Title:

The association between smoking cessation and change in mental health, in people with and without psychiatric disorders: a prospective cohort study using data from a large randomised controlled trial

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Background

Despite many smokers reporting that they want to quit (Zhou et al., 2009) many continue because they attribute smoking as a coping mechanism for stress and offers them mental health benefits (Cookson et al., 2014; Sheals et al., 2016). This behaviour is noted to occur in smokers with and without psychiatric disorders (Clancy et al., 2013; Kerr et al., 2006; Lawn et al., 2002; Lerman et al., 1996; Thompson et al., 2003). Smokers with and without psychiatric disorders may be misattributing the nicotine withdrawal relief provided by cigarettes as mental health benefits. Feelings of irritability and anxiety can manifest when an individual has not smoked for a certain period of time (Guthrie et al., 2004; Hughes, 2007), where these feelings are relieved upon the deliverance of nicotine through cigarettes (Parrott, 1999). Therefore, individuals may perceive that smoking is relieving their psychological distress; however, this distress may have been caused by the act of smoking withdrawal. Smokers, therefore, may be less likely to cease smoking if they believe that their mental health will decline as a result. Additionally, health professionals may also thereby be reluctant to suggest smoking cessation to certain smokers due to impact on mental health (Johnson et al., 2010; McNally et al., 2006).

However, there is a strong association between smoking cessation and improvements in mental health, with similar sized associations seen for both individuals with and without psychiatric disorders (Taylor et al., 2014). Observational studies have also indicated that smoking cessation is associated with lower prescription rates of antidepressants and anxiolytics (Taylor et al., 2019). Given that the rate of smoking in individuals diagnosed with psychiatric disorders is not subsiding to the same level as the general population (Richardson et al., 2019; Taylor et al., 2019), it is, therefore, essential to update the evidence exploring the association between mental health and smoking for populations with and without psychiatric disorders.

It is not feasible to randomly assign participants to continue or quit smoking; therefore, to study the association between smoking cessation on mental health, observational analysis strategies must be used. The primary issue with traditional observational epidemiology is teasing out whether associations are causal. While there are studies that sought to address the association between mental health and smoking cessation, the strength of confidence in making causal inferences is weaker. This study will have a unique opportunity to use triangulation in a large dataset with populations with and without psychiatric disorders in order to derive results with higher causal inference confidence. As we are concerned about residual confounding, we will triangulate effect estimates derived from statistical methods that differ in their ability to produce causal estimates (Lawlor et al., 2017): multivariable regression models, propensity score-adjusted models, and instrumental variable regressions. The combination of three analytical approaches will allow for different levels of control for confounding factors. The multivariable regression model will have the least control for confounding, propensity score-adjusted modelling will have less susceptibility, and confounding factors will unlikely impact instrumental variable analysis. The practice of triangulation facilitates stronger confidence towards answering causal questions if all three statistical approaches point to the same conclusion (Lawlor et al., 2017). Therefore, this study will attempt to overcome the weaknesses of traditional observational epidemiology and use these methods to make a causal inference between the association of smoking cessation and mental health outcomes.

Study Aims

In this study, we aim to investigate the association between stopping smoking and change in mental health, compared to continuing to smoke, in people with and without psychiatric disorders.

Method

We have followed STROBE statement to guide protocol development. We will pre-register this study on the Open Science Framework. All analytical code will be made open access via GitHub.

Study design

We will conduct a longitudinal cohort study using pre-existing data. We will conduct a secondary analysis of individual-level patient data from a double-blind, randomised, placebo-controlled trial of varenicline compared to nicotine replacement therapy or bupropion for smoking cessation, in people with and without psychiatric disorders (EAGLES) (Anthenelli et al., 2016). We will compare the change in mental health outcomes from baseline to follow-up (outcome) in those who quit smoking compared to those who continued to smoke (exposure), rather than by treatment allocation.

Data source

Trial conduct and funding: The trials were conducted and funded jointly by Pfizer and GlaxoSmithKline. The trials took place between 2011 and 2015 and were conducted in 16 countries at 140 centres. Eight thousand one hundred forty-four participants were enrolled in the trials. Only data collected in the United States was provided for this secondary analysis by Pfizer, four thousand two hundred sixty participants.

