UiT The Arctic University of Norway

Faculty of Health Sciences - Department of Community Medicine

SSRI-use, depression, and socioeconomic status among Norwegian adult women – A cross-sectional study with data from the NOWAC-study

Natalie Waag

Master's thesis in Public Health…HEL-3950…December 2022

Supervisor: Marko Lukic

Co-supervisor: Anne Elise Eggen

Foreword

I am grateful to my family, friends and supervisor for their encouragement throughout the process of working on this thesis. Their belief in my abilities kept me motivated and focused during a difficult year.

I would like to express my sincere appreciation to my supervisor, Marko Lukic, for his guidance, support and feedback throughout this process. His expertise and insight have been invaluable in helping me to complete this thesis.

Though the results from my research were not groundbreaking and in many ways were consistent with previous and similar studies, I hope that the insights gained from this work will be useful to others.

Natalie Waag
December 2022

Abstract

Introduction

Depressive disorders affect a significant part of the population, and its effects can be debilitating. Such disorders have a higher prevalence among women and previous studies have shown that there is a consistent association between SES and depression, and between SES and SSRI-use. The primary aim of this cross-sectional study was to investigate the association between SES and the use of SSRIs among adult Norwegian women recruited to the NOWAC-study. The association between SES and depression was also explored. SES refers specifically to education and gross household income.

Methods

Data was provided from the second and third wave of the NOWAC-study with 62 388 participants after exclusion. Descriptive statistics were used to present the prevalence of SSRI-use and depression according to education, income and other health and lifestyle factors. Logistic regression analysis was used to calculate the odds ratios for SSRI-use and depression according to education and income.

Results

Regarding descriptive statistics, 4.7% reported current use of SSRIs, while the prevalence of current and former depression was 15.5%. In the age-adjusted models the odds of using SSRIs were almost twice as large for the lowest education group (OR 1.95, 95% CI 1.72-2.21) compared to the highest education group (OR 1.15, 95% CI 1.02-1.29), while the odds of using SSRIs were 4.59 times higher for the lowest income group (95% CI 3.87-5.45) compared to the second highest income group (OR 1.15, 95% CI 1.02-1.29). The association between education and depression was considerably less apparent in both models compared to the association between education and SSRI-use. For income, the odds of having depression increased threefold for those in the lowest income group (OR 3.24, 95% CI 2.92-3.61) compared to those in the second highest income group (OR 1.16, CI 95% 1.06-1.27).

Conclusion

There was a clear inverse social gradient in all outcomes. The association between income and SSRI-use and income and depression was prominent, while the association between education and SSRI-use and education and depression was less apparent.

Keywords

Depression, SSRI, antidepressants, SES, socioeconomic status, social gradient

Abbreviations

CI: Confidence interval

DAG: Directed acyclic graph

NOWAC: Norwegian Women & Cancer

OR: Odds ratio

SES: Socioeconomic status

SPSS: Statistical Package for the Social Sciences

SSRI: Selected serotonin reuptake inhibitor

Table of Contents

List of tables

List of Figures

1 Introduction

1.1 Mental disorders and depression

Mental health issues and depressive disorders are some of the larger challenges faced in healthcare today. Depression affects over a quarter of a billion people worldwide and is one of the leading causes of disability. Depressive disorders contribute significantly to the global disease burden, and the more severe depressive disorders can have a crippling effect on those who are impacted (1). Depression causes several psychological symptoms, the most prominent including feelings of sadness and emptiness, issues with self-esteem and guilt, loss of interest in activities that were previously enjoyable and suicidal ideation. Symptoms can also be somatic in nature, such as reduced energy, sleep issues and loss of appetite, and patients will generally experience a mix of psychological and somatic symptoms. Depending on symptom profile, severity and duration, depression is usually classified as either mild, moderate, or severe (2). The etiology of depression is complex, and it is commonly associated with social and biological factors such as deprivation, trauma, abuse, illness, age, and gender (1).

The prevalence and incidence of depression in a population can be challenging to measure, as depressive disorders do not have reliable biomarkers and many of those who exhibit symptoms do not reach out to healthcare services for aid. Furthermore, different methodologies and measurement criteria will yield different results. According to the Norwegian Institute of Public Health, in one year, one in ten will experience a depressive disorder, and one in five will experience a depressive disorder during their lifetime (3). In a cross-sectional study on self-reported depression in the Norwegian population, 9.8% of women answered that they had an ongoing depression while the corresponding number for men was 6.8% (4). Another factor to keep in mind is that for many patients, depression is highly recurrent, and for some patients it develops into a chronic condition. Whatever methodology one chooses when measuring depression prevalence, from available research it is apparent that depressive disorders affect a significant part of the population.

1.2 Antidepressants and SSRIs

Medication is a common treatment for depressive symptoms, preferably alongside some type of therapy. Research shows that the greatest benefit for patients suffering from depressive disorders is achieved through approaches where pharmacotherapy and psychotherapy are combined (5, 6). There are several subcategories of antidepressants, among them selective

serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants. Some of these drugs can be prescribed for conditions other than depression, such as anxiety disorders, sleep disorders, eating disorders, premenstrual dysphoric disorders and chronic pain (7). In this thesis, antidepressant utilization refers specifically to the use of SSRIs. In 2020, SSRIs constituted approximately half of total antidepressant use among women of all ages (8).

The way SSRIs work is not completely understood, but it is thought that they prevent a process in the brain referred to as reuptake. Serotonin is a neurotransmitter, which is a chemical that enables communication between neurons. Reuptake occurs when a neuron cell absorbs serotonin, a substance which it originally produces and then releases. When reuptake is prevented, the level of serotonin in the brain increases, and it is thought that this increase alleviates depressive symptoms. SSRIs have fewer adverse side-effects than older antidepressants and they are generally the first choice regarding treatment of depression. Common side-effects, especially during the first weeks of use, include indigestion, constipation, agitation, lethargy, and headaches (9). For some users, there are adverse long-term effects, with sexual dysfunction and weight gain cited as the most common ones (10, 11). Long-term use can also precipitate sexual dysfunction after treatment has ended (12, 13). Pharmacotherapeutic treatment of patients with depressive disorders is not a one-size-fits-all approach and usually requires a process of trial-and-error when choosing which SSRI to administer, and subsequently adjusting the dose.

In the last decades the consumption of antidepressants has increased globally (14), and is likely to continue increasing in the coming years. According to information from the Norwegian Prescription Database, antidepressant prescription rates have gone up among the general population, from 60.77 users per 1000 inhabitants in 2010 to 65.61 users per 1000 inhabitants in 2020. The total number of users receiving prescriptions for antidepressants was 297 119 in 2010, and 352 951 in 2020. As for antidepressant use by sex, in 2010, 7.9% of women were receiving antidepressant prescriptions, while the corresponding number for men was 4.2%. In 2020, 8,7% of women were receiving antidepressants as treatment for depression, while the corresponding number for men was 4.5%. When looking specifically at SSRI-use by sex, in 2010, 4.9% of women received SSRI-prescriptions, compared to 2.5% of men. In 2020 the corresponding figures were 4.6% for women and 2.3% for men (8). So even though general antidepressant use in Norway has increased, similarly to international trends, SSRI-use has had a slight decrease from 2010 to 2020 (see the appendix for all figures provided in this paragraph).

1.3 Serotonin imbalance theory of depression

When researching SSRI-use and depression, it is of interest to note that SSRIs and their effectiveness in treating depression have been contested in scientific literature, the press, and social media for years. It is safe to say that there is still a certain level of stigma and controversy attached to these medications, while at the same time there is more social acceptance of mental illness and the necessity of treatment (15, 16). Much of the debate has centered around the serotonin imbalance theory of depression. This theory was developed in the 1950s and 1960s by numerous researchers and gained traction in the following years, so much so that the ensuing development of antidepressants and SSRIs completely changed both the field of psychiatry and pharmaceutical companies (17). The main tenet of the theory is that depressive disorders are caused by a chemical imbalance in the brain. As an alternative to stringent biomedical models, in the 1970s the biopsychosocial model was developed to better understand the complexities of somatic and mental illnesses. The point of that model was a holistic approach, where biological, psychological, and social factors were considered while studying disease. The biopsychosocial model did not deny biological mechanisms, rather it subsumed them into a larger multidimensional framework. Both models played a prominent part in modern psychiatry, and they have dominated the cultural narrative on depression treatment at different times. Both models have also received their fair share of criticism (18).

In a systematic review that was published this summer and that received a lot of attention in the press (19), the authors concluded that there was no link between low levels of serotonin in the brain and depression, and they suggested that the serotonin imbalance theory of depression should be rejected. Two of the authors stated in a second article published a few months later that SSRIs were not beneficial against depression, and that the field of psychiatry was guilty of endorsing a theory of depression that lacked proper empirical basis (20).

Several psychiatrists and researchers have responded to both articles, stating that the chemical imbalance theory has mostly been rejected, or that its presentation for laypeople has been oversimplified. Others have noted that the belief that modern psychiatry adheres to or has ever adhered to a single cause-theory regarding depression is a myth. Most psychiatrists endorse some version of the biopsychosocial model, and they would argue that depression is multicausal and complex, and that there are several ways to treat depression, both with and without SSRIs. However, looking into the past, the chemical imbalance theory was actively used by pharmaceutical companies to market their respective products, especially in the 90s

and early 2000s (20, 21). Other critics have stressed that the abovementioned systematic review only looked at the association between serotonin levels and depression and did not explore how SSRIs affected depression. As for the efficacy of SSRIs, randomized controlled trials and systematic reviews have demonstrated that there is a small, but positive effect when compared with placebo (22, 23).

