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The Gold Standard Programme (GSP) for Smoking Cessation in Denmark: Effectiveness in smokers with and without a mental disorder—a cohort study

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Abstract

Objectives: We compared the effectiveness of an intensive smoking cessation intervention among smokers with and without severe mental disorder (SMD), and to identify factors associated with successful quitting. The main hypothesis was that smokers with SMD would be less likely to stay continuously smoke-free for 6 months.

Design: A prospective cohort study.

Setting: 302 smoking cessation clinics in Denmark from municipal clinics, pharmacies, hospitals, midwives, primary care facilities, and other private providers who reported data to the national Danish Smoking Cessation Database from 2006–2016.

Participants: 38,293 patients from the Danish Smoking Cessation Database. Patients with SMD were identified by linking data to the Danish National Patient Register. Diagnoses of organic mental disorders (F0 chapter) or intellectual disabilities (F7 chapter) were not included. Smokers ≥18 years old, attending a Gold Standard Programme (GSP) with planned follow-up was included. Smokers not wanting contact after 6 months were excluded.

Interventions: A comprehensive manual-based smoking cessation interventions (the GSP).

Main outcome measures: Self-reported continuous abstinence for 6 months, follow-up rate 69%.

Results: The rate of successful quitting was high overall but significantly lower in SMD smokers (29% versus 38%; odds ratios (OR) 0.74; 95% confidence interval (CI) 0.68-0.80). Variables associated with successful quitting were mainly compliance, but also older age, and male gender as well as not being disadvantaged, a heavy smoker, or recommended by health professionals.

Conclusions: Only one in four smokers with SMD successfully quit smoking, which is significantly lower than the one in three among smokers without SMD. Compliance was the most important predictor for successful quitting.

Strengths and limitations of this study

- This is a prospective cohort study based on 38,293 smokers with or without mental disorder(s).
- Only psychiatric smokers with a mental disorder severe enough to justify hospitalisation (in- or outpatient) were identified in this study. The Smoking Cessation Database might hold information on patients with less severe mental disorder(s).
- Participants with SMD were included independent of the time span from diagnoses to the intervention onset.
- This study was based on routinely collected health data, but since the aim of this study was in line with the purposes of the Smoking Cessation Database, we considered the implications to be minimal.

Introduction

The prevalence of smoking among mentally ill patients is known to be relatively high (1,2). A Danish survey showed that 39% of patients with mental illness were daily smokers compared to 20% in the background population (3). Furthermore, mentally ill patients were 2.5 times more likely to be heavy smokers (3). Overall, patients with severe mental illness had a reduced life expectancy, with a reduction of 15 and 20 years in women and men, respectively (4), and a recent study found that one-third of the 15 lost life years in smokers with a severe mental disorder (SMD) may be attributed to smoking (2). Based on observational studies, it has been shown that successful smoking cessation improves mental health (5) and reduces mortality and morbidity in psychiatric patients (2,6). Most smoking cessation interventions combine behavioural and pharmacological support. A recent review on the efficacy of smoking cessation intervention in patients with severe mental illness concluded that bupropion and varenicline appear to be as effective in psychiatric populations as in the general public (7). However, the effectiveness of behavioural interventions as standing alone, remains unclear (7). Despite these findings, smoking is often ignored in inpatient psychiatry (8).

In 2013, NICE (National Institute for Health and Care Excellence) published a guideline concerning smoking cessation in acute, maternity and mental health services, stating that smokers with mental illness should be offered intensive smoking cessation support (9). The Gold Standard Programme (GSP) is an intensive face-to-face smoking cessation intervention consisting of 5-6 meetings. The programme has been shown to have a good effect on smoking cessation in other subpopulations, as well as for the background population (10–14), but the effectiveness in smokers with SMD remains unknown.

The aim of this study was to compare the effectiveness of the GSP in smokers with and without diagnosed SMD and to identify factors associated with successful quitting. We hypothesised that this vulnerable subgroup of smokers would be less likely to be continuously smoke-free after six months than smokers without a mental disorder.

Method

Study design and setting

We performed a register-based cohort study using data from two national Danish registers: the Smoking Cessation Database (15) and the National Patient Register (16,17). Data have been recorded in the database since 2001 and lists >111,000 smokers who received face-to-face aid to quit smoking. Since 2006, each smoker provided informed consent and was thereafter registered with a unique 10-digit number (a CPR number) assigned to all Danes at birth or at immigration. The number contains information on sex and date of birth (18). The CPR number was used to control for smokers attending more than one intervention and to identify smokers diagnosed with mental disorder(s) using data from the National Patient Register. Since 1995, all contacts (in- or outpatient) from somatic and psychiatric wards of all hospitals have been registered in the National Patient Register using the International Classification of Diseases, 10th edition (ICD-10) (16,17).

All smokers in Denmark, including smokers with a mental disorder, have access to smoking cessation interventions without referral and free of charge. Throughout the study period from

1 January 2006 until 31 December 2016, 302 smoking cessation clinics in different settings, such as hospitals, with midwives, municipal clinics, pharmacies, primary care facilities, and other private institutions, reported data to the Smoking Cessation Database (15). Approximately 80-90% of the face-to-face interventions in Denmark are registered in the Smoking Cessation Database, which is considered to be a representative sample (19).

This project was approved by the Danish Data Protection Agency (2014-41-3370/2010-41-5463/2000-54-0013) and registered with the Scientific Ethical Committee (H-C-FSP-2010-049).

Intervention

GSP is the standard smoking cessation intervention in Denmark, and the details of the intervention have been previously described (10,14,15). In brief, the smoking cessation intervention comprises 5–6 meetings held in groups (2 hours/session) or as individual interventions (a 40-minute first session and approximately 20 minutes/session thereafter) over the course of six weeks. The programme was taught by specially trained staff and was counselling-based with a clearly structured manual-based patient education programme. Each smoker was offered individual counselling on nicotine replacement therapy or other medical support according to their level of dependence, as measured by the Fagerström test score (15,20). To be compliant in terms of meeting adherence, patients had to attend at least 75% of the scheduled meetings as defined by the Steering Committee (21). To follow up on the effect of the intervention, patients registered in the Smoking Cessation Database were contacted by phone six months (±1 month) after the planned quit date and asked about their smoking status (15). Since patients were reached by phone, self-reported smoking status was not validated (15).

Participants

The study cohort included 74,121 smokers who were registered in the Smoking Cessation Database during the study period. If a smoker attended more than one intervention only the latest intervention was included (7,180 smokers were registered more than once, corresponding to 9.3% of the smokers; 9,523 interventions were not included). Smokers were not included in the study if they met any of the following criteria: were younger than 18 years of age at the onset of the intervention (1,146); did not attend a GSP (16,077); or went to a smoking cessation clinic that pre-decided, on the administrative level, not to contact their participants for follow-up after 6 months (8,496).

The remaining 38,879 smokers in the Smoking Cessation Database were cross-referenced with data from the National Patient Register using CPR numbers to identify smokers with mental disorder(s). Psychiatric discharge diagnoses given before the onset of the smoking cessation intervention were extracted. All psychiatric diagnoses (*Chapter V; Mental and behavioural disorders, F00-F99*), except F17 (*Mental and behavioural disorders due to use of tobacco*), were initially linked to the smokers. Patients diagnosed with organic mental disorders (F0 chapter) or intellectual disabilities (F7 chapter) were not included in the study regardless of other psychiatric diagnoses. Smokers without any psychiatric diagnosis composed the control group. Patients were categorised based on the severity and occurrence of a specific SMD according to the following hierarchy: schizophrenia (F20), schizotypal disorder (F21), other psychoses (F22-F25, F28-29), manic episodes (F30), bipolar disorder

(F31), depression (F32-F34), anxiety (F40-F41), obsessive-compulsive disorder (F42), post-traumatic stress disorder (F43.1), personality disorders (F60-F69), and substance use disorder (SUD) (F1). To avoid representing a patient multiple times in the analyses, the most severe diagnosis, defined by the hierarchy above, was considered the main discharge diagnosis. Smokers without SMD but with other diagnosed mental disorder(s) were omitted from the primary outcome analysis. Thus, 38,293 smokers with or without mental disorder(s) were included in this study (see flowchart in Figure 1).

Figure 1. *Patient flow. Smokers of at least 18 years of age attending a GSP between 1 January 2006 and 31 December 2016 were included in this study. A total of 11,534 smokers were lost to follow-up, leaving 25,411 smokers to be included in the outcome analyses.*

Outcome and other variables

The primary outcome was six months of self-reported continuous abstinence, which was defined as not having smoked at all from the intended quit date to the six month follow-up (15).

For each smoker registered in the Smoking Cessation Database, data were collected on socio-demographic parameters, smoking history, their intervention programme and follow-up information. Age and smoking information were collected as continuous variables. The remaining variables were categorically collected and grouped as shown in Table 1 (and appendix A). Confounders and predictors included in the statistical analyses are listed in Table 1.

Smokers were considered heavy smokers if they fulfilled one or more of three criteria: a ≥20 pack-year smoking history, daily consumption of ≥20 cigarettes, or a nicotine dependency ≥7 points according to the Fagerström test score (13,20). Smokers were considered disadvantaged if they fulfilled at least one of two criteria: were unemployed (receiving unemployment benefits) or had a low level of education (no education except for elementary school or short work-related courses) (14).

Data access and cleaning

We had full access to all smokers recorded in the Smoking Cessation Database from 2006-2016. Throughout this time period, smokers were registered using their individual CPR number. All CPR numbers were checked for validity using official validation rules. Invalid numbers were checked in the Civil Registration System and corrected if possible, and age and sex were corrected accordingly. If correction was not possible, the smokers were excluded from the database. In this study, 484 of 67,339 smokers were omitted from the database due to an invalid CPR number, corresponding to 0.7%.

The online registration application of the Smoking Cessation Database supplies automatic data validation rules to ensure that only valid dates and required data are entered. In addition to these rules, daily consumption of tobacco was manually checked. Daily consumption of more than 100 grams was considered unlikely, and data were recoded to “missing”. Likewise,

years of smoking were recoded to "missing" if the years of smoking were greater than the age of the smoker.

