Drug and Alcohol Dependence 200 (2019) 64–70

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Testing the reciprocal association between smoking and depressive symptoms from adolescence to adulthood: A longitudinal twin study

Anu Ranjit[a,*], Tellervo Korhonen[b], Jadwiga Buchwald[b], Kauko Heikkilä[b], Annamari Tuulio-Henriksson[c], Richard J. Rose[d], Jaakko Kaprio[a,b], Antti Latvala[b]

[a] Department of Public Health, University of Helsinki, Helsinki, Finland
[b] Institute for Molecular Medicine Finland, University of Helsinki, Helsinki, Finland
[c] Department of Psychology and Logopedics, University of Helsinki, Helsinki, Finland
[d] Department of Psychological and Brain Sciences, Indiana University, Bloomington, IN, United States

ARTICLE INFO

Keywords:
Cigarette smoking
Depressive symptoms
Twins
Adolescence
Adulthood

ABSTRACT

Background: Longitudinal studies enhance understanding of the complex reciprocal relationship between smoking and depression from adolescence to young adulthood. Examining bi-directional associations between cigarette smoking and depressive symptoms in a genetically informative twin design can help to understand whether the associations are independent of shared genetic and environmental factors.

Methods: We analyzed longitudinal data on smoking and depressive symptoms in twins participating in the adolescent (mean age 17.5) and young adult (mean age 21.9) surveys of the FinnTwin12 study (maximum N = 2,954 individuals; 1,154 twin pairs). At both waves, self-reported depressive symptoms, assessed with the 10-item version of the General Behavior Inventory (GBI), and smoking status were analyzed. The bi-directional associations were first studied among individuals and then within monozygotic and dizygotic twin pairs.

Results: When adjusted for multiple covariates and baseline depressive symptoms, daily smokers at age 17 had higher depressive symptom scores at age 22 than never smokers (Incidence Rate Ratio = 1.17, 95% CI: 1.03–1.33). Similarly, when adjusted for covariates and baseline smoking, higher score in GBI at age 17 was associated with an increased likelihood of being a non-daily (Relative Risk Ratio (RRR) = 1.06, 95% CI: 1.01–1.11) or daily (RRR = 1.05, 95% CI: 1.00–1.10) smoker at age 22. No associations were found in within-pair analyses, suggesting that the individual-level association is explained by shared familial liabilities.

Conclusion: During the developmental period from adolescence to adulthood, cigarette smoking and depressive symptoms are reciprocally associated. However, these associations are confounded by shared genetic and other familial liabilities.

1. Introduction

Cigarette smoking and depressive symptoms are common in adolescence and young adulthood, and they often co-occur (Mathew et al., 2017; Royal College of Physicians, Royal College of Psychiatrists, 2013). Longitudinal studies have supported a bi-directional association: cigarette smoking is associated with subsequent depression, and those suffering from depression are more likely to start smoking and become nicotine dependent (Audrain-McGovern et al., 2009; Chaiton et al., 2009). However, only a few studies have investigated the directionality of the association from adolescence to young adulthood, reporting mixed results (Needham, 2007; Pedersen and von Soest, 2009; Wilkinson et al., 2016). The transition from adolescence into early adulthood is an important phase, as substance use is commonly initiated (Rimpelä et al., 2007) and the first symptoms of depression typically occur within this period (Avenevoli et al., 2015; Hankin et al., 1998). Understanding the mechanisms underlying these associations is crucial for preventive efforts towards smoking and depression.

It has been suggested that cigarette smoking can increase depressive symptoms; for example, long-term exposure to nicotine stimulates changes in serotonergic and adrenocortical function that are associated with depression (Balfour and Ridley, 2000). Further, in nicotine-dependent smokers, withdrawal symptoms resemble depressive symptoms (Epping-Jordan et al., 1998). On the other hand, depression could lead to smoking through a self-medication process, i.e., depressed individuals might smoke to alleviate depressive symptoms and as a result

* Corresponding author at: Department of Public Health, University of Helsinki, Helsinki, PO Box 20, FIN-00014, Finland.
E-mail address: anu.ranjit@helsinki.fi (A. Ranjit).

https://doi.org/10.1016/j.drugalcdep.2019.03.012
Received 11 December 2018; Received in revised form 28 February 2019; Accepted 12 March 2019
Available online 07 May 2019

have an increased risk of becoming nicotine dependent (Khantzian, 1997). A better understanding of the neurobiological and behavioral mechanisms mediating the link between smoking and depression is necessary (Rao, 2006).

