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Editorial

Towards a Canadian evidence base to inform action to prevent and control vaping in Canada

Cynthia Callard, MM (1); Thierry Gagné, PhD (2); Jennifer L. O'Loughlin, PhD (3,4)

The upsurge in the use of electronic nicotine delivery systems (ENDS) in the past decade is a critical issue for tobacco control, characterized by rapidly changing ENDS technologies, shifting usage patterns and contradictory evidence on the added value of vaping products. Policy development in this realm is often based on risk assessments lacking replication or clear consensus on the benefits and harms of ENDS. Further, without homegrown evidence, Canada's approach has been highly reliant on the experience of and evidence in other countries, despite critical differences in regulatory landscapes and time trends in uptake across age groups.[1]

This second offering in a two-part series in *Health Promotion and Chronic Disease Prevention in Canada: Research, Policy and Practice* (the HPCDP Journal) on tobacco and vaping prevention and control presents Canadian data that directly address this knowledge gap. Our call for papers asked for new Canadian evidence on policy implementation challenges, the determinants of ENDS use, including its social distribution, and the associations between ENDS use, smoking cessation and health outcomes. The five papers in this special issue address key evidence gaps that have challenged the development of relevant policy and programs targeting ENDS use in Canada.

In an innovative online scan of vaping product retailers, D'Mello et al.[2] demonstrate the mind-boggling diversity of the online e-cigarette market in Canada in terms of nicotine concentration, availability of higher-concentration salt-base nicotine products, and flavours. The authors decry this diversity and call for reducing the number of e-liquid flavours available on the market and restricting nicotine concentrations to less than 20 mg/mL. Their research reveals disturbingly high levels of noncompliance with federal regulations that prohibit the marketing of candy-flavoured e-liquids.

Two papers, one by Ahmad et al.[3] and one by Shi et al.,[4] identify determinants of vaping initiation and daily use among Canadian youth. These papers indicate that key determinants of youth vaping in Canada likely include ease of access in addition to the constellation of vulnerabilities underpinning substance use in general, as evidenced by the close associations between vaping and other risk-taking behaviours such as cigarette smoking and use of alcohol, energy drinks and marijuana. These results corroborate supporting findings reported by Williams et al. (published in the first part of this HPCDP Journal special issue).[5]

Finally, two papers shed new light on the acute and long-term effects of vaping on health. First, Baker et al.[6] report results from the first year of the Canadian VALI (vaping-associated lung injury) surveillance system. The authors describe encouraging numbers in terms of low occurrence and acute health consequences compared to the US. However, they caution us about our reduced capacity to monitor these outcomes since the COVID-19 pandemic, and they highlight the need to extend surveillance to assess longer-term health impacts. Second, Pound et al.[7] describe a simulation study showing the relative impact of ENDS on population health across contrasting regulatory scenarios, including a complete ban and a prescription-only scenario (i.e. wherein vaping is available to smokers only). While the debate on the benefits of vaping for cessation remains heated, this analysis underscores the high economic and health costs of delaying action to prevent vaping initiation and the subsequent transition to cigarette smoking in future generations.

We believe that, collectively, the evidence presented in this issue of the HPCDP Journal will assist regulators in enhancing interventions to decrease the recreational use of ENDS and to better control the supply of ENDS. On the demand side, the growing number of Canadian publications on youth vaping highlight that some young people are at particularly high risk of initiating and continuing use for reasons similar to those underpinning the use of other substances. In particular, the social distribution of vaping uptake was not evident early on after ENDS entered the market.[8,9] However, as ENDS use progressed through the innovation curve to affect the entire population, the vulnerability characteristic of most substance use behaviours is now recognized as a key determinant of vaping uptake.

These results are highly evocative of research conducted by tobacco companies in the 1980s that aimed to identify psychographic market segments of the Canadian youth population from which they could most easily recruit new users

Author references:

1. Physicians for a Smoke-Free Canada, Ottawa, Ontario, Canada
2. Research Department of Epidemiology and Public Health, University College London, London, United Kingdom
3. Centre de recherche du Centre hospitalier de l'Université de Montréal, Montréal, Quebec, Canada
4. Département de médecine sociale et préventive, École de santé publique de l'Université de Montréal, Montréal, Quebec, Canada

Correspondence: Cynthia Callard, Physicians for a Smoke-Free Canada, 134 Caroline Avenue, Ottawa, ON K1Y OS9; Email: ccallard@smoke-free.ca

using the concepts of independence, freedom and peer acceptance.[10,11] This market research helped legislators recognize that comprehensive and society-wide tobacco control measures were needed to protect youth. Some of the demand-reduction interventions established for tobacco products that proved effective in reducing youth smoking (e.g. advertising bans) are now in place for ENDS, but others (e.g. plain packaging, full bans on vaping flavours) remain to be implemented.

In addition to these insights on the demand side of the equation, D'Mello's findings[2] highlight stark differences between regulatory controls on the supply side of the Canadian ENDS and tobacco markets. The cigarette market is one in which virtually identical products are sold by a vertically integrated oligopoly,[12] and in which manufacturers are required to provide detailed and regular reports to government on their product emissions, their ingredients, their price and their sales volume.[13] In contrast, those who manufacture the many and diverse ENDS products sold in Canada are not required to file any reports with government, leaving key monitoring data unavailable. Without this information, Canadian researchers and regulators have more difficulty measuring the impact that these products have on population health.

Also on the supply side, Pound's team assessed the cost savings of shifting ENDS products from the consumer goods market and instead making them available as a therapeutic product. This regulatory innovation is underway in Australia, where e-cigarettes are now managed as "unapproved" medicines available only under prescription.[14] Canada's policy choice to legalize e-cigarettes as a recreational drug product was presented as an approach that balanced concerns about "protecting youth from nicotine addiction and tobacco use, and allowing adults to legally access vaping products as a less harmful alternative to cigarettes."[15] Pound's cost study suggests that there may be a better way to achieve an optimal balance.

There is now solid international and homegrown evidence that vulnerability to ENDS uptake in youth is similar to, if not higher than, that of tobacco uptake, and this has serious implications for population health in Canada. Three directions for action emerge from this set of papers. First, we can optimally protect young people by applying the set of stringent and comprehensive demand-side measures that have helped reduce tobacco initiation. Second, because Canada's ENDS market is difficult to monitor, assess and regulate, measures to bring supply under better public health management need to be prioritized. The option of limiting ENDS products to a therapeutic supply (for quitting or harm reduction) should be further explored. Third, much more evidence is needed on the short- and long-term consequences of using ENDS, a knowledge gap that can only be addressed if there is sustained support for surveillance and longitudinal research. We hope that Canada's health authorities recognize the important contribution of the five papers presented herein and use the findings to strengthen their policy and programmatic approaches to addressing the enduring public health challenge of nicotine addiction.

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Conflicts of interest

The authors declare no competing interests.

Statement

The content and views expressed in this article are those of the authors and do not necessarily reflect those of the Government of Canada.

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Original quantitative research

Nicotine content, labelling and flavours of e-liquids in Canada in 2020: a scan of the online retail market

Kimberly D'Mello, BSc (1); David Hammond, PhD (1); Syed Mahamad, BSc (1); Danielle Wiggers, MSc (1); Katherine East, PhD (1,2)

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Abstract

Introduction: The e-cigarette market in Canada has rapidly evolved following the implementation of the *Tobacco and Vaping Products Act* in May 2018, which liberalized the promotion and sale of vaping products. To date, there is little data on the market profile of key product attributes, including nicotine content, labelling practices and flavours.

Methods: An online scan of vaping product retailers (manufacturer, two national, five provincial) was conducted in 2020 to assess the e-liquids available on the Canadian market. Data were extracted from websites and product images regarding the nicotine content, labelling and flavours of e-liquids.

Results: We identified 1746 e-liquids, with a total of 4790 different nicotine concentrations. Approximately half of the e-liquids were offered with salt-base nicotine (46.6%) and half with freebase nicotine (53.2%); the remainder were hybrids (0.2%). The mean nicotine concentration of salt-base e-liquids (3.4%) was higher than freebase e-liquids (0.5%) ($p < 0.001$). Labels indicating the presence of nicotine were visible on two-thirds of e-liquid packaging displayed online (63.2%) while three-quarters of packaging displayed the nicotine concentration (73.7%), and more than half of packaging displayed health warnings (58.9%). A variety of flavours were also identified, with fruit being the most common (43.6%), followed by candy/desserts (27.6%) and non-alcoholic drinks (12.5%).

Conclusion: Findings demonstrate the diversity of the online e-cigarette market in Canada, including the availability of higher-concentration salt-base nicotine products. Flavour restrictions have the potential to dramatically reduce the number of e-liquid flavours on the market, while restricting nicotine concentrations to < 20 mg/mL will predominantly restrict salt-based e-liquids.

Keywords: *Canada, electronic cigarettes, flavouring agents, nicotine, public policy, product labelling*

Highlights

- There is little current data on the Canadian e-cigarette market, particularly about nicotine content, labelling and flavours.
- This online retail scan found that half of e-liquids offered were nicotine salt-base, half were freebase, and a few were hybrids.
- Among e-liquids containing nicotine, nicotine concentration was higher among salt-base (mean: 3.4%; range: 0.3%–6.5%) than freebase (mean: 0.5%; range: 0%–1.8%) e-liquids.
- Eleven e-liquid flavour categories were identified, with fruit being the most common, followed by candy/desserts and nonalcoholic drinks.
- Findings demonstrate the diversity of e-liquids sold online in Canada and that flavour restrictions and nicotine limits will restrict a large proportion of e-liquids.

Introduction

Prior to May 2018, Canada had a highly restrictive regulatory framework for e-cigarettes: nicotine-containing vaping products could not be sold or marketed without premarket approval.[1] However, as of May 2018, the *Tobacco and Vaping Products Act* (TVPA) permitted the sale of nicotine-containing e-cigarettes, as well as greater advertising and promotion.[1] The e-cigarette market experienced rapid change following implementation of the TVPA, including the introduction of major international brands such as JUUL and Vype/Vuse.[2,3] The prevalence of past-30-day vaping also increased from approximately 3% in 2017 to 5% in 2019 among Canadians aged 15 years or older.[4-6]

E-cigarettes offer an alternative method of nicotine consumption that is less harmful than smoking tobacco cigarettes.[7] E-cigarettes are among the most common smoking cessation aids used by adult smokers in Canada[8] and evidence suggests that nicotine-containing e-cigarettes can help some smokers to successfully quit if they are used for the purpose of quitting

Author references:

1. School of Public Health Sciences, Faculty of Health, University of Waterloo, Waterloo, Ontario, Canada
2. National Addiction Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom

Correspondence: Katherine East, National Addiction Centre, 4 Windsor Walk, London, UK SE5 8BB; Email: katherine.east@kcl.ac.uk

and on a daily basis.[7,9-11] However, there are concerns about the use of e-cigarettes among youth and nonsmokers; in Canada, 11.6% of high school students reported vaping on a daily basis in 2019, among the highest rates in the world.[12]

A range of policy measures are being proposed or implemented at both the provincial and federal levels in Canada, with the aim of minimizing vaping among young people (Figure 1).[1,13,14] Several of these policies seek to reduce the appeal of vaping products by modifying product attributes, including restricting flavours of e-liquids, limiting nicotine concentration to 20 mg/mL (in line with the European Union)[15] and mandating health warnings and nicotine labelling.

Flavours play an important role in vaping among youth and young adults, as well as among adult smokers who are trying to quit. Availability and liking of flavours are among the main reasons for vaping among youth in the US[16] and England.[7] Research has also demonstrated that flavours can facilitate smoking cessation.[17,18] Fruit flavours are the most popular among both youth and adult vapers,[5,7,19-21] although, in Canada, tobacco flavours are more commonly used by adults than youth.[4,5] Studies have identified thousands of different e-liquid flavours in the US[22] as well as numerous flavour categories;[23] however, we are unaware of any comprehensive study of the flavour profile of the Canadian e-liquid market.

Several Canadian provinces have implemented restrictions on the nicotine concentration of e-liquids, and at the time of this study, Health Canada had proposed a limit of 20 mg of nicotine per mL of e-liquid (Figure 1), similar to existing regulations in the European Union.[15] In Canada, prior to the implementation of the TVPA in May 2018,[1] although no nicotine-containing products were approved for sale, the vast majority of e-liquids did contain less than 2% (or 20 mg/mL) of nicotine.[24] However, since the implementation of the TVPA, an increasing number of brands, such as JUUL, have been introduced to the Canadian market. The most popular variety of JUUL contains 5% nicotine (59 mg/mL) and uses salt-base nicotine e-liquid with a lower pH than freebase e-liquids to enhance the palatability of higher nicotine concentrates.[25-28] The high-concentration salt-base nicotine e-liquid pioneered by JUUL has since been adopted by most other nicotine salt brands; however, the extent to which the Canadian market has shifted toward higher-concentration nicotine salt e-cigarettes has yet to be examined.

There is also little data on the packaging and labelling practices of products in Canada, including the extent to which nicotine levels are consistently and clearly labelled on product packaging or at the point of sale (including online). A retail scan conducted in Ontario in 2018 found that a substantial proportion of e-cigarettes for sale in Canada were not labelled as having nicotine and that the accuracy of nicotine labelling was inconsistent when tested for actual nicotine concentration in the products.[24] Another scan conducted in 2014 found that many e-cigarette products did not include health claims, but instead listed general disclaimers and ingredient information.[29] The display of "voluntary" health warnings on packaging has also been inconsistent across e-cigarette markets in the United States (US), often changing in response to regulatory proposals by the US Food and Drug Administration (FDA).[30,31] In Canada, new federal requirements were implemented in July 2020 mandating maximum nicotine content restrictions and distinct health warnings on product packaging per the *Vaping Products Labelling and Packaging Regulations*,[32] although we are unaware of

FIGURE 1
Overview of retail regulations for vaping products in Canada at the federal level and in Alberta, British Columbia, Nova Scotia, Ontario and Quebec, at time of study (2020)

	CANADA						
	Recommended	Implemented[a]	AB	BC	NS	ON	QC
Ban flavours	!				✓		
Ban flavours except in adult (19+) vape stores				✓			
Ban flavours (except menthol) except in adult (19+) vape stores						✓	
Maximum nicotine concentration (mg/mL)	! 20	66		20	20		
Higher nicotine in vape stores only						✓	
Labelling requirements: Health warning, nicotine concentration	!	✓		✓			

✓	Measure implemented/ intention to implement declared
	Federal measures apply
!	Measure recommended by the Council of Chief Medical Officers of Health, January 2020

Abbreviations: AB, Alberta; BC, British Columbia; NS, Nova Scotia; ON, Ontario; QC, Quebec.
Note: Only the provinces from which data were collected are included in Figure 1.
[a] At the time of this study (2020) the maximum nicotine concentration was 66 mg/mL.

any current studies documenting labelling practices on Canadian vaping products.

Overall, despite the rapidly evolving e-cigarette product market, there is little publicly available data on key product attributes, including the nicotine content, flavours and labelling of e-cigarettes. This information is critically important for understanding how these products are promoted and used by consumers, as well as for understanding the impact of provincial and federal restrictions. Since many consumers purchase vaping products through online retailers,[33] an understanding of the online market environment is of particular importance.[34] In our study, we therefore sought to examine the e-liquids available on the online retail market in Canada, with a focus on nicotine concentration, flavours and labelling.

Methods

Data collection

Data were collected through an online scan of vaping product retailers from January to September 2020 (manufacturer, two national, five provincial). This scan was conducted in three steps to ensure a diverse set of vaping products were identified to adequately characterize the Canadian market.

First, a list of 25 leading brands was constructed from the 2019 International Tobacco Control (ITC) Youth and Tobacco and Vaping Survey: Aspire, blu, Eleaf, FreeMax, Geekvape, IJOY, Innokin, Joyetech, JUSTFOG, JUUL, KangerTech, Lost Vape, Mi-Pod, MYLÉ, SMOK, Smoke NV, Snowwolf, STLTH, Suorin, TeslaCigs, UWELL, V2, Vaporesso, VOOPOO, Vype/Vuse. Collectively, these brands represent more than 90% of brand market share among young people who vape in the ITC survey.[34] Information on all available vaping products for the 25 brands was identified by searching three online sources, in the following order: (1) Canadian website of manufacturer; (2) non-Canadian website of manufacturer (only if Canadian website of manufacturer was not available); and (3) two large, national online retailers. The two national online retailers were selected based on a Google search of terms "vape" and "Canada". The top ten links to online retailers were identified. The two websites that had the greatest coverage of the leading 25 brands were selected for this study. Each of the 25 leading brands except one (V2) were available for sale in Canada.

Second, additional vaping products (i.e. additional to the 25 leading brands) were identified by scanning the same two large, national online retailers described above. Data on all vaping devices and e-liquids were collected.

Third, one local online retailer per each of five Canadian provinces in our study (British Columbia, Alberta, Ontario, Quebec and Nova Scotia) was also selected to identify additional products. Again, retailers were identified through a Google search of "vape shop" followed by the major city in each province (e.g. "vape shop Toronto") and one vape store was randomly selected in each province. Vape shops were only eligible if product information was posted online.

Data extraction and coding

Data were extracted from the information available on the websites (text and images). E-liquid product images including packaging were captured using screenshots from online websites. Variables included e-liquid nicotine type (salt-base, freebase, hybrid [a combination of salt and freebase]), nicotine strength (percent and/or mg/mL), flavour category (fruit, candy/dessert, nonalcoholic drink, alcoholic beverage, tobacco, menthol/mint, coffee, spice, unflavoured, tobacco and menthol, other), as well as an indication of a health warning, the presence of nicotine and nicotine strength (percent and/or mg/mL) on e-liquid packaging.

Nicotine concentrations were presented on websites (text and images) either as mg/mL or as a percentage. For consistency, all nicotine concentrations were converted to percentages for the analysis in this study using the formula 1.0 mg/mL = 0.1%. The components of e-liquid packaging were assessed based on the clarity and visibility of the product's online image. The presence of a health warning, the presence of nicotine and nicotine strength were each recorded as Yes, No or Undiscernible. To establish the reliability of the coding protocol, three researchers independently coded 10% of all product images and reached an agreement on 95.4% of the data.

