Major Depression is a risk factor for Shorter Time to First Cigarette Irrespective of the Number of Cigarettes Smoked Per Day: Evidence from a National Population Health Survey

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Abstract

Introduction: We assessed whether Major Depression (MD) predicts progression of Nicotine Dependence (ND) as measured by reduction in the Time to First Cigarette (TTFC) after waking and the roles of the number of cigarettes smoked per day (CPD) and stress as explanatory variables of this association.

Methods: 10-years of follow-up data from the National Population Health Survey (NPHS) were used. The analyses were based on this nationally representative sample of the Canadian population who were over the age of 12 years in 1996 (n=13,298). The NPHS included measures of MD and TTFC. Shorter TTFC was defined as TTFC within 5 minutes of waking. Heavy smoking (HS) was defined by smoking 20 or more CPD. Using proportional hazard (PH) models, unadjusted and adjusted hazard ratios (HRs) for shorter TTFC were estimated for those with and without MD.

Results: The unadjusted HR for shorter TTFC among those with MD versus those without MD was 3.7 (95% CI: 2.6-5.3, $p<0.001$). MD predicted onset of shorter TTFC even after adjustment for HS and tendency to smoke more under stress (HR: 1.7; 95% CI: 1.1-2.5, $p=0.02$). When TTFC was defined using longer cut-offs (30 minutes and 60 minutes), HS completely accounted for the effect of MD on TTFC onset.

Conclusions: MD appears to be a risk factor for transition to shorter TTFC independent of effects of HS and the tendency to smoke more under stress. As MD is often modifiable, the above association points towards a preventive opportunity in relation to worsening of ND.

Keywords: Major Depression; Nicotine Dependence; Time to First Cigarette; Cigarettes smoked Per Day; Prospective Longitudinal Study; Risk Factors

MD = Major Depression; ND= Nicotine Dependence; TTFC = Time to First Cigarette; CPD = Cigarettes smoked Per Day; PH = Proportional Hazard; HR = Hazard Ratio; CI = Confidence Interval; NPHS = National Population Health Survey; CIDI-SF = Composite International Diagnostic Interview Short Form; FTND = Fagerstrom Test for Nicotine Dependence.

Introduction

Despite public health efforts to raise awareness about the dangers of smoking on health and to encourage smoking cessation among members of the general population, the prevalence of smoking is still quite high. Approximately 25% of the population in developed countries are current smokers (Office for National Statistics, 2008; Rock et al., 2007). This impasse in smoking cessation efforts is often attributed to a multitude of factors; one commonly implicated is Nicotine Dependence (ND). Severe ND is associated with greater risk of quitting failure and relapse after long-term smoking cessation (Killen & Fortmann, 1994; Perkins et al., 2001; Zhoua et al., 2009). The identification of potentially modifiable risk factors for progression to severe ND may lead to improvement of smoking cessation outcomes. Major depression (MD), a condition with a general lifetime population prevalence of 10-20% (Alonso et al., 2004; Kessler et al., 2003; Patten et al., 2006), may be an important modifiable determinant of severe ND, although it should be pointed out that MD itself can be recalcitrant to clinical management.

The majority of prospective studies report strong associations between depression and smoking initiation, progression to daily smoking, and decreased smoking cessation success (Anda et al., 1990; Breslau, Peterson, Schultz, Chilcoat, & Andreski, 1998; Patton et al., 1998; Glassman et al., 1990; Rohde, Kahler, Lewinsohn, & Brown, 2004). Several studies, however, have reported null associations between depression and various smoking stages (Goodman & Capitman, 2000; Hitsman, Borrelli, McChargue, Spring, & Niaura, 2003). However, there is a dearth of population-based longitudinal studies reporting the role of MD as a predictor of ND onset and transition to severe dependency.

This might be largely due to ND's multifaceted nature as a physiological, cognitive, and behavioral construct and its reliance on other smoking milestones. One study (Breslau, Kilbey, & Andreski, 1993) investigated the role of lifetime history of Major Depressive Disorder (MDD) as a predictor of ND onset and progression to severe levels of dependence. The sample consisted of young members of a health maintenance organization and was followed over 14 months. The authors reported that MDD doubled the odds of onset of ND (odds ratio: 2.1, 95% CI: 1.2-3.5) (Breslau et al., 1993). These findings raise the concern that MD may be an important predictor of ND, but the public health implications are unclear as the sample was restricted to a narrow age range (21 to 30 years old) and was not necessarily representative of the general population. Furthermore, this study did not assess specific mechanisms potentially linking MD to ND.