Participants

Participants were adult smokers (aged 18 years), with or without psychiatric disorders. Participants smoked on average, ten or more cigarettes per day during the previous year and were motivated to stop smoking. Participants were assessed using the DSM-IV-TR diagnostic criteria for psychiatric disorders.

Full exclusion criteria can be found in the original trial (Anthenelli et al., 2016). Inclusion criteria are as follows:

Inclusion criteria for the non-psychiatric and psychiatric cohorts

- Male or female cigarette smokers, 18–75 years old, motivated to stop smoking and considered suitable for a smoking cessation attempt
- Smoked an average of ≥10 cigarettes per day during the past year and the month before the screening visit, and exhaled carbon monoxide >10 ppm at screening

Additional inclusion criteria for the psychiatric cohort

- At least one of the following Axis I or II diagnoses, current (during last 30 days) and/or past, per DSM-IV TR, confirmed by SCID
    - Psychotic disorders limited to schizophrenia and schizoaffective disorder
    - Mood disorders limited to major depressive disorder and bipolar I and II disorders (except for participants from Bulgaria, Denmark, Finland, Germany, Slovakia, and Spain where those with bipolar disorder were not included due to the prescribing information for bupropion in these countries)
    - Anxiety disorders limited to panic disorder with or without agoraphobia, post-traumatic stress disorder, obsessive-compulsive disorder, social phobia, generalised anxiety disorder

- Personality disorders limited to a history of borderline personality disorder All subjects with Axis I or II diagnoses must be judged to be clinically stable by a psychiatrist or a mental health professional, including the following:
- No acute exacerbation of their condition in the preceding six months
- If receiving treatment for their condition, they must have been on stable treatment for a minimum of 3 months (e.g., stable drug and dose ≥three months)
- No change in treatment is anticipated for the duration of the study
- In the opinion of the investigator, the patient is not at high risk of self-injury or suicidal behaviour

Variables

Exposure - Smoking cessation

Biological validation, in addition to self-report of tobacco abstinence, was used to assess smoking cessation in participants. Three variables will be evaluated in terms of smoking cessation; carbon monoxide confirmed continuous abstinence for week 9 through 12, carbon monoxide confirmed continuous abstinence for week 9 through 24 and 7-day point prevalence of abstinence. We will use the most stringent measure of continuous abstinence for the longest time point available, with biological verification. Those who fail biological verification, or who have missing smoking data will be classed as continuing smokers.

Primary outcome – Anxiety and depression (HADS)

Measurements of anxiety and depression involved longitudinal assessments of symptoms of anxiety and depression using the Hospital anxiety and depression scale (HADS)(Zigmond & Snaith, 1983). This scale was administered at multiple time points during clinic visits at Baseline and Weeks 1 through 6, 8, 10, 12, 13, 16, 20, and 24.

Primary analysis - The primary analysis will focus on results from the Hospital Anxiety and Depression Scale (HADS)(Zigmond & Snaith, 1983). Participants self-reported anxiety and depression severity. The HADS consists of fourteen individual item responses ranging in increasing severity from 0 (normal) to 3 (most severe) for a total range of 0 to 42. 7 items assess anxiety and seven assess depression, which therefore provides two subscales with ranges of 0 to 21. In each subscale, 0 to 7 is considered normal, while 15 to 21 represents severe symptoms. We will repeat analyses for the subscales for anxiety and depression.

Secondary outcomes – suicidality and neuropsychiatric adverse events

The Columbia- Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2011) was used as a measure of suicidal ideation, intent, or plan, and past suicidal behaviour. The C-SSRS consists of ten categories which consist of binary responses (yes/no) to assess the presence of suicidal behaviour. A numerical score is obtained when combining answers to the ten categories. The categories of C-SSRS are:

- Category 1 – Wish to be Dead
- Category 2 – Non-specific Active Suicidal Thoughts
- Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
- Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan
- Category 5 – Active Suicidal Ideation with Specific Plan and Intent
- Category 6 – Preparatory Acts or Behaviour
- Category 7 – Aborted Attempt
- Category 8 – Interrupted Attempt

- Category 9 – Actual Attempt (non-fatal)
- Category 10 – Completed Suicide.

Any individual who responds yes to categories 1-5 is categorised to have “Suicidal ideation”, “Suicidal behaviour” for yes responses to categories 6-10 and “Suicidal ideation/suicidal behaviour” is a yes response to categories 1 -10.

