Use of selective serotonin reuptake inhibitors and lifestyle among women of childbearing age: a Danish cross-sectional study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-003024
Article Type:	Research
Date Submitted by the Author:	09-Apr-2013
Complete List of Authors:	Laugesen, Kristina; Institute of Clinical Medicine, Aarhus University Hospital, Department of Clinical Epidemiology Telén Andersen, Ane Birgitte; Aarhus University Hospital, Department of Clinical Epidemiology Nørgaard, Mette; Aarhus University Hospital, Department of Clinical Epidemiology Bech Nielsen, Rikke; Aarhus University Hospital, Department of Clinical Epidemiology Wernich Thomsen, Reimar; Aarhus University Hospital, Department of Clinical Epidemiology Breinholt Larsen, Finn; Public Health and Quality Improvement, Central Denmark Region Toft S&#65533;rensen, Henrik; Aarhus University Hospital, Department of Clinical Epidemiology
Primary Subject Heading:	Public health
Secondary Subject Heading:	Mental health, Smoking and tobacco, Nutrition and metabolism
Keywords:	Adult psychiatry < PSYCHIATRY, MENTAL HEALTH, Maternal medicine < OBSTETRICS, PUBLIC HEALTH

Use of selective serotonin reuptake inhibitors and lifestyle among women of childbearing age: A Danish cross-sectional study

Kristina Laugesen[1], Ane Birgitte Telén Andersen[1], Mette Nørgaard[1], Rikke Bech Nielsen[1], Reimar Wernich Thomsen[1], Finn Breinholt Larsen[2], Henrik Toft Sørensen[1]

[1] Department of Clinical Epidemiology, Institute of Clinical Medicine, Aarhus University Hospital, 8200 Aarhus, Denmark

[2] Public Health and Quality Improvement, Central Denmark Region, 8200 Aarhus, Denmark

Corresponding author: Kristina Laugesen, Department of Clinical Epidemiology, Institute of Clinical Medicine, Aarhus University Hospital, Olof Palmes Allé 43-45, 8200 Aarhus N, Denmark. Phone: +4587168063; Fax: +4587167215; E-mail: kristina.laugesen@studmed.au.dk

Keywords: antidepressants, lifestyle, women, fertile

ABSTRACT

Objective To examine the use of selective serotonin reuptake inhibitors (SSRIs) among Danish women of childbearing age according to lifestyle factors.

Design Cross-sectional study.

Setting The Central Denmark Region.

Participants 4,234 women (71.5% of the invited) aged 25-44 years who participated in a public health survey in 2006.

Outcome measures Prevalence and prevalence ratios (PRs) of current and former SSRI use among women characterized by selected lifestyle factors. We obtained information on SSRI use through linkage to the Aarhus University Prescription Database covering all pharmacies in the region.

Results Of 4,234 women in the study, 161 (3.8%) were current SSRI users, 60 (1.4%) were recent users, 223 (5.3%) were former users, and 3,790 (89.5%) were never users. Current use of SSRIs was more prevalent in obese women than in non-obese women (PR = 1.5, 95% CI: 1.0 to 2.3), in current smokers compared with non-current smokers (PR = 1.6, 95% CI: 1.1 to 2.2), in women who consumed more than 14 alcoholic drinks weekly compared with women who drank 14 or fewer drinks weekly (PR = 1.8, 95% CI: 1.2 to 2.8), and in women with an unhealthy diet compared with women with a healthy diet (PR = 1.7, 95%: CI: 1.2 to 2.6). Prevalence of former use of SSRIs was similarly increased except in those with an unhealthy diet (PR= 1.1, 95% CI: 0.8 to 1.7). SSRI use did not differ according to regular physical exercise.

Conclusion Women with an unhealthy lifestyle were about 1.5-fold more likely to be current or former users of SSRIs than those with a healthy lifestyle. These findings may be useful for

quantitative assessment of the contribution of lifestyle factors to uncontrolled confounding in studies of SSRI use in pregnancy.

ARTICLE SUMMARY

Article focus

- To examine whether current and former use of SSRIs differ according to lifestyle factors among women of childbearing age.

Key messages

- Of 4,234 women aged 25-44 years participating in a public health survey, 161 (3.8%) were current SSRI users, 60 (1.4%) were recent users, and 223 (5.3%) were former users.
- Current and former use of SSRIs were at least 1.5-fold or more prevalent in women who were obese, who were current smokers, or who had higher than recommended weekly alcohol intake, as compared with women with a healthier lifestyle. Current but not former use of SSRIs was more common in women with an unhealthy diet. SSRI use did not differ much according to amount of regular physical exercise.

Strengths and limitations of this study

- SSRI use was identified from a comprehensive population-based prescription database, thus eliminating recall bias. The high quality and completeness of data in this database has been documented. Detailed information on lifestyle factors was available from questionnaires.

- Because the study was based on volunteers in a health survey (participation rate of women of childbearing age = 71.5%), participants may have been more health conscious than non-participants.
- Filled prescriptions may not be an entirely perfect measure of actual drug intake and its timing and thus may have led to some misclassification of SSRI use.

