these unique features of ND and their predictors in WP smokers is important to develop tailored interventions to address the rise of WP smoking among youth.

Milestones in the trajectory of ND development, such as the appearance of first ND symptoms and full syndrome of ND syndrome can help elucidate factors that need to be addressed at each stage of adolescents' tobacco use trajectory for effective intervention. This is particularly important for WP smoking given its unique use features that can influence ND development such as its time-consuming preparation and consumption, intermittent use, and strong sensory and social cues(Akl et al., 2013; Maziak et al., 2019; Maziak et al., 2015). Our earlier studies based on a cohort of adolescents in Lebanon, a country with the highest WP use among adolescents(Jawad et al., 2018), showed that the initial ND symptoms and full syndrome of ND manifest more rapidly among WP smokers compared to cigarette smokers(Ebrahimi Kalan et al., 2020). We also found that 50% of both WP and cigarette smokers developed the full ND syndrome within 15 and 22 months after smoking initiation, respectively (Ebrahimi Kalan et al., 2020). As for contextual factors, our studies (Bahelah et al., 2017; Bahelah et al., 2018) showed that having at least

a family member who smokes WP, and more importantly, not resisting WP use while in a restaurant were associated with a higher risk of ND. Building on such a unique cohort, we aim to identify and contrast the factors that predict initial ND symptoms and full-blown ND syndrome in adolescents WP and cigarette smokers. The findings of this study will be effective for developing WP-specific policies to prevent ND among adolescents and design smoking cessation interventions for those already hooked on nicotine.

Methods

Study design and sample

Data were drawn from the Waterpipe Dependence in Lebanese Youth (WDLY) study, an ongoing prospective study of 647 Lebanese 8th and 9th grades adolescent smokers and non-smokers recruited from 38 public and private schools. A brief in-class, self-administered recruitment baseline survey about students' smoking status was administrated to determine eligibility. To compare cigarette and WP smokers in terms of ND patterns, students were eligible to participate if they were either current (use in the last 30 days) cigarette or WP smokers, but not both. Susceptible non-smokers (defined as the likelihood of cigarette/WP smoking initiation in next year) to smoke WP or cigarettes were also included. More details about the study design and procedures can be found elsewhere (Bahelah, Raed et al., 2016a; Ebrahimi Kalan et al., 2020).

The current longitudinal analysis used data from 8 waves and was restricted to participants who reported being current exclusive users of either WP (WP-only) or cigarettes (cigarette-only) during the study with a retention rate of 72.3% at wave 8 (i.e., n=179 were lost to follow-up during waves 2-8). The first 6 data collection waves were conducted between May 2015 and December 2017 with each wave separated by 6 months.

The 7th and 8th waves were conducted in 2019 and 2020, respectively with a 1-year interval between waves. This was done because data collection every 6 months became challenging given political instability in Lebanon. Also, because changes in ND trajectories tend to stabilize as adolescents approach early adulthood (Hu et al., 2012). At each wave, participant age assessed and when a participant reached 18 years old, informed consent was obtained without the need for parental/guardian consent as was required for those younger than 18. The Institutional Review Boards of Florida International University and the American University of Beirut approved this study.

Measures

Predictors

The selection of ND predictors was guided by a review of the literature on adolescent WP (Auf et al., 2012; Bahelah et al., 2016b; Jaber et al., 2015; Maziak et al., 2005; Neergaard et al., 2007) and cigarette smoking(Hu et al., 2006; Kleinjan et al., 2012) as well as theories of ND in this population (Aboaziza and Eissenberg, 2014; DiFranza et al., 2007; DiFranza and Ursprung, 2008; Maziak et al., 2005). A description of these predictor variables follows (the predictor variable levels used as reference categories in regression models are underlined).

a) So*ciodemographic characteristics* included age (years), gender (female/<u>male</u>), school type (public/<u>private</u>), body mass index (BMI= weight/height^2), regular physical activity defined as performing the physical activity at least once a week (yes/<u>no</u>), parental education (< 12 years of education vs <u>≥12</u>), and crowding index (defined as the number of co-residents in a dwelling, excluding infants, divided by the number of rooms in the dwelling, excluding the kitchen and bathrooms (Bejjani

et al., 2012; Melki et al., 2004). Crowding index is an indirect measure of socioeconomic status (SES) that is widely used in studies in the EMR and a higher crowding score indicates lower SES (Bejjani et al., 2012).

b) *Indicators of smoking in the social environment* such as parental WP/cigarette smoking (mother and/or father; yes/no) and having ≥ 1 siblings/friends who smoke WP/cigarettes; yes/no.

c) *Beliefs about smoking* included: WP/cigarette smokers look more attractive, WP/cigarette smokers have more friends, WP/cigarette smoking makes a person lose weight, and WP/cigarette smoking is harmful to health (response choices for all items: agree vs. disagree or don't know). Due to a low number of participants answered "don't know" and to simplify interpretation of results, we collapsed the responses "don't know" with "disagree".

d) *Smoking patterns* included age of initiating WP/cigarette smoking, past-month WP/cigarette smoking frequency (daily vs non-daily), quantity (number of WP heads/bowls and amount of cigarettes smoked in the past 30 days), intention to quit WP/cigarettes (yes/no), and any attempt to quitting WP/cigarettes in the past 6 months (yes/no).

e) *Psychological indicators* included perceived stress (15 items on four-point Likert scale "Not at all (0) to A whole lot (3)" with a possible score of 0–45) (Racicot et al., 2013), depressive symptoms (6 items on a four-point Likert scale "Never (0) to Often (3)" with a total score of 0–18) (Brunet et al., 2014), impulsivity (7 items on a five-point Likert scale "Not at all true (0) to Very true (4)" with 0–28 total score) (DiFranza et al., 2007), novelty-seeking (9 items on a five-point Likert scale "Not

at all true (0) to Very true (4)" with 0–36 total score) (DiFranza et al., 2007), and self-esteem (10 items on a four-point Likert scale "Strongly Disagree (0) to Strongly Agree (3)" with a total score of 0–30) (Waters et al., 2006). The internal consistency of these scales, as measured by Cronbach's alpha in our previous study, ranged from 0.63 to 0.81, indicating acceptable internal consistency (Bahelah et al., 2016b).

Outcomes

a) *Initial ND symptom*

The time interval between first WP/cigarette use and report of experiencing initial ND symptoms was assessed by the Hooked on Nicotine Checklist (HONC) (DiFranza et al., 2002a). HONC is a 10-item measure based on the Autonomy Theory of Tobacco Dependence which posits that the appearance of a single symptom of dependence (initial ND symptom) signals a loss of autonomy over tobacco use (DiFranza et al., 2000). HONC was validated among adolescent cigarette smokers in previous work (O'Loughlin et al., 2002) and WP smokers in the WDLY study (Bahelah et al., 2016a).

b) Full ND syndrome

The WHO's International Classification of Diseases, 10th Version Criteria for Tobacco Dependence (ICD-10) criteria for ND was assessed using 19 dichotomous (yes/no) items (DiFranza et al., 2007; WHO, 1993) across 6 criteria of ND and attainment of ≥ 3 criteria over a 12-month period is the standard threshold for diagnosis of full ND syndrome (DiFranza et al., 2007). The ICD-10 has been

previously validated among adolescent cigarette smokers (DiFranza et al., 2007) and WP smokers in the WDLY study (Bahelah et al., 2016a).

Data preparation

Data were prepared for analysis in 3 steps. First, to calculate the time-to-event (i.e., number of months) from the first WP/cigarette puff to the appearance of initial ND symptoms and development of full ND syndrome, the date of the first puff was subtracted from the date when the initial ND symptom emerged or full ND syndrome developed (Ebrahimi Kalan et al., 2020). Second, those participants who had achieved these outcomes prior to Wave 1 were excluded from the current analysis. This study sample included participants who were at risk of experiencing an initial ND symptom and developing full ND syndrome at bassline and during the follow up (**Figure 1**). Third, a dynamic cohort and analytical approach allow us to use available data to increase the power of the study and represent all cohort members. Therefore, as shown in Supplemental Table 1, adolescent WP-only (n=79) and cigarette-only (n=49) smokers who were lost to follow-up were included in the analyses. As discussed below, the type of analysis (i.e., time-varying inverse probability weights for Cox regression) that we applied in this study produce marginal estimates but also adjust for selection bias resulting from lost to follow-up (Kohl et al., 2015; Robins et al., 2000). Third, time-varying predictors were measured in all 8 waves. In line with previous longitudinal studies, (Moahmed et al., 2014; O'Loughlin et al., 2009; Racicot et al., 2013) missing values for time-varying predictors (i.e., physical activity, BMI, smoking by parents, siblings, and friends, beliefs about smoking, and psychological indicators) were imputed using the "first observation carried backward" and "last observation carried forward" approaches.

Data analysis

Data analysis was performed in 3 steps. First, summary statistics were computed (categorical variables: frequencies/percentages; continuous variables: mean ± standard deviation [SD]). Chi-square or Fisher's exact test (categorical variables) and Student's T-test or Mann-Whitney U/Kruskal-Wallis tests (continuous variables) were used to assess for significant differences in baseline characteristics between adolescent WP and cigarette smokers. Second, to analyze data containing time-varying predictor variables, we applied the Counting Process technique in SAS (Allison, 2010; Andersen and Gill, 1982; Powell and Bagnell, 2012). Specifically, we constructed a new dataset containing multiple records for each individual, with each record corresponding to a time interval during which all predictors remained constant (Allison, 2010; Andersen and Gill, 1982; Powell and Bagnell, 2012). Third, the Cox Proportional Hazard Regression (CPHR) model is based on the assumption of the proportionality of hazards, meaning that the hazard ratio (HR) of each predictor is the same at all study times (Kleinbaum and Klein, 2010). However, this assumption was violated in our sample, hence, the SAS Macro PHSREG (Kohl et al., 2015) was used to apply weighted CPHR to test the unadjusted and adjusted HR's (aHRs) and 95% confidence intervals of outcomes across levels of each predictor (Hosmer et al., 2002). A multivariable weighted CPHR was performed to identify independent predictors of experiencing initial ND symptoms and developing full ND syndrome for each smoking mode. SPSS v.26 and SAS/STATv14.2 for Windows were used for all analyses and statistical significance was set at $p<0.05$. Fourth, we checked for potential effect modification by gender, BMI, and crowding index (a proxy for SES) in univariate models controlling for the age of participants (see Supplemental Table 2). Lastly, frequency and

quantity of WP (Bahelah et al., 2016b; Maziak et al., 2005; Maziak et al., 2004; Robinson et al., 2017) and cigarette (Kleinjan et al., 2012; Lam et al., 2014; O'Loughlin et al., 2003) use can be either risk factors for the development of ND or behavioral manifestations of established ND. Therefore, multivariable models were run both with and without frequency and quantity of use variables included. Associations of individual, environmental, and psychological variables with outcomes did not differ substantially in models that contained versus those that excluded frequency and quantity variables. As such, these variables were retained in the final multivariable models.

