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Original article

Unemployment and initiation of psychotropic medication: a case-crossover study of 2,348,552 Norwegian employees

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ABSTRACT

Objectives: The study investigated initiation of psychotropic medication in relation to unemployment in the months before, during and after job loss to detect the period of greatest risk.

Methods: The Norwegian working population in 2004 (N=2 348 552) was observed from 2005 to 2010 through administrative registries linked to the Norwegian Prescription Database. A case-crossover design was used to analyse within-person relative risk of incident purchases of prescribed psychotropic drugs in relation to timing of unemployment. Control periods were defined 12, 24 and 36 months before the drug purchase. Supplementary analyses were performed on medication for cardiovascular disease, diabetes, obesity, thyroid disorder, pain and musculoskeletal conditions.

Results: Purchases of all psychotropic drugs increased 1-3 months before job loss. Antidepressants had the highest estimate in the month before job loss (odds ratio (OR) 2.68, 95% confidence intervals (CI) 2.39 to 3.01), followed by hypnotics/sedatives (OR 2.21, 95% CI 1.97 to 2.48), anxiolytics (OR 2.18, 95% CI 1.91 to 2.48) and antipsychotics (OR 2.09, 95% CI 1.76 to 2.48). Rises were greatest in males. Risk of starting psychotropic medication remained raised during a spell of unemployment, but returned to close to baseline levels following re-employment. Drugs used to treat somatic and pain conditions showed similar trends but with weaker associations.

Conclusions: Concerns about impending unemployment may influence mental health several months prior to job loss, especially around the time of notification. The clinical implications of this might be a strengthening of preventive health initiatives early in the unemployment process.

INTRODUCTION

The association between unemployment, mental illness and suicide has been well documented, both in earlier times of economic hardship[1] and in the wake of the Great Recession.[2-4] Further, job loss has been related to increased risk of cardiovascular disease, sleeping problems[5] and overall mortality.[6] However, as poor health might lead to unemployment[7-11] and unemployment might affect health,[12-15] revealing causal health effects of unemployment is an ongoing challenge in this field.[16, 17]

People who lose their jobs are usually notified weeks or months before layoff, so the onset of possible health effects may start before the date of actual unemployment. It might be relevant to distinguish between the acute effects (shock) related to the job loss; stress caused by job insecurity[18] and an anticipation of lowered income, and the effect of actually being unemployed, with its economic and social consequences. Despite this, workers' health in the days and months before unemployment is understudied, probably because lack of detailed data makes it difficult to design informative studies. In order to prevent adverse health consequences of unemployment and come up with targeted interventions, it is clinically and politically relevant to know at what time in relation to job loss people's mental health is most likely to be affected.

In this study we investigated how mental health is affected before, during and after an unemployment spell by using first-time purchases of prescribed psychotropic medication as a measure of increased mental distress. While previous studies in this field are mainly based on self-reported and/or aggregated data, we had access to individual data on more than two million Norwegian employees, including exact dates of purchased medication, unemployment, vocational rehabilitation benefits, pensions, emigration and death.

To account for possible confounding factors associated with both unemployment and mental health, study participants were used as their own controls in a case-crossover design.[19] We investigated how the timing of treatment initiation with prescribed psychotropic drugs in the

Norwegian working population varied with unemployment spells over a six year period (2005 to 2010).

We hypothesised that mental distress related to an upcoming and ongoing unemployment spell would increase the likelihood of initiating treatment with psychotropic drugs before and during unemployment, and then decrease when the unemployment spell ended. Furthermore, we hypothesised that the increase in the likelihood of initiating drug treatment would be more pronounced for psychotropic drugs compared with drugs used for somatic conditions and pain. To the best of our knowledge the present study is the first to analyse trajectories of several types of psychotropic and somatic drug purchases in relation to unemployment in a whole working population with detailed longitudinal data.

METHODS

Data provision

The target population comprised all inhabitants aged 18-67, employed and resident in Norway in 2004 (N = 2,348,552). Statistics Norway provided individual level registry data on exact dates of unemployment and social security benefits (participation in vocational rehabilitation programs, disability pension and old age retirement), as well as sex, age, education, emigration and death from 1992 to 2011 (retirement only until 31.12.2010). The Norwegian Prescription Database (NorPD) was established in 2004 and provided individual level data (dates) of all purchased psychotropic drugs from Norwegian pharmacies from 2004 and throughout the observation period (2005-2010). The drugs were identified by the World Health Organization's Anatomical Therapeutic Chemical classification system (ATC) . The registries were linked using the personal identification number unique to all Norwegian inhabitants.

Design and study population

The association between timing of unemployment and incident use of psychotropic medications was analysed using a case-crossover design. In contrast to a conventional case-control design, each individual serves as his/her own control in a case-crossover design.[20] Hence, all time-invariant or slow-varying confounding (e.g. by sex; past psychiatric illness; educational level) is eliminated.[19, 21] However, the case-crossover design still might be susceptible to time varying confounding. [19] The design assumes constant risk of exposure; the person-time in the case period is assumed to be exchangeable with the same individual's person-time during control periods.[19]

From the target population of 2,348,552 employees, we selected case-crossover samples for each group of psychotropic drugs studied; antidepressants (n=34,111), anxiolytics (n=32,570), hypnotics/sedatives (n=26,838) and antipsychotics (n=12,495). Each sample consisted of employees both exposed to at least one unemployment spell and having a prescribed psychotropic drug (outcome) dispensed during the observation period (1 Jan 2005 to 31 Dec 2010). In order to capture incident medication, we excluded those who purchased a psychotropic drug in 2004 (N = 307,622).

16 exposure states of unemployment were defined according to timing of the unemployment spell(s): 1-6 months before, 1, 2, 3, "4 or more" months during and 1-6 months after the end of an unemployment spell. Further, each individual's unemployment state was recorded on the date of the first drug purchase, henceforth called the case period. Control periods were chosen 12, 24 and 36 months before the incident drug purchase took place, and each individual's unemployment state in these control periods was recorded (see supplementary file, S-Figure 1). Regarding unemployment, we only included individuals who had:

1) At least one episode of unemployment lasting for >90 consecutive days during the observation period. Cut off at 90 days was chosen in order to avoid the inclusion of students searching for work in holidays and those who were registered as unemployed but secured a new job within a short time

2) A first episode of unemployment ending no earlier than 180 days before 1 Jan 2005, or an unemployment spell starting within the 180 days after 31 Dec 2010 – enabling everyone to be situated in any of the 16 time-states in the unemployment process.

See sample selection flow-chart in Figure 1.

(Figure 1 here)

Outcome ascertainment

The outcome was having a first-time registered purchase of a psychotropic drug during the observation period (2005 to 2010). Separate analyses on each of the four psychotropic drug (ATC) groups were performed: N06A Antidepressants; N05C Hypnotics and sedatives; N05B Anxiolytics and N05A Antipsychotics. A list specifying the drugs and defined daily dose (DDD)/1000 inhabitants/day in each group is given in the supplementary file (S-Table 1). Right censoring was done at date of death, emigration, retirement (early/old age) or long-term work disability (vocational rehabilitation program participation or any type of disability pension), whichever occurred first.

Exposure to unemployment

The date of unemployment was defined when an employee was registered completely out of income-producing work and signed up as 100% actively job seeking for >90 days, or full-time participating in re-employment programs. The observation period was split in 30-days-intervals with a maximum of 73 periods (also referred to as months). For each of these periods, we generated dichotomous variables indicating unemployment state and first-time drug purchase based on exact dates. The dichotomous unemployment variables identified episodes of ongoing unemployment as well as the 6-month period leading up to and following each unemployment spell.

Main analysis

We compared the odds of being close to an unemployment spell in the case period (initiation of psychotropic drug treatment) with the odds of being in that same unemployment state 12, 24 and 36 months before the drug purchase took place (control periods). This takes into account seasonal variations in exposure trends, as the same months in each year are used as control periods. An indirect measure of relative risk was estimated with the odds ratio (OR) and 95% confidence intervals (CI), using a conditional logistic regression (fixed effect) estimator when comparing the odds of exposure within each individual's case and control periods. Statistical software: Stata/MP 13.

Subgroup analyses

Subgroup (stratified) analyses were performed according to sex, age and educational level to investigate whether associations differed in these groups. Differences between groups were tested using a generalized Hausman specification test.[22] Age was categorized into three groups: 18-29, 30-49 and 50-67. Educational level measured socioeconomic position, three categories were used: 1) compulsory education (primary school, lower secondary school or less) 2) intermediate education (upper secondary school and post-secondary non-tertiary education), 3) tertiary education (undergraduate, graduate and postgraduate).

Supplementary analyses

Previous literature has shown that both length and repeated spells of unemployment are associated with deteriorations in health.[23-25] To explore the effect of having several unemployment spells during the observation period, we compared individuals with multiple unemployment spells with those only experiencing one episode of unemployment.

As health selection to unemployment has been found in previous studies,[7-9, 11] an increase in the likelihood of purchasing psychotropic drugs around the time of unemployment could be attributed to such a selection process; individuals who develop depression may be more likely to lose

their job. It is also possible that people who become depressed or anxious identify their jobs as a source of distress and decide to resign at a period their mental health is deteriorating. To explore this we did supplementary analyses on purchases of drugs related to somatic conditions and pain, using the same working population and methods as the main analysis. We assessed outcomes defined by first-time purchases of medication for diabetes (ATC A10A), obesity (A08A), thyroid disorders (H03A) and cardiovascular disease (C01, C02, C03, C07, C08, C09, C10, whichever occurred first) as well as opioids (N02A), other analgesics/antipyretics (N02B), non-steroid anti- inflammatory medication and topical products for muscular pain (M01A and M02A).

We considered it less likely that purchases of medication for somatic conditions and pain would be systematically related to an unemployment spell. Based on previous literature we anticipated some associations between unemployment status and purchase of cardiovascular disease medications, [5, 26] but overall we expected lower estimates on somatic and pain related drugs compared to psychotropic drugs.

RESULTS

Descriptive statistics at baseline (2004) are presented in table 1. Annual rates of unemployment in Norway over the study period ranged from 3.5% in 2005 steadily decreasing to 1.7% in 2008 and increasing to 2.9% in 2010. Of the 271,971 (12%) individuals in the working population purchasing antidepressants for the first time during the observation period, 34,111 (13%) had at least one unemployment spell during the observation period. Similarly, of the 331,625 (14%) incident purchasers of hypnotics/sedatives, 32,570 (10%) had a period of unemployment. 251,221 individuals (11%) bought anxiolytic drugs in the observation period, 26,838 (11%) of these experienced unemployment. Antipsychotic medication was less commonly used; 95,287 (4%) individuals purchased antipsychotics for the first time between 2005 and 2010, 12,495 (13%) of these were unemployed at some point during the observation period. Of those purchasing antidepressants, hypnotics/sedatives and anxiolytics, 52%, 49% and 52%, respectively, were women, whilst relatively fewer (44%) of those purchasing antipsychotic medication were females. Individuals who experienced unemployment tended to be younger than those prescribed the various psychotropic drugs as a whole.