INTRODUCTION

More than 10% of pregnant women experience depression.[1] In deciding to initiate antidepressant drug treatment in pregnant women, potential negative effects of untreated depression on the mother and fetus [2-7] must be weighed against the risk of adverse pregnancy outcomes associated with in utero exposure to antidepressant drugs.[2]

Selective serotonin reuptake inhibitors (SSRIs) constitute the most commonly used class of antidepressants. Use of these drugs has substantially increased [8,9] in recent years. In Denmark, 2.4% of all pregnant women were treated with SSRIs in 2006, compared with 0.3% in 1997.[10] In a number of studies, SSRI use has been associated with adverse pregnancy outcomes including preterm birth, poor neonatal adaptation, low birth weight, persistent pulmonary hypertension, and cardiac malformations.[11-16] Other studies have not found such associations.[17,18] Studies investigating these associations often have lacked information on maternal lifestyle factors, such as smoking,[12] alcohol consumption,[14-17] and body mass index (BMI),[11,12,15,16]. Thus, they may have been biased by uncontrolled confounding, complicating interpretation of their results.

Unhealthy lifestyle choices during pregnancy, including smoking, alcohol consumption, and obesity, are known to be associated with increased risk of adverse pregnancy outcomes.[19-22] Still, few studies have investigated whether use of antidepressants differs according to lifestyle factors. Available studies have reported that depression and antidepressant use are more frequent among smokers, alcohol consumers, and obese people.[23-25] In the current study, we used data from a Danish public health survey to examine the relation between SSRI use and lifestyle among women of childbearing age.

METHODS

Study design

We conducted a cross-sectional study based on a 2006 public health survey administered in the Central Denmark region.

Setting

Denmark has 5.5 million inhabitants and is administratively divided into five regions. We conducted this study in one of these regions, the Central Denmark Region, with a population of about 1.2 million people. The Danish healthcare system provides tax-supported healthcare to all residents, guaranteeing free and unfettered access to primary and secondary care. Except for emergencies, general practitioners (GPs) are patients' initial contact with the health care system. GPs either treat the patients themselves or refer them to hospitals or specialists in the primary health care sector.

The unique 10-digit central personal registry number (CPR number) assigned to each Danish citizen at birth and to residents upon immigration [26] allows accurate and unambiguous linkage of all medical and administrative registries at the individual level in Denmark.

Study population

The study population was identified through the survey, "Hvordan har du det?"/ "How Are You?", a questionnaire-based public health study conducted by the Centre for Public Health (now Centre for Public Health and Quality Improvement), Central Denmark Region. In 2006, a sample of 31,500 people, living in the region, was invited to participate in the study. Eligible participants, identified through the Civil Registration System, were 25-79 years of age, residents of the Central Denmark Region, and Danish citizens with at least one parent born in Denmark. In total, 21,708 (69%)

invited persons agreed to participate. A questionnaire and stamped return envelope was delivered by mail. In order to maximize participation [27], three reminders were sent to non-respondents. Those who agreed to participate completed a detailed questionnaire containing approximately 400 questions on self-rated health, occurrence of chronic diseases, socioeconomic factors, and lifestyle factors. The current study was based on a subsample of female respondents of childbearing age, defined as age 25-44 years. In this subsample, 4,234 (71.5 %) invited women agreed to participate. The survey has been described in detail elsewhere (available in Danish: http://www.cfk.rm.dk/udgivelser/befolkningsundersøgelser).

Data on lifestyle factors

Lifestyle factors included in the study were BMI, exercise, diet, smoking status, and alcohol intake. BMI was calculated as self-reported weight in kilograms divided by self-reported height in meters squared. BMI was categorized according to WHO criteria as underweight (BMI<18.5), normal weight (BMI 18.5-24.99), overweight (BMI 25-29.99), and obese (BMI ≥30).[28] Physical activity was operationalized as participation in leisure sports or other regular physical activity (yes/no). Diet was categorized based on a detailed food questionnaire with 30 different questions. Responses were first summarized into four diet components (fruit, vegetables, fish, and fat) and then summarized into categories of healthy, reasonably healthy, or unhealthy diet. Smoking status was categorized as never, former, and current (daily or occasional) tobacco smoking. Finally, alcohol use was categorized according to the Danish Health and Medicine Authority's recommendations at the time of the survey, *i.e.*, higher than recommended (>14 drinks weekly) or within recommended guidelines (≤14 drinks weekly).[29]

Data on SSRI antidepressant drugs

In Denmark, antidepressants are available on prescription only. All pharmacies in the Central Denmark Region are equipped with a computerized accounting system that transmits data to the Danish Health Service for reimbursement of prescribed drugs. According to an agreement with Aarhus University, the National Health Service subdivision of the Central Denmark Region transfers individually identifiable prescription redemption data from the pharmacies to the Aarhus University Prescription Database (AUPD). The AUPD contains information on the CPR number of the patient, type of drug prescribed according to name and the Anatomic Therapeutic Chemical classification system (ATC), and date the prescription was redeemed.[30] Data are available from 1996 onwards. We classified current users of SSRIs (ATC code N06AB) as those who redeemed at least one prescription within 90 days before and up to 30 days after completing the survey questionnaire. We defined recent users as those who redeemed a SSRI prescription in the period from 365 until 91 days before completing the questionnaire. Former users were those who redeemed at least one SSRI prescription more than 365 days before completing the questionnaire but had no prescriptions within 365 days before and up to 30 days after questionnaire completion. Never users were defined as women who never had a prescription for a SSRI.