Statistical analysis

After performing initial analyses on the selected predictors (from appendix A) adjusted for sex and age, a multivariable mixed-effect model was fitted to test for differences in continuous abstinence. The predictors were chosen based on the initial analysis and established knowledge. The multivariable analysis was performed by entering all the predictors together (see Table 1). In addition, the analysis was adjusted for hierarchical clustering using the different smoking cessation clinics as the 1st level cluster. The analysis was repeated for relevant subgroups of mental disorders. To examine whether the time span from diagnosing to GPS was of importance to the continuous abstinence, a separate univariate logistical regression was conducted. The span was calculated as time from making a diagnosis until the start of the GSP.

Data were reported according to the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) statement (22). Patients with missing values were excluded from the analyses. The results were presented as odds ratios (ORs) and 95% confidence intervals (95% CIs). Non-respondent analysis was performed using a χ^2-test to compare respondents to non-respondents. A similar analysis was performed to compare the smokers who were intentionally not followed-up to the included smokers. A two-sided p-value of <0.05 was considered statistically significant. All statistical calculations were performed with Stata/IC v. 15.0 (StataCorp).

Results

In this cohort study, 38,293 smokers were linked to the National Patient Register to identify smokers with mental disorder(s). While 25,411 smokers with SMD or without mental disorder(s) were included in the main analysis, 31% were lost to follow-up (29% among smokers without mental illness and 39% among smokers with SMD) (see Figure 1). Non-respondent analyses revealed that except for living with a smoker, all other tested predictors significantly differed between the respondents and the non-respondents. The largest difference (14 percentage points) observed was in participant compliance, with the respondents being most likely to be compliant. Smokers with SMD were more likely to withdraw from the study (schizophrenia spectrum, 43.2%; affective disorders, 38.9%; anxiety, 36.1%; personality disorders, 38.7%; SUD, 36.7%) as were women, disadvantaged smokers, and smokers attending individual counselling; however, heavy smokers and smokers who were recommended to quit by healthcare staff were more likely to be respondents.

The proportion of successful quitters was 29.4% and 38.0% for smokers with SMD and the control group, respectively (see Table 2).

Characteristics of smokers without a mental disorder and smokers with SMD differed considerably (see Table 1, and appendix A). In particular, the proportion of smokers with SMD was highest among young smokers and gradually decreased as age increased. In addition, smokers with SMD were more likely to be heavy smokers, non-compliant, and recommended to stop smoking by healthcare staff and were more often disadvantaged; all of these factors

were predictors of having relapsed after six months. In addition, smokers with SMD were less likely to live with other smokers, and they were more likely to attend individual interventions, which were both predictors of a successful outcome. Approximately half of the smokers in both groups (51% of smokers with SMD and 45% without SMD) were offered pharmaceutical support, i.e., nicotine replacement therapy, varenicline or bupropion, free of charge.

Primary outcome–smoking cessation at 6 months

After adjusting for clustering and confounding factors, we found that smokers with SMD were statistically significantly less likely to stay continuously abstinent six months after attending a GSP (OR=0.74, 95% CI: 0.68-0.80; p<0.001). The time span between the primary discharge diagnosis and the start of the GSP showed a small but statistically significant association with continuous abstinence (OR: 1.02, 95% CI: 1.00-1.03; p=0.013). We identified associations between a higher risk of relapse and being female (p<0.001), disadvantaged (p<0.001), a heavy smoker (p<0.001), and recommended to quit by healthcare staff (p<0.001). Factors associated with successful quitting were being of older age (p=0.013) and compliant with the GSP (p<0.001) and having attended an individual intervention (p<0.001).

Table 1: *Characteristics of the study population and predictors for continuous abstinence. The initial analyses were adjusted for sex and age only. In addition to the listed predictors, the multivariable model was adjusted for the year of intervention as well as hierarchical clustering (smoking cessation clinic). The results were reported as ORs and 95% CIs. P-values of <0.05 were considered statistically significant and were marked with an *.*

	Characteristics				OR for successful quitting			
	Control n (%)		SMD n (%)		Initial analyses OR (95% CI)		Multivariate analyses OR (95% CI)	
							Adjusted for cluster	
Smokers with mental disorder(s)								
No mental disorder	29,783	(80.6%)			1		1	
Yes, SMD			7,162	(19.4%)	0.68	(0.63-0.73) *	0.74	(0.68-0.80) *
Participants								
Age (years)								
18-24	1,304	(4.4%)	389	(5.4%)	1		1	
25-34	3,423	(11.5%)	1,064	(14.9%)	1.50	(1.27-1.78) *	1.33	(1.10-1.61) *
35-44	5,661	(19.0%)	1,388	(19.4%)	1.54	(1.31-1.81) *	1.37	(1.14-1.64) *
45-54	7,579	(25.5%)	1,877	(26.2%)	1.59	(1.36-1.87) *	1.47	(1.23-1.76) *
55-64	7,098	(23.8%)	1,668	(23.3%)	1.70	(1.45-1.99) *	1.53	(1.28-1.84) *
65+	4,718	(15.8%)	776	(10.8%)	1.61	(1.37-1.90) *	1.30	(1.07-0.57) *
Sex								
Men	12,278	(41.2%)	2,937	(41.0%)	1		1	
Women	17,505	(58.8%)	4,225	(59.0%)	0.87	(0.83-0.92) *	0.85	(0.80-0.90) *
Disadvantaged smokers [a]								
No	18,451	(62.0%)	2,746	(38.3%)	1		1	
Yes	10,178	(34.2%)	4,128	(57.6%)	0.79	(0.74-0.83) *	0.84	(0.79-0.89) *
Heavy smokers [b]								
No	7,032	(23.6%)	1,243	(17.4%)	1		1	
Yes	22,044	(74.0%)	5,770	(80.6%)	0.69	(0.64-0.73) *	0.74	(0.69-0.80) *
Compliance with programme [c]								
No	10,661	(35.8%)	3,393	(47.4%)	1		1	
Yes	18,712	(62.8%)	3,684	(51.4%)	3.32	(3.12-3.53) *	3.26	(3.05-3.48) *
Living with a smoker								
No	19,389	(65.1%)	5,168	(72.2%)	1		1	
Yes	10,129	(34.0%)	1,917	(26.8%)	0.90	(0.86-0.96) *	0.90	(0.85-0.96) *
Earlier quit attempts								
No	11,227	(37.7%)	2,985	(41.7%)	1		1	
Yes	17,966	(60.3%)	4,001	(55.9%)	1.09	(1.04-1.15) *	1.03	(0.98-1.10)
Recommendation by healthcare staff [d]								
No	11,322	(38.0%)	2,162	(30.2%)	1		1	
Yes	17,078	(57.3%)	4,690	(65.5%)	0.86	(0.81-0.91) *	0.89	(0.84-0.95) *
Smoking cessation clinic								
Setting								
Municipality	22,653	(76.1%)	5,636	(78.7%)	1		1	
Pharmacy	4,522	(15.2%)	938	(13.1%)	1.06	(0.98-1.13)	1.02	(0.90-1.15)
Hospital (incl. midwives)	1,943	(6.5%)	514	(7.2%)	1.02	(0.92-1.13)	1.13	(0.94-1.36)
Other	665	(2.2%)	74	(1.0%)	0.99	(0.83-1.20)	1.05	(0.81-1.38)
Smoking cessation intervention								
Programme format								
Group	24,925	(83.7%)	5,347	(74.7%)	1		1	
Individual	4,858	(16.3%)	1,813	(25.3%)	1.30	(1.21-1.39) *	1.17	(1.07-1.28) *
Cluster								
Smoking cessation clinic							0.05	(0.03-0.08) *

a) Disadvantaged: ≤12 years of school and/or unemployed.
b) Heavy smoker: ≥20 pack years, Fagerström score of ≥7 points and/or daily consumption of ≥20 cigarettes.
c) Compliance: attended ≥75% of the planned meeting sessions.
d) Healthcare staff: Doctors, nurses, nurses' assistants, midwives, etc.
e) Free medication: Nicotine replacement therapy, varenicline or bupropion.

The proportion of successful quitters was 38.0% in the control group versus 30.0% in patients with any mental disorder(s) (see Table 2). The quit rates differed by 7 percentage points according to the diagnoses of mental disorder; however, for patients within the schizophrenia spectrum, which was the least successful group, the proportion of successful quitters was

25.7%. All subgroups, except anxiety, were statistically significantly less likely to stay continuously abstinent after 6 months compared with the control group.

Table 2: *Crude quit rates and associations of successful quitting according to subgroups of smokers defined by the severity of the mental disorder.*

		Crude quit rate	Multivariate analyses OR (95% CI)	
Diagnoses (IDC-10)	**n**	**%**	**Adjusted for cluster**	**p**
Control: no psychiatric diagnoses	21,044	38.0%	1	
Any mental disorder	5,306	30.0%	0.75 (0.70-0.81) *	<0.000
Severe mental disorder (SMD)	4,404	29.4%	0.74 (0.68-0.80) *	<0.000
Schizophrenia spectrum (F20-F29)	692	25.7%	0.61 (0.50-0.74) *	<0.000
Affective disorders (F30-F34)	1,742	31.0%	0.80 (0.71-0.90) *	<0.000
Anxiety (F40-F42, F43.1)	548	31.9%	0.86 (0.70-1.06)	0.156
Personality disorders (F60-69)	294	26.9%	0.62 (0.46-0.83) *	0.001
SUD (F10-16, F18-F19)	1,128	28.6%	0.68 (0.59-0.79) *	<0.000
Other	902	32.9%	0.83 (0.71-0.98) *	0.027

We examined the occurrence of dual diagnoses, defined as having SUD in addition to any other mental disorder(s), and the effect of these diagnoses on smoking cessation for subgroups of smokers with a mental disorder. The occurrence of dual diagnoses differed between 17 and 41% in the subgroups. Moreover, the proportion of successful quitters was lower in patients with dual diagnoses (18.9-26.9%) than in patients without SUD (27.7-33.9%), corresponding to a reduction in successful outcomes by 18-43%. This should be compared to a quit rate of 30.5% among patients with SUD alone (see Figure 2).

