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Risky Business: A longitudinal study examining cigarette smoking initiation among susceptible and non-susceptible e-cigarette users

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Risky Business: A longitudinal study examining cigarette smoking initiation among susceptible and non-susceptible e-cigarette users

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ABSTRACT:

Objectives: Given that many adolescent e-cigarette users are never smokers, the possibility that e-cigarettes may act as a gateway to future cigarette smoking has been discussed in various studies. Additional longitudinal data are needed to explore the pathway between e-cigarette and tobacco cigarette use, particularly among different risk groups including susceptible and non-susceptible never smokers. The objective of this study was to examine whether baseline use of e-cigarettes among a sample of never-smoking youth was associated with cigarette smoking initiation over a two-year follow-up.

Design: Longitudinal cohort study

Setting: 89 high schools across Ontario and Alberta, Canada.

Participants: A sample of gr. 9-11 never-smoking students at baseline (n=9501) that participated in the COMPASS study over two years.

Primary and Secondary Outcome Measures: Participants completed in-class questionnaires that assessed susceptibility to future smoking and smoking initiation.

Results: Among the baseline sample of non-susceptible never-smokers, 45.2% of current e-cigarette users reported trying a cigarette at the two-year follow-up compared to 13.5% of non-current e-cigarette users. Among the baseline sample of susceptible never-smokers, 62.4% of current e-cigarette users reported trying a cigarette at the two-year follow-up compared to 36.1 % of non-current e-cigarette users. Overall, current e-cigarette users at baseline were more likely to try cigarette smoking 2 years later. This association was even stronger among the sample of non-susceptible never smokers (Adjusted OR = 5.38, 95 % CI 2.85 to 10.17; $p<0.0001$) compared to susceptible never smokers (Adjusted OR= 2.94, 95 % CI 1.94 to 4.46; $p<0.0001$).

Conclusions: The findings from this large, longitudinal study support public health concerns that e-cigarette use may contribute to the development of a new population of cigarette smokers, even among adolescents that held no intentions to smoke in the future. These findings underscore the need for sustained efforts to prevent e-cigarette use among youth populations, especially those at lowest risk for smoking.

Keywords*: e-cigarettes, cigarettes, youth, adolescents, susceptibility*

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Strengths and Limitations of this study:

- This study assessed the relationship between e-cigarette use among never-smoking adolescents and smoking initiation using a large longitudinal sample.
- This study examined transitions in smoking behaviour among adolescents at different risk levels (i.e. susceptible and non-susceptible never smokers).
- The measures of e-cigarette use used within this study did not provide information regarding the types of e-cigarettes being used.
- This study focused solely on cigarette smoking initiation outcomes.

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BACKGROUND

Despite the declining prevalence of smoking in most countries globally, tobacco use remains a threat to global health. In 2013, tobacco use accounted for the loss of approximately 6.1 million lives and 143.5 million disability-adjusted life-years (DALYs) world-wide [1-2]. Considering that the majority of smokers try their first cigarette during adolescence [3], preventing youth smoking initiation represents a key public health priority.

Electronic cigarettes are battery-operated devices that deliver nicotine and vaporize a liquid mixture made up of propylene glycol, nicotine, flavouring agents and other chemicals. The rise in e-cigarette use among youth has created discussion regarding the public health implications. While some within the tobacco control community believe that e-cigarettes could be used as smoking cessation aids and help reduce smoking-related harms [4], others have

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argued against this considering the limited evidence of the long-term effects of e-cigarettes [5]. Additionally, given that many adolescent e-cigarette users are never smokers [6-7], the possibility that e-cigarette use may act as a gateway to future cigarette behaviour has been discussed in various studies [8-9]. A recent meta-analysis by Soneji et al. (2017) found consistent evidence of an association between initial e-cigarette use and subsequent cigarette smoking initiation [10].

Given that intentions to smoke in the future are a strong predictor of future cigarette smoking, it is likely that smoking initiation among youth in these studies primarily occurs among those that are already at risk of (i.e., susceptible to) future smoking. Studies have recently begun to explore the association between e-cigarette use and smoking initiation among different risk groups. Smoking susceptibility, defined as the lack of a firm commitment not to smoke among never smokers, is a validated and reliable predictor of tobacco cigarette smoking initiation among adolescents [11-12]. It is hypothesized that the use of e-cigarettes by never-smoking youth may increase their susceptibility to future smoking. Cross-sectional studies suggest that never smoking youth that have ever and currently use e-cigarettes are at increased odds of being susceptible to future smoking, with a stronger association identified among younger students [13-16]. To our knowledge, only two longitudinal studies have examined the progression from non-susceptible never smoker to susceptible never smoker or ever smoker among e-cigarette and non-e-cigarette users; however, both studies included older adolescent and young adult populations. The first longitudinal study identified that youth and young adult non-susceptible never smokers that used e-cigarettes at baseline were more likely to become susceptible never smokers and try smoking cigarettes at 1 year follow-up [17]. The second longitudinal study

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identified that grade 11 and 12 non-susceptible never smokers that used e-cigarettes at baseline were more likely to initiate cigarette smoking at follow-up [18].

It is evident that additional longitudinal data that use younger students and a longer follow-up period are needed to explore the potential association between e-cigarette use and subsequent cigarette use among different risk groups. This study examined whether baseline use of e-cigarettes among a sample of susceptible and non-susceptible never-smoking youth was associated with cigarette smoking initiation over a two-year follow-up.

METHODS

Design

COMPASS is a prospective cohort study (2012-2021) designed to gather longitudinal and hierarchical data from a sample of secondary school students [19]. This paper reports on longitudinal findings between Year 2 (2013-2014) and Year 4 (2015-2016) of the study among a sample of schools that agreed to the use of active-information passive consent permission procedures. For ease of description, Year 2 will be considered "baseline" and Year 4 will be considered "follow-up". Year 2 data were selected as baseline due to the larger sample size [20] and since this was the first year e-cigarette use was assessed. Data relating to student health behaviours were collected using the COMPASS student questionnaire (Cq). A full description of the COMPASS study along with its methods is available online (www.compass.uwaterloo.ca) and in print [18]. The University of Waterloo Research Ethics Board along with participating school board review panels approved all procedures used.

