

# The associations of smoking dependence motives with depression among daily smokers

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## ABSTRACT

**Aims** To investigate how strongly smoking dependence and smoking dependence motives are associated with depressive symptoms among daily smokers and if these associations are independent of measured confounders and shared familial factors. **Design** Cross-sectional individual-based and within-pair analyses. **Setting** Fourth wave of the population-based Finnish Twin Cohort conducted in 2011. **Participants** 918 daily smokers born 1945–1957 (48% men), mean age 59.5 years including 38 twin pairs discordant for depression. **Measurements** Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression scale with a cut off value  $\geq 20$  for depression. Smoking dependence was assessed using the Fagerström Test for Cigarette Dependence (FTCD) and smoking dependence motives with three subscales from the multi-dimensional Brief Wisconsin Inventory of Smoking Dependence Motives (WISDM): primary dependence motives (PDM), affective enhancement (AE), and Taste. Logistic regressions, using standardized scores of independent variables and adjusted for multiple confounders with correction for sampling as twin pairs, were used in the individual-based analyses. Conditional logistic regression was used to control for shared familial factors in discordant twin pairs. **Findings** Prevalence of depression was 18% ( $n = 163$ : 61 [14%] in men,  $n = 102$  [22%] in women). Higher smoking dependence measured by the FTCD (OR 1.45; 95% CI 1.20, 1.75), and dependence motives measured by the PDM (1.56; 1.30, 1.87) and the AE (1.54; 1.28, 1.85) were associated with higher odds of depression. The associations remained after adjusting for individual confounders, except for neuroticism, which attenuated all associations. FTCD, PDM, and AE showed associations with depression within depression-discordant monozygotic pairs, suggesting an association independent of familial factors. **Conclusions** Depression appears to be associated with smoking dependence and smoking dependence motives related to heavy, automatic use and use to regulate affective states. The associations appear to be confounded or mediated by neuroticism but are independent of shared familial influences.

**Keywords** Dependence, depression, mental health, motive, public health, tobacco smoking.

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## INTRODUCTION

The association of smoking with depression is widely reported in cross-sectional and longitudinal studies [1–5]. However, several other factors, such as living alone and low education, are associated with both smoking and depression [6–8]. Furthermore, familial factors increase vulnerability for both phenotypes [9,10].

Although the causality and direction of the association between smoking and depression are still unclear [1,11],

several mechanisms underlying the association have been suggested [12,13]. One possible mechanism is the self-medication model, whereby smoking is used to alleviate symptoms, particularly those of negative affect [14], (i.e. depressed mood predisposing to smoking initiation and development of nicotine dependence) [1]. Alternatively, long-term smoking predisposes to the development of depression [15]. Notably, the observed associations may be confounded by familial influences, including shared genetic vulnerability [13].

Recent Mendelian randomization studies indicate that smoking is independently associated with depression [11]. However, genetic vulnerability for depression also predisposed participants to long-term smoking in the same analyses, albeit with weaker evidence [11]. Therefore, genetic confounding in the association between smoking and depression remains a challenge. This makes twin studies powerful tools because they control unmeasured familial confounding in epidemiological studies [16], allowing for deeper understanding of complex associations, and further helps developing prevention and treatment interventions.

Although the association of smoking with depression has been widely studied, less is known about the associations of smoking dependence and smoking dependence motives with depression. For instance, dependence is multi-faceted phenomenon, and it is unknown how depression is associated with global measures of dependence versus specific dependence dimensions. Dependence can be assessed using several measures that have been shown to be related to key dependence criteria [17–21]. Smoking dependence is widely assessed using the Fagerström Test for Cigarette Dependence (FTCD) [17, 18], which assesses smokers' level or severity of dependence by tapping heaviness of smoking and tolerance.

The value of multidimensional measures such as the Nicotine Dependence Syndrome Scale (NDSS) [21] and the Wisconsin Inventory of Smoking Dependence Motives (WISDM) [20], is that they reflect the influence of multiple dependence facets or processes that are associated with classic dependence criteria; relapse vulnerability, nicotine self-administration, and withdrawal magnitude [22–24]. In particular, two major WISDM dimensions, (i.e. primary [PDM] and secondary [SDM] dependence motives) have been meaningfully differentially associated with FTCD [25]. The PDM reflects a pattern of heavy automatic smoking resulting in a perceived loss of control over use and high levels of craving and is particularly associated with intransigent tobacco use (e.g. relapse). The SDM reflects the instrumental use of smoking to achieve certain purposes (e.g. coping with negative affect, experience of pleasure) and appears to develop with less tobacco exposure than does PDM. Two validated SDM subscales were used in this study: affective enhancement (AE) assessing smoking to cope with negative affect and enhance positive emotional states and Taste assessing smoking for taste reward [20, 24, 26]. PDM, AE, and Taste differ in their relations with key aspects of the phenotypes such as withdrawal severity [27] and are also known to differ based on their genetic associations with smoking [28, 29].

Previously, associations of smoking dependence or smoking dependence motives with depression have been investigated in a limited number of studies using mainly

uni-dimensional measures [1]. We are not aware of studies addressing the association between multi-dimensional dependence measures and depression among adults, although depression has been associated with the multi-dimensional NDSS among adolescents [30].

## AIMS

We aimed to investigate how smoking dependence measured by the uni-dimensional FTCD and smoking dependence motives measured by three subscales from the multi-dimensional WISDM, are associated with depressive symptoms in daily smokers, and if the associations are independent of measured confounders and non-measured shared familial factors including genetic influences.