Table 1 **Descriptive statistics at baseline (2004) for all individuals who purchased psychotropic medication and for individuals both purchasing medication and being unemployed (study population) during the observation period (2005 to 2010). Gender distribution, age (mean and standard deviation (SD)) and proportion of individuals in each category. Median number of days of unemployment during the observation period in males (m)/females (f). No missing on gender and age.**

Baseline characteristics	**Anti-depressants (N06A)**	**Incident anti-depressants purchase and unemployed**	**Hypnotic/ sedative drugs (N05C)**	**Incident hypnotics/ sedatives purchase and unemployed**	**Anxiolytic drugs (N05B)**	**Incident anxiolytics purchase and unemployed**	**Anti-psychotic drugs (N05A)**	**Incident antipsychotics purchase and unemployed**
N	271971	34111	331625	32570	251221	26838	95287	12495
Women (%)	159979 (59)	16963 (52)	193502 (58)	16068 (49)	149828 (60)	14086 (52)	49993 (52)	5507 (44)
Age (mean/SD)	41(11.8)	35 (10.8)	44 (12.0)	36 (11.6)	43 (12.0)	36 (11.3)	41(12.0)	34 (10.9)
Age cat. (%)								
18-29 years	54816 (20)	12659 (37)	49845 (15)	10679 (33)	41548 (16)	9245 (35)	20094 (21)	5045 (40)
30-49 years	145124 (53)	17605 (52)	159912 (48)	16597 (51)	125006 (50)	13737 (51)	49438 (52)	6081 (49)
50-67 years	72031 (27)	3847 (11)	121686 (37)	5294 (16)	84667 (34)	3856 (14)	25755 (27)	1369 (11)
Education (%)								
Compulsory	73815 (27)	13354 (39)	75846 (23)	12253 (38)	66774 (26)	10920 (41)	27284 (29)	5279 (42)

Intermediate	122005 (45)	13417 (39)	149279 (45)	13083 (40)	114902 (46)	10533 (39)	42296 (44)	4679 (38)
Tertiary	66287 (24)	5049 (15)	97444 (29)	5312 (16)	62166 (25)	3748 (14)	21849 (23)	1623 (13)
Missing (%)	9864 (4)	2291 (7)	9056 (3)	1922 (6)	7379 (3)	1637 (6)	3858 (4)	914 (7)
Median no days unemployed; (male/female)		392 (408/377)		389 (397/379)		392 (406/384)		408 (421/394)

In Figure 2 we present the within-person relative risk of incident psychotropic drug purchases in relation to timing of unemployment. There was an increasing trend in psychotropic drug purchase in all medication groups 1-3 months ahead of the first registered day of unemployment, with the peak one month before unemployment (more than double risk), and a decrease during the unemployment spell and in particular after the end of unemployment. Of the four psychotropic drugs, antidepressants had the highest estimated odds ratios (OR) in the month before unemployment (OR 2.68, 95% confidence interval (CI) 2.39 to 3.01), followed by hypnotics/sedatives (OR 2.21, 95% CI 1.97 to 2.48), anxiolytics (OR 2.18, 95% CI 1.91 to 2.48) and antipsychotics (OR 2.09, 95% CI 1.76 to 2.48). As seen from the category "4 months or more" of the unemployment spell (4+), there was a tendency towards increased risk of first-time psychotropic drug purchase in longer unemployment spells. Overall risk estimates of psychotropic drug purchase during all periods of unemployment (month 1-4+, data not shown) was OR 1.68 (95% CI 1.61 to 1.76) in antidepressants, OR 1.47 (95% CI 1.40 to 1.54) in hypnotics/sedatives, OR 1.45 (95% CI 1.38 to 1.53) in anxiolytics and OR 1.44 (95% CI 1.34 to 1.54) in antipsychotics.

(Figure 2 here)

Subgroup analyses

Analyses stratified by sex (Figure 3) gave slightly higher risk estimates in men, especially in the months before and during unemployment. The differences in antidepressant purchases between males and females were statistically significant ($p < 0.05$) at unemployment states -4, -3, -2, 1, 2 and 4+. Corresponding results in hypnotics/sedatives concerned states -5, -4, -2, 1 and 4+; anxiolytics at states -2, -1, 1, 2, 4+ and +4; antipsychotics at states -5, -4, -1 and 4+.

(Figure 3 here)

Results of the age-stratified analyses (S-Figure 2) showed no large differences between age-groups in the months before and during unemployment. However, compared to their younger peers,

the oldest employees (50-67 years) seemed to have elevated risk of first-time psychotropic drug purchase also in the months after ending an unemployment spell. The analyses stratified by educational level (S-Figure 3) also gave similar results as the main analysis.

Supplementary analyses and robustness checks

Of the employees included in the case-crossover samples, approximately 25% experienced more than one spell of unemployment, regardless of which psychotropic drug was studied. We performed separate analyses on employees with only one unemployment spell and those with two or more spells during the observation period. The result (S-Figure 4) showed that those experiencing only one unemployment spell, generally had higher odds ratios for purchasing psychotropic medication in the three months before and during unemployment, compared to those experiencing two or more spells.

The supplementary analyses on drugs related to more somatic conditions and symptoms are presented in Figure 4. A list of medications included in each group, and descriptive statistics, are presented in the supplementary file (S-Table 1 and S-Table 2). As expected, the associations between unemployment and first-time purchase of these were lower than that of psychotropic drug purchase. However, first-time purchases of several of these drugs showed similar patterns as psychotropic drugs in the months before unemployment. We observed increased risk of first-time purchases in the months before unemployment for anti-diabetic drugs (association in the month before job loss (OR 1.44, 95% CI 1.10 to 1.89)), cardiovascular drugs (OR 1.48, 95% CI 1.32 to 1.66), drugs for thyroid disorders OR 1.22, 95% CI 0.88 to 1.69), opioids (OR 1.77, 95% CI 1.66 to 1.89) and other analgesics/antipyretic drugs (OR 1.46, 95% CI 1.34 to 1.60). The risk of purchasing anti-obesity and anti-inflammatory drugs were quite similar (OR ≈ 1) comparing case and control periods.

(Figure 4 here)

DISCUSSION

Analysing the initiation of psychotropic drugs before, during and after unemployment in the entire Norwegian working population from 2005 to 2010, showed a two to threefold increase in the risk of first-time purchases of psychotropic drugs during the month before the date of unemployment, with an increasing trend in the three months ahead of unemployment. The rises were greater in males than females. The estimated risk decreased steadily during the first three months of unemployment, but stayed on a higher level compared to the six months before unemployment. In the six months after the end of unemployment the risk estimates were close to those of six months before job loss. Supplementary analyses on several drugs prescribed for somatic and pain conditions showed some of the same trends as psychotropic drug purchase, but with a substantially lower level of risk increase.

Strengths and limitations

A major strength of the study is the linkage of several registries, providing individual level data on the entire Norwegian working population over a fairly long time span. The level of precision (exact dates) and objectivity in the ascertainment of outcomes (prescribed drugs) and exposure (unemployment) adds to a literature dominated by self-rated measures and aggregated data. The variety of drugs studied is also a new contribution to the literature.

Another strength is that we could assess purchases of psychotropic medications with a case-crossover design where individuals served as their own control. By design we then eliminated all time-invariant or slow-varying confounding. Such confounding factors include sex, past psychiatric illness, educational level, genetic vulnerability and other stable individual factors relevant for the use of psychotropic drugs. However, the case-crossover design still might be susceptible to time varying confounding and we cannot rule out the influence from such factors in our study. Further, trends in exposure may introduce bias in case-crossover studies,[21] but we consider this less likely to concern our study as the risk of having a prescription of psychotropic drugs was equal (OR ≈ 1) between case and control periods six months before unemployment.

Purchases of prescribed psychotropic drugs were used as a proxy for mental health. Prescription of psychotropic medication is based on clinical evaluation by a doctor, but is only one of several potential treatments for mental illness. Those in our study population suffering from mental illness, but not on medication, or those receiving medications while hospitalized, could not be identified in the data. Further, as we do not have available data on drug prescriptions before 2004 in Norway, "first-time purchases" refer to the observation period and not life-time purchases, some may have had prescriptions before 2004. This may imply that our estimates are lower than they would be if we did not have this exclusion criterion. Also, some people may have been unemployed, but for various reasons did not register as unemployed, hence not included in the study samples.

Context and generalizability

Mental health consequences of unemployment seems to be context-sensitive, and studies from different labour markets over time are needed to add pieces to the puzzle.[4] A Swedish study using monthly data on unemployment and dispensed antidepressants found no evidence of an increase in the prevalence of antidepressant use following unemployment,[27] while a recent study of the Swedish working population showed an increased risk of purchasing antidepressant drugs in workers exposed to workplace downsizing.[28] Evidence from the USA on macro-level data showed that in the Northeast region of the country, antidepressant and anti-anxiety drug prescriptions increased by 10% when employment fell by 1%, while no such relationship was found in other parts of the country.[29] A Dutch paper used 8 waves of the European Community Household Panel (N = 136,556) to investigate how self-perceived health was affected by labour force exit due to unemployment, retirement or economic inactivity. They found a yearly increase in the likelihood of poor self-rated health after unemployment (OR 1.06, 95% CI 1.03-1.09), applying to all educational groups and all European regions, except the Nordic countries.[30]

Previous research indicates that a generous welfare state may buffer negative consequences of unemployment on mental health, measured by suicide rate and other health outcomes.[4, 31] This

may affect the generalizability of our results outside of Norway and Scandinavia, as the social spending, level of social security and unemployment benefits and degree of unionization is high. Also, unemployment rates in Norway have been low (below 4%) compared to most countries in Europe during the entire observation period (including the financial crisis). Martikainen et al. (2006) confirmed previous findings indicating that excess mortality of the unemployed tend to be lower in regions of high unemployment, suggesting a higher degree of health selection effects when unemployment rates are low. This may concern our findings and their generalizability.[32]

Interpretation and previous findings

The case-crossover design does not rule out the possible influence of time varying ill health as a possible cause of job loss (i.e. selection to unemployment). Still, given the detailed information on time, and incident measures of both outcome and exposure, we interpret the steadily increasing trend with a peak one month ahead of unemployment, as stress related to the unemployment process having a causal effect on workers' mental health. The high ORs 3-1 month before unemployment perfectly correlate in time with the general Norwegian notice period, corresponding with a plausible onset of job insecurity. Job insecurity has been found to affect the work environment and employees' mental health negatively,[18, 28] both in the short[33] and long run, and downsizing are often lengthy processes not only limited to the notice period.[34]

Being in a state of actual unemployment also implied higher risk of first-time psychotropic drug purchase compared to the risk 6 months before or 6 months after the end of unemployment. This corresponds to the previous literature on effects of unemployment on mental health referred to in the introduction. The findings that associations were stronger in males than females are in keeping with international studies of suicides during the Great Recession,[2] and studies on unemployment and health from Eastern Europe and Spain,[12] while several Swedish studies found no gender differences in the unemployment effect on mental health.[12, 35, 36] A systematic review recently concluded that

results of subgroup analyses (gender, age, educational level, marital status etc.) in this field are mixed and context dependent.[12]

When stratifying on one versus two or more unemployment spells, those experiencing their first and only spell had higher risk estimates than those experiencing multiple unemployment spells. A possible interpretation of this could be that the first time is the most stressful. Further, those with several spells might be employed in more unstable jobs and have lower expectations regarding stable employment, and that unemployment did not affect their mental health as badly as in those experiencing only one spell.