Familial factors, including both genetic and environmental influences, have been found to be partly shared between smoking and depression (Kendler et al., 1993; Lyons et al., 2008; McCaffery et al., 2008; Rose et al., 2009). Thus, besides direct effects, the observed associations are likely to reflect such shared underlying liabilities. Within-twin pair analysis in monozygotic (MZ) and dizygotic (DZ) twins can elucidate shared familial influences on the association between these two measures. By comparing the levels of the outcome variable in co-twins differing on the predictor variable, the design controls for confounding due to unmeasured genetic and environmental factors influencing both variables (McGue et al., 2010). The basis of the twin design is that co-twins of both MZ and DZ pairs equally share early rearing environment, whereas DZ pairs share 50% and MZ pairs 100% of their segregating genetic alleles. However, to our knowledge, no previous study has investigated the reciprocal associations between smoking and depressive symptoms within twin pairs focusing on the transition from adolescence to early adulthood.

We studied a Finnish twin cohort from adolescence into young adulthood. The first aim was to examine the bi-directional association at the individual level, i.e., the association of smoking in adolescence with depressive symptoms in adulthood, and the association of depressive symptoms in adolescence with smoking in adulthood. The second aim was addressing the role of shared genetic and environmental influences on the associations in within-twin-pair analyses.

2. Methods

2.1. Sample

We used data from FinnTwin12, a longitudinal study of Finnish twins born in 1983–1987 (Kaprio et al., 2002; Kaprio, 2006, 2013). Ethical approval for the data collection procedures were provided by the University of Helsinki, the Helsinki and Uusimaa Hospital District Ethical Committee, and the Institutional Review Board of Indiana University, Bloomington.

FinnTwin12 includes four waves of study conducted when the twins were on average 12, 14, 17, and 22 years old. We included participants from the third and fourth study waves, i.e., twins responding to age 17 (mean age 17.5) and age 22 (mean age 21.9) questionnaires. At age 17, there were 4,236 questionnaires returned out of 4,594 mailed, a response rate of 92.2% for those already participating in earlier study waves. At age 22, 3,402 questionnaires were returned out of 4,833 mailed (70.4% response rate). A total of 2,968 individuals returned the questionnaires at both wave 3 and wave 4.

Questionnaires at both waves included information on the key variables: smoking status and depressive symptoms. For the association between smoking status at age 17 and depressive symptoms at age 22, 2,925 individuals had non-missing information on both variables. Of them, 1,012 were MZ twins (34.6%), 1,786 were DZ twins (same-sex: 30.8%, opposite-sex: 30.2% of total sample), and 127 were of unknown zygosity.

For the association between depressive symptoms at age 17 and smoking status at age 22, there were 2,954 individuals with non-missing information on both variables. Of them, 1,020 were MZ (34.5%), 1,806 were DZ (same-sex: 30.9%, opposite-sex: 30.2% of total sample), and 128 were of unknown zygosity.

2.2. Measures

2.2.1. Depressive symptoms

Depressive symptoms were assessed with the General Behavior Inventory (GBI). GBI is a self-reported inventory for mood-related behaviors such as depressive, hypomanic, and biphasic symptoms (Depue et al., 1981; Depue, 1987). We used a short version of the GBI, developed and used in previous Finnish studies (Kokko and Pulkkinen, 1998; Salmela-Aro et al., 2014). This scale consists of 10 items inquiring the occurrence of depressive symptoms, answered on a 4-point Likert scale from 0 = never to 3 = very often, and the total sum score ranges from 0-30. The coefficient alpha was 0.90 for GBI at age 17 and 0.91 at age 22, indicating excellent internal consistency for the scale.