Secondary analysis – The secondary analysis will consist of investigating the change in reported frequency and severity of suicidality. We will also assess the incidence of mood disorders using odd ratios.

Covariates

All available baseline measures will be included as covariates, and we will control for smoking cessation treatment group. Covariates will consist of: sex, age, race, weight, smoking characteristics, and psychiatric characteristics. We will also examine the dataset for other potential useful baseline variables.

Analytical Plan

To investigate the effects of smoking cessation on mental health, we propose to use three stages of analysis: conventional linear regression, propensity score regression and instrumental variable analysis. We will also examine the dataset for potential useful repeated measures variable to adjust for time-varying measures.

Multivariable linear regression modelling

In our first analysis, we will use conventional multivariable linear regression modelling to assess the relationship between smoking cessation and change in HADS score from baseline to follow-up. All covariates listed above will be adjusted for in the model. Smoking cessation will be treated as a dummy variable (quitting=1, continuing smoking=0). Due to regression to the mean when using within-person, repeated measures data, participants' mean change scores will not be used to measure the change in HADS score from baseline to follow-up; instead, we will use 24-week follow-up HADS scores, with adjustment for baseline HADS score (Vickers & Altman, 2001). Associations will be reported after being adjusted for basic confounders such as age and gender and other confounding factors identified.

Propensity score matching approach

In our second analysis, we will construct propensity scores using logistic regression in this model whereby the predictors are the covariates, and the outcome is smoking cessation (Glynn et al., 2006; Rosenbaum & Rubin, 1983, 1984). All baseline variables recorded in the trial will be included in the model. Therefore, each participant's propensity score will be their conditional probability (odds) of smoking cessation. Individuals who have quit smoking will be matched to a continuing smoker with the closest propensity score on a ratio of 1:1 using the nearest neighbour greedy algorithm with no replacement, and matching will be restricted to the common support region (Taylor et al., 2015). We will subsequently estimate the association of the outcomes through an adjusted linear regression model for the propensity scores, where the exposure is smoking cessation and outcome is mental health.

Instrumental Variable Analysis

In our third analysis, the randomisation of participants into treatment or placebo groups will be used as an instrumental variable, or a proxy for our exposure (quitting versus continuing to smoke), to

measure the causal relationship between smoking cessation and mental health provided that there is sufficient power. Risk differences will be reported in the outcomes through the use of additive structural mean models estimated via the generalised method of moments (Clarke & Windmeijer, 2010; Clarke & Windmeijer, 2012; Davies et al., 2017; Hansen & Singleton, 1982). We will use the Cragg-Donald Wald F statistic and the Hausman test for endogeneity to test for weak instrument bias (Hahn & Hausman, 2002; Stock & Yogo, 2005).

Model adequacy checks

The propensity score model will be checked to ensure that there is a balance of means and variances for covariates in the propensity score-matched sample (Thoemmes & Kim, 2011). We will use standard procedures to compare the relative bias of linear regression and instrumental variable methods. This procedure will consist of comparing the association between exposure and baseline covariates, and the association between the instrument and covariates (Jackson & Swanson, 2015).

Missing data

For the baseline and outcome data, we will use multivariable multiple imputation to impute data for patients missing values (Royston & White, 2011). The imputation procedure will produce twenty imputed datasets, and the imputation model will include all baseline covariates (Royston, 2004).

For missing exposure data, smoking status, we will assume that those with missing data are continuing smokers. This method produces similar results as multivariable multiple imputation (Taylor et al., 2017).

We will present estimates derived from the complete case and imputed models.

Sensitivity analyses

We will compare the effect estimates derived from complete cases, and compare this to effect estimates derived from complete cases with the addition of imputed data.

Ethics approval and dissemination

Access to the EAGLES data is governed by Pfizer. We will comply with all requirements of Pfizer's requirements for publications based on the EAGLES data. Ethical approval is not required for this study as it consists of secondary data analysis from a randomised control trial. Pfizer will not have any role in the analysis, interpretation, write-up or dissemination of the study findings.

We will submit the protocol to Open Science Framework. The data produced, and the analytical code, from this study, will also be made available through open access. Dissemination of results may involve presentation at meetings for lay audiences or relevant support groups. Key results will also be shared through social media platforms such as Twitter. We will also aim to publish our findings in peer-reviewed journals.

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