Data analysis

First, descriptive statistics were calculated on the frequency and proportion of (1) e-liquid products sold in the form of salt, freebase or a hybrid; and (2) e-liquid products within each of the following flavour categories: fruit, candy/dessert, non-alcoholic drink, alcoholic beverage, coffee, spice, tobacco, menthol or mint, tobacco and menthol, unflavoured, or other. Second, mean differences of nicotine concentration were tested between salt and freebase e-liquids (statistical tests were not run for hybrid e-liquids due to low sample size) using an independent samples *t* test. Third, mean differences of nicotine concentration were tested between e-liquid flavour categories using a one-way analysis of variance (ANOVA) and a Games-Howell post hoc test. Fourth, we calculated the frequency and proportion of e-liquid products with packaging visible on the website that indicated the presence of nicotine, stated the nicotine concentration and had health warnings (text and/or pictorial) followed by a chi-square test to examine associations with e-liquid type (salt vs. freebase).

Results

A total of 1746 e-liquids were identified and analyzed. Overall, 53.2% of the e-liquids identified were labelled or defined on the website as freebase or "regular" (n = 929), while 46.6% were salt-base (n = 814) and 0.2% were hybrid (n = 3). Among the 1746 e-liquids, a total of 4790 different nicotine concentrations were available. In other words, each e-liquid was offered in an average of two or three different nicotine concentrations (Table 1).

The vast majority of e-liquids sold contained nicotine (84.5%). Only 30% of all e-liquids had nicotine concentrations over 2%, although this proportion was much higher among salt-based e-liquids (71.4%). Freebase e-liquid nicotine concentrations ranged from 0% to 1.8%, although when restricted to nicotine-containing products only, concentrations ranged from 0.2% to 1.8% (Table 1). Salt-based e-liquids ranged from 0.3% to 6.5%, although most had nicotine concentrations of 2.1% to 5.0% and fewer had nicotine concentrations over 5%. Among all products (including 0% nicotine), the mean nicotine concentration was higher among salt-base e-liquids (3.4%) than freebase e-liquids (0.5%; $t_{2278} = 88.5$, $p < 0.001$). Among nicotine-containing products only (> 0%), the mean nicotine concentration was also higher among salt-base e-liquids (3.4%)

TABLE 1
Nicotine concentration[a] of e-liquids by nicotine type and overall[b] products in Canada, 2020

	Salt-base n = 2013	Freebase n = 2768	Hybrid n = 9	Overall n = 4790
Nicotine concentration—categorical [% (n)]				
0%	0 (0)	26.8 (741)	0 (0)	15.5 (741)
0.1%–2.0%	28.6 (576)	73.2 (2027)	100 (9)	54.5 (2612)
2.1%–5.0%	68.6 (1380)	0 (0)	0 (0)	28.8 (1380)
> 5.0%	2.8 (57)	0 (0)	0 (0)	1.2 (57)
Nicotine concentration (in %)—continuous				
All e-liquids (n = 4790)				
Mean (SD)	3.4 (1.4)	0.5 (0.4)	1.2 (0.7)	1.7 (1.7)
Range	0.3–6.5	0.0–1.8	0.5–2.0	0.0–6.5
E-liquids containing nicotine only (> 0% nicotine; n = 4049)				
Mean (SD)	3.4 (1.4)	0.6 (0.4)	1.2 (0.7)	2.0 (1.7)
Range	0.3–6.5	0.2–1.8	0.5–2.0	0.2–6.5

Abbreviation: SD, standard deviation.

[a] Nicotine concentrations that were provided in mg/mL were converted to percentages; 1.0 mg/mL = 0.1%.

[b] Data were collected for a total of 1746 e-liquid products; however, many of these products were available in multiple concentrations, resulting in 4790 separate concentrations for analysis.

than freebase e-liquids (0.6%; $t_{2310} = 83.2$, $p < 0.001$; Table 1).

Based on the principal display area of the e-liquid product packaging that was visible online, an indication that the product contained nicotine was available on 63% of all e-liquids, the nicotine concentration was visible on 74% and a health warning was visible on 59% (Table 2). The proportion of products with labels was greater when analyses were restricted to nicotine-containing e-liquids only, such that an indication that the product contained nicotine was available on 66% of all e-liquids, the nicotine concentration was visible on 74% and a health warning was visible on 61%. Between e-liquid types, all labelling was more common among nicotine salt compared to freebase products (Table 2): indication that the product contained nicotine (all products: $\chi^2_2 = 600.4$, $p < 0.001$; > 0% nicotine-containing only: $\chi^2_2 = 308.0$, $p < 0.001$), nicotine content (all products: $\chi^2_2 = 253.8$, $p < 0.001$; > 0% nicotine-containing only: $\chi^2_2 = 188.4$, $p < 0.001$), health warning (all products: $\chi^2_2 = 773.9$, $p < 0.001$; > 0% nicotine-containing only: $\chi^2_2 = 499.8$, $p < 0.001$).

TABLE 2
E-liquid product packaging indicating the presence of nicotine, nicotine concentration, or health warning, overall and by nicotine type in the online Canadian retail market, 2020

	Visible on e-liquid packaging		
	Indication of the presence of nicotine	Nicotine concentration	Health warnings
	% (n)	% (n)	% (n)
All e-liquids (n = 1746)	63.2 (1103)	73.7 (1284)	58.9 (1025)
Salt (n = 814)	76.5 (623)	81.4 (663)	74.2 (604)
Freebase (n = 929)	51.3 (477)	66.5 (618)	45.0 (418)
Hybrid (n = 3)	100.0 (3)	100.0 (3)	100.0 (3)
E-liquids containing nicotine only (> 0% nicotine, n = 4049)[a]	66.0 (2674)	74.4 (3014)	60.9 (2464)
Salt (n = 2013)	79.0 (1590)	83.8 (1686)	77.9 (1568)
Freebase (n = 2027)	53.0 (1075)	65.1 (1319)	43.8 (887)
Hybrid (n = 9)	100.0 (9)	100.0 (9)	100.0 (9)

[a] Data were collected for a total of 1746 e-liquid products; however, many of these products were available in multiple concentrations, resulting in 4790 separate concentrations for analysis.

E-liquid products were available in a variety of different flavours, with the three most common categories being fruit (43.6%), candy/desserts (27.6%) and nonalcoholic drinks (12.5%; Figure 2). The mean nicotine concentration differed between flavour categories (all products: $F_{10\ 192.84} = 7.1$, $p < 0.001$; > 0% nicotine only: $F_{10\ 168.8} = 6.6$, $p < 0.001$) such that flavours in the category "other" had the highest mean nicotine concentration, more than candy or coffee, while menthol/mint was higher than candy or tobacco, and fruit was higher than tobacco or candy (all $p < 0.05$; Table 3).

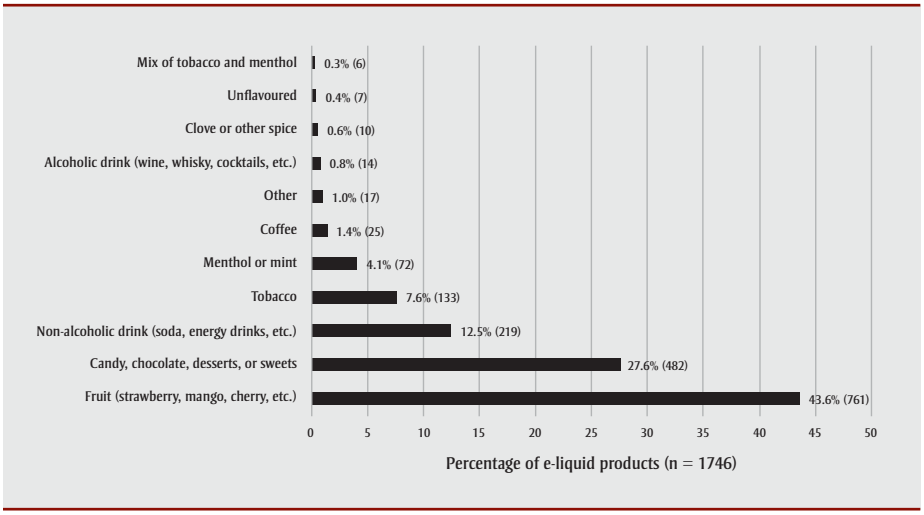
Discussion

In 2020, e-liquids were available in a wide variety of nicotine concentrations and flavours, demonstrating the diversity of the vaping product market in Canada. There were three key findings from this study, discussed in turn below.

First, the e-liquids available on the market were evenly split between salt-base and freebase products, although nicotine concentration was higher and more variable among the salt-base products. In contrast to the salt-base products, which had nicotine concentrations between 0.3% and 6.5%, all freebase products identified in our study had nicotine concentrations at or below 2% (20 mg/mL).[35] This is consistent with the theory that salt-base formulations are critical for enhancing the palatability of higher nicotine concentrates.[35] As of 2020, it was estimated that approximately 30% of all e-liquids in Canada contained freebase nicotine, compared with 70% containing salt-base nicotine; virtually all of the latter contained more than 20 mg/mL.[36] Products without nicotine are rare: for example, one report in 2019 suggested that less than 1% of sales of vaping products at gas and convenience stores in the US were for non–nicotine containing products.[2] Our Canadian data are also consistent with the shift toward higher-nicotine salt-base products seen in the US market.[37]

Interestingly, three products were labelled as hybrid e-liquids, with both salt-base and freebase nicotine. Some consumer blogs and social media indicate that some consumers have been mixing salt-base and freebase nicotine e-liquids to achieve their desired sensory effects; however, hybrid products remain rare and have

FIGURE 2
Summary of e-liquid products by flavour category in Canada, 2020



received little attention in the published literature.

Second, this study found that nicotine labelling and health warnings were not always visible on the packaging on retailers' online images. Slightly more than half of the e-liquid product images available on the websites displayed an indication of the presence of nicotine, nicotine concentration and health warnings. This contrasts with very few e-cigarette products containing health warnings in 2014.[29] Salt-base nicotine products were more likely to include labelling of nicotine and health warnings compared to freebase products, although comparisons must be interpreted with caution given that not all packaging was visible for data collection. In July 2020 (during this study), federal legislation in Canada mandated exterior packaging labels displaying nicotine concentration and health warnings on vaping products.[32,38] Given that many consumers purchase vaping products through online retailers,[33] clear and consistent labelling practices including labelling displays online are important to ensure that consumers have adequate information at the point of purchase.

Third, this study identified a wide range of e-liquid flavours on the Canadian market. The most common flavour category was fruit, consistent with survey data suggesting that fruit is the most popular flavour among both youth and adult vapers,[4,5,19-21] Despite this, "other" flavours had the highest nicotine concentrations. Data suggest an expansion in the availability of flavours since 2014, when the only flavour categories identified were fruit, candy/desserts, drinks and tobacco,[29] compared with the 11 flavour categories identified in this 2020 scan. In the US and England, the availability and liking of e-liquid flavours have been a primary reason for e-cigarette

TABLE 3
Summary of e-liquid products by flavour category and nicotine concentration in Canada, 2020

	Nicotine % continuous		Nicotine concentration % categories			
	All e-liquids (n = 4790)	E-liquids containing nicotine only (n = 4049)	0%	0.1%–2.0%	2.1%–5.0%	> 5.0%
Flavour category	Mean (SD)	Mean (SD)	% (n)	% (n)	% (n)	% (n)
Other[a,b]	2.7 (2.0)	3.0 (1.9)	8.8 (3)	41.2 (14)	41.2 (14)	8.8 (3)
Menthol or mint[c,d]	2.0 (1.8)	2.3 (1.7)	12.2 (24)	53.3 (105)	32.5 (64)	2.0 (4)
Fruit (strawberry, mango, cherry, etc.)[e,f]	1.8 (1.8)	2.2 (1.8)	14.8 (305)	50.8 (1050)	32.7 (677)	1.7 (36)
Alcoholic drink (wine, whisky, cocktails, etc.)	1.8 (1.9)	2.2 (1.9)	18.2 (6)	45.5 (15)	33.3 (11)	3.0 (1)
Mix of tobacco and menthol	1.6 (1.3)	1.7 (1.3)	5.3 (1)	68.4 (13)	26.3 (5)	0 (0)
Clove or other spice	1.7 (1.5)	2.0 (1.5)	12.5 (4)	59.4 (19)	28.1 (9)	0 (0)
Nonalcoholic drink (soda, energy drinks, etc.)	1.6 (1.7)	2.0 (1.7)	16.2 (104)	55.8 (359)	27.5 (177)	0.5 (3)
Tobacco[d,e]	1.6 (1.5)	1.8 (1.5)	14.1 (60)	63.5 (271)	22.3 (95)	0.2 (1)
Candy, chocolate, desserts or sweets[a,c,f]	1.4 (1.7)	1.7 (1.7)	17.5 (215)	56.7 (698)	25.2 (311)	0.7 (8)
Unflavoured	1.8 (1.4)	1.6 (1.4)	15.4 (4)	69.2 (18)	15.4 (4)	0 (0)
Coffee[b]	1.4 (1.4)	1.6 (1.6)	19.0 (15)	63.3 (50)	16.5 (13)	1.3 (1)
Total	**1.7 (1.7)**	**2.0 (1.7)**	**15.5 (741)**	**54.5 (2612)**	**28.8 (1380)**	**1.2 (57)**

Abbreviation: SD, standard deviation.

Note: Nicotine concentrations that were presented in mg/mL were converted to percentages; 1.0 mg/mL = 0.1%.

[a] Games-Howell post hoc comparisons $p < 0.05$: other vs. candy

[b] Games-Howell post hoc comparisons $p < 0.05$: other vs. coffee

[c] Games-Howell post hoc comparisons $p < 0.05$: menthol/mint vs. candy

[d] Games-Howell post hoc comparisons $p < 0.05$: menthol/mint vs. tobacco

[e] Games-Howell post hoc comparisons $p < 0.05$: fruit vs. tobacco

[f] Games-Howell post hoc comparisons $p < 0.05$: fruit vs. candy

use among youth,[7,16,39] although flavours can also help adult smokers to quit smoking.[17,18] An increasing number of Canadian provinces are restricting e-liquid flavours, including Nova Scotia and Prince Edward Island;[14] however, the impact of flavour restrictions on vaping among both adult smokers and youth remains unclear.

The e-cigarette market continues to evolve, and new provincial restrictions have come into force since completion of this study. For example, Nova Scotia has banned the sale of all nontobacco flavours, British Columbia has restricted the sale of nontobacco flavours in stores that permit minors, and similar restrictions have been implemented in Ontario for nontobacco and nonmenthol flavours.[14] Future studies should examine how the industry adapts its products to comply with these restrictions, as well as the impact on consumer patterns of use.

Strengths and limitations

This study has important strengths. We provide the most comprehensive online scan of the e-cigarette market in Canada to date, considering 25 popular e-cigarette brands and using two large national retailers as well as five provincial vape stores and manufacturer websites. Data were collected online, where many consumers purchase their vaping products, thus enhancing ecological validity. The inter-rater reliability of the coding protocol was also high.

However, our findings must be considered in the light of several limitations. First, data collection was limited to products accessible through online retailers (including manufacturers), and so the results may not generalize to the broader Canadian market (e.g. brick-and-mortar stores). However, our findings align with national estimates of sales data on attributes such as flavour profile and nicotine concentration.[2,3] Second, data were restricted to the information available from websites and product images and, in some cases, only a partial view of the e-liquid's packaging was available. Many e-liquids are sold with additional exterior packaging that may have included details relevant to the study, but were not shown on the website. Thus, we are unable to establish the extent to which e-liquids complied with regulations. Third, nicotine concentrations expressed in mg/mL were assumed to be equivalent to nicotine concentrations expressed as percentages (e.g. 20 mg/mL = 2.0%). However, in practice, these numbers are not always equivalent; for example, JUUL's leading formulation of 59 mg/mL is labelled as 5.0% nicotine. Fourth, reliability checks were only performed on 10% of the data.

Conclusion

Our findings demonstrate the diversity of e-liquids available in the Canadian market including the availability of higher-concentration salt-base nicotine products. Findings also suggest that regulations restricting flavours will restrict the vast majority of products sold online in Canada, while Health Canada's proposed restrictions limiting nicotine concentrations to 20 mg/mL or less would predominantly restrict salt-based e-liquids. Future research should evaluate the impact of these restrictions on the product market as well as patterns of consumer use.

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Conflicts of interest

DH has served as a paid expert witness in legal challenges against tobacco and vaping companies. All other authors have no conflicts of interest to declare.

Authors' contributions and statement

- KDM: analysis and interpretation of the data; drafting and revising the paper; approval of the final manuscript for submission.
- DH: design; conceptualization; acquisition, analysis and interpretation of the data; drafting and revising the paper; approval of the final manuscript for submission.
- SM: acquisition of the data; revising the paper; approval of the final manuscript for submission.
- DW: acquisition of the data; revising the paper; approval of the final manuscript for submission.
- KE: acquisition, analysis and interpretation of the data; drafting and revising the paper; approval of the final manuscript for submission.

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Original quantitative research

Predictors of pod-type e-cigarette device use among Canadian youth and young adults

Safa Ahmad, MPH; Tianru Wang, MPH; Robert Schwartz, PhD; Susan J. Bondy, PhD

This article has been peer reviewed.

Abstract

Introduction: Changes to federal legislation allowed nicotine-based e-cigarettes legal entry into the Canadian market in 2018. This included pod-type e-cigarettes (pods), such as JUUL, that were later found to be associated with steeply increasing prevalence and greater frequency of e-cigarette use among US and Canadian youth. Multiple studies of risk factors of JUUL use and use initiation have been conducted among various population groups in the US, but little evidence exists pointing to similar risk factors of pod use among Canadian youth and young adults. Understanding these risk factors can inform use prevention and intervention strategies in Canadian and other jurisdictions.

Methods: A total of 668 Canadian youth and young adults recruited by the 2018-19 Youth and Young Adult Panel Study were provided a baseline survey 3 months before and a follow-up survey 9 months after the relaxation of federal nicotine e-cigarette regulations. We used multivariable logistic regression to understand and rank importance of baseline predictors of future pod use among respondents.

Results: Past-month cannabis use (OR [odds ratio] = 2.66, 95% CI: 1.66–4.21, $p < 0.001$), established cigarette use (OR = 3.42, 1.53–7.65, $p < 0.01$), past cigarette experimentation (OR = 2.40, 1.34–4.31, $p < 0.01$), having many friends who vaped (OR = 2.15, 1.37–3.34, $p < 0.001$), age below 18 compared to age over 22 (OR = 5.26, 2.63–10.00, $p < 0.001$) and male sex (OR = 1.69, 1.16–2.50, $p < 0.01$) were significant and the most influential predictors of future pod use.