## METHODS

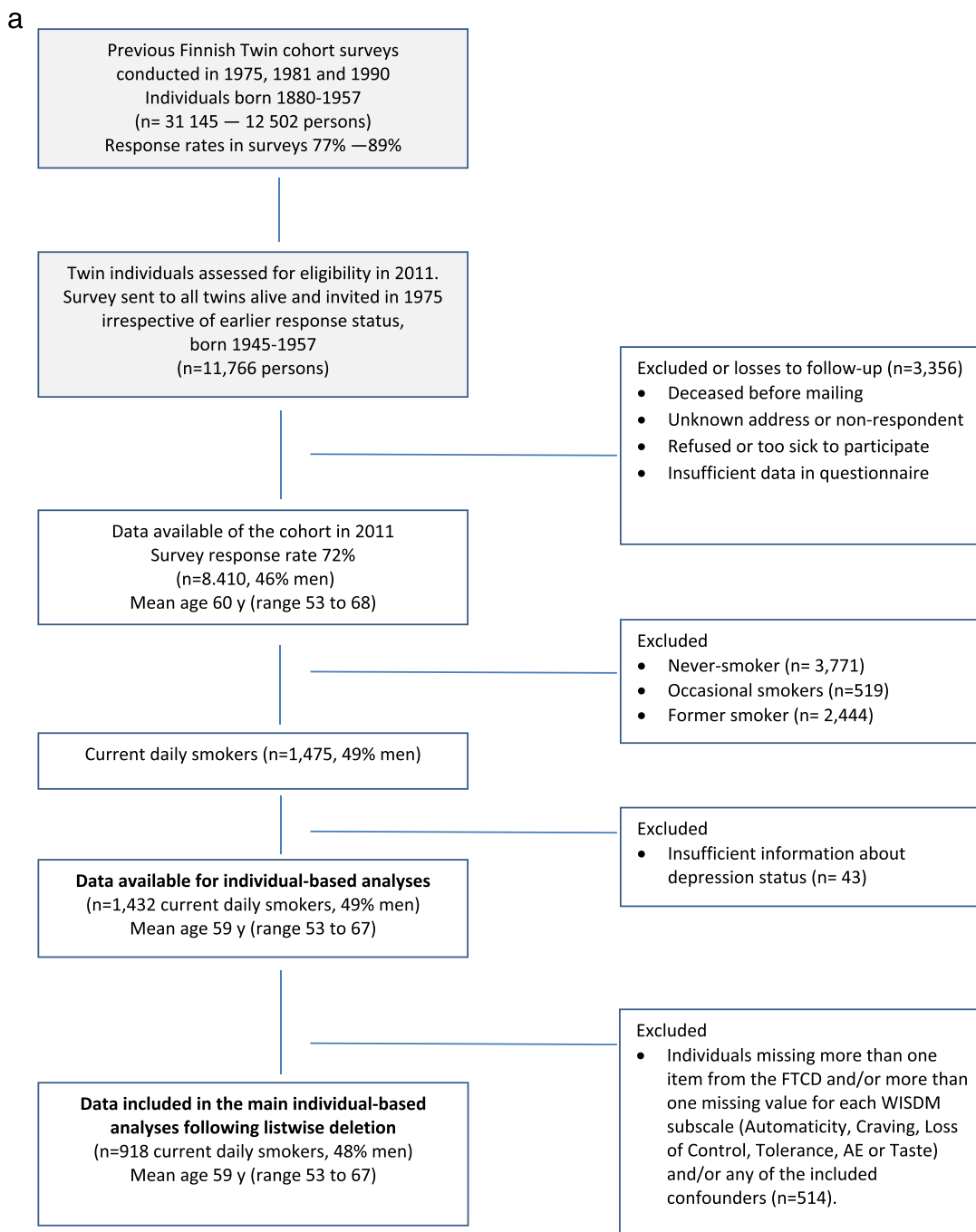
### Participants

Individual-based data came from the fourth survey of the Finnish Twin Cohort conducted in 2011 (participation rate 72%,  $n = 8410$ , 55% (4657) women, mean age 60 years, born in 1945–1957) [31]. In 2011, 18% ( $n = 1475$ ) of the participants reported current daily cigarette smoking. Main analyses were performed for 918 individuals (48% men) following listwise deletion method (Fig. 1a). Supplemental analyses were conducted with all participants who had enough information on depressive symptoms ( $n = 1432$  [97%]; 708 [49%] men). Smoking behavior was assessed similarly in each survey as described in detail elsewhere [32].

Within-pair data came from responses of 198 same-sexed twin pairs (54% female), where both co-twins were daily smokers; 105 were dizygotic (DZ) and 84 monozygotic (MZ, i.e. genetically identical) pairs (Fig. 1b). Nine pairs with uncertain zygosity were excluded from pairwise analyses. Of the 189 pairs, 38 pairs were discordant for depression (18 MZ and 20 DZ) with complete data.

### Dependent variable

The dependent variable was depression (yes/no), assessed with the Center for Epidemiologic Studies Depression (CES-D) scale [33]. A total sum score (range from 0–60) of current depressive symptoms was calculated from 20 items (scored 0–3) reflecting major facets of depression; depressed mood, feelings of guilt and worthlessness, feelings of helplessness and hopelessness, psychomotor retardation, loss of appetite, and sleep disturbance. CES-D sum distribution was skewed with a floor effect (Supporting information Fig. S1). A cut off value  $\geq 20$  was used to classify a participant with clinically relevant level of depressive symptoms



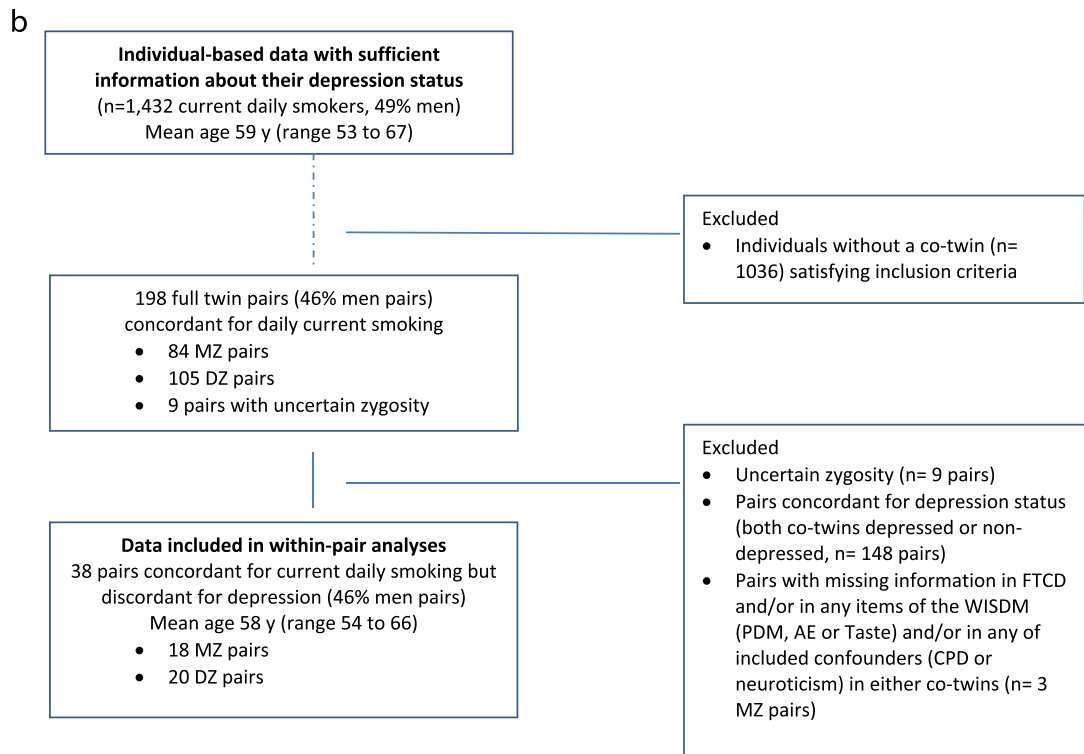
**FIGURE 1a** Flow chart of samples included in the individual-based analyses. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