Results

Descriptive statistics

Of the 367 adolescents included in this study, 228 (62%) were current WP-only smokers and 139 (38%) were current cigarette-only smokers. Compared to cigarette smokers, a higher percentage of WP smokers were females (WP: 61.4%; cigarettes: 18%; $p<0.001$). WP smokers were also younger than cigarette smokers (WP:13.9±1.1years; cigarettes:15.0±1.2; $p<.001$). Table 1 shows the baseline characteristics of adolescents WP and cigarette smokers. Of the 647 participants, 9.1%(n=61) were dual users with a mean age of 14.1 years, males (85.2%) and enrolled in private schools (68.9%) at baseline (data not shown).

Predictors of Initial Symptoms and the Full Syndrome of ND among WP smokers

Between waves 1 and 8, of the 193 WP smokers who were at risk of experiencing initial ND symptoms, 43.5% (n=84) did so and of the 228 WP smokers who were at risk of developing Full Syndrome of ND, 12.3% (n=28) did so. As shown in Table 2, predictors of experiencing initial ND symptoms among WP smokers were having a mother with <12

years of education and ≥ 1 sibling who smoke WP, and high BMI, whereas regular physical activity, being older, and smoking initiation at an older age were protective. There was an interaction effect between gender and school type, showing that for experiencing initial ND symptoms, the estimated marginal mean was higher for females at private schools. However, these two variables were not significant predictors in our multivariable models, therefore, there was no effect modification in the final model. Predictors of experiencing full ND syndrome were believing that WP smokers have more friends, greater depressive symptomatology, and being more impulsive, while older age and smoking initiation at an older age were protective factors.

Predictors of Initial Symptoms and the Full Syndrome of ND among cigarette smokers

Between waves 1 and 8, of the 134 cigarette smokers who were at risk of experiencing initial ND symptoms, 51.5% (n=69) did so and among 139 cigarette smokers who were at risk of developing ICD-10 ND, 17.3% (n=24) did so. As shown in Table 3, predictors of experiencing initial ND symptoms among cigarette smokers were having ≥1 sibling who smokes cigarettes and living in a crowded household (lower SES), whereas being female, older age, smoking initiation at an older age, and lower BMI were protective factors. Being at an older age and initiating smoking at an older age were protective factors of experiencing full ND syndrome. In other words, smoking initiation at a younger age was a risk factor for experiencing full ND syndrome.

Discussion

Adolescents are at a higher risk for ND because of nicotine's irreversible and profound effect on their developing brain (Yuan et al., 2015). Generally, it is well-established that a

younger age of exposure to addictive substances is strongly associated with lifelong addiction (Bonnie et al., 2015). Specifically for tobacco, early symptoms, and full ND syndrome can appear within days to weeks of the onset of WP (Bahelah et al., 2016a; Ebrahimi Kalan et al., 2020) and cigarette smoking (DiFranza et al., 2000; Ebrahimi Kalan et al., 2020; Gervais et al., 2006). While nicotine effect on the developing brain is likely to be universal, nuances related to the vehicle of delivery of nicotine and its context-specific factors and cues will likely shape the development and composition of ND among youth(Aboaziza and Eissenberg, 2014; CDC, 2010, 2012; Maziak et al., 2005). In fact, ND predicts smoking consistency and quantity across teenage years into young adulthood, therefore, understanding these nuances is important to develop tailored approaches to reduce tobacco use and addiction among youth and young adults (Bonnie et al., 2015; Allem and Unger, 2016). We already have extensive knowledge about the development of ND among young cigarette smokers and its predictors, but the same is not true for the most popular tobacco use method among adolescents in the EMR, the WP (Maziak et al., 2005; Maziak et al., 2015). Our cohort in the EMR is uniquely set to address this topic being the only such cohort that follows adolescent WP and cigarette smokers as they develop ND. In this study, for both tobacco use methods, we observed some commonalities in predictors of ND milestones (e.g. age of initiation, sibling tobacco use), which allows us to apply some of the experience of targeting these predictors among cigarette smokers. At the same time, there were substantial differences in the predictors of these ND milestones between the two tobacco use methods (e.g., the role of physical activity, BMI), which will be important to inform the development of tailored interventions targeting these popular tobacco use methods in the EMR.

Our findings show that the initiation of tobacco at a younger age is associated with a greater risk of experiencing initial ND symptoms and developing full ND syndrome for both WP and cigarette smokers. This study is the first to show that early initiation of WP is an independent risk factor for experiencing initial symptoms and developing the full syndrome of ND among adolescents; a finding that is already known for cigarette smoking (Breslau et al., 1993). Another shared predictor of the development of initial ND symptoms between WP and cigarette smokers is having at least one sibling who smokes the same product. This could be an important driver of WP smoking in the EMR context where family attitude and norms are important (Ali and Jawad, 2017), and where WP is rooted in this culture and is more tolerated than cigarettes (Akl et al., 2015; Hammal et al., 2008). Therefore, existing strategies to reduce cigarette smoking among youth such as those based on resisting peer pressure (in this case siblings) can be effective for both products (Akl et al., 2013; CDC, 2012). Special attention perhaps in the EMR context is the focus on communicating WP harmful and addictive properties to family members as a means to protect their children (Akl et al., 2013; Roohafza et al., 2015; Tobacco-Free Kids, 2009). Evidence shows, for example, that family discussion regarding the dangers of WP smoking (e.g., life-long dependency) significantly reduced the likelihood of being a current WP smoker among youth(Alzyoud et al., 2013). As universally effective for both tobacco methods perhaps, are upstream strategies to limit youth access to tobacco products (e.g., taxation, age restrictions) (Jawad et al., 2015).

Apart from commonalities, this study highlighted for the first time differences in the risk factors for experiencing ND symptoms between adolescent WP and cigarette smokers. For example, in contrast to cigarette smoking used often as a means for weight control

among youth (girls in particular), a higher BMI and low physical activity levels were risks of developing initial ND symptoms among WP smokers. Population-based studies from Syria indicated that WP smokers, compared to never-users, had higher BMI, translating into 6 extra kg on average, and were 3 times more likely to be obese (Ward, Kenneth D., et al., 2015). This can be explained with the social context and prolonged sessions of WP smoking (an hour or more) and its association with the WP café/restaurant setting where food is served and consumed around the WP (Aboaziza and Eissenberg, 2014; Baalbaki et al., 2019). In fact, our earlier results from this cohort show that inability to resist WP smoking in these venues was the strongest predictor of ND symptoms progression (Bahelah et al., 2019). This was further supported by our findings showing that regular physical activity was inversely predicting the development of initial ND symptoms among WP but not cigarette smokers. Accordingly, strategies to promote a healthy diet and physical activities among youth, combined with upstream restrictions on underage access to WP venues and clean indoor air policies particularly in restaurants, bars, and cafes can be effective to reduce WP smoking among youth in the EMR.

Another unique aspect of the development of ND among WP compared to cigarette smokers in our cohort was that psychosocial factors (impulsivity and depression) were strong predictors of developing full ND syndrome in WP smokers, but not in cigarette smokers. Differences in who uses and why these tobacco methods are used, may shed some light on these findings. In the EMR context, and unlike cigarettes, WP is looked at as a way to spend good time in the company of friends and family, and as a mood enhancer, while cigarette smoking is looked at as a mundane addiction (Hammal et al., 2008). In fact, having positive beliefs about WP in this study was an independent predictor of developing

full ND syndrome in WP smokers, but not in cigarettes. Evidence shows that positive WP outcome expectancies (e.g. connecting WP smoking with relaxation and socialization) are associated with ND, less motivation to quit, and reduced ability to quit WP tobacco smoking (Barnett et al., 2017; Aboaziza and Eissenberg, 2014; Maziak et al., 2015). The positive attitude towards WP in the EMR context is intertwined with its social acceptability compared to cigarettes, being considered as part of the local culture (Ebrahimi Kalan and Ben Taleb, 2018; Maziak et al., 2015). The effect of such norms is most noticeable for females, where WP smoking is way more tolerated than cigarette smoking in the EMR (Abdulrashid et al., 2018; Hammal et al., 2008). This explains the high prevalence of WP smoking among females in our sample compared to males (61.4% vs 38.6%, respectively) with the opposite is true for cigarette smoking (18% vs 82%, respectively). Being a female was a protective factor against experiencing initial ND symptoms for cigarettes but not WP in this study. As such, our findings indicate that at the individual level, adolescent WP smokers with depressive symptoms represent an important subgroup in need of targeted smoking cessation interventions in the EMR (Dierker et al., 2015). At the population level, strategies to increase awareness about the harmful effects of WP smoking and de-normalize its use, are warranted to counterbalance the "cultural endorsement" of this tobacco use method.

This study has some limitations. First, the longitudinal nature of the study makes possible errors in recalling dates of ND milestones. We tried to minimize such possibilities using techniques that improve event recall (e.g., personal landmarks, bounded recall, decomposition, and a visual aid) (Bahelah et al., 2017; DiFranza et al., 2002b). Third, our findings may not be generalizable to adolescent WP and cigarette smokers in other

countries and there is a need for additional research elsewhere as context-specific factors will likely be important (e.g. tobacco control policies). Fourth, although we included those exclusive WP and cigarette smokers who were lost to follow-up in the main analysis, a statistical approach and dynamic characteristic of this cohort study made it possible to use available data to increase the power of the study and represent all cohort members who were exclusive WP and exclusive cigarette smokers. Finally, data were collected only from students who attended public or private schools, so our findings may be less generalizable to youths who are home-schooled or have dropped out of school. However, almost 97% of Lebanese youths aged 11-18 years were enrolled in a public or private school in 2015 (Chaaban and El Khoury, 2015). Also, the findings from this study can be informative for other countries in the MER due to the shared culture and factors related to WP smoking among youth in this region(Maziak et al., 2014, 2015).

Despite these limitations and given the commonalities in the EMR cultural context that is driving the huge epidemic of WP smoking among adolescents, our findings are important to guide tailored approaches to reduce tobacco use among adolescents in the EMR.

Conclusions

We previously hypothesized that ND in WP smokers is shaped by factors unique to its social context and cues beyond the addictive effects of nicotine. In this study, we further advance our knowledge about WP-specific nuances affecting the development of ND among youth. Taken together, our findings indicate that focusing on communicating WP's harmful and addictive properties, de-normalizing its use, promoting a healthy diet and physical activity, and targeting at-risk children for cessation intervention as promising

strategies to reduce WP smoking among youth. At the population level, our findings indicate the importance of limiting underage access to tobacco products and venues, and clean indoor air policies particularly in cafés and restaurants serving the WP.