2.2.2. Smoking status

For smoking behavior, individuals were asked “Have you ever smoked (or tried smoking, at least one cigarette)?” and the responses were either “Yes” or “No”. Those who replied “No” were considered never smokers. Never smokers served as the reference category in the analyses. Those who replied “Yes” were invited to answer more detailed smoking-related questions. To determine smoking status at the time of each survey, participants were asked “Which of the following best describes your present smoking habits?” The original responses were “I smoke 20 cigarettes or more each day”, “I smoke 10–19 cigarettes each day”, “I smoke 1–9 cigarettes each day”, “I smoke once or more a week, but not every day”, “I smoke less often than once a week”, “I am trying to or have quit smoking”, and “I have tried smoking, but I don’t smoke.” Based on these responses, a 4-class smoking status variable was created. The smoking frequency categories were combined into “Daily smokers” who smoked at least one cigarette per day, and “Non-daily smokers” who smoked less often (once a week or more often but not daily, or less often than once a week). The other categories included those reporting they had already quit or were trying to quit and were not smoking during the study period (“Quitters or trying to quit”), and those who had tried smoking but were not smoking at the time of the assessment (“Experimenters”). Furthermore, smoking status was also used as a dichotomous variable: “Never smokers” versus “Ever smokers”. Never smokers were those without any exposure, whereas ever smokers included all other smoking categories.

2.2.3. Covariates

Potential confounders to be included in the analyses were selected based on existing literature (Chaiton et al., 2015). Age, sex, educational attainment, drinking alcohol to intoxication and family structure were derived from the age 17 questionnaire. Parental smoking and educational level were derived from each parent’s questionnaire at the study baseline (wave 1). For educational attainment at age 17, a binary variable for “lower than high-school education” and “at least high-school education”, including both completed and ongoing studies, was created. High school in the Finnish context means academically oriented secondary education after the compulsory 9-year comprehensive school ends at age 16. “Lower than high-school” included individuals who did not attend school at all after age 16, repeated the last grade of compulsory school, or attended vocational training (i.e., non-academic secondary education). For assessing drinking alcohol to the point of intoxication, participants were inquired about their drinking behavior, and the responses were categorized as “never” and “drinking alcohol to intoxication”, which included all those who reported drinking to intoxication at least once a year. For determining the family structure, respondents were asked about their family members with whom they were residing, and the responses were categorized as “mother and father” and “other than mother and father” (a combined category consisting of mother and stepfather, father and stepmother, only mother, only father, or other relatives). Parental smoking was based on each parent’s questionnaire. The mother and the father were asked individually: “Have you smoked more than 5–10 packs of cigarettes in your lifetime?”. Responses from both parents were used for classifying either “both mother and father are never-smokers”, or “either mother or father, or both are ever smokers”. For parents’ educational level, both parents were asked “What is your basic education?”, with responses categorized as “lower or equal to intermediate level, i.e.,

comprehensive school with or without vocational schooling", or "academic high-school or university degree", and the highest educational level of either parent was considered.

2.3. Statistical analyses

We used negative binomial regression and multinomial logistic regression to analyze the bi-directional association between smoking status and depressive symptoms. In these analyses, twins were treated as individuals accounting for the non-independence of observations by using a robust variance estimator (Williams, 2000). We estimated Incidence Rate Ratios (IRR) and Relative Risk Ratios (RRR) with 95% confidence intervals (CI) and considered $p < 0.05$ as statistically significant.

Because of the positively skewed outcome variable with unequal mean and variance, negative binomial regression was used for the association between smoking at age 17 and depressive symptoms at age 22. The outcome variable was analyzed as a continuous count variable. In the analysis, we first adjusted for age and sex; second, we adjusted for educational attainment, drinking alcohol to intoxication, family structure, parents' educational level, and parental smoking. The final model was adjusted for all the previous covariates as well as depressive symptoms at age 17. Males and females were pooled together in the analysis because there was no evidence for a sex × smoking interaction for depressive symptoms (p = 0.45). Further, we also conducted a sensitivity analysis including only those who had a depression score of either 0 or 1 at age 17 (N = 718), reflecting none or a very low level of depressive symptoms. Participants scoring 0 or 1 constituted the first quartile of the GBI distribution. This analysis was conducted to observe whether smoking at age 17 predicted depressive symptoms at age 22 also among those who had almost no depressive symptoms at age 17, ruling out the effect of pre-existing depression.