[34]. Those with depression ( $\text{CES-D} \geq 20$ ) were compared to those with no depression ( $\text{CES-D} < 20$ ).

#### Independent variables

We considered two dependence measures; smoking dependence assessed with the FTCD and smoking dependence motives assessed with three subscales from the multi-dimensional brief WISDM [26]; PDM, AE, and Taste. PDM was used as a latent profile for the core of

smoking dependence and is constructed from four WISDM subscale scores (automaticity, craving, loss of control, and tolerance) based on 16 items (four items/subscale). Automaticity reflects tendency to smoking automatically and without conscious awareness or intention, whereas craving assesses frequency and severity of urges to smoke and smoking in response to cravings. The loss of control subscale assesses the perceived loss of volitional control over smoking behavior. Last, tolerance assesses needing



**FIGURE 1b** Flow chart of twin pairs included in the within-pair analyses. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

to smoke more to experience desired effects or ability to smoke heavily without adverse consequences. AE (three items) reflects smoking to ameliorate negative internal states or enhance positive feeling states and consists of both negative and positive smoking reinforcement motives from the original WISDM-68 scale whereas Taste (three items) reflects smoking to experience the gustatory sensations associated with smoking [20]. Whereas the FTCD attempts to measure dependence largely by assessing its downstream consequences, the WISDM does so by assessing the motivational drives and effects produced by it.

To manage overall participant burden, the current study included 22 items from the total 37 Brief WISDM items. Each statement was rated with a Likert scale ranging from 1 (Not true of me at all) to 7 (Extremely true of me). A value for each subscale (automaticity, craving, loss of control, tolerance, AE, and Taste) was calculated as a mean of included items per subscale and the PDM is the mean of the automaticity, craving, loss of control, and tolerance subscales [26]. The features of these dependence phenotypes (PDM, AE, and Taste) have been defined during development of the WISDM and validated with several independent samples [22, 24, 26]. The exact full text questions for items included in each subscale have been presented in the Appendix of the article by Smith *et al.* [26].

The item numbers are as follows: PDM; automaticity (1,10,14,25), craving (4,7,23,29), loss of control (2,16,21,35), tolerance (3,28,31,36), and SDM; AE (9,33,37), and Taste (5,15,20).

Participants also completed the global dependence measure FTCD with a sum score of responses to six items that include heaviness of smoking and latency to smoke in the morning (range 0–10) [17, 18].

#### Confounders

Relevant variables associated with depression or smoking were chosen from the literature [6–8, 35] and considered as potential confounders (Supporting information Table S1). All potential confounders were tested separately for each independent variable (FTCD, PDM, AE, and Taste) and depression. To be included as a confounder, a variable had to be associated ( $P < 0.15$ ) with both the depression and a primary independent variable (PDM, AE, and FTCD) [36]. As shown in Supporting information Table S2, several confounders were included in the analyses in addition to age and sex. The questionnaires including all variables used in the Finnish Twin Cohort 2011 survey are available online [37]. Categorization of confounders, including amount of missing data are shown in Table 1. Validation and origin of each variable are shown in Supporting information Table S1.

**TABLE 1** Characteristics of the study variables among all current daily cigarette smokers with sufficient information on their depression status ( $n = 1432$ ) by CES-D categorization in the Finnish Twin Cohort in 2011.

Confounder/independent variable	Depression status		Inferential statistic <sup>a</sup> P value
	Non-depressed CES-D <20 N = 1145 n (%)	Depressed CES-D ≥20 N = 287 n (%)	
Sex			
Man	596 (52.1)	112 (39.0)	7.90e−05
Woman	549 (47.9)	175 (61.0)	
Missing	0	0	
Marital status			
Married or living together	714 (62.4)	137 (47.7)	7.43e−05
Single	160 (14.0)	54 (18.8)	
Divorced or widowed	263 (23.0)	95 (33.1)	
Missing	8 (0.7)	1 (0.4)	
Working status			
At work	618 (54.0)	79 (27.5)	1.10e−14
Not at work	524 (45.8)	207 (72.1)	
Missing	3 (0.3)	1 (0.4)	
Self-rated health			
Excellent/very good	688 (60.1)	75 (26.1)	7.76e−33
Good	384 (33.5)	140 (49.8)	
Fair/poor	63 (5.5)	70 (24.4)	
Missing	10 (0.9)	2 (0.7)	
Leisure time physical activity			
Active (>1.5 MET-h/day)	581 (50.7)	118 (41.1)	7.03e−03
Inactive (≤1.5 MET-h/day)	542 (47.3)	159 (55.4)	
Missing	22 (1.9)	10 (3.5)	
Number of pass outs due to alcohol in the last year			
Never	960 (83.8)	210 (73.2)	1.07e−06
1–3 times	133 (11.6)	52 (18.1)	
At least 4 times	25 (2.2)	21 (7.3)	
Missing	27 (2.4)	4 (1.4)	
Sleep length			
7–9 hours	772 (67.4)	148 (51.6)	9.63e−06
<7 hours	290 (25.3)	110 (38.3)	
≥9 hours	78 (6.8)	26 (9.1)	
Missing	5 (0.4)	3 (1.1)	
Sleep quality			
Well	323 (28.2)	31 (10.8)	6.88e−24
Rather well	639 (55.8)	134 (46.7)	
Rather poorly	138 (12.1)	81 (28.2)	
Poorly	33 (2.9)	35 (12.2)	
Missing	12 (1.1)	6 (2.1)	
Life satisfaction			
Satisfied	274 (23.9)	7 (2.4)	3.5e−109
Intermediate	773 (67.5)	85 (29.6)	
Dissatisfied	98 (8.6)	194 (67.6)	
Missing	0 (0)	1 (0.4)	
Emotional support			
Strong support	1041 (90.9)	207 (72.1)	6.37e−17
Some support	61 (5.3)	42 (14.6)	
Not any support	37 (3.2)	37 (12.9)	
Missing	6 (0.5)	1 (0.4)	
Negative life events (weighted sum score)			
Quartile 1 (lowest)	368 (32.1)	31 (10.8)	1.98e−20
Quartile 2	186 (16.2)	31 (10.8)	
Quartile 3	251 (21.9)	56 (19.5)	

