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**Changes in prevalence of depression and anxiety following  
smoking cessation: results from an international cohort study  
(ATTEMPT)**

**Short title: Smoking cessation, depression and anxiety**

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**Abstract**

**Background:** Smoking cessation improves physical health but it has been suggested that in vulnerable individuals it may worsen mental health. This study aimed to identify the short- and longer-term effects of stopping smoking on depression and anxiety in the general population and those with a history of these disorders.

**Methods:** Socio-demographic and smoking characteristics, mental and physical health were assessed using established measures in the ATTEMPT cohort, an international longitudinal study of smokers (N=3,645). Smokers who had stopped for at least 3 months or less than 3 months at 12 months follow-up were compared with current smokers (N=1,640).

**Results:** At follow-up, 9.7% (95%CI 8.3-11.2) of smokers had stopped for less than three months and 7.5% (95%CI 6.3-8.9) for at least three months. Compared with current smokers, prevalence of depression prescriptions obtained in the last two weeks was lower for those who had stopped for less than (OR 0.37, 95%CI 0.14-0.96) or at least three months (OR 0.25, 95%CI 0.06-0.94) after adjusting for baseline prescription levels and confounding variables. Adjusted prevalence of recent depression symptoms was also lower for ex-smokers who had stopped for less than (OR 0.34, 95%CI 0.15-0.78) or at least three months (OR 0.24, 95%CI 0.09-0.67) than among continuing smokers. There was no change in anxiety measures in the general population nor any increase in anxiety or depression symptoms in ex-smokers with a past history of these conditions.

**Conclusions:** Smoking cessation does not appear to be associated with an increase in anxiety or depression and may lead to reduced incidence of depression.

**Key words:** smoking, smoking cessation, mental health, anxiety, depression, longitudinal

## Introduction

Smoking cessation improves physical health and reduces the risk of premature death (Taylor *et al.* 2002; Doll *et al.* 2004). However, its effect on mental health is uncertain (West & Jarvis, 2005). Cross-sectional studies consistently show a clear association between smoking and poor mental health, with current smokers having a higher prevalence of several psychiatric disorders including depression and anxiety than never- and ex-smokers (Glassman *et al.* 1990; Breslau *et al.* 1994; Breslau 1995; Breslau & Klein, 1999; Farrell *et al.* 2001; Degenhardt *et al.* 2001; Benjet *et al.* 2004; Grant *et al.* 2004; Wiesbeck *et al.* 2008). This may be due to several reasons.

Smoking behaviour and poor mental health may share a common aetiology based on genetic vulnerability (Kendler *et al.* 1993), early childhood environment (Goodwin *et al.* 2004) and personality traits (Goodwin & Hamilton, 2002). In addition, smoking may worsen mental health and stopping may improve it, or people with worse mental health could be more likely to start smoking and find it more difficult to stop, e.g. because they self-medicate (Breslau *et al.* 1998). Indeed, longitudinal studies show both that psychiatric illnesses leads to later smoking uptake (Brown *et al.* 1996; Patton *et al.* 1998; Breslau *et al.* 1998; Breslau *et al.* 2004) and that starting to smoke increases the risk of subsequent psychiatric morbidity (Johnson *et al.* 2000; Klungsoyr *et al.* 2006; Steuber & Danner, 2006; Boden *et al.* 2010; Kang & Lee, 2010), suggesting a reciprocal relationship. However, most research has focused on either the onset of mental illness following uptake of smoking or uptake of smoking following the onset of mental illness. Less is known about the effects of smoking cessation on mental health in general and depression and anxiety in particular.

A large body of opinion postulates that smoking may, through the actions of nicotine, have beneficial effects on mental health, for example acting as an anxiolytic, and aid in self-medication to relieve perceived psychological or physiological symptoms (Morrell & Cohen, 2006; Morissette *et al.* 2007; Ziedonis *et al.* 2008). If that were the

case, one might expect mental health to deteriorate, particularly in vulnerable individuals who stop smoking. In agreement with this, some reports indicate increased incidence of depressive episodes in people with a history of major depressive disorder who have stopped smoking, linking these to cessation (Flanagan & Maany, 1982; Glassman *et al.* 1990; Glassman *et al.* 2001; Aubin 2009). Moreover, general population studies have shown that mood disturbances do not necessarily resolve following a month of abstinence from smoking (Gilbert *et al.* 1999; Gilbert *et al.* 2002) and that smokers with a history of depression or those who experience more negative affect during a quit attempt are more likely to relapse (Kassel *et al.* 2003; Piasecki *et al.* 2003; Rohde *et al.* 2004).

Yet, short to longer-term cessation has also been associated with a decrease in stress and anxiety and no worsening of depressed mood in the general population (West & Hajek, 1997; Hajek *et al.* 2010; Bolam *et al.* 2011) and with a faster recovery among those with a current diagnosis of depression or anxiety (Jamal *et al.* 2012). While there is evidence that acute negative affect may precipitate relapse (Shiffman & Waters, 2004), meta-analyses have failed to corroborate findings that a history of depression predicts smoking cessation outcomes (Hitsman *et al.* 2003; Covey *et al.* 2006). In addition, randomised controlled trials of smoking cessation interventions show that smokers with mental illness can achieve abstinence rates comparable to those of general population samples (Banham & Gilbody, 2010).

Given these contradictory findings, more research is needed into the association of mental health with smoking cessation to better understand causal relationships (Morrell & Cohen, 2006). However, much of what we know about the impact of smoking cessation on mental health comes from randomised controlled trials rather than naturalistic, observational studies, and cohort studies that can address the issue by comparing continuing smokers with those who stop are relatively rare (Ziedonis *et*

*al.* 2008). Most large-scale studies in this area tend to be cross-sectional and retrospective (Mykletun *et al.* 2008; McClave *et al.* 2009) and prospective studies have often parochial and small sample sizes (Covey *et al.* 1997; Glassman *et al.* 2001; Gilbert *et al.* 2002) limiting the conclusions that can be drawn.

Thus there is an expressed need for longitudinal data on this issue with regular follow up in a sample that is representative of the general population of smokers. This paper reports on the impact of smoking cessation on self-reported depression and anxiety using data from ATTEMPT, the largest longitudinal, multi-national general population study yet to be conducted on this topic. Specifically, we investigate the following questions:

- 1.) What is the impact of short- (<3 months) and longer-term ( $\geq 3$  months) smoking cessation on the prevalence of depression and anxiety in a general population sample?
- 2.) What is the impact of short- and longer-term smoking cessation on the prevalence of depression and anxiety among smokers with a history of these conditions?