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Tables and Figures

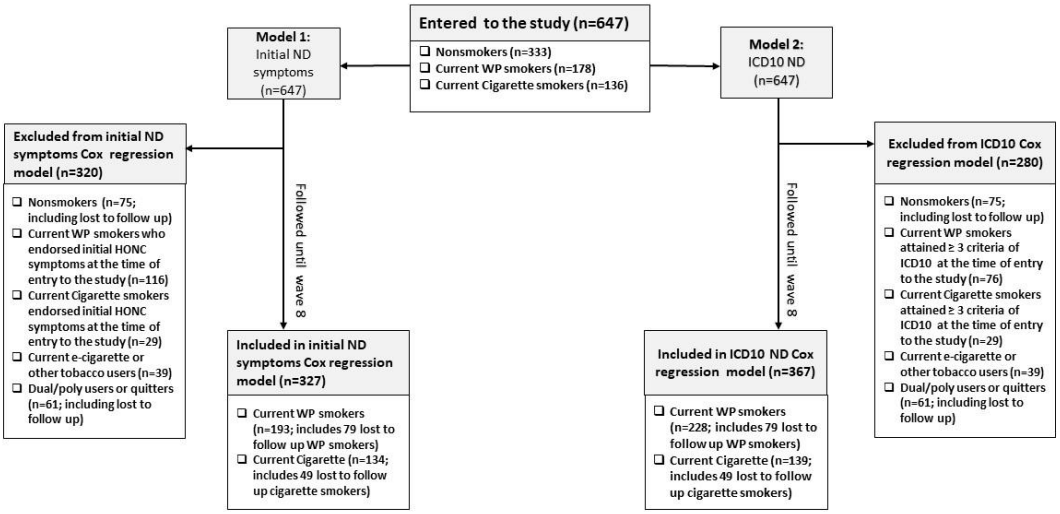

Figure 1. Study sample flowchart. In the first model, we excluded those WP (n=116) and cigarette (n=29) smokers who endorsed ND symptoms at the baseline. In the second model, we excluded those WP (n=76) and cigarette (n=29) smokers who had already attained ICD10 criteria at the baseline. Note, the retention rate at wave 8 was 72.3% (i.e., n=179 were lost to follow up at wave 8); among adolescents who were lost to follow up, we excluded those who were either non-smokers or dual users at the time of loss to follow up (n=51). However, adolescents WP (n=79) and cigarette (n=49) smokers who were lost to follow up were included in the analysis (i.e., whether they were diagnosed as dependent or not at the end of the study) to increase the power. E-cigarettes module was added to the WDLY study at wave 8 and current e-cigarette users were excluded from current analysis.

Table 1. Baseline characteristics of adolescents waterpipe and cigarette smokers (n=367)

	Study characteristics	Total (n=367)	Waterpipe smokers (n=228)	Cigarette smokers (n=139)	p-value
Individual characteristics	Gender, n(%)				
	Male	202 (55.0)	88 (38.6)	114 (82.0)	<.001
	Female	165(45.0)	140 (61.4)	25 (18.0)	
	School type, n (%)				
	Private	182 (49.6)	94 (41.2)	88 (63.3)	<.001
	Public	185 (50.4)	134 (58.8)	51 (36.7)	
	Physical activity (at least once/week) (yes), n (%)	270 (73.6)	163 (71.5)	107 (77.0)	.273
	Father's years of education (< 12 years/ illiterate) [a]	219 (59.7)	141 (61.8)	78 (56.1)	.324
	Mother's years of education (< 12 years/ illiterate) [a]	185 (50.4)	122 (53.5)	63 (45.3)	.133
	Age, years M±SD	14.3±1.2	13.9± 1.1	15.0± 1.0	.001
	BMI (weight/height^2) M±SD	21.7±4.3	21.2±4.1	22.4±4.5	<.001
	Crowding index, M±SD	1.6±0.8	1.4±0.6	1.9±0.9	<.001
Indicators of smoking	Parent smokes cigarette (yes), n (%)	243 (66.2)	151 (66.2)	92 (66.2)	1.00
	Parent smokes WP (yes), n (%)	171 (46.6)	122 (53.5)	49 (35.3)	.001
	≥1 sibling smoke cigarette, n (%)	96 (26.2)	57 (25.0)	39 (28.1)	.542
	≥1 sibling smoke WP, n (%)	144 (39.2)	109 (47.8)	35 (25.2)	<.001
	≥1 friend smoke cigarette, n (%)	226 (61.6)	106 (46.5)	120 (86.3)	<.001
	≥1 friend smoke WP, n (%)	311 (84.7)	189 (82.9)	122 (87.8)	.233
Beliefs about smoking	WP smokers looks attractive (agree)[b], n (%)	60 (16.3)	47 (20.6)	13 (9.4)	.005
	Cigarette smokers looks attractive (agree)[b], n (%)	52 (14.2)	24 (10.5)	28 (20.1)	.013
	WP smokers have more friends (agree)[b], n (%)	97 (26.4)	68 (29.8)	29 (20.9)	.067
	Cigarette smokers have more friends (agree)[b], n (%)	59 (16.1)	35 (15.4)	24 (17.3)	.662
	WP smoking makes a person lose weight (agree)[b], n (%)	48 (13.1)	27 (11.8)	21 (15.1)	.425
	Cigarette smoking makes a person lose weight (agree)[b], n (%)	55 (15.0)	24 (10.5)	31 (22.3)	.004
	WP smoking is harmful to health (agree)[b], n (%)	357 (97.3)	221 (96.9)	136 (97.8)	.748
	Cigarette smoking is harmful to health (agree)[b], n (%)	359 (97.8)	221 (96.9)	138 (99.3)	.268
Smoking patterns	Age of initiation, years, M±SD	—	13.3±1.9	13.9±1.9	.007
	Frequency of use (daily)[c] n (%)	—	22 (9.6)	80 (57.6)	—
	No of WPs/cigarettes smoked in the past month, M±SD	—	12.3±17.7	249.9±23.8	—
	Intention to quit (yes), n (%)	—	84 (36.8)	35 (25.2)	—
	Made quit attempt (yes), n (%)	—	60 (26.3)	51(36.7)	—
Psychosocial	Stress, M±SD	5.9±5.6	7.2±5.9	3.9±4.3	<.001
	Depression, M±SD	6.1±4.2	6.9±4.2	4.9±4.1	<.001
	Distractibility, M±SD	6.6±4.5	7.5±4.4	5.1±4.4	<.001
	Novelty seeking, M±SD	12.3±7.1	13.1±6.5	11.0±7.7	.005
	Impulsivity, M±SD	8.3±6.1	9.3±5.7	6.6±6.4	<.001
	Self-esteem, M±SD	19.2±4.6	20.7±4.1	16.7±4.4	<.001

[a] Compared to ≥12 years of education, [b] Compared to Disagree/or don't, [c] Compared to non-daily use

Table 2. Weighted Cox regression of the association between predictors and experiencing initial ND symptoms and developing full syndrome of ND among WP smokers, WDLY Study, 2015-2020

Study characteristics		Initial ND symptoms (n=193)		Full syndrome of ND (n=228)	
		Unadjusted HRs (95%CI)	**Adjusted HRs (95%CI)**	**Unadjusted HRs (95%CI)**	**Adjusted HRs (95%CI)**
Individual characteristics	Gender (Female vs Male) ¥	1.22 [0.95-1.57] #	1.04 [0.58-1.84]	0.68 [0.42-1.11] #	0.50 [0.19-1.32]
	School (Public vs. Private) ¥	1.11 [0.86-1.44]	1.21 [0.68-2.15]	**1.62 [1.06- 2.65] ***	1.51 [0.66-3.48]
	Physical activity (at least once/week) (yes vs no)	**0.63 [0.49- 0.82] ***	**0.69 [0.50-0.95] ***	0.97 [0.46-2.05]	—
	Father's years of education (< 12 years/ illiterate vs ≥12 years) ¥	**1.30 [1.02-1.68] ***	0.97 [0.55-1.72]	0.74 [0.45-1.22]	—
	Mother's years of education (< 12 years/ illiterate vs ≥12 years) ¥	**2.110 1.62-2.74] ***	**1.99 [1.09-3.63] ***	0.91 [0.56-1.48]	—
	Age, years	**0.68 [0.64-0.78] ***	**0.68 [0.59-0.79] ***	**0.77 [0.67-0.89] ***	**0.76 [0.62-0.96] ***
	BMI (weight/height^2)	1.02 [0.99-1.05] #	**1.06 [1.01-1.12] ***	**1.05 [1.01-1.09] ***	1.07 [0.97-1.18]
	Crowding index ¥	**0.80 [0.67-0.96] ***	0.72 [0.43-1.20]	1.16 [0.74-1.84]	—
Indicators of smoking in social	Parents smokes cigarette (yes vs no)	0.95 [0.74-1.23]	—	0.98 [0.58-1.62]	—
	Parents smokes WP (yes vs no)	0.72 [0.46-1.10] #	0.77 [0.50-1.18]	0.92 [0.56-1.50]	—
	≥1 sibling smoke cigarette	0.99 [0.76-1.30]	—	0.53 [0.27-1.05]	—
	≥1 sibling smoke WP	**1.43 [1.12-1.83] ***	**1.43 [1.07-2.24] ***	0.71 [0.43-1.17] #	0.65 [0.27-1.54]
	≥1 friend smoke cigarette	0.52 [0.40-1.00]	—	**0.34 [0.19-0.60] ***	0.25 [1.00-0.73]
	≥1 friend smoke WP	0.92 [0.58-1.44]	—	1.04 [0.40-2.49]	—
Beliefs about smoking	WP smokers looks attractive	**2.03 [1.44-2.85] ***	1.23 [0.77-1.96]	1.39 [0.71-2.73]	—
	Cigarette smokers looks attractive	0.85 [0.530-1.38]	—	1.00 [0.45-2.18]	—
	WP smokers have more friends	**1.39 [1.05-1.85] ***	0.98 [0.64-1.49]	**2.44 [1.47-4.05] ***	**2.76 [1.05-7.30] ***
	Cigarette smokers have more friends	1.62 [1.14-2.31]	—	0.48 [0.19-1.19]	—
	WP smoking makes a person lose weight	0.91 [0.56-1.50]	—	0.53 [0.21-1.34]	—
	Cigarette smoking makes a person lose weight	0.37 [0.14-1.01]	—	0.90 [0.41-1.97]	—
	WP smoking is harmful to health	**0.53 [0.33-0.86] ***	0.65 [0.33-1.26]	2.10 [0.29-15.13]	—
	Cigarette smoking is harmful to health	1.72 [0.54-5.45]	—	1.67 [0.22-12.35]	—
Smoking patterns	Age of initiation	**0.87 [0.84-0.91] ***	**0.84 [0.79-0.89] ***	**0.90 [0.82-0.98] ***	**0.88 [0.78-0.98] ***
	Frequency of use (daily vs non-daily)	1.03 [0.80-1.34] #	0.95 [0.57-1.59]	0.67 [0.38-1.20] *	0.85 [0.26-2.82]
	No of WPs smoked in the past month	**1.05 [1.01-1.09] ***	1.00 [0.99-1.02]	**1.06 [1.01-1.12] ***	**1.04 [1.02-1.08] ***
	Intention to quit (yes vs no)	1.12 [0.71-1.78]	—	**1.89 [1.15-3.09] ***	1.68 [0.83-3.41]
	Having quit attempt (yes vs no)	0.85 [0.54-1.35]	—	**1.70 [1.03-2.82] ***	1.12 [0.36-3.47]
Psychosocial indicators	Stress	1.05 [0.99-1.12]	—	**1.08 [1.04-1.12] ***	0.99 [0.91-1.06]
	Depression	1.03 [0.98-1.09]	—	**1.15 [1.09-1.21] ***	**1.13 [1.02-1.25] ***
	Distractibility	0.93 [0.87-1.01]	—	**1.10 [1.05-1.15] ***	1.02 [0.93-1.12]
	Novelty seeking	**1.05 [1.04-1.07] ***	1.02 [0.99-1.04]	**1.06 [1.03-1.09] ***	0.99 [0.93-1.07]
	Impulsivity	**1.07 [1.05-1.09] ***	**1.03 [1.01-1.07] ***	**1.08 [1.05-1.11] ***	**1.06 [1.02-1.11] ***
	Self-esteem	**1.06 [1.03-1.10] ***	0.98 [0.94-1.02]	1.05 [0.98-1.12]	—