Figure 2*: Crude quit rates according to specified mental disorder(s) with or without SUD.*

Intentional lack of follow-up

Smokers who were intentionally not followed up due to an administrative decision in the smoking cessation clinic were compared with the included smokers regarding the characteristics shown in Table 1. The analyses showed that there were statistically significant differences between the two groups with regard to mental diagnoses, heavy smoking, compliance, living with a smoker, earlier quit attempts, arena, setting, and year of intervention. The differences were most pronounced in relation to arena (22 percentage points), where smokers attending an intervention in a municipal clinic were most likely to receive a follow-up call. The year of intervention (9 percentage points) revealed that smokers were less likely to receive follow-up before 2010. All other factors differed by less than 5 percentage points, and smokers with mental disorder(s) were more likely to receive follow-up than heavy smokers, non-compliant smokers, smokers not living with another smoker, and smokers attending a group intervention.

Discussion

Overall, one in four smokers with SMD, compared to one in three without SMD, stayed continuously smoke-free for at least 6 months after undergoing a GSP intervention. This was in agreement with our main hypothesis. Compliance was by far the most important predictor of a successful outcome. Dual diagnoses lowered the proportion of successful quitters to 19-27%, depending on the diagnoses.

Smokers with SMD were as likely to want to quit smoking as the general public (3), but the evidence of smoking cessation intervention is sparse among this group of smokers. A recent review concluded that while bupropion and varenicline seem to be effective among smokers with SMD, the efficacy of nicotine replacement therapy and behavioural treatment is still unclear (7). Another review illuminating the effect of specialised advice to smokers with SMD revealed only one ongoing trial investigating this topic (23).

Promising results were presented in a randomised trial on treating tobacco dependence among inpatients at a psychiatric ward with a complete smoking ban. Prochaska et al. found a point prevalence after 6 months of 14% in smokers undergoing an intervention combining behavioural treatment and nicotine patches, in contrast to 7% in the usual care control group (8). Even unmotivated patients were able to successfully quit, and the long-term results after 18 months were positive (8).

In our study, one in four participants with SMD continued to abstain after 6 months. The smokers diagnosed within the schizophrenia spectrum benefitted the least from the GSP. While meta-analyses have also shown a lower effect in this group (24), smokers with depression showed higher quit rates (25). A review reported that only two small studies have been published concerning smokers with bipolar disorders (26), and both trials had difficulties recruiting smokers within this subgroup. In our subgroup analysis, smokers with anxiety (F4 Chapter) were also likely to have been slightly underpowered, which was also the case for the subgroup of smokers diagnosed with “other diagnoses”.

The GSP programme is a package consisting of several elements, including an extensive patient education programme, individual counselling and pharmaceutical support (10,15). In our study, it was not possible to pinpoint which elements were the most important or whether some of the elements were unnecessary for different groups of smokers. In addition to the different mental diagnoses, variations in the severity of the mental disease may impact the quit rates. On the one hand, one could expect that smokers with SMD are more likely to be successful in their quit attempt when they are well-treated and close to discharge. On the other hand, a hospital stay in completely smoke-free surroundings has been shown to be supportive—for SMD smokers as well (8).

Dual diagnoses seem to have a great impact on the ability to quit smoking, and it would be relevant to evaluate combined interventions of both smoking and SUD. The evidence is also sparse, but smoking cessation intervention has been shown to be effective for smokers in short-term substance abuse treatment (27).

This study has strengths as well as limitations. Since the aim of this study was in line with the purposes of the Smoking Cessation Database, we considered the implications of using these routinely collected health data to be minimal. However, one potential weakness was that the participants with SMD were included independent of the time span from diagnoses to the

intervention onset. Surprisingly, we found only a somewhat significant association between time span and continuous abstinence, and this association should be investigated in more detail in future intervention studies. Using the National Patient Register, we identified only psychiatric smokers with a mental disorder severe enough to justify hospitalisation (in- or outpatient). There might be patients in the Smoking Cessation Database with mental disorders who did not undergo hospital care, but we must assume that the mental disorder would have then been much less severe.

One of the strengths of this study was the large nationwide study cohort and the inclusion of all settings (municipalities, hospitals, pharmacies, etc.) where smoking cessation interventions occur in Denmark. Data from both registries used in this study provide a high degree of completeness and precision, and the amount of missing data was very low (15,17). We were unable to identify possible misclassifications, but the occurrence was expected to be very low (15,17).

The use of continuous abstinence instead of point prevalence was a strength, but the self-reporting without biomarker validation was a limitation (28) that might have introduced a reporting bias (29). Contrary to the logical presumption that this would prove more precise, a Canadian study showed no significant difference between self-reporting of smoking status and urinary cotinine levels (30), and the use of carbon monoxide tests to validate smoking status showed that validation increased the detection of smokers with short- and long-term quit rates by only 0.5% and 0.2%, respectively (31,32).

Due to different national and cultural traditions as well as smoking habits, socio-economic conditions and the identification of SMD, the external validity of these results is limited and should be considered carefully before extrapolating to other developed countries.

Overall, it is important for smokers with mental disorder(s) to be offered clinical help to quit smoking due to the many positive effects of smoking cessation on both physical and mental health (5). However, the evidence on how to best help this group of smokers is sparse. Randomised controlled trials have shown that smoking cessation interventions can be effective, and this study reports that it is feasible to help a clinically relevant part of this vulnerable subgroup of smokers; however, with a lower quit rate than smokers without SMD. More evidence is needed concerning the treatment of competing addictions and dual diagnoses.

Conclusion

Only one in four smokers with SMD successfully quit smoking, which is significantly lower than the one in three among smokers without SMD. The lowest quit rates were observed among patients with dual diagnoses. The most important predictor of successful quitting was compliance.

Competing interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Data sharing

Protocol, anonymised data and statistical codes are available from the corresponding author.

Contributions

MR, MK and HT contributed to the study conception and design. MR and HT headed the data acquisition. MR contributed to the data analysis. MR, MK, JK, MN and HT contributed to the data interpretation. MR drafted the manuscript, and MK, JK, MN and HT revised it critically for important intellectual content. All the authors gave final approval of the version to be published. MR is the guarantor.

Transparency declaration

The lead author (study guarantors) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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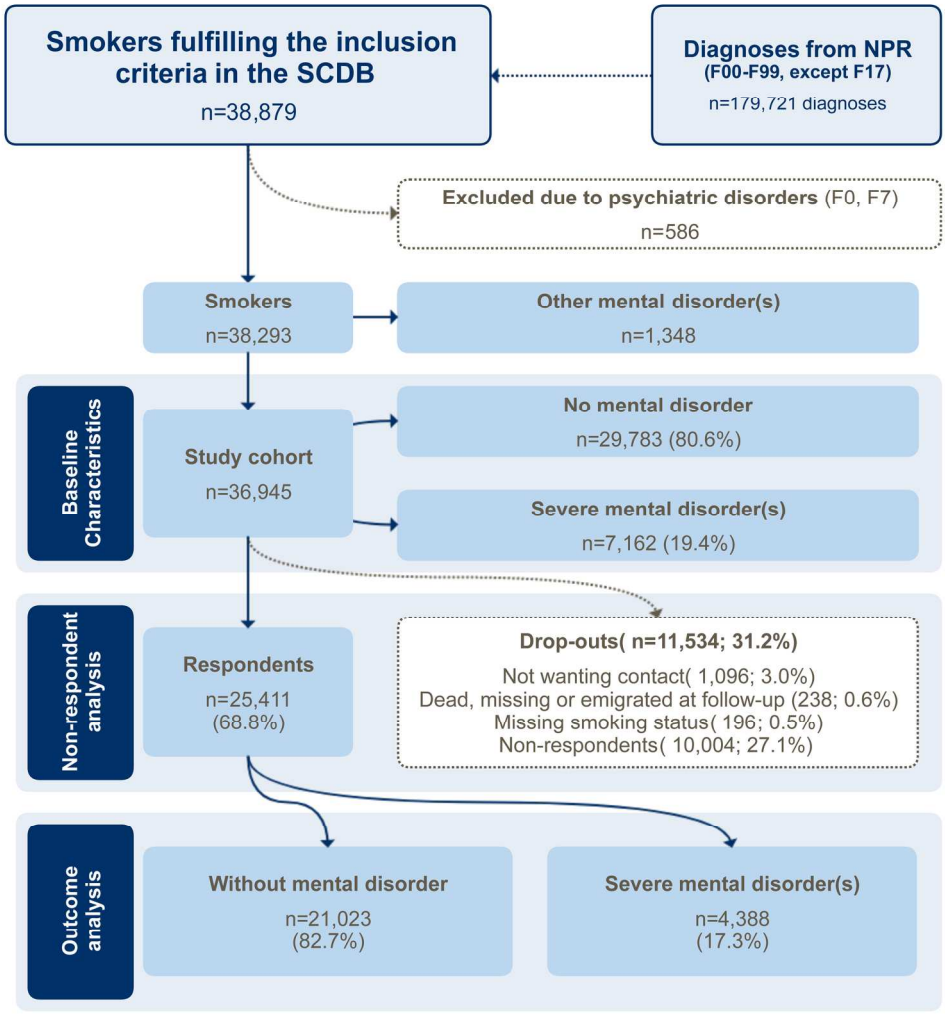

Figure 1. Patient flow. Smokers of at least 18 years of age attending a GSP between 1 January 2006 and 31 December 2016 were included in this study. A total of 11,534 smokers were lost to follow-up, leaving 25,411 smokers to be included in the outcome analyses.