## **Methods**

### Study population and design

Participants were selected from the ATTEMPT cohort; a multinational prospective study examining physical and mental health outcomes in individuals as a function of their smoking status. Full details of the study methodology are provided elsewhere (West *et al.* 2006). Briefly, participants were recruited via Harris Interactive, Inc. which maintains a market research panel with several million panellists in over 125 countries. These panel members are internet users who have registered voluntarily and have agreed to complete regular online surveys for research purposes in exchange for points that can be redeemed for merchandise. The current analysis reports on phase two of this study, set up in 2004 in the USA, Canada, the UK, France and Spain. Following email invitations sent to a random sample of panellists in these countries, those that smoked at least five cigarettes a day, intended to quit within the following three months and were aged between 35-65 years were included. A total of 3,645 respondents met eligibility criteria. At baseline participants completed a self-report questionnaire received via email, and detailed follow-up questionnaires were completed via email approximately every three months for up to 18 months. Only participants who provided complete and consistent responses at both the baseline and 12 months follow-up (N=1,640) were included in the current analysis (see Table 1 for sample characteristics).

### Measures

Smoking history and standard smoking characteristics, socio-demographic characteristics including age, sex, marital and employment status, ethnicity and educational attainment were collected at baseline and follow-up surveys and standardised across countries.

At baseline, smokers were asked to indicate length of time of smoking and recent quit attempts were determined by asking: “During the past 3 months (90 days), have you made a serious attempt to stop smoking for good that lasted for at least a day (24h)?”. Smokers were also asked if any cessation medications were used to support their quit attempt. Motivation to stop smoking was measured using a 10-point Likert scale: “In the following 10-point scale, please select the number that best describes your current motivation to quit smoking cigarettes” (1=not at all motivated, 10=highly motivated). Nicotine dependence was measured using the Fagerstrom Test of Nicotine Dependence (Heatherton *et al.* 1991), which places smokers on a ten point scale based on six items: time to first cigarette (0=60+ min; 1=31-60 min; 2=6-30 min; 3=within 5 min); daily cigarette consumption (0= $\leq$ 10, 1=11-20, 2=21-30, 3=31+); smoking when ill; more frequent smoking shortly after awakening; difficulty refraining from smoking in no-smoking areas (for all: 0=no; 1=yes); and the cigarette smokers hate most to give up (1=first in the morning, 0=any other).

Smoking status at 12 months follow-up was assessed by asking participants “Are you currently a smoker?” and “Have you smoked any cigarettes today?”. Those who answered ‘yes’ to either or both questions were classified as ‘current smokers’. Participants who answered ‘no’ to both questions were further asked “How many days has it been since you last smoked a cigarette?” and a free-text response was recorded. Those who claimed to have not had a cigarette within the last 3 months were asked “Just to confirm, in the last 3 months (90 days) have you smoked any cigarettes (even a puff)?” Participants who answered ‘no’ were classified as ‘ex-smokers  $\geq$ 3 months’. Participants whose response suggested they had stopped smoking within the last 3 months were asked to confirm they had not smoked either in the last 30 days, 7 days or today. Those who answered ‘no’ to any of these options were classified as ‘ex-smokers <3 months’. Inconsistent responders (N=40) were excluded.



Physical and mental health was assessed at both baseline and follow-up.

Participants were asked to provide their height and weight in order to calculate their body-mass-index. Respondents also completed the EuroQol (EQ-5D), a widely used measure of health-related quality of life (Rabin & de Charro, 2001). Mental health was determined by yes/no responses to single item measures which have been found to have good congruence with structured clinical interviews (McChargue & Werth, 2007). Life-time mental health diagnoses were assessed by asking “Have you ever been told by a doctor or other health care professional that you had any of the following conditions? 1) Depression, 2) Anxiety”. Recent mental health status was determined by asking “During the past 3 months, have you had symptoms or been bothered by any of the following conditions? 1) Depression, 2) Anxiety”. Respondents also noted their medication prescriptions, being asked “During the past 2 weeks, did you take medications that require a prescription from your doctor for the following conditions? 1) Depression, 2) Anxiety”. For ease of analysis, measures of depression and anxiety were also combined into a single measures of ‘any’ mental health problem.

### Analysis

Data were analysed using SPSS 20.0 (IBM, New York). In unadjusted analyses between and within group differences were assessed with  $X^2$  test, Wilcoxon signed-rank test or ANOVAs for categorical and continuous variables, respectively. Adjusting for all other factors in the model, logistic regressions were carried out providing odds ratios (OR) with 95% confidence intervals (CIs) in order to evaluate which, if any, of the variables were independently associated with mental health outcomes.

Generalised estimating equations were used to compute mean-value adjusted levels of mental health outcomes by smoking status. Statistical significance was set at the

standard level ( $p < 0.05$ ) and in post-hoc analyses, the Sidak correction was applied to control for multiple comparisons.

## Results

A total of 45% of participants (N=1,640) completed both baseline and follow-up online questionnaires. Those lost to follow-up differed on a number of socio-economic and smoking but on only few physical and mental health characteristics. Those lost to follow-up were slightly more likely to report a life-time diagnosis of any mental health problem, in particular depression ( $X^2=4.6, df=1, p=0.032$ ), but no other differences were apparent. Life-time prevalence of depression and anxiety in the retained sample was 22.3% (95%CI 20.2-24.2) and 27.4% (95%CI 25.1-29.4), respectively. Overall, a third (37.5%, 95%CI 35.2%-39.8%) reported any life-time diagnosis (Table 1).

(Table 1 about here)

At 12 months, 7.5% (95%CI 6.3-8.9) of smokers had stopped for at least three months and 9.7% (95%CI 8.3-11.2) for less than three months. There were few differences in baseline variables according to smoking status at follow-up (Table 1). Those who were smokers at 12 month follow up had been more nicotine dependent ( $F=10.5, df_{\text{between}}=2, df_{\text{within}}=1610, p<0.001$ ) and less likely to have previously made a quit attempt at baseline ( $X^2=16.4, df=2, p<0.001$ ) than recent ex-smokers. They also scored marginally lower on the EQ-5D than longer-term ex-smokers ( $F=3.4, df_{\text{between}}=2, df_{\text{within}}=1603, p=0.035$ ).

### 1.) Impact of short- and longer-term smoking cessation on depression and anxiety prevalence in the general population

At follow-up, current smokers were more likely to have received a prescription in the last two weeks for 'any' mental health problem than longer-term ( $\geq 3$  months) ex-smokers (Table 2). More specifically, longer-term ex-smokers were less likely to report receiving a prescription for depression, but not anxiety, than current smokers

(OR 0.26, 95%CI 0.09-0.71,  $p=0.009$ ). There were no differences between current and recent (<3 months) ex-smokers. These results were broadly mirrored when looking at 'any' mental health symptoms experienced in the last three months (Table 2). Longer-term and recent ex-smokers were less likely to report symptoms of depression, but not anxiety, than current smokers (OR 0.31, 95%CI 0.14-0.67,  $p=0.003$  and OR 0.53, 95%CI 0.31-0.92,  $p=0.025$ , respectively).