The literature on unemployment effects on physical health measures (except suicide) is scarce with mixed findings. There are few relevant studies on other outcomes than cardiovascular disease.[5, 26] A Swedish study did not find any effects of job loss on severe cardiovascular diseases,[37] while a French study claimed that unemployment may impair cardiovascular health.[38] Empirical evidence from Finland found only modest effects on mortality of unemployment due to downsizing.[32]In our study, incident purchases of drugs other than psychotropics increased in the months ahead of unemployment. A plausible explanation could be an increase in morbidity (e.g. pain and cardiovascular symptoms) as a response to stress and depression related to unemployment. Another explanation could be that mental distress in relation to job loss increases doctor visits *per se*. Doctor visits will in itself trigger medical examinations likely to detect other medical problems in need of treatment. This detection aspect could contribute to an increased observed morbidity amongst the unemployed, previously discussed in a systematic review concluding that unemployed people may be more likely than employed people to visit physicians, take medications or be admitted to general hospitals.[39] The increasing drug purchases may support the health selection hypothesis of vulnerable employees being more prone to lose their job.[7] Nevertheless, the rapidly increasing odds ratios close to the unemployment period points towards unemployment triggering ill health.

One could expect the relationship between personal finances (which may vary over time within individuals) and medication prices to affect the demand for drugs, especially when the household economy is under pressure during unemployment. However, the Norwegian reimbursement system to a large extent covers the expenses for psychotropic drugs and other drugs related to chronic conditions like diabetes, thyroid disease and cardiovascular disease. In countries with high prices on medication, personal finances and market forces could confound the association between drug purchase and unemployment, but we do not consider this to be a problem in our study.

Interventions for the unemployed targeting mental health are sparsely studied. A systematic review from 2010 concluded that the evidence supporting the use of vocational interventions to improve reemployment and reduce mental distress was weak.[40] However, evidence from the US[41] and Finland [42] indicate that psychological interventions targeting the unemployed effectively improved mental health and were positively associated with reemployment. A two to threefold risk increase in purchasing psychotropic drugs in the months before unemployment, compared to other periods of peoples' lives, means that the potential for conducting preventive health care should be high during this period – especially in plants going through major downsizing or closure. These are often lengthy processes that imply job insecurity for both those being laid off and those surviving in a downsizing firm. An implication of our findings could be a strengthening of preventive health initiatives early in the unemployment process, for example through joint working between employees, employers, occupational health services, organisers of public reemployment programs and general practitioners.

CONCLUSION

Although the detrimental effects of unemployment are widely recognized, the present study's results underscore that mental health may deteriorate in the period prior to the actual date of job loss. The

clinical implications of this might be a strengthening of preventive health initiatives early in the unemployment process.

What this paper adds

- Numerous studies have reported an adverse effect of unemployment on mental health, but few studies have been able to analyse the whole unemployment process, especially how mental health is affected around the time of job-loss notification, before actual unemployment begins.
- The level of precision (exact dates) and objectivity in the ascertainment of outcomes (prescribed and purchased drugs) and exposure (registered unemployment spells) adds to a literature dominated by self-reported health measures and aggregated unemployment data.
- We found that the risk of having a first purchase of prescribed psychotropic drugs was highest one month *before* unemployment, indicating that preventive health initiatives should be strengthened around the time of notification, early in the unemployment process.
- Sensitivity analyses on a range of drugs for somatic and pain conditions, not studied in the previous literature, showed similar trends as psychotropics, but with weaker associations.

SUPPLEMENTARY FILE WITH STROBE STATEMENT

A supplementary file with descriptive statistics, results from supplementary analyses and a STROBE statement is available online.

DECLARATION of COMPETING INTERESTS

All authors confirm that the recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations 2013) were followed. We declare that (1) SL Kaspersen and K Pape have support from the Liaison Committee between the Central Norway Regional Health Authority and the Norwegian University of Science and Technology (PhD position and postdoctoral funding) for the submitted work; (2) SL Kaspersen, K Pape, SO Ose, D Gunnell and JH Bjørngaard have no relationships with any companies that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; (4) D Gunnell is a NIHR Senior Investigator; (5) Silje L. Kaspersen is an employee (researcher) at SINTEF Technology and Society, Department of Health. The authors declare no other relationships or activities that could appear to have influenced the submitted work.

CONTRIBUTORSHIP STATEMENT

Silje L Kaspersen designed the study protocol, administered the data collection process, wrote the statistical analysis plan/PhD protocol (in which the study was included), cleaned and analysed the data, and wrote most of the text in the paper. She is guarantor. Kristine Pape and Johan Håkon Bjørngaard contributed in designing the PhD protocol, analysed the data, and drafted and revised the paper. Solveig O Ose contributed by designing the PhD protocol, gave suggestions on data purchases and drafted and revised the paper. David Gunnel gave advices in the analysis process, drafted and revised the paper. Consultants at Statistics Norway and the Norwegian Prescription Database

prepared the data, including identifying the study participants in the registries and cooperated on registry linkages. We would also like to thank the three reviewers who contributed with useful comments in the review process.

PERMISSIONS

ETHICS APPROVAL

The study was approved by the Norwegian Regional Committee for Medical Research Ethics (ref. 2012/1941b).

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DATA SHARING

No additional data is available due to restrictions from the Norwegian Data Protection Authority

(Reference 13/00023-2/EOL).

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Figures

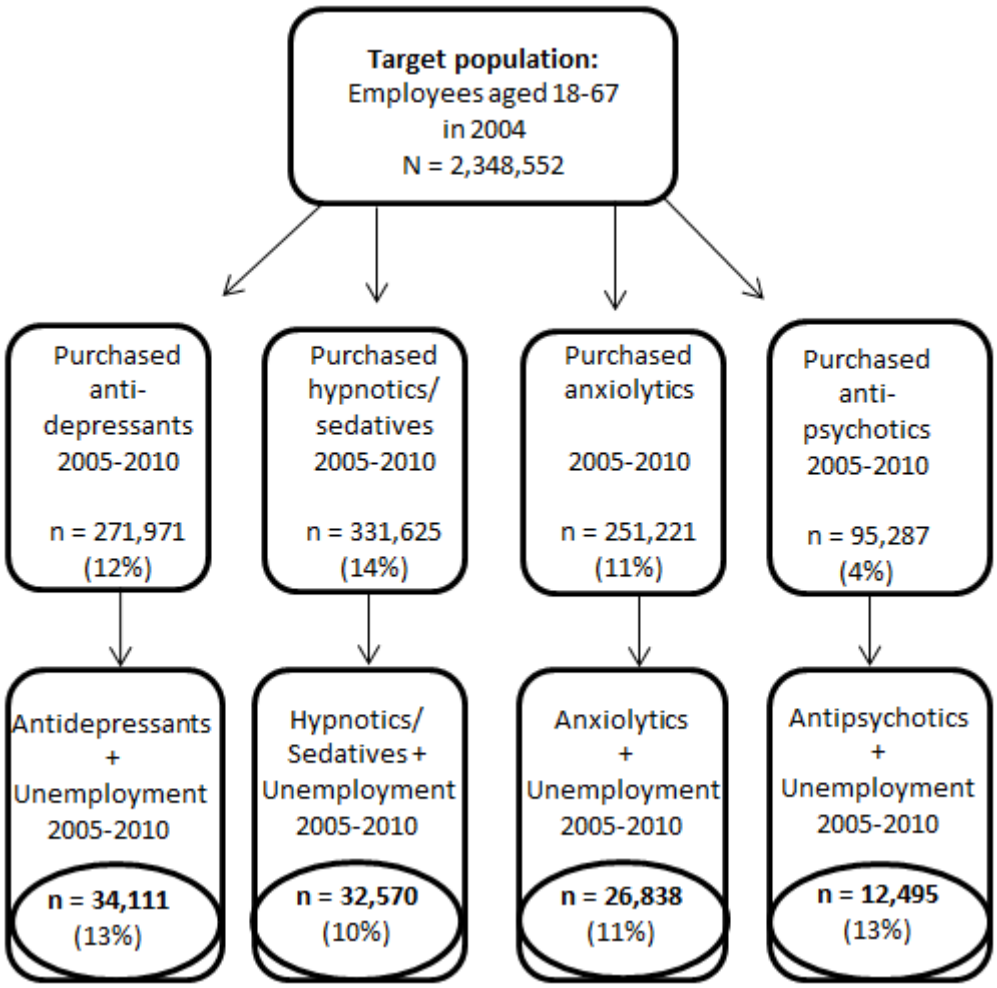


Figure 1 **Flowchart of study population within each ATC-group. Those with at least one purchase of prescribed psychotropic drugs (outcome) and one or more unemployment spells lasting for >90 days (exposure) were included in the case-crossover samples (those within the oval lines).**