180x186mm (300 x 300 DPI)

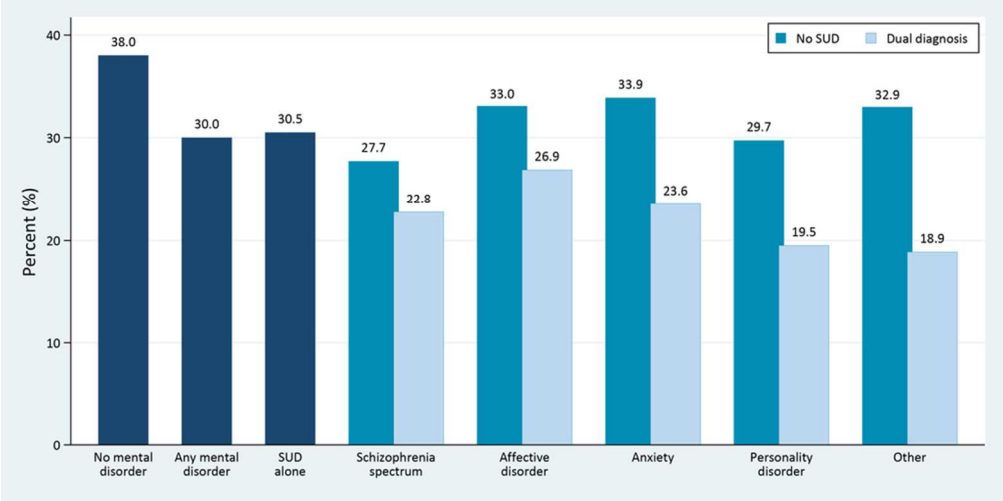

Figure 2: Crude quit rates according to specified mental disorder(s) with or without SUD.

86x43mm (300 x 300 DPI)

Appendix A

Table 1: Characteristics of the study population.

	Population without prior mental diagnosis n (%)	Population with SMD n (%)
All	29,783 (80.6%)	7,162 (19.4%)
Previously attempted smoking cessation		
Yes	17,966 (60.3%)	2,985 (55.9%)
No	11,227 (37.7%)	2,985 (41.7%)
Heavy smoker [b]		
Yes	22,044 (74.0%)	5,770 (80.6%)
No	7,032 (23.6%)	878 (17.4%)
Unknown	707 (2.4%)	149 (2.1%)
Smoking		
<20 pack years	9,355 (31.4%)	2,106 (29.4%)
≥20 pack years	19,461 (65.3%)	4,798 (67.0%)
Fagerström score [a] 0-6	23,100 (77.6%)	4,191 (58.5%)
Fagerström score 7-10	6,683 (22.4%)	2,971 (41.5%)
<20 cigarettes per day	13,842 (46.5%)	2,430 (33.9%)
≥20 cigarettes per day	15,941 (53.5%)	4,732 (66.1%)
Age (years)		
18-24	1,304 (4.4%)	389 (5.4%)
25-34	3,423 (11.5%)	1,064 (14.9%)
35-44	5,661 (19.0%)	1,388 (19.4%)
45-54	7,579 (25.5%)	1,877 (26.2%)
55-64	7,098 (23.8%)	1,668 (23.3%)
65+	4,718 (15.8%)	776 (10.8%)
Sex		
Men	12,278 (41.2%)	2,937 (41.0%)
Women	17,505 (58.8%)	4,225 (59.0%)
Living with smoker		
Yes	10,129 (34.0%)	1,917 (26.8%)
No	19,389 (65.0%)	5,168 (72.2%)
Unknown	265 (0.9%)	77 (1.1%)
Medication [c] offered for free		
Yes	13,526 (45.4%)	3,632 (50.7%)
No	12,880 (43.3%)	3,115 (43.5%)
Unknown	3,377 (11.3%)	415 (5.8%)
Compliant with programme [d]		
Yes	18,712 (62.8%)	3,684 (51.4%)
No	10,661 (35.8%)	3,393 (47.4%)
Unknown	410 (1.4%)	85 (1.2%)
Recommendation by healthcare staff [e]		
Yes	17,078 (57.3%)	4,690 (65.5%)
No	11,322 (38.0%)	2,162 (30.2%)
Unknown	1,383 (4.6%)	310 (4.3%)
Disadvantaged [g]		
Yes	10,178 (34.2%)	4,128 (57.6%)
No	18,451 (62.0%)	2,746 (38.3%)
Unknown	1,154 (3.9%)	288 (4.0%)
Education level [f]		
Low	7,979 (26.8%)	2,448 (34.2%)
Medium	6,257 (21.0%)	1,430 (20.0%)
High	14,532 (48.8%)	2,971 (41.5%)
Unknown	1,015 (3.4%)	313 (4.4%)
Employment		
Employed	18,079 (60.7%)	2,480 (34.7%)

Unemployed	3,964 (13.3%)	3,055 (42.7%)
Student	1,174 (3.9%)	428 (6.0%)
Retired	5,747 (19.3%)	967 (13.5%)
Unknown	819 (2.68%)	230 (3.2%)
Setting		
Municipality	22,653 (76.0%)	5,636 (78.7%)
Pharmacy	4,522 (15.2%)	938 (13.1%)
Hospital	1,943 (6.5%)	514 (7.2%)
Other	665 (2.2%)	74 (1.0%)
Programme format		
Individual	4,858 (16.3%)	1,813 (25.3%)
Group	24,925 (83.7%)	5,347 (74.7%)
Unknown	0 (0.0%)	2 (0.0%)
GSP year		
2006	3,628 (12.1%)	460 (6.4%)
2007	4,210 (14.1%)	538 (7.5%)
2008	3,332 (11.2%)	570 (8.0%)
2009	3,203 (10.8%)	669 (9.3%)
2010	3,063 (10.3%)	698 (9.8%)
2011	2,123 (7.1%)	526 (7.3%)
2012	1,882 (6.3%)	505 (7.0%)
2013	1,256 (4.2%)	422 (5.9%)
2014	1,264 (4.2%)	450 (6.3%)
2015	2,489 (8.4%)	992 (13.9%)
2016	3,333 (11.2%)	1,332 (18.6%)

a) Fagerström score: a standard for quantifying nicotine addiction.
b) Heavy smoker: defined as having ≥20 pack years, a Fagerström score of ≥7 points and/or a daily consumption of ≥20 cigarettes.
c) Free medication: Either nicotine replacement therapy, varenicline or bupropion.
d) Compliance: defined as having participated in at least 75% of the planned meeting sessions.
e) Healthcare staff: doctors, nurses, nurses' assistants.
f) Education level: low: ≤12 years of school, medium: >12 years of school but <3 years of higher education, high: ≥3 years of higher education.
g) Disadvantaged: ≤12 years of school and/or unemployed.

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	✓ a) Page 1 ✓ b) Page 2	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	✓ Page 2 ✓ Page 1+2 ✓ Page 2
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	✓ Page 3		
Objectives	3	State specific objectives, including any prespecified hypotheses	✓ Page 3		
Methods					
Study Design	4	Present key elements of study design early in the paper	✓ Page 3		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	✓ Page 3-4		
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the	✓ Page 4	RECORD 6.1: The methods of study population selection (such as codes or	✓ Page 4-5

		sources and methods of selection of participants. Describe methods of follow-up ~~*Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls~~ ~~*Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants~~ *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed ~~*Case-control study* - For matched studies, give matching criteria and the number of controls per case~~	Not relevant – not a matched study	algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Not relevant ✓ Page 4-5 + figure 1 (this study includes linkage to one register).
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	✓ Page 5 + table 1	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	✓ Page 5 + table 1 (characteristics) and supp. online appendix
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	✓ Page 5-6		
Bias	9	Describe any efforts to address potential sources of bias	✓ Page 10-11(bias and limitations in discussion)		

Study size	10	Explain how the study size was arrived at	✓ Page 4-5 + figure 1		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	✓ Page 4-6		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed ~~*Case-control study* - If applicable, explain how matching of cases and controls was addressed~~ ~~*Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy~~ (e) Describe any sensitivity analyses	✓ Page 6		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	✓ Page 5-6
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-	✓ Page 4

				level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	✓ Page 4-5 + figure 1	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	✓ Page 4-5 + figure 1
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	✓ Page 8; table 1, + supp. online appendix		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time ~~*Case-control study* - Report numbers in each exposure category, or summary measures of exposure~~ ~~*Cross-sectional study* - Report numbers of outcome events or summary measures~~	✓ Page 6 + figure 1		
Main results	16	(a) Give unadjusted estimates	✓ Page 8-9; table		

		and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	1-2 ✓ Page 8; table 1 + supp. online appendix Not relevant		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	✓ Page 6-9		
Discussion					
Key results	18	Summarise key results with reference to study objectives	✓ Page 10		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	✓ Page 10-11	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	✓ Page 10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	✓ Page 10-11		
Generalisability	21	Discuss the generalisability (external validity) of the study results	✓ Page 11		

Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	✓ Page 12 (Acknowledgements)		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	✓ Page 12 (data sharing)

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

BMJ Open

Effectiveness of the Gold Standard Programme (GSP) for Smoking Cessation on smokers with and without a severe mental disorder—a Danish cohort study

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Effectiveness of the Gold Standard Programme (GSP) for Smoking Cessation on smokers with and without a severe mental disorder—a Danish cohort study

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Abstract

Objectives: We compared the effectiveness of an intensive smoking cessation intervention among smokers with and without a severe mental disorder (SMD) and identified factors associated with successful quitting. The main hypothesis was that smokers with an SMD would be less likely to stay continuously smoke-free for 6 months.

Design: A prospective cohort study.

Setting: In all, 302 smoking cessation clinics in Denmark from municipal clinics, pharmacies, hospitals, midwives, primary care facilities, and other private providers who reported data to the national Danish Smoking Cessation Database from 2006–2016 participated in this study.

Participants: A total of 38,293 patients from the Danish Smoking Cessation Database. Patients with an SMD were identified by linking data to the Danish National Patient Register. Diagnoses of organic mental disorders (F0 chapter) or intellectual disabilities (F7 chapter) were not included. Smokers ≥18 years old who were attending a Gold Standard Programme (GSP) with planned follow-up were included. Smokers not wanting contact after 6 months were excluded.