(Table 2 about here)

These findings were further substantiated using logistic regression models to control for potential confounders. Smoking status at follow-up did not impact reported prescriptions for anxiety in the last two weeks or experiencing symptoms of anxiety in the last three months at 12 months follow-up (Table 3a). However, the prevalence of receiving a prescription for depression in the last two weeks at follow-up was significantly lower among recent (7.0%; OR 0.37, 95%CI 0.14-0.96,  $p=0.041$ ) and longer-term ex-smokers (6.2%; OR 0.25, 95%CI 0.06-0.94,  $p=0.040$ ) than among current smokers (11.4%, Figure 1a). Similarly, prevalence of reported symptoms of depression experienced within the last three months was significantly lower among recent (10.2%; OR 0.34, 95%CI 0.15-0.78,  $p=0.011$ ) and longer-term ex-smokers (8.1%; OR 0.24, 95%CI 0.09-0.67,  $p=0.006$ ) than among current smokers (16.5%) at 12 months follow-up (Figure 1b).

(Table 3 about here)

As expected, baseline prescription levels and symptoms of depression or anxiety were the strongest predictors of a recent prescription and experiencing symptoms of depression or anxiety at 12 months-follow up (Table 3a). There were some country-level differences, with participants from the US reporting highest levels of depression

prescriptions and symptoms. In addition, those who were married, employed and showed an increase in their health-related quality of life from baseline were less likely to report receiving a prescription for, or experiencing, depression symptoms at follow-up. Conversely, those who were male, employed, less nicotine dependent and had improved health-related quality of life, and to a lesser degree those who were less motivated to quit and had made no recent quit attempt at baseline, were less likely to report receiving a prescription for, or experiencing, anxiety symptoms at follow-up (Table 3a).

## 2.) Impact of short and longer term smoking cessation on depression and anxiety prevalence among those with a history of mental health problems

As expected the prevalence of indicators of recent mental health problems, depression and anxiety symptoms experienced in the last three months and relevant prescriptions received in the last two weeks, was higher in this vulnerable population than in the general population (Figure 1). Ex-smokers of at least three months were less likely to report receiving prescriptions for, or experiencing, 'any' mental health problem than current smokers in unadjusted analysis (Table 2). This was the case for prescriptions for depression (OR 0.27, 95%CI 0.09-0.76,p=0.014) and experiencing symptoms of depression (OR 0.33, 95%CI 0.14-0.75,p=0.008) but not anxiety. Ex-smokers of less than three months were also less likely to report experiencing depression symptoms in the last three months (OR 0.50, 95%CI 0.27-0.92,p=0.026) than those who continued smoking (Table 2).

(Figure 1 about here)

As Figure 1 shows, differences between current and ex-smokers with a history of mental health problems were largely attenuated in adjusted analysis with two exceptions: the prevalence of having received a prescription for 'any' mental health

problem in the last two weeks was significantly lower among longer-term ex-smokers (20.5%) than current smokers (35.6%; OR 0.24, 95%CI 0.07-0.77,  $p=0.016$ ) and the prevalence of experiencing symptoms of depression in the last three months was significantly lower among recent ex-smokers (23.7%) than current smokers (36.6%; OR 0.36, 95%CI 0.14-0.92,  $p=0.033$ ; Table 3b). Generally, odds ratios were comparable to those from the general population.

As before, baseline prescription levels and symptoms of depression or anxiety were the strongest predictors of a recent prescription and experiencing symptoms of depression or anxiety at 12 months-follow up (Table 3b). The level of depression prescription and symptom was again higher in the US compared with other countries. In addition, as in the general population, those who were married, employed and showed an increase in their health score from baseline were less likely to report receiving a prescription for, or experiencing, depression symptoms at follow-up. Likewise, those who were male were less likely to report receiving a prescription for, or experiencing, anxiety symptoms at follow-up and those who were more motivated to quit and had made a recent quit attempt at baseline were also more likely to report receiving a prescription for anxiety in the last two weeks (Table 3b).

(Figure 2 about here)

In order to delineate the causal direction of the observed association of smoking cessation with mental health, sensitivity analyses were carried out. It was reasoned that the findings may be an artefact. Self-selection could account for the results as smokers who are more prone to become depressed upon cessation may be more likely to relapse and continue to smoke. In this scenario, there would be no change over time in the total prevalence of mental health problems in the cohort. The decrease in prevalence of mental health problems among ex-smokers - those who

are less vulnerable to psychiatric morbidities and are therefore able to stop - would be offset by an increase in the prevalence of mental health problems in the remaining pool of current smokers - those who are more vulnerable to psychiatric morbidities and find it difficult to stop (Figure 2A). Alternatively, if smoking cessation improved mental health, one would expect that with an increase in ex-smokers in the cohort, there should be an overall decrease in the prevalence of mental health problems as there would be no change among current smokers but a decline among ex-smokers (Figure 2A).

Figures 2B and C show a pattern of no change or a decrease in the prevalence of reported mental health outcomes among current smokers and a pronounced decrease among ex-smokers, consistent with the latter but not former interpretation. There was a non-significant overall decrease in prescriptions from 15.5% to 14.9% in the total population, no change among current smokers and a decline among ex-smokers resulting in significant differences between ex- and current smokers at follow-up ( $X^2=4.2, df=1, p=0.04$ ) but not at baseline (Figure 2B). There was also a significant decrease in prescriptions among those with mental health problems from 41.5% to 34.3% (Wilcoxon  $Z=3.69, p<0.001$ ). Whilst this was the case for both continuing smokers (Wilcoxon  $Z=2.04, p=0.041$ ) and ex-smokers (Wilcoxon  $Z=3.13, p=0.002$ ), possibly reflecting regression towards the mean, this decline was steeper among ex-smokers who were less likely than smokers to report receiving prescriptions for 'any' mental health problems in the last two weeks at follow-up ( $X^2=4.7, df=1, p=0.03$ ) but not baseline.

The pattern was broadly similar for mental health problems experienced in the last three months, reducing significantly from 28.7% to 26.1% in the overall sample (Wilcoxon  $Z=2.45, p=0.014$ ). This decline was only present among those who had stopped smoking (Wilcoxon  $Z=3.37, p<0.001$ ; Figure 2C). Among those with a history

of mental health problems, there was also an overall significant decline from 76.6% to 55.8% (Wilcoxon  $Z=2.45, p=0.014$ ). As before this may be a result of regression towards the mean, being present among both current (Wilcoxon  $Z=7.09, p<0.001$ ) and ex-smokers (Wilcoxon  $Z=2.54, p=0.019$ ). However, the decline was again steeper among ex-smokers since there were no differences between groups at baseline but there were at follow up ( $X^2=7.4, df=1, p=0.007$ ).



## Discussion

Depression and anxiety as assessed in this cohort of smokers was common, with one in three reporting a life-time diagnosis of either condition and one in four experiencing recent symptoms. These estimates are broadly similar to previous studies confirming much higher incidence and prevalence rates among smokers than non-smokers (Perez-Stable *et al.* 1990; Breslau *et al.* 1991; Grant *et al.* 2004; McClave *et al.* 2009; Lawrence *et al.* 2009). In agreement with previous research (West & Hajek, 1997; McClave *et al.* 2009; Bolam *et al.* 2011), this study provides evidence that smoking cessation in the general population does not result in an increase in mental health problems and may be associated with a decrease in depression. Similar to a cross-sectional analysis, these effects appeared largely independent of the length of abstinence (Mykletun *et al.* 2008).