HR = Hazard Ratio; CI = Confidence Interval. BMI=Body Mass Index. Sign (*) indicate p-value <0.05. Sign (#) indicate p-value <0.25 (selected variables for multivariable analysis). Sign (¥) indicates time-invariant predictors. Note, for continuous variables, the HR approximates the risk change for every one-unit increase in the age, BMI, crowding index, age of initiation, number of WP/cigarettes smoked, and psychological indicators.

Table 3. Weighted Cox regression of the association between predictors and experiencing initial ND symptoms and developing full syndrome of ND among cigarette smokers, WDLY Study, 2015-2020

	Study characteristics	Initial ND symptoms (n=193)		Full syndrome of ND (n=228)	
		Unadjusted HRs (95%CI)	Adjusted HRs (95%CI)	Unadjusted HRs (95%CI)	Adjusted HRs (95%CI)
Individual characteristics	Gender (Female vs Male) ¥	0.49 [0.23-1.02] #	**0.43 [0.19-0.93] ***	0.18 [0.02-1.32] #	0.50 [0.07-3.71]
	School (Public vs. Private) ¥	1.39 [0.82-2.33]	1.67 [0.88-3.13]	1.16 [0.49-2.71]	1.17 [0.46-2.99]
	Physical activity (at least once/week) (yes vs no)	0.94 [0.57-1.57] #	0.97 [0.63-1.53]	1.74 [0.65-4.66]	—
	Father's years of education (< 12 years/ illiterate vs ≥12 years) ¥	**1.30 [1.02-1.68] ***	1.22 [0.76-1.97]	—	1.37 [0.87-2.17]
	Mother's years of education (< 12 years/ illiterate vs ≥12 years) ¥	**2.110 1.62-2.74] ***	1.00 [0.62-1.61]	—	**1.96 [1.24-3.09] ***
	Age, years	**0.85 [0.81-0.91] ***	**0.76 [0.70-0.83] ***	**0.81 [0.66- 0.99] ***	**0.75 [0.65-0.87] ***
	BMI (weight/height^2)	0.98 [0.95-1.00] #	**0.95 [0.93-0.97] ***	0.94 [0.85-1.04]	—
	Crowding index ¥	**1.44 [1.09-1.91] ***	**1.40 [1.01-1.93] ***	1.37 [0.89-2.10] #	1.50 [0.89-2.52]
Indicators of smoking in social	Parents smokes cigarette (yes vs no)	0.95 [0.74-1.23]	**1.84 [1.08-3.16] ***	1.47 [0.87-2.53]	1.86 [0.74-4.69] #
	Parents smokes WP (yes vs no)	0.69 [0.43-1.13]	—	2.17 [0.93-5.08] #	1.69 [0.61-4.69]
	≥1 sibling smoke cigarette	**1.73 [1.07-2.78] ***	**1.86 [1.19-2.93] ***	0.78 [0.33-1.83]	—
	≥1 sibling smoke WP	0.99 [0.58-1.67]	—	0.81 [0.32-2.06]	—
	≥1 friend smoke cigarette	1.13 [0.49-2.61]	—	1.14 [0.26-4.87]	—
	≥1 friend smoke WP	0.64 [0.28-1.49]	—	1.53 [0.20-11.33]	—
Beliefs about smoking	WP smokers looks attractive	**2.03 [1.44-2.85] ***	1.27 [0.46-3.50]	—	2.99 [0.89-10.08] #
	Cigarette smokers looks attractive	0.85 [0.530-1.38]	1.21 [0.65-2.25]	—	0.55 [0.16-1.85]
	WP smokers have more friends	**1.39 [1.05-1.85] ***	**1.98 [1.12-3.51] ***	1.14 [0.68-1.93]	**2.81 [1.16-6.79] ***
	Cigarette smokers have more friends	1.62 [1.14-2.31]	1.22 [0.58-2.55]	—	1.78 [0.61-5.23]
	WP smoking makes a person lose weight	0.91 [0.56-1.50]	1.13 [0.58-2.22]	—	1.77 [0.66-4.76]
	Cigarette smoking makes a person lose weight	0.37 [0.14-1.01]	1.35 [0.78-2.34] #	1.03 [0.61-1.73]	0.59 [0.17-1.97]
	WP smoking is harmful to health	**0.53 [0.33-0.86] ***	0.66 [0.21-2.09]	—	0.34 [0.08-1.47]
	Cigarette smoking is harmful to health	1.72 [0.54-5.45]	1.12 [0.27-4.57] #	0.80 [0.36-1.73]	0.86 [0.11-6.39]
Smoking patterns	Age of initiation	**0.85 [0.81-0.91] ***	**0.79 [0.74-0.84] ***	**0.81 [0.66- 0.99] ***	**0.76 [0.67-0.86] ***
	Frequency of use (daily vs non-daily)	1.03 [0.80-1.34] #	**2.68 [1.44-5.01] ***	**2.19 [1.16-4.13] ***	**2.62 [0.89-7.68]** #
	No of WPs smoked in the past month	**1.05 [1.01-1.09] ***	**1.04 [1.02-1.08] ***	**1.02 [1.01-1.04] ***	1.01 [0.97-1.03] #
	Intention to quit (yes vs no)	1.02 [0.59-1.76]	—	**1.75 [1.09-2.80] ***	1.45 [0.41-5.09]
	Having quit attempt (yes vs no)	0.97 [0.59-1.59]	—	**1.69 [1.08-2.64] ***	1.20 [0.41-3.49]
Psychosocial indicators	Stress	1.02 [0.96-1.09]	—	1.07 [0.98-1.18]#	1.04 [0.97-1.11]
	Depression	1.00 [0.94-1.06]	—	0.96 [0.85-1.09]	—
	Distractibility	0.99 [0.89-1.10]	—	1.03 [0.93-1.14]	—
	Novelty seeking	1.00 [0.97-1.03]	—	1.03 [0.98-1.08] #	1.02 [0.96-1.07]
	Impulsivity	0.98 [0.94-1.02]	—	1.02 [0.96-1.08]	—
	Self-esteem	**1.10 [1.01-1.18] ***	1.06 [0.98-1.13]	**1.19 [1.09-1.30] ***	1.10 [1.00-1.18]

HR = Hazard Ratio; CI = Confidence Interval. BMI=Body Mass Index. Sign (*) indicate p-value <0.05. Sign (#) indicate p-value <0.25 (selected variables for multivariable analysis). Sign (¥) indicates time-invariant predictors. Note, for continuous variables, the HR approximates the risk change for every one-unit increase in the age, BMI, crowding index, age of initiation, number of WP/cigarettes smoked, and psychological indicators.

Supplementary materials

Supplementary Table 1. Baseline characteristics of participants who retained up to wave 8 and lost to follow up during waves 2-8 (N=647)

Study characteristics	Retained in the study (n=468)	Lost to follow up (n=179)	p-values	Total (n=647)
Gender, n (%)			0.929	
Male	263 (56.2)	102 (57.0)		365 (56.4)
Female	205(43.8)	77 (43.0)		282 (43.6)
School type, n (%)			0.429	
Private	216(46.2)	89 (49.7)		305 (47.1)
Public	252(53.8)	90(50.3)		342 (52.9)
Outcomes of study				
Endorsing initial ND symptoms among WP-only smokers (n=193)			0.001	
yes	33(29.0)	51 (64.5)		84 (43.5)
no	81 (71.0)	28 (34.5)		109 (56.5)
Endorsing initial ND symptoms among cigarette-only smokers (n=134)			0.001	
yes	39 (45.9)	30 (61.2)		69 (51.5)
no	46 (54.1)	19 (38.8)		65 (48.5)
Attaining full ND syndrome among WP-only smokers (n=228)			0.768	
yes	54(36.2)	30 (38.0)		84 (38.5)
no	95 (63.8)	49 (62.0)		144 (61.5)
Attaining Full ND syndrome among cigarette-only smokers (n=139)			0.469	
yes	14 (15.5)	10 (20.4)		24 (17.3)
no	76 (84.5)	39 (79.6)		115 (82.7)

Abbreviations: ND, nicotine dependence; WP, waterpipe

Supplementary Table 2. Modification effects of gender, school, BMI, and crowding index on outcome of interest among waterpipe and cigarette smokers

	Initial ND symptoms		Full syndrome of ND	
	WP Parameter Estimate (SE)	Cigarettes Parameter Estimate (SE)	WP Parameter Estimate (SE)	Cigarettes Parameter Estimate (SE)
Gender*school	-0.67 (0.27) *	0.59 (0.42)	-0.85(0.44)	0.71 (0.63)
Gender* BMI	0.04 (0.30)	0.09 (0.05)	0.21 (0.05)	-0.04(0.12)
Gender* Crowding index	-0.16(0.22)	0.13 (0.03)	-0.05 (0.33)	-0.58 (0.50)

SE, standard error; waterpipe; ND, nicotine dependence. WP, *p<0.05. Referent (school=public vs private); gender (female vs male). All analyses were controlled for the age variable. The crowding index is defined as the number of co-residents in a dwelling, excluding infants, divided by the number of rooms in the dwelling, excluding the kitchen and bathrooms.

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MANUSCRIPT 3

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Abstract

Background and objective

Adolescence represents a critical period in which nicotine dependence (ND) symptoms are developing. Little is known about waterpipe (WP) smoking and developmental trajectories of ND criteria across adolescence. Here, we aimed to identify ND trajectories from early to late adolescence in current (past 30 days) WP smokers and examine baseline correlates of each identified trajectory, using the International Classification of Diseases, 10th Version (ICD10).