Participants

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At baseline, data were gathered from 45,298 grade 9 to 12 students (response rate of 79.2%) attending 89 Ontario and Alberta secondary schools. At follow-up, data were gathered from 40,436 grade 9 to 12 secondary students (response rate of 79.9 %) attending 81 Ontario and Alberta secondary schools. The vast majority of missing respondents were a result of students being absent or on a spare during the data collection period; missing respondents due to parental refusal was limited (~0.4 %).

Data Linkage

To examine longitudinal changes among individuals, we linked student responses at baseline and follow-up using a unique code generated by each student [21]. A total of 11,215 students in grades 9, 10 and 11 from 79 schools could be linked across both time points. We excluded students who reported ever having tried a cigarette at baseline (n=1,527) or who had missing data for any predictors/covariates (n=187), leaving a final linked sample of 9,501 students.

Measures

Susceptibility to future smoking among never smoking students was measured using three validated measures: “Do you think in the future you might try smoking cigarettes?”, “If one of your best friends were to offer you a cigarette, would you smoke it?”, and “At any time during the next year, do you think you will smoke a cigarette?” Consistent with Pierce’s validated construct [11], individuals who responded “definitely not” to all three questions were categorized as non-susceptible to future smoking (i.e., low risk). Individuals who responded positively to at least one item were categorized as susceptible to future smoking (i.e., high risk).

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Current (past 30 day) use of e-cigarettes was measured by asking students the following question: "In the last 30 days, did you use any of the following? (Mark all that apply)". Students could choose one or more tobacco/nicotine products, including e-cigarettes (electronic cigarettes that look like cigarettes/cigars, but produce vapour instead of smoke). Respondents who reported having used e-cigarettes in the past 30 days were categorized as current e-cigarette users, while all others were categorized as non-current users.

Students also self-reported their gender (male or female), grade (9, 10, 11, 12) and ethnicity (Black, White, Asian, Latin-American, Aboriginal, Other/Mixed). Students' social environment was measured by asking "How many of your closest friends smoke cigarettes?" ("None" to "5 or more friends").

ANALYSES

Changes to self-reported susceptibility to future smoking were identified between baseline and follow-up among the sample of current and non-current e-cigarette users. Simple descriptive statistics examined the baseline characteristics of current and non-current e-cigarette users; chi-square tests identified differences between current and non-current e-cigarette users at baseline. We conducted two logistic regression models. The first, a multinomial logistic regression model, assessed whether e-cigarette use among non-susceptible youth at baseline predicted susceptibility to future smoking and smoking initiation at follow-up. The second, a binary logistic regression model assessed whether e-cigarette use among susceptible youth at baseline predicted smoking initiation at follow-up. Both models controlled for gender, grade, self-reported ethnicity, the number of friends that smoke cigarettes at baseline and student-level clustering within schools, as these covariates have been seen to influence smoking susceptibility outcomes.

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RESULTS

Table 1 presents the baseline characteristics of current and non-current e-cigarette users. At baseline, significantly more male students, grade 10 students, students with friends that smoked cigarettes, and susceptible never-smokers reported current e-cigarette use than non-current e-cigarette use.

Table 1. Baseline characteristics of current and non-current e-cigarette users among students that reported never smoking cigarettes at baseline, 2013-2016 COMPASS study

Variable				Chi-square	
		Non-Current E-cigarette Users (n=9295)	Current E-cigarette Users (n=206)	df	p-value
Grade	9	54.8 (5098)	51.5 (106)	2	0.6117
	10	42.2 (3923)	45.6 (94)		
	11	2.9 (274)	2.9 (6)		
Gender	Female	52.6 (4889)	37.9 (78)	1	<.0001
	Male	47.4 (4406)	62.1 (128)		
Race	White	70.9 (6590)	65.0 (134)	5	0.0015
	Black	2.6 (239)	4.9 (10)		
	Asian	4.7 (440)	1.0 (2)		
	Off-Reserve Aboriginal	0.9 (83)	1.9 (4)		
	Hispanic/Latin American	1.0 (97)	2.4 (5)		
	Other/Mixed	19.9 (1846)	24.8 (51)		
Number of friends that smoke cigarettes	None	81.7 (7594)	63.6 (131)	3	<.0001
	1	10.7 (997)	19.4 (40)		
	2	4.4 (408)	8.7 (18)		
	3 or more	3.2 (296)	8.3 (17)		
Susceptibility to future cigarette smoking	Not susceptible	71.2 (6616)	35.4 (73)	1	<.0001
	Susceptible	28.8 (2679)	64.6 (133)		

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Figure 1 presents the smoking status of current and non-current e-cigarette users at follow-up among baseline non-susceptible never smokers. It is apparent that more current e-cigarette users reported trying tobacco cigarettes at follow-up relative to non-current e-cigarette users; roughly half of current e-cigarette users at baseline proceeded to trying a cigarette at follow-up. Figure 1 also presents the smoking status of current and non-current e-cigarette users at follow-up among baseline susceptible never smokers. Similarly, a larger proportion of current e-cigarette users reported trying cigarette smoking at follow-up, in comparison to non-current e-cigarette users.

Figure 2 presents the adjusted odds of being susceptible to future smoking or trying cigarette smoking at follow-up among susceptible and non-susceptible current e-cigarette users at baseline (relative to non-current users). After controlling for relevant covariates, non-susceptible current e-cigarette users at baseline were significantly more likely to become susceptible to future smoking and try cigarette smoking at follow-up relative to non-current e-cigarette users. Similarly, susceptible current e-cigarette users at baseline were significantly more likely to try cigarette smoking at follow-up relative to non-current e-cigarette users.

DISCUSSION

Within the sample of never cigarette smokers at baseline, this study found that current e-cigarette users were at a higher risk of cigarette smoking initiation after a two-year follow-up period. These findings were consistent with previous studies that have demonstrated that adolescents with a history of e-cigarette use were a greater risk for future cigarette use [9, 13]. Of concern, the observed association between e-cigarette use and smoking initiation was found to be even stronger among individuals that were not susceptible to future smoking (i.e., low risk).