(Continues)

Table 1. (Continued)

Confounder/independent variable	Depression status		Inferential statistic <sup>a</sup> P value
	Non-depressed CES-D <20 N = 1145 n (%)	Depressed CES-D ≥20 N = 287 n (%)	
Quartile 4 (Highest)	306 (26.7)	148 (51.6)	
Missing	34 (3.0)	21 (7.3)	
Involvement in a serious traffic accident in adulthood*			
No	866 (75.6)	195 (67.9)	2.91e-02
Yes	86 (7.5)	28 (9.8)	
Missing	193 (16.9)	64 (22.3)	
Injured by physical assault in adulthood*			
No	823 (71.9)	152 (53.0)	1.46e-10
Yes	144 (12.6)	77 (26.8)	
Missing	178 (15.6)	58 (20.2)	
Victim of sexual assault in childhood*			
No	1028 (89.8)	216 (75.3)	2.12e-12
Yes	19 (1.7)	24 (8.4)	
Missing	98 (8.6)	47 (16.4)	
Victim of sexual assault in adulthood*			
No	906 (79.1)	176 (61.3)	8.08e-15
Yes	55 (4.8)	51 (17.8)	
Missing	184 (16.1)	60 (20.9)	
Victim of or witness to a violent crime in adulthood*			
No	927 (81.0)	207 (72.1)	9.18e-04
Yes	39 (3.4)	21 (7.3)	
Missing	179 (15.6)	59 (20.6)	
Parental divorce or separation in childhood*			
No	958 (83.7)	221 (77.0)	3.00e-02
Yes	86 (7.5)	30 (10.5)	
Missing	101 (8.8)	36 (12.5)	
Dichotomy of traumatic life events <sup>ab</sup>			
None	615 (53.7)	90 (31.4)	5.46e-10
At least one	237 (20.7)	89 (31.0)	
Missing info in 1–5 traumas	277 (24.2)	101 (35.2)	
Missing info in all 6 traumas	16 (1.4)	7 (2.4)	
	Mean (SD)	Mean (SD)	
Age (years, range 53.3–67.3)	59.5 (3.5)	59.2 (3.6)	2.05e-01
Missing, n (%)	0 (0)	0 (0)	
Education by 1981 (years, range 3–16) <sup>c</sup>	8.0 (2.5)	7.6 (2.3)	2.41e-02
Missing, n (%)	2 (0)	1 (0)	
Alcohol consumption (drinks [12 g alcohol]/day, range 0–22.6)	1.4 (2.1)	1.7 (2.9)	6.85e-01
Missing, n (%)	2 (0)	1 (0)	
Number of cigarettes (per day, range 0–40)	14.0 (7.4)	15.5 (8.4)	3.35e-01
Missing, n (%)	4 (0)	2 (1)	
Neuroticism (sum score, range 0–10)	3.0 (2.2)	6.6 (2.1)	5.0e-108
Missing, n (%)	30 (3)	7 (2)	
FTCD (sum score, range 0–10)	3.8 (2.3)	4.6 (2.4)	4.67e-08
Missing, n (%)	13 (1)	1 (0)	
WISDM PDM motives (sum, range 16–112)	55.3 (23.6)	67.4 (26.8)	3.00e-13
Missing, n (%)	39 (3)	13 (5)	
WISDM AE motives (sum, range 3–21)	10.9 (4.8)	13.3 (5.1)	6.43e-14
Missing, n (%)	14 (1)	6 (2)	
WISDM Taste motives (sum, range 3–21)	11.6 (4.7)	12.2 (5.3)	9.35e-02
Missing, n (%)	13 (1)	6 (2)	

CES-D = The Center for Epidemiological Studies-Depression; WISDM = The Wisconsin Inventory of Smoking Dependence Motives; PDM = primary dependence motives; AE = affective enhancement motives; FTCD = Fagerström Test for Cigarette Dependence; MET = metabolic equivalent <sup>a</sup>Pearson  $\chi^2$  test for categorical variables and two-sample *t*-test for continuous variables. <sup>b</sup>A dichotomous variable (none vs at least one) of traumatic life events includes those traumatic life events that were related to depression and smoking dependence/motives (\*). <sup>c</sup>The latest information in data from 1981; corresponding information from the 1975 survey was used for those with missing information on their education in 1981.



## STATISTICAL ANALYSES

### Missing data

For the main analyses, we imputed some missing data in the CES-D, WISDM, and FTCD, but no missing information were allowed in any of the independent variables or confounders. In CES-D, no more than two missing items were allowed, and those values were imputed by the mean of the remaining items. In the WISDM measure, one missing value for each subscale (automaticity, craving, loss of control, tolerance, AE, or Taste) was allowed, a missing item being imputed as mean of the non-missing values within a subscale. In the FTCD, one missing value was allowed and replaced with a mean of non-missing values. Because of missing values in the confounders, we created a “missing” category for the categorical variables that we used in one part of sensitivity analyses.