Interventions: A comprehensive manual-based smoking cessation intervention comprising 5 meetings over a 6-week period (the GSP).

Main outcome measures: Self-reported continuous abstinence at the 6-month follow-up.

Results: In all, 69% of the participants participated in the follow-up after six months. The overall rate of successful quitting was high but significantly lower in SMD smokers (29% versus 38%; odds ratio (OR) 0.74; 95% confidence interval (CI) 0.68-0.80). Variables associated with successful quitting were compliance (defined as attending ≥75% of the planned meetings), older age, and male gender as well as not being disadvantaged, heavy smoking, or recommendation of intervention by health professionals.

Conclusions: Only 29% of smokers with an SMD successfully quit smoking, which was significantly lower than the 38% of smokers without an SMD. Compliance was the most important predictor for successful quitting.

Strengths and limitations of this study

- This was a prospective cohort study based on 38,293 smokers with or without mental disorder(s).
- Quit rates at the 6-month follow-up were based on unvalidated self-reporting.
- When identifying smokers with psychiatric issues in this study, only smokers with a mental disorder severe enough to justify hospitalisation (in- or outpatient) were recognised. This cohort might contain patients with less severe mental disorder(s), who (in this study) were categorised as smokers without severe mental disorder (SMD).
- Participants with an SMD were included independent of the time span from diagnoses to intervention onset.
- This study was based on routinely collected health data, but because the aim of this study was in line with the purposes of the Smoking Cessation Database, we considered the implications minimal.

Introduction

The prevalence of smoking among mentally ill patients is relatively high (1,2). A Danish survey showed that 39% of patients with a mental illness were daily smokers compared to 20% of the general population (3). Furthermore, mentally ill patients were 2.5 times more likely to be heavy smokers (3). Overall, patients with a severe mental illness had reduced life expectancies of 15 and 20 years in women and men, respectively (4), and a recent study found that one-third of the 15 lost life years in smokers with a severe mental disorder (SMD) may be attributed to smoking (2). Based on observational studies, successful smoking cessation has been shown to improve mental health (5) and reduce mortality and morbidity in patients with psychiatric issues (2,6). Most smoking cessation interventions combine behavioural and pharmacological support. A recent review on the efficacy of smoking cessation intervention in patients with a severe mental illness concluded that bupropion and varenicline appear to be as effective in populations with psychiatric issues as in the general public (7). However, the effectiveness of behavioural interventions alone remains unclear (7). Despite these findings, smoking is often ignored in inpatient psychiatry (8).

In 2013, NICE (National Institute for Health and Care Excellence) published a guideline concerning smoking cessation for individuals requiring acute, maternity and mental health services, stating that smokers a with mental illness should be offered intensive smoking cessation support (9). The Gold Standard Programme (GSP) is an intensive face-to-face smoking cessation intervention consisting of 5-6 meetings. The programme has been shown to have a good effect on smoking cessation in other subpopulations, as well as for the general population (10–14), but its effectiveness in smokers with an SMD remains unknown.

The aim of this study was to compare the effectiveness of the GSP in smokers with and without a diagnosed SMD and to identify factors associated with successful quitting. We hypothesised that this vulnerable subgroup of smokers would be less likely to be continuously smoke-free after six months than smokers without a mental disorder.

Method

Study design and setting

We performed a register-based cohort study using data from two national Danish registers: the Smoking Cessation Database (15) and the National Patient Register (16,17). The Smoking Cessation Database was established to evaluate the effect of smoking cessation interventions offered throughout Denmark, and data has been prospectively collected since 2001. The database now includes >111,000 smokers who received face-to-face assistance to quit smoking.

At birth or upon immigration, all people in Denmark are assigned a unique personal 10-digit identification number known as a CPR ("Central Person Register") number, which contains information on sex and date of birth of the individual (18). The CPR number is used as the unique identification number in the National Patient Register as well as in many other Danish registers, making it possible to link information relating to an individual (19).

Since 2006, each smoker provided informed consent and was thereafter registered in the Smoking Cessation Database with their CPR number. The CPR number was used to control for smokers attending more than one intervention and to identify smokers diagnosed with mental disorder(s) using data from the National Patient Register. Since 1995, all contacts (in- or outpatient) with somatic and psychiatric wards of all hospitals in Denmark have been registered in the National Patient Register using the International Classification of Diseases, 10th edition (ICD-10) (16,17).

All smokers in Denmark, including smokers with a mental disorder, have access to smoking cessation interventions without referral and free of charge. Throughout the study period from 1 January 2006 until 31 December 2016, 302 smoking cessation clinics in different settings, such as hospitals, midwife interactions, municipal clinics, pharmacies, primary care facilities, and other private institutions, reported data to the Smoking Cessation Database (15). Approximately 80-90% of the face-to-face interventions in Denmark are registered in the Smoking Cessation Database, and are considered a representative sample (20).

In Denmark, the prevalence of daily smokers (≥15 years) dropped from 25% in 2006 to 16% in 2016 (21). This corresponds to a drop from 1,100,000 to 765,000 smokers. Thus, the SCDB contains information on 6–9% of the daily smokers in Denmark.

This project was approved by the Danish Data Protection Agency (2014-41-3370/2010-41-5463/2000-54-0013) and was registered with the National Committee on Health Research Ethics (H-C-FSP-2010-049).

Intervention

GSP is the standard smoking cessation intervention in Denmark (15). The GSP comprises 5 meetings held either in groups (2 hours/session) or as an individual session (first session lasting 40 minutes and approximately 20-minute/sessions thereafter) over a 6-week period. The programme was presented by specially trained staff and was counselling-based with a clearly structured manual-based patient education programme. The quit date was planned between the 2nd and the 3th meeting. Each smoker was offered individual counselling on nicotine replacement therapy or other medical support according to their level of dependence, as measured by the Fagerström test score (15,22). It was recommended (but not mandatory) after 3 months to offer a 6th meeting after 3 months focusing on relapse prevention. To follow up on the effect of the intervention, patients registered in the Smoking Cessation Database were contacted by phone six months (±1 month) after the planned quit date and asked about their smoking status (15). Because patients were reached by phone, the self-reported smoking status was not validated (15). The intervention has been previously described in detail (10,14,15).

Participants

The study cohort included 74,121 smokers registered in the Smoking Cessation Database during the study period. If a smoker attended more than one intervention, only the latest intervention was included (7,180 smokers (corresponding to 9.3% of all smokers) were registered more than once; 9,523 interventions were not included). Smokers were not included in the study if they met any of the following criteria: younger than 18 years of age at the onset of the intervention (1,146); no attendance at a GSP (16,077); or attendance at a

smoking cessation clinic that pre-decided, on the administrative level, not to contact their participants for follow-up after 6 months (8,496).

To identify smokers with a mental disorder(s), the remaining 38,879 smokers in the Smoking Cessation Database were cross-referenced with data from the National Patient Register using CPR numbers. Psychiatric discharge diagnoses given before the onset of the smoking cessation intervention were extracted. All psychiatric diagnoses (*Chapter V; Mental and behavioural disorders, F00-F99*), except F17 (*Mental and behavioural disorders due to use of tobacco*), were initially linked to the smokers. Patients diagnosed with organic mental disorders (F0 chapter) or intellectual disabilities (F7 chapter) were not included in the study regardless of other psychiatric diagnoses. Smokers without any psychiatric diagnosis composed the control group. Patients were categorised based on the severity and occurrence of a specific SMD according to the following hierarchy: schizophrenia (F20), schizotypal disorder (F21), other psychoses (F22-F25, F28-29), manic episodes (F30), bipolar disorder (F31), depression (F32-F34), anxiety (F40-F41), obsessive-compulsive disorder (F42), post-traumatic stress disorder (F43.1), personality disorders (F60-F69), and substance use disorder (SUD) (F1). To avoid representing a patient multiple times in the analyses, the most severe diagnosis as defined by the hierarchy above was considered the primary discharge diagnosis. Smokers without an SMD but with other diagnosed mental disorders were omitted from the primary outcome analysis. Thus, 38,293 smokers with or without a mental disorder were included in this study (see flowchart in Figure 1).

Figure 1. *Flow chart of patient inclusion in the study. Smokers at least 18 years of age who attended a GSP between 1 January 2006 and 31 December 2016 were included in this study. A total of 11,534 smokers were lost to follow-up, leaving 25,411 smokers for inclusion in the outcome analyses.*

Patient and Public Involvement

This study is based on data from any smokers participating in smoking cessation interventions available to the public without referral and free of charge. Patients or public were not otherwise involved in this study.

Outcome and other variables

The primary outcome was self-reported continuous abstinence measured six months after quitting. Continuous abstinence was defined as not having smoked at all from the quit date to the six-month follow-up contact (15).

For each smoker registered in the Smoking Cessation Database, data relating to socio-demographic characteristics, smoking history, intervention programme and follow-up information were collected. Age and smoking information were collected as continuous variables, whereas the remaining variables were categorical and grouped as shown in Table 1 (and appendix A). Confounders and predictors included in the statistical analyses are listed in Table 1.

Compliance with regard to meeting adherence was defined as attending at least 75% of the scheduled meetings as defined by the Steering Committee (23).

Smokers were considered heavy smokers if they fulfilled one or more of three criteria: a ≥20 pack-year smoking history, daily consumption of ≥20 cigarettes, or a nicotine dependency ≥7 points according to the Fagerström test score (13,22). Smokers were considered disadvantaged if they fulfilled at least one of two criteria: unemployment (receiving unemployment benefits) or low level of education (no education except for elementary school or short work-related courses) (14).

Data access and cleaning

We had full access to data relating to all smokers recorded in the Smoking Cessation Database from 2006-2016. Throughout this period, smokers were registered using their individual CPR number. All CPR numbers were checked for validity using official validation rules. Invalid numbers were checked in the Civil Registration System and corrected if possible, and age and sex were corrected accordingly. If correction was not possible, the smokers were excluded from the database. In this study, 484 of 67,339 smokers (corresponding to 0.7%) were omitted from the database due to an invalid CPR number.