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These results support public health concerns that electronic cigarette use may contribute towards the development of a new population of cigarette smokers [13, 16], even among adolescents at low risk of future smoking experimentation.

Our results demonstrated an increased risk of smoking experimentation with current e-cigarette use at baseline; however, only a small percentage of non-smoking students reported using e-cigarettes in the past 30 days (4.0 %). Though this may be seen as having a small overall effect with regards to the public health implications, it should be noted that prior work has demonstrated that a substantial number of adolescents have tried using e-cigarettes and that never smokers comprise the largest population of youth [21-22]. As such, continued surveillance is crucial to monitor the use of e-cigarettes among non-smoking and smoking youth populations.

The use of e-cigarettes by non-susceptible never smoking youth may be explained in part by the availability of appealing flavouring agents including candy or fruit-flavours. Currently, there are over 7000 distinct flavours available for the e-liquid solutions used in e-cigarettes [23]. A recent review identified that the preference for sweetened tobacco products was higher among youth than adult populations [24]. Previous research has also shown the growing appeal of flavoured tobacco products among Canadian adolescents [25]. Banning e-cigarette flavours to limit their attractiveness may be an important step to reduce the appeal of these products to youth.

Additionally, e-cigarette promotion has proliferated through a number of channels including billboards, radio, television advertising, celebrity endorsement and online media platforms [26-27]. It may be that the widespread promotion of these products have had unintended consequences of re-normalizing cigarette smoking and shifting social norms

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surrounding smoking, especially among low risk youth populations [28-29]. These marketing strategies may undermine wider tobacco control policies by inadvertently promoting smoking.

Although some evidence exists to support the notion that e-cigarettes may be a less harmful alternative to cigarette smoking [30], it is also important to simultaneously consider the potential for harm creation among a population of non-smoking youth who would not have normally considered trying tobacco cigarettes. E-cigarettes may potentially lead to a rise in tobacco initiation rates, if youth who would not have otherwise tried smoking begin experimenting with e-cigarettes and then transition to using other tobacco products. Our findings reinforce the need for a comprehensive approach that addresses all forms of tobacco products in youth-focused prevention efforts, moving forward.

The findings from this study hold important implications at a time when regulation surrounding the sales and promotion of e-cigarettes is either being tabled or passed in various jurisdictions [31]. For instance, within Canada, Bill S-5 will take existing regulations and restrictions on tobacco products and extend them to vaping products (http://www.parl.ca/DocumentViewer/en/42-1/bill/S-5/third-reading). Our findings lend support to the need for appropriate regulations that will reduce the appeal of e-cigarettes and discourage use among non-smoking youth.

The study has various strengths including the use of a large, longitudinal, school-based sample from two jurisdictions, Ontario and Alberta. Another key strength of this study included the use of passive consent procedures, which reduces the chances of producing a biased sample and increases participation rates [32]. However, the study is also subject to some limitations. For instance, the study was not able to assess the reasons behind e-cigarette use among the baseline sample of current e-cigarette users, as this question was only introduced in Year 4 of COMPASS

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(2015-2016). However, moving forward, future longitudinal work may assess the main reasons driving youth e-cigarette use. In addition, the measures of e-cigarette use did not provide any information about the types of e-cigarettes used (e.g. flavoured/non-flavoured, with/without nicotine, mod/tank). Thus, associations between specific kinds of e-cigarettes and cigarette smoking initiation could not be examined. Lastly, this study focused solely on cigarette smoking initiation; future research should focus on examining other outcomes (e.g. smoking progression) and also examine relationships between e-cigarette use and initiation of other tobacco products (e.g. cigars, cigarillos) among different risk groups.

CONCLUSIONS

Among non-smoking youth that were current e-cigarette users, our findings showed an increased risk of progressing to cigarette use after two years, even among adolescents that held no intentions to smoke in the future. These findings reinforce the need to adopt regulations aimed at reducing the appeal of e-cigarettes and deterring use among youth population. Additionally, our results point towards the need for sustained efforts focused on deterring the use of all forms of tobacco products, including e-cigarettes.

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Figure 1: Smoking status of current and non-current e-cigarette users among baseline non-susceptible and susceptible never smokers, 2013-2016 COMPASS study

Figure 2: Adjusted odds ratio estimate of becoming susceptible to future smoking and trying tobacco cigarette smoking at follow-up among baseline non-susceptible and susceptible never smokers, 2013-2016 COMPASS study

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Contributors: SL designed the study. SA and AC formulated the research objectives and plan. Analysis of data was performed by WQ. SA and AC prepared the manuscript. All authors made revisions to the original draft and approved the final submitted version.

Conflict of Interest: The authors declare they have no conflicts of interest.

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Ethics Approval: Ethics approval was received by the University of Waterloo's Office of Research Ethics and all participating school boards' research ethics bodies.

Data sharing: COMPASS data is stored at the University of Waterloo on a secure server. The principal investigator of COMPASS, Dr. Leatherdale, maintains ownership of all COMPASS data, and will grant access to COMPASS research collaborators, external research groups and students. For researchers looking to gain access to COMPASS data, individuals must successfully complete the COMPASS data usage application form, which is then reviewed and approved/declined by Dr. Leatherdale.