STATISTICAL ANALYSES

We computed the prevalence of SSRI use (current, former, and never use) according to the available lifestyle factors. We then calculated prevalence ratios (PRs) with 95% confidence intervals (CIs) for current SSRI use and former SSRI use, comparing obese (BMI $\geq$ 30) to non-obese women (BMI < 30), current smokers to non-current smokers (never and former smokers), women with higher than weekly recommended alcohol use to women who used alcohol within the

recommended amount, women with an unhealthy diet to women with a healthy diet (healthy and reasonably healthy), and women who exercised regularly to women who did not.

In a sensitivity analysis, we added recent SSRI users to the group of current users and estimated PRs for current/recent use with 95% CIs associated with lifestyle factors. This analysis was undertaken to investigate whether potential misclassification between current and recent users could have affected our estimates.

All statistical analyses were conducted using Stata software (Release 12, StataCorp LP). The study was approved by the Danish Data Protection Agency (Record no. 2009-41-3866).

RESULTS

In total, 4,234 women (71.5% of those invited) aged 25 - 44 years participated in the survey. Of these, 161 (3.8%) were current SSRI users, 223 (1.4%) were former users, 60 (5.3%) were recent users, and 3,790 (89.5%) were never users. Table 1 shows the distribution of SSRI use (current, former, and never use) according to lifestyle factors.

Table 2 shows PRs for current, current/recent, and former use of SSRIs according to the lifestyle factors. Obese women had a higher prevalence of current SSRI use than non-obese women (PR = 1.5, 95% CI: 1.0 to 2.3). Current smokers had a higher prevalence of current SSRI use than non-current smokers (PR = 1.6, 95% CI: 1.1 to 2.2). Women with higher than recommended weekly alcohol intake had a higher prevalence of current SSRI use than women whose weekly alcohol intake was within the recommendations (PR = 1.8, 95% CI: 1.2 to 2.8). Women with an unhealthy diet had a higher prevalence of current SSRI use than women with a healthy diet (PR= 1.7, 95% CI: 1.2 to 2.6). Women who engaged in or did not engage in regular physical exercise had a similar prevalence of current SSRI use. The prevalence of former SSRI use by lifestyle factors followed the same pattern as current use. The only exception was unhealthy diet (PR = 1.1, 95% CI: 0.8-1.7).

In the sensitivity analysis, which added recent users to the group of current users, the PRs for SSRI use were very similar to those in the main analysis (Table 2).

DISCUSSION

In our study, women with unhealthy lifestyles were more often current or former users of SSRIs compared with women with healthier lifestyles. However, the prevalence of current and former SSRI use among women not engaging in regular exercise was similar to that among women who exercised regularly. Current but not former use of SSRIs was more common in women with an unhealthy diet. Our study contributes to knowledge of how use of SSRIs differs according to lifestyle choices among women of childbearing age.

Our study differs from earlier studies [23-25] by focusing on women of childbearing age. Therefore, our findings are applicable for assessing potential confounding in studies of birth outcomes in women using SSRIs.

However, our findings are in line with the previous findings in populations consisting of both men and women, thus underlining the reliability of our results. A French questionnaire-based public health survey including 10,252 men and women over age 18 years found that both non-smokers and former smokers had 30% lower risk of being prescribed an antidepressant drug than current smokers.[25] An American study including 43,093 men and women found that abusers of alcohol had an increased risk of major depression compared with lifetime abstainers [OR = 2.1 (95% CI: 1.3 to 3.4) for young adults not attending college and OR = 1.3 (95% CI: 1.0 to 1.6) for adults over age 30, respectively].[23] Also, a meta-analysis including in total 58,745 men and women found that obese persons were at increased risk of developing depression over time [pooled OR = 1.55 (95% CI: 1.23 to 2.01)].[24]

We identified use of SSRIs from a comprehensive population-based prescription database thus eliminating recall bias. This database is complete regarding SSRIs.[30] Furthermore, our use of questionnaires permitted collection of detailed information on the selected lifestyle factors.

Our study also has limitations. The study was cross-sectional and based on responses of women who volunteered to participate in a health survey. Because participants in such surveys might be more health conscious than non-participants, our cohort may not be representative of lifestyle choices in the general population. Survey participation was 69% overall and 71.5% among women aged 25 - 44 years. It is possible that non-participants may have differed from participants not only in lifestyle but also in the prevalence of major depression. This may have led us to underestimate the prevalence of SSRI use among women with unhealthy lifestyles. Furthermore, as information on lifestyle factors was self-reported, it is possible that unhealthy lifestyles were underreported. Also, redeemed prescriptions may be an imperfect measure of actual drug intake and timing. This may have led to misclassification of some non-users as SSRI users due to non-compliance. While this would not explain our finding of a higher prevalence of current SSRI use among women with an unhealthy lifestyle, it could have led us to underestimate the association.

In conclusion, women with an unhealthy lifestyle were about 1.5-fold more likely to be current or former SSRI users than women with a healthier lifestyle. These results may be useful in quantifying the degree to which uncontrolled confounding by lifestyle factors may affect studies of SSRI use during pregnancy.

Table 1. Distribution of selective serotonin reuptake inhibitor (SSRI) use in women aged 25-44 years according to lifestyle factors.