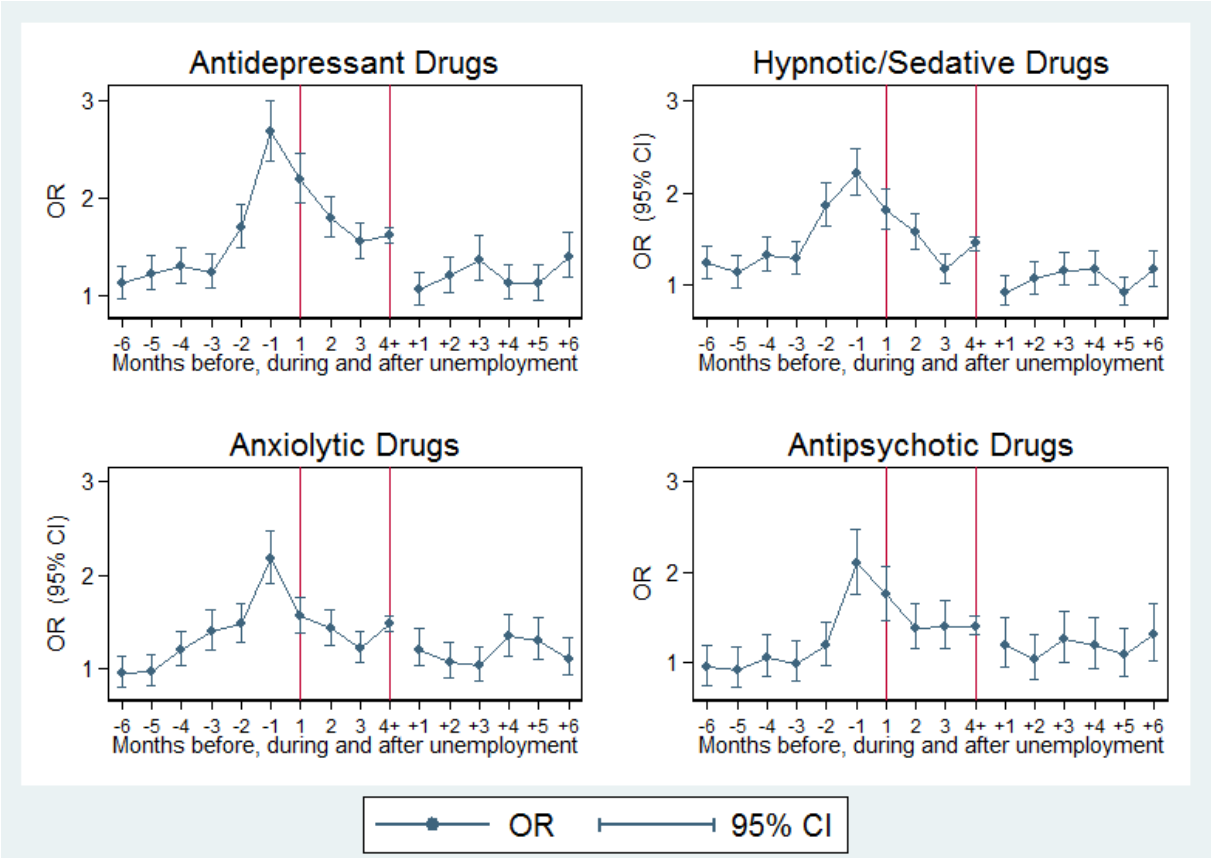


Figure 2 Odds ratios (OR) with 95% Confidence Intervals (CI) of having a first purchase of antidepressants, hypnotic/sedative drugs, anxiolytic drugs and antipsychotic drugs, respectively, while being in a state of unemployment (1-6 months before, 1,2,3,4 or more months during (between vertical lines) and 1-6 months after the end of unemployment). Control periods = 12, 24 and 36 months before the date of drug purchase. Start of the observation period was January 1st 2005, ending on December 31st 2010.

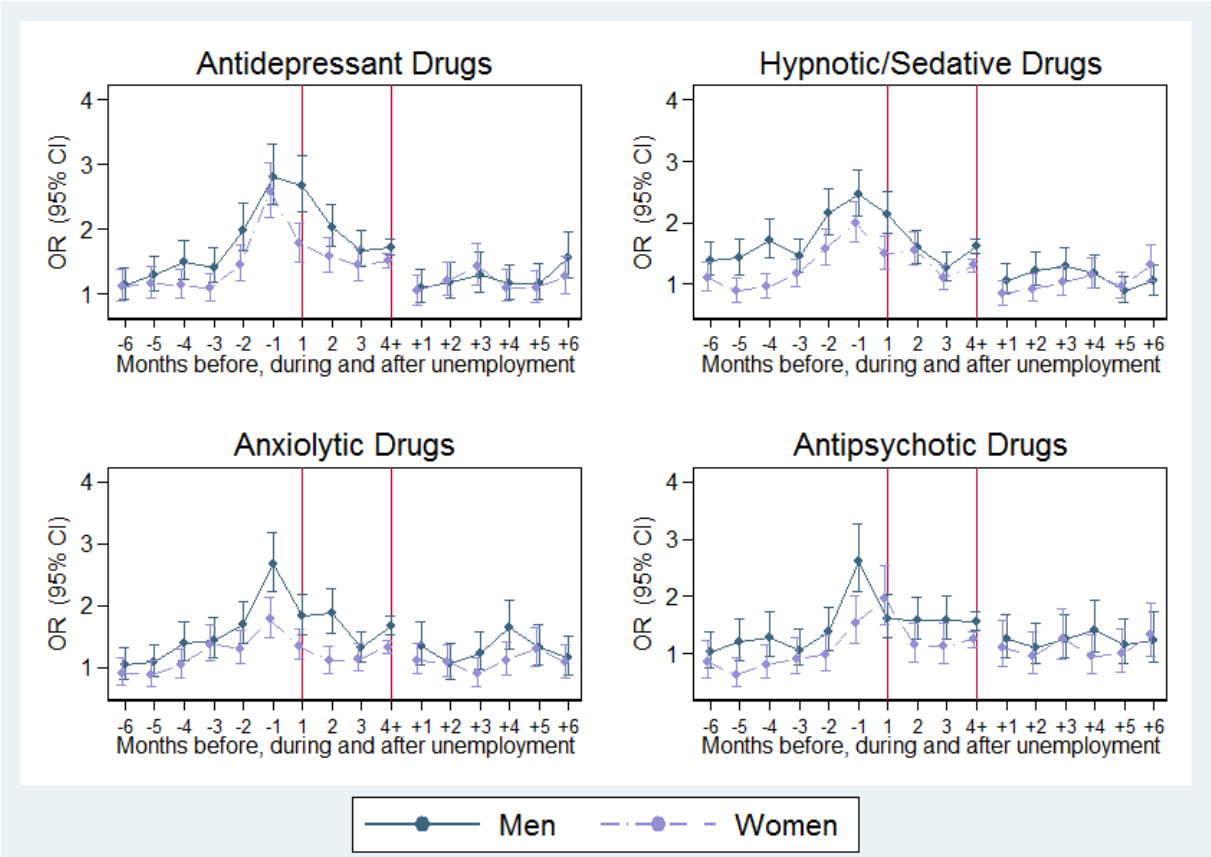


Figure 3 Odds ratios (OR) with 95% Confidence Intervals (CI) of having a first purchase of antidepressants, hypnotic/sedative drugs, anxiolytic drugs and antipsychotic drugs, respectively, while being in a state of unemployment (1-6 months before, 1,2,3,4 or more months during (between vertical lines) and 1-6 months after the end of unemployment). Control periods = 12, 24 and 36 months before the date of drug purchase. Start of the observation period was January 1st 2005, ending on December 31st 2010. Stratified by gender.

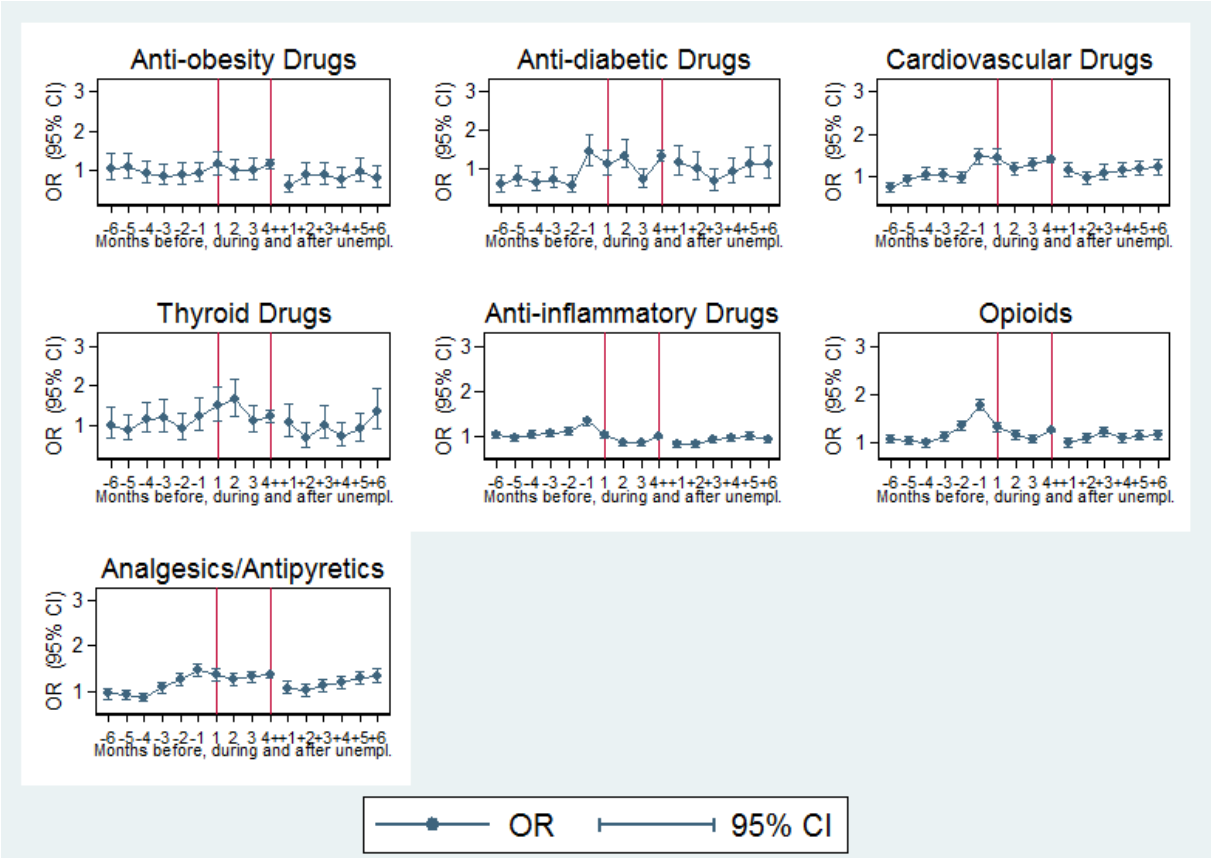
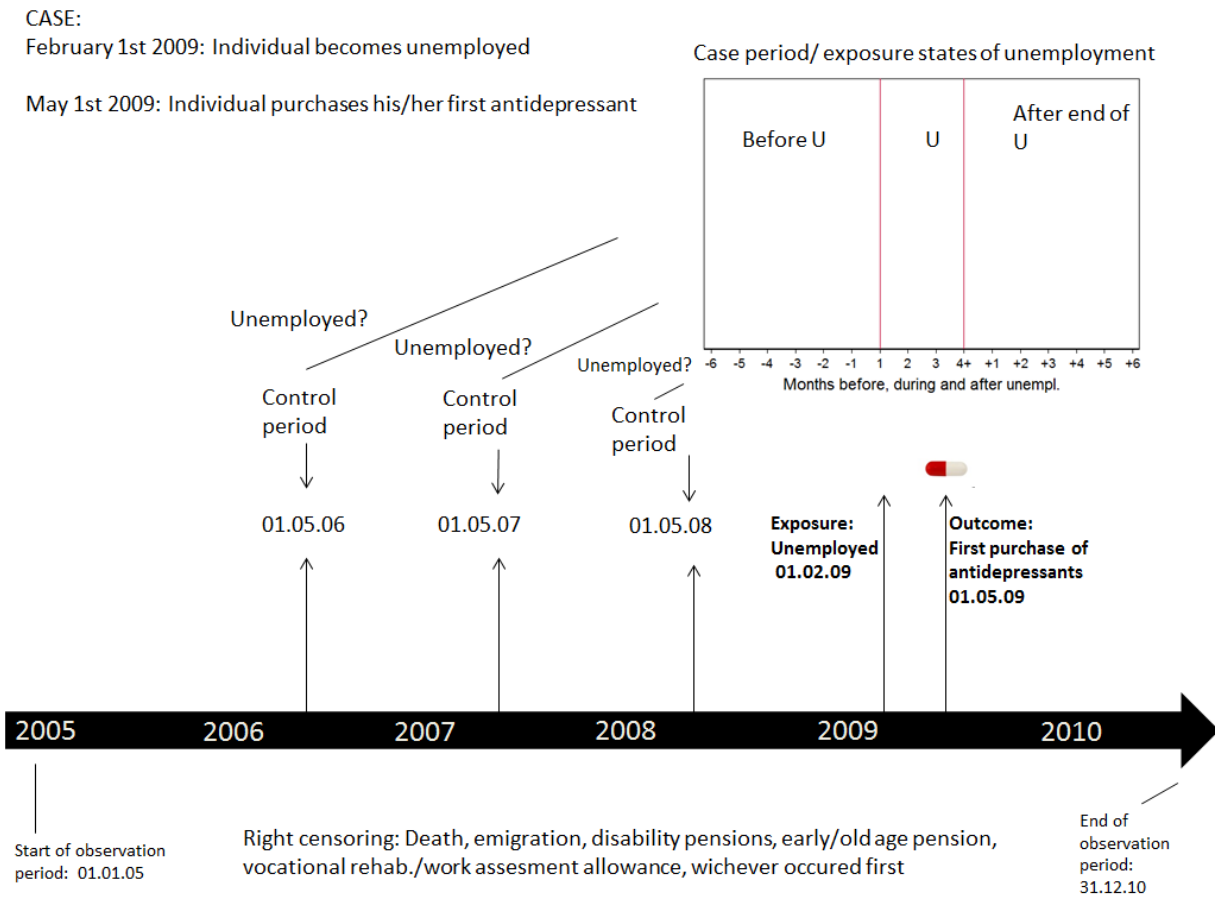