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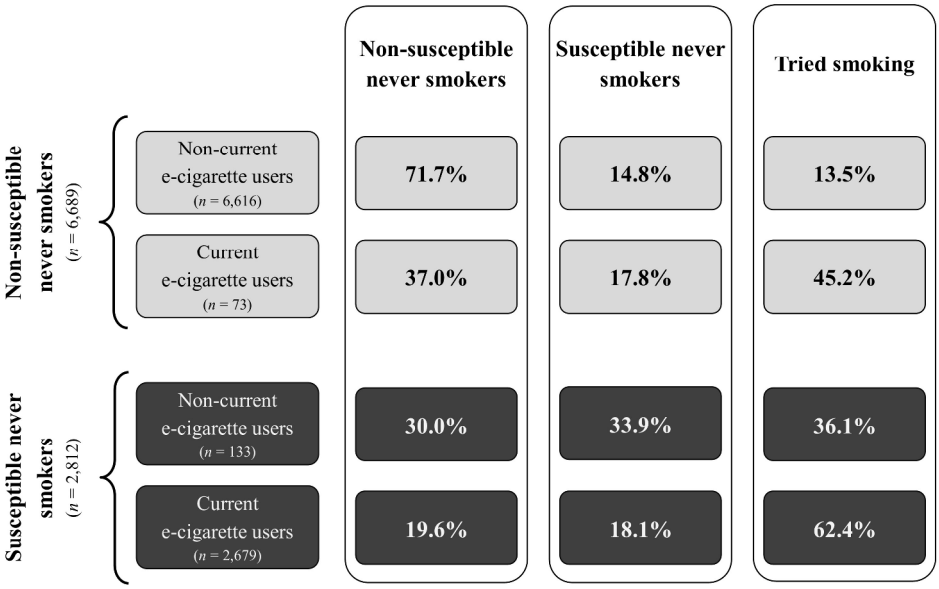

Figure 1: Smoking status of current and non-current e-cigarette users among baseline non-susceptible and susceptible never smokers, 2013-2016 COMPASS study

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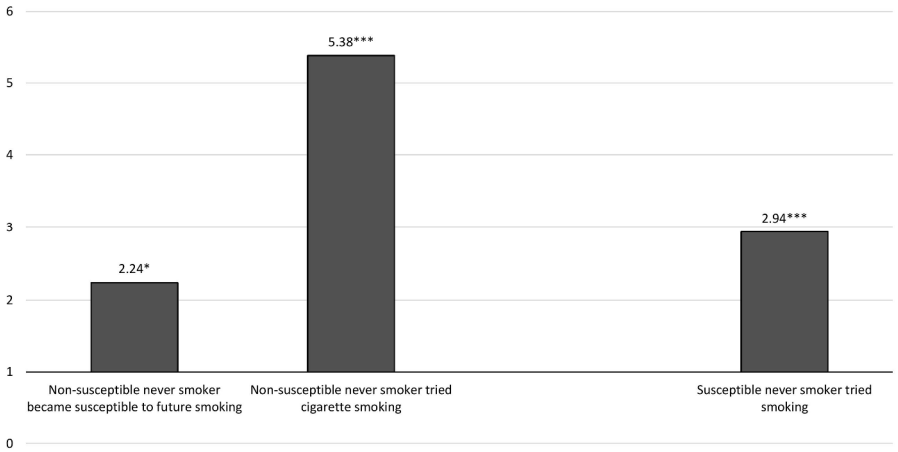

Note: Logistic regression models controlled for gender, grade, self-reported ethnicity, the number of friends that smoke cigarettes at baseline and student-level clustering within schools.

* p<0.05; ** p<0.01; *** p<0.001

Figure 3. Adjusted odds ratio estimate of becoming susceptible to future smoking and trying tobacco cigarette smoking at follow-up among baseline non-susceptible and susceptible never smokers, 2013-2016 COMPASS study

Figure 2: Adjusted odds ratio estimate of becoming susceptible to future smoking and trying tobacco cigarette smoking at follow-up among baseline non-susceptible and susceptible never smokers, 2013-2016 COMPASS study

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	**1- 2**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	**2**
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	**3-5**
Objectives	3	State specific objectives, including any prespecified hypotheses	**4-5**
Methods			
Study design	4	Present key elements of study design early in the paper	**5**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	**5-6**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	**5-6**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	**N/A**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	**6-7**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	**6- 7**
Bias	9	Describe any efforts to address potential sources of bias	**5, 10**
Study size	10	Explain how the study size was arrived at	**5-6**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	**7**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	**7**
		(*b*) Describe any methods used to examine subgroups and interactions	**7**
		(*c*) Explain how missing data were addressed	**6**
		(*d*) If applicable, explain how loss to follow-up was addressed	**6**
		(*e*) Describe any sensitivity analyses	**N/A**
Results			

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	**5-6**
		(b) Give reasons for non-participation at each stage	**5-6**
		(c) Consider use of a flow diagram	**N/A**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	**7-8**
		(b) Indicate number of participants with missing data for each variable of interest	**5-6**
		(c) Summarise follow-up time (eg, average and total amount)	**N/A**
Outcome data	15*	Report numbers of outcome events or summary measures over time	**7-8**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	**7-8**
		(*b*) Report category boundaries when continuous variables were categorized	**N/A**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	**N/A**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	**N/A**
Discussion			
Key results	18	Summarise key results with reference to study objectives	**7-8**
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	**8-11**
Generalisability	21	Discuss the generalisability (external validity) of the study results	**10**
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	**12**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Risky Business: A longitudinal study examining cigarette smoking initiation among susceptible and non-susceptible e-cigarette users in Canada

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Manuscripts

Risky Business: A longitudinal study examining cigarette smoking initiation among susceptible and non-susceptible e-cigarette users in Canada

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ABSTRACT:

Objectives: Given that many adolescent e-cigarette users are never smokers, the possibility that e-cigarettes may act as a gateway to future cigarette smoking has been discussed in various studies. Longitudinal data are needed to explore the pathway between e-cigarette and cigarette use, particularly among different risk groups including susceptible and non-susceptible never smokers. The objective of this study was to examine whether baseline use of e-cigarettes among a sample of never-smoking youth predicted cigarette smoking initiation over a two-year period.

Design: Longitudinal cohort study

Setting: 89 high schools across Ontario and Alberta, Canada.

Participants: A sample of gr. 9-11 never-smoking students at baseline (n=9501) that participated in the COMPASS study over two years.

Primary and Secondary Outcome Measures: Participants completed in-class questionnaires that assessed smoking susceptibility and smoking initiation.