	Current use of SSRIs N (%)	Recent use of SSRIs N (%)	Former use of SSRIs N (%)	Never use of SSRIs N (%)	Total N (%)
BMI					
<18.5	5 (5.1)	3 (3.1)	3 (3.1)	87 (88.8)	98 (100)
18.5-24.9	72 (3.0)	36 (1.5)	128 (5.2)	2,245 (90.5)	2,481 (100)
25.0-29.9	49 (4.9)	11 (1.1)	47 (4.7)	890 (89.3)	997 (100)
≥30.0	30 (5.3)	8 (1.4)	38 (6.8)	486 (86.5)	562 (100)
Missing	5 (5.2)	2 (2.1)	7 (7.3)	82 (85.4)	96 (100)
Smoking					
Current	44 (5.1)	20 (2.3)	67 (7.8)	725 (84.7)	856 (100)
Former	33 (3.2)	12 (1.2)	59 (5.5)	912 (89.8)	1,016 (100)
Never	82 (3.5)	27 (1.2)	95 (4.1)	2,136 (91.3)	2,340 (100)
Missing	2 (9.1)	1 (4.5)	2 (9.1)	17 (77.3)	22 (100)
Diet					
Unhealthy	26 (6.1)	12 (2.8)	24 (5.6)	366 (85.5)	428 (100)
Reasonable healthy	95 (3.5)	33 (1.2)	144 (5.3)	2,465 (90.1)	2,737 (100)
Healthy	38 (3.8)	14 (1.4)	48 (4.8)	895 (90.0)	995 (100)
Missing	2 (1.5)	59 (44.7)	7 (5.3)	64 (48.5)	132 (100)
Intake of alcohol					
More than 14 drinks weekly	23 (6.3)	2 (0.5)	23 (6.3)	320 (87.0)	368 (100)
14 drinks or less weekly	124 (3.5)	49 (1.4)	165 (4.7)	3,197 (90.4)	3,535 (100)
Missing	14 (4.2)	9 (2.7)	35 (10.6)	273 (82.5)	331 (100)
Regular physical exercise					
Yes	77 (3.6)	24 (1.1)	102 (4.8)	1,935 (90.5)	2,138 (100)
No	83 (4.1)	35 (1.7)	119 (5.8)	1,803 (88.4)	2,040 (100)
Missing	1 (1.8)	1 (1.8)	2 (3.6)	52 (92.9)	56 (100)

Diet: Responses were first summarized into four diet components (fruit, vegetables, fish, and fat) and then summarized into categories of healthy, reasonably healthy, or unhealthy diet.

Regular physical exercise: Physical activity was operationalized as participation in leisure sports or other regular physical activity (yes/no)

Table 2. Prevalence ratios (PRs) and 95% confidence intervals (95% CIs) for use of selective serotonin reuptake inhibitors (SSRIs) in women aged 25-44 years, according to different lifestyle factors.

SSRI use	PRs comparing obese vs. non-obese women [95% CIs]	PRs comparing current smokers vs. non-current smokers [95% CIs]	PRs comparing alcohol intake above 14 drinks weekly vs. alcohol intake of 14 drinks or less weekly [95% CIs]	PRs comparing unhealthy diet vs. healthy diet [95% CIs]	PRs comparing regular exercise vs. no regular exercise [95% CIs]
Never use	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Current use	1.5 [1.0 – 2.3]	1.6 [1.1 – 2.2]	1.8 [1.2 – 2.8]	1.7 [1.2 – 2.6]	0.9 [0.6 – 1.2]
Current/recent use	1.4 [1.0 – 2.0]	1.7 [1.3 – 2.2]	1.4 [0.9 – 2.1]	1.8 [1.3 – 2.6]	0.8 [0.6 – 1.0]
Former use	1.4 [1.0 – 1.9]	1.8 [1.3 – 2.3]	1.4 [0.9 – 2.1]	1.1 [0.8 – 1.7]	0.8 [0.6 – 1.0]

Current/recent use: In this group, we added recent use to current use. Current use was defined as women who redeemed at least one prescription within 90 days before and up to 30 days after completing the survey questionnaire. And recent use was defined as women who redeemed a prescription in the period from 365 until 91 days before completing the questionnaire.

Acknowledgements: We wish to thank all the participants who helped us conduct this study by completing questionnaires.

Funding: This research was supported by the Clinical Epidemiology Research Foundation, Aarhus University Hospital, Denmark. The Department of Clinical Epidemiology, Aarhus University Hospital, receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of these studies have any relation to the present study.

Competing interests: None declared.

Data sharing statement: No additional data available.

Contributorship statement: KL, ABTA and MN made primary contributions to writing the manuscript. All authors contributed to the study conception and study design. RN made the data collection and KL the statistical analyses. All authors contributed to interpretation of results, all revised the manuscript critically, and all approved the final manuscript.

REFERENCES

*1 Bennett HA, Einarson A, Taddio A, et al. Prevalence of depression during pregnancy; systematic review. Obstet Gynecol 2004;**103**:698-709.*

*2 Bennett HA, Einarson A, Taddio A, et al. Depression during Pregnancy: Overview of Clinical Factors. Clin Drug Investig 2004;**24**:157-179.*

*3 Pajulo M, Savonlahti E, Sourander A, et al. Antenatal depression, substance dependency and social support. J Affect Disord 2001;**65**:9-17.*

*4 Zuckerman B, Amaro H, Baucher H, et al. Depressive symptoms during pregnancy: relationship to poor health behaviors. Am J Obstet gynecol 1989;**160**:1107-1111.*

*5 Lejoyeux M, Leon E, Rouillon F. Prevalence and risk factors of suicide and attempted suicide. Encephale 1994;**20**:495-503.*

*6 Bonari L, Pinto N, Ahn E, et al. Perinatal risks of untreated depression during pregnancy. Can J Psychiatry 2004;**49**:726-735.*