Methods

The analytical sample consisted of 278 current WP smokers from 8 waves of an ongoing longitudinal cohort of 8th-9th graders in Lebanon. Group-based trajectory modeling was estimated to identify trajectory classes for ICD10 ND criteria over ages 11-18.

Results

A group-based modeling approach yielded a four-class solution that best fit the data and reflected differences in the timing of ND onset during adolescence: no-onset of ND

(43.9%), early (16.2%), mid (26.6%), and late-onset (13.3%) of ND criteria. Having a less-educated mother and siblings who smoke WP, exposure to favorite WP-specific advertisements, and being a novelty seeker were associated with early-onset of ND. Daily or weekly WP smokers (vs monthly) and having higher stress level were associated with mid-onset trajectory. Believing that WP smoking is harmful to health and spending more than 60 minutes on a WP smoking session were associated with late-onset ND trajectory class. Finally, WP smoking initiation at a younger age was associated with early and mid-onset while initiating smoking at an older age was associated with late-onset trajectory.

Conclusions

Monitoring the development of ND trajectories among WP smokers may identify an individual as belonging to one of these four groups with distinct individual and socio-environmental factors, and allow the individual and healthcare providers opportunities to inform initiate and on-time WP-specific tailored prevention and cessation interventions.

Introduction

Waterpipe (WP; hookah, shisha) tobacco smoking is a widespread addictive and harmful behavior among young people in the Eastern Mediterranean Region (EMR) (Maziak et al., 2015a; WHO, 2015). In many EMR countries, WP tobacco smoking is already more common than cigarette smoking, especially among youth (Soweid, 2005; WHO, 2015). For example, in 2017, current (past 30 days) tobacco use (mostly WP) was reported by 31.5% of Lebanese youth (age 13-15) compared with 11.2% who smoked cigarettes (WHO, 2019). Adolescence represents an important developmental period in which exposure to nicotine can cause nicotine dependence (ND), and harm the developing

brain, negatively impacting learning ability and attention (CDC, 2004, 2014; Waziry et al., 2017).

Understanding the characteristics of ND development in young WP smokers is needed to develop effective strategies and intervention to deal with it. WP tobacco smoking has several unique features that impact ND development in a way distinctive from cigarettes. Unlike smoking cigarettes, which is typically a solitary activity that takes about 5 minutes, a WP tobacco smoking session takes ~45 minutes, occurs in a relaxed socialized atmosphere, is stationary (WP is not portable like cigarettes), and produces a pleasant aroma and taste that can serve as reinforcing sensory cues (Alam et al., 2020).

The pace of development of ND seems also to be generally more rapid in WP smokers compared to cigarettes (Aboaziza and Eissenberg, 2015; Ebrahimi Kalan et al., 2020a; WHO, 2015). This is perhaps due to WP tobacco smoking's unique features and use patterns (Aboaziza and Eissenberg, 2015; Bahelah et al., 2016a). However, within the general time to ND anatomy, certain subgroups show unique patterns—pace—of ND development referred to usually as trajectories (Hu et al., 2012). In cigarette smokers knowledge of such trajectories has led to different developmental course over time, which varies by the timing of onset, level of escalation, duration, and remission of symptoms (Hu et al., 2008, 2012). While related trajectories are expected in young WP smokers, such analysis has not been conducted to date, mostly due to the lack of longitudinal data that documents the development of ND in young WP and cigarette smokers. Utilizing our pioneer prospective cohort data from the Waterpipe Dependence in Lebanese Youth (WDLY) study, we aim to 1) identify the distinctive developmental trajectory (latent

classes) of ND among young people during an 8-year time span, and 2) determine individual and environmental risk factors that are associated with participants' membership in each ND trajectory class. Understanding the varied trajectories of WP ND and their associated socio-demographic characteristics will have important implications for cessation efforts in terms of when and what specific interventions are needed.

Methods

Study design

Data for the present study were drawn from 8 waves of an ongoing interview-based longitudinal study (WDLY) among 647 adolescents who were enrolled in eighth and ninth grades at baseline in spring 2015. Study design and procedures have been described elsewhere (Bahelah et al., 2016a; Ebrahimi Kalan et al., 2020a). In brief, students from 38 (out of 178) public and private schools located in four regions of Lebanon (Beirut, Mount Lebanon, Nabatiye, South Lebanon) were interviewed at 6-month intervals for waves 1-6 (2015-2018) and annually for waves 7-8 (2019-2020).

Ethical considerations

For participants ≥18 years old, written informed consent was obtained without the need for parental/guardian consent as opposed to those younger than 18 who provided parental consent in addition to their assents. This study was approved by the Institutional Review Boards of Florida International University and the American University of Beirut.

Cohort for analysis

The current study assessed data from 278 current WP smokers who reported WP smoking at least once in the 30 days prior to each prospective interview during 8 waves follow-up. For this study sample (n=278), while there was no loss to follow up from wave 1 to 2, the retention rate from wave 2 to wave 8 were 96% (n=267), 92% (n=256), 88% (n=245), 76.2% (n=212), 75.1% (n=209), and 71.6% (199), respectively. Overall, n=79 WP smokers were lost to follow-up by wave 8, 49 (62.0%) of whom have already met ND criteria (see below for outcome variable information). Private and confidential face-to-face interviews were administrated to collect the data on WP use patterns, symptoms of ND, individual and environmental characteristics known to be associated with tobacco initiation, use behaviors or ND (Aboaziza and Eissenberg, 2015; DiFranza et al., 2000; O'Loughlin et al., 2003). We also collected the dates for smoking milestones such as initiation or appearance of ND symptoms (Bahelah et al., 2016a; DiFranza et al., 2007). During each interview, we employed techniques (e.g., personal calendar) to facilitate the accurate recall of dates and events (DiFranza et al., 2007).

Measures

Outcome variable

Nicotine dependence (ND) was defined based on the International Classification of Diseases, 10th Revision (ICD-10), which includes 19 items with Yes/No response choices for each item. In this study, the ICD-10 was grouped into 6 criteria and the number of ND criteria (ranged between 0 and 6) was treated as an outcome variable. Full ND syndrome was defined when 3+ criteria were met within a 12-month period. The ICD-10 has shown

high reliability in adolescent smokers both in the WDLY study(Bahelah et al., 2016b) and others. (DiFranza et al., 2007; O'Loughlin et al., 2003)

Covariates

The bassline covariates associated with ND were selected based on our previous work from the same cohort (Bahelah et al., 2016a; Ebrahimi Kalan et al., 2020b) and published literature (Akl et al., 2015; Maziak et al., 2005).

Sociodemographic variables include age, gender, school type (public/private), mother/father education (< 12 years of education vs ≥12), parents smoke WP, body mass index (BMI = weight in kg /height in m^2), regular physical activity defined as performing the physical activity at least once a week (yes/no)

Smoking-related characteristics include having ≥ 1 siblings/friends who smoke WP (yes/no), believing that WP smokers have more friends (agree vs. disagree), believing that WP/cigarette smoking is harmful to health (agree vs. disagree), having favorite WP ads (yes/no), percentage of monthly income/allowance spend for WP (≤10% vs >10%), age of initiating WP smoking, frequency (daily/weekly/monthly) and quantity (number of WP heads/bowls) of use in the past month, and time spent during a typical WP smoking session (less than 30 minutes/30-60/more than 60).

Psychological indicators include perceived stress (15 items on a four-point Likert scale "Not at all (0) to A whole lot (3)" with a possible score of 0–45) (Racicot et al., 2013), depressive symptoms (6 items on a four-point Likert scale "Never (0) to Often (3)" with a total score of 0–18) (Brunet et al., 2014), impulsivity (7 items on a five-point Likert scale

"Not at all true (0) to Very true (4)" with 0–28 total score) (DiFranza et al., 2007), novelty-seeking (9 items on a five-point Likert scale "Not at all true (0) to Very true (4)" with 0–36 total score) (DiFranza et al., 2007), and self-esteem (10 items on a four-point Likert scale "Strongly Disagree (0) to Strongly Agree (3)" with a total score of 0–30) (Waters et al., 2006). For all measures, a higher score indicates that the participant is showing a higher endorsement of the psychological indicator. In this cohort, Cronbach's alpha of the psychological measures ranged from 0.63 to 0.81, indicating acceptable internal consistency (Bahelah et al., 2016b).

Statistical analysis

Semiparametric group-based modeling (SGM), an analytical tool that is available through a customized PROC TRAJ SAS macro developed by Nagin and colleagues (Jones et al., 2001), was used to identify distinctive developmental trajectories of self-reported ICD10 ND criteria among WP smokers from age 11 to 18 years (Jones et al., 2001; Nagin et al., 2018). Due to the unequal time intervals between the interviews, we used a one-time varying covariate to adjust the dependent variable at each time point, — namely the participants' age at the time of attaining ICD10 criteria. PROC TRAJ allowed us to utilize all available data (including missing observations at some time points due to loss to follow-up) to estimate model parameters (Andruff et al., 2009; Nagin et al., 2018; Nagin and Nagin, 2005). Because ND criteria were treated as a count outcome and were not normally distributed—due to a large number of zero responses for an outcome that resulted in skewed distributions— we applied zero-inflated Poisson distribution in the SGM (Collins et al., 2001; Enders, 2001; Lanza et al., 2020).

To determine the appropriate number of trajectory classes and shape for each class, a series of linear and quadratic growth models (adjusted for age of smoking initiation) were estimated by fitting one to six classes. These growth models were estimated starting with a single class model followed by consecutively increasing the number of specified classes. Since the cubic term was not significant for all classes, we applied quadratic term for all subsequent models. The appropriate number of classes was not known a priori; therefore, in order to determine the optimal and interpretable number of trajectory classes we considered Bayesian Information Criteria (BIC) and Akaike Information Criteria (AIC) as indicators of model goodness of fit(Nagin and Nagin, 2005). The lower BIC and AIC values mirror model parsimony, favoring a high log-likelihood estimate along with a lower number of parameters (Muthén, 2001; Nagin, 1999). The obtained posterior probability was used to assign each individual membership to the trajectory (class) that best fits their profile of change. The lowest membership probabilities were considered as 5% and values of the average posterior probability of membership > 0.7 were considered since it indicates acceptable internal reliability (Andruff et al., 2009). Our sample size was sufficient for SGM since this analysis approach can be applied to data sets of at least 100 cases (Nagin and NAGIN, 2005).

To ascertain whether baseline covariates varied by trajectory classes of ND, we performed a chi-square test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables. Baseline covariates with $p<0.2$ in the univariate analyses (Bursac et al., 2008) and theoretically ND-related covariates (e.g., gender and school type) were entered into the multinomial logistic regression models to estimate adjusted odds ratios (aORs) and corresponding 95% confidence intervals (95% CIs) in a

relationship to ND trajectory classes. All analyses were conducted in SAS/STAT statistical software (Version 9.4; SAS Institute Inc., Cary, NC) and a two-sided $p<0.05$ was statistically significant.