Multinomial logistic regression was used to study the association between depressive symptoms at age 17 and smoking status at age 22. We conducted three models following a similar pattern as described above. However, the final model was additionally adjusted for smoking status at age 17, whereas drinking alcohol to intoxication was excluded because of high multicollinearity with smoking status at age 17. Further, in a sensitivity analysis, we included only those who were never smokers at age 17 (N = 914).

The individual-level analyses were also conducted using a dichotomous smoking variable (never/ever) to allow for direct comparison of estimates with those derived from within-pair analyses below. Logistic regression was used for studying the association between depressive symptoms and subsequent smoking status.

To account for shared genetic and other familial factors, we conducted within twin pair analyses. These analyses are stratified by twin pair and by design adjust for all unmeasured factors which are constant within the pair (Allison, 2009). We estimated Incidence Rate Ratios (IRR) and Odds Ratios (OR) with 95% confidence intervals (CI) and considered $p < 0.05$ as statistically significant.

For the within-pair analysis, we used fixed effects negative binomial regression for the association between smoking status at age 17 and depressive symptoms at age 22. For the association between depressive symptoms at age 17 and smoking status at age 22, we used conditional (fixed effects) logistic regression. Both analyses used the binary smoking status variable (never vs. ever smoker) in order to highlight co-twin differences related to having any experiences with smoking. The within-pair analyses were first conducted combining twin pairs of both zygosities and then separately in MZ and DZ pairs, also adjusted for sex (in DZ pairs), baseline depressive symptoms and baseline smoking status. The number of pairs discordant for smoking at age 17 and 22 was 76 and 34 in MZ twins, respectively, and 301 and 91 in DZ twins, respectively. For depressive symptoms at age 17 and 22, there were 576 and 411 MZ pairs, respectively, where the co-twins had different values. For DZ pairs, the corresponding numbers of pairs with different values were 1137 and 721, respectively. While the point estimates in the fixed effects models are derived from pairs where co-twins have different values, concordant pairs provide information for the other model parameters. Further, to capture persistent smoking exposure and depressive symptoms during adolescence, we conducted additional analyses including data also from the age 14 survey (Supplement). All statistical analyses were conducted with Stata (version 13) (StataCorp, 2013).

Table 1
Descriptive statistics of cigarette smoking and depressive symptoms by sex.

Smoking status at age 17 N (%)	Total (N = 4,200)	Male (N = 2,026)	Female (N = 2,174)
Never smokers	1,240 (29.5%)	628 (31.0%)	612 (28.1%)
Experimenters	1,189 (28.3%)	577 (28.5%)	612 (28.1%)
Quitters or trying to quit	255 (6.1%)	121 (6.0%)	134 (6.2%)
Non-daily	452 (10.8%)	183 (9.0%)	269 (12.4%)
Daily	1,064 (25.3%)	517 (25.5%)	547 (25.2%)
$\chi^2 = 13.9$, df = 4, $p < 0.01$			
Smoking status at age 22 N (%)	Total (N = 3,392)	Male (N = 1,463)	Female (N = 1,929)
Never smokers	325 (9.6%)	135 (9.2%)	190 (9.8%)
Experimenters	1,019 (30.0%)	379 (25.9%)	640 (33.2%)
Quitters or trying to quit	719 (21.2%)	301 (20.6%)	418 (21.7%)
Non-daily	400 (11.8%)	205 (14.0%)	195 (10.1%)
Daily	929 (27.4%)	443 (30.3%)	486 (25.2%)
$\chi^2 = 34.1$, df = 4, $p < 0.001$			
Depressive symptoms at age 17	Total (N = 4,222)	Male (N = 2,036)	Female (N = 2,186)
Mean (SD)	5.1 (4.9)	3.7 (4.0)	6.3 (5.4)
Median (Q1, Q3)	4 (1, 7)	3 (1, 5)	5 (2, 9)
Mann-Whitney U test: z = 18.2, $p < 0.001$			
Depressive symptoms at age 22	Total (N = 3,372)	Male (N = 1,458)	Female (N = 1,914)
Mean (SD)	4.5 (4.7)	3.6 (4.3)	5.1 (4.9)
Median (Q1, Q3)	3 (1, 7)	2 (1, 5)	4 (1, 7)
Mann-Whitney U test: z = 10.2, $p < 0.001$			

SD = Standard deviation.
Q = Quartile.