The online registration application of the Smoking Cessation Database supplies automatic data validation rules to ensure that only valid dates and required data are entered. In addition to these rules, daily consumption of tobacco was manually checked. Daily consumption of more than 100 grams was considered unlikely, and these data were recoded to "missing". Likewise, years of smoking was recoded to "missing" if the years of smoking were greater than the age of the smoker.

Statistical analysis

After performing initial analyses on the selected predictors (from appendix A) adjusted for sex and age, a multivariable mixed-effect model was fitted to test for differences in continuous abstinence. The predictors were chosen based on the initial analysis and established knowledge (24). The multivariable analysis was performed by entering all the predictors together (see Table 1). In addition, the analysis was adjusted for hierarchical clustering using the different smoking cessation clinics as the 1st level cluster. The analysis was repeated for relevant subgroups of mental disorders. To examine whether the time span from diagnosis to participation in a GSP was related to continuous abstinence, a separate univariate logistical regression was conducted. The span was calculated as time from initial diagnosis of an SMD until the start of the GSP.

Data were reported according to the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) statement (25). Patients with missing values were excluded from the analyses. The results were presented as odds ratios (ORs) and 95% confidence intervals (CIs). Non-respondent analysis was performed using a χ^2-test to compare respondents to non-respondents. A similar analysis was performed to compare the smokers who were intentionally not followed-up to the included smokers. A two-sided p-value <0.05 was considered statistically significant. All statistical calculations were performed with Stata/IC v. 15.0 (StataCorp).

Results

In this cohort study, 38,293 smokers were linked to the National Patient Register to identify smokers with a mental disorder. While 25,411 smokers with or without an SMD were included in the main analysis, 31% were lost to follow-up (29% among smokers without a mental illness and 39% among smokers with an SMD) (see Figure 1). Non-respondent analyses revealed that except for living with a smoker, all other tested predictors significantly differed between the respondents and the non-respondents. The largest difference (14 percentage points) observed was in participant compliance with the respondents showing more compliance with the programme. Smokers with an SMD were more likely to withdraw from the study (schizophrenia spectrum, 43.2%; affective disorders, 38.9%; anxiety, 36.1%; personality disorders, 38.7%; SUD, 36.7%) as were women, disadvantaged smokers, and smokers who attended individual counselling; however, heavy smokers and smokers who were recommended to quit by healthcare staff were more likely to be respondents.

The percentage of individuals who successfully quit was 29.4% and 38.0% for smokers with an SMD and the control group, respectively (see Table 2).

The characteristics of smokers without a mental disorder and smokers with an SMD differed considerably (see Table 1, and appendix A). In particular, the proportion of smokers with an SMD was highest among young smokers and gradually decreased as age increased. In addition, smokers with an SMD were more likely to be heavy smokers, non-compliant, and recommended to stop smoking by healthcare staff and were more often disadvantaged; all these factors were predictors of relapsing within six months of completing the GSP. In addition, smokers with an SMD were less likely to live with other smokers and more likely to attend individual interventions, both of which were predictors of a successful outcome. Approximately half the smokers in both groups (51% of smokers with an SMD and 45% without an SMD) were offered pharmaceutical support, e.g., nicotine replacement therapy, varenicline or bupropion, free of charge.

Primary outcome–smoking cessation at 6 months

After adjusting for clustering and confounding factors, we found that smokers with an SMD were significantly less likely to maintain continuous abstinence six months after attending a GSP (OR=0.74, 95% CI: 0.68-0.80; p<0.001). The time span between the primary discharge diagnosis and the start of the GSP showed a small but statistically significant association with continuous abstinence (OR: 1.02, 95% CI: 1.00-1.03; p=0.013). We identified associations between a higher risk of relapse and female gender (OR: 0.85, 95% CI: 0.80-0.90), disadvantaged status (OR: 0.84, 95% CI: 0.79-0.89), heavy smoking (OR: 0.74, 95% CI: 0.69-0.80), and recommendations to quit by healthcare staff (OR: 0.89, 95% CI: 0.84-0.95). Factors associated with successful quitting were older age (OR: 1.30, 95% CI: 1.07-1.57) compliance with the GSP (OR: 3.26, 95% CI: 3.05-3.48) and attendance of an individual intervention (OR: 1.17, 95% CI: 1.07-1.28).

Table 1: *Characteristics of the study population and predictors for continuous abstinence. The initial analyses were adjusted for sex and age only. In addition to the listed predictors, the multivariable model was adjusted for the year of intervention as well as hierarchical clustering (smoking cessation clinic). The results were reported as ORs and 95% CIs. P-values <0.05 were considered statistically significant and are marked with an *.*

	Characteristics				OR for successful quitting			
	Control n (%)		SMD n (%)		Initial analyses OR (95% CI)		Multivariate analyses OR (95% CI)	
							Adjusted for cluster	
Smokers with a mental disorder								
No mental disorder	29,783	(80.6%)			1		1	
Yes, SMD			7,162	(19.4%)	0.68	(0.63-0.73) *	0.74	(0.68-0.80) *
Participants								
Age (years)								
18-24	1,304	(4.4%)	389	(5.4%)	1		1	
25-34	3,423	(11.5%)	1,064	(14.9%)	1.50	(1.27-1.78) *	1.33	(1.10-1.61) *
35-44	5,661	(19.0%)	1,388	(19.4%)	1.54	(1.31-1.81) *	1.37	(1.14-1.64) *
45-54	7,579	(25.5%)	1,877	(26.2%)	1.59	(1.36-1.87) *	1.47	(1.23-1.76) *
55-64	7,098	(23.8%)	1,668	(23.3%)	1.70	(1.45-1.99) *	1.53	(1.28-1.84) *
65+	4,718	(15.8%)	776	(10.8%)	1.61	(1.37-1.90) *	1.30	(1.07-0.57) *
Sex								
Men	12,278	(41.2%)	2,937	(41.0%)	1		1	
Women	17,505	(58.8%)	4,225	(59.0%)	0.87	(0.83-0.92) *	0.85	(0.80-0.90) *
Disadvantaged smoker [a]								
No	18,451	(62.0%)	2,746	(38.3%)	1		1	
Yes	10,178	(34.2%)	4,128	(57.6%)	0.79	(0.74-0.83) *	0.84	(0.79-0.89) *
Heavy smoker [b]								
No	7,032	(23.6%)	1,243	(17.4%)	1		1	
Yes	22,044	(74.0%)	5,770	(80.6%)	0.69	(0.64-0.73) *	0.74	(0.69-0.80) *
Compliance with programme [c]								
No	10,661	(35.8%)	3,393	(47.4%)	1		1	
Yes	18,712	(62.8%)	3,684	(51.4%)	3.32	(3.12-3.53) *	3.26	(3.05-3.48) *
Living with a smoker								
No	19,389	(65.1%)	5,168	(72.2%)	1		1	
Yes	10,129	(34.0%)	1,917	(26.8%)	0.90	(0.86-0.96) *	0.90	(0.85-0.96) *
Earlier quit attempts								
No	11,227	(37.7%)	2,985	(41.7%)	1		1	
Yes	17,966	(60.3%)	4,001	(55.9%)	1.09	(1.04-1.15) *	1.03	(0.98-1.10)
Recommendation by healthcare staff [d]								
No	11,322	(38.0%)	2,162	(30.2%)	1		1	
Yes	17,078	(57.3%)	4,690	(65.5%)	0.86	(0.81-0.91) *	0.89	(0.84-0.95) *
Smoking cessation clinic								
Setting								
Municipality	22,653	(76.1%)	5,636	(78.7%)	1		1	
Pharmacy	4,522	(15.2%)	938	(13.1%)	1.06	(0.98-1.13)	1.02	(0.90-1.15)
Hospital (incl. midwives)	1,943	(6.5%)	514	(7.2%)	1.02	(0.92-1.13)	1.13	(0.94-1.36)
Other	665	(2.2%)	74	(1.0%)	0.99	(0.83-1.20)	1.05	(0.81-1.38)
Smoking cessation intervention								
Programme format								
Group	24,925	(83.7%)	5,347	(74.7%)	1		1	
Individual	4,858	(16.3%)	1,813	(25.3%)	1.30	(1.21-1.39) *	1.17	(1.07-1.28) *
Cluster								
Smoking cessation clinic							0.05	(0.03-0.08) *

a) Disadvantaged: ≤12 years of school and/or unemployed.
b) Heavy smoker: ≥20 pack years, Fagerström score of ≥7 points and/or daily consumption of ≥20 cigarettes.
c) Compliance: attended ≥75% of the planned meeting sessions.
d) Healthcare staff: Doctors, nurses, nurses' assistants, midwives, etc.
e) Free medication: Nicotine replacement therapy, varenicline or bupropion.

The proportion of successful quitters was 38.0% in the control group versus 30.0% in patients with any mental disorder (see Table 2). The quit rates among the SMD subgroups differed by approximately 7 percentage points; however, for patients within the schizophrenia spectrum, which was the least successful group, the proportion of successful quitters was 25.7%. All the

subgroups, except anxiety, were significantly less likely to stay continuously abstinent after 6 months than the control group.

Table 2: *Crude quit rates and associations of successful quitting according smoker subgroups stratified by the severity of the mental disorder.*

		Crude quit rate	Multivariate analyses OR (95% CI)	
Diagnoses (IDC-10)	**n**	**%**	**Adjusted for cluster**	**p**
Control: no psychiatric diagnoses	21,044	38.0%	1	
Any mental disorder	5,306	30.0%	0.75 (0.70-0.81) *	<0.000
Severe mental disorder (SMD)	4,404	29.4%	0.74 (0.68-0.80) *	<0.000
Schizophrenia spectrum (F20-F29)	692	25.7%	0.61 (0.50-0.74) *	<0.000
Affective disorders (F30-F34)	1,742	31.0%	0.80 (0.71-0.90) *	<0.000
Anxiety (F40-F42, F43.1)	548	31.9%	0.86 (0.70-1.06)	0.156
Personality disorders (F60-69)	294	26.9%	0.62 (0.46-0.83) *	0.001
SUD (F10-16, F18-F19)	1,128	28.6%	0.68 (0.59-0.79) *	<0.000
Other	902	32.9%	0.83 (0.71-0.98) *	0.027

We examined the occurrence of dual diagnoses, defined as having SUD in addition to any other mental disorder(s), and the effect of these diagnoses on smoking cessation for subgroups of smokers with a mental disorder. The occurrence of dual diagnoses differed between 17 and 41% in the subgroups. Moreover, the proportion of successful quitters was lower in patients with dual diagnoses (18.9-26.9%) than in patients without SUD (27.7-33.9%), corresponding to a reduction in successful outcomes by 18-43%. This should be compared to a quit rate of 30.5% among patients with SUD alone (see Figure 2).