One challenge in this area of research is the lack of consensus as to the best measure of ND and severe dependency. Some of the widely used instruments in epidemiological studies are the Fagerstrom Test of Nicotine Dependence (FTND) and the Heaviness of Smoking Index (HSI) (Fagerstrom, 1978; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991; Heatherton, Kozlowski, Frecker, Rickert, & Robinson, 1989). Despite their popularity, ambiguity still persists around the ability of these instruments to predict dependence and severity relative to simpler measures. For example, much of the predictive value of the FTND (a six-item instrument) is attributable to a single item: time to first cigarette [TTFC] after waking (Baker et al., 2007; Dale et al., 2001; Haberstick et al., 2007). In fact, recent studies have identified TTFC as the best predictor of ND due to its capability of capturing withdrawal and relapse vulnerability, hence its implication in

smoking cessation outcomes (Baker et al., 2007; Fagerstrom, 2003). Therefore, we used TTFC as an indicator of ND and shorter TTFC to index progression to severe levels of ND.

Originally, TTFC was conceptualized as a categorical variable with the following levels in minutes: ≤ 5, 6-30, 31-60, and >60 with reduced TTFC indicating greater severity of dependence (Heatherton et al., 1989). Reduced TTFC has also been associated with higher expiratory carbon monoxide, wider variability in amount of cigarettes smoked per day (CPD), higher cotinine levels [a major metabolite of nicotine] (Heatherton et al., 1991; Heatherton et al., 1989; Muscat, Stellman, Caraballo, & Richie, 2009), and poor cessation outcomes (Baker et al., 2007; Foulds et al., 2006; Hymowitz et al., 1997). Although there is no consensus as to the ideal cut-off denoting shorter versus longer TTFC and contradictory results regarding the association between CPD and TTFC in different ethnic groups have been reported (Ahijevych, Weed, & Clarke, 2004; Royce, Hymowitz, Corbett, Hartwell, & Orlandi, 1993). These discrepancies have been attributed to the cut-off used to define reduced TTFC (Luo et al., 2008). Whether the effect of MD on TTFC depends on a particular TTFC cut-off remains unexplored. For the purpose of this study, TTFC ≤ 5 minutes is referred to as shorter TTFC hereafter.

Other explanatory variables that may influence the relationship between MD and TTFC are heavy smoking (HS) and stress since both are strongly associated with MD and severe levels of ND (Breslau, 1995; Carmody, 1989; Kassel, Stroud, & Paronis, 2003; Perkins & Grobe, 1992; Pomerleau & Pomerleau, 1987; Pomerleau et al., 2005). In addition, there are various smoking transitions that may lead to severe ND, which makes smoking status at baseline an important covariate, specially, in light of evidence

suggesting that MD maybe more strongly associated with some smoking milestones than others. For example, MD has been inconsistently associated with smoking cessation success, with conflicting results arising from different studies (Glassman et al., 1991; Hitsman et al., 2003). However, MD has been consistently associated with smoking persistence, transition to daily smoking, and dependence (Anda et al., 1990; Breslau et al., 1993; Breslau et al., 1998; Dierker, Avenevoli, Merikangas, Flaherty, & Stolar, 2001) such that there maybe differential effects of MD within various categories of smoking status at baseline.

The objective of the current study was to assess whether MD predicts progression to severe levels of ND, as measured by reduction in TTFC, after accounting for HS, stress, and baseline smoking status (current versus never or former smokers). We also assessed whether our results were sensitive to the definition of TTFC and whether shorter TTFC predicted MD incidence.

Methods

Study Design

The current study is based on data from the National Population Health Survey (NPHS). The NPHS used probability-based multistage sampling methods to select a representative community sample of Canadian household residents of all ages initially interviewed in 1994 by Statistics Canada. The longitudinal cohort has been prospectively followed and re-interviewed every second year in subsequent cycles for 7 cycles to date. Detailed information on this sample and sampling methods are described elsewhere (Swain, Catlin, & Beaudet, 1999; Tambay & Catlin, 1995).