### Individual-based analyses

Men and women were analyzed together because there were no interactions between sex and any independent variable on depression in the Likelihood-ratio tests ( $P$  values  $>0.3$ ) [38]. Descriptive analyses were performed with Pearson  $\chi^2$  or two-sample  $t$  test by depression status. The WISDM and FTCD scores were standardized to mean of 0 and SD of 1 for comparisons. Logistic regression (OR with 95% CI) was used in analyzing the associations of PDM, AE, Taste, or FTCD with depression. Basic regression analyses were adjusted for sex and age (model 1). In model 2, the effect of a variable of interest (PDM, AE, Taste, or FTCD) was tested after adjusting for sex, age, and a single confounder. To allow comparison, the same confounders were included for all four independent variables. In model 3, all WISDM subscales (PDM, AE, and Taste) were jointly entered in the model with age and sex to reveal orthogonal relations within the various subscales [25]. In addition, two multiple adjusted analyses (model 4 without neuroticism and model 5 with neuroticism) were performed including all confounders showing  $<0.5$  correlation with each other. In all analyses, a cluster option was used to control for the effect of sampling twins as pairs on standard errors of the estimates [39].

### Within-pair analyses

Conditional logistic regression was used to control for the effect of familial factors in twin pairs concordant for smoking (i.e. both co-twins were daily smokers), but discordant for depression, (i.e. one was depressed twin [CES-D  $\geq 20$ ] and the other was not [CES-D  $< 20$ ]), with information on FTCD, all WISDM items, and relevant confounders (Fig. 1b). Analyses were performed MZ/DZ pairs combined and separately for DZ and MZ pairs with

a test for heterogeneity between zygosity using the likelihood–ratio test. Implementing and interpreting within-pair analyses are described in Supporting information Text S1. Within-pair analyses were adjusted for cigarettes smoked per day (CPD) to control for differences in amount of smoking between co-twins, which might account for some within-pair discrepancies in smoking dependence or dependence motives. Neuroticism was adjusted because of substantial confounding in the individual-based analyses, unlike the other tested confounders.

### Sensitivity analyses

Sensitivity analyses are described and reported in the Supporting information Text S2 and Supporting information Tables S3–S5.

Stata SE versions 15/16 (StataCorp, College Station, TX) were used for all the analyses.

The primary research question and analysis plan of this study have not been pre-registered on a publicly available platform.

## RESULTS

### Individual-based analyses

Characteristics of studied variables by depression status in the whole sample ( $n = 1432$ ) are shown in Table 1. Among the 918 daily smokers (48% men), the prevalence of depression (CES-D  $\geq 20$ ) was 18% ( $n = 163$ : 61 men [14%]; 102 women [22%]) in 2011.

In age- and sex-adjusted analyses, we found statistically significant associations of FTCD, PDM, and AE with depression and the associations remained significant after adjusting for most of the confounders (Table 2). The associations of PDM and AE with depression also remained significant when all three WISDM dimensions were simultaneously included in the model (model 3). PDM and AE, but not FTCD, were statistically significantly associated with depression when all confounders except neuroticism were simultaneously included in the models (model 4). The variable confounding the associations most was neuroticism, which strongly attenuated the associations of FTCD, PDM, and AE with depression (models 2 and 5). Associations of each confounder with depression by each dependence measure are shown in the Supporting information Table S2. Sensitivity analyses demonstrate that findings were robust over different choices for handling missing data (Supporting information Tables S3 and S4).

The Taste dimension behaved differently from the PDM and AE in that it showed a lack of association with depression (Table 2), even before including confounders. Including Taste in the model along with the other smoking

**TABLE 2** Associations of standardized values of FTCD and WISDM measures with depression (CES-D  $\geq$  20) among current daily cigarette smokers ( $n = 918$  with 163 cases) in the Finnish Twin Cohort.

Individual-based analyses	Confounders	WISDM dimensions			
		FTCD	PDM	AE	Taste
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Model 1 <sup>a</sup>		<b>1.45 (1.20, 1.75)</b>	<b>1.56 (1.30, 1.87)</b>	<b>1.54 (1.28, 1.85)</b>	1.01 (0.85, 1.21)
Model 2 <sup>b</sup>	Education	<b>1.44 (1.20, 1.74)</b>	<b>1.55 (1.29, 1.87)</b>	<b>1.54 (1.28, 1.85)</b>	1.02 (0.85, 1.22)
	Marital status	<b>1.42 (1.17, 1.72)</b>	<b>1.54 (1.28, 1.85)</b>	<b>1.52 (1.26, 1.83)</b>	1.01 (0.85, 1.20)
	Working status	<b>1.35 (1.11, 1.63)</b>	<b>1.47 (1.22, 1.80)</b>	<b>1.49 (1.24, 1.79)</b>	1.01 (0.85, 1.21)
	Self-rated health	1.19 (0.98, 1.45)	1.33 (1.10, 1.60)	1.37 (1.13, 1.66)	0.99 (0.83, 1.19)
	LTPA	<b>1.42 (1.17, 1.71)</b>	<b>1.53 (1.27, 1.85)</b>	<b>1.52 (1.26, 1.82)</b>	1.01 (0.85, 1.21)
	Alcohol consumption	<b>1.44 (1.19, 1.74)</b>	<b>1.55 (1.29, 1.86)</b>	<b>1.53 (1.27, 1.84)</b>	1.01 (0.84, 1.21)
	Pass outs due to alcohol	<b>1.39 (1.15, 1.68)</b>	<b>1.50 (1.25, 1.80)</b>	<b>1.48 (1.23, 1.78)</b>	0.97 (0.81, 1.17)
	Number of cigarettes	<b>1.51 (1.19, 1.93)</b>	<b>1.61 (1.29, 2.01)</b>	<b>1.50 (1.23, 1.83)</b>	0.95 (0.79, 1.15)
	Sleep length	<b>1.41 (1.17, 1.71)</b>	<b>1.54 (1.28, 1.85)</b>	<b>1.50 (1.25, 1.81)</b>	1.00 (0.84, 1.19)
	Sleep quality	<b>1.41 (1.16, 1.72)</b>	<b>1.53 (1.27, 1.85)</b>	<b>1.49 (1.23, 1.80)</b>	1.03 (0.85, 1.24)
	Life satisfaction	1.19 (0.97, 1.46)	1.33 (1.09, 1.62)	1.41 (1.13, 1.76)	0.93 (0.75, 1.14)
	Emotional support	<b>1.38 (1.14, 1.66)</b>	<b>1.51 (1.25, 1.81)</b>	<b>1.51 (1.25, 1.82)</b>	1.03 (0.85, 1.24)
	Negative life events	<b>1.41 (1.16, 1.16)</b>	<b>1.51 (1.25, 1.82)</b>	<b>1.46 (1.21, 1.77)</b>	0.99 (0.82, 1.20)
	Traffic accident in adulthood *	<b>1.45 (1.20, 1.75)</b>	<b>1.56 (1.29, 1.87)</b>	<b>1.53 (1.28, 1.84)</b>	1.01 (0.85, 1.21)
	Physical assault in adulthood *	<b>1.40 (1.16, 1.69)</b>	<b>1.51 (1.26, 1.81)</b>	<b>1.49 (1.24, 1.80)</b>	1.00 (0.84, 1.20)
	Sexual abuse in childhood *	<b>1.45 (1.20, 1.75)</b>	<b>1.57 (1.30, 1.88)</b>	<b>1.51 (1.25, 1.81)</b>	1.01 (0.84, 1.21)
	Sexual abuse in adulthood *	<b>1.40 (1.15, 1.69)</b>	<b>1.53 (1.27, 1.84)</b>	<b>1.52 (1.25, 1.84)</b>	1.02 (0.85, 1.22)
	Victim/witness of violent crime in adulthood *	<b>1.43 (1.19, 1.72)</b>	<b>1.54 (1.28, 1.85)</b>	<b>1.50 (1.25, 1.81)</b>	1.03 (0.86, 1.23)
	Parental divorce in childhood*	<b>1.44 (1.20, 1.74)</b>	<b>1.56 (1.30, 1.88)</b>	<b>1.54 (1.29, 1.85)</b>	1.01 (0.85, 1.21)
	Dichotomy of traumatic life events (none/at least one)**	<b>1.39 (1.15, 1.68)</b>	<b>1.52 (1.26, 1.83)</b>	<b>1.51 (1.26, 1.82)</b>	1.01 (0.85, 1.21)
	Neuroticism	1.13 (0.93, 1.39)	1.12 (0.91, 1.38)	1.09 (0.88, 1.35)	0.97 (0.78, 1.20)
Model 3 <sup>c</sup>			<b>1.45 (1.09, 1.93)</b>	<b>1.51 (1.13, 2.03)</b>	<b>0.66 (0.52, 0.83)</b>
Model 4 <sup>d</sup>		1.09 (0.77, 1.54)	<b>1.42 (1.06, 1.92)</b>	<b>1.36 (1.02, 1.82)</b>	0.87 (0.66, 1.14)
Model 5 <sup>e</sup>		0.98 (0.68, 1.40)	1.16 (0.84, 1.62)	1.10 (0.81, 1.50)	0.82 (0.60, 1.12)