In contrast to some (Glassman *et al.* 1990; Covey *et al.* 1997; Glassman *et al.* 2001) but not other work (Haustein *et al.* 2002; Jamal *et al.* 2012), there was no evidence of an exacerbation of symptoms following smoking cessation among those with a history of mental health problems. This divergence may be due to a number of factors. This analysis provides a larger sample than most previous studies and includes participants from several countries. In addition, it is possible that the association of smoking cessation and deterioration in mental health may be a function of the severity of past mental health problems which was not assessed in the current study. However, even in studies reporting an increased risk of depressive episodes following cessation, rates were very low (Morrell & Cohen, 2006; Ziedonis *et al.* 2008) suggesting that this may be an issue for only a small proportion of smokers with a history of mental health problems.

In line with previous studies in general or patient populations, being married (Weissman *et al.* 1996; Frech & Williams, 2007) or in employment (Murphy &

Athanasou, 1999) was independently associated with lower rates of depression and men were less likely than women to display anxiety symptoms (West & Hajek, 1997; Lewinsohn *et al.* 1998; Pigott 1999; McClave *et al.* 2009). In addition, as shown previously, greater nicotine dependence was associated with anxiety (Goodwin *et al.* 2011), and improvement in general health was associated with better mental health (Wise & Taylor, 1990; Sherbourne *et al.* 1996; Patten 2001; Ruo *et al.* 2003; Evans *et al.* 2005; Beard *et al.* 2007; Janney *et al.* 2008; Carek *et al.* 2011).

This study has some limitations. As data were collected online, smoking status and mental health were assessed by self-report rather than clinical assessment. However, self-report in surveys has been shown to be a valid indicator of both current smoking (Patrick *et al.* 1994) and mental health status (McChargue & Werth, 2007). While the use of prescription as an indicator is problematic as prescription policies and practices vary between countries of included participants, several measures of mental health were used to increase reliability, yielding similar results, and country was included as a confounder in analysis. Moreover, prevalence estimates and observed associations with a range of socio-demographic variables replicate previous findings of studies using standard measures of mental health, further corroborating this approach. Whilst numerous covariates were included in the analysis, it is possible that inclusion of other uncontrolled variables, for instance common vulnerability factors for both mental health and smoking such as impulsivity or neuroticism (Bienvenu *et al.* 2001; Hooten *et al.* 2005), could have altered results. In addition, self-selection cannot be excluded as an explanation for the findings. However, this problem could only be overcome using a randomised controlled design which would be unethical and sensitivity analysis showed that it is unlikely that self-selection alone can account for the observed associations. Lastly, given that this sample comprises internet users, aged 35-64, who volunteered to participate this may affect the generalizability of findings. However, previous analysis has shown that

characteristics of this sample show high congruence with characteristics of equivalent national probability-based samples of the respective countries of participants (West *et al.* 2006). This study also had strengths. The longitudinal design allowed for an analysis of temporal associations in a large sample drawn from the general population across different countries, controlling for a multitude of confounders which strengthens the generalizability of findings.

Our findings add substantially to a growing literature suggesting that smoking cessation may not only be beneficial for physical but also mental health in the general population and that it does not exacerbate symptoms of depression or anxiety among those with a history of these conditions. These outcomes may be explained by the adverse effects that chronic smoking has on neurophysiological substrates, being linked to changes in monoamine oxidase activity (Fowler *et al.* 1996) and levels of brain-derived neurotrophic factor (Kim *et al.* 2007) which have been implicated in the aetiology of psychopathology (Pintar & Breakefield, 1982; Sen *et al.* 2008). It has also been postulated that the frequent unpleasant withdrawal symptoms experienced by smokers may lead to the development and maintenance of mental health problems (Parrott 2006). In this context it is important to reiterate that smokers with mental health problems are just as motivated to stop smoking as those in the general population and that smoking cessation interventions are equally effective in this group of smokers (Ziedonis *et al.* 2008; Champion *et al.* 2008). Thus smokers with and without current psychiatric comorbidities should be encouraged to stop smoking given the great benefits that smoking cessation provides.

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## Tables

Table 1: Baseline sample characteristics by follow-up status and smoking status at follow-up

	Total Sample (N=3645)	Lost to follow-up (N=2005)	Followed-up (N=1640)	Smoking status at 12 months follow-up		
				Ex-smoker ≥ 3 months (N=123)	Ex-smoker < 3 months (N=159)	Current smoker (N=1358)
<b>Sociodemographic characteristics</b>						
Mean (SD) Age	45.8 (7.3)	45.4 (7.1)	46.3 (7.5)***	47.1 (7.9)	46.7 (7.8)	46.2 (7.4)
% (N) Women	48.0 (1750)	50.3 (1009)	45.2 (741)**	45.5 (56)	40.9 (65)	45.7 (620)
% (N) Married	47.4 (1729)	44.4 (890)	51.2 (839)***	50.4 (62)	47.8 (76)	51.6 (701)
% (N) Employed <sup>#</sup>	72.2 (2632)	71.4 (1427)	73.6 (1205)	77.2 (95)	76.6 (121)	72.9 (989)
% (N) White	93.3 (3400)	93.7 (1879)	92.7 (1521)	95.1 (117)	95.0 (151)	92.3 (1253)
% (N) Education <sup>^</sup>						
No high school	4.5 (163)	5.5 (109)	3.3 (54)*	4.9 (6)	4.4 (7)	3.0 (41)
Some high school	5.9 (215)	6.5 (129)	5.3 (86)	1.6 (2)	5.0 (8)	5.6 (76)
High school	31.6 (1150)	33.6 (672)	29.2 (478)*	30.1 (37)	28.3 (45)	29.2 (396)
Some college	27.8 (1014)	25.7 (514)	30.5 (500)**	30.1 (37)	28.9 (46)	30.8 (417)
College	8.9 (324)	8.8 (176)	9.0 (148)	11.4 (14)	10.7 (17)	8.6 (117)
Graduate school	21.2 (771)	20.0 (399)	22.7 (372)	22.0 (27)	22.6 (36)	22.8 (309)
% (N) Country						
US	19.9 (725)	14.4 (288)	26.6 (437)***	22.8 (28)	21.4 (34)	27.6 (375)
Canada	2.8 (102)	2.2 (45)	3.5 (57)	4.1 (5)	2.5 (4)	3.5 (48)
UK	33.0 (1203)	38.3 (767)	26.6 (436)***	38.2 (47)	30.8 (49)	25.0 (340)
France	33.2 (1209)	35.0 (702)	30.9 (507)*	22.8 (28)	34.0 (54)	31.3 (425)
Spain	11.1 (406)	10.1 (203)	12.4 (203)	12.2 (15)	11.3 (18)	12.5 (170)
<b>Cigarette smoking characteristics</b>						
Mean (SD) Years of smoking	28.5 (9.4)	28.2 (9.3)	29.0 (9.4)**	29.8 (9.4)	29.8 (9.0)	28.8 (9.5)
Mean (SD) Nicotine Dependence score <sup>~</sup>	4.7 (2.4)	4.7 (2.4)	4.7 (2.4)	4.4 (2.6) <sup>a,b</sup>	3.9 (2.5) <sup>a</sup>	4.8 (2.4) <sup>b</sup>
Mean (SD) Motivation to quit	6.8 (1.9)	6.8 (1.9)	6.9 (1.8)	7.0 (1.7)	7.1 (1.8)	6.9 (1.9)
% (N) Quit attempt in past 3 months <sup>‡</sup>	29.1 (983)	30.9 (572)	27.0 (411)*	20.5 (23) <sup>a</sup>	40.1 (61) <sup>b</sup>	26.0 (327) <sup>a</sup>