Measures

Major Depression Assessment

The NPHS interview included a brief fully structured diagnostic interview for MD, the Composite International Diagnostic Interview Short Form (CIDI-SF) (Kessler et al., 1998). This interview assesses the presence of past-year major depressive episodes (MDEs). The CIDI-SF algorithm is scored using a 90% predictive probability cut-point validated against DSM-III-R diagnostic criteria (American Psychiatric Association, 1987). These criteria closely resemble those of the DSM-IV-TR (American Psychiatric Association, 2000): an endorsement of minimum of 5 out of 9 symptom-based criteria for MDE, at least one of which must be either depressed mood or loss of interest or pleasure. The CIDI-SF was validated for assessment of MDEs in adolescents as young as 15 years of age (Kessler et al., 1998). In the current sample, there were some subjects between the ages of 12-14 years. No validation data is currently available for this group. A decision was made not to exclude these subjects in view of the face-validity of the instrument and because the longutdinal nature of the study meant that these respondents moved into the 15+ age group within one or two data collection cycles.

Heavy smoking & Nicotine Dependence Assessment

HS was assessed asking the question: "how many cigarettes do you usually smoke each day?" The question "how soon after you wake up do you smoke your first cigarette?" assessed TTFC. Both of these were only administered to current daily smokers (smoked ≥100 cigarettes in their lifetime and currently smoking at least 1 CPD). The HS question was open-ended while the TTFC question was categorical. HS was modeled both as a continuous variable and as a dichotomous variable with 20 CPD as the cut-off (Heatherton et al., 1991). TTFC was dichotomized in the primary analysis using smoking

within 5 minutes to distinguish those who were highly dependent from those with low to moderate levels of dependence. This cut-off was chosen as it is usually the most heavily weighted in instruments such as the FTND (Heatherton et al., 1991). We carried out sensitivity analysis with other cut-offs for TTFC: within 30 and within 60 minutes.

Other Covariates Assessment

Alcohol dependence was assessed using a module of the CIDI-SF (Kessler et al., 1998). A predictive cut-point of 0.85 was used to define probable alcohol dependence status. Stress was assessed using a 16-items scale based on the work of Pearlin and Schooler (1978). This scale was an abbreviated version adapted by Statistics Canada for use in surveys. The abbreviated version has not been independently validated. The scale captures the extent of exposure to daily stressors in different life domains (personal, financial, relationship, environmental, and family). This variable was modeled as a dichotomous variable with the median score as a cut-point designating higher levels of stress. A decision to dichotomize this variable was made to alleviate a breakdown of the linearity assumption at the upper end of the stress scale when stress was modeled as predictor of shorter TTFC, as recommended by Streiner (2002). The tendency to smoke more under stress was assessed using a single item from a coping style questionnaire included in the survey in 2002 (Lazarus & Folkman, 1984)**.** The Kessler 6-item (K6) non-specific psychological distress scale [range 0-24] (Kessler et al., 2002) as a non-specific indicator of severe mental illness. This variable was modeled on a continuum and categorically with scores of 13 or more indicating severe levels of distress.

Study Population

The initial longitudinal cohort included 17,276 participants. The current study was

restricted to those who, in 1996, were: either (1) current smokers who did not smoke their first cigarette within 5 minutes after waking or (2) were non-smokers (never or former). To be eligible, a respondent must also have responded to CIDI-SF (n=12,907). Non-smokers were not excluded because the duration between cycles was long enough for non-smokers at baseline to initiate daily smoking between follow-up interviews, potentially transitioning to shorter TTFC in the same interval. From the original sample of 12,907 followed to 2006, 7,525 (58.3%) subjects had complete data compared to 3,666 (28.4%) non-respondents at one or more time points on key survey questions. The balance had partial response, were institutionalized or deceased during follow-up (see supplementary figure). Whenever possible, respondents were included in the analysis and censored when they left the sampling frame.

Analytical Procedures

The 2-year prevalence of different TTFC categories stratified by baseline MD and HS status were calculated. Next, the 10-year cumulative incidence or risk of shorter TTFC stratified by baseline MD and HS status was estimated. Based on previous findings from the literature, a list of other covariates (see above) including the tendency to smoke more under stress were prepared and the 10-year risk of shorter TTFC was then stratified by these variables. In these preliminary stratified analyses, any factor that substantially reduced the MD-shorter TTFC association was subsequently added to proportional hazard (PH) models estimating the HR for the entire follow-up period and making simultaneous covariate adjustments.