Results

Descriptive results

At baseline, adolescents in the analyzed sample (n=278) were on average 14.1 years old (SD=1.2), 62.2% were female, 53.2% were enrolled in private school, and more than half had a parent (mother or father) with less than high school education (Table 1).

Trajectory class characteristics

Table 2 presents fit statistics for the latent class growth modeling with 1 to 4 classes since the five-class solution was not viable due to false convergence in the model, meaning that PROC TRAJ failed to estimate model parameters for ≥5 classes. Therefore, we chose the growth model to specify the presence of 4 classes based on smaller BIC and AIC statistics with the proportion of classes (>5%) and the average posterior probability (for classes 1 to 4) as 0.98, 0.87, 0.94, and 0.95, respectively. As shown in Figure 1, each time point represents the estimated number of ICD10 criteria (mean with corresponding 95% CI). Based on the aforementioned probabilities, it is estimated that 43.9% (n=122) of the study sample belongs to class 1 (no onset of ND symptoms; hereafter "no-onset"), 16.2% (n=45) to class 2 (early-adolescence ND onset; "early-onset"), 26.6% (n=74) to class 3 (mid-adolescence ND onset; "mid-onset"), and 13.3% (n=37) to class 4 (late-adolescence ND onset; "late-onset").

Overall, 56.1% (n=156) of adolescent WP smokers experienced ≥ 1 ICD-10 criterion and 27% (n=75) attained full syndrome of ND (i.e., reached ≥3 of 6 ICD10 ND criteria) between ages 11-18 years. Of these 75 WP smokers, 32.0% (n=24) were in early-onset, 46.7% (n=35) in mid-onset, and 21.3% (n=16) in late-onset trajectory (Figure 1). more than half of the participants experienced ≥ 1 ICD-10 criterion spanning from 11 to18 years old, from which 27% met the full criteria for ND

Correlates of trajectories membership

As displayed in Table 3, compared with the no-onset trajectory class: adolescents in the early-onset class initiated WP smoking at an earlier age (aOR=0.52, 95%CI: 0.40-0.67; p<.001) and were more likely to have favorite WP-associated advertisements (aOR=3.33, 95%CI:1.03-10.85; p=0.048), adolescents in the mid-onset class were more likely to be daily (aOR=2.20, 95%CI: 1.05-4.62; p=0.04) and weekly smokers (aOR=3.48, 95%CI: 1.08-11.23; p =0.04) compared to monthly, and report higher stress level (aOR=1.07 (1.01-1.14); p=0.049), and adolescents in the late-onset class were less likely to believe that WP smoking is harmful to health (aOR=0.11, 95%CI: 0.02-0.82; p=0.03), more likely to initiate WP smoking at an older age (aOR=1.36, 95%CI: 1.06-1.75; 0.02) and spend an average of more than 60 minutes on a WP smoking session (aOR=5.62, 95%CI: 1.20-26.44; p=0.03).

Compared with the mid-onset trajectory class, adolescents in the early-onset class were more likely to have a less-educated mother (aOR=4.08, 95%CI: 1.01-16.53; p=0.04), have at least one sibling who smokes WP (aOR=3.95, 95%CI: 1.08-14.42; p=0.04) and report higher score in novelty-seeking (aOR=1.12, 95%CI: 1.02-1.23; p=0.02), and less likely to believe that WP smokers have more friends and initiate smoking WP at a younger age, and

report lower stress (aOR=0.86, 95%CI: 0.76-0.97; p=0.01) and self-esteem (aOR=0.74, 95%CI: 0.61-0.90; p<0.01) levels. Compared with the late-onset trajectory class, adolescents in the early-onset class were less likely to initiate smoking WP at an older age (aOR=0.39, 95%CI: 0.24-0.63; p<0.001).

As shown in Figure 1, we classified adolescents into three groups based on their age of WP smoking imitation. Among those adolescents who started WP smoking at age 12 or below, 33% belong to early-onset, while it was 10.1% for those who started to smoke WP at age 13-15 and 0% for those who started at age 16 or over. This finding indicates a clear link between the age of smoking initiation and belonging to ND trajectory classes as was evident in regression analysis.

Discussion

This pioneer longitudinal study sought to identify empirically ND developmental trajectory classes among adolescent WP smokers and their predictors using group-based trajectory modeling. In this study, more than half of the participants experienced ≥ 1 ICD-10 criterion spanning from 11 to18 years old, from which 27% met the full criteria for ND. Four classes provided the best fitting model with a spectrum of developmental trajectories of ND ranging from showing no symptoms (no-onset; class 1) to meeting diagnostic criteria for ND during early-adolescence (i.e., early-onset; class 2), mid-adolescence (i.e., mid-onset; class 3)and late- adolescence (late-onset; class 4).

Our findings revealed several differences among the identified ND classes in terms of sociodemographic, smoking patterns, and psychological characteristics. For example, compared with those without symptoms (no-onset), adolescents in the early-onset ND

trajectory class were more receptive/exposed to tobacco advertising, in the mid-onset ND trajectory, there was a strong association with the magnitude of smoking frequency (i.e., daily/weekly vs monthly) and they reported a higher stress and self-esteem level, and in the late-onset trajectory, adolescents were less likely to believe that WP smoking can harm health and more likely to report a long smoking session. Compared to mid or late-onset trajectory classes, adolescents showing early-onset ND had a mother with less than high school education, siblings who smoke WP, were novelty seekers and reported low self-esteem.

In this study, the age-specific manifestations of ND symptoms allowed us to specify the ages (11-18 years) at which ND symptoms occur. Consistent with our previous studies from the same cohort (Bahelah et al., 2016b; Ebrahimi Kalan et al., 2020b) and cigarette literature (DiFranza et al., 2000; Hu et al., 2008, 2012), this latent class analysis showed that the younger the age of smoking initiation, the faster ND symptoms appear. In our analysis, a higher percentage of adolescents who developed full ND syndrome (46.7%) belonged to the mid-onset class that showed a strong association with frequency of use (daily/weekly). One interpretation for this finding is that the availability of WP and opportunities for smoking probably are much higher for this age group (13-15 years) than other age groups during adolescence, which partially supports why World Health Organization uses this age range to reports smoking prevalence among adolescents across the countries, especially in Lebonan (WHO, 2019).

Adolescents in the early-onset class were more receptive to tobacco advertising than their counterparts in the no-onset class. Most of the adolescents in this class began smoking

WP when they were less than 13 years old, and this explains the fact that why they are one of the main target population for WP advertisements in Lebanon. (Jawad et al., 2015a) This is not surprising since the WP tobacco industry (Jawad et al., 2015b), especially in the EMR, operates in an almost entirely unregulated market and employs deceptive marketing techniques to entice children as young as 13 years old with no policies in place to restrict underage access to WP smoking in WP-serving premises. (Jawad et al., 2013; Jawad et al., 2015a; Khalil et al., 2009) This regulatory-relaxed environment facilitates youth smoking rates which leads to the early appearance of ND symptoms as evident in our study. (Jawad et al., 2013, 2015a, 2015b; Loddenkemper et al., 2015)

Our team and others previously highlighted some of the WP marketing tactics that attract youth. These include, but not limited to, promoting WP smoking on social media (e.g., Instagram), (Ben Taleb et al., 2018; Salloum et al., 2016) WP home delivery (Ebrahimi Kalan et al., 2020c), and marketing campaigns targeting youth and women. (Soweid, 2005) Although some of the WP-related policy interventions are similar to that of cigarettes (e.g., taxation), unique policies are needed to curb WP use (e.g., restrictions on underage access to WP venues, clean indoor air policies particularly in restaurants, bars, and cafes, regulating WP design and packaging (targeting the novelty effect), health warning labels specific to WP, and outlawing home delivery of ready-to-consume WPs). (Asfar et al., 2019; Bahelah et al., 2018; Salloum et al., 2016)

The observed nuances in the pace of development of ND symptoms during adolescence and associated predictors between trajectory classes that alluded to above can help to implement early (i.e., prior to or in the first years of middle and high school) tailored

intervention programs to reduce WP consumption, prevent the development of ND symptoms, and support cessation programs. These programs specifically include school-based educational interventions (e.g., stress management techniques, increased self-esteem, educating parents especially for those adolescents who have WP smokers in their family and are at greater risk of early WP smoking initiation and subsequently rapid experience of ND symptoms. For those adolescents who already developed full ND syndrome at an early age, several tailored behavioral-counseling services could be helpful. For example, public health practitioners can assist adolescents with WP smoking cessation by following the “Five A's” - Ask, Advise, Assist, Arrange Follow-up, and Anticipatory Guidance. (Larzelere and Williams, 2012) These programs should address the specific features of WP smoking, such as its social dimension, unique experiences, and cues. (Maziak et al.,2005, 2015a, 2015b)

This study has some limitations. First, since ND trajectories were examined only for WP smokers, developmental patterns cannot be extended to cigarette smokers (due to the low sample size) in the WDLY study. Nevertheless, data from the next wave (wave 9) of the WDLY study will provide a unique opportunity to examine latent class analysis for cigarette smoking and how it differs from the trajectory classes among WP smokers in the same population extended to early adulthood. Second, the longitudinal nature of this study makes it prone to errors in recalling dates of ND milestones. However, we minimized such possibilities through employing techniques that improve event recall (e.g., personal landmarks, bounded recall, decomposition, and a visual aid) (Bahelah et al., 2016b; DiFranza et al., 2007). Despite these limitations, our findings suggest that every ND trajectory class during adolescence could have distinctive characteristics and therefore

provide new insights into the process of ND in terms of when and what specific interventions are needed to curb the development of ND, and long-term WP smoking among youth.

Conclusions

Using a cohort of adolescents WP smokers, we showed that the developmental trajectories of ND vary during adolescence by the time of ND symptoms onset. We also revealed that the correlates of ND differ according to the developmental course. Identifying class membership among youth should be critical for the development of cessation interventions tailored to their specific characteristics.