Results: Among the baseline sample of non-susceptible never-smokers, 45.2% of current e-cigarette users reported trying a cigarette after two years compared to 13.5% of non-current e-cigarette users. Among the baseline sample of susceptible never-smokers, 62.4% of current e-cigarette users reported trying a cigarette after two years compared to 36.1 % of non-current e-cigarette users. Overall, current e-cigarette users were more likely to try a cigarette 2 years later. This association was stronger among the sample of non-susceptible never smokers (AOR = 5.28, 95 % CI 2.81 to 9.94; $p<0.0001$) compared to susceptible never smokers (AOR= 2.78, 95 % CI 1.84 to 4.20; $p<0.0001$).

Conclusions: Findings from this large, longitudinal study support public health concerns that e-cigarette use may contribute to the development of a new population of cigarette smokers. They also support the notion that e-cigarettes are expanding the tobacco market by attracting low-risk youth who would otherwise be unlikely to initiate using cigarettes. Careful consideration will be needed in developing an appropriate regulatory framework that prevents e-cigarette use among youth.

Keywords*: e-cigarettes, cigarettes, youth, adolescents, susceptibility*

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Strengths and Limitations of this study:

- This study assessed the relationship between e-cigarette use among never-smoking adolescents and smoking initiation using a large longitudinal sample.
- This study examined transitions in smoking behaviour among adolescents at different risk levels (i.e. susceptible and non-susceptible never smokers).
- The measures of e-cigarette use used within this study did not provide information regarding the types of e-cigarettes being used.
- This study focused solely on cigarette smoking initiation outcomes.

BACKGROUND

Despite the declining prevalence of smoking in most countries globally, tobacco use remains a threat to global health. In 2013, tobacco use accounted for the loss of approximately 6.1 million lives and 143.5 million disability-adjusted life-years (DALYs) world-wide [1-2]. Considering that the majority of smokers try their first cigarette during adolescence [3], preventing youth smoking initiation represents a key public health priority.

Electronic cigarettes are battery-operated devices that deliver nicotine and vaporize a liquid mixture made up of propylene glycol, nicotine, flavouring agents and other constituents. The rise in e-cigarette use among youth has created discussion regarding the public health implications. While some evidence does exist to support the potential of e-cigarettes to be used as smoking cessation aids and help reduce smoking-related harms among adults [4,5], others

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have argued against this considering the limited evidence of the long-term effects of e-cigarettes [6]. On the other hand, given that many adolescent e-cigarette users are never smokers [7-8], the possibility that e-cigarette use may attract new cigarette smokers among youth populations has been discussed in various studies [5,9-10]. A recent meta-analysis by Soneji et al. (2017) found consistent evidence from 9 longitudinal studies of an association between initial e-cigarette use among non-smoking adolescents and adults and subsequent cigarette smoking initiation [11]. Despite substantial evidence supporting this association [11], most longitudinal studies to date examining this relationship have been based out of the U.S., with an absence of studies assessing whether this pattern also exists within a Canadian context, where the regulatory environment for e-cigarettes differs from the U.S. Within Canada, nicotine e-cigarettes are considered medical devices requiring market authorization before advertisement or sale. Currently, no e-cigarettes with nicotine have received market approval in Canada. It is important to consider whether Canada's distinct regulatory policies that limit the sale of nicotine-containing e-cigarettes may have an impact on the relationship between adolescent e-cigarette use and subsequent cigarette smoking initiation.

Though substantial evidence exists to support the association between e-cigarette use and subsequent smoking initiation [11], few studies to date have assessed the differential association between e-cigarette use and subsequent smoking initiation among distinct risk groups, including non-susceptible never smokers (i.e., low risk) versus susceptible never smokers (i.e., high risk). Susceptibility to future smoking, defined as the lack of a firm commitment not to smoke among never smokers, is a validated and reliable predictor of tobacco cigarette smoking initiation among adolescents [12-13]. It is hypothesized that the use of e-cigarettes by never-smoking youth may increase their susceptibility to future cigarette smoking. Cross-sectional studies

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suggest that never smoking youth that have ever and currently use e-cigarettes are at increased odds of being susceptible to future smoking, with a stronger association identified among younger students [14-16]. To our knowledge, only two longitudinal studies have examined the progression from non-susceptible never smoker to susceptible never smoker or ever smoker among e-cigarette and non-e-cigarette users; however, both studies included older adolescent and young adult populations. The first longitudinal study identified that youth and young adult non-susceptible never smokers that used e-cigarettes at baseline were more likely to become susceptible never smokers and try smoking cigarettes at 1 year follow-up, compared to those who did not smoke e-cigarettes at baseline [17]. The second longitudinal study identified that among a sample of older adolescents, non-susceptible never smokers that used e-cigarettes at baseline were more likely to initiate cigarette smoking after 16 months, compared to never users of e-cigarettes at baseline [18].

Previous longitudinal studies assessing the potential association between e-cigarette use and subsequent cigarette smoking initiation among non-smoking youth have focused on older adolescents and young adults and generally had shorter follow-up periods [17-18]. These studies have also all taken place in the United States. Additional longitudinal work incorporating a sample of younger adolescents, a longer follow-up period, and different regulatory contexts is needed to explore the potential association between e-cigarette use and subsequent cigarette use among different risk groups and in different contexts. This study examined whether baseline use of e-cigarettes among a Canadian sample of susceptible and non-susceptible never-smoking youth was associated with cigarette smoking initiation over a two-year follow-up.

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METHODS

Design

COMPASS is a prospective cohort study (2012-2021) designed to gather longitudinal and hierarchical data from a sample of secondary school students in Canada [19]. This paper reports on longitudinal findings between Year 2 (2013-2014) and Year 4 (2015-2016) of the study among a sample of schools that agreed to the use of active-information passive consent permission procedures. Year 2 data were selected as baseline due to the larger sample size [20] and since this was the first year e-cigarette use was assessed. Data relating to student health behaviours were collected using the COMPASS student questionnaire (Cq). A full description of the COMPASS study along with its methods is available online (www.compass.uwaterloo.ca) and in print [19]. The University of Waterloo Research Ethics Board along with participating school board review panels approved all procedures used.

Participants

In Year 2, data were gathered from 45,298 grade 9 to 12 students (response rate of 79.2%) attending 89 secondary schools located within the Canadian provinces of Ontario and Alberta. In Year 4, data were gathered from 40,436 grade 9 to 12 secondary students (response rate of 79.9 %) attending 81 Ontario and Alberta secondary schools. The vast majority of missing respondents were a result of students being absent or on a spare (i.e., scheduled free period) during the data collection period; missing respondents due to parental refusal was limited (~0.4 %).