Conclusion: Similar factors drove pod use among Canadian and US youth and young adults. Appropriate preventive strategies can benefit from considering polysubstance use among high school–aged youth.

Keywords: *vaping, nicotine, electronic nicotine delivery systems, risk factors, Canada, young adult, adolescent, cannabis*

Highlights

- Cannabis use, cigarette smoking or past experimentation, male sex, age below 18 and having friends who vape all significantly increased the likelihood that a Canadian youth or young adult in our sample was to use pod-type nicotine e-cigarettes such as JUUL after the products legally entered the Canadian market in mid-2018.
- These factors have also been identified either as predictors of future pod use or characteristics of current pod users in various US studies.

Introduction

In May 2018, the *Tobacco and Vaping Products Act* allowed nicotine-based e-cigarettes legal entry into the Canadian market without requiring premarket approval.[1] Market liberalization was accompanied by increased exposure to e-cigarette promotion among Canadian youth between 2017 and 2019.[2] It also coincided with the beginning of sharp increases in the prevalence and frequency of e-cigarette use: in 2019, the proportion of a national sample of Canadian youth aged 16 to 19 who indicated vaping for 20 days or more in the past month was more than three times the proportion in 2017.[3] The proportion of Canadians aged 15 to 19, 20 to 24 and 25 and up indicating they vaped in the past month remained roughly constant between 2019 and 2020.[4,5]

With its lightweight and ultraportable design, the latest-generation e-cigarette device, namely the pod-type e-cigarette ("pod"), is engineered for convenient use.[6] A combined free-nicotine and nicotine salt–based formulation helps increase efficiency of nicotine delivery by reducing its harsh impact on the upper respiratory system, potentially enabling repeated and increased nicotine intake and facilitating dependence.[7,8] The most well-known pod brand, JUUL, accounted for nearly 80% of the retail e-cigarette market in the United States by the end of 2018.[9] In a nationally representative longitudinal sample of US youth and young adults, JUUL use and more frequent e-cigarette use both increased significantly between 2018 and 2019.[10] Similar findings resulted from repeat national samples of Canadian adolescents, wherein 17.7% of past-30-day e-cigarette users indicated using JUUL in 2019, compared to 10.3% in 2018.[7]

Upward trends in frequency of vaping add to the severity of the risks e-cigarettes

Author reference:

Ontario Tobacco Research Unit, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada

Correspondence: Safa Ahmad, Ontario Tobacco Research Unit, Dalla Lana School of Public Health, 155 College St., Toronto, ON M5T 3M7; Tel: 647-208-6100; Email: safa.ahmad@mail.utoronto.ca

pose to youth and young adults. Daily use of psychoactive or rewarding substances and use on a high proportion of days are associated with dependence, decreased probability of quitting and increased risk of any adverse health effect due to dose. These links are well demonstrated for cigarette smoking[11,12] and increasingly demonstrated with e-cigarettes.[13]

Understanding predictors of initiation of pod use can help identify groups of youth at high risk of frequent exposure to nicotine via e-cigarettes. Previous studies of the correlates of JUUL use among US youth and subpopulations have identified cigarette use,[10,14,15] lower harm perception,[14,16] sensation seeking,[10,14] peers' and household members' use,[10,14,17] flavour appeal,[17] higher socioeconomic status,[14,15,18] younger age,[14,15] male sex[15] and White ethnic background.[14,18] However, cross-sectional studies cannot assess the temporality of risk factor and outcome association where it is relevant and make it difficult to identify risk factors of future use.[19]

Peer tobacco use and cannabis use have been identified as predictors of JUUL and other e-cigarette initiation in a 2017/18 cohort of Texas adolescents.[20] Exposure to advertisements, cigarette use and lower perception of harm have been identified as predictors of future JUUL use in a 2018 cohort of young adults enrolled in colleges in North Carolina and Virginia.[21]

The Youth and Young Adult Panel Study collected data from Canadian youth and young adult e-cigarette users and nonusers in March 2018 and again in a follow-up survey in March 2019. The legislative changes occurred in May 2018, during the period between the administration of the baseline and follow-up surveys.[1] This timing provided us a unique opportunity to identify risk factors of pod use in a population that was relatively naïve to pod-type e-cigarettes, and to compare them with findings about high-risk population groups in the US.

Methods

Setting and participants

The Youth and Young Adult Panel was a longitudinal study aiming to track patterns of e-cigarette use among Canadian residents aged 16 to 25 years during an 18-month period, and has been described elsewhere.[22] Most participants were recruited using social media, including Instagram, Reddit and Google Ads, while 4% were recruited from a recontact list obtained from Leave the Pack Behind, a provincially funded program offering cessation support and services.

Data were collected using purposive sampling to ensure 60%/40% distribution of regular and irregular/never e-cigarette users and an adequate sample of hard-to-reach youth and young adult age ranges. To ensure this quota criterion was met, the following question was asked during screening: "In the past 4 weeks, did you vape e-cigarettes every week?" Those who responded "Yes" were considered part of the regular quota while those who responded "No" were considered part of the irregular quota. Multilingual participants were eligible if they could complete the online survey in English.

The panel enrolled 1048 participants at baseline, of which 578 were regular e-cigarette users. Of the baseline participants, 18 unsubscribed and 65% (668/1030) of the remaining participants responded to the 12-month survey. All eligible participants received a $10 e-gift card honorarium and a chance to win one of two $250 gift cards.

Variables

Outcome measures

Respondents to the 12-month follow-up survey were asked if they had "used a pod system or pod vape that uses pods or cartridges and may look like a flash drive (e.g. JUUL, myblu, Vype, Logic, Breeze 2, etc.)" in the last six months. Given the dates of introduction of these devices, pod or cartridge device use at follow-up reflected use of these devices after their legal and widespread introduction to the market in the context of the study.

Potential predictors of pod use considered

Baseline predictors examined were: reported importance of the intention to quit or to reduce smoking in the decision to vape; reported importance of flavours in the decision to vape; sensation seeking; perception of risk of vaping regularly with nicotine; cannabis use in the past month; frequency of e-cigarette use; smoking status; proportion of friends who vape; past-month exposure to billboard, gas station or outdoor vaping advertisement; past-month exposure to TV, radio or online vaping advertisement; age group; sex; and province or territory of residence.

Sensation seeking was assessed by asking participants whether they agreed or disagreed with the statement, "I like new and exciting experiences, even if I have to break the rules." Responses were divided in two categories for analysis (Strongly agree/Somewhat agree, Strongly disagree/Somewhat disagree/Neither). Participants' responses about perception of risk of regularly vaping with nicotine were divided into two categories (Great risk/Moderate risk, No risk/Slight risk/Unknown risk). Smoking status was divided into five categories. Current smokers were self-reported current smokers and had smoked at least 100 cigarettes during their lifetime, while current experimenters were smokers who had smoked fewer than 100 cigarettes. Past experimenters and former smokers were nonsmokers who had smoked fewer or more than 100 cigarettes, respectively, in the past. Never smokers had never tried cigarettes.

Responses to "How often do you vape?" were divided into three categories (Daily/Almost daily, At least weekly/At least monthly, Less than monthly/Never). Responses to "proportion of friends who vape" were divided into two categories (None/Some, Many).

Age was categorized for analysis into three categories based on typical age brackets for high school–aged, postsecondary-aged and older individuals (15–17, 18–21, 22–26). Provinces and territories of residence were categorized into three separate provinces (Ontario, Alberta, British Columbia) while a fourth category included the remaining provinces and territories (Other).

Analysis

We fitted a predictive multivariable model to identify the most influential predictors of future pod use among participants in our sample. Steps were guided by Harrell's generic predictive model-building strategy.[23] We considered all a priori predictors, obtained standard effect size estimates for the predictor variables and validated the rank position of influence of each predictor.

The response indicating frequency of vaping was missing in 21% (140/668) of observations, proportion of friends who

vape was missing in 13%, smoking status in 7%, sensation seeking in 2% and risk perception in 1%. We used multiple imputation to obtain less biased and valid estimates despite missing predictor data.[24] We did this by applying the semiparametric predictive mean matching approach and bootstrapping to create a set of imputations as described by Harrell.[25,26] We used all the variables in the final model to create 23 imputations, given that 22.8% (152/668) of observations had one or more missing values.[25] Five logistic regression models were created using completed datasets and all five sets of coefficients averaged to produce effect estimates.[25]

Age was treated as a categorical variable due to interest in nonarbitrary cutoff points that divided participants into typically high school–aged, postsecondary-aged and older individuals with narrow age ranges within categories. The number of predictors included was maintained below $m/15$ where m = min ($N_{outcome=1}$, $N_{outcome=0}$).[23] Variance inflation factors were used to assess multicollinearity. Predictor influence was ranked based on the difference between Wald chi-square values and predictor degrees of freedom (df). The ranking process was bootstrapped to obtain 95% confidence intervals (CIs) containing the true rank measure.[27] Model validation was performed with 1000 bootstrap resamples with replacement to assess overfitting.[28]

The magnitudes of association between predictors remaining in the model and the likelihood of participants using a pod within six months before filling out the follow-up survey were reported as odds ratios (ORs) with 95% CIs. All analyses were conducted in R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Sample characteristics

Table 1 presents the demographic characteristics of the sample, baseline measures of vaping and other substance use characteristics, and remaining potential predictive factors considered in the analysis. Of the 668 respondents who provided baseline and 12-month survey data, 59.3% (396/668) indicated that they used a pod at some point within six months before responding to the follow-up survey. The composition of sex (χ^2 = 9.42, p < 0.01,

TABLE 1
Participant characteristics of 2018-19 Youth and Young Adult Panel Study participants

Variable	Incomplete respondents (N = 380) (%)[a]	Complete respondents (N = 668) (%)[a]
Pod use within 6 months before follow-up		
No	—	272 (41)
Yes	—	396 (59)
Baseline sociodemographic characteristics		
Sex		
Male	281 (74)	417 (62)
Female	99 (26)	251 (38)
Province/territory		
Ontario	171 (45)	335 (50)
Alberta	63 (17)	115 (17)
British Columbia	67 (18)	111 (17)
Other[b]	79 (21)	107 (16)
Age group		
15–17	161 (42)	286 (43)
18–21	186 (49)	289 (43)
22–26	33 (9)	93 (14)
Baseline substance use		
Smoking status		
Current smoker	62 (16)	90 (13)
Current experimenter	36 (9)	42 (6)
Former smoker	42 (11)	72 (11)
Past experimenter	68 (18)	104 (16)
Never smoker	171 (45)	353 (53)
Missing	1 (0.3)	7 (1)
Past-month cannabis use		
No	204 (54)	452 (68)
Yes	176 (46)	216 (32)
Vaping frequency		
Daily or almost daily	162 (43)	244 (37)
Weekly or monthly	120 (32)	165 (25)
Less than monthly or never	59 (16)	119 (18)
Missing	39 (10)	140 (21)
Other baseline vaping-related characteristics		
Importance to decision to vape Flavours		
No	191 (50)	357 (53)
Yes	189 (50)	311 (47)
Attempt to quit/reduce smoking		
No	294 (77)	554 (83)
Yes	86 (23)	114 (17)

Continued on the following page

TABLE 1 (continued)
Participant characteristics of 2018-19 Youth and Young Adult Panel Study participants

Variable	Incomplete respondents (N = 380) (%)[a]	Complete respondents (N = 668) (%)[a]
Perceived risk of regular vaping with nicotine		
Moderate risk/great risk	223 (59)	438 (66)
No risk/slight risk/do not know	156 (41)	229 (34)
Missing	1 (0.3)	1 (0.1)
Baseline psychosocial/environmental factors		
Proportion of friends who vape		
None/some	180 (47)	414 (62)
Many	196 (52)	241 (36)
Missing	4 (1)	13 (2)
Past-month outdoor exposure to advertisements		
No	175 (46)	273 (41)
Yes	205 (54)	395 (59)
Past-month media exposure to advertisements		
No	185 (49)	293 (44)
Yes	195 (51)	375 (56)
Like new and exciting experiences, even if have to break rules		
Strongly agree/somewhat agree	249 (66)	417 (62)
Do not agree/strongly disagree/ somewhat disagree	129 (34)	249 (37)
Missing	2 (0.5)	2 (0.3)

Notes: Similar predictors have been grouped for easier understanding. In total, 668 youth and young adults responded to both the baseline survey and the 12-month survey, while 380 youth and young adults responded only to the baseline survey.

[a] Percentages may not total 100, due to rounding.

[b] This category includes all remaining provinces and territories, including 5.8% of 668 follow-up respondents from the Atlantic provinces, 4.2% from Saskatchewan, 3.0% from Quebec, 2.7% from Manitoba and 0.3% from Yukon.

df = 1), past-month cannabis use ($\chi 2$ = 14.07, $p < 0.001$, df = 1) and proportion of participants' friends who vaped (χ^2 = 12.83, $p < 0.001$, df = 1) differed significantly among the 668 follow-up respondents compared to the total 1048 respondents at baseline.

Full model

Table 2 presents results from the multivariable logistic regression model fit to predict likelihood of using a pod between 6 and 12 months after filling out the baseline survey. All variance inflation factors were below 10 and did not indicate multicollinearity. With a concordance statistic of 0.81 and, after correcting for overfitting, 0.79, the model's predictive discrimination suggests some utility in predicting individual subject responses[27] and only a small degree of overfitting (corrected C-index 95% CI: 0.76–0.83).

Respondents who, in the baseline survey, indicated using cannabis in the past month had significantly greater odds of using a pod in the future than those who did not; those who indicated vaping daily or almost daily had significantly greater odds of using a pod in the future than those who indicated not vaping or vaping less than monthly; those who indicated that "many" of their friends vaped had greater odds than those who indicated "none" or "some" of their friends vaped; those who agreed they liked new experiences even if they had to break the rules had greater odds than those who did not. Typically postsecondary-aged and older participants both had lower odds of using a pod in the future compared with those under 18.

Male sex predicted significantly greater odds of future pod use. Current established smokers and past experimenters each had greater odds of using a pod in the future than respondents who had never smoked.

In order, the most important baseline predictors in the top five highest ranks, where 1 is the most important predictor, are age group, smoking status, past-month cannabis use, proportion of friends who vaped and male sex (Figure 1). The 95% CIs of the ranks of smoking status and age group do not overlap with the CIs of the rank of outdoor advertisement exposure nor of the rank of vaping to quit or reduce smoking. The 95% CIs of all five important predictors overlap with all remaining predictors (Figure 1).

Discussion

We found cannabis use, peer influence on vaping, age, sex and smoking status to be among the more important predictors of future pod use among the respondents in our sample. This is in line with previous research on correlates of pod use, which included male sex, co-use of cigarettes, younger age and peers' use, and previous research on predictors of future pod use, including co-use of cigarettes, peers' use, and cannabis use.

Although this study did not assess the prevalence of polysubstance use in its panel of participants, it is important to note that the prevalence of the phenomenon has been increasing among Canadian youth. The proportion of substance-using students indicating use of multiple substances rose from 40% in 2013 to over 50% between 2017 and 2018.[29] E-cigarette use drove much of this increase between 2017 and 2018,[29] and, in a sample of over 74 000 Canadian high school students, e-cigarettes were the substance most often combined with others.[30] These results are significant, considering evidence linking polysubstance use among adolescents with a myriad of poor health and education outcomes,[30] and in the aftermath of cannabis legalization for Canadian adults in 2018.[31]

Cannabis was legalized during the study period, and this may have affected the association between cannabis use and future pod use. However, studies in various legal environments across multiple Western countries have found an association between cannabis and e-cigarette use.[32] Although many of these longitudinal studies have found an association in the opposite direction, with e-cigarette use predicting future cannabis use, bidirectional effects have also been found in a US college sample.[33]

TABLE 2
Full multivariable logistic regression model predicting pod-type e-cigarette device use, 2018-19 Youth and Young Adult Panel Study

Predictors	Odds ratio (95% CI)	*p*-value
Intercept	**0.75 (0.55–1.02)**	**0.3782**
Age group (years)		
15–17	1.00 (ref)	—
18–21	0.63 (0.41–0.98)*	0.0391
22–26	0.19 (0.10–0.38)***	< 0.0001
Sex		
Male	1.00 (ref)	—
Female	0.59 (0.40–0.86)**	0.0061
Province/territory		
Ontario	1.00 (ref)	—
Alberta	1.42 (0.85–2.39)	0.1813
British Columbia	0.86 (0.51–1.45)	0.5833
Others[a]	0.85 (0.50–1.46)	0.5633
Vaping-related characteristics		
Importance to vaping of flavours		
No	1.00 (ref)	—
Yes	1.38 (0.90–2.10)	0.1407
Importance to vaping of attempt to quit/reduce smoking		
No	1.00 (ref)	—
Yes	1.05 (0.52–2.09)	0.8969
Regular nicotine vaping risk perception		
No risk/slight risk/do not know	1.00 (ref)	—
Moderate risk/great risk	0.80 (0.51–1.24)	0.3114
Vaping frequency at baseline		
Less than monthly or never	1.00 (ref)	—
Weekly or monthly	1.47 (0.83–2.60)	0.1823
Daily or almost daily	2.25 (1.14–4.44)*	0.0189
Polysubstance use		
Past-month cannabis use		
No	1.00 (ref)	—
Yes	2.66 (1.66–4.21)***	< 0.0001
Smoking status		
Never smoker	1.00 (ref)	—
Current experimenter	2.20 (0.86–5.57)	0.0983
Former smoker	0.83 (0.37–1.86)	0.6479
Past experimenter	2.40 (1.34–4.31)**	0.0034
Current smoker	3.42 (1.53–7.65)**	0.0027
Psychosocial and environmental factors		
Past-month outdoor exposure to advertisements		
No	1.00 (ref)	—
Yes	1.35 (0.88–2.00)	0.1706

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Our results are also significant because they favour a holistic approach to substance use problems among youth over singling out a particular substance for control and prevention efforts. Preventive approaches involving school support and good quality parental connection have been implicated in the literature as worthwhile interventions for polysubstance use.[30] High school–aged youth had greater odds of pod use than older individuals, revealing the appeal of these devices in this demographic.[7] Consistent with previous US findings,[20] we found that peer use also predicted future pod use, underscoring the need for substance use interventions that target communities, such as those found in schools.