*7 Grote NK, Bridge JA, Gavin AR, et al. A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. Arch Gen Psychiatry 2010;**67**:1012-1024.*

*8 Cooper WO, Willy ME, Pont SJ, et al. Increasing use of antidepressants in pregnancy. Am J Obstet Gynecol 2007;**196**:544.e1-e5.*

*9 Andrade SE, Raebel MA, Brown J, et al. Use of antidepressant medications during pregnancy: a multisite study. Am J Obstet Gynecol 2008;**198**:194.e1-e5.*

10 Available at: http://www.sst.dk/Nyhedscenter/Nyheder/2007/nye_tal_20-07.aspx . Accesed 3/29 2013.

*11 Chambers CD, Johnson KA, Dick LM, et al. Birth outcomes in pregnant women taking fluoxetine. N Engl J Med 1996;**335**:1010-1015.*

*12 Wen SW, Yang Q, Garner P, et al. Selective serotonin reuptake inhibitors and adverse pregnancy outcomes. Am J Obstet Gynecol 2006;**194**:961-966.*

*13 Lund N, Pedersen LH, Henriksen TB. Selective serotonin reuptake inhibitor exposure in utero and pregnancy outcomes. Arch Pediatr Adolesc Med 2009;**163**:949-954.*

*14 Reis M, Kallen B. Delivery outcome after maternal use of antidepressant drugs in pregnancy: an update using Swedish data. Psychol Med 2010;**40**:1723-1733.*

*15 Pedersen LH, Henriksen TB, Vestergaard M, et al. Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study. BMJ 2009;**339**:b3569.*

*16 Kieler H, Artama M, Engeland A, et al. Selective serotonin reuptake inhibitors during pregnancy and risk of persistent pulmonary hypertension in the newborn: population based cohort study from the five Nordic countries. BMJ 2012;**339**:d8012.*

*17 Reis M, Kallen B. Combined use of selective serotonin reuptake inhibitors and sedatives/hypnotics during pregnancy: risk of relatively severe congenital malformations or cardiac defects: A register study. BMJ Open 2013;**3**.*

*18 Alwan S, Reefhuis J, Rasmussen SA, et al. Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth defects. N Engl J Med 2007;**356**:2684-2692.*

*19 Rogers JM. Tobacco and pregnancy: overview of exposures and effects. Birth Defects Res C embryo Today 2008;**84**:1-15.*

*20 Dennedy MC, Avalos G, O´Reilly MW, et al. The impact of maternal obesity on gestational outcomes. Ir Med J 2012;**105**:23-25.*

*21 Erickson AC, Arbour LT. Heavy smoking during pregnancy as a marker for other risk factors of adverse birth outcomes: a population-based study in British Columbia, Canada. BMC Public Health 2012;**12**:102.*

*22 Mateja WA, Nelson DB, Kroelinger CD, et al. The association between maternal alcohol use and smoking in early pregnancy and congenital cardiac defects. J Womens Health (Larchmt) 2012;**21**:26-34.*

*23 Dawson DA, Grant BF, Stinson FS, et al. Psychopathology associated with drinking and alcohol use disorders in the college and general adult populations. Drug Alcohol Depend 2005;**77**:139-150.*

*24 Luppino FS, de Wit LM, Bouvy PF, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch gen Psychiatry 2010;**67**:220-229.*

*25 Cheron-Launay M, Le Faou AL, Sevilla-Dedieu C, et al. Smoking and the consumption of antidepressants, anxiolytics and hypnotic drugs: results of a large, French epidemiological study in 2005. Addict Behav 2011;**36**:743-748.*

*26 Pedersen CB. The Danish Civil Registration System. Scand J Public Health 2011;**39**:22-25.*

*27 Edwards P, Roberts I, Clarke M, et al. Increasing response rates to postal questionnaires: systematic review. BMJ 2002;**324**:1183.*

28 Available at: http://apps.who.int/bmi/index.jsp?introPage=intro_3.html . Accessed 3/29 2013.

29 Available at: www.sst.dk/Sundhed%20og%20forebyggelse/Alkohol/UdmeldingerOmAlkohol.aspx. Accessed 3/29 2013.

*30 Ehrenstein V, Antonsen S, Pedersen L. Existing data sources for clinical epidemiology: Aarhus University Prescription Database. Clin Epidemiol 2010;**2**:273-279.*

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6,7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7,8
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	7,8
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8,9
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	9
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	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9,12
		(b) Indicate number of participants with missing data for each variable of interest	12
Outcome data	15*	Report numbers of outcome events or summary measures	9,12
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	14
		(*b*) Report category boundaries when continuous variables were categorized	7,12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10,14
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
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	15

*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.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Use of selective serotonin reuptake inhibitors and lifestyle among women of childbearing age: a Danish cross-sectional survey

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-003024.R1
Article Type:	Research
Date Submitted by the Author:	07-Jun-2013
Complete List of Authors:	Laugesen, Kristina; Institute of Clinical Medicine, Aarhus University Hospital, Department of Clinical Epidemiology Telén Andersen, Ane Birgitte; Aarhus University Hospital, Department of Clinical Epidemiology Nørgaard, Mette; Aarhus University Hospital, Department of Clinical Epidemiology Bech Nielsen, Rikke; Aarhus University Hospital, Department of Clinical Epidemiology Wernich Thomsen, Reimar; Aarhus University Hospital, Department of Clinical Epidemiology Breinholt Larsen, Finn; Public Health and Quality Improvement, Central Denmark Region Toft S&#65533;rensen, Henrik; Aarhus University Hospital, Department of Clinical Epidemiology
Primary Subject Heading:	Public health
Secondary Subject Heading:	Mental health, Smoking and tobacco, Nutrition and metabolism
Keywords:	Adult psychiatry < PSYCHIATRY, MENTAL HEALTH, Maternal medicine < OBSTETRICS, PUBLIC HEALTH