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Data Linkage

To examine longitudinal changes among individuals, we linked student responses at Year 2 and Year 4 using a unique code generated by each student [21]. The process of linking student-level data across multiple waves is described in greater depth by Qian and colleagues [22]. The linked sample consisted of students that could be followed across both time points. As such, it was not possible to link grade 11 and 12 students in Year 2 that had already graduated and grade 9 and 10 students that were newly admitted to high school in Year 4. A total of 11,215 students who were in grades 9, 10 and 11 at Year 2 could be linked across both time points. Grade 11 students within the linked sample represented students who had not graduated high school with their peers and as such were able to participate in the study at both time points. Furthermore, students who reported ever having tried a cigarette at baseline (n=1,527) or who had missing data for any predictors/covariates (n=187) were excluded, leaving a final linked sample of 9,501 students. For ease of description, Year 2 will be considered "baseline" and Year 4 will be considered "follow-up".

Measures

Smoking initiation at baseline and follow-up was assessed by asking students: "Have you ever tried smoking a cigarette, even a puff or two?" Individuals who responded "yes" were classified as ever-smokers, while all others were classified as never smokers. We further classified the "never smokers" group as susceptible or non-susceptible to future smoking. Susceptibility to future smoking among never smoking students was assessed at baseline and follow-up using a three-item validated measure: "Do you think in the future you might try

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smoking cigarettes?", "If one of your best friends were to offer you a cigarette, would you smoke it?", and "At any time during the next year, do you think you will smoke a cigarette?" Consistent with Pierce's validated construct [12], individuals who responded "definitely not" to all three questions were categorized as non-susceptible to future smoking (i.e., low risk). Individuals who responded positively to at least one item were categorized as susceptible to future smoking (i.e., high risk).

Current (past 30 day) use of e-cigarettes at baseline was measured by asking students the following question: "In the last 30 days, did you use any of the following? (Mark all that apply)". Students could choose one or more tobacco/nicotine products, including e-cigarettes ("electronic cigarettes that look like cigarettes/cigars, but produce vapour instead of smoke"). Respondents who reported having used e-cigarettes in the past 30 days were categorized as current e-cigarette users, while all others were categorized as non-current users.

Students also self-reported their gender (male or female), grade (9, 10, 11, 12) and ethnicity (Black, White, Asian, Latin-American, Aboriginal, Other/Mixed) at baseline. Students' social environment was measured by asking "How many of your closest friends smoke cigarettes?" ("None" to "5 or more friends") at baseline. Students' weekly spending money at baseline was also measured by asking "About how much money do you usually get each week to spend on yourself or to save?" with response options of zero, $1 to $5, $6 to $10, $11 to $20, $21 to $40, $41 to $100, more than $100 and "I do not know how much I get each week".

Patient and Public Involvement

There were no patients involved in the development of the research questions and outcome measures, the design of the study or the recruitment to and conduct of the study.

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ANALYSES

Descriptive statistics were used to examine changes in self-reported susceptibility to future smoking at follow-up among never smokers, stratifying by e-cigarette use and cigarette smoking susceptibility at baseline. Descriptive statistics examined the baseline characteristics of current and non-current e-cigarette users; chi-square tests identified differences between current and non-current e-cigarette users at baseline.

For longitudinal analyses, the PROC GENMOD procedure (present on SAS 9.4) was used to fit Generalized Estimating Equation (GEE) models using the repeated statement. GEE models are an extension of generalized linear models that allow for the analysis of correlated observations (i.e., students clustered within schools) [23]. Using GEE, two logistic regression models assessed the relationship between baseline e-cigarette use and smoking susceptibility at follow-up, stratifying by smoking susceptibility at baseline. The first, a multinomial logistic regression model, assessed whether e-cigarette use among non-susceptible (i.e., low-risk) youth at baseline predicted susceptibility to future smoking and smoking initiation at follow-up. The second, a binary logistic regression model, assessed whether e-cigarette use among susceptible (i.e., high-risk) youth at baseline predicted smoking initiation at follow-up. Both models controlled for gender, grade, self-reported ethnicity, self-reported spending money and the number of friends that smoke cigarettes at baseline, as these covariates have been seen to influence smoking susceptibility outcomes. The alpha level used for all statistical analyses was 0.05.

RESULTS

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Table 1 presents the baseline characteristics of current and non-current e-cigarette users. At baseline, a significantly higher proportion of current (past-30 day) e-cigarette users reported being male, relative to those who had not used e-cigarettes in the past 30 days. A significantly higher proportion of current e-cigarette users also reported having friends that smoked cigarettes and reported being susceptible to smoking cigarettes in the future, relative to those who had not used e-cigarettes in the past 30 days.

Table 1. Baseline characteristics of current and non-current e-cigarette users among students that reported never smoking cigarettes at baseline, 2013-2016 COMPASS study

Variable		Current (Past-30 day) E-cigarette Users		Chi-square	
		No (n=9295)	Yes (n=206)	df	p-value
Grade	9	54.8 (5098)	51.5 (106)	2	0.6117
	10	42.2 (3923)	45.6 (94)		
	11	2.9 (274)	2.9 (6)		
Gender	Female	52.6 (4889)	37.9 (78)	1	<.0001
	Male	47.4 (4406)	62.1 (128)		
Race	White	70.9 (6590)	65.0 (134)	5	0.0015
	Black	2.6 (239)	4.9 (10)		
	Asian	4.7 (440)	1.0 (2)		
	Off-Reserve Aboriginal	0.9 (83)	1.9 (4)		
	Hispanic/Latin American	1.0 (97)	2.4 (5)		
	Other/Mixed	19.9 (1846)	24.8 (51)		
Number of friends that smoke cigarettes	None	81.7 (7594)	63.6 (131)	3	<.0001
	1	10.7 (997)	19.4 (40)		
	2	4.4 (408)	8.7 (18)		
	3 or more	3.2 (296)	8.3 (17)		
Susceptibility to future cigarette smoking	Not susceptible	71.2 (6616)	35.4 (73)	1	<.0001
	Susceptible	28.8 (2679)	64.6 (133)		
Weekly Spending Money	Zero	21.8 (2022)	11.2 (23)	4	<0.0001
	$1-20	38.6 (3584)	36.9 (76)		
	$21-100	20.4 (1898)	29.1 (60)		