	Total Sample (N=3645)	Lost to follow-up (N=2005)	Followed-up (N=1640)	Smoking status at 12 months follow-up		
				Ex-smoker ≥ 3 months (N=123)	Ex-smoker < 3 months (N=159)	Current smoker (N=1358)
% (N) Use of cessation medication in past 3 months	25.7 (937)	27.9 (559)	23.0 (378)**	15.4 (19)	25.2 (40)	23.5 (319)
<b>Physical / mental health characteristics</b>						
Mean (SD) Body Mass Index	26.8 (5.5)	26.5 (5.5)	27.1 (5.4)***	27.8 (4.9)	27.9 (5.6)	27.0 (5.5)
Mean (SD) EQ-5D Score <sup>~</sup>	0.76 (0.26)	0.75 (0.27)	0.76 (0.26)	0.82 (0.22) <sup>a</sup>	0.78 (0.23) <sup>a,b</sup>	0.76 (0.27) <sup>b</sup>
% (N) Life time diagnosis						
<i>Any</i>	39.5 (1439)	41.1 (824)	37.5 (615)*	35.8 (44)	39.6 (63)	37.4 (508)
Depression <sup>†</sup>	24.0 (870)	25.4 (506)	22.3 (364)*	16.3 (20)	20.3 (32)	23.1 (312)
Anxiety <sup>†</sup>	28.0 (1016)	28.5 (569)	27.4 (447)	25.2 (31)	28.5 (45)	27.5 (371)
% (N) Prescription in past 2 weeks						
<i>Any</i>	15.4 (561)	15.3 (306)	15.5 (255)	9.8 (12)	15.7 (25)	16.1 (218)
Depression	10.1 (369)	10.5 (210)	9.7 (159)	4.9 (6)	9.4 (15)	10.2 (138)
Anxiety	9.4 (341)	9.0 (180)	9.8 (161)	5.7 (7)	8.8 (159)	10.3 (140)
% (N) Symptom in past 3 months						
<i>Any</i>	29.5 (1075)	30.1 (604)	28.7 (471)	26.8 (33)	30.2 (48)	28.7 (390)
Depression <sup>†</sup>	16.0 (581)	16.5 (330)	15.3 (251)	10.6 (13)	13.2 (21)	16.0 (217)
Anxiety <sup>†</sup>	21.5 (781)	21.8 (437)	21.0 (344)	18.7 (23)	24.5 (39)	20.8 (282)

<sup>~</sup>80 missing; <sup>#</sup>9 missing; <sup>^</sup>8 missing; <sup>‡</sup>267 missing; <sup>“</sup>84 missing; <sup>†</sup>18 missing; 6 missing; \*p<0.05, \*\*p<0.01, \*\*\*p<0.001; Different letters in superscript indicate significant differences (p<0.05); SD: standard deviation

Table 2: Mental health outcomes at follow-up by smoking status and mental health history

	Total Follow-up	Current smoker (1)	Ex-smoker < 3 months (2)	Ex-smoker ≥ 3 months (3)	2 vs 1	3 vs 1
General population	N=1640	N=1358	N=159	N=123	Odds ratio (95%CI)	
% (N) Prescription in past 2 weeks						
Any	14.9 (245)	15.8 (214)	13.8 (22)	7.3 (9)	0.86 (0.54-1.38)	0.42 (0.21-0.85)*
Depression	10.4 (171)	11.5 (156)	6.9 (11)	3.3 (4)	0.57 (0.30-1.08)	0.26 (0.09-0.71)**
Anxiety	9.0 (147)	9.2 (125)	9.4 (15)	5.7 (7)	1.03 (0.59-1.80)	0.60 (0.27-1.31)
% (N) Symptom in last 3 months						
Any	26.1 (428)	27.4 (372)	22.0 (35)	17.1 (21)	0.75 (0.51-1.11)	0.55 (0.34-0.89)*
Depression <sup>a</sup>	15.0 (245)	16.5 (223)	9.5 (15)	5.7 (7)	0.53 (0.31-0.92)*	0.31 (0.14-0.67)**
Anxiety <sup>a</sup>	19.1 (313)	19.7 (267)	17.1 (27)	15.6 (19)	0.84 (0.54-1.30)	0.75 (0.45-1.25)
Population with mental health history <sup>^</sup>	N=615	N=508	N=63	N=44		
% (N) Prescription in past 2 weeks						
Any	34.3 (211)	36.2 (184)	31.7 (20)	15.9 (7)	0.82 (0.47-1.44)	0.33 (0.15-0.76)**
Depression	24.9 (153)	27.2 (138)	17.5 (11)	9.1 (4)	0.57 (0.29-1.12)	0.27 (0.09-0.76)*
Anxiety	21.1 (130)	22.0 (112)	20.6 (13)	11.4 (5)	0.92 (0.48-1.75)	0.45 (0.18-1.18)
% (N) Symptom in past 3 months						
Any	55.8 (343)	58.3 (296)	47.6 (30)	38.6 (17)	0.65 (0.39-1.10)	0.45 (0.24-0.85)*
Depression	33.7 (207)	36.6 (186)	22.2 (14)	15.9 (7)	0.50 (0.27-0.92)*	0.33 (0.14-0.75)**
Anxiety	42.1 (259)	43.5 (221)	36.5 (23)	34.1 (15)	0.75 (0.43-1.28)	0.67 (0.35-1.28)

<sup>a</sup>5 missing; \*p<0.05; \*\*p<0.01; <sup>^</sup>With history of depression and/or anxiety; CI: confidence interval