We found that current, established smokers and past experimenters were more likely to initiate pod use once they appeared prominently in the market than those who had never smoked. Whether or not respondents were attempting to quit or reduce smoking was a significantly less influential predictor, supporting research that found that pods appealed significantly to Canadian youth, who are not likely to be trying to quit smoking.[3,7]

A previous longitudinal cohort study discovered a 655% growth in prevalence of dual cigarette and e-cigarette users in a sample of Alberta and Ontario secondary school students.[34] This result is important, considering the greater risk of higher frequency cigarette and e-cigarette use among dual users compared to exclusive e-cigarette or cigarette users, and adds to concerns about nicotine dependence among youth.[34] The finding is also important because dual cigarette and e-cigarette users in another sample of Canadian secondary students were more likely to use cannabis, alcohol and other drugs with greater frequency,[35] adding to earlier concerns about potential polysubstance use.[30]

Contrary to other research findings, however, future pod use was not predicted by low or unknown perceived risk of nicotine vaping,[14,16] nor by exposure to advertisements.[2,21] The latter may be because respondents' exposure to marketing was assessed in the baseline survey three months before nicotine e-cigarette marketing regulations were relaxed by a change in the *Tobacco and Vaping Products Act*.[1,2] Indeed, though our study did not find an effect of advertising exposure, prior findings about the likely effect of e-cigarette

TABLE 2 (continued)
Full multivariable logistic regression model predicting pod-type e-cigarette device use, 2018-19 Youth and Young Adult Panel Study

Predictors	Odds ratio (95% CI)	*p*-value
Past-month media exposure to advertisements		
No	1.00 (ref)	—
Yes	0.93 (0.61–1.43)	0.7319
Proportion of friends who vape		
None/some	1.00 (ref)	—
Many	2.15 (1.37–3.34)***	0.0009
Sensation seeking (like new and exciting experiences, even if have to break rules)		
Do not agree/strongly disagree/somewhat disagree	1.00 (ref)	—
Strongly agree/somewhat agree	1.47 (1.00–2.17)	0.0527

Abbreviation: CI, confidence interval.

Note: Model based on the 668 participants who responded to both the baseline survey and the 12-month survey.

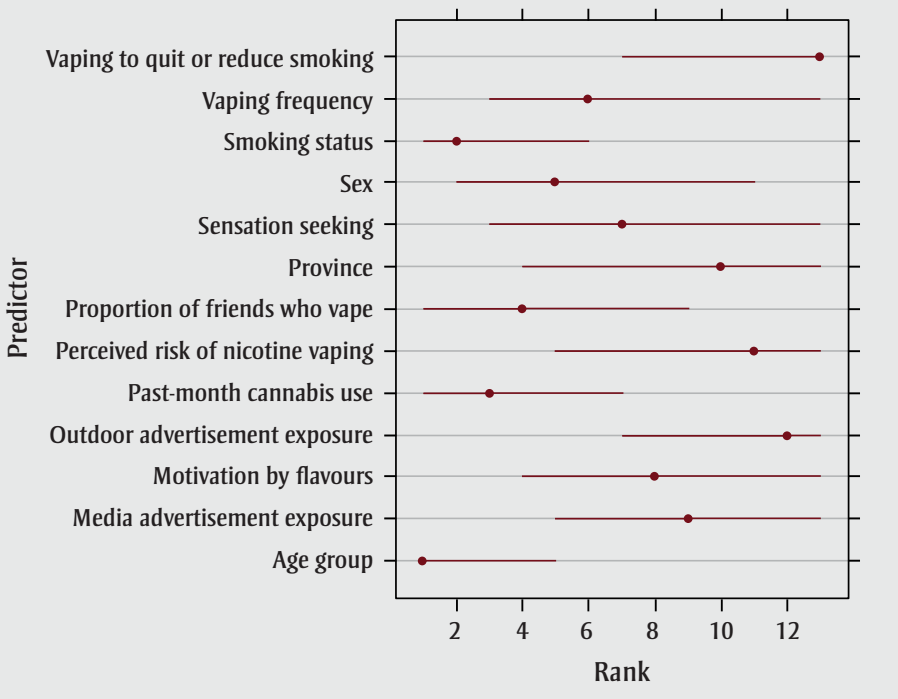
[a] This category includes all remaining provinces and territories, including 5.8% of 668 follow-up respondents from the Atlantic provinces, 4.2% from Saskatchewan, 3.0% from Quebec, 2.7% from Manitoba and 0.3% from Yukon.

*$p \leq 0.05$

**$p \leq 0.01$

***$p \leq 0.001$

FIGURE 1
Rank measures[a] and associated bootstrapped 95% rank CIs for model predictors of pod use, 2018-19 Youth and Young Adult Panel Study



Abbreviation: CI, confidence interval.

Note: Model based on the 668 participants who responded to both the baseline survey and the 12-month survey.

[a] Rank measures are calculated based on the difference between the Wald chi-square statistic and predictor degrees of freedom. They are shown in descending order, with 1 being the highest rank and 13 the lowest.

marketing on prevalence of e-cigarette use among Canadian youth were credible enough to have resulted in a federal ban on promotion that may be viewed by youth as of July 2020.[2,36]

Numerous other bans have been put into effect in various provinces, including bans on flavours,[37,38] retail sales other than in specialty vape stores,[39,40] liquids with nicotine concentrations exceeding 20 mg/mL[37,40] and point-of-sale advertising. Other regulatory changes include higher taxes,[41-43] higher minimum sales age,[44] and packaging restrictions.[40] It is expected that these changes contributed to plateauing national rates of e-cigarette use in 2020[4] and will likely continue to have an impact in the future. However, there is significant variation in provincial regulation, with only some changes implemented in each jurisdiction, making it important for public health to continue health promotion efforts to curb use among youth.

Strengths and limitations

Our panel study and its timing allowed us to draw more robust conclusions about differences in youth who did and did not choose to use pods after changes in federal legislation. Our study drew from a large sample of Canadian youth and young adults from across Canada and from comprehensive surveys that allowed multiple potential risk factors to be studied. These surveys addressed various psychosocial, motivational and substance use–related risk factors, and, unlike most large, population-based surveys, were engineered specifically to study e-cigarette use.

Limitations included the use of a sample of youth and young adults that was not representative of the national population, limiting generalization of results across the country. Over 35% of baseline survey respondents did not respond to the 12-month survey, possibly introducing selection bias and further limiting generalization beyond our sample. Obtaining participants from a smoking cessation service recontact list might have resulted in oversampling from the subgroup of youth who are current or former smokers and could potentially have introduced bias. However, only 4% of all respondents at baseline were recruited using this list.

Conclusion

Like previous studies, ours supports the assertion that pod-type e-cigarette devices

with high nicotine concentration are popular among adolescents who have used cannabis and who are not primarily attempting to quit or reduce cigarette use. Our findings support previous recommendations that prevention efforts be targeted at communities, especially schools, and at polysubstance and cannabis use among youth and young adults. Because our findings parallel those in some US populations, public health in other jurisdictions may benefit from these considerations, especially those where youth polysubstance or cannabis use is significant, and where high-nicotine e-cigarettes are either currently legal or will soon enter the marketplace.

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Conflicts of interest

None to be declared.

Authors' contributions, declaration and statement

SA and SB conceptualized the study. SA and TW conducted formal analysis with software and wrote the original draft. SB provided supervision and resources and was involved with project administration, software, and writing, review and editing. RS provided supervision and was involved in funding acquisition, investigation and with review and editing.

All relevant ethical guidelines have been followed, and any necessary IRB and/or ethics committee approvals have been obtained. Ethics approval was obtained from the University of Toronto Research Ethics Board; RIS Human Protocol Number 34887.

The content and views expressed in this article are those of the authors and do not necessarily reflect those of the Government of Canada.

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Original quantitative research

A machine learning approach to predict e-cigarette use and dependence among Ontario youth

Jiamin Shi, MPH (1,2); Rui Fu, MSc (2,3); Hayley Hamilton, PhD (1,2); Michael Chaiton, PhD (1,2)

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Abstract

Introduction: We developed separate random forest algorithms to predict e-cigarette (vaping) ever use and daily use among Ontario youth, and subsequently examined predictor importance and statistical interaction.

Methods: This cross-sectional study used a representative sample of Ontario elementary and high school students in 2019 (N = 6471). Vaping frequency over the last 12 months was used to define ever-vaping and daily vaping. We considered a large set of individual characteristics as potential correlates for ever-vaping (176 variables) and daily vaping (179 variables). Using cross-validation, we developed random forest algorithms and evaluated model performance based on the C-index, a measure to assess the discriminatory ability of a model, for both outcomes. Further, the top 10 correlates were identified by relative importance score calculation and their interaction with sociodemographic characteristics.

Results: There were 2064 (31.9%) ever-vapers, and 490 (7.6%) of the respondents were daily users. The random forest algorithms for both outcomes achieved high performance, with C-index over 0.90. The top 10 correlates of daily vaping included use of caffeine, cannabis and tobacco, source and type of e-cigarette and absence in last 20 school days. Those of ever-vaping included school size, use of alcohol, cannabis and tobacco; 9 of the top 10 ever-vaping correlates demonstrated interactions with ethnicity.

Conclusion: Machine learning is a promising methodology for identifying the risks of ever-vaping and daily vaping. Furthermore, it enables the identification of important correlates and the assessment of complex intersections, which may inform future longitudinal studies to customize public health policies for targeted population subgroups.

Keywords: *machine learning, vaping, smoking, Ontario, youth*

Highlights

- This study applied a machine learning methodology that allowed the inclusion of a wide range of correlates in tobacco research among youth.
- The top 10 correlates of daily vaping included use of caffeine, cannabis and tobacco, source and type of e-cigarette and absence in last 20 school days. Those of ever-vaping included school size, and use of alcohol, cannabis and tobacco.
- Future longitudinal studies could verify the most important correlates of ever-vaping and daily vaping identified, potentially informing policies to prioritize strategies for issues related to substance use.
- Analysis of interactions quantified interaction strengths amongst important correlates and sociodemographic characteristics, which could be further explored by future longitudinal studies.

Introduction

Research has shown that the prevalence of vaping nicotine increased rapidly among North American youth aged 16 to 19 years from 2017 to 2018.[1] In particular, the ever-vaping percentage increased from 29.3% to 37.0%, and the percentage of vaping in the past 30 days increased from 8.4% to 14.6% among youth in Canada. Youth are also increasingly reporting symptoms of vaping dependence, defined as "the constellation of behaviors and symptoms that are distressing to the user and promote the compulsive use of vaping due to nicotine and non-nicotine factors."[2,p.257] A prospective cohort study suggests that vaping dependence is potentially related to future tobacco use persistence and escalation among Grade 12 students in the US.[3] As of 2020, approximately 3000 hospitalizations and deaths reported by the US Centers for Disease Control and Prevention (CDC) were linked to use of vaping products.[4]

Previous studies of vaping dependence, including those that used validated scales such as the PROMIS-E and the Penn State Electronic Cigarette Dependence Index, have attributed the rise of vaping dependence symptoms to older age, longer duration of use, greater vaping frequency, higher nicotine concentrations and current cigarette smoking.[5,6] However, these

Author references:

1. Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada
2. Institute for Mental Health Policy Research, Centre for Addiction and Mental Health, Toronto, Ontario, Canada
3. Institute of Health Policy, Management and Evaluation, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada

Correspondence: Michael Chaiton, Institute for Population Mental Health Research, Centre for Addiction and Mental Health, Toronto, ON M5T 1R8; Tel: 416-535-8501; Email: Michael.Chaiton@camh.ca

studies have limitations associated with traditional statistical regressions. The use of *p*-values to select features for model building based on statistical significance may limit insight into predictors not selected. Moreover, as vaping dependence may correlate with a wide variety of characteristics, it can be challenging for a regression model to completely capture these complex relationships. This complexity can further limit study findings with statistical issues such as multicollinearity and overfitting.

To address the aforementioned limitations, we applied a machine learning approach in this study. Machine learning—defined as "a group of data-driven analytical methods that rely on computational power to perform statistical tasks"[7,p.1317]—is an emerging technique found in health research.[8-11] Compared to conventional statistical methods, machine learning may prove better able to make accurate predictions, with proper guidelines to mitigate risks of overfitting.[12] We use the machine learning definition of "predictor" throughout this paper to refer to a prediction model; it does not necessarily imply a temporal or causal relationship.

This methodology focusses on the variables that are most "important" to prediction in terms of improving the performance of the model area under the curve (AUC) of the receiver operating curve (ROC), rather than relying on estimates of variance and *p*-value hypothesis testing. Although there are studies that have applied machine learning methods such as classification trees[13] and random forest[14] in tobacco research, a recent scoping review suggested that these applications are rarely linked to public health impacts.[15]

Thus, the aim of our study was to investigate further ever-vaping and daily vaping (as a proxy for vaping dependence) among the youth population, using machine learning methods with interpretable findings. In particular, our objectives were to develop machine learning algorithms that predict both ever-vaping and daily vaping among Ontario youth, and to perform post hoc analysis including ranking the importance of individual risk factors on both outcomes and illustrating statistical intersections to identify particularly susceptible youth subgroups.

Methods

Data and participants

This study used data from the 2019 Ontario Student Drug Use and Health Survey (OSDUHS), which included responses from 14 142 students from 992 classes in 263 elementary or secondary schools from 47 Ontario school boards.[16] The OSDUHS had a complex survey sampling design—schools were clustered within the 26 geographical strata. There were four different questionnaire types in total. We obtained a total of 6471 respondents after including only the survey types that contained the question "In the last 12 months, how often did you smoke e-cigarettes?" and excluding students who did not respond to this question. The sample used to examine daily vaping was limited to ever-vapers, including a total of 2064 respondents.

Measures

Outcome

We created binary outcome variables to represent daily vaping and ever-vaping using the same survey question. Participants who reported never having used an e-cigarette in their lifetime were "never-vapers," while others were "ever-vapers." Participants who vaped at least daily were classified as vaping dependent. Those who did not meet this criterion were considered to be participants without daily vaping.

Potential determinants

We regarded 179 and 176 variables capturing person-level characteristics as potentially predicting daily vaping and ever-vaping, respectively[16] (see the Appendix at https://osf.io/x36p8/ for full list of variables.) These variables described administrative information, demographics, school life, family life, physical health, mental health, driving behaviours, experience of having been a passenger with an intoxicated driver, vaping behaviours, substance use, perceptions and exposures, sociodemographic characteristics and other risk behaviours of substance use. We excluded any variables that were conditional on either daily vaping or ever-vaping based on survey design (i.e. questions that were conditional on having ever vaped were not included as predictors of ever-vaping). We collapsed levels of several variables to facilitate subsequent analysis. Numeric variables were scaled using z-score normalization prior to model building.

Analysis

Descriptive statistics and imputation of missing values

We summarized demographic characteristics of the respondents and prevalence of ever-vaping and daily vaping. Over 90% of the variables had missingness lower than 5% or between 5% and 10%. A variable describing different types of special education had 10% missingness. Categorical variables were either collapsed with their reference levels or available options representing uncertainty of how to respond. We imputed the missing value as the median for all numeric variables.

Random forest algorithm

Using the R version 3.6.3 package "caret,"[17] we developed a random forest algorithm—an ensemble machine learning algorithm formed by a large number of classification trees—to classify respondents of primary outcomes.[18] For instance, in the algorithm of daily vaping, each tree classified respondents either as being daily vapers or as not being daily vapers. When all the class predictions from trees were summed, the class with the majority of votes became the prediction of the random forest. This "wisdom of the crowd" approach had the potential to make the random forest a highly accurate and robust algorithm for prediction.[19]

Development and validation of a random forest for daily vaping and ever-vaping

We included all the candidate predictors to train the model, excluding variables that were conditional on the outcome (i.e. we excluded questions for ever-vaping that were only asked to students who vaped). Using a ratio of 7:3, we randomly split the dataset into a training set (n = 1612 or 4680) and a test set (n = 691 or 2006) for the sample to classify daily vaping and ever-vaping. Both ever-vaping and daily vaping were imbalanced. To facilitate model training efficiency, we performed a Synthetic Minority Oversampling Technique (SMOTE) procedure on the training data to reach two balanced samples for model training.[20] In a 10-fold cross-validation procedure during model training, the dataset was randomly partitioned into 10 equally sized subsamples. At each iteration, nine subsamples were used to train the model, while the one subsample retained was used to validate

the model. The above procedure was repeated 10 times. To evaluate model performance, we reported accuracy, sensitivity, specificity and AUC regarding the classification of daily vaping and ever-vaping on the test set. We considered the average performance of the 10 iterations as overall performance of the model. AUC exceeding 0.80 represented good discriminatory ability, a common threshold for classification models.[21]

Ranking of individual risk factors of daily vaping and ever-vaping

To identify the top 10 correlates of daily vaping and ever-vaping, we ranked all of the correlates based on scaled relative importance scores (0–100)—a measure calculated from total loss of accuracy due to exclusion of a correlate for every tree divided by the total number of trees.[22,23] One-way partial dependence plots of the top 10 correlates were used to understand their marginal effects on the predicted risks of daily vaping and ever-vaping, while other correlates were kept constant.[24] A partial dependence plot of one correlate illustrated probabilities of outcomes, given different values of that correlate. The higher the probability, the greater the risk of outcome observed under the influence of that correlate. These methods were applied to sociodemographic characteristics as well.

Exploration of interactions

We examined two-way interactions of the top 10 correlates identified and sociodemographic correlates that can robustly predict inequities of smoking-related outcomes.[25] Further, we explored the interaction effects of the following pairs of sociodemographic characteristics—age and sex, age and ethnicity, age and socioeconomic status (SES), sex and ethnicity, sex and SES, ethnicity and SES—using a simple feature importance ranking measure approach.[26] SES is subjectively determined by respondents based on their rating of their own SES on a ladder scaled from zero to 10.[27] Two-way partial dependence plots were used to illustrate daily vaping and ever-vaping risks on the proposed pairs with interaction strengths above a threshold of 0.1. The calculations of partial dependence probabilities were based on the variation of the two predictors, while holding other predictors constant.[28]

Sensitivity analysis

We conducted two sets of sensitivity analyses using the same oversampled training set for both outcomes. First, we fitted random forest algorithms with only the top 10 correlates identified. Second, we built base multivariate logistic regression models composed of age, sex, ethnicity and SES. Performance of these logistic models was assessed by accuracy, sensitivity, specificity and AUC on the test set and compared to these measures of the random forest.