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	More than $100	4.9 (454)	9.7 (20)		
	I don't know how much money I get each week/Not stated	14.1 (1337)	13.1 (27)		

Figure 1 presents the smoking status at follow-up among baseline never-smokers of tobacco cigarettes. The results are stratified by e-cigarette use and cigarette smoking susceptibility at baseline. Among non-susceptible never smokers, it is apparent that a higher proportion of current e-cigarette users reported trying tobacco cigarettes at follow-up compared to those who did not report using e-cigarettes in the past 30 days; roughly half of current e-cigarette users at baseline proceeded to trying a cigarette at follow-up. Similarly, among susceptible never smokers, a larger proportion of current e-cigarette users reported trying cigarette smoking at follow-up compared to those who did not report using e-cigarettes in the past 30 days.

Figure 2 presents the adjusted odds of being susceptible to future smoking or trying cigarette smoking at follow-up among susceptible and non-susceptible current e-cigarette users at baseline (relative to non-current users). After controlling for relevant covariates, non-susceptible current e-cigarette users at baseline were significantly more likely to become susceptible to future smoking and try cigarette smoking at follow-up relative to non-current e-cigarette users. Similarly, susceptible current e-cigarette users at baseline were significantly more likely to try cigarette smoking at follow-up relative to non-current e-cigarette users.

DISCUSSION

Within the sample of never cigarette smokers at baseline, this study found that current e-cigarette users were at a higher risk of cigarette smoking initiation after a two-year follow-up

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period. These findings were consistent with previous studies that have demonstrated that adolescents with a history of e-cigarette use were at greater risk for future cigarette use compared to non-users of e-cigarettes [10, 14]. Of concern, the observed association between e-cigarette use and smoking initiation was even stronger among individuals that were not susceptible to future smoking (i.e., low risk). These results support public health concerns that electronic cigarette use may contribute towards the development of a new population of cigarette smokers [14, 17], even among adolescents at low risk of future smoking experimentation.

The study findings demonstrated that only a small percentage of non-smoking students reported using e-cigarettes in the past 30 days (4.0 %). The small proportion of e-cigarette users may be interpreted as unlikely to result in large effects when assessing public health harms brought on by non-smoking youth that transition from using e-cigarettes to traditional cigarettes. However, it should be noted that prior work has demonstrated that a substantial number of Canadian youth have tried using e-cigarettes and that never smokers comprise the largest population of youth [24-25]. Furthermore, our findings clearly demonstrate that never smokers that reported using e-cigarettes in the past 30 days were at an increased risk of transitioning to cigarette smoking after two years. As such, continued surveillance and monitoring of e-cigarette use and its relationship with cigarette smoking among youth populations should be considered a public health priority.

The use of e-cigarettes by non-susceptible never smoking youth may be explained in part by the availability of appealing flavouring agents including candy or fruit-flavours. Currently, there are over 7000 distinct flavours available for the e-liquid solutions used in e-cigarettes [26]. A recent review identified that the preference for sweetened tobacco products was higher among youth than adult populations [27]. Previous research has also shown the growing appeal of

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flavoured tobacco products among Canadian adolescents [28]. Banning e-cigarette flavours may be an important step to reduce the appeal of these products to youth.

Additionally, e-cigarette promotion has proliferated through a number of channels including billboards, radio, television advertising, celebrity endorsement and online media platforms [29-30]. It may be that the widespread promotion of these products have had unintended consequences of re-normalizing cigarette smoking and shifting social norms surrounding smoking, especially among low risk youth populations [31-32]. These marketing strategies may undermine wider tobacco control policies by inadvertently promoting smoking.

Although some evidence exists to support the notion that e-cigarettes may be a less harmful alternative to cigarette smoking [33], it is also important to simultaneously consider the potential for harm creation among a population of non-smoking youth who would not have normally considered trying tobacco cigarettes. E-cigarettes may potentially lead to a rise in cigarette smoking initiation rates, if youth who would not have otherwise tried smoking begin experimenting with e-cigarettes and then transition to using cigarettes and other tobacco products [6]. In addition to the harms associated with transitioning to traditional cigarettes, it is also important to consider the health risks nicotine-containing e-cigarettes pose to youth, as nicotine has been seen to alter the developing adolescent brain [34-35]. Our findings reinforce the need for a comprehensive approach that addresses all forms of tobacco products in youth-focused prevention efforts, moving forward.

The findings from this study hold important implications at a time when regulation surrounding the sales and promotion of e-cigarettes is either being tabled or passed in various jurisdictions [36]. For instance, within Canada, Bill S-5 will aim to regulate the manufacturing, sale, labelling and promotion of e-cigarettes. Some of the measures within this Bill include

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banning the sale of vaping products to Canadians under the age of 18, restricting the promotion of flavours that are appealing among youth populations (e.g., dessert flavours) and limiting promotional activities that would be considered appealing to youth. Our findings lend support to the need for appropriate regulations that will reduce the appeal of e-cigarettes and discourage use among non-smoking youth.