Use of selective serotonin reuptake inhibitors and lifestyle among women of childbearing age: A Danish cross-sectional survey

Kristina Laugesen[1], Ane Birgitte Telén Andersen[1], Mette Nørgaard[1], Rikke Beck Nielsen[1], Reimar Wernich Thomsen[1], Finn Breinholt Larsen[2], Henrik Toft Sørensen[1]

[1] Department of Clinical Epidemiology, Institute of Clinical Medicine, Aarhus University Hospital, 8200 Aarhus, Denmark

[2] Public Health and Quality Improvement, Central Denmark Region, 8200 Aarhus, Denmark

Corresponding author: Kristina Laugesen, Department of Clinical Epidemiology, Institute of Clinical Medicine, Aarhus University Hospital, Olof Palmes Allé 43-45, 8200 Aarhus N, Denmark. Phone: +4587168063; Fax: +4587167215; E-mail: kristina.laugesen@studmed.au.dk

Keywords: antidepressants, lifestyle, women, fertile

ABSTRACT

Objective To examine the use of selective serotonin reuptake inhibitors (SSRIs) among Danish women of childbearing age according to lifestyle factors.

Design Cross-sectional survey.

Setting The Central Denmark Region.

Participants 4,234 women (71.5% of the invited) aged 25-44 years who participated in a public health survey in 2006.

Outcome measures Prevalence and prevalence ratios (PRs) of current and former SSRI use among women characterized by selected lifestyle factors. We obtained information on SSRI use through linkage to the Aarhus University Prescription Database covering all pharmacies in the region.

Results Of 4,234 women in the study, 161 (3.8%) were current SSRI users, 60 (1.4%) were recent users, 223 (5.3%) were former users, and 3,790 (89.5%) were never users. Current use of SSRIs was more prevalent in obese women than in non-obese women (PR = 1.5, 95% CI: 1.0 to 2.3), in current smokers compared with non-current smokers (PR = 1.6, 95% CI: 1.1 to 2.2), in women who drank more than seven alcoholic drinks weekly compared with women who drank seven or fewer drinks weekly (PR = 1.8, 95% CI: 1.2 to 2.8), and in women with an unhealthy diet compared with women with a healthy diet (PR = 1.7, 95%: CI: 1.2 to 2.6). Prevalence of former use of SSRIs was similarly increased except in those with an unhealthy diet (PR= 1.1, 95% CI: 0.8 to 1.7). SSRI use did not differ according to participation in regular physical activity.

Conclusion Women with an unhealthy lifestyle were about 1.5-fold more likely to be current or former users of SSRIs than those with a healthy lifestyle. These findings may be useful for

quantitative assessment of the contribution of lifestyle factors to uncontrolled confounding in studies of SSRI use in pregnancy.

ARTICLE SUMMARY

Article focus

- To examine whether current and former use of SSRIs differ according to lifestyle factors among women of childbearing age.

Key messages

- Of 4,234 women aged 25-44 years participating in a public health survey, 161 (3.8%) were current SSRI users, 60 (1.4%) were recent users, and 223 (5.3%) were former users.
- Current and former use of SSRIs were at least 1.5-fold or more prevalent in women who were obese, who were current smokers, or who had a weekly alcohol intake above seven drinks, as compared with women with a healthier lifestyle. Current but not former use of SSRIs was more common in women with an unhealthy diet and in women with intake of alcohol of more than 14 drinks weekly. SSRI use did not differ much according to participation in regular physical activity.

Strengths and limitations of this study

- SSRI use was identified from a comprehensive population-based prescription database, thus eliminating recall bias. The high quality and completeness of data in this database has been documented. Detailed information on lifestyle factors was available from questionnaires.

- Because the study was based on volunteers in a health survey (participation rate of women of childbearing age = 71.5%), participants may have been more health conscious than non-participants.
- Filled prescriptions may not be an entirely perfect measure of actual drug intake and its timing and thus may have led to some misclassification of SSRI use.

INTRODUCTION

More than 10% of pregnant women experience depression.[1] In deciding to initiate antidepressant drug treatment in pregnant women, potential negative effects of untreated depression on the mother and fetus [2-6] must be weighed against the risk of adverse pregnancy outcomes associated with in utero exposure to antidepressant drugs.[2]

Selective serotonin reuptake inhibitors (SSRIs) constitute the most commonly used class of antidepressants. Use of these drugs has substantially increased [7,8] in recent years. In Denmark, 2.4% of all pregnant women were treated with SSRIs in 2006, compared with 0.3% in 1997.[9]

In a number of studies, SSRI use has been associated with adverse pregnancy outcomes including preterm birth, poor neonatal adaptation, low birth weight, persistent pulmonary hypertension, and cardiac malformations.[10-15]. One study reported an elevated risk of risk of cardiac malformations after prenatal exposure to SSRI, but concluded that this was due to unaccounted confounding.[15] However, other studies did not find such associations.[16,17] Studies investigating these associations often have lacked information on maternal lifestyle factors, such as smoking,[10] alcohol consumption,[12-14] and body mass index (BMI),[10,13,14]. Thus, they may have been biased by uncontrolled confounding, complicating interpretation of their results.