Results

Sample characteristics

The 6471 respondents were divided into 10 age groups (0 to 11, individual years between ages 12 and 19, and 20+ years); 54.6% of them were females; the majority (68.6%) came from a family positioned from 6 to 8 on the SES ladder; and 62.1% of them were White (Table 1). There were 2064 (31.9%) ever-vapers and 490 (7.6% of the entire sample or 23.7% of ever-vapers) respondents who were daily vapers.

Performance of the random forest algorithms

The random forest algorithms for both outcomes achieved high performance. The algorithm for ever-vaping had a testing accuracy of 0.82 (95% confidence interval [CI]: 0.81–0.84), sensitivity of 0.83 (0.80–0.86), specificity of 0.82 (0.80–0.84) and an AUC of 0.90. The algorithm for daily vaping had a testing accuracy of 0.83 (0.80–0.86), sensitivity of 0.85 (0.77–0.90), specificity of 0.82 (0.78–0.86) and an AUC of 0.90.

Top 10 correlates of ever-vaping and daily vaping

The algorithms demonstrated different top 10 correlates for daily vaping and ever-vaping (Figure 1). The top 10 correlates for ever-vaping were: having used cannabis in lifetime; having drunk alcohol in past 12 months; source of cannabis; having used waterpipe in lifetime; having used tobacco in lifetime; school size; having used cannabis in past 12 months; the number of drinks containing alcohol when typically drinking; having had an energy drink with alcohol in last 12 months; and having been drunk. The top 10 correlates for daily vaping were: source of e-cigarette/tried a friend's; having smoked e-cigarettes with nicotine; having used cannabis in lifetime; source of cannabis; having smoked e-cigarettes without nicotine; having had a caffeine drink in the last 12 months; having had a caffeine drink in the last seven days; absence in the last 20 school days; source of e-cigarette/having bought e-cigarettes at a vape shop; and having used tobacco in lifetime. For both daily vaping and ever-vaping, all of the sociodemographic correlates showed minimal influence, with relative importance lower than three; thus, none of the corresponding partial dependence plots were reported.

Partial dependence on the top 10 predictors

According to partial dependence plots for ever-vaping, we found higher risks of ever-vaping among respondents who had used cannabis in the last 12 months or their lifetime, had drunk alcohol with or without high energy drinks in the last 12 months, had used tobacco or waterpipe in their lifetime, and had been drunk, compared to those who had not (see Appendix at https://osf.io/x36p8/). Across sources of cannabis, respondents who had ever used cannabis demonstrated a higher risk of ever-vaping than never-users. Respondents who had two to three drinks containing alcohol when they typically drank had approximately a 25% higher risk of ever-vaping than other alcohol and non-alcohol users. Risk of ever-vaping increased as school size increased in a range of up to 500 students, and remained high until the school size reached approximately 1850. There was a tiny decline in risk for schools with 1850 to 2000 students.

In regard to daily vaping, an increased risk of daily vaping was found among respondents who had used cannabis or tobacco in their lifetime or had drunk a caffeine drink in the last 12 months or seven days, compared with those who had not (see Appendix at https://osf.io/x36p8). Across sources of e-cigarette, there was a vast difference in the risk of being a daily vaper for respondents who borrowed an e-cigarette from a friend compared to those who purchased one in a retail environment. Across types of e-cigarettes, respondents who smoked e-cigarettes without nicotine had a 25% lower risk of being a daily vaper than those who did not. Never-users of cannabis showed a slightly lower risk of being a daily vaper than respondents who used cannabis across various sources. Any absence in

TABLE 1
Demographic characteristics of sample eligible respondents to OSDUHS 2019

	Overall (N = 6471)
Age (years)	
11 or younger	20 (0.3%)
12	727 (11.2%)
13	954 (14.7%)
14	1042 (16.1%)
15	1225 (18.9%)
16	1100 (17.0%)
17	981 (15.2%)
18	386 (6.0%)
19	27 (0.4%)
20 or older	9 (0.1%)
Sex	
Female	3535 (54.6%)
Male	2936 (45.4%)
Socioeconomic status[a]	
1	6 (0.1%)
2	40 (0.6%)
3	122 (1.9%)
4	280 (4.3%)
5	675 (10.4%)
6	1061 (16.4%)
7	1805 (27.9%)
8	1575 (24.3%)
9	657 (10.2%)
10	250 (3.9%)
Ethnicity	
White	4017 (62.1%)
Chinese	374 (5.8%)
South Asian	648 (10.0%)
Black	563 (8.7%)
Indigenous	157 (2.4%)
Filipino	368 (5.7%)
Latin American/Central American/South American	282 (4.4%)
Southeast Asian	125 (1.9%)
West Asian or Arab	344 (5.3%)
Korean	56 (0.9%)
Japanese	31 (0.5%)
Not sure about ethnicity	256 (4.0%)
Ever-vaping	
No	4407 (68.1%)
Yes	2064 (31.9%)
Daily vaping	
No	5981 (76.3%)
Yes	490 (23.7%)

Abbreviations: OSDUHS, Ontario Student Drug Use and Health Survey; SES, socioeconomic status.

[a] SES was subjectively determined by respondents based on their rating of their own SES on the MacArthur Scale of Subjective Social Status, a ladder scaled from zero to 10.

the last 20 school days was associated with an increased risk of daily vaping; while it is possible that daily vaping could have led to more school absence, our model was not designed to demonstrate such a relationship.

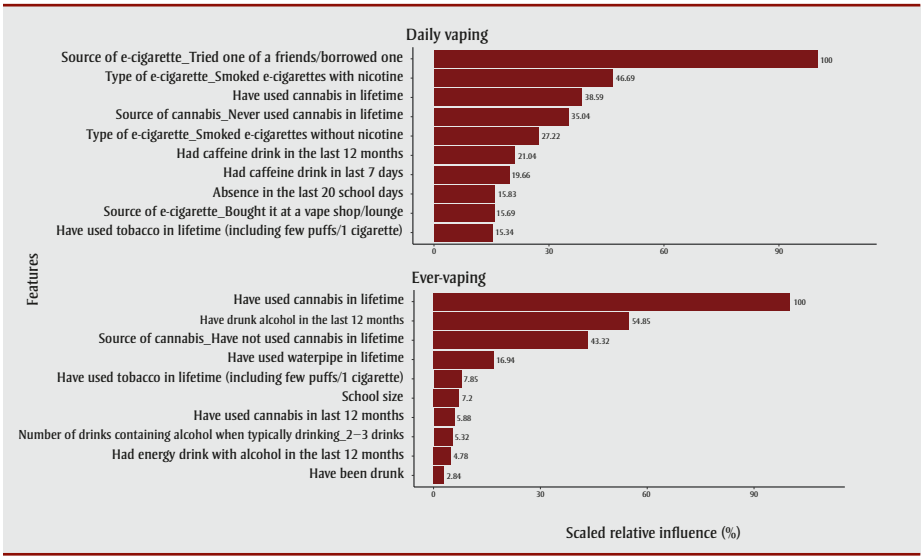
Interactions

All of the top 10 correlates for ever-vaping, except for having been drunk, demonstrated interactions with ethnicity (see Appendix at https://osf.io/x36p8). Having tobacco or cannabis in lifetime and having drunk alcohol in last 12 months showed interactions with ethnicity, SES and age. Japanese ethnicity demonstrated a higher probability of ever-vaping than non-Japanese ethnicity for all school sizes, while opposite relationships were found among those of Southeast Asians and Korean ethnicity. Across all sources of cannabis, being of non-Japanese ethnicity was associated with lower probabilities of ever-vaping than being of Japanese ethnicity. Regardless of ethnic group, having two to three drinks on a typical day had the highest probability of ever-vaping, compared to other sources of alcohol. While being of Japanese ethnicity was positively associated with the probability of ever-vaping, being of Southeast Asian or Korean ethnicity was inversely associated with ever-vaping. There were smaller differences in the probability of ever-vaping between those of Japanese compared to non-Japanese ethnicity for having had cannabis or alcohol and having had alcohol combined with energy drinks in last 12 months. This relationship was also found for having had tobacco or cannabis in lifetime. Across all the SES groups, being of Southeast Asian or Korean ethnicity was associated with a slightly lower probability of ever-vaping compared to being non-Southeast Asian or non-Korean.

Age interacted with past-year alcohol use, ever use of tobacco and ever use of cannabis; in these interactions, the use of a substance was a more important predictor among younger students compared to older students. Similarly, these variables were more important predictors among higher SES students compared to lower SES students.

Weak interaction was found between caffeine consumption and ethnicity for daily vaping (see the Appendix at https://osf.io/x36p8/). The interaction strength of

FIGURE 1
Scaled relative importance plots of the top 10 correlates of daily vaping and ever-vaping, OSDUHS 2019



Abbreviation: OSDUHS, Ontario Student Drug Use and Health Survey.

having had a caffeine drink in the last seven days and being uncertain of ethnicity was 0.111. Having had a caffeine drink in the last seven days was associated with a slightly higher probability of daily vaping, regardless of the uncertainty of ethnicity.

Sensitivity analysis

In line with the results of the primary analysis, high performance was found in parsimonious random forest algorithms with only the top 10 correlates. The parsimonious model of daily vaping had an accuracy of 0.81 (95% CI: 0.78–0.84), a sensitivity of 0.80 (0.72–0.86), a specificity of 0.82 (0.78–0.85) and an AUC of 0.87; the parsimonious model of ever-vaping had an accuracy of 0.78 (0.76–0.79), a sensitivity of 0.78 (0.74–0.81), a specificity of 0.78 (0.75–0.80), and an AUC of 0.86. By contrast, base logistic regressions of both outcomes had lower performance than the random forest models from the primary analysis. Specifically, the logit model of daily vaping had an accuracy of 0.53 (0.49–0.57), a sensitivity of 0.63 (0.54–0.71), a specificity of 0.50 (0.45–0.54) and an AUC of 0.60; the logit model of ever-vaping had an accuracy of 0.61 (0.59–0.64), a sensitivity of 0.82 (0.79–0.85), a specificity of 0.52 (0.49–0.55) and an AUC of 0.73.

Discussion

We applied a machine learning approach to investigate correlates of daily vaping and ever-vaping, using data from the OSDUHS conducted on a representative sample of Ontario youth attending elementary or secondary schools. The final random forest algorithms demonstrated high performance. The top 10 correlates for daily vaping differed from those for ever-vaping, as is consistent with various predictors found for cigarette onset and escalation in tobacco research.[29-31] While we found no interactions among pairs of predictors proposed for daily vaping, we did find interactions between predictors of ever-vaping, particularly by ethnicity.

Our study suggests the key correlates for ever-vaping and daily vaping were different. While a previous study concluded that social influences are the most powerful predictors for ever-vaping,[32] our study highlights the importance of three substances, namely cannabis, alcohol and tobacco, to risk of ever-vaping. These findings align with the emerging trend of cannabis vaping,[33] and indicate that nicotine, a highly addictive compound in tobacco, is the most common substance in vaping devices.[34] We also identified school size as an important sociodemographic correlate to the risk of ever-vaping.

Across sources of e-cigarette, since the lowest risk of daily vaping was found among respondents who tried an e-cigarette from a friend or borrowed one, social influences may play a limited role in the development of daily vaping. The use of nicotine-containing e-cigarettes was found to be associated with the highest risk of daily vaping—unsurprisingly, since addiction to vaping depends on nicotine.[35] Our results suggest that caffeine, cannabis and tobacco are important substances for increased risk of daily vaping. While the literature suggests school grade and age might be the strongest sociodemographic correlates of drug use,[36] our study shows increased number of absences in the last 20 school days might contribute more to increased risk of daily vaping.

Strengths and limitations

Methodologically, our study provides further evidence on the utility of machine learning in devising predictive modelling in tobacco control.[37] The high performance of random forests yields interpretable findings, such as identification of important features, that are potentially meaningful for policy makers. As research indicates that e-cigarette use in adolescence is associated with higher odds of smoking cigarettes,[38] features selected can identify important correlates, potentially preventing youth from proceeding to cigarette use. Days absent from school and school size, indicators not commonly found in the literature, were identified as important correlates of outcomes, because of the use of machine learning methods.

Furthermore, the high performance found in this study is in line with research that demonstrates that machine learning can outperform conventional statistical modelling on some occasions. For example, a systematic review reports that machine learning models have higher performance than logistic regression in neurosurgical outcome predictions.[39] Similarly, machine learning models exhibit higher C-indexes than clinical risk scores in prognostic performance among patients with acute gastrointestinal bleeding.[40]

Regarding limitations, as our study was cross-sectional, we were only able to identify the top 10 important correlates rather than the true predictors of daily vaping or ever-vaping. Despite the robustness of random forest algorithms,[41] the relative importance of correlates did not imply causality, and we did not conduct hypothesis testing in this analysis. Future longitudinal studies with a causal design and analysis would help address this limitation. More research is also required to validate the findings about interactions, since the ethnic groups reported had

relatively small sample sizes (n < 150). While our models demonstrated high performance with simple imputation of missing data, it would be worthwhile for future research to consider more sophisticated pipelines such as multiple imputation if precision of correlates is of major interest.[42]

Furthermore, current tools for developing random forest algorithms are unable to incorporate a cluster sampling. However, this limitation only affects the variance of the correlates, which was not the focus of this study. Finally, our analysis has limitations that are inherent to survey studies, such as potential recall bias and response bias. Nevertheless, we expect the results to remain robust, since we believe the OSDUHS survey has been structured with instruments that optimize response quality.

Conclusion

By training and testing random forest algorithms, we identified different sets of top 10 correlates for daily vaping and ever-vaping in a Canadian youth population. We found interactions among important correlates and sociodemographic characteristics for ever-vaping. Identification of correlates for daily vaping and ever-vaping for targeting purposes may inform future longitudinal studies to improve policies designed for subpopulations, irrespective of causality.

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Conflicts of interest

The authors have no conflicts of interest.

Authors' contributions and statement

JS, HH and MC conceptualized the manuscript. JS led the writing, statistical analysis and data interpretation, with the guidance of RF and MC. All authors provided feedback, edited drafts and approved the final version of the manuscript.

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Original quantitative research

A cost-utility analysis of the impact of electronic nicotine delivery systems on health care costs and outcomes in Canada

Catherine M. Pound, MD, MSc (1,2); Doug Coyle, PhD (2)

This article has been peer reviewed.

Abstract

Introduction: We determined the impact of electronic nicotine delivery systems (ENDS) on health outcomes and costs in Canada, based on their effect on smoking cessation and smoking initiation rates.

Methods: We used gender-specific Markov models to estimate lifetime discounted life years, quality-adjusted life years (QALYs) and smoking-related health care costs for cohorts of males and females aged 15 to 19 years, in scenarios in which (1) ENDS are available (status quo); (2) ENDS are completely unavailable; and (3) ENDS are available for smoking cessation through health care provider prescription, in addition to currently recognized smoking cessation tools. Analysis was from the perspective of a publicly funded health care system.

Results: Outcomes are expressed per 1000 individuals and based on expected values obtained through a Monte Carlo simulation of 10 000 replications. For males aged 15 to 19 years, life years, QALYs and smoking-related health care costs were 41 553, 35 871 and CAD 79 645 964, respectively, when ENDS were available; 41 568, 35 894 and CAD 79 645 960 when ENDS were unavailable; and 41 570, 35 897 and CAD 79 605 869 when ENDS were available through prescription only. For females, life years, QALYs and smoking-related health care costs were 43 596, 37 416 and CAD 69 242 856, respectively, when ENDS were available; 43 610, 37 438 and CAD 69 085 926 when ENDS were unavailable; and 43 611, 37 438 and CAD 69 076 034 when ENDS were available through prescription only. Thus, situations in which ENDS are unavailable, or available through prescription only are dominant over the status quo.

Conclusion: These results show that a policy change whereby ENDS were unavailable to the Canadian population or available through prescription only would likely increase population health and reduce health care costs.

Keywords: *tobacco products, smoking, smoking cessation, electronic nicotine delivery systems, vaping, cost-benefit analysis*

Highlights

- Vaping is commonly used by smokers to try to quit smoking.
- Vaping may increase smoking initiation in youth, resulting in negative long-term impacts on health.
- The results of this study show that, under our study assumptions, restricting access to vaping is likely to result in increased population health and reduced health care costs.
- Policy changes restricting access to vaping need to be examined with caution to avoid unintended consequences such as negative health impacts for current and former smokers who rely on vaping as a harm reduction strategy.

Introduction

Despite a considerable decrease in smoking prevalence over the last 50 years,[1] smoking continues to be the most common cause of preventable disease and mortality in Canada.[2] The costs of tobacco use in 2012 were CAD 16 billion, with the majority of indirect costs (CAD 9.5 billion) related to lost wages from long-term disability and premature mortality, and the largest portion of direct costs (CAD 6.5 billion) associated with health care costs.[2] Given the impact of smoking on the Canadian population, the Government of Canada has set a target to reduce smoking prevalence to below 5% by 2035.[3] Reaching that target requires a careful examination of smoking cessation strategies, as well as strategies preventing smoking initiation.