Table 3: Association of baseline characteristics and smoking status at follow-up with mental health outcomes at follow-up

a) Total Sample	Prescription for condition in past 2 weeks (OR, 95% CI)			Symptom in past 3 months (OR, 95% CI)		
	Any (N=1423)	Depression (N=1423)	Anxiety (N=1423)	Any (N=1423)	Depression (N=1417)	Anxiety (N=1417)
Age	1.03 (1.00-1.05)*	1.01 (0.99-1.04)	1.02 (0.98-1.05)	1.02 (1.00-1.04)	1.01 (0.99-1.04)	1.00 (0.98-1.02)
Gender <sup>1</sup>	1.44 (0.98-2.12)	1.03 (0.66-1.61)	2.34 (1.42-3.86)**	1.72 (1.28-2.33)***	1.05 (0.71-1.57)	1.93 (1.39-2.68)***
Marriage Status <sup>2</sup>	0.75 (0.51-1.09)	0.53 (0.34-0.82)**	1.06 (0.66-1.72)	1.02 (0.76-1.37)	0.54 (0.37-0.80)**	1.04 (0.76-1.43)
Employment Status <sup>3</sup>	0.51 (0.34-0.75)***	0.47 (0.30-0.73)**	0.49 (0.30-0.82)**	0.64 (0.46-0.88)**	0.44 (0.29-0.66)***	0.65 (0.46-0.92)*
Ethnicity <sup>4</sup>	0.53 (0.27-1.03)	0.53 (0.25-1.13)	0.46 (0.20-1.06)	0.67 (0.39-1.16)	0.81 (0.40-1.66)	0.73 (0.40-1.33)
Education						
No high school	1	1	1	1	1	1
Some high school	0.77 (0.22-2.74)	2.52 (0.50-12.6)	0.10 (0.02-0.55)**	0.54 (0.19-1.54)	1.41 (0.32-6.20)	0.30 (0.10-0.91)*
High school	1.04 (0.38-2.87)	2.75 (0.70-10.8)	0.42 (0.13-1.33)	1.00 (0.43-2.36)	2.14 (0.62-7.35)	0.75 (0.32-1.79)
Some college	1.07 (0.38-3.02)	2.06 (0.50-8.41)	0.56 (0.17-1.80)	0.85 (0.36-2.03)	1.60 (0.45-5.66)	0.74 (0.31-1.79)
College	1.48 (0.48-4.63)	3.04 (0.67-13.8)	0.44 (0.12-1.67)	1.19 (0.46-3.05)	2.40 (0.62-9.25)	0.83 (0.32-2.19)
Graduate school	0.99 (0.35-2.83)	1.86 (0.45-7.76)	0.36 (0.11-1.17)	0.86 (0.36-2.07)	1.54 (0.43-5.51)	0.72 (0.30-1.74)
Country						
US	1	1	1	1	1	1
Canada	0.63 (0.23-1.76)	0.79 (0.24-2.57)	0.50 (0.13-1.87)	0.90 (0.41-2.00)	0.83 (0.30-2.27)	1.02 (0.41-2.55)
UK	0.84 (0.49-1.45)	0.67 (0.37-1.22)	0.69 (0.31-1.51)	0.95 (0.62-1.46)	0.65 (0.38-1.10)	1.01 (0.62-1.65)
France	0.73 (0.44-1.21)	0.47 (0.26-0.85)*	1.15 (0.60-2.21)	1.10 (0.73-1.64)	0.42 (0.24-0.72)**	1.55 (1.00-2.42)
Spain	0.85 (0.41-1.77)	0.38 (0.14-0.99)*	1.63 (0.70-3.80)	0.82 (0.47-1.44)	0.38 (0.17-0.86)*	1.15 (0.63-2.10)
Nicotine Dependence score	1.08 (1.00-1.18)	1.04 (0.95-1.15)	1.14 (1.03-1.27)*	1.08 (1.01-1.15)*	1.01 (0.93-1.10)	1.10 (1.03-1.18)**
Motivation to quit	1.07 (0.97-1.19)	0.99 (0.88-1.11)	1.21 (1.06-1.38)**	1.04 (0.96-1.12)	0.94 (0.85-1.05)	1.06 (0.98-1.16)
Quit attempt in past 3 months	1.27 (0.82-1.96)	1.05 (0.63-1.76)	2.02 (1.19-3.42)**	1.43 (1.03-2.00)*	1.33 (0.84-2.09)	1.26 (0.88-1.81)
Cessation medication used in past 3 months <sup>5</sup>	1.06 (0.67-1.69)	0.89 (0.51-1.55)	1.05 (0.59-1.89)	1.35 (0.94-1.93)	1.15 (0.71-1.85)	1.30 (0.87-1.89)

a) Total Sample	Prescription for condition in past 2 weeks (OR, 95% CI)			Symptom in past 3 months (OR, 95% CI)		
	Any (N=1423)	Depression (N=1423)	Anxiety (N=1423)	Any (N=1423)	Depression (N=1417)	Anxiety (N=1417)
Change in Body Mass Index <sup>6</sup>	1.03 (0.95-1.12)	0.99 (0.91-1.09)	1.02 (0.92-1.13)	1.04 (0.97-1.12)	1.06 (0.98-1.15)	0.99 (0.92-1.07)
Change in Health Score <sup>6</sup>	0.36 (0.16-0.80)*	0.24 (0.09-0.60)**	0.47 (0.17-1.26)	0.20 (0.10-0.40)***	0.16 (0.07-0.36)***	0.36 (0.18-0.74)**
Baseline equivalent to dependent variable	26.8 (17.9-40.1)***	35.9 (21.8-59.2)***	46.1 (27.0-78.8)***	14.1 (10.3-19.1)***	33.1 (21.6-50.8)***	13.2 (9.5-18.5)***
<b>Smoking status</b>						
<b>Smoker</b>	<b>1</b>	<b>1</b>	<b>1</b>	<b>1</b>	<b>1</b>	<b>1</b>
<b>Ex-smoker (&lt; 3 months)</b>	<b>0.74 (0.37-1.46)</b>	<b>0.37 (0.14-0.96)*</b>	<b>1.38 (0.63-3.04)</b>	<b>0.52 (0.31-0.88)*</b>	<b>0.34 (0.15-0.78)*</b>	<b>0.67 (0.38-1.17)</b>
<b>Ex-smoker (≥ 3 months)</b>	<b>0.28 (0.10-0.78)*</b>	<b>0.25 (0.06-0.94)*</b>	<b>0.57 (0.18-1.76)</b>	<b>0.38 (0.20-0.73)**</b>	<b>0.24 (0.09-0.67)**</b>	<b>0.67 (0.34-1.31)</b>