3. Results

3.1. Descriptive results

One fourth of the participants were daily smokers at age 17 (Table 1). By age 22, there was a slight increase in the proportion of current smoking (non-daily and daily smokers). At age 17 there were more never smokers among males (χ^2 (4) = 13.9, $p < 0.01$), but at age 22 there were more never smokers among females (χ^2 (4) = 34.1, $p < 0.001$). Depressive symptom scores were higher among females compared to males both at age 17 (Mann-Whitney U = 18.2, $p < 0.001$) and at age 22 (Mann-Whitney U = 10.2, $p < 0.001$).

3.2. Association between smoking status at age 17 and depressive symptoms at age 22

Smoking status at age 17 was associated with depressive symptoms at age 22 (Table 2). In the age and sex adjusted model, depressive symptom scores were 37% higher in quitters or those trying to quit, compared to never smokers, and 22% and 44% higher in non-daily and daily smokers, respectively. When adjusted for multiple covariates, the associations were slightly attenuated. Finally, when baseline depressive symptom scores were also included in the model, there was still evidence for an association of daily smoking (IRR = 1.17, 95% CI: 1.03–1.33) with the outcome. As a sensitivity procedure, we repeated the analysis including only those who had a depression score of 0 or 1 at

Table 2
Incidence rate ratios (IRR) and 95% confidence intervals (CI) for depressive symptoms at age 22 by smoking status at age 17.

	Adjusted for age and sex			Adjusted for all covariates[a]			Adjusted for all covariates[a] and age 17 depressive symptoms		
Smoking status predicting depressive symptoms	IRR	95% CI	*P*	IRR	95% CI	*P*	IRR	95% CI	*P*
Never smokers	1.00			1.00			1.00		
Experimenters	1.12	1.00-1.24	0.042	1.10	0.98-1.24	0.095	1.03	0.92-1.15	0.634
Quitters or trying to quit	1.37	1.17-1.61	8.9e-05	1.32	1.12-1.55	0.001	1.13	0.97-1.32	0.110
Non-daily smokers	1.22	1.04-1.43	0.012	1.21	1.02-1.42	0.024	1.03	0.89-1.20	0.666
Daily smokers	1.44	1.28-1.61	4.9e-10	1.34	1.18-1.54	1.1e-05	1.17	1.03-1.33	0.014

[a] Adjusted for age, sex, educational attainment, drinking alcohol to intoxication, family structure, parent's educational level, and parental smoking.

age 17 (Table S1). In this restricted sub-sample, there were no significant associations. However, the point estimate was similar to that of the main analysis for daily smoking at age 17 (IRR = 1.28, 95% CI: 0.94–1.74).

3.3. Association between depressive symptoms at age 17 and smoking status at age 22

Depressive symptoms at age 17 predicted smoking status at age 22 (Table 4). In the age and sex adjusted model, a 1-unit higher depression symptom score at age 17 was associated with a 12% increased likelihood of being a non-daily or daily smoker at follow-up as compared to being a never smoker. When adjusted for other covariates, the point estimates were slightly attenuated. When further adjusted for baseline smoking status, there was still evidence for a weak association of depressive symptoms with non-daily (RRR = 1.06, 95% CI: 1.01–1.11) and daily smoking (RRR = 1.05, 95% CI: 1.00–1.10).

In a sensitivity analysis, we restricted the model to those who were never smokers at baseline (Table S2). Having higher depressive symptom scores was associated with increased likelihood of becoming a daily smoker (RRR = 1.09, 95% CI: 1.00–1.18). A similar but non-significant point estimate for non-daily smoking was observed.