Vaping, the act of using electronic nicotine delivery systems (ENDS), is a common smoking cessation strategy. In Canada, almost one-third of current and former smokers report having vaped as a way to try to quit smoking.[4] There are, however, concerns that vaping could lead to increased cigarette smoking initiation in youth.[5,6] This association, though, has been debated, with some studies suggesting a negligible risk of youth vaping-related smoking initiation at the population level.[7,8] In Canada, 11% of youth aged under 25 years and 32% of teens aged 15 to 17 years who ever smoked daily used ENDS prior to

Author references:

1. Department of Pediatrics, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada
2. School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada

Correspondence: Catherine Pound, Division of Pediatric Medicine, Children's Hospital of Eastern Ontario, 401 Smyth Road, Ottawa, ON K1H 8L1; Tel: 613-737-7600, ext. 2701; Email: cpound@cheo.on.ca

initiating traditional cigarette smoking.[5] Also of concern is the rising prevalence of vaping over time. Between 2013 and 2019, the proportion of Canadian youth aged 15 to 19 years who endorsed vaping increased from 20% to 36%, while that of those aged 20 to 24 years jumped from 20% to 48%.[9,10]

While ENDS can have a positive effect on smoking cessation,[11,12] their impact on youth smoking initiation is concerning. In order to determine whether the benefits incurred from ENDS through smoking cessation alone are sufficient to offset the negative health consequences of increased smoking initiation, we conducted a cost-utility analysis to determine the impact of ENDS on life expectancy, quality-adjusted life years (QALYs) and smoking-related health care costs in Canada under three different scenarios: (1) the status quo, i.e. current access to ENDS; (2) a complete ban of ENDS; and (3) limited access to ENDS for smoking cessation only, as prescribed by a medical professional. Sales of nicotine-containing vaping products are currently permitted to adults aged 18 years and older in Canada,[13] although some provinces have a higher minimum age.

Methods

We used gender-specific Markov models to examine smoking behaviours of nonsmokers and current and former smokers in relation to ENDS, as well as the impact of ENDS on mortality and smoking-related illnesses in cohorts of males and females aged 15 to 19 years. We estimated life years, QALYs and smoking-related health care costs in three different scenarios: (1) the status quo, in which ENDS are widely available; (2) a complete ban on ENDS; and (3) limited access to ENDS through prescription by health care professionals, for smoking cessation purposes. In the prescription-based scenario, we modelled the impact of ENDS as an increment on current smoking cessation tools, and not as a replacement for currently approved tools.

The perspective of the reference-case analysis was that of publicly funded health care system. While public health care costs are under the jurisdiction of provincial ministries, the results are generalizable to all ministries, since data were extracted from national population-based surveys. A lifetime horizon was adopted to take into consideration the overall lifetime costs and health effects.

Data collection

Data from population-based surveys of the Canadian population were used where possible and supplemented with data available through literature review. Although the Canadian Community Health Survey[14] was initially considered because it collects information on a large number of Canadians (over 100 000 Canadians 12 years of age and over), specific data on smoking and vaping status were extracted from the Canadian Tobacco, Alcohol and Drugs Survey (CTADS), 2017.[4] While the sample size is smaller (approximately 16 000 Canadians 15 years and over), the CTADS offers more vaping- and smoking-specific data, and oversamples the 15 to 24 year age group, which comprises the population at highest risk for smoking initiation.[4] We stratified data by age groups and gender.

Model design

We extracted age-specific distributions for each of the smoking states (nonsmokers, current smokers and former smokers) from the 2017 CTADS,[4] and simulated how the cohort progresses through life, from 15 to 105 years of age (Figure 1).

In the scenarios in which ENDS are available, we examined their impact on smoking initiation between ages 15 and 24, and their impact on smoking cessation for ages 25 to 105. An age of 25 was chosen as a cut-off between youth and adults, since Canadian population-based survey data[4,14] show that the number of nonsmokers initiating smoking or vaping after the age of 25 is extremely small.

In the scenario in which ENDS are available for smoking cessation through prescription only, we assumed a reduced access to ENDS for smokers, since almost 15% of Canadians over the age of 12 do not have access to a primary health care provider.[15] A cycle length of six months was used, since smoking cessation is traditionally defined as sustained abstinence of at least six months' duration.[16] This timeframe therefore represents the minimum time period required to go from current to former smoker.

We extracted smoking status from the CTADS based on the traditional smoking categories used in the survey (current daily smoker; current occasional smoker; former daily smoker; former occasional smoker; experimental smoker; lifetime abstainer), and regrouped them into the following new categories:

- Current daily smokers: current daily smokers
- Former daily smokers: former daily smokers and current occasional smokers who were once daily smokers
- Never/experimental/occasional (never-daily) smokers: experimental smokers, lifetime abstainers, former occasional smokers and current occasional smokers who were never daily smokers

Current occasional smokers who were once daily smokers were grouped together with former daily smokers to allow for a conservative estimate of costs and QALY losses associated with smoking-related illnesses. Current occasional smokers who once were daily smokers are likely at higher risk of smoking-related illnesses than former daily smokers who are now completely abstinent, but are also likely at lower risk of smoking-related illnesses than current daily smokers. Grouping current occasional smokers who were once daily smokers with current daily smokers would inflate illness-related costs and QALY losses, which were based on risk estimates for current daily smokers.

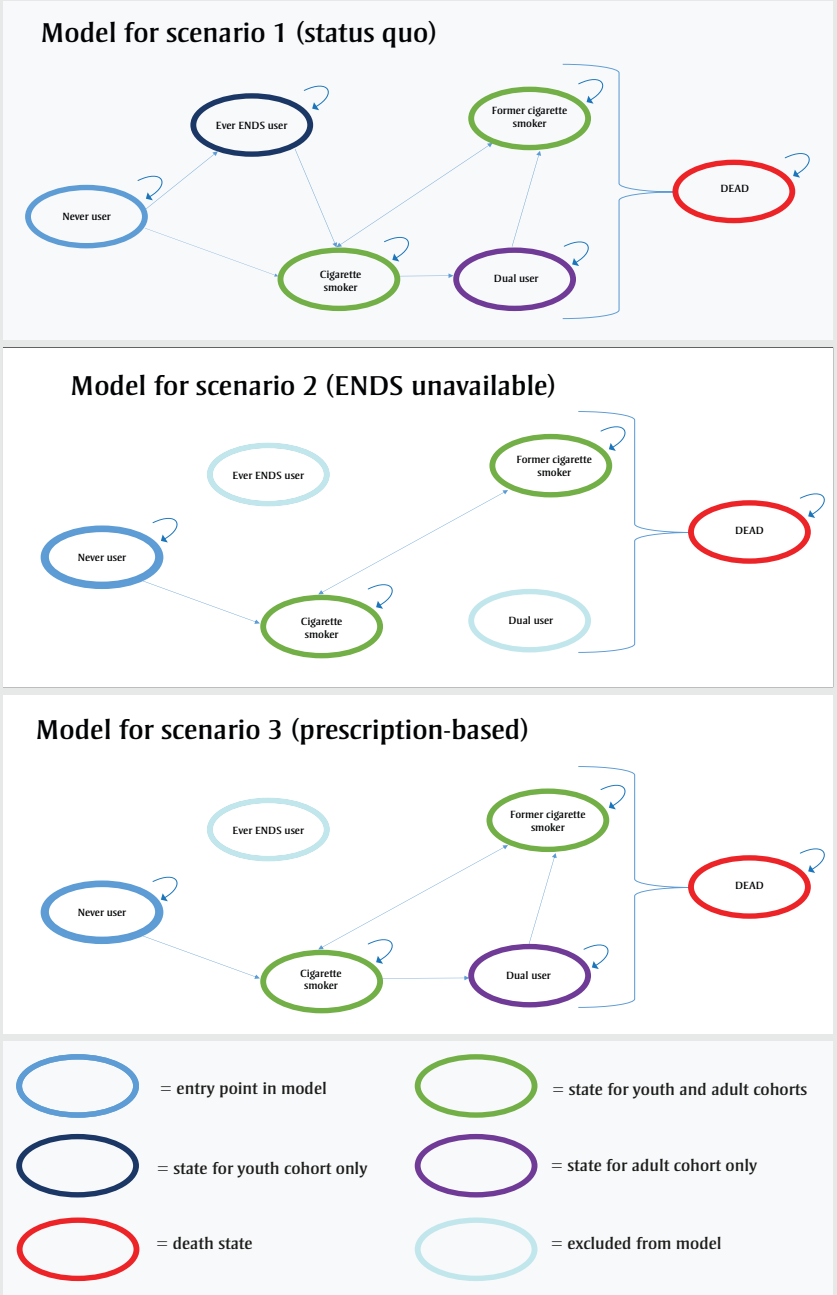
Current occasional smokers who never were daily smokers were grouped together with the "Never/experimental/occasional (never daily) smokers," since these individuals are also unlikely to experience the same costs and QALY losses associated with smoking-related illnesses that daily smokers experience.

These groupings therefore allow for the most conservative approach for estimating costs and QALY losses associated with smoking-related illnesses.

In addition to the smoking states, we also included the following:

- Ever ENDS users (15–24 years of age model): individuals who have ever vaped
- Dual users (25–105 years of age model): individuals who used e-cigarettes to quit smoking in the two years before the survey

FIGURE 1
Markov Models illustrating smoking behaviours in three scenarios with differing availability of electronic nicotine delivery systems (ENDS)



Abbreviation : ENDS, electronic nicotine delivery system.

- Death

Schematics of the models for each scenario are shown in Figure 1.

Data requirements

Transition probabilities

Age- and gender-specific transition probabilities were obtained for smoking initiation, continuation and cessation in all three main scenarios.

CTADS allows determination of the proportion of a given age-gender cohort by smoking status (current daily smoker, current occasional smoker, former daily smoker, former occasional smoker, experimental smoker and lifetime abstainer) at the time of the survey. One can also derive both the age at which a daily smoker started smoking and the time since a former daily smoker quit smoking. From this information, it was possible to determine the proportion of a given age-gender cohort by smoking status at the start of each age-gender cohort. By assuming that the transition from one smoking status to another (i.e. the probability of initiation of smoking and the probability of smoking cessation) remains constant within a specific age-gender group, we were able to obtain transition probabilities by calibration of the data by determining the probabilities that replicate the proportion in each smoking status category (current, former and never smoker) both at the time of beginning of age cohort and at the time of survey (calculation example available in transition probabilities document at https://osf.io/w7ndg/).

We used a relative risk (RR) for smoking initiation in ENDS users versus nonusers obtained from the literature[17] (RR = 2.18, 95% CI: 1.65–2.83), as it was more conservative than the RR we extracted from CTADS-derived data (RR = 7.83 in males and 9.09 in females). The large RR difference was felt to be related to the small sample size of the CTADS. The RR obtained from the literature was applied to both male and female 15-to-24-years cohorts to determine transition probabilities relating to daily smoking initiation for ENDS users versus nonusers through a further calibration process. A slightly more conservative adjusted odds ratio (AOR) of 1.79 was described in an observational Canadian study;[18] however, the RR of 2.18 mentioned above was chosen for this study because the RR measure is more generalizable to populations other than the AOR. Finally, the RR of smoking cessation in ENDS users versus nonusers (RR = 1.05 in males and 1.08 in females) was obtained from CTADS data and applied to the 25-years-and-above cohort, so as to determine transition probabilities for ENDS users versus ENDS nonusers. This RR represents the additional smoking cessation benefits conferred by ENDS over and above those seen with other currently available smoking cessation tools.

Mortality by smoking status

Annual probabilities of mortality for each age-gender cohort were obtained from Statistics Canada.[19] We then estimated the six-month probabilities of dying for each age-gender cohort by smoking status, through a calibration process combining the Statistics Canada mortality data with the baseline CTADS smoking status data.

We also estimated the age- and gender-specific RR of mortality by smoking status from the literature[20] (sample calculation available in calculation of probabilities document at https://osf.io/w7ndg/)

Smoking-related diseases

We obtained the prevalence of age- and gender-specific smoking-related illnesses (chronic obstructive pulmonary disease[21] [COPD], coronary heart disease[22] [CHD], stroke[22]) from Canadian population-based data (data available in supplementary tables at https://osf.io/w7ndg/). For lung cancer,[23] only the incidence was available, but given the short median survival of lung cancer (16.9 months),[24] incidence was felt to correlate closely with yearly prevalence. We chose to include these diseases as they represent approximately 75% of the smoking-related mortality in developed countries.[25] The RR of developing these diseases for each smoking status was obtained from the literature.[20] Age- and gender-specific probabilities of developing each condition were obtained through calibration.

Vaping-related diseases

Given the paucity of data about the long-term health impacts of the prolonged use of ENDS, we assumed there were none. This is unlikely to be true, as there is some emerging evidence that ENDS may be associated with the development of COPD,[26,27] independent of cigarette smoking. However, given the lack of clear evidence, this assumption allows for the most conservative approach.

Costs

Average six-monthly costs related to the treatment of individuals with lung cancer,[28] COPD,[29] CHD[30] and stroke[31] were obtained from the literature. Costs obtained from previous years were inflated to current-year costs using the Bank of Canada Inflation Calculator. All costs are presented in 2020 Canadian dollars (data available in supplementary tables at https://osf.io/w7ndg/).

Utility values

We obtained age- and gender-specific utility values for never smokers from Canadian population data,[14] to which we applied disutility data related to smoking status.[32] The disutility data for each of the smoking-related illnesses (lung cancer, COPD, myocardial infarction, CHD and stroke) was obtained from a study based in the United Kingdom[33] (data available in supplementary tables at https://osf.io/w7ndg/). We had planned on using Canadian- disutility data; however, the available Canadian data did not report on lung cancer separately from other cancers.[34] Disutility values for the other smoking-related illnesses were comparable between the UK and Canadian studies.

Analysis

All analyses were in the form of a cost-utility analysis to capture monetary and utility costs and benefits. A cost-utility approach was chosen given the possibility that one scenario could lead to more QALYs but not necessarily to reduced health care costs, since health and economic impacts related to smoking initiation occur many years later than those related to smoking cessation.

Probability distributions were used to account for uncertainty around the parameters of interest. We used beta distributions for transition probabilities and utility values, lognormal distributions for relative risks and gamma distributions for disutility values and uncertain costs (data available in supplementary tables at https://osf.io/w7ndg/). The probabilistic analysis was performed using a Monte Carlo simulation with 10 000 replications to ensure stability of the data. We used a threshold value of willingness to pay CAD 50 000 per QALY for interpretation of the results. All outcomes were weighted equally, regardless of the characteristics of people affected by the intervention. As per the CADTH guidelines,[35] an annual discount rate of 1.5% was applied to all costs and utilities. Confidence intervals were not produced because they are not considered meaningful for economic evaluations, the purpose of which is to inform binary decisions. Confidence intervals in this setting are not considered best practice.[35,36] Research Ethics Board approval was not needed for this study, given its use of publicly available data.

Assumptions

Two main general assumptions underlie the analysis proposed in this framework. First, we assumed no vaping-related long-term impacts, as ENDS are still relatively new. As already discussed, this is unlikely to be true. However, since most long-term vaping health impacts are not yet known, this assumption allows for the most conservative approach. Second, we assumed a stable smoking relapse rate across age groups, as no age-stratified smoking relapse rate was identified in our literature review. However, as people age, they may be less likely to relapse as more time elapses since their quit date.

Sensitivity analyses

In order to account for the uncertainty of assumptions upon which the analysis is built, we performed multiple sensitivity analyses. These include

- a relapse rate increasing by 10% in each decade of life;
- a relapse rate decreasing by 10% in each decade of life;
- a RR of 1.79 for vaping-related smoking initiation;[18]
- a 90% decrease in ENDS access (instead of 100%) for all individuals in scenario 2, and for youth in scenario 3, to account for black market access and online ordering;
- an 80% decrease in ENDS access (instead of 100%) for all individuals in scenario 2, and for youth in scenario 3, to account for black market access and online ordering;
- a 50% decrease in ENDS access (instead of 15%) because of difficulty in accessing health care in the scenario in which ENDS are only available through prescription;
- a 10% decrease ENDS access (instead of 15%) because health care access may be easier than anticipated in the scenario in which ENDS are only available through prescription;
- a discount rate of 0%;
- a discount rate of 5%;
- a scenario in which youth vaping increases by 50%;
- a scenario in which youth vaping does not increase risk of smoking initiation; and
- a scenario in which vaping does not increase quitting rates.

Results

Table 1 summarizes the impact of ENDS on life expectancy, quality-adjusted life years (QALYs) and smoking-related health care costs in Canada under our three

different scenarios: (1) the status quo, with current access to ENDS; (2) a complete ban of ENDS; and (3) limited access to ENDS for smoking cessation only, as prescribed by a medical professional. Results are presented per 1000 individuals. Incremental cost effectiveness ratios (ICERs) were not relevant, as all other scenarios are dominant over scenario 1.

In the sensitivity analyses, scenarios 2 and 3 were cost-saving for women in all situations compared to the status quo scenario, except for the one in which we assumed no association between youth vaping and smoking initiation. For men, scenarios 2 and 3 were cost-saving in most sensitivity analyses (except, again, when no association was assumed between youth vaping and smoking initiation), and otherwise would be considered cost-effective based on a willingness to pay of CAD 50 000 (relapse rate decreasing by 10% in each decade of life: ICER CAD 628 for scenario 2 vs. 1; increased access to physician to 90%: ICER CAD 28 for scenario 2 vs. 1; discount rate of 0%: ICER CAD 285 for scenario 2 vs. 1; data available in sensitivity analyses at https://osf.io/w7ndg/).

Discussion

Our results show that, based on the study assumptions, a scenario in which ENDS are completely unavailable to the Canadian population would result in an increase in population health, as well as a reduction in health care costs, when compared to the status quo. A scenario in which ENDS are restricted to a prescription-based system would lead to even greater benefits and reduction in health care costs as compared to the other two scenarios analyzed.

The significant health and economic benefits conferred by smoking cessation are the rationale for harm reduction strategies. The main purpose of harm reduction is to decrease the impact of behaviours that are typically associated with negative consequences,[37] which, in the case of smoking, involve inhalation of toxins related to the combustion of tobacco. Because ENDS do not require tobacco combustion,[38] they are felt to be safer than cigarettes, and can therefore act as harm reduction tools by helping smokers transition to a less harmful habit.

Smoking cessation is known to result in important health and economic gains. For instance, the European Study on Quantifying Utility of Investment in Protection from Tobacco (EQUIPT) showed that, for each smoker who does not quit within a 12-month period, the system incurs an additional lifetime cost of USD 6460, and that smoker experiences a decreased life expectancy of 0.66 years and a reduction in lifetime QALYs of 1.09, as compared to a smoker who quits within the same period of time.[39]

However, the results of our study are concerning: the dominance of scenario 2 (ENDS completely unavailable) over the status quo suggests that long-term harms incurred through increased smoking initiation in vaping youth outweigh the smoking cessation benefits of ENDS. This is even more apparent in scenario 3, in which ENDS are unavailable to youth but remain accessible for smoking cessation, leading to the most significant positive outcomes.