At the modeling stage, discrete PH models were used for covariate adjustments because the interviews were conducted two years apart (Singer & Willett, 2003). We

initially modeled the 10-year risk of shorter TTFC as the primary outcome. Discrete-time models using the complementary log-log link function (Singer & Willett, 2003) were fit using Stata version 11.0. We tested the PH assumption by comparing models with and without MD by time interactions using the likelihood ratio test. Time-invariant and time-varying predictors were then added to these models. MD effects on the risk of shorter TTFC were modeled as a lagged time-varying variable with MDE ascertainment 2 to 3 years prior to TTFC assessment. Similarly, CPD was modeled as lagged (two years prior to TTFC assessment) time-varying variable. However, to ensure that our results were robust regardless of the assessment duration, we also modeled CPD as non-lagged variable (assessment of CPD assessment at the same cycle as TTFC). We modeled the effects of CPD and MD as time-varying rather than fixed in order to minimize the potential of misclassification bias. Other covariates were also treated as time-varying where appropriate.

As a secondary endpoint, we also modeled the 10-year risk of MD and delineated the effect of shorter TTFC on the risk of MD. The same modeling strategies and covariate-adjustments were used as those employed in modeling the TTFC-MD pathway.

In all our analyses, estimates were weighted to adjust for survey design effects: variation in the probability of selection and non-response. Replicate bootstrap weights accounted for clustering and stratification in variance estimation.

Results

Sample Characteristics

The sample consisted of slightly higher proportions of females (51.3%) than males (48.7%). Respondents aged 12-25 years comprised 22.9% of the sample compared to

37.9% of those aged 26-45 years, and 39.2 % of those 46 years and over. Table 1 compares those with and without MD at baseline on various potential risk factors for shorter TTFC. MD was positively associated with current smoking status, alcohol dependence, low income, separated or divorced marital status, and chronic stress. MD was negatively associated with never smoking status. The corresponding confidence intervals did not overlap suggesting that these associations are unlikely due to sampling variability**.** The current sample (n=12,907) was slightly older, less likely to be current smokers, and more likely to report higher levels of stress at baseline than the original sample (n=17,276).

Prevalence & Incidence of TTFC by MD

Table 2 shows the prevalence of TTFC at baseline (1996) by MD status and the amount smoked in 1996. Irrespective of their HS status, individuals with MD compared to those without MD had significantly higher frequencies of shorter TTFC [58.3% versus 34.7%, $p<0.001$; 24.6% versus 11.0%, $p<0.001$]. This pattern was not evident for other TTFC cut-offs

Figure 1 shows the 10-year risk of shorter TTFC by MD and HS status in 1996. Among those with MD who were heavy smokers, the risk of shorter TTFC was approximately 3 times higher at each follow-up point when compared to those without MD who were not HS. [Cycle 1: 17.0% versus 5.9%, ($p<0.05$); Cycle 2: 26.9% versus 9.8%, ($p<0.05$); Cycle 3: 30.9% versus 11.5% ($p<0.05$); Cycle 4: 34.0% versus 12.8% ($p<0.05$); and Cycle 5: 35.5% versus 13.5% ($p<0.05$)] .

Only 1.2% of all incident cases of shorter TTFC were respondents who were 12-14 years of age at baseline and who reported having MDEs between 1996 and 1998.

Therefore, their contribution to the risk of shorter TTFC was negligible, which alleviates concern that the CIDI-SF has not been formally validated in this group.

In preliminary stratified analyses (not shown), there was no evidence of effect modification by any covariate. However, a number of covariates were found to account for some of the MD-TTFC association, which necessitated adjustment in multivariate modeling (see below). No evidence against the PH assumption was found. Similarly, the likelihood ratio test with and without MD by time interactions was not significant (p=0.08**).**

Statistical Models

Controlling for age, sex, marital status, education, alcohol dependence, and chronic stress did not substantially alter our results. Only controlling for HS and "smoke more under stress" reduced the hazard ratio (HR) compared to the unadjusted HR. Therefore, we report results on models including these two covariates.

Models for Shorter TTFC (within 5 minutes)

In a model with HS and MD alone (not shown), the HR for heavy versus non-heavy smokers independent of MD was 2.6 (95% CI: 2.1-3.3; p<0.001), while the adjusted HR for MD was 1.9 (95% CI: 1.3-2.7; p<0.001) compared to the unadjusted HR of 3.7 (95% CI: 2.6-5.3). Similarly, in a model with "smoke more under stress" and MD alone (not shown), the adjusted HR for "smoke more under stress" was 7.5 (95% CI: 5.5-10.2; p<0.001) while the HR for MD was reduced to 2.3 (95% CI: 1.5-3.6; p<0.001). In a model with all three variables, the effect of MD independent of HS and "smoke more under stress" was further reduced to 1.7 (95% CI: 1.1-2.5), but remained statistically significant (p=0.02) (see Table 3).

