



Confounders or intermediate variables? Testing mechanisms for the relationship between depression and smoking in a longitudinal cohort study



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HIGHLIGHTS

- The relationship of depressive symptoms and smoking is a complex one.
- Care must be taken to differentiate between intermediate variables and confounders.
- Pathways between depressive symptoms and smoking varied by the direction of effect.
- Stress and friend smoking were important intermediate variables.

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ABSTRACT

Introduction: The relationship between the onset of smoking and the onset of depression among adolescents has been well documented, but the mechanisms underlying the relationship are unclear. This paper uses an empirical method to assess potential intermediate variables in the pathway between changes in depressive symptoms and cigarette smoking in a longitudinal cohort of adolescents.

Methods: 837 participants from a cohort in Montreal, Canada who had not smoked and did not have elevated depressive symptoms at baseline were followed for five years from 1999 to 2003. The role of a set of 15 variables previously identified in the literature as potential confounders were systematically evaluated as predictors of exposure and outcome, for attenuation of the association by more than 10%, and for intra-individual change in the variable after onset of exposure.

Results: The magnitude of the association between smoking and depressive symptoms was fully attenuated after adjustment for all variables included indiscriminately. A concept map was developed detailing the empirical associations between the variables within this data set. Stress, worry about weight, and worry about parents were identified as intermediate variables for both smoking predicting depressive symptoms and depressive symptoms predicting smoking. Cox regressions with appropriate confounders maintained statistical significance.

Conclusion: Cigarette smoking is associated with higher depressive symptoms prior to and after inclusion of empirical confounders. Inclusion of intermediate variables in multivariable models can lead to the erroneous conclusion that there is no association between smoking and depression.

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1. Introduction

The association between smoking and depression or depression symptoms has been well documented over the last 30 years, but to

date there is neither consensus on the mechanisms underlying the relationship, nor on the potential temporal order—that is, whether smoking precedes depression, or depression precedes smoking (Chaiton, Cohen, O'Loughlin, & Rehm, 2009; Paperwalla, Levin, Weiner, & Saravay, 2004). An estimated 150 million adolescents worldwide use tobacco and nearly 5 million deaths are attributed to tobacco use annually. Further, depression is the number one cause of disability worldwide.

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The magnitude of the association between smoking and depression has been shown to be substantially reduced after controlling for potential confounders (Black, Zimmerman, & Coryell, 1999; Brown, Lewinsohn, Seeley, & Wagner, 1996; Dierker, Avenevoli, Stolar, & Merikangas, 2002; Federman, Costello, Angold, Farmer, & Erkanli, 1997). Chaiton et al. (2009) compiled a list of variables (Table 1) previously incorporated as confounders in longitudinal cohort analyses of the relationship between smoking and depression (Chaiton et al., 2009). These variables were included in multivariate models to, explicitly or implicitly, account for the theory that the apparent association between smoking and depression is spurious due to a common underlying variable (Breslau, Peterson, Schultz, Chilcoat, & Andreski, 1998; Park & Romer, 2007). Because these variables have been included as potential confounders in previous analyses, it is possible to suggest that, based on previous literature, all these variables should be included in future analyses.

A confounder must be associated with both the exposure and the outcome; and in addition must affect the value of the estimate of the relationship between the exposure and the outcome (Boslaugh, 2008). A 10 percent difference between the unadjusted and adjusted estimate of effect has been proposed as a guideline for whether or not the variable affects the estimate of the relationship between the exposure and the outcome substantively (Rothman, Greenland, & Lash, 2008). Similar to a confounder, an intermediate variable (also termed a “mediator”) is associated with both exposure and outcome, and will also affect the estimate of the relationship of the exposure and the outcome. In contrast to a confounder, an intermediate variable is a consequence of the exposure as it lies on the causal pathway between the exposure and the outcome (Greenland, 2008). That is, the onset of the exposure should lead to changes in the mediator which occur prior to the onset of the outcome. Adding intermediate variables into the model could obscure a real association between depression and smoking by over-controlling for the causal impact (Greenland, 2008).