b.) Sample with mental health history <sup>^</sup>	Prescription for condition in past 2 weeks (OR, 95% CI)			Symptom in past 3 months (OR, 95% CI)		
	Any (N=536)	Depression (N=536)	Anxiety (N=536)	Any (N=536)	Depression (N=536)	Anxiety (N=536)
Age	1.05 (1.02-1.08)**	1.03 (1.00-1.07)	1.02 (0.98-1.06)	1.04 (1.01-1.07)	1.03 (0.99-1.06)	1.00 (0.97-1.03)
Gender <sup>1</sup>	1.16 (0.73-1.84)	0.82 (0.49-1.38)	1.88 (1.07-3.32)*	1.48 (1.00-2.18)	0.96 (0.59-1.57)	1.50 (1.01-2.23)*
Marriage Status <sup>2</sup>	0.72 (0.46-1.12)	0.47 (0.28-0.79)**	1.04 (0.60-1.78)	0.92 (0.63-1.34)	0.42 (0.26-0.69)**	0.93 (0.63-1.36)
Employment Status <sup>3</sup>	0.54 (0.34-0.87)*	0.47 (0.28-0.79)**	0.60 (0.33-1.07)	0.64 (0.42-0.98)	0.37 (0.22-0.62)***	0.75 (0.49-1.14)
Ethnicity <sup>4</sup>	0.54 (0.23-1.27)	0.73 (0.29-1.86)	0.42 (0.16-1.12)	0.64 (0.30-1.38)	0.98 (0.40-2.42)	0.76 (0.36-1.58)
Education						
No high school	1	1	1	1	1	1
Some high school	0.64 (0.15-2.79)	1.16 (0.19-6.98)	0.16 (0.03-1.06)	0.31 (0.08-1.18)	0.77 (0.14-4.07)	0.23 (0.06-0.88)*
High school	1.48 (0.46-4.72)	2.71 (0.64-11.4)	0.65 (0.17-2.55)	0.85 (0.28-2.57)	1.77 (0.47-6.69)	0.72 (0.24-2.10)
Some college	1.36 (0.42-4.48)	1.96 (0.45-8.57)	0.72 (0.18-2.90)	0.74 (0.24-2.27)	1.43 (0.37-5.55)	0.67 (0.22-2.00)
College	2.45 (0.65-9.17)	3.44 (0.69-17.2)	0.58 (0.12-2.80)	0.80 (0.24-2.71)	1.50 (0.33-6.83)	0.63 (0.19-2.10)
Graduate school	1.07 (0.32-3.57)	1.44 (0.32-6.53)	0.37 (0.09-1.54)	0.72 (0.23-2.24)	1.13 (0.29-4.50)	0.66 (0.22-2.00)

b.) Sample with mental health history <sup>^</sup>	Prescription for condition in past 2 weeks (OR, 95% CI)			Symptom in past 3 months (OR, 95% CI)		
	Any (N=536)	Depression (N=536)	Anxiety (N=536)	Any (N=536)	Depression (N=536)	Anxiety (N=536)
Country						
US	1	1	1	1	1	1
Canada	0.42 (0.11-1.57)	0.92 (0.19-4.37)	0.17 (0.03-0.88)*	0.46 (0.14-1.48)	0.38 (0.09-1.63)	0.71 (0.20-2.49)
UK	0.71 (0.37-1.38)	0.55 (0.27-1.11)	0.64 (0.27-1.55)	0.69 (0.39-1.22)	0.45 (0.23-0.87)*	0.70 (0.39-1.27)
France	0.46 (0.25-0.84)*	0.33 (0.17-0.65)**	0.74 (0.35-1.53)	0.62 (0.37-1.05)	0.26 (0.13-0.49)***	0.92 (0.54-1.57)
Spain	0.61 (0.25-1.46)	0.34 (0.12-0.99)*	1.17 (0.44-3.15)	0.53 (0.26-1.10)	0.29 (0.11-0.75)*	0.83 (0.40-1.73)
Nicotine Dependence score	1.06 (0.96-1.17)	1.01 (0.91-1.13)	1.11 (0.99-1.25)	1.07 (0.99-1.16)	1.00 (0.90-1.11)	1.07 (0.98-1.16)
Motivation to quit	1.07 (0.94-1.21)	1.02 (0.89-1.17)	1.19 (1.02-1.38)*	1.02 (0.92-1.13)	0.97 (0.85-1.10)	1.04 (0.93-1.15)
Quit attempt in past 3 months	1.04 (0.61-1.77)	0.78 (0.42-1.45)	2.03 (1.10-3.74)*	1.56 (1.00-2.43)	1.12 (0.62-2.00)	1.31 (0.85-2.04)
Cessation medication used in past 3 months <sup>5</sup>	0.93 (0.53-1.64)	0.82 (0.43-1.57)	0.84 (0.43-1.65)	1.21 (0.75-1.93)	0.95 (0.52-1.73)	1.26 (0.79-2.03)
Change in Body Mass Index <sup>6</sup>	1.00 (0.90-1.10)	0.95 (0.85-1.06)	1.01 (0.90-1.13)	1.05 (0.96-1.15)	1.05 (0.94-1.17)	1.00 (0.91-1.09)
Change in Health Score <sup>6</sup>	0.56 (0.23-1.36)	0.36 (0.13-1.00)*	0.64 (0.23-1.83)	0.39 (0.18-0.85)	0.28 (0.11-0.74)*	0.50 (0.23-1.09)
Baseline equivalent to dependent variable	11.5 (7.13-18.5)*	13.6 (7.92-23.4)***	23.9 (13.0-44.0)***	3.94 (2.47-6.27)	12.6 (7.63-21.0)***	5.24 (3.41-8.06)*
<b>Smoking status</b>						
<b>Smoker</b>	<b>1</b>	<b>1</b>	<b>1</b>	<b>1</b>	<b>1</b>	<b>1</b>
<b>Ex-smoker (&lt; 3 months)</b>	<b>0.76 (0.35-1.65)</b>	<b>0.40 (0.15-1.09)</b>	<b>1.28 (0.52-3.18)</b>	<b>0.53 (0.28-0.98)</b>	<b>0.36 (0.14-0.92)*</b>	<b>0.66 (0.34-1.25)</b>
<b>Ex-smoker (≥ 3 months)</b>	<b>0.24 (0.07-0.77)*</b>	<b>0.26 (0.06-1.05)</b>	<b>0.48 (0.13-1.80)</b>	<b>0.39 (0.18-0.85)</b>	<b>0.33 (0.11-1.02)</b>	<b>0.65 (0.29-1.43)</b>

<sup>1</sup>Referent: Men; <sup>2</sup>Referent: Not Married; <sup>3</sup>Referent: Unemployed; <sup>4</sup>Referent: Non-white; <sup>5</sup>At follow-up; <sup>6</sup>Positive score indicates increase from baseline; \*p<0.05,

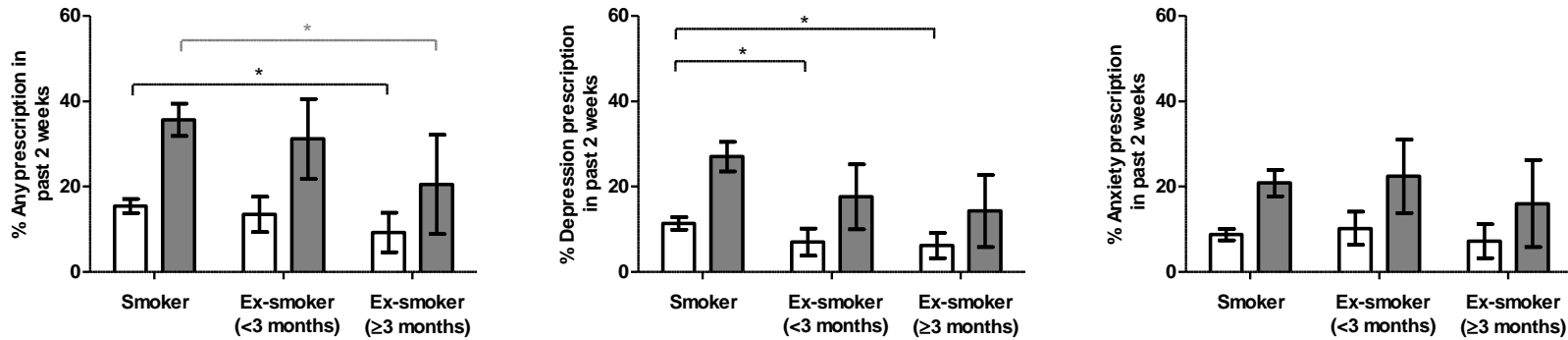
\*\*p<0.01, \*\*\*p<0.001; <sup>^</sup>With history of depression and/or anxiety; CI: confidence interval