Figure 2*: Crude quit rates according to the specified mental disorder with or without SUD.*

Intentional lack of follow-up

The characteristics shown in Table 1 were also compared between smokers who were intentionally not followed up due to an administrative decision in the smoking cessation clinic and the included. The analyses showed that there were statistically significant differences between the two groups with regard to mental diagnoses, heavy smoking, compliance, living with a smoker, earlier quit attempts, setting, programme format and year of intervention. The differences were most pronounced in relation to arena (22 percentage points), where smokers attending an intervention in a municipal clinic were most likely to receive a follow-up call. The year of intervention (9 percentage points) revealed that smokers were less likely to receive follow-up before 2010. All other factors differed by fewer than 5 percentage points, and smokers with a mental disorder were more likely to receive follow-up than heavy smokers, non-compliant smokers, smokers not living with another smoker, and smokers attending a group intervention.

Discussion

Overall, 28% of the smokers with an SMD stayed continuously smoke-free for at least 6 months after undergoing a GSP intervention compared to 38% without an SMD. This was in agreement with our main hypothesis. Compliance was by far the most important predictor of a successful outcome. Dual diagnoses of SMDs lowered the proportion of successful quitters to 19-27%, depending on the diagnoses.

Smokers with an SMD were as likely to want to quit smoking as the general population (3), but the evidence of smoking cessation intervention is sparse among this group. A recent review concluded that although bupropion and varenicline appear to be effective among smokers with an SMD, the efficacy of nicotine replacement therapy and behavioural treatment is still unclear (7). Another review illuminating the effect of specialised advice to smokers with an SMD revealed only one ongoing trial investigating this topic (26).

Promising results were presented in a randomised trial on treating tobacco dependence among inpatients at a psychiatric ward with a complete smoking ban. Prochaska et al. observed a point prevalence of 14% in smokers undergoing an intervention combining behavioural treatment and nicotine patches at 6 months after intervention in contrast to 7% in the usual care control group (8). Even unmotivated patients were able to successfully quit, and the long-term results after 18 months were positive (8).

In our study, 28% of the participants with an SMD continued to abstain after 6 months. Smokers diagnosed within the schizophrenia spectrum benefitted the least from the GSP. Although meta-analyses have also shown a lower effect in this group (27), smokers with depression showed higher quit rates (28). A review reported that only two small studies have been published concerning smokers with bipolar disorders (29), and both trials had difficulties recruiting smokers within this subgroup. In our subgroup analysis, smokers with anxiety (F4 Chapter) were also likely to have been slightly underpowered, which was also the case for the subgroup of smokers classified as “other diagnoses”.

The GSP is a package consisting of several elements, including an extensive patient education programme, individual counselling and pharmaceutical support (10,15). In our study, it was not possible to pinpoint which elements were the most important or whether some of the elements were unnecessary for different groups of smokers. In addition to the different mental diagnoses, variations in the severity of mental disease may impact the quit rates. On the one hand, one could expect that smokers with an SMD are more likely to be successful in their quit attempt when they are well-treated and close to discharge. On the other hand, a hospital stay in completely smoke-free surroundings has been shown to be supportive— for SMD smokers as well (8).

Dual diagnoses appear to have a great impact on the ability to quit smoking, and it would be relevant to evaluate combined interventions for both smoking and substance abuse. Although the evidence is also sparse, smoking cessation intervention has been shown to be effective for smokers in short-term substance abuse treatment (30).

This study has strengths as well as limitations. Because the aim of this study was in line with the purposes of the Smoking Cessation Database, we considered the implications of using these routinely collected health data to be minimal. However, one potential weakness was that participants with an SMD were included independent of the time span from diagnoses to

the intervention onset. Surprisingly, we found only a small significant association between time span and continuous abstinence, and this association should be investigated in more detail in future intervention studies. Using the National Patient Register, we identified only smokers with a mental disorder severe enough to justify hospitalisation (in- or outpatient). There might be patients in the Smoking Cessation Database with mental disorders who did not receive hospital care, but we must assume that their mental disorders are much less severe. The proportion of participants lost to follow-up was moderate (31%). In this study, we only included respondents in the final analysis, thus assuming that the quit rates among non-respondents were similar to the quit rates estimated in this study. Because the non-respondent analysis showed a higher proportion of non-compliant participants among the non-respondents, it is likely that the quit rates in this study are overestimated.

One strength of this study was the large nationwide cohort and the inclusion of all settings (municipalities, hospitals, pharmacies, etc.) where smoking cessation interventions in Denmark are conducted. Data from both registries used in this study provide a high degree of completeness and precision, and the amount of missing data was very low (15,17). We were unable to identify possible misclassifications, but the occurrence of these was expected to be very low (15,17).

The use of continuous abstinence instead of point prevalence was a strength, but self-reporting without biomarker validation was a limitation (31) that might have introduced reporting bias (32). Contrary to the logical presumption that the use of this outcome would prove more precise, a Canadian study showed no significant difference between self-reported smoking status and urinary cotinine levels (33). The use of carbon monoxide tests to validate smoking status showed that validation increased the detection of smokers with short- and long-term quit rates by only 6 and 3 percentage points, respectively (34,35). Similar results were observed in a Danish study where self-reported and validated abstinence differed by 3-4 percentage points (36).

Due to differences in national and cultural traditions, smoking habits, socio-economic conditions and the diagnosis of SMDs, the external validity of these results is limited and should be considered carefully before extrapolating to other developed countries.

Overall, it is important for smokers with a mental disorder to be offered clinical help to quit smoking due to the many positive effects of smoking cessation on both physical and mental health (5). However, the evidence on how to best help this group of smokers is sparse. Randomised controlled trials have shown that smoking cessation interventions can be effective, and this study reports that it is feasible to help a clinically relevant part of this vulnerable subgroup of smokers; however, these individuals have a lower quit rate than smokers without an SMD. More evidence is needed concerning the treatment of competing addictions and dual diagnoses.

Conclusion

Only 28% of the smokers with an SMD successfully quit smoking, which is significantly lower than the rate observed among smokers without an SMD (38%). The lowest quit rates were observed among patients with dual diagnoses, and the most important predictor of successful quitting was compliance.

Competing interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Data sharing

The protocol, anonymised data and statistical codes are available from the corresponding author.

Contributions

MR, MK and HT contributed to the study conception and design. MR and HT headed the data acquisition. MR contributed to the data analysis. MR, MK, JK, MN and HT contributed to the data interpretation. MR drafted the manuscript, and MK, JK, MN and HT revised it critically for important intellectual content. All the authors gave final approval of the version to be published. MR is the guarantor.

Transparency declaration

The lead author (study guarantors) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Figure 1. *Flow chart of patient inclusion in the study. Smokers at least 18 years of age who attended a GSP between 1 January 2006 and 31 December 2016 were included in this study. A total of 11,534 smokers were lost to follow-up, leaving 25,411 smokers for inclusion in the outcome analyses.*

Figure 2*: Crude quit rates according to the specified mental disorder with or without SUD.*

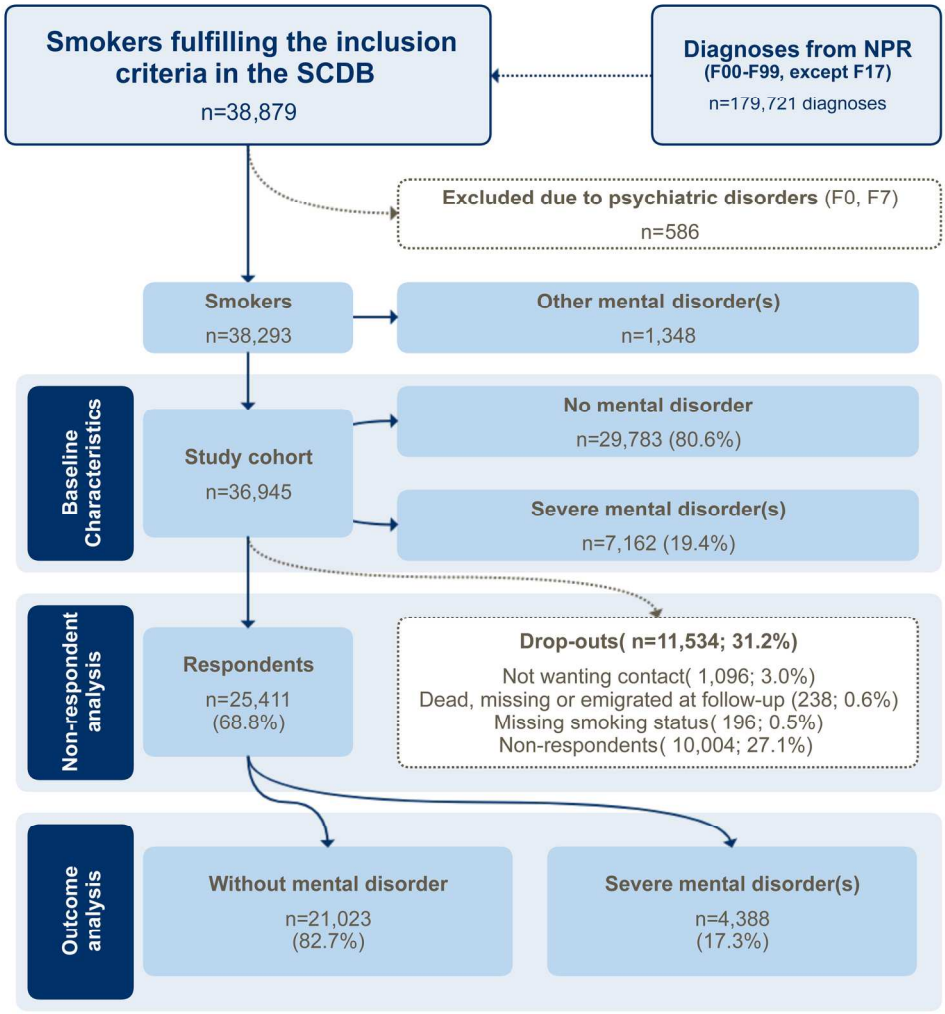

Figure 1. Patient flow. Smokers of at least 18 years of age attending a GSP between 1 January 2006 and 31 December 2016 were included in this study. A total of 11,534 smokers were lost to follow-up, leaving 25,411 smokers to be included in the outcome analyses.