1.4 Socioeconomic status and the social gradient

Socioeconomic status (SES) is a measure of a person's social standing, and it is used in many fields of research to gauge a person's "differential access (realized and potential) to desired resources" (24). In health research SES is frequently used to identify inequalities in health outcomes and inequities in distribution of healthcare services. Researchers use SES to measure in what way it is related to a certain outcome, and it can also be used as a control variable when researching other associations of interest. The way SES is measured is not standardized, but variables such as education, income and occupation are typically included in the analysis. Other variables of interest can include self-reported socioeconomic status and parents' education and income levels. Some researchers choose to construct a composite SES-variable to use in their analysis, while other researchers investigate associations for separate variables such as income and education, particularly in regression analysis (24). In this thesis SES refers specifically to participants' education or income level.

The social gradient in public health refers to the relationship between SES and health outcomes. It is well-established in scientific literature that people with lower SES tend to have worse health outcomes, such as shorter life expectancy and increased morbidity rates, than those with higher SES. This relationship is often referred to as the "social gradient" because it typically follows a gradient or slope, with health outcomes worsening as SES decreases. The social gradient is also apparent when examining how healthcare services are utilized. In 2021, Statistics Norway published a report which indicated many of these inequities (25). For example, groups with high education and income were more prone to use the services of medical specialists, physical therapists, and dentists, while lower education and income groups were more likely to utilize general practitioners and receive inpatient care. The proportion who had received inpatient care decreased for each increase in income. Disparities were also observed regarding vaccination. Among people taking the flu shot, most were in higher income brackets, also when the researchers adjusted for participants' health condition.

For women specifically, a social gradient according to education and income was observed when surveying which patients were getting a mammography or a pap-smear.

1.5 Distribution of depression

Disparities in mental health problems among different socioeconomic groups have been demonstrated previously in the literature. There is a consistent association between lower SES and higher rates of depression prevalence. A Norwegian longitudinal study with repeated measurements, examined national trends among adolescents and found such disparities in mental health with no significant changes over the years in how these disparities were distributed (26). Likewise, similar trends in other countries are found in numerous studies and systematic reviews (27-30).

1.6 Distribution of antidepressant prescriptions

The existence of inequalities in healthcare utilization is also well-established in the literature, and the distribution of antidepressant prescriptions is no exception. In a Norwegian study from 2020, the authors looked at new depression diagnoses in 2015 among the general population, and then checked for antidepressant prescriptions dispensed within 12 months of diagnosis. One of the independent variables they used was education, and they found that women with lower education were more likely to receive a prescription compared with women with higher education. Similar differences were not found among men (31). In a separate report on social inequalities in healthcare utilization, the authors found that antidepressant consumption was higher in groups with lower SES (32). In a longitudinal study on young Norwegian adults (33), the authors found that low SES was linked with increased antidepressant prescription rates. This was apparent for all indicators of SES, except for parents' level of education. Similar results have been observed in research from other countries (34-37).

1.7 Basis for thesis, objective, and research question

The relationship between SES and SSRI-utilization is not fully understood, though a higher prevalence of depressive disorders and other mental illnesses among lower SES-groups partly explains why there are also higher antidepressant prescription rates in these groups. As women generally have higher rates of SSRI-use than men, and differences in use between SES-groups have been identified in other studies, it is of interest to assess this association with data from a representative sample of adult Norwegian women. As a secondary goal, it is of interest to analyze the association between SES and depression.

By using data from the NOWAC-study, this cross-sectional study aims to explore the relationship between SES and the use of SSRIs among women above the age of 45. This will be the first time such a study is undertaken with a representative sample of adult Norwegian women. As the use of SSRIs and depression prevalence are so closely entwined, this thesis will also attempt to ascertain the relationship between SES and depression in the same cohort. My research questions therefore are as follows:

Primary objective:

What is the relationship between socioeconomic status and the use of antidepressants among adult women, aged 46 - 64, living in Norway?

Secondary objective:

What is the relationship between socioeconomic status and depression in the same population?

2 Materials and methods

2.1 Study population and data collection

The NOWAC-study is a prospective cohort study, with data collected for the first time in 1991. The objective of that study was primarily cancer research, with a focus on examining possible associations between the use of oral contraceptives and breast cancer. Over 300 000 women have been invited to participate in the study, and of these, 170 000 women, aged 30 to 70 years, have been recruited to this day. The women who participated in NOWAC were recruited at random from the Norwegian Central Person Register (38).

In addition to questions on SSRI-use and socioeconomic factors, the questionnaire includes queries on menstruation, menopause, pregnancy, breastfeeding, hormone therapy, contraceptives, morbidity, nutrition, tobacco and alcohol use, levels of physical activity and sunbathing habits.

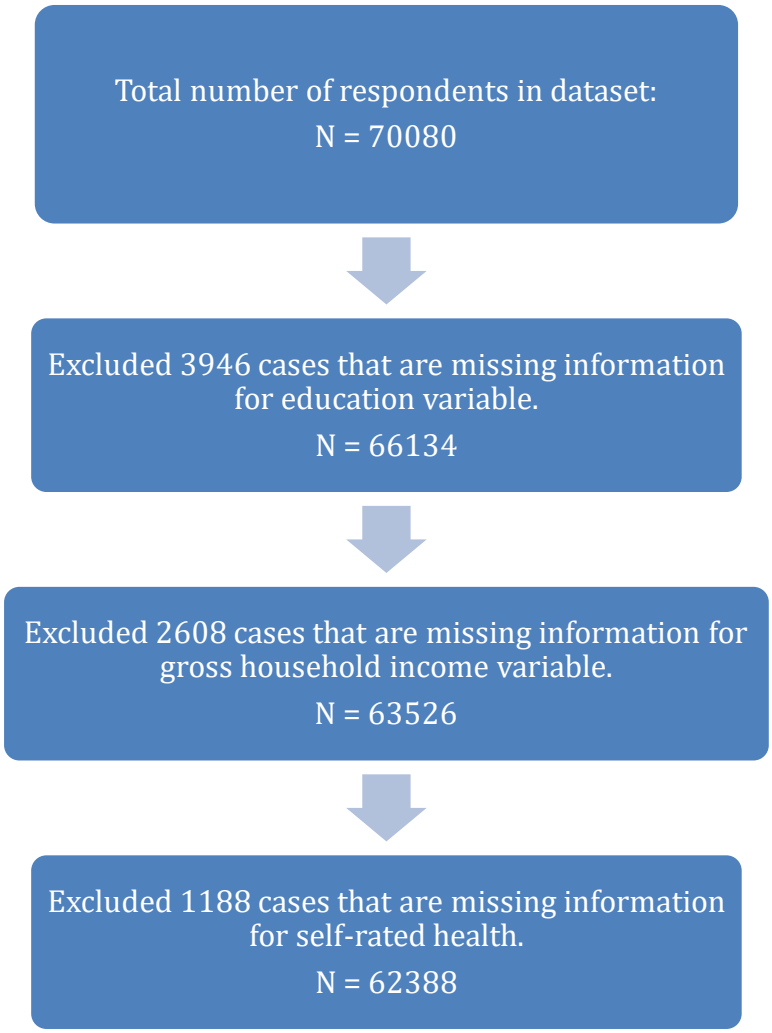
The NOWAC-study has been conducted in four waves. In this thesis, the analysis used data from the second and third waves only, as the questionnaire from the first wave did not contain questions on SSRI-use and data from the fourth wave was not ready at this time. Furthermore, the NOWAC-study has included follow-up questionnaires every five years approximately. The analysis in this cross-sectional study made use of data from the first questionnaire in the second and third waves, and no data from the follow-up questionnaires.

The second wave was conducted from 2003 - 2006, and here 130 577 women were invited to participate, and of these, 63 232 were recruited. The third wave was conducted in 2007 and 6 711 women were recruited. The response rate at baseline for the first three waves was 52.7% (38).

2.2 Criteria for inclusion or exclusion

As for inclusion criteria, participants must have answered questions concerning antidepressant use, income, education, marital status, and self-rated health in the questionnaire. Cases with missing data for these variables were removed from the dataset.

Figure 1: Flow chart for excluded cases in dataset.



The variables for depression and marital status were also checked for missing data, but both included information for all cases at N = 62388.

2.3 Variables

In total, 55 variables were included in the NOWAC-dataset.

2.3.1 Outcome

The first outcome variable of interest was SSRI-use, which was measured in two ways, current use at time of questionnaire response and ever-use. Respondents were also asked about duration of use, both currently and in the past. The questions and response options were phrased like this:

Other medication

Do you currently use any of these preparations daily? Yes/No

Fontex, Fluoxetin

Cipramil, Citalopram, Desital

Seroxat, Paroxetin

Zoloft

Fevarin

Cipralex

If Yes; for how long time have you used this preparation continuously? Months..... Years.....

Have you ever used any of these preparations? Yes/No

If Yes; For how long time did you use these preparations continuously? Months..... Years.....