Unhealthy lifestyle choices during pregnancy, including smoking, alcohol consumption, and obesity, are known to be associated with increased risk of adverse pregnancy outcomes.[18-21] Still, few studies have investigated whether use of antidepressants differs according to lifestyle factors. Available studies have reported that depression and antidepressant use are more frequent among smokers, alcohol consumers, and obese people.[22-24] In the current study, we used data from a Danish public health survey to examine the relation between SSRI use and lifestyle among women of childbearing age.

METHODS

Study design

We conducted a cross-sectional study based on a 2006 public health survey administered in the Central Denmark region.

Setting

Denmark has 5.5 million inhabitants and is administratively divided into five regions. We conducted this study in one of these regions, the Central Denmark Region, with a population of about 1.2 million people. The Danish healthcare system provides tax-supported healthcare to all residents, guaranteeing free and unfettered access to primary and secondary care. Except for emergencies, general practitioners (GPs) are patients' initial contact with the health care system. GPs either treat the patients themselves or refer them to hospitals or specialists in the primary health care sector.

The unique 10-digit central personal registry number (CPR number) assigned to each Danish citizen at birth and to residents upon immigration [25] allows accurate and unambiguous linkage of all medical and administrative registries at the individual level in Denmark.

Study population

The study population was identified through the survey, "Hvordan har du det?"/ "How Are You?", a questionnaire-based public health study conducted by the Centre for Public Health (now Centre for Public Health and Quality Improvement), Central Denmark Region. In 2006, a random sample of 31,500 people, living in the region, was invited to participate in the study. Eligible participants,

identified through the Civil Registration System, were 25-79 years of age, residents of the Central Denmark Region, and Danish citizens with at least one parent born in Denmark. In total, 21,708 (69%) invited persons agreed to participate. A questionnaire and stamped return envelope was delivered by mail. In order to maximize participation [26], three reminders were sent to non-respondents. Those who agreed to participate completed a detailed questionnaire containing approximately 400 questions on self-rated health, occurrence of chronic diseases, socioeconomic factors, and lifestyle factors. The current study was based on a subsample of female respondents of childbearing age, defined as age 25-44 years. In this subsample, 4,234 (71.5 %) invited women agreed to participate.

The survey has been described in detail elsewhere (available in Danish: http://www.cfk.rm.dk/udgivelser/befolkningsundersøgelser).

Data on lifestyle factors

Lifestyle factors included in the study were BMI, participation in regular physical activity, diet, smoking status, and alcohol intake.

BMI was calculated as self-reported weight in kilograms divided by self-reported height in meters squared. BMI was categorized according to WHO criteria as underweight (BMI<18.5), normal weight (BMI 18.5-24.99), overweight (BMI 25-29.99), and obese (BMI ≥30).[27] Physical activity was in the questionnaire asked as participation in leisure sports or other regular physical activity (yes/no). To assess diet, this health survey used a score system developed by the Research Centre for Prevention and Health, the Capital Region of Denmark.[28] This included 30 different questions regarding intake of fruit, vegetables, fish, and fat. By the score system the responses were summarized into categories of healthy (high amount of fruit, vegetables, fish, and low amount of saturated fat), reasonably healthy (median high intake of fruit, vegetables, fish, and saturated fat),

or unhealthy diet (low amount of fruit, vegetables, fish, and high amount of saturated fat). Smoking status was categorized as never, former, and current (daily or occasional) tobacco smoking. Finally, alcohol use was in the questionnaire asked as how many drinks per week you drink. First, we categorized alcohol use according to the Danish Health and Medicine Authority's recommendations, *i.e.*, higher than recommended (> seven drinks weekly) or within recommended guidelines (≤ seven drinks weekly).[29] Second, we categorized alcohol in > 14 drinks weekly and ≤ 14 drinks weekly.

Data on SSRI and antiepileptic, anti-diabetics and antipsychotic use

In Denmark, antidepressants are available on prescription only. All pharmacies in the Central Denmark Region are equipped with a computerized accounting system that transmits data to the Danish Health Service for reimbursement of prescribed drugs. According to an agreement with Aarhus University, the National Health Service subdivision of the Central Denmark Region transfers individually identifiable prescription redemption data from the pharmacies to the Aarhus University Prescription Database (AUPD). The AUPD contains information on the CPR number of the patient, type of drug prescribed according to name and the Anatomic Therapeutic Chemical classification system (ATC), and date the prescription was redeemed.[30] Data are available from 1996 onwards. In Denmark, a prescription for SSRI generally lasts between 28 days and 100 days given that the daily use is one DDD. We classified current users of SSRIs (ATC code N06AB) as those who redeemed at least one prescription within 90 days before and up to 30 days after completing the survey questionnaire. We defined recent users as those who redeemed a SSRI prescription in the period from 365 until 91 days before completing the questionnaire. Former users were those who redeemed at least one SSRI prescription more than 365 days before completing the

questionnaire but had no prescriptions within 365 days before and up to 30 days after questionnaire completion. Never users were defined as women who never had a prescription for a SSRI.

We further defined use of anti-diabetic (ATC code A10), antiepileptic (ATC code N03), and antipsychotic (ATC code N05A) drugs as ever having redeemed a prescription on these drugs before filling in the questionnaire.