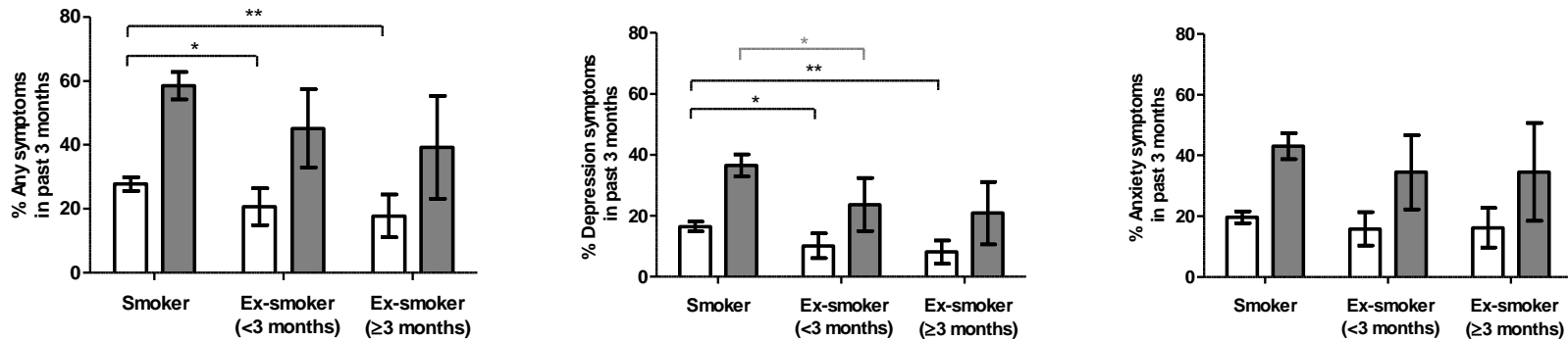
**Figures**

Figure 1: Adjusted prevalence<sup>#</sup> of recent (A) medication prescription and (B) mental health symptoms by smoking status at 12 months follow-up in total sample and those with history of mental health illness<sup>^</sup>

**A**



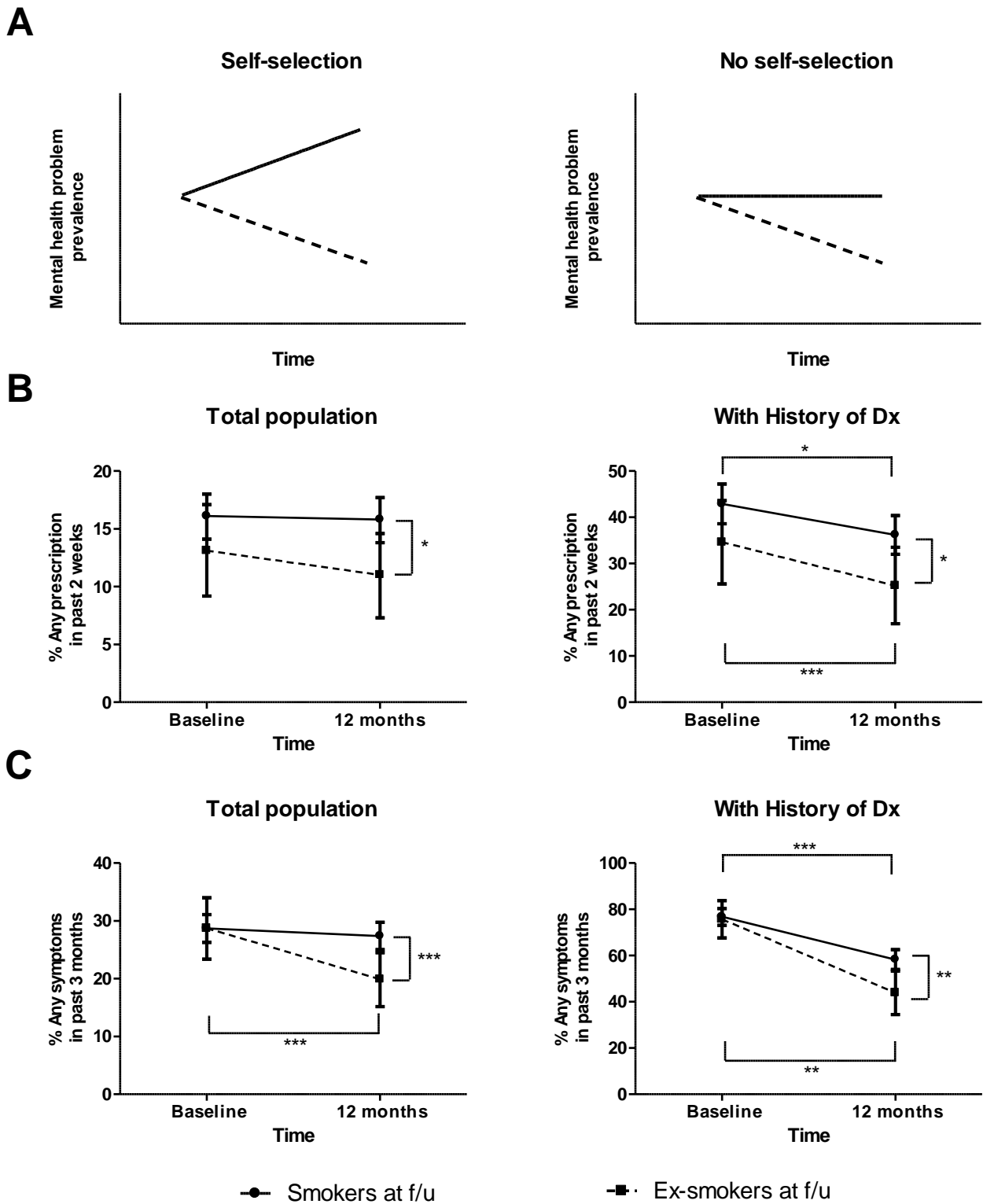
**B**



All respondents       Respondents with history of mental health problems

<sup>#</sup>Estimated marginal means with confounders set at average values (error bars show 95% confidence intervals); <sup>^</sup>With history of depression and/or anxiety; \*p<0.05, \*\*p<0.01

Figure 2: Changes in indices of mental health by smoking status and history of mental health problems; (A) Postulated change scenario as function of selection; (B) Change in medication prescription prevalence; (C) Change in symptom prevalence



\*p<0.05, \*\*p<0.01, \*\*\*p<0.001; Error bars show 95% confidence intervals