3.4. Within-pair analyses

The bi-directional associations between ever versus never smoking and depressive symptoms in the individual-level and within-pair analyses (in all pairs, DZ pairs, and MZ pairs) are shown in Tables 3 and 5. For smoking at age 17 predicting depressive symptoms at age 22, the age and sex adjusted analysis found an association within DZ pairs (ever smokers: IRR = 1.17, 95% CI: 1.00–1.36) but not within MZ pairs (IRR = 0.90, 95% CI: 0.76–1.08). In the fully adjusted model, the DZ estimate also dropped, and no association remained. For the reverse association, the age- and sex-adjusted models suggested an association between depressive symptom scores at age 17 and smoking at age 22 within DZ pairs, although it did not reach statistical significance (ever smokers: OR = 1.10, 95% CI: 1. 00–1.20), but not within MZ pairs (OR = 1.04, 95% CI: 0.82–1.32). The results of the fully adjusted models were difficult to interpret due to wide confidence intervals.

3.5. Analyses with persistent smoking and depressive symptoms in adolescence

Persistent smoking at ages 14 and 17 robustly predicted depressive symptoms at age 22 (Table S3). The association was attenuated within DZ pairs, and no association was found within MZ pairs (Table S4). Similarly, reporting high depressive symptoms at ages 14 and 17 strongly predicted current smoking at age 22, even when adjusted for persistent smoking in adolescence (Table S5). Within-pair analyses showed elevated but non-significant point estimates (Table S6).

4. Discussion

We examined the longitudinal bi-directional associations between cigarette smoking and depressive symptoms from adolescence to young adulthood. Our individual-level results of cigarette smoking being associated with subsequent depressive symptoms, and depressive symptoms being associated with increased risk of cigarette smoking, are in line with previous findings in adolescents (Chaiton et al., 2009) and adults (Fluharty et al., 2017). However, our within-pair results suggest that the observed reciprocal associations are not independent of shared familial liabilities.

When analyzing twins as individuals, non-daily and daily smokers at age 17 were likely to have higher depressive symptom scores at age 22 compared to never smokers, yet after full adjustment the association remained significant only among daily smokers. In the other direction,

Table 3
Incidence rate ratios (IRR) and 95% confidence intervals (CI) for depressive symptoms at age 22 by smoking status at age 17: Individual and within-pair analysis.

Smoking status predicting depressive symptoms		Model 1 IRR (95% CI)	Model 2 IRR (95% CI)
Individual	Never smokers	1.00	1.00
	Ever smokers	1.26 (1.15-1.38)***	1.09 (1.00-1.18)*
Pairwise			
All	Never smokers	1.00	1.00
	Ever smokers	1.08 (0.96-1.21)	1.02 (0.92-1.14)
DZ	Never smokers	1.00	1.00
	Ever smokers	1.17 (1.00-1.36) *	1.06 (0.92-1.22)
MZ	Never smokers	1.00	1.00
	Ever smokers	0.90 (0.76-1.08)	0.92 (0.76-1.12)

Individual, Model 1: Adjusted for age and sex; Model 2: Further adjusted for baseline depressive symptoms.
All pairs, Model 1: Adjusted for sex; Model 2: Further adjusted for baseline depressive symptoms.
DZ, Model 1: Adjusted for sex; Model 2: Further adjusted for baseline depressive symptoms.
MZ, Model 1: Crude model; Model 2: Adjusted for baseline depressive symptoms.
* $P < 0.05$.
*** $P < 0.001$.

Table 4
Relative risk ratios (RRR) and 95% confidence intervals (CI) for smoking status at age 22 by depressive symptoms at age 17.

	Adjusted for age and sex			Adjusted for all covariates[a]			Adjusted for all covariates[b] and age 17 smoking status		
Depressive symptoms predicting smoking status	RRR	95% CI	*P*	RRR	95% CI	*P*	RRR	95% CI	*P*
Never smokers	1.00			1.00			1.00		
Experimenters	1.03	0.99-1.08	0.158	1.01	0.97-1.05	0.665	1.00	0.96-1.04	0.875
Quitters or trying to quit	1.08	1.04-1.13	4.2e-04	1.05	1.01-1.09	0.019	1.03	0.99-1.08	0.157
Non-daily smokers	1.12	1.07-1.17	5.8e-07	1.09	1.04-1.14	1.7e-04	1.06	1.01-1.11	0.010
Daily smokers	1.12	1.07-1.16	3.9e-07	1.07	1.03-1.12	0.001	1.05	1.00-1.10	0.035

[a] Adjusted for age, sex, educational attainment, drinking alcohol to intoxication, family structure, parent's educational level and parental smoking.
[b] Adjusted for all previous co-variates except drinking alcohol to intoxication which was not adjusted for due to multicollinearity with smoking status at age 17. Smoking status at 17 was included as a dichotomous variable (0 = never smokers, 1 = ever smokers).