Fontex and Fluoxetin are different brands but with the same active ingredient, and this similarly applies to the second and third rows of SSRIs above. For the analysis, the six dichotomous variables referring to current use of any of the abovementioned medications were recoded into one single dichotomous variable signifying current use or non-use of SSRIs.

The secondary outcome of interest was depression. In the questionnaire the response options were yes or no to ever having experienced depression, phrased like so:

Disease

Do you have or have you ever had any of the following diseases? Yes/No

	Yes	No
Cancer		
High blood pressure		
Heart failure		
Heart attack		
Stroke		
Diabetes		
Depression		

Depression was coded as a dichotomous variable for the analysis.

2.3.2 Exposure

The exposure variables were income and education. In the questionnaire the response options on income were divided into six subgroups, while education was measured as the number of years spent at school. Those questions were phrased like this in the questionnaire:

Social conditions

How many years of school, including higher and lower education, do you have in total?

What is your yearly gross income?

Under 150.000 kr.	151.000-300.000 kr.
301.000-450.000 kr.	451.000-600.000 kr.
601.000-750.000 kr.	Over 750.000 kr.

For the analysis, the continuous variable referring to length of education was recoded into a categorical variable with four categories: Equal to or under 9 years, 10 – 12 years, 13 – 16 years and finally equal to or over 17 years. The group with the highest education was coded as the reference category for the regression analysis.

Gross household income was coded as a single categorical variable, with the six categories referring to the six income brackets as seen above. The group with the highest income was coded as the reference category for the regression analysis.

For this thesis, the exposure variables were not merged into a composite variable but used separately in statistical models.

2.3.3 Covariates

2.3.3.1 Age

Age is a possible confounder when analyzing the association between SES and SSRI-use and SES and depression, as both outcomes tend to have a higher prevalence among young women and some groups of seniors. For the analysis, age was calculated from data on year of birth, which was originally retrieved from the Norwegian Central Person Register.

2.3.3.2 Marital status

For the analysis, marital status was coded as a dichotomous variable. Married included those cohabiting, while not married included divorcees and widows. This variable was calculated by recoding five dichotomous variables from the dataset: Married, cohabiting, unmarried, divorced and widow.

2.3.3.3 Self-rated health

NOWAC includes information on comorbidities and other lifestyle factors, many of which are associated with symptoms of depression and poor mental health. To simplify the statistical regression model, self-rated health was used as a proxy for comorbidities and lifestyle factors,

such as smoking and BMI. Though it is a subjective measure, research has demonstrated that it is a highly valid and reliable measure of health (39). It can capture nuances that a so-called objective outside observer might not perceive. A person with a chronic disease might rate their health as good, due to their quality of life being satisfactory despite having a chronic disease. In the same way, someone with an invisible illness like an autoimmune disease or mental illness, might rate their health as very poor, though to an outsider they would appear to be in perfect health. In the dataset, self-rated health was coded as a categorical variable with four categories: very good, good, poor, and very poor. Very good was coded as the reference category for the regression analysis.

2.3.3.4 Education

As earlier mentioned, the exposure variables were used separately in two statistical models. In the second model where income was the main exposure, education was treated as a potential confounder. The highest education level was coded as the reference category.

2.3.4 Lifestyle factors

The lifestyle variables referring to smoking status, alcohol abstinence, BMI and physical activity were not used in the final regression models, but they were included in the first part of the analysis concerning descriptive statistics. Cases with missing data on these four variables were not removed from the dataset. Smoking status was coded as a categorical variable with three categories: never, former, and current smoker. Alcohol abstinence was coded as a dichotomous variable. The variable for BMI was calculated from the variables for height and weight, and then recoded into a categorical variable with the following categories: underweight (18.5 or less), normal weight (18.5 to <25), overweight (25.0 to <30) and obese (30.0 or higher). Physical activity was coded as a categorical variable with three categories: low, medium, and high.

2.3.5 Directed acyclic graphs and sensitivity analysis

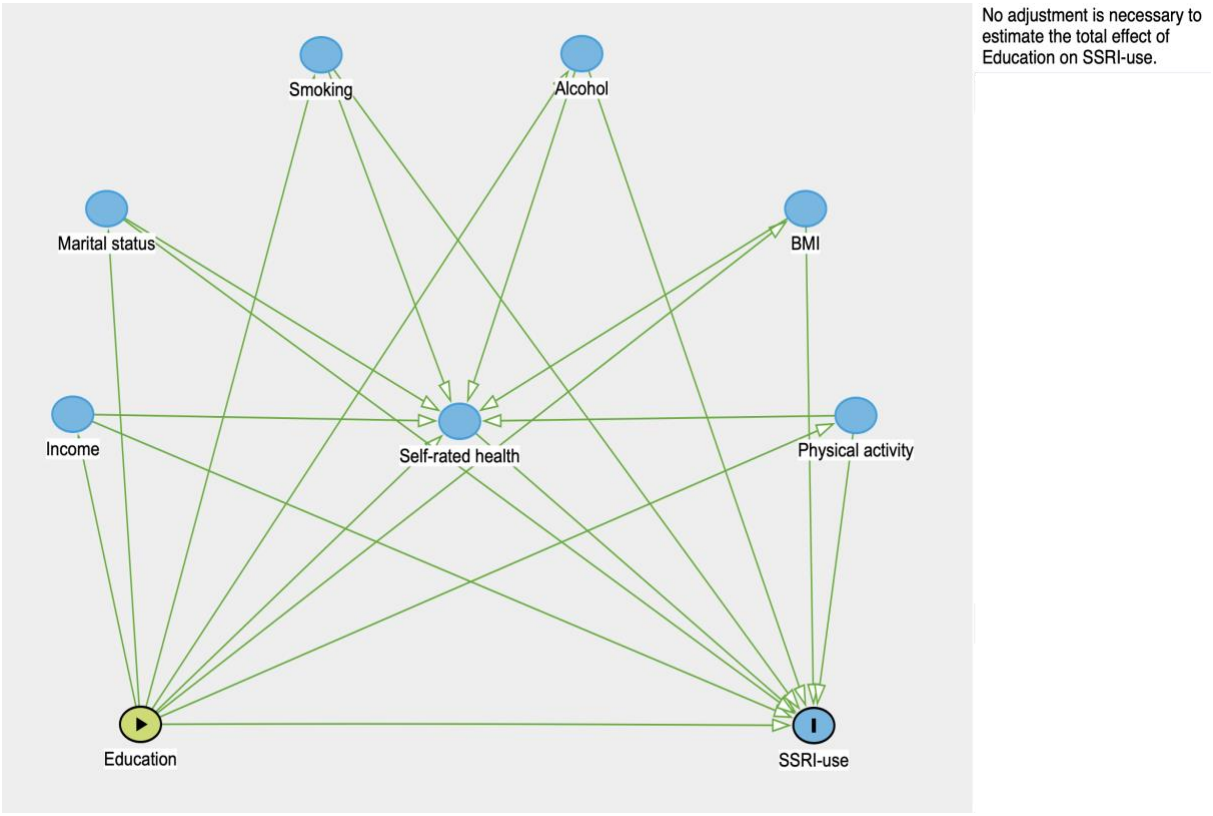
Depression, SSRI-use, and SES are complex topics, and they are all associated with many risk factors, something which can make it challenging to ascertain the direction of an effect when building a statistical model. What compounds this difficulty is that the NOWAC-study contains a wealth of information, so choosing the appropriate variables for the statistical models required some planning. To systematically determine which variables to be included in the analysis, and whether they should be identified as having a confounding or mediating effect or other role, several directed acyclic graphs (DAGs) were created using DAGitty's

online software. DAGs are a tool increasingly used in health research to help visualize and analyze causal structures and separate confounders, mediators, and colliders (40).

In the first DAG presented here, education was the exposure variable and SSRI-use was the outcome. By looking at relevant literature, it was determined that all the independent variables in the DAG could be associated with both the exposure and the outcome (10, 41-45). Furthermore, it was assessed that it was more likely that they were in the causal pathway between the exposure and the outcome, hence it would not be necessary to adjust for them in the regression analysis.