Figure 4 Odds ratios (OR) with 95% Confidence Intervals (CI) of having a first purchase of anti-obesity drugs, anti-diabetic drugs, cardiovascular drugs, thyroid drugs, anti-inflammatory drugs, opioids and other analgesics and antipyretics while being in a state of unemployment (1-6 months before, 1,2,3,4 or more months during (between vertical lines) and 1-6 months after the end of unemployment). Control periods = 12, 24 and 36 months before the date of drug purchase. Start of the observation period was January 1st 2005, ending on December 31st 2010.

Supplementary File

Study design

In order to illustrate the case period (the 16 time states in relation to unemployment around the time of drug purchase) and the three control periods, we made a figure illustrating a case (S-Figure 1). We estimated the risk (odds ratio) of being exposed to unemployment around the date of having a *first* purchase of a psychotropic drug (here: antidepressant). Dichotomous variables indicating each person's time-state according to unemployment and psychotropic drug purchase were generated, making it possible to analyse the data with a conditional logistic fixed-effects estimator (within person), eliminating time-invariant confounding. In the analyses we compared the odds of exposure of unemployment within each individual's case and control periods.



S-Figure 2 **Case-crossover study design indicating the time of the event (drug purchase) and the exposure states of unemployment 1-6 months before the date of unemployment, the 1,2,3, 4 or more months during unemployment and 1-6 months after end of unemployment.**

Medication list

S-Table 1 **Medications included in each outcome-group; N05A Antipsychotics, N05B Anxiolytics, N05C Hypnotics and sedatives, N06A Antidepressants. Daily defined doses (DDD) per 1000 inhabitants per day in the Norwegian population 2006-2010. See the report "Drug consumption in Norway 2006-2010" published by the Norwegian Institute of Public Health (2011:1) for details of consumption on each specific drug.**

ATC	ATC level name	DDDs/1000 inhabitants/day					
		2005	2006	2007	2008	2009	2010
N05A	Antipsychotics	8.4	8.7	8.9	8.9	9.0	9.1
N05B	Anxiolytics	19.6	19.2	19.1	19.3	18.9	18.0
N05C	Hypnotics and sedatives	39.5	41.2	43.1	44.2	44.6	44.3
N06A	Antidepressants	48.4	49.0	51.0	51.7	51.6	52.8
A08A	Anti-obesity preparations, excl. diet products	2.6	2.3	2.7	3.0	3.1	0.9
A10A	Insulins and analogues	17.1	17.5	17.8	18.5	18.5	18.7
C01+C02+C03 +C07+C08+C09 +C10	Cardiac therapy; Antihypertensives; Diuretics; Beta blocking agents; Calcium channel blockers; Agents acting on the renin-angiotensin system; Lipid modifying agents	46.6	49.2	51.8	54.7	55.7	57.0
H03A	Thyroid therapy	19.0	19.6	20.4	21.2	21.5	22.3
M01A +M02A	Antiinflammatory and antirheumatic products, nonsteroids; Topical products for joint and muscular pain	33.2	33.5	33.7	32.9	32.1	32.2
N02A	Opioids	17.1	17.3	17.4	18.0	18.1	17.7
N02B	Other analgesics and antipyretics	5.6	6.6	7.7	9.2	10.6	11.9

N05A	**Antipsychotics**
N05AA	Phenothiazines with aliphatic side chain
N05AA01	Chlorpromazine
N05AA02	Levomepromazine
N05AB	Phenothiazines with piperazine structure
N05AB01	Dixyrazine
N05AB02	Fluphenazine
N05AB03	Perphenazine
N05AB04	Prochlorperazine
N05AB06	Trifluoperazine
N05AB08	Thioproperazine
N05AC	Phenothiazines with piperidine structure

N05AC01	Periciazine
N05AC02	Thioridazine
N05AC04	Pipotiazine
N05AD	Butyrophenone derivatives
N05AD01	Haloperidol
N05AD03	Melperone
N05AD08	Droperidol
N05AE03	Sertindole
N05AE04	Ziprasidone
N05AE05	Lurasidone
N05AF	Thioxanthene derivatives
N05AF01	Flupentixol
N05AF03	Chlorprothixene
N05AF05	Zuclopenthixol
N05AG	Diphenylbutylpiperidine derivatives
N05AG02	Pimozide
N05AG03	Penfluridol
N05AH	Diazepines, oxazepines, thiazepines and oxepines
N05AH01	Loxapine
N05AH02	Clozapine
N05AH03	Olanzapine
N05AH04	Quetiapine
N05AH05	Asenapine
N05AL	Benzamides
N05AL01	Sulpiride
N05AL03	Tiapride
N05AL05	Amisulpride
N05AN	Lithium
N05AN01	Lithium
N05AX	Other antipsychotics
N05AX07	Prothipendyl

N05AX08	Risperidone
N05AX12	Aripiprazole
N05AX13	Paliperidone
N05B	**Anxiolytics**
N05BA	Benzodiazepine derivatives
N05BA01	Diazepam
N05BA02	Chlordiazepoxide
N05BA04	Oxazepam
N05BA05	Potassium clorazepate
N05BA06	Lorazepam
N05BA08	Bromazepam
N05BA09	Clobazam
N05BA12	Alprazolam
N05BB	Diphenylmethane derivatives
N05BB01	Hydroxyzine
N05BC	Carbamates
N05BC01	Meprobamate
N05BE	Azaspirodecanedione derivatives
N05BE01	Buspirone
N05C	**Hypnotics and sedatives**
N05CA	Barbiturates, plain
N05CA01	Pentobarbital
N05CA04	Barbital
N05CA06	Secobarbital
N05CB	Barbiturates, combinations
N05CB02	Barbiturates in combination with other drugs
N05CC	Aldehydes and derivatives
N05CC01	Chloral hydrate
N05CD	Benzodiazepine derivatives
N05CD01	Flurazepam
N05CD02	Nitrazepam

N05CD03	Flunitrazepam
N05CD04	Estazolam
N05CD05	Triazolam
N05CD08	Midazolam
N05CF	Benzodiazepine related drugs
N05CF01	Zopiclone
N05CF02	Zolpidem
N05CF03	Zaleplon
N05CH	Melatonin receptor agonists
N05CH01	Melatonin
N05CM	Other hypnotics and sedatives
N05CM02	Clomethiazole
N05CM05	Scopolamine
N05CM06	Propiomazine
N05CM09	Valerianae radix
N05CM11	Bromides
N05CM18	Dexmedetomidine
N06	Psychoanaleptics
N06A	**Antidepressants**
N06AA	Non selective monoamine reuptake inhibitors
N06AA01	Desipramine
N06AA02	Imipramine
N06AA04	Clomipramine
N06AA05	Opipramol
N06AA06	Trimipramine
N06AA07	Lofepramine
N06AA08	Dibenzepin
N06AA09	Amitriptyline
N06AA10	Nortriptyline
N06AA11	Protriptyline
N06AA12	Doxepin

N06AA21	Maprotiline
N06AB	Selective serotonin reuptake inhibitors
N06AB03	Fluoxetine
N06AB04	Citalopram
N06AB05	Paroxetine
N06AB06	Sertraline
N06AB08	Fluvoxamine
N06AB10	Escitalopram
N06AF	Monoamine oxidase inhibitors, non selective
N06AF01	Isocarboxazid
N06AF03	Phenelzine
N06AF04	Tranylcypromine
N06AG	Monoamine oxidase a inhibitors
N06AG02	Moclobemide
N06AX	Other antidepressants
N06AX01	Oxitriptan
N06AX02	Tryptophan
N06AX03	Mianserin
N06AX05	Trazodone
N06AX06	Nefazodone
N06AX09	Viloxazine
N06AX11	Mirtazapine
N06AX12	Bupropion
N06AX14	Tianeptine
N06AX16	Venlafaxine
N06AX18	Reboxetine
N06AX21	Duloxetine
N06AX22	Agomelatine
N06AX25	Hyperici herba
N06AX26	Vortioxetine
A08A	**Antiobesity preparations, excl. diet products**

A08AA	Centrally acting antiobesity products
A08AA01	Phentermine
A08AA02	Fenfluramine
A08AA04	Dexfenfluramine
A08AA05	Mazindol
A08AA10	Sibutramine
A08AA56	Ephedrine, combinations
A08AB	Peripherally acting antiobesity products
A08AB01	Orlistat
A08AX	Other antiobesity drugs
A08AX01	Rimonabant
A10A	**Insulins and analogues**
A10AB	Insulins and analogues for injection, fast acting
A10AB01	Insulin (human)
A10AB03	Insulin (pork)
A10AB04	Insulin lispro
A10AB05	Insulin aspart
A10AB06	Insulin glulisine
A10AC	Insulins and analogues for injection, intermediate acting
A10AC01	Insulin (human)
A10AC03	Insulin (pork)
A10AC30	Combinations
A10AD	Insulins and analogues for injection, intermediate or long combinded with fast acting
A10AD01	Insulin (human)
A10AD03	Insulin (pork)
A10AD04	Insulin lispro
A10AD05	Insulin aspart
A10AE	Insulins and analogues for injection, long acting
A10AE01	Insulin (human)
A10AE02	Insulin (beef)