*Models for Longer TTFC (within 30 and 60 minute*s)

In a model predicting TTFC within 30 minutes with HS and MD alone (not shown), the HR for heavy versus non-heavy smokers was 2.1 (95% CI: 1.6-2.7; p<0.001), but the adjusted HR for MD was reduced to 1.0 (95% CI: 0.6-1.5) and was no longer significant (p=0.9) compared to unadjusted HR for MD of 2.1 (95% CI: 1.4-3.1; p<0.001). When controlling for both HS and "smoke more under stress" simultaneously, the HR for MD did not change in value and did not predict TTFC (HR=1.0, 95% CI: 0.5-1.7; p=0.9). Additionally, both variables remained significant predictors of TTFC. Similar results were obtained for MD (HR=0.7, 95% CI: 0.4-1.3; p=0.6) when modeling TTFC within 60 minutes with the exception that after adjustment for HS status (HR=1.7, 95% CI: 1.2-2.8; p=0.04) the HR for "smoke more under stress" was greatly reduced to a value of 1.1 (95% CI: 0.8-1.6). This variable was no longer a significant predictor of TTFC (p=0.4), and was removed from the model shown in Table 3.

Similar results were obtained when number of CPD was modeled as continuous variable rather than dichotomous HS status; when CPD was modeled as non-lagged variable relative to TTFC ascertainment; and when distress was added to these models. These results are available upon request.

To assess the effects of MD on risk of shorter TTFC as a function of baseline smoking status, an interaction term between MD and smoking status was added to a model (not shown) with main effects of MD, HS, and smoking status. There was no evidence of effect modification (p=0.8). We also re-ran separate analyses restricted to baseline current smokers at risk for shorter TTFC and baseline never or former smokers

(see supplementary table). Our main results were found to be robust when the analysis was approached in these differing ways.

Models for Shorter TTFC-MD pathway

We also modeled the effect of shorter TTFC on the risk of MD onset. The same modeling strategies and covariate-adjustments were used. Unlike previous analyses, controlling for age and sex in shorter TTFC-MD analyses substantially changed our results. Therefore, all reported models for these analyses were adjusted for age and sex accordingly. In a model with HS and shorter TTFC (not shown), the HR relating heavy versus non-heavy smokers was 1.4 (95% CI: 1.2-1.7; $p<0.001$), while the adjusted HR for shorter TTFC was 1.3 (95% CI: 1.1-1.6; $p<0.05$) compared to unadjusted HR of 1.6 (95% CI: 1.2-2.1). Similarly, in a model with "smoke more under stress" and shorter TTFC (not shown), the adjusted HR for "smoke more under stress" was 1.8 (95% CI: 1.4-2.3; $p<0.001$) while the HR for shorter TTFC was reduced to 1.2 (95% CI: 0.9-1.5) and was no longer statistically significant ($p=0.2$). In a model with all three covariates, only the effect of "smoke more under stress" remaining a predictor of MD onset (1.7, 95% CI: 1.2-2.4; $p<0.01$), neither the effect of shorter TTFC (HR=1.0, 95% CI: 0.7-1.5; $p=0.9$) nor HS status was statistically significant (HR=1.4, 95% CI: 1.0-2.0; $p=0.05$).

Discussion

To our knowledge, this is the first population-based prospective investigation reporting associations between MD and TTFC. Our results show that MD is a significant risk factor for progression to severe levels of dependence as characterized by transition to shorter TTFC after controlling for HS and tendency to smoke more under stress. However, when

defining TTFC using longer cut-offs, HS completely accounted for the effect of MD on TTFC.

There are substantial pharmacologic effects (Benowitz, 2010) as well as reported craving, withdrawal, reduction of negative affect and increasing positive affect after smoking the first cigarette of the day (Toll, Schepis, O'Malley, McKee, & Kirshnan-Sarin, 2007). Our findings implicate MD in shorter TTFC etiology and consequently to neurochemical processes that presumably result in these subjective changes in response to the first cigarette of the day. Although the underlying biological mechanisms that link MD to shorter TTFC are currently unknown, the biological plausibility of this association has been previously reported (Balfour & Ridley, 2000; Camordy, 1989; Lerman et al., 1996). Our findings with respect to MD-shorter TTFC may have important implications for smoking cessation interventions.