However, Duncan and Rees argued that several purported confounders (i.e., stress, academic performance, self-esteem) might in fact be intermediate (rather than confounding) variables that lie on the causal pathway between smoking and depression (Duncan & Rees, 2005). Several theories have been proposed to explain the mechanisms underlying the association between smoking and depression (Breslau

et al., 1998; Johnson, Rhee, Chase, & Breslau, 2004; Kendler et al., 1993) and, depending on the theory, the same set of variables could quite legitimately be considered either as confounders or intermediate variables or both in the causal pathway. Consequently, existing theory offers little guidance as to the appropriate role of variables.

This paper examines the effect of a wide range of variables previously conceptualized as confounders, on the longitudinal relationship between smoking and depressive symptoms. It quantifies the effect of the variables on the relationship between smoking and depressive symptoms, and it then uses the empirical information to develop a concept map of the factors that affect the relationship between smoking and depressive symptoms.

2. Materials and methods

2.1. Population and design

The NDI Study is a longitudinal cohort study (1999–2005) designed to investigate the natural course of early cigarette use and the development of nicotine dependence in novice smokers. The cohort included 1293 students initially aged 12–13 years recruited from all grade seven classes in a sample of ten secondary schools in Montreal, Canada. Secondary schools were purposively selected to include a mix of French and English schools, urban, suburban, and rural schools, and schools located in high and low socioeconomic neighbourhoods, all with a relatively low turnover of students. Thirteen schools were approached and agreed to participate. However, two schools were excluded due to a low return of signed parental consent forms, and one school was excluded because the school administrators could not guarantee cooperation over the entire study.

All students in all Secondary I (grade 7) classes at participating schools were invited to participate. Potential participants were given an information letter to bring home to their parents. Signed informed guardian consent and student consent were obtained from all participants and from a parent or guardian. Over half of eligible students (56.2%) participated in the baseline data collection. This relatively low response was due, in part, to a labour dispute that resulted in teachers in several schools refusing to collect consent forms. Blood sampling needed for genetic analysis also likely affected the response adversely.

Table 1

Variables included in final multivariate models reported in longitudinal studies that examined the association between smoking and depression in adolescents (Eppel, O’Loughlin, Paradis, & Platt, 2006).

Variable	Variable included in current study	Citation numbers of study(ies) that included variable in the final multivariate model
Age	Age	(all)
Sex	Sex	(all)
Alcohol use	Alcohol use	Audrain-McGovern, Lerman, Wileyto, Rodriguez, & Shields (2004), Fergusson, Goodwin, & Horwood (2003), Killen et al. (1997), Patton et al. (1998), Skara, Sussman, & Dent (2001), Windle & Windle (2001), Wu & Anthony (1999)
Parental education	Parent education	Brook, Schuster, & Zhang (2004), Brown et al. (1996), Duncan & Rees (2005), Escobedo et al. (1998), Silberg et al. (2003), Skara et al. (2001)
Race/ethnic group	Percent life in Canada	Audrain-McGovern et al. (2004), Brown et al. (1996), Escobedo et al. (1998), Fergusson et al. (2003), Goodman & Capitman (2000), Skara et al. (2001), Wu & Anthony (1999)
Smoking among peers	Friends smoking	Audrain-McGovern et al. (2004), Fergusson et al. (2003), Killen et al. (1997), Patton et al. (1998), Silberg et al. (2003), Skara et al. (2001), Windle & Windle (2001)
Parental smoking	Parental smoking	Escobedo et al. (1998), Patton et al. (1998), Silberg et al. (2003), Skara et al. (2001)
Academic performance	Academic Performance	Audrain-McGovern et al. (2004), Escobedo et al. (1998), Fergusson et al. (2003), Skara et al. (2001)
Physical activity	Physical Activity	Audrain-McGovern et al. (2004), Patton et al. (1998)
Stress/anxiety	Stress/Worry about parents/Worry about weight	Costello, Erkanli, Federman, & Angold (1999), Fergusson et al. (2003), O’Loughlin et al. (2002)
Novelty-seeking	Novelty-seeking	Fergusson et al. (2003)
Temperament	Impulsivity	Windle & Windle (2001)
Self-esteem	Self-esteem	Fergusson et al. (2003)
Parental attachment	—	Fergusson et al. (2003)
Social support	—	Windle & Windle (2001)
Marijuana/other drug use	—	Audrain-McGovern et al. (2004), Brook et al. (2004), Skara et al. (2001), Windle & Windle (2001)
Childhood adversity	—	Fergusson et al. (2003)
Conduct problems	—	Fergusson et al. (2003), Silberg et al. (2003)

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