FTCD = Fagerström Test for Cigarette Dependence; WISDM = Brief Wisconsin Inventory of Smoking Dependence Motives; PDM = primary dependence motives; AE = affective enhancement;  $n$  = number of individuals with depression in the analysis by dependence motive; LTPA = leisure time physical activity; CES-D = depression defined by the Center for Epidemiologic Studies Depression scale with a cut-off value of 20 (depression CESD  $\geq$  20). Analyses were performed with logistic regression providing OR with 95% CI including observations without missing values in any variables. In all individual-based analyses, a robust variance estimator was used to adjust for the non-independence of observations within twin pairs. Associations with  $P$  values  $< 0.05$  are in bold. <sup>a</sup>Model 1: individual models for FTCD and each WISDM dimension, adjusted for age and sex (basic model). <sup>b</sup>Model 2: individual models for FTCD and each WISDM dimension, adjusted for age, sex and separately for each significant covariate. <sup>c</sup>Model 3: a multiple adjusted model with all three WISDM dimensions, adjusted for age and sex. <sup>d</sup>Model 4: individual multiple adjusted models for FTCD and each WISDM dimension, with all confounders except neuroticism. <sup>e</sup>All traumatic life events related to depression and smoking dependence/motives were added to the model as a dichotomous variable. \*\* (none vs at least one traumatic life event). <sup>f</sup>Model 5: individual multiple adjusted models for FTCD and each WISDM dimension with all confounders (as in the model 4) including also neuroticism.

dependence motives revealed that higher Taste scores were associated with a reduced depression likelihood.

### Within-pair analyses

Altogether there was 38 smoking concordant but depression discordant twin pairs (18 MZ, 20 DZ) (Figs. 1b, Supporting information Figs. S2 and S3). In the conditional logistic regression analyses, FTCD, PDM, and AE showed statistically significant associations with depression when MZ and DZ pairs were combined (Table 3). The associations of FTCD, PDM, and AE with depression were evident also in MZ pairs with similar effect sizes (Supporting information

Text S1). Adjusting within-pair differences for CPD did not fundamentally change these associations except for PDM in MZ pairs where the association became stronger. When adjusted for neuroticism all associations attenuated.

### DISCUSSION

Our analyses showed that FTCD, PDM and AE are associated with depression. Our findings also indicate that in daily smokers, depression is related to core dependence processes, such as craving and automatic smoking arising from a history of heavy smoking, as well as from the



**TABLE 3** Within-pair associations of standardized mean values of smoking dependence (FTCD) and dimensions from the WISDM with depression (CES-D  $\geq 20$ )<sup>a</sup> among twin pairs discordant for depression, where both co-twins are current daily cigarette smokers with no missing values in any factors of interest or covariates in the Finnish Twin Cohort.