Table 5
Odds ratios (OR) and 95% confidence intervals (CI) for smoking status at age 22 by depressive symptoms at age 17: Individual and within-pair analysis.

Depressive symptoms predicting smoking status		Model 1 OR (95% CI)	Model 2 OR (95% CI)
Individual	Never smokers	1. 00	1.00
	Ever smokers	1.08 (1.04-1.12)***	1.01 (0.97-1.05)
Pairwise			
All	Never smokers	1.00	1.00
	Ever smokers	1.06 (0.98-1.15)	1.03 (0.91-1.17)
DZ	Never smokers	1.00	1.00
	Ever smokers	1.10 (1. 00 -1.20)	1.18 (0.95-1.45)
MZ	Never smokers	1.00	1.00
	Ever smokers	1.04 (0.82-1.32)	0.93 (0.69-1.26)

Individual, Model 1: Adjusted for age and sex; Model 2: Further adjusted for baseline smoking status.
All pairs, Model 1: Adjusted for sex; Model 2: Further adjusted for baseline smoking status.
DZ, Model 1: Adjusted for sex; Model 2: Further adjusted for baseline smoking status.
MZ, Model 1: Crude model; Model 2: Adjusted for baseline smoking status.
*** P < 0.001.

higher depressive symptom scores at baseline were associated with an increased likelihood of being a non-daily or a daily smoker. Previous bi-directional studies among the young populations have reported similar findings (Audrain-McGovern et al., 2009; Brown et al., 1996; Wilkinson et al., 2016; Windle and Windle, 2001). However, mixed results have also been reported. Some studies have suggested that smoking is associated with poor mental health such as depression but that depression might not be associated with subsequent smoking (Beal et al., 2014; Pedersen and von Soest, 2009; Wu and Anthony, 1999) or moderately increases the likelihood for smoking onset (Brown et al., 1996). Taken together, the mixed results on the directionality are compatible with, and likely reflect, our findings on shared genetic and other familial liabilities explaining the association between smoking and depressive symptoms.

We adjusted the analyses for multiple measured factors that were presumed to confound the association between smoking and depression (Chaiton et al., 2015). Adjusting for baseline depressive symptom scores and baseline smoking status enabled us to account for a major confounding effect which partly explained the observed relationship between the exposure and outcome. Furthermore, in a subsequent sensitivity analysis including only participants with a very low level of baseline depressive symptoms, the association between smoking status and later depression was not statistically significant, although the point estimates were elevated. However, this may reflect limited statistical power due to the reduced sample size.

In addition to taking into account measured confounders, we investigated whether smoking and depressive symptoms were associated when possible confounding by shared genetic and other familial influences was accounted for. Within-pair analyses suggested familial confounding for the association between smoking at 17 and depressive symptoms at 22. More precisely, point estimates in the age- and sex-adjusted analyses in DZ pairs were similar to the individual-level results, whereas the estimates dropped within MZ pairs. This suggests that there is no evidence of a causal association, and the existing association is likely to be due to genes rather than environmental factors shared by siblings and affecting both smoking and depression. Within-pair analysis of the reverse association between depressive symptoms at 17 and smoking status at 22 also suggested potential confounding by shared genetic factors, although the pattern of results was somewhat less clear. Considering that the pattern of within-pair estimates in MZ and DZ pairs was not completely unambiguous, our findings are best interpreted as showing confounding by familial (i.e., genetic and shared environmental) influences. Previous twin studies have suggested shared genetic and/or environmental factors for the association between smoking and depression (Leventhal et al., 2012; Unger et al., 2011). Interestingly, in one study, the comorbidity between smoking and depression was mostly explained by shared genetic factors among girls but by shared environmental factors among boys (Silberg et al., 2003). Similarly, McCaffery et al. (2008) suggested a strong genetic correlation among smoking and depression for females ($r_A = 0.62$), and Unger et al. (2011) suggested for overlapping genetic risk. Furthermore, among adults, genome-wide association studies reported low to moderate genetic correlation between lifetime smoking and depressive symptoms (Brainstorm Consortium et al., 2018). Our study did not aim to estimate the genetic correlation between smoking and depressive symptoms but rather to test the reciprocal association between smoking and depression when shared genetic and environmental influences were considered in analyses of relatives with different genetic relatedness. Our findings highlight the fact that in order to properly understand the relationship between smoking behavior and depressive symptoms, shared genetic and environmental influences need to be taken into account (Martin et al., 2018).