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Tables and figures

Table 1. Prevalence or mean of covariates, overall and by nicotine dependence trajectory class, WDLY (n=278)

Variables	Overall, n=278	No ND onset n= 122	Early ND onset n=45	Mid ND onset n= 74	Late ND onset n=37	p-value*
Gender (female vs male)	173 (62.2)	76 (62.3)	27 (60.0)	41 (55.4)	29 (78.4)	.129
School (private vs public)	148 (53.2)	71 (58.2)	23 (51.1)	37 (50.0)	17 (45.9)	.496
Age at baseline (mean±SD)	14.1±1.2	13.9±1.5	13.5±0.9	14.0±0.9	15.4±1.4	<.001
Mother' education	160 (57.6)	62 (50.8)	30 (66.7)	43 (58.1)	25 (67.6)	.150
Father' education	182 (65.5)	70 (57.4)	30 (66.7)	54 (73.0)	28 (75.7)	.068
BMI, weight/height^2, (mean**±SD)**	21.3±4.0	20.8±4.1	21.8±4.5	21.5±3.9	21.9±3.4	.354
Physical activity (at least once/week)	199 (71.6)	83 (68.0)	30 (66.7)	60 (81.1)	26 (70.3)	.203
Parents smoke WP (yes)	153 (55.0)	66 (54.1)	24 (53.3)	46 (62.2)	17 (45.9)	.415
Having ≥ 1 siblings who smoke WP	149 (53.6)	63 (51.6)	33 (73.3)	34 (45.9)	19 (51.4)	**.029**
Having ≥ 1 friends who smoke WP	236 (84.9)	97 (79.5)	40 (88.9)	63 (85.1)	36 (97.3)	.051
WP is harmful to health	43 (95.6%)	73 (98.6%)	32 (86.5%)	268 (96.4%)	120 (98.4%)	**.005**
Cigarette is harmful to health	272 (97.8)	119 (97.5)	44 (97.8)	73 (98.6)	36 (97.3)	.954
WP smokers have more friends	92 (33.1)	31 (25.4)	15 (33.3)	31 (41.9)	15 (40.5)	.080
Age of initiating WP smoking	13.3±1.9	13.7±1.7	11.6±1.8	13.2±1.4	14.4±2.1	**<.001**
Frequency of WP use, Monthly	132 (47.5)	72 (59.0)	18 (40.0)	29 (39.2)	13 (35.1)	**.011**
Frequency of WP use, Weekly	93 (33.5)	37 (30.3)	14 (31.1)	29 (39.2)	13 (35.1)	
Frequency of WP use, Daily	53 (19.1)	13 (10.7%)	13 (28.9)	16 (21.6)	11 (29.7)	
Quantity (number of WP heads/bowls)	9.5±19.0	6.4±12.9	17.1±35.5	7.9±10.4	13.7±18.3	**.005**
Time spend during a WP smoking session						**.009**
Less than 30 minutes	147 (52.9)	77 (63.1)	19 ()42.2	37 (50.0)	14 (37.8)	
30 – 60 minutes	102 (36.7)	38 (31.1)	20 (44.4)	30 (40.5)	14 (37.8)	
More than 60 minutes	29 (10.4)	7 (5.7)	6 (13.3)	7 (9.5)	9 (24.3)	
Do you have favorite WP ads? (yes)	35 (12.6)	7 (5.7)	11 (24.4)	11 (14.9)	6 (16.2)	**.008**
Monthly income/allowance spend for WP						
≤10% of income/allowance	252 (96.9)	113 (97.4)	37 (92.5)	70 (97.2)	32 (100.0)	.289
>10% of income/allowance	8 (3.1)	3 (2.6)	3 (7.5)	2 (2.8)	0 (0.0)	
Stress	7.6±6.2	6.6±5.7	8.0±7.1	8.6±5.9	8.6±6.8	.112
Depression	7.1±4.2	6.5±4.4	8.0±4.3	7.5±3.9	7.3±4.2	.157
Impulsivity	9.8±6.0	9.2±5.7	10.7±6.6	10.0±6.0	10.5±6.3	.403
Self esteem	20.9±4.1	20.6±4.0	20.2±4.0	21.9±4.0	21.4±4.6	.086
Novelty seeking	13.8±7.0	12.7±7.0	16.0±6.4	13.6±7.4	15.4±6.1	**.030**
Distractibility	7.9±4.7	7.3±4.6	8.3±4.3	8.5±4.9	8.7±5.0	.232
Full syndrome of ND (yes) [a]	75 (27.0)	0 (0.0)	24 (53.3)	35 (47.3)	16 (43.2)	<.001

Note: Class 1, resistant to ND symptoms onset); class 2, onset in early adolescence; class 3, onset in mid-adolescence); and class 4, onset in late adolescence. All measure are based on n(%) or mean±SD. Father's and mother's education is based on (< 12 years of education vs ≥12) * Chi-square test for categorical variables and ANOVA for continuous variables. a Logistic regression analysis (accounted for gender, school type, and age at smoking initiation did not show any significant differences between classes 2, 3, and 4 in terms of attaining full ND syndrome.

Table 2. Test statistics for trajectories nicotine dependence (ICD10 criteria) classes (N=278)

Model	Bayesian Information Criteria (BIC)	Akaike Information Criteria (AIC)	Class size
1	1206.44	1278.86	278
2	1131.85	1119.15	186, 92
3	1070.70	1050.74	175, 58, 45
4	**1023.73**	**994.71**	**122, 74, 45, 37**

Note: The five-class solution was not viable due to the failed convergence, meaning that the Proc Traj failed to estimate model parameters for ≥5 classes. The lowest value of BIC and AIC, highlighted in **bold**, was selected as an optimal model

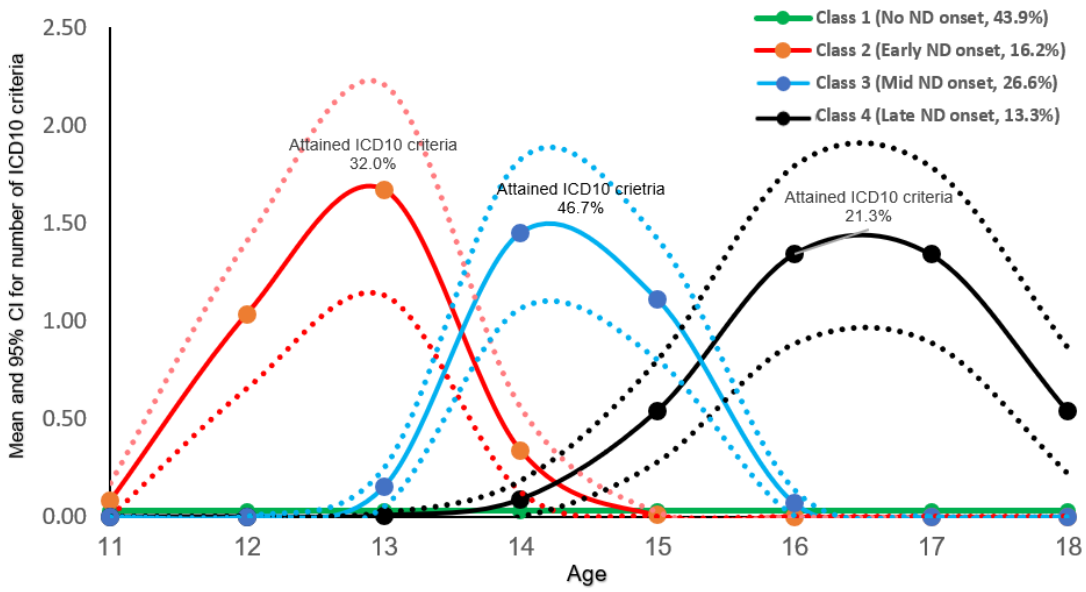

Figure 1. Trajectories of ICD10 nicotine dependence criteria in a 4-class group-based trajectory model. Note: Class membership is based on average posterior probabilities without covariates in the model. Each time point (age) represents the mean and 95% CI (*dotted lines*) of the number of ICD10 criteria. The onset of ICD10 nicotine dependence is reported as early, mid, and late adolescence. Note: Latent growth model was controlled for age at smoking initiation and age at the entry to the study to get a clear picture of ND trajectories during adolescence

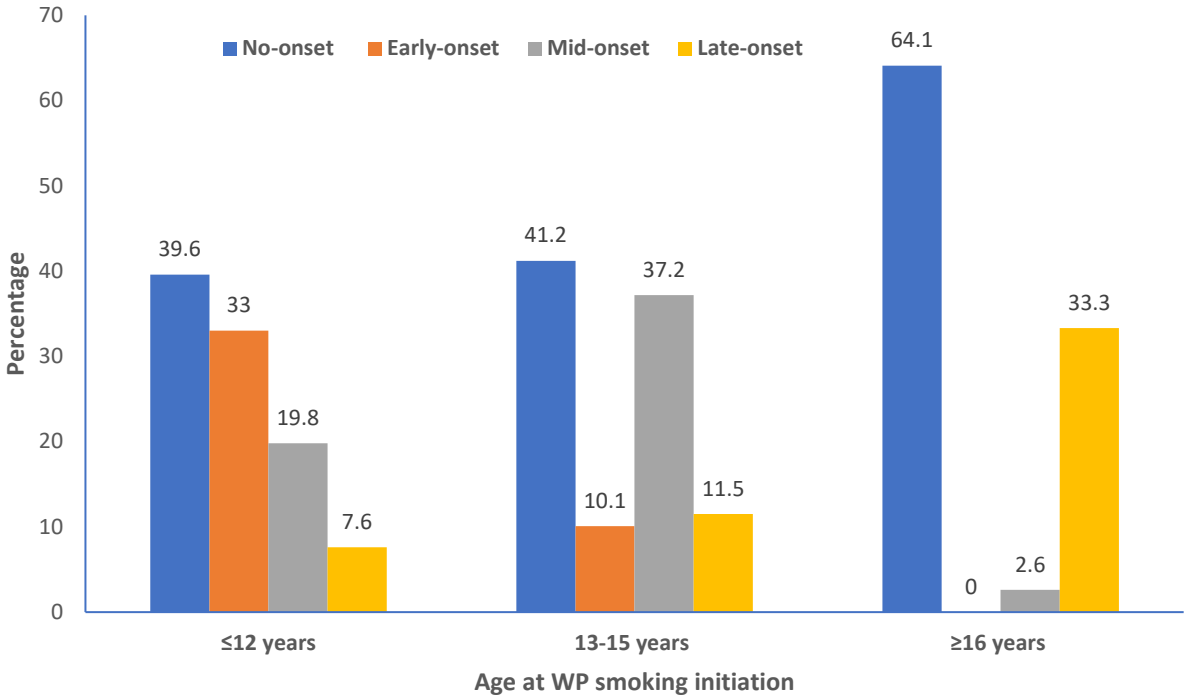

Figure 2. Age at waterpipe smoking initiation and 4-class trajectories of nicotine dependence in WDLY study

Table 3. Factors associated with developmental trajectories of nicotine dependence in four-class group-based modeling, WDLY (n=278)