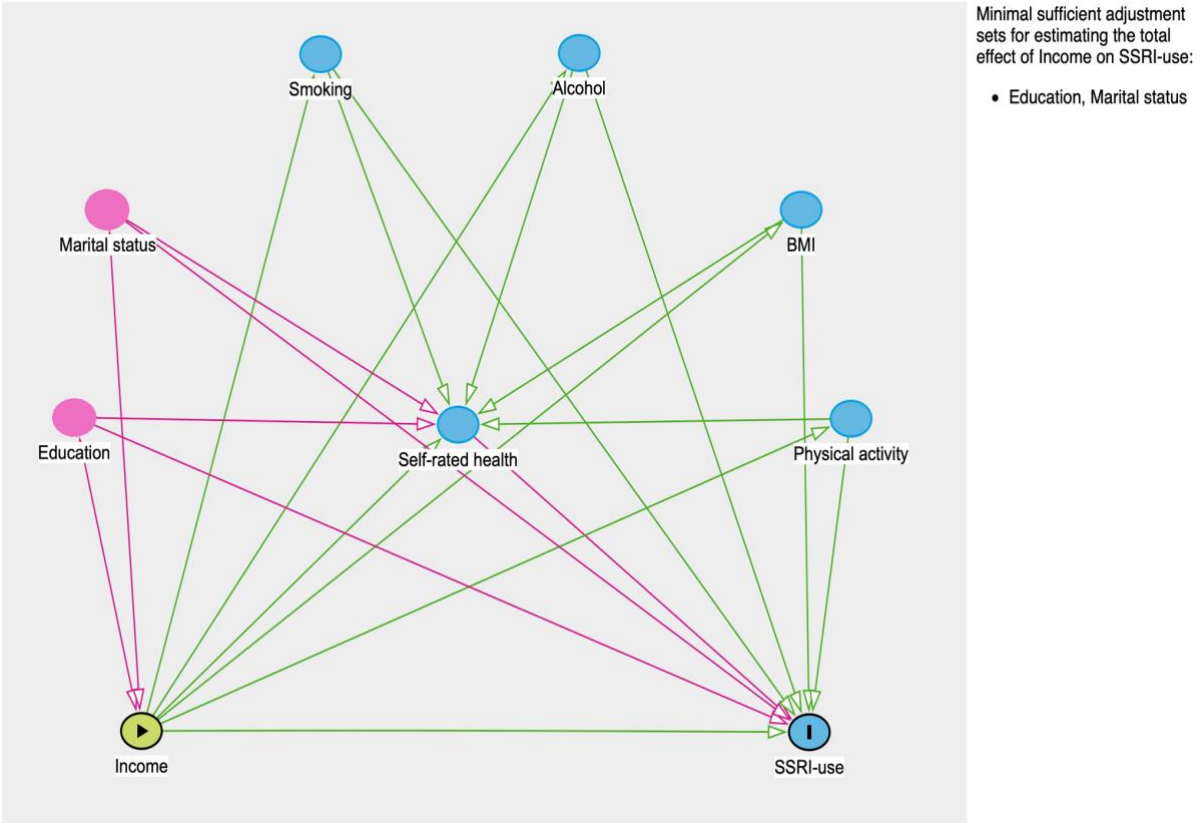
Nevertheless, in epidemiological research and especially cross-sectional studies, one can never be sure about the relationship between variables, and one must rely on assumptions. However, there are ways to examine these assumptions. Sensitivity analysis is a method used in statistical research to evaluate how sensitive the results of a study are to changes in the assumptions and inputs that are used in the analysis. This can help researchers determine the robustness of their results and identify potential sources of uncertainty or bias. Sensitivity analysis can also be used to identify the most important factors or variables that may have the greatest impact on the results of a study (46). The variable self-rated health could be used as a proxy for other lifestyle factors, and in this thesis, as part of the sensitivity analysis, adjustments were made for that variable in the last statistical model to see how this affected results.

Figure 2: DAG representing the relationship between education and SSRI-use, with possible confounders including income, marital status, smoking, alcohol use, BMI, physical activity, and self-rated health.



In the second DAG, income was the exposure variable, while SSRI-use was the outcome. Education was thought to be a confounder as it affects what kind of employment one gets, and therefore how much income. Marital status was also considered to be a confounder, as a marriage or cohabitation will often significantly increase a person's household income, and gross household income was the measurement used in the NOWAC-study. As these two variables were deemed to be confounders in this DAG, it was necessary to adjust for them in the regression analysis. A sensitivity analysis with education as the exposure and with adjustment for self-rated health was conducted to check any impact on the results.

Figure 3: DAG representing the relationship between income and SSRI-use, with possible confounders including education, marital status, income, smoking, alcohol use, BMI, physical activity, and self-rated health.



Assessing relevant literature regarding depression produced similar results to those above, and it was inferred that the independent variables were most likely to be in the causal pathway between the exposure and outcome (47). Consequently, using depression as the outcome instead of SSRI-use produced the same DAGs as those presented above with SSRI-use as the outcome. A sensitivity analysis was conducted with adjustment for self-rated health.

2.4 Statistical analysis

Descriptive statistics were used for the first part of the analysis, to present the prevalence of SSRI-use and depression among women participating in the NOWAC-study. Prevalence of SSRI-use and depression was calculated according to education, gross household income, marital status, self-rated health, smoking status, alcohol abstinence, BMI, and level of physical activity. The results for SSRI-use are presented in Table 1 and the results for depression are presented in Table 2.

For the second part of the analysis, logistic regression was used to determine the association between education and SSRI-use, income and SSRI-use, education and depression and

income and depression. Odds ratios (ORs) with 95% confidence intervals (CI) were calculated for SSRI-use according to education or income, and depression according to education or income. Model 1a included education as the exposure, while adjusting for age. In model 1b adjustments were additionally made for self-rated health. Model 2a included income as the exposure, while adjusting for age. Model 2b adjusted for education and marital status while model 2c also adjusted for self-rated health. This process was repeated with depression as the outcome. P-values lower than 0.05 were considered statistically significant. The analysis was done using IBM SPSS statistics, version 28 (48).

2.5 Ethical aspects and data storage

The collection of data for the NOWAC-study was approved by The Norwegian Data Protection Authority and The Regional Committees for Medical and Health Research Ethics (38). The dataset was stored on my laptop while I worked on the thesis and will be deleted once the thesis is submitted and graded.

3 Results

3.1 Descriptive statistics

The total number of participants in the sample was 62388 women, and of these, 4.7% reported current use of SSRIs (table 1). Participants had a mean age of 54.1, while the difference in mean age between those using and not using antidepressants was negligible. As for education, 52.3% of the participants belonged in the higher education groups, 13 – 16 years and 17 years, respectively. As for current SSRI-use by education level, from 10 – 12 years with increasing education levels, the proportion using SSRIs declined, from 35.1% to 27.9% to 16.2%. With respect to gross household income, over half the population sample, 53.6%, were in the three highest income brackets. Of those using SSRIs, 64.3% were in the three lowest income brackets. Regarding marital status, a substantial proportion, 77.4% of participants were married or cohabiting. For self-rated health, most participants, 92.5% rated their health as good or very good. SSRI-use was excessively prevalent among those with poor and very poor self-rated health.

The last part of the table contains data on lifestyle factors that were not used in the final model. Regarding smoking, 24.9% of the population sample smoked currently, and the proportion of those using SSRIs was larger for former and current smokers (36.4% and 38.6%), compared to never smokers (25.1%). For alcohol abstinence, 8% of the population sample described themselves as abstinent. As for BMI, 55.4% of participants were in the healthy weight category (18.5 to <25). 55.9% of those using SSRIs were in the overweight and obese categories. For physical activity, 70% had a moderate level of physical activity. 86.6% of those using SSRIs were in the moderate and low categories for physical activity, while the corresponding number for those not using SSRIs was 79,6%.

Table 1: Selected characteristics of participants according to use of SSRIs in the NOWAC-study.

Characteristics	**No current use of**	**Current use of**	**Total sample**
Participants, n (%)	59479 (95.3)	2909 (4.7)	62388 (100)
Age at baseline (y), mean (SD)	54.1 (4.4)	54.3 (4.4)	54.1 (4.4)
Education level, n (%)			
≤ 9 years	8264 (13.9)	607 (20.9)	8871 (14.2)
10 - 12 years	19874 (33.4)	1020 (35.1)	20894 (33.5)
13 - 16 years	18817 (31.6)	812 (27.9)	19629 (31.5)
≥ 17 years	12524 (21.1)	470 (16.2)	12994 (20.8)
Gross household income, n (%)			
< NOK 150 000,-	2342 (3.9)	279 (9.6)	2621 (4.2)
NOK 151 000 – 300 000,-	10096 (17.0)	770 (26.5)	10866 (17.4)
NOK 301 000 – 450 000,-	14671 (24.7)	819 (28.2)	15490 (24.8)
NOK 451 000 – 600 000,-	12968 (21.8)	515 (17.7)	13483 (21.6)
NOK 601 000 – 750 000,-	8228 (13.8)	236 (8.1)	8464 (13.6)
> NOK 750 000	11174 (18.8)	290 (10.0)	11464 (18.4)
Marital status, n (%)			
Married	46285 (77.8)	1975 (67.9)	48260 (77.4)
Not married	13194 (22.2)	934 (32.1)	14128 (22.6)
Self-rated health, n (%)			
Very good	19572 (32.9)	284 (9.8)	19856 (31.8)
Good	35876 (60.3)	1976 (67.9)	37852 (60.7)
Poor	3904 (6.6)	619 (21.3)	4523 (7.2)
Very poor	127 (0.2)	30 (1.0)	157 (0.3)
Smoking status, n (%)			
Never	19889 (33.6)	725 (25.1)	20614 (33.2)
Former	24973 (42.2)	1052 (36.4)	26025 (41.9)
Current	14311 (24.2)	1115 (38.6)	15426 (24.9)
Alcohol abstinence, n (%)			
Not abstinent	54402 (92.1)	2582 (89.8)	56984 (92.0)
Abstinent	4637 (7.9)	293 (10.2)	4930 (8.0)
BMI, n (%)			
Underweight (<18.5)	707 (1.2)	43 (1.5)	750 (1.2)
Healthy weight (18.5 to <25)	32509 (56.0)	1205 (42.5)	33714 (55.4)
Overweight (25.0 to <30)	18447 (31.8)	1009 (35.6)	19456 (32.0)
Obese (30.0 or higher)	6372 (11.0)	575 (20.3)	6947 (11.4)
Level of physical activity, n (%)			
Low	5335 (9.3)	596 (21.3)	5931 (9.9)
Medium	40164 (70.3)	1829 (65.3)	41993 (70.0)
High	11662 (20.4)	375 (13.4)	12037 (20.1)

The second table presents the same characteristics and lifestyle factors of the population sample, including SSRI-use, according to depression. 15.5% of participants reported experiencing depression, either currently or earlier in life. Of those who had ever experienced depression, 20.8% were currently using SSRIs, while 79,2% were not currently using SSRIs. 1.7% of those who had never experienced depression reported using SSRIs. One noticeable difference when comparing tables, was that the prevalence of depression according to education was more evenly distributed in each category compared to the prevalence of SSRI-use in the first table. Regarding gross household income, 58.3% of those who had experienced depression were in the three lowest household income brackets. As for marital status, depression prevalence was overrepresented among those who were not married or cohabiting, which was comparable to SSRI-use among those not married in table 1. For self-rated health, depression was more prevalent among those with poor or very poor self-rated health. As for other lifestyle factors, depression was more likely among current and former smokers compared to never smokers, and more likely among women with low or medium levels of physical activity compared with women with high physical activity.