Our results align with those of some previous studies. Soneji et al.[40] demonstrated that, although ENDS are associated with increased years of life gained through their smoking cessation effect, they disproportionately increase years of life lost through increased youth-related smoking initiation. A similar conclusion was reached by Kalkhoran et al.,[41] who, through modelling of various scenarios in the US and the UK, showed that net harms resulted from all situations in which ENDS increased smoking initiation.

However, other studies have shown conflicting results. Cherng et al[42] showed that, under multiple scenarios, ENDS seemed to affect smoking cessation more than smoking initiation. Their study, however, only examined smoking prevalence and did not take into account other health or economic measures. Finally, a study by Levy et al.[43] projected a 21% reduction in smoking-attributable death and a 20% decrease in life years lost based on projected patterns of ENDS use in the US at the time of their study. The study projected a greater than 35% decrease in cigarette smoking by age 25 when ENDS were available; however, the authors assumed that only 5% of never-smoking youth ENDS users would go on to become daily smokers, which is about half of the proportion seen in Canadians under 25 years old.[4]

Although our results show that limiting the availability of ENDS to the Canadian population, either completely or through

TABLE 1
The impact of ENDS on life years, QALYs and smoking-related health care costs per 1000 individuals under different scenarios, discounted at 1.5%

	ENDS widely available (scenario 1)	ENDS completely unavailable (scenario 2)	Difference between scenarios 2 and 1	ENDS available through prescription for smoking cessation (scenario 3)	Difference between scenarios 3 and 1
Males					
Life years	41 553	41 568	15	41 570	17
QALYs	35 871	35 894	23	35 897	26
Costs	CAD 79 645 964	CAD 79 645 960	CAD -3	CAD 79 605 869	CAD -40 095
Females					
Life years	43 596	43 610	14	43 611	15
QALYs	37 416	37 438	21	37 438	22
Costs	CAD 69 242 856	CAD 69 085 926	CAD -156 930	CAD 69 076 034	CAD -166 821

Abbreviations: CAD, Canadian dollars; ENDS, electronic nicotine delivery systems; QALY, quality-adjusted life year.

Note: Due to rounding, the data in the "difference between scenarios" columns may differ slightly from calculated values derived from the reported data in this table.

prescription, could result in population health benefits and reduced health care costs, this conclusion must be seen through a realistic lens. A complete ENDS prohibition would offer the greatest protection to the smoking-naïve population; however, it would negate health gains accrued by smokers who have reduced or eliminated their cigarette consumption by switching over to ENDS.

Additionally, there are concerns that banning ENDS could result in the emergence of a black market,[44] with a potential increase in unsafe products. Scenario 3, which would allow smokers to access ENDS through a physician, demonstrated the greatest positive outcomes. This scenario would allow smokers to continue benefitting from ENDS while limiting youth exposure. Provincial health insurance program coverage could be explored, potentially resulting in decreasing financial barriers. However, this scenario also raises significant equity issues. Low-income Canadians are much more likely to have unmet health care needs[45] and potential difficulties in accessing physicians, yet they are also more likely to smoke.[46] These factors need to be taken into account when considering policy options.

Strengths and limitations

Our study's major strength is that it relies on population-based Canadian data. Our assumptions about the impact of ENDS on smoking initiation, their use and their long-term health impacts were very conservative, so as to ensure the potential benefits of ENDS were not understated. The consistency of our findings across sensitivity analyses also lends credibility to our results.

There are, however, some populations that are not represented by the CTADS (i.e. residents of the Yukon, Northwest Territories and Nunavut, full-time residents of institutions and people without access to a land or cellular phone,[47]) limiting generalizability of our findings to these groups. Also, concerns have been raised that CTADS may underestimate smoking prevalence due to higher nonresponse rates felt to be related to the inclusion of alcohol- and drug-related issues, which tend to be strongly associated with cigarette smoking.[48] It is therefore plausible that this would result in an under-estimation of the costs and health care costs reported in this analysis. In addition, having been created in 2003, ENDS represent a fairly new technology, and long-term safety data are not yet available, making long-term assumptions difficult.[38]

Finally, in the prescription-only scenario, we based our ENDS-related smoking cessation estimate on individuals who used ENDS to quit smoking in the last two years. A scenario in which ENDS are prescribed by health care professionals would likely change risk perceptions and social norms around vaping, as well as potentially reduce the cost of ENDS, because they might then become subsidized by provincial health programs. This could lead to an increase in the proportion of smokers using ENDS as a smoking cessation tool, as compared to the estimate used in this evaluation, making the prescription-based scenario even more cost-saving as compared to the status quo.

Conclusion

Studies such as this one examining the impact of ENDS on health care costs and outcomes provide valuable information. Although our results suggest that restricting access to ENDS, either through a complete ban or through a prescription-based system, would be cost effective, factors such as equity and feasibility need to be considered. Alternative policy tools such as increased taxation[49] and strict marketing regulations have been shown to impact ENDS use. Further research should focus on determining the ideal policy mix that would achieve a balance between reducing ENDS-associated smoking initiation and offering support as a smoking cessation tool. More data is also needed about the long-term impact of ENDS on health.

Conflicts of interest

The authors have no conflicts of interest to disclose.

Authors' contributions and statement

CP conceptualized and designed the study, carried out the analyses, interpreted the data, drafted the initial manuscript, and reviewed and revised the manuscript. DC participated in the conceptualization and design of the study, reviewed the analyses, participated in the interpretation of the data, and reviewed and revised the manuscript. Both authors approved the final manuscript as submitted and are accountable for all aspects of the work.

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Original qualitative research

Vaping-associated lung illness (VALI) in Canada: a descriptive analysis of VALI cases reported from September 2019 to December 2020

Melissa M. Baker, PhD; Theresa D. Procter, MSc; Lisa Belzak, MPH; Susanna Ogunnaike-Cooke, MSc

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Abstract

Introduction: The aim of this study was to explore demographic and clinical characteristics of vaping-associated lung illness (VALI) cases reported in Canada from September 2019 to December 2020; compare the epidemiology of VALI cases in Canada to e-cigarette or vaping product use-associated lung injury (EVALI) cases in the US; and examine possible explanations for differences between the two countries.

Methods: A federal/provincial/territorial task group developed a national outbreak definition, minimum dataset and case report form for identification and surveillance of VALI cases in Canada. Descriptive analysis explored the characteristics and epidemiology of reported VALI cases.

Results: Of the 20 VALI cases reported, none resulted in a death. Of all cases, 5 (25%) involved youth aged 15 to 19 years, 10 (50%) adults aged 20 to 49 years and 5 (25%) aged 50 years and older. Sixty percent of patients were men. Half (50%) required breathing assistance. Three-quarters (75%) reported using nicotine-containing vaping products, and 40% reported use of cannabis-containing vaping products; of those who reported frequency of vaping, most (71%) reported vaping daily. VALI cases were reported at a lower prevalence (0.9 per million) than EVALI (8.5 per million). Demographics and vaping behaviour also differed.

Conclusion: VALI cases were reported in Canada between September 2019 and December 2020; however, there was a much lower prevalence and they may have been caused by different factors from the EVALI outbreak in the US. The factors influencing VALI in Canada are complex and multifactorial. Research is needed to understand the short- and long-term health effects of nicotine and cannabis vaping.

Keywords: *e-cigarette use, electronic cigarette, nicotine vaping, tetrahydrocannabinol (THC), cannabis vaping, lung illness, lung injury, vape*

Highlights

- In Canada, the use of e-cigarettes has been increasing, particularly among youth.
- Between September 2019 and December 2020, 20 cases of vaping-associated lung illness (VALI) were reported in Canada.
- Canada experienced a lower per-population prevalence of VALI compared to e-cigarette or vaping product use-associated lung injury (EVALI) in the US; differences in patient demographics and products used were also found.

Introduction

In Canada, the use of electronic cigarettes (e-cigarettes or vaping devices) has been increasing, particularly among youth. Between 2015 and 2019, the number of Canadians aged 15 years and older who reported ever-vaping (nicotine) increased from 13% to 16%,[1,2] with younger age groups reporting the highest frequency: 36% of youth aged 15 to 19 years and 48% of young adults (20 to 24 years), compared to 12% of adults (25 years and over) in 2019.[2] Among students in grades 7 to 12 in Canada, 20% reported past- 30-day use of e-cigarettes in 2018-2019, double the number of students who reported past 30-day use in 2016-2017 (10%).[1,3]

Similar findings were reported in 2019: past 30-day use of a vaping device was higher among youth and young adults (15% each, respectively) compared to adults (3%) in Canada.[2] Ever-vaping cannabis-containing products was reported by 9% of Canadians 15 years of age and older in 2019; past 30-day use was reported by 3% of Canadians, with young adults (7%) reporting past 30-day use more than youth and adults (3% each, respectively).[2]

E-cigarettes and vaping products have been marketed as a potentially less harmful alternative to combustible products; however, long-term risks, both acute and chronic, remain mostly unknown.[4] The exposure to potentially harmful chemicals while vaping is variable and depends on the composition of the vaping liquid or product, the legal status and source of

Author reference:

Public Health Agency of Canada, Ottawa, Ontario, Canada

Correspondence: Melissa M. Baker, Substance-related Harms Division, Centre for Surveillance and Applied Research, Public Health Agency of Canada, 785 Carling Avenue, Ottawa, ON K1S 5H4; Tel: 343-542-1186; E-mail: vapingillness-maladievapotage@phac-aspc.gc.ca

product and how the product is used. Across both nicotine-containing and cannabis-containing vaping products in the United States, more than 500 chemicals have been identified in vaping cartridges and liquids, including various amounts of nicotine, cannabinoids, volatile organic compounds, vitamin E acetate, silicon conjugated compounds and various terpenes, metals and pesticides.[5,6]

In August 2019, the US Centers for Disease Control and Prevention (CDC) reported an outbreak of e-cigarette or vaping product use-associated lung injury (EVALI). At the request of the Chief Public Health Officer of Canada, the Public Health Agency of Canada (PHAC) alerted provincial and territorial health authorities of the potential for cases and the need for enhanced vigilance.

Studies of EVALI cases in the US have examined the common factors and clinical features associated with EVALI; however, no specific substance, product or device was linked to all cases. Nonetheless, vitamin E acetate, an additive found in cannabis products (and typically not in nicotine products) from informal sources such as friends, family and the illegal market was found to be strongly linked to the EVALI outbreak in the US; 82% of EVALI patients reported using cannabis-containing vaping products, of which 78% reported acquiring these products from informal sources. However, evidence was not sufficient to rule out the contribution of other chemicals found in any vaping product whether cannabis-containing or not, as EVALI occurred among those who did not report vaping cannabis-containing products.[7-9]

The severity and nonspecificity of vaping-associated lung illness (VALI) symptoms present a diagnostic challenge for physicians, particularly if a patient does not disclose having recently vaped. Patients who might have VALI may visit primary care clinics or outpatient hospital emergency services, and treatment can vary from hospital or intensive care unit (ICU) admission, to being placed on a regimen of antibiotics or steroids, to receiving supplementary oxygen or ventilation, or even to being placed on life support.[10] Exploring trends in VALI cases in Canada contributes to the evidence base for improved understanding of severe vaping-related harms and clinical management of suspected VALI cases. Accordingly, the objectives of this study were to (1) explore the demographic and clinical patient characteristics in VALI cases reported in Canada from September 2019 to December 2020; (2) compare the epidemiology of VALI in Canada to EVALI in the US; and (3) examine possible explanations for the differences in the epidemiology between Canada and the US.

Methods

Case data

To coordinate a national investigation, in September 2019, the Canadian Council of Chief Medical Officers of Health (CCMOH) approved the formation of the federal, provincial and territorial (F/P/T) VALI Task Group to develop a common approach to detect, investigate and report on cases of VALI in their respective jurisdictions. The F/P/T VALI Task Group created data collection tools, a national outbreak case definition for severe pulmonary disease associated with vaping or dabbing (Table 1), a minimum dataset for standardized data collection and a case report form. "Vaping" is the act of inhaling an aerosol produced by a vaping product. "Dabbing" is inhaling very hot vapours from heated cannabis oils, concentrates or extracts.

Self-reported vaping behaviours were obtained during initial and follow-up interviews with either the patient or close family members, if the patient was unable to participate. Provincial and territorial (P/T) public health authorities submitted de-identified case data to PHAC after a VALI case was verified as probable or confirmed against the national case definition in their jurisdiction. Health Canada (HC) also actively searched existing databases for self-reported and industry-reported adverse reactions to nicotine, non-nicotine and cannabis vaping products, and e-cigarette or vaping devices. Four possible incidents of lung injury related to vaping in Canada were identified and shared with PHAC.

Investigative efforts and reporting in Canada focussed on hospitalized patients, using a similar case definition and strategy as the US investigation; however, Alberta, British Columbia, New Brunswick and Quebec expanded their investigations to include outpatient visits and family physician settings. In March 2020, when COVID-19 transmission became widespread in Canada, active surveillance of VALI was paused and surveillance was limited to monitoring and reporting adverse reactions and to incidents event reporting through existing HC regulatory surveillance programs. Characteristics of EVALI cases were sourced from public health data and published literature. This study, which covered the reporting period of September 2019 to December 2020, and this paper were approved by the F/P/T VALI Task Group of the CCMOH. Ethics approval was not required, as this study falls within routine public health surveillance activities.

Laboratory testing

Health Canada's Regulatory Operations and Enforcement Branch Laboratories (HC-ROEB-Laboratories) conducted analytical testing of vaping product samples to identify and quantify substances of interest in support of VALI investigations. When possible, patients provided samples of the substances vaped prior to onset of symptoms. HC-ROEB-Laboratories also purchased and tested samples of the same brands that patients reported using, to act as control samples. HC-ROEB-Laboratories carried out the chemical analyses of e-liquids using validated analytical methods employing gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-photodiode array (HPLC-PDA) techniques. Analytes were reported as detected only if their presence in the sample was confirmed by both methods. Health Canada's Healthy Environments and Consumer Safety Branch–Product Safety Laboratory (HC-HECSB-PSL) also provided laboratory services for testing vaping devices linked to cases via visual evaluation, heater coil resistance measurement and testing coils for the presence of heavy metals using a portable x-ray fluorescence analyzer.

Analysis

Given the small number of cases, descriptive analysis was performed using MS Excel spreadsheets that detailed the characteristics and epidemiology of all 20 VALI cases in Canada. Statistical associations and significance tests were not conducted, due to insufficient statistical power resulting from small sample size and the level of availability and completeness of data. Due to low case counts, confirmed and probable cases were combined for analyses.

TABLE 1
Outbreak case definitions of confirmed and probable cases of vaping-associated lung illness (VALI) and e-cigarette or vaping product use-associated lung injury (EVALI)

	Vaping-associated lung illness (VALI)	E-cigarette or vaping product use-associated lung injury (EVALI)
Confirmed	History of vaping or dabbing[a] in the 90 days prior to symptom onset	Using an e-cigarette (vaping) or dabbing[a] in 90 days prior to symptom onset
	AND	AND
	Pulmonary infiltrate, such as opacities, on plain film chest radiograph or ground-glass opacities on chest CT	Pulmonary infiltrate, such as opacities, on plain film chest radiograph or ground-glass opacities on chest CT
	AND	AND
	Absence of pulmonary infection on initial work-up: Minimum criteria are: negative respiratory viral panel, influenza PCR or rapid test, if local epidemiology supports testing. All other clinically indicated respiratory infectious disease testing (e.g. urine antigen for *Legionella*, sputum culture if productive cough, BAL culture if done, blood culture, HIV-related opportunistic respiratory infections if appropriate) must be negative	Absence of pulmonary infection on initial work-up: Minimum criteria are: a negative respiratory viral panel and a negative influenza PCR or rapid test, if local epidemiology supports influenza testing. All other clinically indicated respiratory infectious disease testing (e.g. urine antigen for *Streptococcus pneumoniae* and *Legionella*, sputum culture if productive cough, BAL culture if done, blood culture, HIV-related opportunistic respiratory infections if appropriate) are negative
	AND	AND
	No evidence in medical records of alternative plausible diagnoses (e.g. cardiac, rheumatologic or neoplastic process)	No evidence in medical record of alternative plausible diagnoses (e.g. cardiac, rheumatologic, or neoplastic process)
Probable	History of vaping or dabbing in the 90 days prior to symptom onset	Using an e-cigarette (vaping) or dabbing in 90 days prior to symptom onset
	AND	AND
	Pulmonary infiltrate, such as opacities, on plain film chest radiograph or ground-glass opacities on chest CT	Pulmonary infiltrate, such as opacities, on plain film chest radiograph or ground-glass opacities on chest CT
	AND	AND
	Infection identified via culture or PCR, but clinical team believes this is not the sole cause of the underlying respiratory disease process	Infection identified via culture or PCR, but clinical team believes this infection is not the sole cause of the underlying lung injury
	OR	OR
	Minimum criteria to rule out pulmonary infection not met (testing not performed) and clinical team believes infection is not the sole cause of the underlying respiratory disease process	Minimum criteria to rule out pulmonary infection not met (testing not performed) and clinical team believes infection is not the sole cause of the underlying lung injury
	AND	AND
	No evidence in medical record of alternative plausible diagnoses (e.g. cardiac, rheumatologic or neoplastic process)	No evidence in medical record of alternative plausible diagnoses (e.g. cardiac, rheumatologic, or neoplastic process)

Sources: VALI: Government of Canada. National outbreak case definitions: severe pulmonary disease associated with vaping or dabbing [Internet]. Ottawa (ON): Government of Canada; 2019 [modified 2019 Oct 11; cited 2021 Oct 5]. Available from: https://www.canada.ca/en/public-health/services/diseases/vaping-pulmonary-illness/health-professionals/national-case-definition.html

EVALI: Centers for Disease Control and Prevention (CDC). 2019 lung injury surveillance primary case definitions, September 18, 2019 [Internet]. Atlanta (GA): CDC; 2019 [cited 2021 Oct 05]. Available from: https://www.cdc.gov/tobacco/basic_information/e-cigarettes/assets/2019-Lung-Injury-Surveillance-Case-Definition-508.pdf

Abbreviations: BAL, bronchoalveolar lavage; CT, computed tomography; HIV, human immunodeficiency virus; PCR, polymerase chain reaction.

[a] Inhaling very hot vapours from heated cannabis oils, concentrates or extracts.