A10AE04	Insulin glargine
A10AE05	Insulin detemir
A10AE06	Insulin degludec
C01	**Cardiac therapy**
C01A	Cardiac glycosides
C01AA	Digitalis glycosides
C01AA04	Digitoxin
C01AA05	Digoxin
C01AB	Scilla glycosides
C01AB01	Proscillaridin
C01B	Antiarrhythmics, class i and iii
C01BA	Antiarrhythmics, class ia
C01BA01	Quinidine
C01BA02	Procainamide
C01BA03	Disopyramide
C01BA05	Ajmaline
C01BB	Antiarrhythmics, class ib
C01BB01	Lidocaine
C01BB02	Mexiletine
C01BC	Antiarrhythmics, class ic
C01BC03	Propafenone
C01BC04	Flecainide
C01BD	Antiarrhythmics, class iii
C01BD01	Amiodarone
C01BD02	Bretylium tosilate
C01BD05	Ibutilide
C01BD07	Dronedarone
C01BG	Other antiarrhythmics, class i and iii
C01BG11	Vernakalant
C01C	Cardiac stimulants excl. cardiac glycosides
C01CA	Adrenergic and dopaminergic agents

C01CA01	Etilefrine
C01CA02	Isoprenaline
C01CA03	Norepinephrine
C01CA04	Dopamine
C01CA06	Phenylephrine
C01CA07	Dobutamine
C01CA09	Metaraminol
C01CA10	Methoxamine
C01CA13	Prenalterol
C01CA14	Dopexamine
C01CA17	Midodrine
C01CA24	Epinephrine
C01CA26	Ephedrine
C01CE	Phosphodiesterase inhibitors
C01CE01	Amrinone
C01CE02	Milrinone
C01CX	Other cardiac stimulants
C01CX08	Levosimendan
C01D	Vasodilators used in cardiac diseases
C01DA	Organic nitrates
C01DA02	Glyceryl trinitrate
C01DA08	Isosorbide dinitrate
C01DA14	Isosorbide mononitrate
C01DX	Other vasodilators used in cardiac diseases
C01DX12	Molsidomine
C01DX16	Nicorandil
C01E	Other cardiac preparations
C01EA	Prostaglandins
C01EA01	Alprostadil
C01EB	Other cardiac preparations
C01EB03	Indometacin

C01EB09	Ubidecarenone
C01EB10	Adenosine
C01EB15	Trimetazidine
C01EB16	Ibuprofen
C01EB17	Ivabradine
C01EB18	Ranolazine
C01EB21	Regadenoson
C02	**Antihypertensives**
C02A	Antiadrenergic agents, centrally acting
C02AB	Methyldopa
C02AB01	Methyldopa (levorotatory)
C02AC	Imidazoline receptor agonists
C02AC01	Clonidine
C02AC05	Moxonidine
C02C	Antiadrenergic agents, peripherally acting
C02CA	Alpha adrenoreceptor antagonists
C02CA01	Prazosin
C02CA04	Doxazosin
C02CC	Guanidine derivatives
C02CC02	Guanethidine
C02D	Arteriolar smooth muscle, agents acting on
C02DB	Hydrazinophthalazine derivatives
C02DB01	Dihydralazine
C02DB02	Hydralazine
C02DC	Pyrimidine derivatives
C02DC01	Minoxidil
C02DD	Nitroferricyanide derivatives
C02DD01	Nitroprusside
C02K	Other antihypertensives
C02KD	Serotonin antagonists
C02KD01	Ketanserin

C02KX	Antihypertensives for pulmonary arterial hypertension
C02KX01	Bosentan
C02KX02	Ambrisentan
C02KX03	Sitaxentan
C02KX04	Macitentan
C02KX05	Riociguat
C03	**Diuretics**
C03A	Low ceiling diuretics, thiazides
C03AA	Thiazides, plain
C03AA01	Bendroflumethiazide
C03AA03	Hydrochlorothiazide
C03AA06	Trichlormethiazide
C03AB	Thiazides and potassium in combination
C03AB01	Bendroflumethiazide and potassium
C03B	Low ceiling diuretics, excl. Thiazides
C03BA	Sulfonamides, plain
C03BA04	Chlortalidone
C03BA05	Mefruside
C03BA08	Metolazone
C03C	High ceiling diuretics
C03CA	Sulfonamides, plain
C03CA01	Furosemide
C03CA02	Bumetanide
C03CA04	Torasemide
C03CB	Sulfonamides and potassium in combination
C03CB02	Bumetanide and potassium
C03CC	Aryloxyacetic acid derivatives
C03CC01	Etacrynic acid
C03D	Potassium sparing agents
C03DA	Aldosterone antagonists
C03DA01	Spironolactone

C03DA02	Potassium canrenoate
C03DA04	Eplerenone
C03DB	Other potassium sparing agents
C03DB01	Amiloride
C03DB02	Triamterene
C03E	Diuretics and potassium sparing agents in combination
C03EA	Low ceiling diuretics and potassium
C03EA01	Hydrochlorothiazide and potassium sparing agents
C03X	Other diuretics
C03XA	Vasopressin antagonists
C03XA01	Tolvaptan
C07	**Beta blocking agents**
C07A	Beta blocking agents
C07AA	Beta blocking agents, non selective
C07AA01	Alprenolol
C07AA02	Oxprenolol
C07AA03	Pindolol
C07AA05	Propranolol
C07AA06	Timolol
C07AA07	Sotalol
C07AA12	Nadolol
C07AB	Beta blocking agents, selective
C07AB02	Metoprolol
C07AB03	Atenolol
C07AB07	Bisoprolol
C07AB09	Esmolol
C07AB12	Nebivolol
C07AG	Alpha and beta blocking agents
C07AG01	Labetalol
C07AG02	Carvedilol
C07B	Beta blocking agents and thiazides

C07BB	Beta blocking agents, selective, and thiazides
C07BB07	Bisoprolol and thiazides
C07BB12	Nebivolol and thiazides
C08	**Calcium channel blockers**
C08C	Selective calcium channel blockers with mainly vascular effects
C08CA	Dihydropyridine derivatives
C08CA01	Amlodipine
C08CA02	Felodipine
C08CA03	Isradipine
C08CA05	Nifedipine
C08CA06	Nimodipine
C08CA13	Lercanidipine
C08CX	Other selective calcium channel blockers with mainly vascular effects
C08CX01	Mibefradil
C08D	Selective calcium channel blockers with direct cardiac effects
C08DA	Phenylalkylamine derivatives
C08DA01	Verapamil
C08DB	Benzothiazepine derivatives
C08DB01	Diltiazem
C09	**Agents acting on the renin angiotensin system**
C09A	Ace inhibitors, plain
C09AA	Ace inhibitors, plain
C09AA01	Captopril
C09AA02	Enalapril
C09AA03	Lisinopril
C09AA04	Perindopril
C09AA05	Ramipril
C09AA09	Fosinopril
C09AA10	Trandolapril
C09AA15	Zofenopril
C09B	Ace inhibitors, combinations

C09BA	Ace inhibitors and diuretics
C09BA02	Enalapril and diuretics
C09BA03	Lisinopril and diuretics
C09BA15	Zofenopril and diuretics
C09BB	Ace inhibitors and calcium channel blockers
C09BB02	Enalapril and lercanidipine
C09C	Angiotensin ii antagonists, plain
C09CA	Angiotensin ii antagonists, plain
C09CA01	Losartan
C09CA02	Eprosartan
C09CA03	Valsartan
C09CA04	Irbesartan
C09CA06	Candesartan
C09CA07	Telmisartan
C09CA08	Olmesartan medoxomil
C09D	Angiotensin ii antagonists, combinations
C09DA	Angiotensin ii antagonists and diuretics
C09DA01	Losartan and diuretics
C09DA02	Eprosartan and diuretics
C09DA03	Valsartan and diuretics
C09DA04	Irbesartan and diuretics
C09DA06	Candesartan and diuretics
C09DA07	Telmisartan and diuretics
C09DA08	Olmesartan medoxomil and diuretics
C09DB	Angiotensin ii antagonists and calcium channel blockers
C09DB01	Valsartan and amlodipine
C09DB02	Olmesartan medoxomil and amlodipine
C09DX	Angiotensin ii antagonists, other combinations
C09DX01	Valsartan, amlodipine and hydrochlorothiazide
C09DX03	Olmesartan medoxomil, amlodipine and hydrochlorothiazide
C09X	Other agents acting on the renin angiotensin system

C09XA	Renin inhibitors
C09XA02	Aliskiren
C09XA52	Aliskiren and hydrochlorothiazide
C10	**Lipid modifying agents**
C10A	Lipid modifying agents, plain
C10AA	Hmg coa reductase inhibitors
C10AA01	Simvastatin
C10AA02	Lovastatin
C10AA03	Pravastatin
C10AA04	Fluvastatin
C10AA05	Atorvastatin
C10AA06	Cerivastatin
C10AA07	Rosuvastatin
C10AA08	Pitavastatin
C10AB	Fibrates
C10AB01	Clofibrate
C10AB02	Bezafibrate
C10AB04	Gemfibrozil
C10AB05	Fenofibrate
C10AC	Bile acid sequestrants
C10AC01	Colestyramine
C10AC02	Colestipol
C10AC04	Colesevelam
C10AD	Nicotinic acid and derivatives
C10AD01	Niceritrol
C10AD02	Nicotinic acid
C10AD06	Acipimox
C10AD52	Nicotinic acid, combinations
C10AX	Other lipid modifying agents
C10AX02	Probucol
C10AX06	Omega 3 triglycerides incl. other esters and acids

C10AX09	Ezetimibe
C10B	Lipid modifying agents, combinations
C10BA	Hmg coa reductase inhibitors in combination with other lipid modifying agents
C10BA02	Simvastatin and ezetimibe
C10BA05	Atorvastatin and ezetimibe
H03A	**Thyroid preparations**
H03AA	Thyroid hormones
H03AA01	Levothyroxine sodium
H03AA02	Liothyronine sodium
H03AA03	Combinations of levothyroxine and liothyronine
H03AA04	Tiratricol
H03AA05	Thyroid gland preparations
M01A	**Antiinflammatory and antirheumatic products, non steroids**
M01AA	Butylpyrazolidines
M01AA01	Phenylbutazone
M01AB	Acetic acid derivatives and related substances
M01AB01	Indometacin
M01AB02	Sulindac
M01AB05	Diclofenac
M01AB15	Ketorolac
M01AB16	Aceclofenac
M01AB55	Diclofenac, combinations
M01AC	Oxicams
M01AC01	Piroxicam
M01AC06	Meloxicam
M01AE	Propionic acid derivatives
M01AE01	Ibuprofen
M01AE02	Naproxen
M01AE03	Ketoprofen
M01AE14	Dexibuprofen
M01AE17	Dexketoprofen