Within pair analyses	np	WISDM dimensions			
		FTCD OR (95% CI) <sup>b</sup>	PDM OR (95% CI) <sup>b</sup>	AE OR (95% CI) <sup>b</sup>	Taste OR (95% CI) <sup>b</sup>
Basic model <sup>c</sup>					
DZ and MZ pairs together	38	<b>1.77 (1.02, 3.08)</b>	<b>2.30 (1.16, 4.50)</b>	<b>1.77 (1.08, 2.89)</b>	1.35 (0.89, 2.06)
DZ pairs	20	1.52 (0.82, 2.81)	1.62 (0.83, 3.16)	1.47 (0.85, 2.51)	1.24 (0.75, 2.06)
MZ pairs	18	2.55 (0.87, 7.49)	30.3 (0.88, 1045)	3.15 (0.96, 10.3)	1.61 (0.75, 3.44)
LR test for MZ/DZ difference (P value)		P = 0.396	<b>P = 0.023</b>	P = 0.208	P = 0.573
Model 1 <sup>d</sup>					
DZ and MZ pairs together	38	2.03 (0.91, 4.55)	<b>2.87 (1.13, 7.32)</b>	1.81 (0.99, 3.31)	1.24 (0.78, 1.97)
DZ pairs	20	1.45 (0.55, 3.85)	1.54 (0.59, 3.98)	1.35 (0.68, 2.69)	1.09 (0.61, 1.95)
MZ pairs	18	3.62 (0.86, 15.3)	<b>55.6 (1.21, 2552)</b>	3.55 (0.95, 13.2)	1.54 (0.69, 3.46)
LR test for MZ/DZ difference (P value)		P = 0.448	<b>P = 0.029</b>	P = 0.207	P = 0.489
Model 2 <sup>e</sup>					
DZ and MZ pairs together	38	1.14 (0.59, 2.23)	1.51 (0.70, 3.24)	1.35 (0.79, 2.31)	1.16 (0.68, 2.00)
DZ pairs	20	1.19 (0.56, 2.54)	1.21 (0.56, 2.62)	1.28 (0.70, 2.32)	1.00 (0.49, 2.03)
MZ pairs	18	0.99 (0.21, 4.57)	23.2 (0.48, 1119)	1.83 (0.46, 7.25)	1.43 (0.62, 3.39)
LR test for MZ/DZ difference (P value)		P = 0.828	P = 0.094	P = 0.723	P = 0.526

FTCD = Fagerström Test for Cigarette Dependence; WISDM = Brief Wisconsin Inventory of Smoking Dependence Motives; PDM = primary dependence motives; AE = affective enhancement; DZ = dizygotic; MZ = monozygotic; np = number of twin pairs discordant for depression; LR test = Likelihood-ratio test for difference between MZ and DZ pairs. Associations are presented by zygosity and for all pairs of known zygosity. <sup>a</sup>Depression defined by the Center for Epidemiologic Studies Depression (CES-D) scale with a cut-off value of 20 (depression CES-D  $\geq 20$ ). <sup>b</sup>Conditional logistics regression odds ratios with 95% CI. Statistically significant associations ( $P < 0.05$ ) are in bold. <sup>c</sup>Basic model: age and sex are automatically adjusted in the model (data includes only same-sexed twin pairs). <sup>d</sup>Model 1: adjusted with age, sex, and number of cigarettes smoked per day. <sup>e</sup>Model 2: adjusted with age, sex, and neuroticism.

instrumental use of smoking for affect regulation. Taste and sensory motivations to smoke are not associated with depression. The associations for AE and PDM but not for FTCD remained after adjusting for multiple confounders except neuroticism, which alone attenuated all associations. Further, based on the MZ pairs, associations of FTCD, PDM, and AE with depression appear to be independent of familial factors. Notably, all within-pair effects were independent of smoking heaviness. Therefore, our analyses add to the evidence of the robust association of two different measures of dependence (FTCD and WISDM) with depression, not explained by smoking quantity.

Whereas FTCD and PDM both reflect heavy smoking [40], in our study, the OR estimates were higher for PDM relative to FTCD in MZ pairs, although with overlapping CIs. This may be because the PDM captures a wider array of information about the “core” features of dependence (e.g. only the PDM measures automaticity, craving, and loss of control). The FTCD may also tap unintended environmental features that do not sensitively index dependence *per se* (e.g. contextual factors that prohibit or permit heavy smoking). Interestingly, all the PDM subscales accounted for similar amounts of total variability for depression in the sensitivity analyses. However, whether the PDM total value or any of the PDM subscores alone can be used to examine relations between smoking dependence motives and depression, needs further investigation.

The localization of the effects to PDM and AE indicates that the mechanisms linking depression and dependence may operate by promoting heavy and automatic smoking to suppress cravings and smoking to cope with affective distress, supporting previous findings [14]. However, this does not mean that other SDM motives do not play any role. However, among SDM scales, the AE motive may be especially relevant because of the need to reduce negative moods associated with depression. Regardless of which SDM subscales might contribute to depression related smoking, their influence may be most apparent early in the development of dependence. Namely, SDM motives appear to influence smoking early in its development [23, 24], but escalating smoking because of SDM motives may then stimulate heavier smoking, which augments PDM.

Our individual-based and within-pair results consistently suggest that depressed persons are not smoking because of Taste or taste-reward related to smoking. Smokers, who have taste-related motives for their smoking behavior, may comprise a specific subgroup of daily smokers behaving differently from others in relation to mood. Rather, depression seems to be related to primary dependence motives and to affect regulation. This finding is also supported by a study in which positive and negative reinforcement subscales used from the original WISDM-68 predicted depression level in smoking college students [41]. Vinci *et al.* [41] also reported that friendship-like

attachment to smoking (affiliative attachment) explained significant variance of depression level in college smokers. Unfortunately, we did not include the affiliative attachment subscale in our questionnaire in 2011.

Our analyses highlight the role of neuroticism in the association between dependence and depression. Neuroticism is robustly related to depression and anxiety and may account for the comorbidity of many mood disorders [42]. There is also a strong genetic correlation between neuroticism and major depression [43]. According to our analyses, when neuroticism is used as a confounder, a major portion of the smoking dependence motives-depression relationship is attenuated. This may occur because the statistical control of depression via neuroticism may greatly reduce meaningful information in the depression variable [44] or neuroticism may play a role as a mediator between smoking and depression.

Finally, our analyses yield new evidence about the associations between addictions and depression, because this is one of the first studies using both uni- and multi-dimensional measures of smoking dependence in the study of depression. Although depression is more common among adult women [35, 45] and depressed women are at higher risk for nicotine dependence [46], we did not find sex-interactions in the associations of depression with smoking dependence or smoking dependence motives. Therefore, based on our data, the association between depression and such dependence is not moderated by sex.

### Strengths and limitations

This study has several strengths. First, the data are from a population-based cohort with a high participation rate. Second, we controlled for multiple potential confounders. Third, a twin sample enables co-twin control design, which controls for familial confounding on the associations. Therefore, the generalization of our findings is high among a population of European ancestry with 53–67 years of age.