Variables	**Early-onset vs No-onset**	**Mid-onset vs No-onset**	**Late-onset vs No-onset**	**Early-onset vs Mid-onset**	**Early-onset vs Late-onset**	**Mid-onset vs Late-onset**
	aOR (95% CI); *p-value*	**aOR (95% CI); *p-value***	**aOR (95% CI); *p-value***	**aOR (95% CI); *p-value***	**aOR (95% CI); *p-value***	**aOR (95% CI); *p-value***
Gender (female vs male)	0.91 (0.35-2.33); 0.84	0.63 (0.30-1.29); 0.20	1.79 (0.62-5.19); 0.28	0.93 (0.26-3.30); 0.91	0.43 (0.08-2.42); 0.34	0.47 (0.13-1.67); 0.24
School (private vs public)	0.95 (0.40-2.24); 0.90	0.62 (0.31-1.22); 0.16	0.71 (0.29-1.75); 0.46	2.40 (0.65-8.84); 0.19	2.12 (0.46-9.82); 0.34	0.90 (0.30-2.74); 0.85
Age at bassline (mean±SD)	**0.51 (0.29- 0.91); 0.02**	0.93 (0.64-1.34);0.71	**2.55 (1.57- 4.14);0.001**	**0.27 (0.11- 0.67);0.04**	**0.08 (0.01-0.45);.005**	**0.12 (0.04-0.35);.001**
Mother' education (< 12 years vs ≥12)	1.45 (0.56-3.79); 0.45	0.84 (0.40-1.73); 0.63	2.14 (0.79-5.78); 0.13	**4.08 (1.01-16.53); 0.04**	1.48 (0.27-8.06); 0.65	1.76 (0.36-8.61); 0.48
Father education (< 12 years vs ≥12)	0.81 (0.31-2.12); 0.67	1.94 (0.89-4.22); 0.10	1.69 (0.60-4.76); 0.32	0.23 (0.05-1.02); 0.05	0.50 (0.08-3.04); 0.45	0.29 (0.07-1.22); 0.09
Having ≥ 1 siblings who smoke WP	1.55 (0.62-3.86); 0.35	0.63 (0.32-1.23); 0.18	0.69 (0.28-1.72); 0.43	**3.95 (1.08-14.42); 0.04**	2.26 (0.40-12.69); 0.36	0.69 (0.23-2.02); 0.49
Having ≥ 1 friends who smoke WP	1.17 (0.33-4.21); 0.81	1.19 (0.49-2.87); 0.70	6.86 (0.81-57.98); 0.08	0.23 (0.03-1.88); 0.17	0.07 (0.00-3.62); 0.18	**0.07 (0.01-0.87); 0.04**
WP smoking is harmful to health (agree vs. disagree),	0.76 (0.04-13.42); 0.85	1.83 (0.11-30.73); 0.68	**0.11 (0.02-0.82); 0.03**	0.30 (0.01-6.40); 0.44	15.53 (0.40-601.53); 0.14	10.48 (0.58-189.67); 0.11
Believing that WP smokers have more friends (agree vs. disagree),	0.77 (0.28-2.09); 0.60	1.72 (0.85-3.46); 0.13	1.45 (0.56-3.77); 0.44	**0.20 (0.05-0.80); 0.02**	0.51 (0.07-3.62); 0.50	1.09 (0.32-3.70); 0.90
Age of initiating WP smoking	**0.52 (0.40-0.67); <.001**	0.87 (0.71-1.05); 0.15	**1.36 (1.06-1.75); 0.02**	**0.40 (0.25-0.64); 0.01**	**0.39 (0.24-0.63); <0.001**	**0.56 (0.39-0.81); <0.001**

Table 3 (continue)

Frequency of WP use (referent: monthly use)						
Weekly	0.89 (0.32-2.49); 0.82	**2.20 (1.05-4.62); 0.04**	1.48 (0.54-4.07); 0.45	0.33 (0.09-1.25); 0.10	0.62 (0.10-3.76); 0.61	1.28 (0.35-4.71); 0.71
Daily	1.93 (0.49-7.62); 0.35	**3.48 (1.08-11.23); 0.04**	0.90 (0.19-4.32); 0.90	0.24 (0.03-2.33); 0.22	2.33 (0.14-39.52); 0.56	5.02 (0.56-44.69); 0.15
Quantity (number of WP heads/bowls)	1.01 (0.99-1.04); 0.35	0.99 (0.95-1.02); 0.39	1.00 (0.97-1.04); 0.78	1.06 (0.98-1.16); 0.16	1.00 (0.96-1.04); 0.91	0.96 (0.91-1.01); 0.14
On average, time spend in 1 WP session (referent: Less than 30 minutes)						
30 – 60 minutes	1.25 (0.48-3.29); 0.65	1.35 (0.66-2.77); 0.41	1.47 (0.56-3.86); 0.44	1.11 (0.32-3.89); 0.87	0.96 (0.17-5.34); 0.97	1.22 (0.34-4.33); 0.76
More than 60 minutes	1.00 (0.20-5.06); 1.00	1.33 (0.35-5.11); 0.68	**5.62 (1.20-26.44); 0.03**	0.88 (0.11-7.19); 0.90	0.45 (0.03-7.36); 0.58	0.31 (0.05-2.05); 0.22
Do you have favorite WP ads? (yes)	**3.33 (1.03-10.85); 0.05**	2.01 (0.68-5.89); 0.20	2.47 (0.62-9.84); 0.20	1.95 (0.49-7.83); 0.35	2.21 (0.36-13.65); 0.39	0.66 (0.13-3.34); 0.62
Stress	0.97 (0.89-1.07); 0.55	**1.07 (1.00-1.14); 0.05**	1.05 (0.97-1.14); 0.20	**0.86 (0.76-0.97); 0.01**	0.93 (0.80-1.07); 0.28	1.01 (0.92-1.11); 0.89
Depression	1.05 (0.93-1.18); 0.47	1.04 (0.94-1.15); 0.43	0.94 (0.83-1.08); 0.38	1.01 (0.84-1.20); 0.94	1.25 (0.98-1.61); 0.07	1.12 (0.95-1.33); 0.18
Novelty seeking	1.04 (0.98-1.10); 0.22	0.98 (0.93-1.03); 0.35	1.04 (0.97-1.11); 0.31	**1.12 (1.02-1.23); 0.02**	0.99 (0.87-1.12); 0.82	0.95 (0.88-1.02); 0.12
Self esteem	0.95 (0.85-1.06); 0.35	**1.11 (1.02-1.20); 0.01**	1.06 (0.96-1.18); 0.26	**0.74 (0.61-0.90); <0.01**	0.86 (0.72-1.03); 0.10	1.05 (0.92-1.19); 0.51

Supplementary e-Table. WHO's ICD-10 nicotine dependence criteria

1.	**Strong desire or sense of compulsion to use tobacco**
a.	Have you ever had strong cravings to smoke waterpipe?
b.	Have you ever felt like you were addicted to waterpipe?
c.	Have you ever felt like you really needed a waterpipe?
d.	Is it hard to keep from smoking waterpipe in places where you are not supposed to, like school?
2.	**Difficulties in controlling tobacco-taking behavior in terms of its onset, termination, or levels of use**
a.	Have you ever tried to quit waterpipe smoking but could not do it?
b.	Do you smoke waterpipe now because it is really hard to quit?
c.	Are you smoking waterpipe more now than you planned to when you started?
3.	**A physiological withdrawal state**
a.	Did you find it hard to concentrate because you could not smoke waterpipe?
b.	Did you feel more irritable because you could not smoke waterpipe?
c.	Did you feel a strong need or urge to smoke waterpipe?
d.	Did you feel nervous, restless, or anxious because you could not smoke waterpipe?
e.	Do you smoke waterpipe to avoid withdrawal symptoms?
4.	**Evidence of tolerance**
a.	Do you find that you need to smoke waterpipe more often than you used to?
b.	Do you have to smoke waterpipe more often now to feel relaxed than you used to?
5.	**Neglect of alternative pleasures**
a.	Do you find that you are spending more of your free time trying to get waterpipe?
b.	Have you cut down on your physical activities or sports because you smoke waterpipe?
c.	Do you ever give up going places or doing things because waterpipe smoking is not allowed?
d.	Have you stopped hanging out with certain friends because you smoke waterpipe?
6.	**Use despite harm**
a.	Has a doctor or nurse told you that you should quit smoking waterpipe because it was damaging your health?

Note: All responses are as Yes or No.

Conclusions

WP's configuration, smoking patterns (long intermittent sessions), and setting (e.g. café and social environment) can result in a unique trajectory of nicotine dependence (ND) symptoms compared to cigarette smoking. This pioneer longitudinal study provides the first comprehensive information about the development and trajectories of ND and their time-variant predictors among a cohort of adolescent WP and cigarette smokers.

The first manuscript revealed that early development of symptoms of ND that are important in relapse and cessation appears earlier with low frequency and quantity of use in adolescent WP smokers compared to cigarette smokers. Half of adolescent WP smokers who experienced initial ND symptoms did so within 10 months of the first puff on WP, compared to 19 months for cigarette smokers. Similarly, half of adolescent WP smokers who met ICD10 criteria did so within 15.1 months after smoking initiation, compared to 22.3 months for cigarette smokers. More cigarette smokers expressed difficulty in refraining from smoking in places where it is not allowed compared to WP smokers. These findings highlight the potential role of WP-unique features, use patterns, and social setting in ND development, and the need to address early ND symptoms appearance, composition, and contextual factors in WP smoking cessation interventions.

Building on the first manuscript, the second manuscript identifies and contrasts the factors that predict initial ND symptoms and full-blown ND syndrome in adolescents WP and cigarette smokers. For both tobacco use methods, we found some commonalities in predictors of ND milestones (e.g. age of initiation, sibling tobacco use), which allows us to apply some of the experience of targeting these predictors among cigarette smokers. At

the same time, there were substantial differences in the predictors of these ND milestones between the two tobacco use methods (e.g., the role of physical activity, BMI), which will be important to inform the development of tailored interventions targeting these popular tobacco use methods in the EMR.

The third manuscript identifies 4 unobserved latent classes of ND over ages 11-18 as class 1 (no-onset of ND symptoms), class 2 (early-adolescence ND onset), class 3 (mid-adolescence ND onset), and class 4 (late-adolescence ND onset). Compared with those without symptoms (no-onset), adolescents in the early-onset class were more receptive/exposed to tobacco advertising, in the mid-onset, there was a strong association with the magnitude of smoking frequency (i.e., daily/weekly vs monthly) and they reported higher stress and self-esteem level, and in the late-onset trajectory, adolescents were less likely to believe that WP smoking can harm health and more likely to report a long smoking session. Our findings suggest that every ND trajectory class during adolescence could have distinctive characteristics and therefore provide new insights into the process of ND in terms of when and what specific interventions are needed to curb the development of ND, and long-term WP smoking among youth.

Together, our findings underscore a deeper understanding of the natural course of initial ND symptoms and full ND syndrome and their time-constant and time-varying predictors among adolescents WP and cigarette smokers in a developing country. This study also reveals latent classes of the developmental trajectories of WP-specific ND criteria during the adolecence. This information will help guide healthcare providers and

regulatory bodies to curb the burgeoning WP use epidemic in Lebonan and other countries with the same cultural context.

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