M01AE52	Naproxen and esomeprazole
M01AG	Fenamates
M01AG02	Tolfenamic acid
M01AH	Coxibs
M01AH01	Celecoxib
M01AH02	Rofecoxib
M01AH03	Valdecoxib
M01AH04	Parecoxib
M01AH05	Etoricoxib
M01AH06	Lumiracoxib
M01AX	Other antiinflammatory and antirheumatic agents, non steroids
M01AX01	Nabumetone
M01AX05	Glucosamine
M02A	**Topical products for joint and muscular pain**
M02AA	Antiinflammatory preparations, non steroids for topical use
M02AA07	Piroxicam
M02AA10	Ketoprofen
M02AA13	Ibuprofen
M02AA15	Diclofenac
M02AB	Capsaicin and similar agents
M02AB01	Capsaicin
M02AC	Preparations with salicylic acid derivatives
M02AX	Other topical products for joint and muscular pain
M02AX10	Various
N02A	**Opioids**
N02AA	Natural opium alkaloids
N02AA01	Morphine
N02AA03	Hydromorphone
N02AA05	Oxycodone
N02AA08	Dihydrocodeine
N02AA51	Morphine, combinations

N02AA55	Oxycodone, combinations
N02AA59	Codeine, combinations excl. psycholeptics
N02AB	Phenylpiperidine derivatives
N02AB01	Ketobemidone
N02AB02	Pethidine
N02AB03	Fentanyl
N02AB72	Pethidine, combinations with psycholeptics
N02AC	Diphenylpropylamine derivatives
N02AC01	Dextromoramide
N02AC03	Piritramide
N02AC04	Dextropropoxyphene
N02AC54	Dextropropoxyphene, combinations excl. psycholeptics
N02AD	Benzomorphan derivatives
N02AD01	Pentazocine
N02AE	Oripavine derivatives
N02AE01	Buprenorphine
N02AG	Opioids in combination with antispasmodics
N02AG01	Morphine and antispasmodics
N02AG02	Ketobemidone and antispasmodics
N02AG03	Pethidine and antispasmodics
N02AX	Other opioids
N02AX02	Tramadol
N02AX06	Tapentadol
N02AX52	Tramadol, combinations
N02B	**Other analgesics and antipyretics**
N02BA	Salicylic acid and derivatives
N02BA01	Acetylsalicylic acid
N02BA11	Diflunisal
N02BA51	Acetylsalicylic acid, combinations excl. psycholeptics
N02BB	Pyrazolones
N02BB01	Phenazone

N02BB02	Metamizole sodium
N02BB51	Phenazone, combinations excl. psycholeptics
N02BB54	Propyphenazone, combinations excl. psycholeptics
N02BE	Anilides
N02BE01	Paracetamol
N02BE05	Propacetamol
N02BE51	Paracetamol, combinations excl. psycholeptics
N02BE71	Paracetamol, combinations with psycholeptics
N02BG	Other analgesics and antipyretics
N02BG07	Flupirtine
N02BG08	Ziconotide
N02BG10	Cannabinoids

Descriptive statistics of the "supplementary" study population (other drugs than psychotropics)

S-Table 2 Descriptive statistics at baseline (2004) for individuals on medication and individuals both on medication and unemployed (study population) during the observation period (2005-2010). Gender distribution, age (mean and standard deviation (SD)) and proportion of individuals in each category. No missing on gender and age.

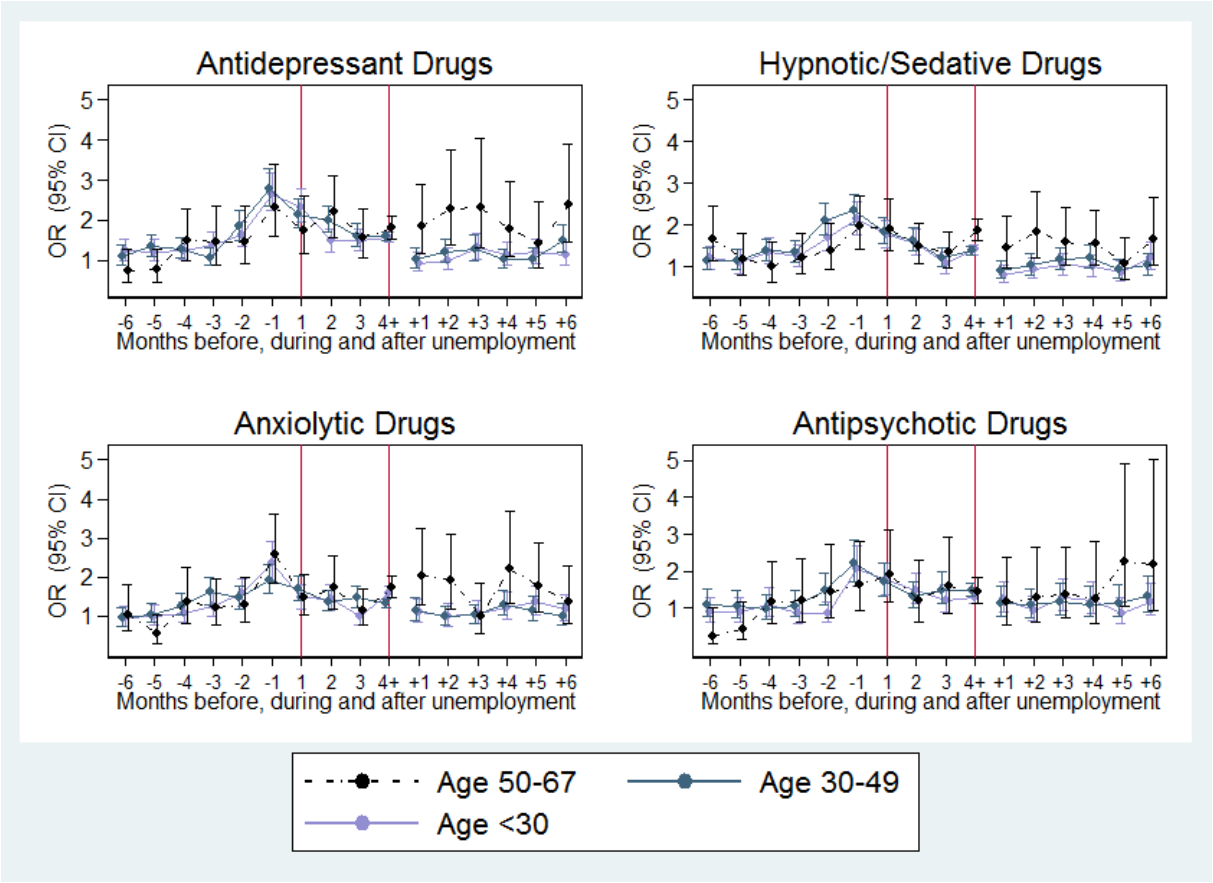
Baseline characteristics	**Anti-obesity drugs (A08)**	**A08 + unempl.**	**Anti-diabetic drugs (A10A)**	**A10A + unempl.**	**Heart therapy (C01+ C02+ C03+ C07+ C08+C09+ C10)**	**C01-C10 + unempl.**	**Thyroid therapy (H03A)**	**H03A + unempl.**	**Anti-inflammatory and anti-rheumatic drugs (M01A+M02A)**	**M01A+M02A + unempl.**
N	69 636	7577 (11)	82446	7085 (9)	582862	37015 (6)	101090	7 148 (7)	1509625	130032 (9)
Women (%)	52 376 (75)	5 795 (76)	32090 (39)	2910 (41)	261209 (45)	15735 (43)	81524 (81)	5685 (80)	739845 (49)	59449 (46)
Age (mean/SD)	39(11.2)	34 (10.1)	46 (11.8)	40 (12.0)	48 (10.5)	43 (11.6)	45(11.6)	38 (11.6)	40 (12.1)	35 (11.3)
Age cat. (%)										
18-29 years	14842 (21)	3045 (40)	9301 (11)	1575 (22)	34750 (6)	5344 (14)	11982 (12)	1822 (25)	326446 (21)	50046 (39)
30-49 years	40013 (58)	3895 (52)	35005 (43)	3606 (51)	244080 (42)	18720 (51)	18808 (48)	3845 (54)	780856 (52)	62912 (48)
50-67 years	14781 (21)	637 (8)	38140 (46)	1904 (27)	304032 (52)	12951 (35)	40300 (40)	1481 (21)	402323 (27)	17074 (13)
Education (%)										
Compulsory	17712 (25)	2849 (38)	19269 (23)	2406 (34)	121467 (21)	11686 (31)	18956 (19)	2050 (29)	335896 (22)	47386 (36)
Intermediate	34436 (50)	3334 (44)	40882 (50)	3121 (44)	291762 (50)	17653 (48)	46561 (46)	3052 (43)	715790 (47)	54016 (42)
Tertiary	15005 (22)	956 (12)	19657 (24)	1037 (15)	158531 (27)	5902 (16)	33196 (33)	1604 (22)	415297 (28)	20081 (15)
Missing (%)	2033 (3)	438 (6)	2638 (3)	521 (7)	11102 (2)	1774 (5)	2377 (2)	442 (6)	42642 (3)	8549 (7)

S-Table 2 (cont.) Descriptive statistics at baseline (2004) for individuals on medication and individuals both on medication and unemployed (study population) during the observation period (2005-2010). Gender distribution, age (mean and standard deviation (SD)) and proportion of individuals in each category. No missing on gender and age.