Results

During the study period, 20 VALI cases and zero deaths were reported to PHAC by P/T health authorities. Of the 20 VALI cases, 8 were classified as confirmed and 12 as probable, as defined by the national outbreak case definition.

Detailed case information was submitted for 75% (15 of 20 cases) of reported VALI cases in Canada between 1 September 2019 and 31 December 2020.

Data on basic demographics, symptoms, symptom onset, hospitalization status and substance(s) vaped were available for all cases. Detailed information was available for the cases as follows: medical history (13 of 20 cases), medical interventions (13 of 20 cases), source and frequency of substance(s) and devices used for vaping (14 of 20 cases) and use of other substances (combustible or other means of consumption; 16 of 20 cases).

Demographic characteristics

Of all cases, 25% (5 of 20 cases) were among youth aged 15 to 19 years; 50% (10 of 20 cases) were among those aged 20 to 49 years and 25% (5 of 20 cases) were among those aged 50 years and older. Cases were reported in Quebec, British Columbia, Ontario, New Brunswick, Alberta and Newfoundland and Labrador.

Symptoms

Cases reported between 1 September 2019 and 31 December 2020 involved symptom onset dates ranging from 5 May 2019 to 11 April 2020. Half (50%; 10 of 20 cases) had a symptom onset date between August 2019 and October 2019.

All 20 patients reported respiratory symptoms, of which 25% (5 of 20 cases)

reported exclusively respiratory symptoms (e.g. cough, shortness of breath), and 75% (15 of 20 cases) reported a combination of respiratory, gastrointestinal (e.g. nausea, diarrhea), constitutional (e.g. chills, fatigue) and/or other symptoms (e.g. fever, poor appetite/weight loss). Eight patients (40%) reported a fever. Of all 20 patients, 3 (15%) experienced acute respiratory distress syndrome (ARDS). Other symptoms reported included back pain, numbness or tingling, confusion, short-term memory loss, runny nose, sinus pressure, sore throat, sweating, fecal incontinence, lack of balance and urinary symptoms.

By sex, men more commonly reported cough and constitutional symptoms compared to women (cough: 10 of 12 [83%] males compared to 4 of 8 [50%] females; constitutional symptoms: 10 of 12 [83%] males compared to 3 of 8 females [38%]).

Medical history

Detailed case information about pre-existing conditions and other risk factors was available for 65% (13 of 20) of VALI cases. Of those with information available, 62% of patients (8 of 13 cases) reported having one or more pre-existing conditions or risk factors. Of those who reported a pre-existing condition or risk factor, 63% (5 of 8 cases) reported a pre-existing respiratory or lung condition, including asthma and chronic obstructive pulmonary disease (COPD). The majority of patients that reported pre-existing conditions or risk factors (75%; 6 of 8 cases) were aged 40 years and older. No differences were observed in the number of pre-existing conditions or risk factors reported by sex.

Hospitalization and intensive care unit (ICU) admission

Of all 20 VALI patients, 80% (16 of 20 cases) were hospitalized. Detailed case information on date of hospital admission and discharge was available for 14 of the 16 hospitalized patients. The median length of hospitalization was 6 days (range of 2 to 54 days). Of the 14 patients with information available, 86% (12 of 14 cases) were hospitalized for 10 days or less. Of the 16 patients hospitalized, 50% (8 of 16 cases) were admitted to the ICU.

Medical intervention and treatments

Of all 20 VALI patients, 55% (11 of 20 cases) required respiratory intervention. Of the 11 patients who did, 55% (6 of 11 cases) received oxygen support via nasal cannula, while the remaining patients required more intensive or supportive interventions such as ventilation (3 of 11 cases), continuous positive airway pressure (CPAP; 1 of 11 cases) or extracorporeal membrane oxygenation (ECMO; 1 of 11 cases). Additional medical treatments were provided to several patients, including treatment with antimicrobials and/or steroids. A higher percentage of VALI patients aged 40 years or older (6 of 9 cases; 67%) than those VALI patients aged 39 years or younger (5 of 11 cases; 45%) required respiratory interventions. No differences were observed in the type of intervention by sex.

Vaping behaviours

Of all VALI patients, 75% (15 of 20 cases) self-reported having vaped nicotine products. Of these 15 patients, 12 (80%) reported exclusively vaping nicotine products. Seven patients reported vaping nicotine products with flavouring. Most of these reported using more than one flavour (5 of 7 cases). Flavours reported included tobacco (2 cases), fruit (e.g. green apple, strawberry guava, "very berry," and mango, among others; 6 cases) and other flavours (e.g. cotton candy, bubble gum, mint, vanilla; 3 cases). Vaping or dabbing of cannabis-containing products was reported by 40% of all VALI patients (8 of 20 cases). Of these 8 patients, 5 (63%) reported exclusive cannabis vaping (representing a broad category of inhaled substances containing cannabis extracts).

Exclusive nicotine vaping was reported by both men and women in all age groups. Exclusive cannabis vaping use was reported by both men and women less than 60 years of age. Of those who reported vaping using both nicotine- and cannabis-containing products, all were men and under 20 years of age. More women than men (60%; 3 of 5 cases) reported vaping cannabis exclusively, while more men than women (58%; 7 of 12 cases) reported exclusive nicotine vaping.

Different types of devices can be used to vape, creating an inhalable aerosol of nicotine, flavoured substance and/or cannabis extracts; the latter may be in liquid, semi-solid or solid forms (e.g. "shatter," "wax"). Detailed information on type of vaping or dabbing device used was available for 14 of 20 VALI cases. Device types included vape pens with either a tank (refillable), a pre-filled (single use) cartridge, or disposable cartridges. A dab device (dab rig, bong, nail) and other devices were also reported. Most patients (71%; 10 of 14 cases) reported using their device on a daily basis. Information on the amount of substance used each time or how many times each day was not provided. No patients reported using a modified device; however, one reported modifying the vaping substance.

In addition to substances vaped, data on nicotine products and other substances consumed via other means (e.g. inhaled, injected, ingested, combusted) were available for 70% of cases (14 of 20). Of these patients, three-quarters (79%; 11 of 14 cases) reported prior or current combustible tobacco use, while 57% (8 of 14 cases) reported prior or current combustible cannabis use.

Laboratory results of substances and devices

As of 3 June 2020, HC-ROEB-Laboratories had received and analyzed 59 samples related to 8 cases (35 control samples, 16 product samples from patients and 8 samples collected from one patient's device—comprising the substance and swabs of different parts of the device). Vitamin E acetate was detected in one control sample at a very low concentration (0.279 mg/mL). At this concentration, there is no evidence to indicate it could have caused VALI-like symptoms. No specific substance detected or quantified could be pinpointed as a responsible agent for VALI symptoms, based on a risk analysis of the exposure and toxicity information related to samples tested from VALI patients. While the substances that were detected have very low toxicity via the oral route, the inhalation toxicity of most of the substances is currently unknown. Vaping liquid was also tested for the presence of heavy metals such as cadmium, arsenic, lead and mercury. No heavy metals were detected in the liquids tested (Table 2).

HC-HECSB-PSL received 11 devices and evaluated 7 of them. HC-HECSB-PSL's analysis of the devices revealed no key

findings via either visual evaluation or heater coil resistance measurement, and no heavy metals were detected above the limit of detection of the x-ray fluorescent analyzer (< 10 parts per million).

Discussion

From September 2019 to December 2020, 20 VALI cases were reported in Canada, representing a prevalence of 0.9 cases per 1 million population.* As of 18 February 2020, the CDC reported 2807 EVALI cases and 68 deaths in the US, representing a prevalence of approximately 8.5 cases per 1 million population. Given the smaller number of cases in Canada, as well as the differing regulatory and health care systems, it is difficult to compare the characteristics of EVALI in the US with VALI in Canada. While the EVALI outbreak in the US was characterized by a sharp increase in emergency department visits through the summer of 2019 followed by a peak in September 2019,[11] in Canada, a small number of cases (1–4) was reported each month from September 2019 to April 2020.†

Geographically, in the US, EVALI cases were reported by all 50 states, the District of Columbia and two US territories (Puerto Rico and the US Virgin Islands); rates varied by state, with states in the northern Midwest (e.g. Illinois, Minnesota, Indiana) reporting a higher rate of cases than other states.[11,12] Although vaping regulations vary by province, the majority of VALI cases in Canada (80%) were reported in British Columbia, Ontario and Quebec, Canada's three most populous provinces, which account for 75% of the Canadian population. This suggests there is no geographic centre to VALI cases in Canada, as there appears to be the US.

Almost half of all VALI cases in Canada (45%) were among those aged 40 years and older, and there was a higher number of cases among men compared with women (60% male). Comparatively, three-quarters (76%) of US EVALI cases were among those aged 34 years and under, and there was a higher number of men (66%) compared to women;[11] a greater proportion of patients with VALI in Canada are therefore older than those diagnosed with EVALI in the US, while men account for a larger proportion of both VALI and EVALI cases.

TABLE 2
Summary of vaping liquid analysis by HC-ROEB-Laboratories related to VALI cases in Canada, September 2019 to December 2020

Type of vaping liquid sample	Results
Control (n = 35)	**Nicotine** • Present in 22 samples; content is consistent with label claim for all samples • For the remaining 13 samples, nicotine was below the limit of detection; content is consistent with label claim for all samples **Additional substances** • Flavouring agents (e.g. vanillin, benzyl benzoate, benzaldehyde, among others) • Diluents (benzyl alcohol)
Patient (n = 16)	**Nicotine** • Present in 11 samples • Nicotine concentration was consistent with label claim in 6 samples; 5 samples were not large enough to quantify; and in 5 samples, nicotine was not detected (below the limit of detection), which is aligned with label claim **THC** • Present in 4 samples (from 1 patient) **Additional substances** • Vanillin identified in 1 sample
Liquid extracted from patients' devices (n = 8)	**Nicotine** • Present in 8 samples[a]—not enough sample to quantify **Additional substances** • Vanillin identified in 3 samples; traces of cocaine (on the mouthpiece of the vaporizer) identified in 1 sample

Abbreviations: HC-ROEB, Health Canada's Regulatory Operations and Enforcement Branch; THC, tetrahydrocannabinol; VALI, vaping-associated lung injury.

[a] In addition to collecting a sample of the liquid in devices, additional samples were also taken from the device itself by swabbing different components or sections, thus resulting in more samples than the number of devices submitted for testing.

From August to November 2019, approximately 95% of EVALI patients in the US had been hospitalized.[13] Most (80%) VALI patients in Canada were hospitalized; however, this was likely due to case-finding strategies that were limited to hospitalized patients in the majority of the provinces and territories. Expanding the case finding beyond hospitals, as was done by some provinces, led to the detection of additional cases in clinics and emergency departments. It is possible that focussing on hospitalized patients resulted in underreporting of cases that may have involved milder symptoms or were resolved with outpatient interventions, thus not requiring hospitalization.

In Canada, the most common substance vaped by VALI patients was nicotine. In the US, the majority of EVALI patients self-reported using cannabis-containing products obtained from informal sources.[11] For example, 91% of EVALI cases in Minnesota and three patient clusters in Wisconsin (8 cases) involved cannabis-containing vaping products obtained from informal sources such as friends, family or in-person or online dealers, and 75% of THC-containing products reported in California also came from such informal sources.[14-16] In Canada, one VALI patient reported modifying vaping substances, which may have changed the chemistry of the liquid vaped, potentially contributing to adverse effects.[10] Similarly, traces of cocaine detected on one device may indicate the individual was experimenting to produce a different user experience, which may have resulted in adverse health effects. The difference in prevalence between VALI and EVALI cases may be due to the increased proportion of patients reporting vaping cannabis-containing products from informal sources in the US.

More than one potential factor contributing to illness may have been present in Canada at the same time as the US EVALI outbreak. The outbreak of EVALI in the US was strongly associated with vitamin E

* Population estimates were calculated based on Statistics Canada Table 17-10-0009-01, Population estimates, quarterly (2020 Q1). Prevalence is presented per population per year.

† Surveillance is ongoing; additional data and cases may be reported outside the surveillance period included in this report.

acetate added to cannabis-containing vaping products obtained from informal sources;[11,17,18] however, it was not linked to any of the Canadian cases in sufficient amounts. A vitamin E acetate concentration of 0.279 mg/mL (0.03%) was detected in one Canadian control sample; concentrations of 23% to 88% were detected in samples from EVALI cases.[19] Other chemicals that may be present in vaping products cannot be ruled out as contributing factors;[20] furthermore, pre-existing conditions add complexity to case evaluation.

Regulatory differences may have contributed to the differences between case characteristics in Canada and the US as well. Canada's October 2019 legislation regulating inhaled cannabis extracts, including cannabis vaping products, closely restricts additives, carrier ingredients and substances and contaminants (e.g. pesticides and heavy metals) that may pose a risk of injury to human health.[21-23] However, inhaled cannabis extracts frequently used with accessories such as vaping devices did not enter the legal marketplace until December 2019; products used during some of this investigation, prior to December 2019, may not have adhered to these regulations. In the US, there was no federal oversight of these products at the time of the outbreak, requiring each state to develop its own set of regulations and restrictions, resulting in regulations that varied from state to state. States such as Colorado and California, where the adult use of cannabis is legalized, reported lower rates of EVALI cases compared to states where cannabis use is illegal.[24] The variability of product regulations in the US likely did not impact the products used by Canadians, as importation of cannabis-containing products by consumers is prohibited in Canada. Thus the likelihood of adulterated products from the US being legally imported into the Canadian marketplace is reduced.[25]

It is likely that the EVALI outbreak in the US led to increased surveillance and awareness of the potential for vaping-related harms in Canada, which may have contributed to the detection or identification of cases that might not have been reported otherwise or aggregated at the national level.[26-28] Long-established governance structures and relations with the Pan-Canadian Public Health Network, the CCMOH,[29] provincial and territorial health authorities and the media may have expedited timely information sharing, raised awareness and enhanced surveillance of the potential for harm related to vaping products. Furthermore, an information update to the general Canadian population warning of the potential risk of VALI in September 2019[30] may have encouraged self-regulating behaviours such as refraining from using illicit products and discontinuing the use of vaping products if feeling sick. Further research and surveillance are needed to understand the effect of this messaging on behavioural change.

Strengths and limitations

Our study exploring the trends in VALI cases in Canada contributes to the evidence base and consequently to improved understanding of severe vaping-related harms and the clinical management of suspected VALI cases.

However, our results should be viewed in light of certain limitations. The small sample size (20 cases) and limited case histories of patients in the study limited the analyses and interpretation of results, making it difficult to identify a particular risk factor. The data may be subject to reporting biases from patients, their families and health care providers, as most were collected retrospectively and some patients could not remember the products used. Individuals may have been hesitant to disclose use of cannabis-containing vaping products, given these products were illegal in the Canadian marketplace until December 2019, fearing the stigma of using illegal products and the repercussions of admitting use. Due to the small sample of products tested by HC-ROEB-Laboratories and HC-HECSB-PSL, the results of the laboratory tests should not be interpreted as identified causes of VALI. Furthermore, no bronchoalveolar lavage samples were tested for Canadian cases, which was a key factor in identifying vitamin E acetate in the US investigation. Underreporting of cases and vaping behaviours likely occurred in a similar extent in both Canada and the US.

VALI is a diagnosis of exclusion and its symptoms may occur along a spectrum. Patients who presented to emergency departments with mild symptoms and/or whose symptoms resolved with outpatient interventions may be underreported or not identified. Without a baseline, it is difficult to know if rates of VALI-like presentations differ as a function of frequency and duration of use, which cannot be known from counts among vaping patients alone. Given the prevalence of vaping in the population in Canada, especially among youth, and the nonspecific nature of the case definition and symptom presentation, the possibility that vaping is coincidentally associated with VALI in at least some cases cannot be excluded. Additionally, with more than half of the cases classified as probable, some caution must be exercised regarding misdiagnosis and confounders; patients with respiratory infections or other conditions causing infiltrates may have been captured as VALI due to a vaping history that may not have been related to their symptoms.

Furthermore, more than two-thirds of VALI patients reported prior or current use of combustible tobacco or cannabis or both, thus exposing these patients to lung damage potentially unrelated to vaping. Many also reported pre-existing conditions that may have affected lung function and contributed to greater severity of illness in certain cases. Since February 2020, when the COVID-19 epidemic began in Canada, probable or confirmed COVID-19 cases could have confounded potential VALI cases, given the overlap of symptoms and disease progression.[31] While provinces and territories continue to monitor for and report on VALI cases, the de-escalation of active surveillance of VALI due to COVID-19 transmission in Canada may have contributed to underreporting of cases since March 2020.

Conclusion

While vaping is generally considered to lead to lower exposure to known toxicants than combustible smoking, there are still many unknowns about vaping of substances, and it is not without risks. VALI was detected in Canada between September 2019 and December 2020; however, it was at a much lower rate and possibly through a differing mechanism than EVALI in the US. Unlike in the US, where vitamin E acetate was identified as a novel adulterant in cannabis-containing products obtained from informal sources, it was not identified in sufficient amounts in any products tested related to VALI cases in Canada. Although nicotine products were reported to have been used by the majority of VALI patients and detected in several product samples, a causal relationship cannot be assumed at this time. No single

causative agent responsible for VALI could be identified.

As the prevalence of using nicotine and cannabis-containing vaping products increases in Canada, especially among youth who have previously never smoked, additional research is needed to clarify how changing patterns of vaping product use, including the frequency and intensity of use, may contribute to acute and chronic harms, including VALI, nicotine or cannabis addiction and future smoking trends. In addition, continuing education to primary care physicians, emergency department clinicians and other primary care or outpatient health care providers (e.g. nurse practitioners) is important to maintain awareness of VALI as a potential diagnosis.

The factors influencing VALI in Canada are likely complex and multifactorial. While evidence is lacking in this area, it is important to investigate both the short- and long-term health effects of nicotine and cannabis vaping, including the possible influence on susceptibility to infectious diseases. Maintaining awareness and vigilance for the detection and reporting of VALI cases by health care providers is important to capture a complete picture of VALI in Canada and better characterize factors influencing VALI.

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Conflicts of interest

The authors have no conflicts of interest to disclose.

Authors' contributions and statement

MB, LB and SOC contributed to the study conception and design. Material preparation, data acquisition, analysis and interpretation were performed by MB and TP. The first draft of the manuscript was written by MB and TP with comments from all authors. All authors read and approved the final manuscript.

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