Table 2: Selected characteristics of participants according to depression in the NOWAC-study.

Characteristics	No depression	Depression (all-	Total sample
Participants, n (%)	52731 (84.5)	9657 (15.5)	62388 (100)
Age at baseline (y), mean (SD)	54.1 (4.4)	54.0 (4.4)	54.1 (4.4)
SSRI-use			
Current use of SSRIs	905 (1.7)	2004 (20.8)	2909 (4.7)
No current use of SSRIs	51826 (98.3)	7653 (79.2)	59479 (95.3)
Education level, n (%)			
≤ 9 years	7382 (14.0)	1489 (15.4)	8871 (14.2)
10 - 12 years	17791 (33.7)	3103 (32.1)	20894 (33.5)
13 - 16 years	16607 (31.5)	3022 (31.3)	19629 (31.5)
≥ 17 years	10951 (20.8)	2043 (21.2)	12994 (20.8)
Gross household income, n (%)			
< NOK 150 000,-	1927 (3.7)	694 (7.2)	2621 (4.2)
NOK 151 000 – 300 000,-	8601 (16.3)	2265 (23.5)	10866 (17.4)
NOK 301 000 – 450 000,-	12825 (24.3)	2665 (27.6)	15490 (24.8)
NOK 451 000 – 600 000,-	11604 (22.0)	1879 (19.5)	13483 (21.6)
NOK 601 000 – 750 000,-	7480 (14.2)	984 (10.2)	8464 (13.6)
> NOK 750 000	10294 (19.5)	1170 (12.1)	11464 (18.4)
Marital status, n (%)			
Married	41810 (79.3)	6450 (66.8)	48260 (77.4)
Not married	10921 (20.7)	3207 (33.2)	14128 (22.6)
Self-rated health, n (%)			
Very good	18320 (34.7)	1536 (15.9)	19856 (31.8)
Good	31319 (59.4)	6533 (67.7)	37852 (60.7)
Poor	3000 (5.7)	1523 (15.8)	4523 (7.2)
Very poor	92 (0.2)	65 (0.7)	157 (0.3)
Smoking status, n (%)			
Never	18132 (34.6)	2482 (25.8)	20614 (33.2)
Former	22174 (42.3)	3851 (40.0)	26025 (41.9)
Current	12138 (23.1)	3288 (34.2)	15426 (24.9)
Alcohol abstinence, n (%)			
Not abstinent	48294 (92.3)	8690 (90.8)	56984 (92.0)
Abstinent	4054 (7.7)	876 (9.2)	4930 (8.0)
BMI, n (%)			
Underweight (<18.5)	598 (1.2)	152 (1.6)	750 (1.2)
Healthy weight (18.5 to <25)	29007 (56.4)	4707 (50.0)	33714 (55.4)
Overweight (25.0 to <30)	16366 (31.8)	3090 (32.8)	19456 (32.0)
Obese (30.0 or higher)	5477 (10.6)	1470 (15.6)	6497 (11.4)
Level of physical activity, n (%)			
Low	4414 (8.7)	1517 (16.2)	5931 (9.9)
Medium	35657 (70.5)	6336 (67.6)	41993 (70.0)
High	10520 (20.8)	1517 (16.2)	12037 (20.1)

3.2 Logistic regression

In table 3, the ORs with 95% CI for SSRI-use are presented for each level of educational attainment. Model 1a was age-adjusted while model 1b was also adjusted for self-rated health as part of the sensitivity analysis. The estimated effect of education on the use of SSRIs was statistically significant for all levels in model 1a. In model 1b, the effect was only significant for the first two levels, while the effect for 13 – 16 years was not statistically significant (OR 1.07, 95% CI 0.96-1.21). In model 1a, the odds of using SSRIs were almost twice as large for the lowest education group (OR 1.95, 95% CI 1.72-2.21) compared to the highest education group (OR 1.15, 95% CI 1.02-1.29). In both models, the OR decreased for each increased level of education.

Table 3: Multivariable model 1 with odds ratios and 95% confidence intervals for current SSRI-use according to education in the NOWAC-study.

Exposure	**Model 1a** **OR (95% CI)**	**Model 1b** **OR (95% CI)**
Education level		
≤ 9 years	1.95 (1.72-2.21)	1.41 (1.24-1.60)
10 - 12 years	1.37 (1.22-1.53)	1.14 (1.01-1.27)
13 - 16 years	1.15 (1.02-1.29)	1.07 (0.96-1.21)
≥ 17 years	Ref	Ref
With education as the exposure and adjusted for age in model 1a, additionally adjusted for self-rated health in model 1b.		

In table 4, the ORs with 95% CI for SSRI-use are presented for each income level. Model 2a was age-adjusted, while model 2b was adjusted for age, education, and marital status. Model 2c was additionally adjusted for self-rated health. The estimated effect of gross household income on the use of SSRIs was statistically significant for the first four income levels in all three models, and not significant for the second highest income level (OR 1.11, 95% CI 0.93-1.32, OR 1.08, 95% CI 0.91-1.29 and OR 0.97, 95% CI 0.81-1.16). In all three models, the OR decreased for each increased level of income. In model 2a the odds of using SSRIs were 4.59 times higher for the lowest income group (95% CI 3.87-5.45) compared to the second highest income group. The odds of using SSRIs declined by half to 2.24 in model 2c for the lowest income group (95% CI 1.84-2.73).

Table 4: Multivariable model 2 with odds ratios and 95% confidence intervals for current SSRI-use according to gross household income in the NOWAC-study.

Exposure	**Model 2a OR (95% CI)**	**Model 2b OR (95% CI)**	**Model 2c OR (95% CI)**
Gross household income			
< NOK 150 000	4.59 (3.87-5.45)	3.87 (3.19-4.69)	2.24 (1.84-2.73)
NOK 151 000 – 300 000	2.94 (2.56-3.38)	2.60 (2.22-3.03)	1.85 (1.58-2.17)
NOK 301 000 – 450 000	2.15 (1.88-2.47)	1.99 (1.72-2.29)	1.55 (1.34-1.80)
NOK 451 000 – 600 000	1.53 (1.32-1.77)	1.46 (1.26-1.70)	1.23 (1.06-1.43)
NOK 601 000 – 750 000	1.11 (0.93-1.32)	1.08 (0.91-1.29)	0.97 (0.81-1.16)
> NOK 750 000	Ref	Ref	Ref
With gross household income as the exposure and adjusted for age in model 2a, adjusted for age, education, and marital status in model 2b, additionally adjusted for self-rated health in model 2c.			

In table 5, the ORs with 95% CI for depression are presented for each level of educational attainment. Model 3a was age-adjusted while model 3b was also adjusted for self-rated health. The estimated effect of education on depression was only statistically significant for the lowest education level in 3a with an OR of 1.11 (95% CI 1.03-1.19). In model 3b, all education levels had a significant, yet slightly protective effect. The association between education and depression was considerably less apparent in both models compared to the association between education and SSRI-use.

Table 5: Multivariable model 3 with odds ratios and 95% confidence intervals for depression according to education in the NOWAC-study.

Exposure	**Model 3a OR (95% CI)**	**Model 3b OR (95% CI)**
Education level		
≤ 9 years	1.11 (1.03-1.19)	0.84 (0.77-0.90)
10 - 12 years	0.94 (0.89-1.00)	0.80 (0.75-0.85)
13 - 16 years	0.98 (0.92-1.04)	0.92 (0.87-0.98)
≥ 17 years	Ref	Ref
With education as the exposure and adjusted for age in model 3a, additionally adjusted for self-rated health in model 3b.		

In table 6, the ORs with 95% CI for depression are presented for each income level. Model 4a was adjusted for age, model 4b was adjusted for age, education, and marital status, while model 4c was additionally adjusted for self-rated health. The estimated effect of gross household income on depression was statistically significant for every single income level in all three models and the OR decreased with each increase in income level. The association between income and depression was more prominent than the association between education and depression. The odds of having depression increased threefold for those in the lowest income group (OR 3.24, 95% CI 2.92-3.61) compared to those in the second highest income group (OR 1.16, CI 95% 1.06-1.27) in model 4a. The odds decreased to just under twofold when comparing those in the lowest and second highest income groups in model 4c (OR 1.85, 95% CI 1.64-2.10 and OR 1.09, 95% CI 1.00-1.20).