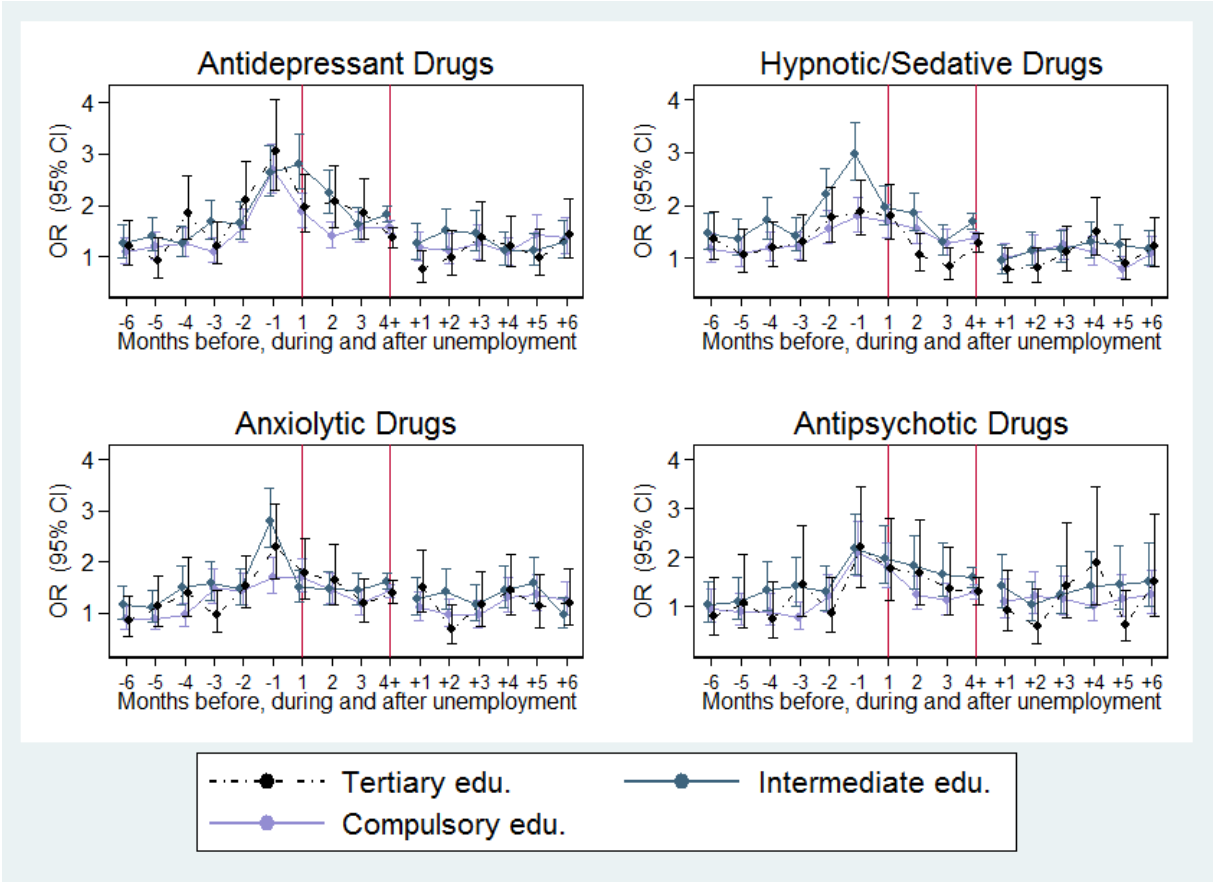
Baseline characteristics	**Opioids (N02A)**	**N02A + unempl.**	**Analgesics/ antipyretics (N02B)**	**N02B + unempl.**
N	939357	87301 (9)	469107	42518 (9)
Women (%)	454445 (48)	39358(45)	251132 (54)	21125 (50)
Age (mean/SD)	41(12.2)	35 (11.3)	42 (12.0)	36 (11.4)
Age cat. (%)				
18-29 years	199247 (21)	33616 (39)	78886 (17)	14372 (34)
30-49 years	477729 (51)	42352 (48)	239428 (51)	21753 (51)
50-67 years	262381 (28)	11333 (13)	150793 (32)	6393 (15)
Education (%)				
Compulsory	222486 (24)	33404 (39)	114966 (25)	16398 (38)
Intermediate	444198 (47)	35747 (41)	227336 (48)	17740 (42)
Tertiary	245383 (26)	12501 (14)	112703 (24)	5350 (13)
Missing (%)	27290 (3)	5649 (6)	14102 (3)	3030 (7)

Psychotropic drug purchase stratified by age and educational level

In order to reduce the number of figures in the paper, we present the stratified analyses of the main analysis in S-Figure 2 and S-Figure 3 below. The results are commented in the paper.



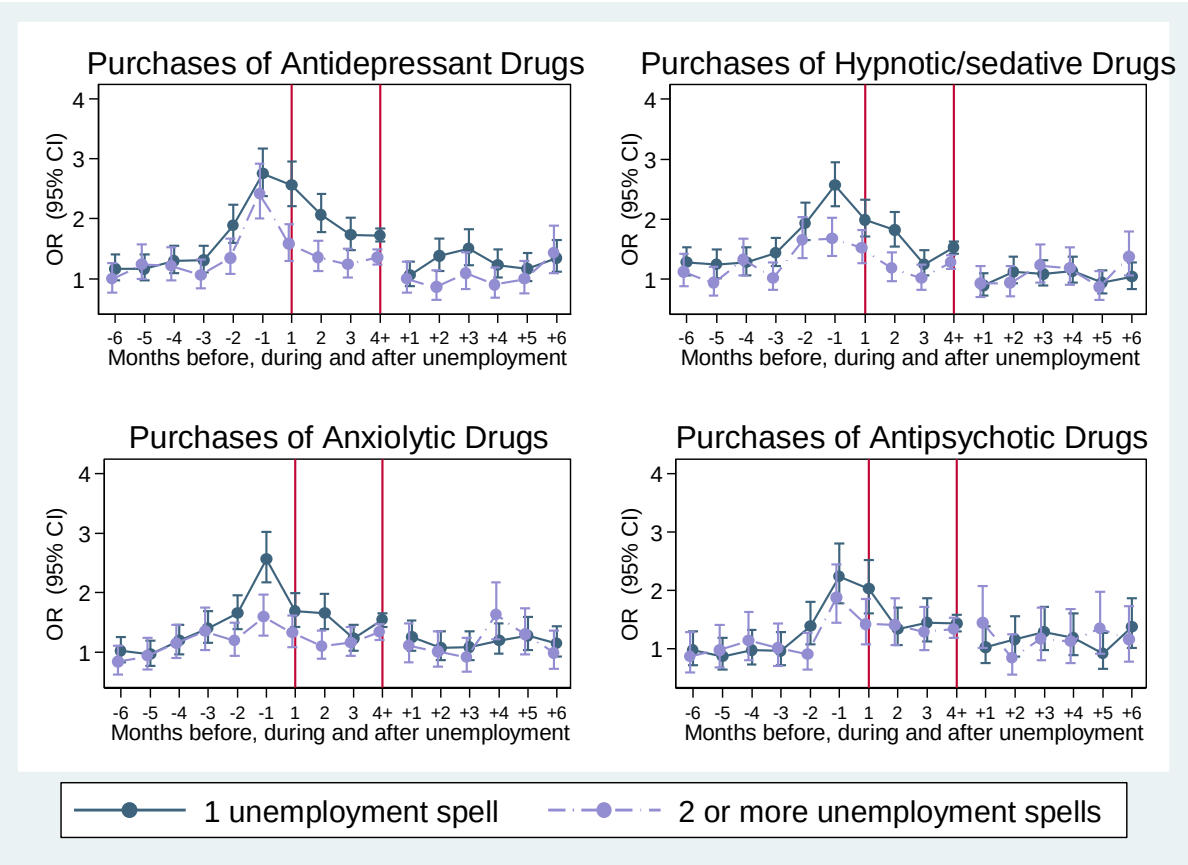
S-Figure 2 **Odds ratios (OR) with 95% Confidence Intervals (CI) of having a first purchase of antidepressants, hypnotic/sedative drugs, anxiolytic drugs and antipsychotic drugs, respectively, while being in a state of unemployment (1-6 months before, 1,2,3,4 or more months during (between vertical lines) and 1-6 months after the end of unemployment). Control periods = 12, 24 and 36 months before the date of drug purchase. Start of the observation period was January 1st 2005; the end was December 31st 2010. Stratified by age.**



S-Figure 3 **Odds ratios (OR) with 95% Confidence Intervals (CI) of having a first purchase of antidepressants, hypnotic/sedative drugs, anxiolytic drugs and antipsychotic drugs, respectively, while being in a state of unemployment(1-6 months before, 1,2,3,4 or more months during (between vertical lines) and 1-6 months after the end of unemployment). Control periods = 12, 24 and 36 months before the date of drug purchase. Start of the observation period was January 1st 2005; the end was December 31st 2010. Stratified by educational level.**

Unemployment frequency during the observation period (2005 to 2010)

As having repeated unemployment spells can be associated with deteriorated health (see main manuscript), we wanted to explore the effect of potentially having several unemployment spells during the observation period. We compared individuals with multiple unemployment spells with those only experiencing one episode of unemployment. The results are commented in the paper:



S-Figure 4 **Odds ratios (OR) with 95% Confidence Intervals (CI) of having a first purchase of antidepressants, hypnotic/sedative drugs, anxiolytic drugs and antipsychotic drugs, respectively, while being in a state of unemployment (1-6 months before, 1,2,3,4 or more months during (between vertical lines) and 1-6 months after the end of unemployment). Control periods are 12, 24 and 36 months before the date of drug purchase. Start of the observation period was January 1st 2005; the end was December 31st 2010. Stratified by 1 vs. 2 or more unemployment spells during the observation period.**

STROBE statement

The authors confirm that the STROBE checklist was followed in this article:

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Author: Study design(case-crossover) is included in the title
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Author: See abstract.**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Author: See sections one and two in the introduction.**
Objectives	3	State specific objectives, including any prespecified hypotheses **Author: See sections three, four and five in the introduction.**
Methods		
Study design	4	Present key elements of study design early in the paper **Author: See sections under the subheadings "Data provision" and "Design and study population". Also, see the illustration of the study design in S-table 1 in the supplementary file.**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Author: See sections under the subheadings "Data provision" and "Design**

		and study population"
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the 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 **Author: Case-crossover study: See sections under the subheadings "Data provision" and "Design and study population". Also, see figure 1.**
		(*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 **Author: In the case-crossover design, individuals are matched with themselves – at different times in life. See sections under the subheading "Design and study population"**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Author: See sections under subheadings "Outcome ascertainment" and "Exposure to unemployment". Confounding is commented in the first section under the subheading "Design and study population".**
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 **Author: All data was provided from national registries. See sections under subheading "Data provision".**
Bias	9	Describe any efforts to address potential sources of bias **Author: See first sections under subheadings "Design and study population" and "Main analysis".**
Study size	10	Explain how the study size was arrived at **Author: See sections under subheadings "Data provision", Design and study population". Also, see figure 1.**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Author: See sections under subheadings "Data provision", "Main analysis" and "Subgroup analyses"**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **Author: See sections under subheadings "Main analysis" and "Subgroup analyses"**
		(*b*) Describe any methods used to examine subgroups and interactions **Author: See section under subheading "Subgroup analyses". Also, see comments on stratified analyses in the supplementary file.**
		(*c*) Explain how missing data were addressed **Author: There were no missing data in the main analyses, as commented**

		in table 1.
		(*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 **Author: Case-crossover. Right censoring (loss to follow-up) was described under the subheading "Outcome ascertainment".**
		(*e*) Describe any sensitivity analyses **Author: Sensitivity/supplementary analyses are described under the subheading "Supplementary analyses".**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Author: See Figure 1 and Table 1.**
		(b) Give reasons for non-participation at each stage **Author: See "Design and study population" under Methods.**
		(c) Consider use of a flow diagram **Author: See Figure 1.**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Author: See Table 1 in the manuscript and S-Table 1 and S-Table 2 in the**

		supplementary file. Also, see the first section under "Results".
		(b) Indicate number of participants with missing data for each variable of interest Author: **See Table 1 in the manuscript and S-Table 2 in the supplementary file.**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) Author: Not relevant in a case-crossover. The observation period was 2005 to 2010, as described in the second section under the subheading "Design and study population".
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 **Author: Case-crossover study – all study participants are both exposed and have the outcome, as described in "Methods" under the subheading "Design and study population" and in Figure 1.**
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	*(a)* Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Author: See the second section under "Results". Also, see Figure 2-4 providing odds rations with 95% confidence intervals.**
		(b) Report category boundaries when continuous variables were categorized **Author: See Table 1.**
		(c) If relevant, consider translating estimates of relative risk into absolute risk

		for a meaningful time period **Author: Not relevant.**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **Author: See Figure 3-4 in the manuscript and S-Figure 2-4 in the supplementary file.**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Author: See section one under "Discussion".**
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 **Author: See subheading "Strengths and limitations".**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Author: See subheadings **"Strengths and limitations", "Previous studies" and "Interpretation".**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Author: See section under subheading "Context and generalizability"**
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 **Author: See section under subheading "Funding".**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.