180x186mm (300 x 300 DPI)

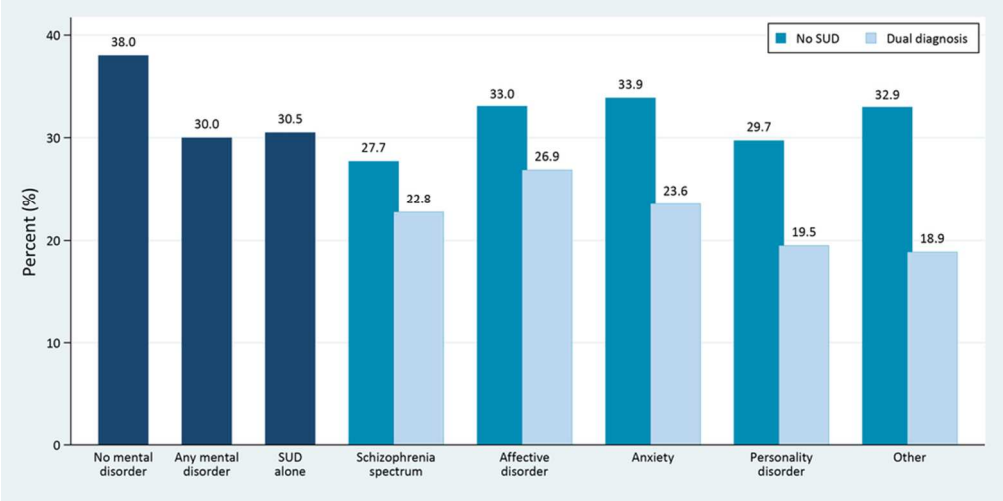

Figure 2: Crude quit rates according to specified mental disorder(s) with or without SUD.

86x43mm (300 x 300 DPI)

Appendix A

Table 1: Characteristics of the study population.

	Population without prior mental diagnosis n (%)	Population with SMD n (%)
All	29,783 (80.6%)	7,162 (19.4%)
Previously attempted smoking cessation		
Yes	17,966 (60.3%)	2,985 (55.9%)
No	11,227 (37.7%)	2,985 (41.7%)
Heavy smoker [b]		
Yes	22,044 (74.0%)	5,770 (80.6%)
No	7,032 (23.6%)	878 (17.4%)
Unknown	707 (2.4%)	149 (2.1%)
Smoking		
<20 pack years	9,355 (31.4%)	2,106 (29.4%)
≥20 pack years	19,461 (65.3%)	4,798 (67.0%)
Fagerström score [a] 0-6	23,100 (77.6%)	4,191 (58.5%)
Fagerström score 7-10	6,683 (22.4%)	2,971 (41.5%)
<20 cigarettes per day	13,842 (46.5%)	2,430 (33.9%)
≥20 cigarettes per day	15,941 (53.5%)	4,732 (66.1%)
Age (years)		
18-24	1,304 (4.4%)	389 (5.4%)
25-34	3,423 (11.5%)	1,064 (14.9%)
35-44	5,661 (19.0%)	1,388 (19.4%)
45-54	7,579 (25.5%)	1,877 (26.2%)
55-64	7,098 (23.8%)	1,668 (23.3%)
65+	4,718 (15.8%)	776 (10.8%)
Sex		
Men	12,278 (41.2%)	2,937 (41.0%)
Women	17,505 (58.8%)	4,225 (59.0%)
Living with smoker		
Yes	10,129 (34.0%)	1,917 (26.8%)
No	19,389 (65.0%)	5,168 (72.2%)
Unknown	265 (0.9%)	77 (1.1%)
Medication [c] offered for free		
Yes	13,526 (45.4%)	3,632 (50.7%)
No	12,880 (43.3%)	3,115 (43.5%)
Unknown	3,377 (11.3%)	415 (5.8%)
Compliant with programme [d]		
Yes	18,712 (62.8%)	3,684 (51.4%)
No	10,661 (35.8%)	3,393 (47.4%)
Unknown	410 (1.4%)	85 (1.2%)
Recommendation by healthcare staff [e]		
Yes	17,078 (57.3%)	4,690 (65.5%)
No	11,322 (38.0%)	2,162 (30.2%)
Unknown	1,383 (4.6%)	310 (4.3%)
Disadvantaged [g]		
Yes	10,178 (34.2%)	4,128 (57.6%)
No	18,451 (62.0%)	2,746 (38.3%)
Unknown	1,154 (3.9%)	288 (4.0%)
Education level [f]		
Low	7,979 (26.8%)	2,448 (34.2%)
Medium	6,257 (21.0%)	1,430 (20.0%)
High	14,532 (48.8%)	2,971 (41.5%)
Unknown	1,015 (3.4%)	313 (4.4%)
Employment		
Employed	18,079 (60.7%)	2,480 (34.7%)

Unemployed	3,964 (13.3%)	3,055 (42.7%)
Student	1,174 (3.9%)	428 (6.0%)
Retired	5,747 (19.3%)	967 (13.5%)
Unknown	819 (2.68%)	230 (3.2%)
Setting		
Municipality	22,653 (76.0%)	5,636 (78.7%)
Pharmacy	4,522 (15.2%)	938 (13.1%)
Hospital	1,943 (6.5%)	514 (7.2%)
Other	665 (2.2%)	74 (1.0%)
Programme format		
Individual	4,858 (16.3%)	1,813 (25.3%)
Group	24,925 (83.7%)	5,347 (74.7%)
Unknown	0 (0.0%)	2 (0.0%)
GSP year		
2006	3,628 (12.1%)	460 (6.4%)
2007	4,210 (14.1%)	538 (7.5%)
2008	3,332 (11.2%)	570 (8.0%)
2009	3,203 (10.8%)	669 (9.3%)
2010	3,063 (10.3%)	698 (9.8%)
2011	2,123 (7.1%)	526 (7.3%)
2012	1,882 (6.3%)	505 (7.0%)
2013	1,256 (4.2%)	422 (5.9%)
2014	1,264 (4.2%)	450 (6.3%)
2015	2,489 (8.4%)	992 (13.9%)
2016	3,333 (11.2%)	1,332 (18.6%)

a) Fagerström score: a standard for quantifying nicotine addiction.
b) Heavy smoker: defined as having ≥20 pack years, a Fagerström score of ≥7 points and/or a daily consumption of ≥20 cigarettes.
c) Free medication: Either nicotine replacement therapy, varenicline or bupropion.
d) Compliance: defined as having participated in at least 75% of the planned meeting sessions.
e) Healthcare staff: doctors, nurses, nurses' assistants.
f) Education level: low: ≤12 years of school, medium: >12 years of school but <3 years of higher education, high: ≥3 years of higher education.
g) Disadvantaged: ≤12 years of school and/or unemployed.

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	✓ a) Page 1 ✓ b) Page 2	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	✓ Page 2 ✓ Page 1+2 ✓ Page 2
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	✓ Page 3		
Objectives	3	State specific objectives, including any prespecified hypotheses	✓ Page 3		
Methods					
Study Design	4	Present key elements of study design early in the paper	✓ Page 3		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	✓ Page 3-4		
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the	✓ Page 4	RECORD 6.1: The methods of study population selection (such as codes or	✓ Page 4-5

		sources and methods of selection of participants. Describe methods of follow-up ~~*Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls~~ ~~*Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants~~ *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed ~~*Case-control study* - For matched studies, give matching criteria and the number of controls per case~~	Not relevant – not a matched study	algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Not relevant ✓ Page 4-5 + figure 1 (this study includes linkage to one register).
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	✓ Page 5 + table 1	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	✓ Page 5 + table 1 (characteristics) and supp. online appendix
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	✓ Page 5-6		
Bias	9	Describe any efforts to address potential sources of bias	✓ Page 10-11(bias and limitations in discussion)		

Study size	10	Explain how the study size was arrived at	✓ Page 4-5 + figure 1		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	✓ Page 4-6		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed ~~*Case-control study* - If applicable, explain how matching of cases and controls was addressed~~ ~~*Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy~~ (e) Describe any sensitivity analyses	✓ Page 6		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	✓ Page 5-6
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-	✓ Page 4

				level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	✓ Page 4-5 + figure 1	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	✓ Page 4-5 + figure 1
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	✓ Page 8; table 1, + supp. online appendix		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time ~~*Case-control study* - Report numbers in each exposure category, or summary measures of exposure~~ ~~*Cross-sectional study* - Report numbers of outcome events or summary measures~~	✓ Page 6 + figure 1		
Main results	16	(a) Give unadjusted estimates	✓ Page 8-9; table		

		and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	1-2 ✓ Page 8; table 1 + supp. online appendix Not relevant		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	✓ Page 6-9		
Discussion					
Key results	18	Summarise key results with reference to study objectives	✓ Page 10		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	✓ Page 10-11	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	✓ Page 10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	✓ Page 10-11		
Generalisability	21	Discuss the generalisability (external validity) of the study results	✓ Page 11		

Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	✓ Page 12 (Acknowledgements)		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	✓ Page 12 (data sharing)

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.