Recent research has found TTFC to be the single best predictor of ND (Fagerstrom et al., 2003). Further, reduction in TTFC is closely implicated in poor smoking cessation outcomes (Baker et al., 2007). Our findings point to MD as a risk factor for transitions to shorter TTFC especially among daily smokers. A clinical implication of this finding is that early detection and treatment of MD may help prevent worsening of ND, which may in turn lead to improvement in smoking cessation outcomes in this subset of the general population. In addition, TTFC appears to be an effective determinant of dosage strength in ND treatment allocation (Shiffman et al., 2002). TTFC can be easily assessed during a brief clinical encounter in primary care compared to other instruments. Therefore, the use of TTFC to approximate ND and index its severity in patients with MD may be warranted in clinical practice and deserves further exploration.

Previous studies have reported the lack of one-to-one concordance between CPD and different measures of ND in both adults and adolescents (Colby, Tiffany, Shiffman, & Niaura, 2000; Dierker & Donny, 2008; Dierker et al., 2007; Muscat et al., 2009). Our results replicate these findings for shorter TTFC, but not for longer TTFC. In addition, our results contribute to the current literature as MD may be a potential source for some of the discrepant findings. In particular, MD may account for some of the idiosyncrasies in sensitivity to nicotine at comparable levels of CPD.

Our results also point to the importance of the role of an ineffective coping style (tendency to smoke more under stress) as an independent predictor of transition to shorter TTFC. Although we have adjusted for this covariate in our models, its role as mediator in the MD-shorter TTFC pathway should not be ruled out especially with evidence from the literature pointing to its role in MD etiology (Kassel, Stroud, & Paronis, 2003; Lerman et al., 1996). If so, adjustment for this variable may result in underestimation of the association of interest. As a mediating factor, the self-medication of depressive symptoms is an emotion-focused coping strategy potentially amenable to psychosocial interventions that facilitate problem-focused coping strategies. This may potentially have valuable clinical or public health implications in prevention of escalation to severe dependence.

As for the influence of baseline smoking status on findings from this study, MD appears to be implicated in the transition from longer to shorter TTFC while the effects of MD on shorter TTFC among never and former smokers are more equivocal. However, since less than 2% of individuals transitioned from non-smoking to shorter TTFC, the lack of statistical significance of the association in may be the result of Type II error.

While our data is non-experimental and causal inferences cannot be drawn, it is still valuable to assess the plausibility of other unmeasured variable(s) accounting for our findings. To this end, the latter half of our analyses focused on the reverse direction vis-à-vis shorter TTFC-MD pathway. Breslau et al. (1993) reported the bidirectional association between lifetime MDD and ND (defined by DSM-III) while our findings only support a unidirectional association: MD as predictor of shorter TTFC. Different covariate adjustments as well as different ND assessment methods may have contributed to this discrepancy. With respect to the latter, there is a lack of consensus on how well some ND criteria in the DSM predict smoking cessation outcomes. In contrast, the predictive validity of TTFC has recently been confirmed against both traditional and newer measures of dependence (Baker et al., 2007). Nevertheless, our results are preliminary and need further replication by future studies.

There are various limitations to our findings. One limitation is the self-report nature of the data and narrow scope of ND assessment**.** Second, the brief nature of CIDI-SF makes it susceptible to misclassification of MD status among respondents. Nevertheless, this type of bias is likely to be non-differential with an expected direction of bias is towards the null (Kleinbaum, Kupper, & Morgenstern, 1982). This form of bias cannot account for the significant associations reported in this study. Third, the relatively long assessment duration between antecedent CPD and consequent development of TTFC may contribute to some misclassification with regards to CPD status. However, a similar pattern of results was observed with and without CPD as lagged time-varying variable. Hence, it is unlikely that such bias would invalidate our findings. Finally, the lack of direct assessment of psychiatric comorbidity (except alcohol dependence) is another

potential limitation of this study. Our results do not rule out the possibility that other mental disorders accounted for the presented results.

In conclusion**,** the current study provides evidence in support of MD as a strong predictor of developing shorter TTFC independent of the amount of CPD and the tendency to smoke more under stress. TTFC provides a convenient way of assessing severity of ND in clinical practice and since MD is treatable, the association of MD with shorter TTFC may possibly point towards a promising preventive opportunity. People with MD may deserve closer monitoring and support in clinical settings as they are at risk of transitioning to ND.

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Declaration of Interests

None declared

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