Table 6: Multivariable model 4 with odds ratios and 95% confidence intervals for depression according to gross household income in the NOWAC-study.

Exposure	**Model 4a**	**Model 4b OR (95% CI)**	**Model 4c OR (95% CI)**
Gross household income			
< NOK 150 000	3.24 (2.92-3.61)	2.89 (2.57-3.26)	1.85 (1.64-2.10)
NOK 151 000 – 300 000	2.36 (2.19-2.55)	2.15 (1.96-2.34)	1.63 (1.49-1.79)
NOK 301 000 – 450 000	1.85 (1.72-1.99)	1.75 (1.62-1.89)	1.45 (1.33-1.57)
NOK 451 000 – 600 000	1.43 (1.32-1.54)	1.48 (1.37-1.60)	1.29 (1.19-1.40)
NOK 601 000 – 750 000	1.16 (1.06-1.27)	1.19 (1.09-1.30)	1.09 (1.00-1.20)
> NOK 750 000	Ref	Ref	Ref
With gross household income as the exposure and adjusted for age in model 4a, adjusted for age, education, and marital status in model 4b, additionally adjusted for self-rated health in model 4c.			

4 Discussion

4.1 Summary

The main results in this study demonstrated an inverse social gradient, where the odds of using SSRIs or experiencing depression decreased with each increase in education or income level. This gradient was apparent for all models, age-adjusted and multivariable. Low levels of education and income were associated with an increase in the odds of using SSRIs and experiencing depression. This association was especially prominent according to income, while the association between education level and the use of SSRIs and depression was less prominent.

4.2 Comparison with other results

The results in this study were expected and consistent with previous Norwegian and international studies. Regarding medication, other referenced studies have largely looked at general antidepressant use and not solely SSRI-use. Several Norwegian studies that demonstrated an association between SES and antidepressant-use and SES and depression were referred to in the Introduction, and similar patterns were found in research from other countries. In a study from Australia, the authors argued that their results indicated a prescribing bias towards patients with low SES and that they were not merely a corollary of higher depression prevalence in that group (34). In a study from England the authors compared healthcare access in deprived and less deprived areas. They found that antidepressants were prescribed more frequently to patients with low SES, and that this was a persistent pattern in deprived neighbourhoods (36).

Concerning depression, in a cross-sectional study surveying populations from Finland, Poland and Spain, the authors found that every increase in SES-level reduced the odds of depression. Interestingly, higher levels of education reduced the odds of depression substantially, while income did not have the same impact, and this was observed in all three countries (27). The results of a study on Japanese adults indicated that both educational attainment and household income were separately linked to the occurrence of depression. Household income appeared to have a stronger connection to depression than education and the authors implied that having a higher household income could have a compensatory effect and reduced the risk of depression for individuals with lower levels of education (30). There is a lack of studies on these associations in low, lower-middle, and upper-middle income countries, but available research demonstrates similar trends (49-51).

As for overall impact on antidepressant-use and depression, it is difficult to conclude whether this is stronger for income or education, as studies have found different results. It is likely that the relative strength of these associations may vary depending on the specific population being studied and according to how measurements are made, but there is also an impression that income is generally a stronger predictor.

4.3 Mechanisms behind the association

There are several factors that may contribute to this association between SES and antidepressant use and SES and depression. These include, but are not limited to, access to mental healthcare, stigma surrounding mental health treatment, attitudes to antidepressants and the effects of poverty and other social determinants of health on mental well-being.

First, the overlap between SSRI-use and depression is worth a closer look. When exploring the second table from the section on descriptive statistics, it might be considered surprising that so few with depression are on SSRIs. Here it is important to note that the SSRI-variable is about current use and not ever use, while the depression variable is about former and current depression. The women in the sample with depression and no SSRI-use could be on other medications, they could have used SSRIs in the past, they might have opted to use completely different strategies to handle their symptoms, or they were simply not depressed when they were surveyed. Some women with depression might have made a conscious choice not to use SSRIs as adverse side-effects can be severe and they might have had prior negative experiences with these medications. In addition, spontaneous remission of untreated depression, particularly mild and moderate depression, is frequent, and not all depressions require treatment (52, 53).

As for differences in SSRI-use between SES-groups, it is possible that they could be due to affluent groups having less severe depressive symptoms, which in turn might require less use of medication. According to Norwegian national guidelines, an SSRI-prescription is generally recommended to patients suffering from moderate and severe depression, while those with mild symptoms ideally should be recommended therapy first (54). It is also possible that mental health services providing talk therapies are not sufficiently available for poorer groups, which might partly explain why they are being prescribed SSRIs at a higher rate. Affluent groups will also have the resources to choose other types of interventions, such as therapy, physical activity, and other lifestyle changes. For less wealthy groups, SSRI-use is an available and usually an affordable treatment option. Waiting lists for therapists in public

mental healthcare can be long, while seeing a therapist who maintains a private practice might prove too expensive.

It is possible that there are differences in attitudes to SSRIs between SES-groups, but scientific literature on this topic is scarce. One Norwegian study referenced in the Introduction found that women with lower education were more likely to receive an antidepressant prescription than women with higher education, while the same pattern could not be observed for men. The authors speculated that this might reflect a mistrust of medication use among women with higher education (31). In an observational study from 2019 where researchers surveyed patients in general practices, they found that most patients preferred talk therapy with their GP. When looking at differences according to sex, age and SES, they found that a preference for talk therapy with their GP and medication use was associated with men, older people and lower education levels, while a preference for referrals was associated with women, younger people and higher education levels (55).

As this is a cross-sectional study, neither causality nor the direction of any potential causal effects can be determined. It is possible that the relationship between SES and SSRI-use and SES and depression, is bidirectional. For example, depression and poverty could be linked in a cyclical relationship. Poverty and deprivation could lead to depression, as the stress and challenges of living with limited financial resources take a toll on a person's mental health. At the same time, depression could also lead to poverty, as the symptoms of depression, such as lack of motivation and difficulty concentrating, make it difficult for a person to hold down a job or manage their finances effectively. This could create a cycle in which poverty exacerbates depression, and depression in turn makes it more difficult to escape poverty. In what was reportedly one of the first meta-analyses on the association between SES and depression from 2003, the authors argued that there was a bidirectional association between them, but also that their results more strongly supported SES as the explanatory variable, so it is likely that these two processes are taking place concurrently (56).

Finally, concerning the inverse social gradient in health, which was evident from the results, it is often seen in a variety of health indicators, including life expectancy, morbidity, and mortality rates (57, 58). One possible explanation for the inverse gradient is that lower socio-economic groups often have less access to healthcare and other resources that can help improve health outcomes. They may also be more likely to live in environments that are more hazardous to health, such as neighborhoods with higher levels of air pollution or poor housing

conditions. In addition, lower socio-economic groups may be more vulnerable to the negative health effects of stress and other psychosocial factors. When examining systematic reviews and other studies on the topic of socioeconomic disparities in health, one finds that these inequities have been acknowledged for decades, as far back as 1969 (59).

4.4 Strengths and limitations

Studies in public health and other fields of research are considered strong if they are designed and conducted in such a way that the potential for bias and confounding is reduced. There are several characteristics that contribute to the strength of this study. First, the sample size is large. This increases the statistical power of the study and makes it possible to assess the association between the exposure and outcome in an accurate manner. Second, the response rate was 52.7%, which is acceptable. Response rates for surveys in several research fields have declined sharply since the 1950s, and that could produce selection bias, but even response rates much lower than 52.7% do not necessarily translate to imprecise effect estimates. Throughout scientific literature there are many examples of studies with extremely low response rates, where differences in effect estimates are slight, when compared with studies with higher response rates (60). Third, women participating in the NOWAC-study were randomly sampled. This is a useful method for producing representative samples because it reduces the potential for bias and allows for the generalization of findings from the sample to the population. However, it is not a guarantee that the sample will be representative of the population. As for external validity, which refers to the extent to which the results of a study can be generalized to the population at large, there were no differences between participants and those who were eligible, apart from education and parity. 26.0% of participants reported having more than 12 years of education while the corresponding number for eligible women was 21.9% (61). Although education was one of the exposures in this study, it is doubtful whether the above-mentioned difference would have impacted the results in a substantial way. Regarding self-reported current SSRI-use, the authors of a recently published study concluded that this information had high validity. They conducted their research by linking records with the Norwegian Prescription Database and analyzing plasma concentrations. Discrepancies between data sources were small and related to employment status, low education level, marital status, and other indicators of ill health (62).