This study has also weaknesses. First, smoking status is based on self-reports without biochemical verification. Second, we used a cross-sectional design, because the FTCD, WISDM, and the CES-D measures were available only in one survey. Therefore, without temporal order, we cannot draw conclusions regarding the direction of a causal pathway between dependence and development or worsening of depression. A longitudinal incidence analysis is needed to test if depression leads to dependence among baseline non-dependent smokers or if dependence leads to depression among baseline non-depressed smokers. Third, because we studied only three WISDM dimensions, associations between other smoking dependence motives and depression need further investigation. Fourth, multiple imputation was not used in all variables to replace missing

observations, which might have some influence on the findings. However, zero missingness in the CES-D items in our main analysis sample ( $n = 918$ ; 94%) did not differ significantly from the whole survey sample ( $n = 8410$ ; 90%) in 2011. Further, sensitivity analyses show that our results are not significantly affected by the number of observations included in the analyses. On the other hand, we cannot rule out a possibility of overfitting our multiple adjusted models. Notably, our sample is restricted to adults with 53–67 years of age [47, 48]. Further, the observed associations may be underestimated because both dependent smokers and seriously depressed persons likely had higher attrition because of premature death or other reasons [49–51]. However, we acknowledge that in the Finnish Twin Cohort, the general participation rates have been relatively high (72–89%) compared to many other population-based cohort surveys [47]. Finally, although the original surveys included thousands of twin pairs [48], our pairwise analyses include only 18 MZ pairs discordant for depression but concordant for daily smoking and therefore, lack optimal statistical power resulting in large CIs. However, pairwise analyses are powerful in controlling for familial confounding on the associations and therefore, our results deepen knowledge of the relationships between dependence and depression.

### CONCLUSION

Depression and smoking dependence are associated with one another independently of shared familial influences, a relationship found with FTCD and two WISDM dimensions, with the latter capturing motives related to heavy, out of control automatic smoking, with high levels of craving, and smoking to regulate affective states. These associations are robust with adjustment for several single or a combination of confounders, except neuroticism, which attenuates the association. Regarding clinical implications, higher dependence and smoking to regulate affect should be considered while helping depressed smokers to quit their habit.

### Declaration of interest

T.K. has consulted for Pfizer on nicotine dependence 2011–2017. There are no other conflicts of interest.

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### Author contributions

**Maarit Piirtola:** Conceptualization; data curation; formal analysis; investigation; methodology; software; validation; visualization. **Jaakko Kaprio:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization. **Timothy Baker:** Conceptualization; data curation; investigation; methodology; validation. **Thomas Piasecki:** Conceptualization; formal analysis; methodology; software; validation. **Megan Piper:** Conceptualization; methodology; validation. **Tellervo Korhonen:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation.

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### Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Crude associations of potential confounders with depression (CES-D  $\geq$  20) and smoking dependence (FTCD score) and smoking dependence motives (WISDM subscales) among current daily cigarette smokers ( $n = 1432$ ) in the Finnish Twin Cohort in 2011.

**Table S2** The associations (OR with 95% CI) of each confounder with depression (CES-D  $\geq$  20) a by standardized values of smoking dependence (FTCD) /smoking dependence motives (WISDM) measures after controlling for sex and age among daily current cigarette smokers ( $n = 918$ ) in the Finnish Twin Cohort (each confounder and each dependence variable simultaneously in the model).

**Table S3** Individual-based sensitivity analyses 1. Associations of standardized values of smoking dependence or smoking dependence motive measures with depression (CES-D  $\geq$  20) among current daily cigarette smokers ( $n = 1327$  with 264 cases) in the Finnish Twin Cohort. Analyses were performed with logistic regression providing OR with 95% CI and including the same, fixed number of observations in all analyses\*. In all individual-based analyses, a robust variance estimator was used to adjust for the non-independence of observations within twin pairs. Associations with  $P$  values  $<0.05$  are in bold.

**Table S4** Individual-based sensitivity analyses 2. Associations of standardized values of smoking dependence or smoking dependence motive measures with depression



(CES-D  $\geq 20$ ) among current daily cigarette smokers ( $n = 1432$ ) in the Finnish Twin Cohort. Analyses were performed with logistic regression providing OR with 95% CI allowing number of included observations to vary between models\*. In all individual-based analyses, a robust variance estimator was used to adjust for the non-independence of observations within twin pairs. Associations with  $P$  values  $< 0.05$  are in bold.

**Table S5** Within-pair sensitivity analyses 1. Associations (OR with 95% CI) of standardized mean values of smoking dependence (FTCD) and dimensions from the Brief WISDM with depression (CES-D  $\geq 20$ ) among all twin pairs discordant for depression, where both co-twins are current daily cigarette smokers in the Finnish Twin Cohort. Associations are presented by zygosity and for all pairs of known zygosity.

**Figure S1** Distribution and normality of the Center for Epidemiologic Studies Depression (CES-D) scale in smokers in 2011 ( $n = 918$ ).

**Figure S2** Within-pair differences in the Center for Epidemiologic Studies Depression (CES-D) sums by zygosity in twin pairs discordant for depression but concordant for smoking in 2011. The mean CESD sum was 10.5 points in twin without depression and 27.7 points in his/her co-twin with depression. The mean difference in CESD

sum was 16.7 (SD 11.1) in MZ pairs and 17.6 (SD 8.2) in DZ pairs discordant for depression (depression cut-off 20 points).

**Figure S3** Scatter plots for within-pair comparisons of standardized (sdt) mean scores for Brief Wisconsin Inventory of Smoking Dependence Motives (WISDM); (A) primary dependence motives (PDM), (B) affective enhancement (AE), and (C) Taste by zygosity (monozygotic [MZ] and dizygotic [DZ]) for twin pairs discordant for depression ( $n = 38$  pairs). Both twins are current smokers. Each plot compares WISDM scores by smoking dependence motive within each twin pair: the score of a twin with depression is plotted on y-axis and the score of his/her co-twin without depression is plotted on x-axis. The green line illustrates regression coefficient 1.00 (i.e. there would be no within pair difference in WISDM scores by depression status). The interpretation of the figure is that if the observations (twin pair values) are situated on the left upper corner, the twin with depression reported generally higher WISDM scores compared to his/her co-twin without depression (e.g. MZ pairs in the A square). Plots in which observations are located on both sides of the line (e.g. DZ pairs in the A square), the twin with depression reported both higher and lower WISDM scores compared to his/her co-twin without depression.