The study has various strengths including the use of a large, longitudinal, school-based sample from two Canadian jurisdictions, Ontario and Alberta. This is one of the few studies documenting the transition from e-cigarette use to cigarette smoking initiation among a non-U.S. sample of non-smoking youth, illustrating that this pattern of behaviour is not specific to U.S. adolescents. Another key strength of this study included the use of passive consent procedures, which reduces the chances of producing a biased sample and increases participation rates [37]. However, the study is also subject to some limitations. First, the study used non-probability sampling methods and as such was not representative of all Ontario and Alberta high schools [19]. As such, these findings may not be generalizable to other Canadian high schools outside of the study sample. Second, the study was not able to assess the reasons behind e-cigarette use among the baseline sample of current e-cigarette users, as this question was only introduced in Year 4 of COMPASS (2015-2016). However, future longitudinal work may assess the main reasons driving youth e-cigarette use. In addition, the measures of e-cigarette use did not provide any information about the types of e-cigarettes used (e.g. flavoured/non-flavoured, with/without nicotine, mod/tank). Thus, associations between specific kinds of e-cigarettes and cigarette smoking initiation could not be examined. Lastly, this study focused solely on cigarette smoking initiation; future research should focus on examining other outcomes (e.g. smoking progression)

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and also examine relationships between e-cigarette use and initiation of other tobacco products (e.g. cigars, cigarillos) among different risk groups.

CONCLUSIONS

Among non-smoking youth that were current e-cigarette users, our findings showed an increased risk of progressing to cigarette use after two years. Of concern, low-risk youth at baseline were at an even greater risk of cigarette smoking initiation at follow-up. These results suggest that e-cigarettes are expanding the tobacco cigarette market by attracting low-risk youth who would not have otherwise tried using cigarettes. These findings reinforce the need to adopt regulations aimed at reducing the appeal of e-cigarettes and deterring use among youth populations. Additionally, our results point towards the need for sustained efforts focused on deterring the use of all forms of tobacco products, including e-cigarettes.

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Figure 1: Smoking status of current and non-current e-cigarette users among baseline non-susceptible and susceptible never smokers, 2013-2016 COMPASS study

Figure 2: Adjusted odds ratio estimate of becoming susceptible to future smoking and trying tobacco cigarette smoking at follow-up among baseline non-susceptible and susceptible never smokers, 2013-2016 COMPASS study

Contributors: SL designed the study. SA and AC formulated the research objectives and plan. Analysis of data was performed by WQ. SA and AC prepared the manuscript. All authors made revisions to the original draft and approved the final submitted version.

Conflict of Interest: The authors declare they have no conflicts of interest.

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Ethics Approval: Ethics approval was received by the University of Waterloo's Office of Research Ethics and all participating school boards' research ethics bodies.

Data sharing: COMPASS data is stored at the University of Waterloo on a secure server. The principal investigator of COMPASS, Dr. Leatherdale, maintains ownership of all COMPASS data, and will grant access to COMPASS research collaborators, external research groups and

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students. For researchers looking to gain access to COMPASS data, individuals must successfully complete the COMPASS data usage application form, that is available online (https://uwaterloo.ca/compass-system/information-researchers), which is then reviewed and approved/declined by Dr. Leatherdale.

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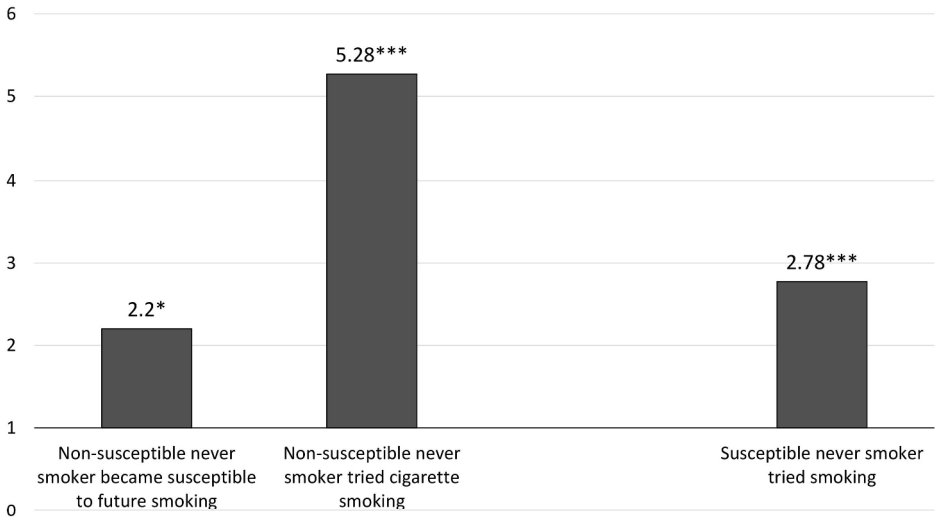

Note: Logistic regression models accounted for student-level clustering within schools and controlled for gender, grade, self-reported ethnicity, the number of friends that smoke cigarettes at baseline, and weekly spending money at baseline.

* p<0.05; ** p<0.01; *** p<0.001

Figure 2: Adjusted odds ratio estimate of becoming susceptible to future smoking and trying tobacco cigarette smoking at follow-up among baseline non-susceptible and susceptible never smokers, 2013-2016 COMPASS study

254x190mm (300 x 300 DPI)

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	**1- 2**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	**2**
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	**3-5**
Objectives	3	State specific objectives, including any prespecified hypotheses	**4-5**
Methods			
Study design	4	Present key elements of study design early in the paper	**6**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	**6-7**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	**6-7**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	**N/A**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	**7-8**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	**7-8**
Bias	9	Describe any efforts to address potential sources of bias	**6, 14**
Study size	10	Explain how the study size was arrived at	**6-7**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	**8-9**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	**8-9**
		(*b*) Describe any methods used to examine subgroups and interactions	**9**
		(*c*) Explain how missing data were addressed	**7**
		(*d*) If applicable, explain how loss to follow-up was addressed	**7**
		(*e*) Describe any sensitivity analyses	**N/A**
Results			

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	**6-7**
		(b) Give reasons for non-participation at each stage	**6-7**
		(c) Consider use of a flow diagram	**N/A**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	**9-10**
		(b) Indicate number of participants with missing data for each variable of interest	**7**
		(c) Summarise follow-up time (eg, average and total amount)	**N/A**
Outcome data	15*	Report numbers of outcome events or summary measures over time	**10-11**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	**9-11**
		(*b*) Report category boundaries when continuous variables were categorized	**N/A**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	**N/A**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	**N/A**
Discussion			
Key results	18	Summarise key results with reference to study objectives	**11-12**
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	**11-14**
Generalisability	21	Discuss the generalisability (external validity) of the study results	**14**
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	**16**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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