This study does have several limitations. As data was retrieved from a prospective cohort study, there is a risk of selection bias, specifically what is referred to as a healthy selection

bias. This is an effect that often occurs in cohort studies when people who participate are healthier than the general population. This can lead to an overestimation of the benefits of an intervention or treatment or an underestimation of risk factors or other associations. It is possible that healthier women were more inclined to take part in the NOWAC-study, and this might mean that there is an underestimation of the prevalence of SSRI-use and depression (63). Regarding medications, it could be considered a limitation that no information exists for other types of antidepressant-use for this cohort. Though there is scientific value in separately analyzing categories of antidepressants, as they have very different active ingredients, on a population level SSRIs account for approximately half of all antidepressant use. As other antidepressant categories were not part of the survey, no conclusions can be drawn on general antidepressant use among participants in the NOWAC-study. In addition, the bulk of the information in this study was derived from self-reported data, which could potentially introduce information bias. As earlier mentioned, the data on SSRI-use has a high validity. However, it is more challenging to assess the validity of the other outcome, self-reported depression. There is still stigma attached to mental health disorders, so underreporting from participants is possible. Misclassification for other categories, such as income level, lifestyle factors and health indicators are also conceivable. Misclassification can produce overestimates or underestimates of the effect, depending on whether it is differential or non-differential and other factors. Misclassification will always occur to some degree when collecting data, and in this study, one cannot categorically establish whether it was random or not. For example, it is possible that self-diagnosis of depression occurred more frequently among women with higher education or that women with depression underestimated or overestimated exposures and other lifestyle factors. As for depression, there is not sufficient information to determine its measurement accuracy, however its prevalence does match results from other studies. Finally, as this is a cross-sectional study, meaning data on exposures and outcomes were collected at a single point in time, determinations on causality and the direction of the effect cannot be made with certainty. Several DAGs were created to explore the causal structures in this thesis and determine what adjustments should be made. The DAGs were based on cross-sectional data, defined as a snapshot of a population at a specific time, so assumptions had to be made about the temporal relationships between variables, but one cannot be certain that these models accurately reflect reality.

4.5 Future implications

As cross-sectional study designs cannot establish cause and effect relationships, future research should focus on prospective study designs, and employ more stringent measures of SSRI-use and mental health disorders. There are several subjects that merit further exploration, among them long-term effects of SES on medication use and mental health and the effect of treatments for depression and other mental disorders among patients with low SES or stratified by SES.

Prospective design refers to a type of research in which the study is conducted prospectively, meaning that data is collected as events occur in the future, rather than retrospectively, after the events have already taken place. The research question is defined before the study begins, and there are several advantages to using this type of design. It allows for the collection of data on many subjects over a longer timeframe, which can provide a more comprehensive understanding of the research question. Another advantage is that data collected on exposures, confounders and outcomes might have a higher accuracy than data collected for a retrospective or a cross-sectional study, especially if the data is collected from registries. However, this design can be expensive and time-consuming due to the long follow-up period required to collect data. As a result, this study design may be less efficient compared to other types of research designs (64).

Prospective study designs cannot prove causality, but they can indicate causal relationships, as they can be used to determine whether an exposure precedes an outcome, which is a key criterion for establishing causality. The data on SES in the present study was collected only at one point in time, while in reality SES is dynamic and changes throughout a person's lifetime, though to what degree is uncertain. A prospective design would let researchers trace these changes in detail and provide a more complete understanding of the relationship between SES and other outcomes that may not be immediately apparent. An example of this is a prospective study on Norwegian adolescents that was referenced in the Introduction, where the authors' findings indicated that mental health issues among high school students were on the rise since 2014. This was apparent in all socioeconomic groups, and girls were particularly vulnerable to this development (26).

4.6 Conclusion

The objective of this study was to assess the association between SES and SSRI-use, and SES and depression with data from the NOWAC-study, with SES referring to education and gross household income. Income was plainly the more substantial predictor compared to education. The association between income and SSRI-use and income and depression was strong in every single model, while the association with education was less pronounced. These associations clearly manifested as an inverse social gradient in all outcomes and these results were consistent with similar research on this subject. In view of this, there are several subjects that future research should investigate further, among these, the long-term effects of SES on mental health and the use of medication, including the potential for cumulative effects over the life course and the impact of depression treatment among those with low SES.

Works cited

1. World Health Organization. Depression: World Health Organization; 2020 [Available from: https://www.who.int/news-room/fact-sheets/detail/depression.
2. World Health Organization. ICD-11 : International Statistical Classification of Dseases and Related Health Problems : 11th revision. Geneva: World Health Organization; 2019.
3. Norwegian Institute of Public Health. Psykisk helse i Norge. 2018.
4. Bonsaksen T, Grimholt TK, Skogstad L, Lerdal A, Ekeberg Ø, Heir T, et al. Self-diagnosed depression in the Norwegian general population - associations with neuroticism, extraversion, optimism, and general self-efficacy. BMC public health. 2018;18(1):1076-.
5. Cuijpers P, Sijbrandij M, Koole SL, Andersson G, Beekman AT, Reynolds III CF. Adding psychotherapy to antidepressant medication in depression and anxiety disorders: a meta-analysis. World Psychiatry. 2014;13(1):56-67.
6. Karyotaki E, Smit Y, Holdt Henningsen K, Huibers MJH, Robays J, de Beurs D, et al. Combining pharmacotherapy and psychotherapy or monotherapy for major depression? A meta-analysis on the long-term effects. Journal of Affective Disorders. 2016;194:144-52.
7. The Norwegian Medicines Manual for Health Personnel. L5.3 Antidepressiva: Foreningen for utgivelse av Norsk legemiddelhåndbok; 2015.
8. Norwegian Institute of Public Health. Statistics from the Norwegian Prescription Database 2021 [Available from: http://www.norpd.no/Prevalens.aspx.
9. The Norwegian Medicines Manual for Health Personnel. L5.3.1 Selektive serotoninreopptakshemmere: Foreningen for utgivelse av Norsk legemiddelhåndbok; 2015.
10. Gafoor R, Booth HP, Gulliford MC. Antidepressant utilisation and incidence of weight gain during 10 years' follow-up: population based cohort study. Bmj. 2018;361:k1951.
11. Jing E, Straw-Wilson K. Sexual dysfunction in selective serotonin reuptake inhibitors (SSRIs) and potential solutions: A narrative literature review. Mental Health Clinician. 2016;6(4):191-6.
12. Reisman Y. Post-SSRI sexual dysfunction. BMJ. 2020;368:m754.
13. Bala A, Nguyen HMT, Hellstrom WJ. Post-SSRI sexual dysfunction: a literature review. Sexual medicine reviews. 2018;6(1):29-34.
14. OECD. OECD Health Statistics 2021 2021 [Available from: https://www.oecd.org/els/health-systems/health-data.htm.
15. Castaldelli-Maia JM, Scomparini LB, Andrade AG, Bhugra D, de Toledo Ferraz Alves TC, D'Elia G. Perceptions of and attitudes toward antidepressants: stigma attached to their use--a review. J Nerv Ment Dis. 2011;199(11):866-71.
16. Pescosolido BA, Halpern-Manners A, Luo L, Perry B. Trends in Public Stigma of Mental Illness in the US, 1996-2018. JAMA Netw Open. 2021;4(12):e2140202.
17. Leo J, Lacasse JR. The Media and the Chemical Imbalance Theory of Depression. Society. 2008;45(1):35-45.
18. Lugg W. The biopsychosocial model – history, controversy and Engel. Australasian Psychiatry. 2021;30(1):55-9.
19. Moncrieff J, Cooper RE, Stockmann T, Amendola S, Hengartner MP, Horowitz MA. The serotonin theory of depression: a systematic umbrella review of the evidence. Molecular Psychiatry. 2022.
20. Ang B, Horowitz M, Moncrieff J. Is the chemical imbalance an ‘urban legend’? An exploration of the status of the serotonin theory of depression in the scientific literature. SSM - Mental Health. 2022;2:100098.
21. Healy D. Serotonin and depression. BMJ : British Medical Journal. 2015;350:h1771.

22. Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. The Lancet. 2018;391(10128):1357-66.
23. Hieronymus F, Emilsson JF, Nilsson S, Eriksson E. Consistent superiority of selective serotonin reuptake inhibitors over placebo in reducing depressed mood in patients with major depression. Molecular Psychiatry. 2016;21(4):523-30.
24. Oakes JM, Rossi PH. The measurement of SES in health research: current practice and steps toward a new approach. Soc Sci Med. 2003;56(4):769-84.
25. Statistics Norway. Sosial ulikhet i bruk av helsetjenester - 2. 2021.
26. Myhr A, Anthun KS, Lillefjell M, Sund ER. Trends in Socioeconomic Inequalities in Norwegian Adolescents' Mental Health From 2014 to 2018: A Repeated Cross-Sectional Study. Frontiers in Psychology. 2020;11(1472).
27. Freeman A, Tyrovolas S, Koyanagi A, Chatterji S, Leonardi M, Ayuso-Mateos JL, et al. The role of socio-economic status in depression: results from the COURAGE (aging survey in Europe). BMC Public Health. 2016;16(1):1098.
28. Patel V, Burns JK, Dhingra M, Tarver L, Kohrt BA, Lund C. Income inequality and depression: a systematic review and meta-analysis of the association and a scoping review of mechanisms. World Psychiatry. 2018;17(1):76-89.
29. Schlax J, Jünger C, Beutel ME, Münzel T, Pfeiffer N, Wild P, et al. Income and education predict elevated depressive symptoms in the general population: results from the Gutenberg health study. BMC Public Health. 2019;19(1):430.
30. Hinata A, Kabasawa K, Watanabe Y, Kitamura K, Ito Y, Takachi R, et al. Education, household income, and depressive symptoms in middle-aged and older Japanese adults. BMC Public Health. 2021;21(1):2120.
31. Hansen AB, Baste V, Hetlevik O, Haukenes I, Smith-Sivertsen T, Sabine R. General practitioners' drug treatment for depression by patients' educational level: registry-based study. BJGP Open. 2021;5(2):BJGPO.2020.0122.
32. Statistics Norway. Sosial ulikhet i bruk av helsetjenester. En kartlegging 2017 [Available from: https://www.ssb.no/helse/artikler-og-publikasjoner/_attachment/312917?_ts=15cbf99fcd8.
33. von Soest T, Bramness JG, Pedersen W, Wichstrøm L. The relationship between socio-economic status and antidepressant prescription: A longitudinal survey and register study of young adults. Epidemiology and Psychiatric Sciences. 2012;21(1):87-95.
34. Butterworth P, Olesen SC, Leach LS. Socioeconomic differences in antidepressant use in the PATH through life study: Evidence of health inequalities, prescribing bias, or an effective social safety net? Journal of Affective Disorders. 2013;149(1):75-83.
35. Roer K, Fonager K, Bingley P, Mortensen JT. The use of antidepressants and introduction of new types in different socio-economic groups: A Danish registry-based cross-sectional study. Nordic Journal of Psychiatry. 2010;64(4):268-72.
36. Giebel C, Corcoran R, Goodall M, Campbell N, Gabbay M, Daras K, et al. Do people living in disadvantaged circumstances receive different mental health treatments than those from less disadvantaged backgrounds? BMC Public Health. 2020;20(1):651.
37. Lalji HM, McGrogan A, Bailey SJ. An analysis of antidepressant prescribing trends in England 2015-2019. J Affect Disord Rep. 2021;6:100205.
38. Lund E, Dumeaux V, Braaten T, Hjartåker A, Engeset D, Skeie G, et al. Cohort Profile: The Norwegian Women and Cancer Study—NOWAC—Kvinner og kreft. International Journal of Epidemiology. 2008;37(1):36-41.
39. Schnittker J, Bacak V. The increasing predictive validity of self-rated health. PLoS One. 2014;9(1):e84933.

40. Tennant PWG, Murray EJ, Arnold KF, Berrie L, Fox MP, Gadd SC, et al. Use of directed acyclic graphs (DAGs) to identify confounders in applied health research: review and recommendations. International Journal of Epidemiology. 2020;50(2):620-32.
41. Gidlow C, Johnston LH, Crone D, Ellis N, James D. A systematic review of the relationship between socio-economic position and physical activity. Health Education Journal. 2006;65(4):338-67.
42. Pearce M, Garcia L, Abbas A, Strain T, Schuch FB, Golubic R, et al. Association Between Physical Activity and Risk of Depression: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2022;79(6):550-9.
43. Hämäläinen J, Kaprio J, Isometsä E, Heikkinen M, Poikolainen K, Lindeman S, et al. Cigarette smoking, alcohol intoxication and major depressive episode in a representative population sample. Journal of Epidemiology and Community Health. 2001;55(8):573-6.
44. Kim H, Yoo J, Han K, Fava M, Mischoulon D, Park MJ, et al. Associations Between Smoking, Alcohol Consumption, Physical Activity and Depression in Middle-Aged Premenopausal and Postmenopausal Women. Frontiers in Psychiatry. 2021;12.
45. Yan XY, Huang SM, Huang CQ, Wu WH, Qin Y. Marital status and risk for late life depression: a meta-analysis of the published literature. J Int Med Res. 2011;39(4):1142-54.
46. Thabane L, Mbuagbaw L, Zhang S, Samaan Z, Marcucci M, Ye C, et al. A tutorial on sensitivity analyses in clinical trials: the what, why, when and how. BMC Med Res Methodol. 2013;13:92.
47. Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BWJH, et al. Overweight, Obesity, and Depression: A Systematic Review and Meta-analysis of Longitudinal Studies. Archives of General Psychiatry. 2010;67(3):220-9.
48. IBM Corp. IBM SPSS Statistics for Macintosh, Version 28.0. Armonk, NY: IBM Corp; 2021.
49. Lund C, Breen A, Flisher AJ, Kakuma R, Corrigall J, Joska JA, et al. Poverty and common mental disorders in low and middle income countries: A systematic review. Soc Sci Med. 2010;71(3):517-28.
50. Maselko J, Bates L, Bhalotra S, Gallis JA, O'Donnell K, Sikander S, et al. Socioeconomic status indicators and common mental disorders: Evidence from a study of prenatal depression in Pakistan. SSM Popul Health. 2018;4:1-9.
51. Araya R, Lewis G, Rojas G, Fritsch R. Education and income: which is more important for mental health? Journal of Epidemiology and Community Health. 2003;57(7):501.
52. Whiteford HA, Harris MG, McKeon G, Baxter A, Pennell C, Barendregt JJ, et al. Estimating remission from untreated major depression: a systematic review and meta-analysis. Psychol Med. 2013;43(8):1569-85.
53. Mekonen T, Ford S, Chan GCK, Hides L, Connor JP, Leung J. What is the short-term remission rate for people with untreated depression? A systematic review and meta-analysis. Journal of Affective Disorders. 2022;296:17-25.
54. Helsedirektoratet. Nasjonale retningslinjer for diagnostisering og behandling av voksne med depresjon i primær- og spesialisthelsetjenesten. 2022.
55. Hetlevik Ø, Garre-Fivelsdal G, Bjorvatn B, Hjørleifsson S, Ruths S. Patient-reported depression treatment and future treatment preferences: an observational study in general practice. Family Practice. 2019;36(6):771-7.
56. Lorant V, Deliège D, Eaton W, Robert A, Philippot P, Ansseau M. Socioeconomic Inequalities in Depression: A Meta-Analysis. American Journal of Epidemiology. 2003;157(2):98-112.
57. Chan MS, van den Hout A, Pujades-Rodriguez M, Jones MM, Matthews FE, Jagger C, et al. Socio-economic inequalities in life expectancy of older adults with and without

multimorbidity: a record linkage study of 1.1 million people in England. International Journal of Epidemiology. 2019;48(4):1340-51.
58. Mackenbach JP, Stirbu I, Roskam AJ, Schaap MM, Menvielle G, Leinsalu M, et al. Socioeconomic inequalities in health in 22 European countries. N Engl J Med. 2008;358(23):2468-81.
59. Hollingshead AB. Social Status and Psychological Disorder. By B. P. Dohrenwend and B. S. Dohrenwend. New York: Wiley, 1969. 207 pp. $9.50. Social Forces. 1970;49(2):319-.
60. Morton S, Bandara D, Robinson E, Atatoa-Carr P. In the 21st Century, what is an acceptable response rate? Australian and New Zealand journal of public health. 2012;36:106-8.
61. Lund E, Kumle M, Braaten T, Hjartåker A, Bakken K, Eggen E, et al. External validity in a population-based national prospective study--the Norwegian Women and Cancer Study (NOWAC). Cancer Causes Control. 2003;14(10):1001-8.
62. Waaseth M, Havelkova M, Forsdahl G, Lund E, Log T. Use of Selective Serotonin Reuptake Inhibitors - Validity of Self-Report versus Plasma Concentrations and Pharmacy Dispensations - A Cross-Sectional Analysis of the Norwegian Women and Cancer Study. Clin Epidemiol. 2022;14:815-26.
63. Webb P. Essential epidemiology : an introduction for students and health professionals / Penny Webb and Chris Bain. Bain C, editor. New York: Cambridge University Press; 2019.
64. Celentano DD, Szklo M. Gordis epidemiology / by David D. Celentano and Moyses Szklo. Sixth edition. ed. Philadelphia, PA: Elsevier; 2019.

Appendix

Data on antidepressant use and SSRI-use for 2010 and 2020 among both sexes and separately for men and women from the Norwegian Prescription Database:

Norwegian Prescription Database

Report date: 15/11/2022 22:40

http://www.norpd.no
The Norwegian Institute of Public

					Number of users	Users per 1000 inhabitants	Population base
Antidepressants	2010	All ages	Both sexes	Entire country	297 119	60,77	4 889 252
			Men	Entire country	102 905	42,11	2 443 800
			Women	Entire country	194 214	79,42	2 445 452
	2020	All ages	Both sexes	Entire country	352 951	65,61	5 379 474
			Men	Entire country	121 106	44,64	2 712 910
			Women	Entire country	231 845	86,95	2 666 564
N06AB	2010	All ages	Both sexes	Entire country	180 607	36,94	4 889 252
			Men	Entire country	61 250	25,06	2 443 800
			Women	Entire country	119 357	48,81	2 445 452
	2020	All ages	Both sexes	Entire country	184 263	34,25	5 379 474
			Men	Entire country	61 990	22,85	2 712 910
			Women	Entire country	122 273	45,85	2 666 564

ATC/DDD version: 2021

Note:
If the number of users is less than five, all unit of measurements on the same row, except 'population', will be empty.

Selected unit of measurement:
Number of users
Users per 1000 inhabitants
Population base

Selected search criteria:
Drug:
- N06AB -Selective serotonin reuptake inhibitors
- Antidepressants comprises "N06A - Antidepressants".

Period: 2020, 2010
Age: All ages
Gender: Both sexes, Women, Men
Residence: Entire country