In our study, depressive symptoms at age 17 similarly predicted non-daily and daily smoking at age 22. However, only daily smoking at

17 was associated with an increased risk of depressive symptoms at age 22. It should be noted that the non-daily and daily smoking categories may be quite similar; many of those who smoke on a non-daily basis could consume a similar number of cigarettes as daily smokers do and have similar nicotine intake and metabolism rates (Shiffman et al., 2014). Cigarette smoking was self-reported, and there was no biochemical assessment of exposure (e.g., cotinine level) available. Thus, it remains unclear whether there may be underreporting of the real exposure among those reporting non-daily smoking.

4.1. Limitations and strengths

First, the measurement of depressive symptoms was based on a non-diagnostic, self-reported scale. We used the 10-item version of the GBI, where depressive symptoms were measured as a continuous score, and higher values indicated a greater degree of psychopathology. However, the strength of the GBI was its high internal consistency. Furthermore, studies have suggested the validity of the original GBI (Danielson et al., 2003; Findling et al., 2002; Gjerde, 1995); for example, Danielson et al. (2003) found that GBI did well in differentiating any mood disorder versus no mood disorder. A second limitation was the assessment of cigarette smoking based on self-reports, which is vulnerable to response bias. Third, statistical power in the within-pair analysis was reduced because of smaller numbers of pairs with co-twins differing in exposures and outcomes. Reduced power is a well-known limitation of fixed effects models, whereas their strength is the ability to rule out all unobserved factors which are constant within the defined strata (Allison, 2009). Clearly, further studies with other informative methods such as the newly developed Mendelian Randomization in the context of the Direction of Causation twin model (Minica et al., 2018) should investigate the mechanisms underlying the associations between smoking and depression.

The major strength of this study was the study design including genetically informative, prospective data to analyze the bi-directional associations between smoking and depressive symptoms while accounting for baseline levels of smoking and depression as well as unmeasured genetic and other familial confounding factors. Furthermore, the participants were followed from adolescence to young adulthood, which is a critical phase for substance use initiation and onset of psychopathology. Our study was based on a nationwide sample of Finnish twins with high response rates, supporting the generalizability of our results.

5. Conclusion

During the developmental phase from adolescence to adulthood, cigarette smoking and depressive symptoms are reciprocally associated. However, such associations reflect shared familial liabilities rather than the effects of smoking on the development of depressive symptoms or vice versa. These findings do not reduce the significance of treating depressive symptoms and preventing smoking in young age. Knowledge on shared risks can contribute to early identification of individuals with elevated risks for both smoking and depression.

Role of Funding Source

This work was supported by the National Institute of Alcohol Abuse and Alcoholism (AA-12502, AA-00145 and AA-09203 to RJR); Academy of Finland (100499, 205585, 118555, 141054, 265240, 263278, 264146, 308248, 312073 to JK, 277209, 308698 to AL and 309119 to TK); Juho Vainio Foundation; University of Helsinki; and the Foundation of the Finnish Anti-Tuberculosis Association to AR. The funding agencies played no role in analysis and interpretation of the data, preparation of the manuscript, and decision to submit the report for publication.

Contributors

AR, TK, JK and AL designed the study. RJR and JK collected the data. AR conducted the statistical analysis and wrote the first draft of the manuscript. TK, JB and AL assisted with the statistical analysis. TK, JB, KH, ATH, RJR, JK and AL provided feedback and contributed to subsequent versions of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of Interest

Dr. Kaprio and Dr. Korhonen have consulted for Pfizer on nicotine dependence 2011-2015 and 2011-2017, respectively. Other authors declare none.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2019.03.012.

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