STATISTICAL ANALYSES

We computed the prevalence of SSRI use (current, former, recent and never use) according to the available lifestyle factors and according to use of anti-diabetic, antiepileptic, and antipsychotic drugs . We then calculated prevalence ratios (PRs) and 95% confidence intervals (CIs) by the Clopper-Pearson exact method for current SSRI use and former SSRI use, comparing obese (BMI ≥ 30) to non-obese women (BMI < 30), current smokers to non-current smokers (never and former smokers), women with alcohol intake of more than seven drinks weekly to women with alcohol intake of seven drinks or less weekly, women with alcohol intake of more than 14 drinks to women with alcohol intake of 14 drinks or less weekly, women with an unhealthy diet to women with a healthy diet (healthy and reasonably healthy), and women who participated in regular physical activity to women who did not. Women with missing data were excluded from the analyses.

In a sensitivity analysis, we added recent SSRI users to the group of current users and estimated PRs for current/recent use with 95% CIs associated with lifestyle factors. This analysis was undertaken to investigate whether potential misclassification between current and recent users could have affected our estimates.

All statistical analyses were conducted using Stata software (Release 12, StataCorp LP). The study was approved by the Danish Data Protection Agency (Record no. 2009-41-3866).

RESULTS

In total, 4,234 women (71.5% of those invited) aged 25 - 44 years participated in the survey. Of these, 161 (3.8%) were current SSRI users, 223 (1.4%) were former users, 60 (5.3%) were recent users, and 3,790 (89.5%) were never users. We investigated the number of pregnant women in our study population as the number of women who gave birth up to nine month after filling in the questionnaire. In total, we identified 232 pregnant women. Among these, 3 (1.3%) were current users, 3 (1.3%) were recent users, and 11(4.7%) were former users. The small number of pregnant women in our study population did not allow us to examine the relation between use of SSRI and lifestyle factors in pregnancy. Table 1 shows the distribution of SSRI use (current, recent, former, and never use) according to lifestyle factors and use of anti-diabetic, antiepileptic, and antipsychotic drugs.

Table 2 shows PRs for current, current/recent, and former use of SSRIs according to the lifestyle factors. Obese women had a higher prevalence of current SSRI use than non-obese women (PR = 1.5, 95% CI: 1.0 to 2.3). Current smokers had a higher prevalence of current SSRI use than non-current smokers (PR = 1.6, 95% CI: 1.1 to 2.2). Women with an intake of alcohol of more than seven drinks weekly had a higher prevalence of current SSRI use than women whose weekly alcohol intake was seven drinks or less (PR = 1.8, 95% CI: 1.2 to 2.8). Using 14 drinks per week as level for overuse, the PR increased (PR = 2.9 , 95% CI: 1.7 to 5.3). Women with an unhealthy diet had a higher prevalence of current SSRI use than women with a healthy diet (PR= 1.7, 95% CI: 1.2 to 2.6). Women who participated in regular physical activity and women, who did not participate in regular physical activity had a similar prevalence of current SSRI use. The prevalence of former SSRI use by lifestyle factors followed the same pattern as current use. The only exception was unhealthy diet (PR = 1.1, 95% CI: 0.8 to1.7) and alcohol intake of more than 14 drinks weekly (PR = 1.1, 95% CI: 0.5 to 2.6).

In the sensitivity analysis, which added recent users to the group of current users, the PRs for SSRI use were very similar to those in the main analysis (Table 2).

DISCUSSION

In our study, women with unhealthy lifestyles were more often current or former users of SSRIs compared with women with healthier lifestyles. However, the prevalence of current and former SSRI use among women not participating in regular physical activity was similar to that among women who participated in regular physical activity. Current but not former use of SSRIs was more common in women with an unhealthy diet and an alcohol intake of more than 14 drinks weekly. Our study contributes to knowledge of how use of SSRIs differs according to lifestyle choices among women of childbearing age.

Our study differs from earlier studies [22-24] by focusing on women of childbearing age. Therefore, our findings are applicable for assessing potential confounding in studies of birth outcomes in women using SSRIs.

However, our findings are in line with the previous findings in populations consisting of both men and women, thus underlining the reliability of our results. A French questionnaire-based public health survey including 10,252 men and women over age 18 years found that both non-smokers and former smokers had 30% lower risk of being prescribed an antidepressant than current smokers.[24] An American study including 43,093 men and women found that abusers of alcohol had an increased risk of major depression compared with lifetime abstainers [OR = 2.1 (95% CI: 1.3 to 3.4) for young adults not attending college and OR = 1.3 (95% CI: 1.0 to 1.6) for adults over age 30, respectively].[22] Also, a meta-analysis including in total 58,745 men and women found that obese persons were at increased risk of developing depression over time [pooled OR = 1.55 (95% CI: 1.23 to 2.01)].[23]

We identified use of SSRIs from a comprehensive population-based prescription database thus eliminating recall bias. This database is considered complete regarding SSRIs, as SSRIs are available by prescription only and therefore not sold as over-the-counter drugs.[30] Furthermore, our use of questionnaires permitted collection of detailed information on the selected lifestyle factors.

Our study also has limitations. The study was cross-sectional and based on responses of women who volunteered to participate in a health survey. Because participants in such surveys might be more health conscious than non-participants, our cohort may not be representative of lifestyle choices in the general population. Survey participation was 69% overall and 71.5% among women aged 25 - 44 years. It is possible that non-participants may have differed from participants not only in lifestyle but also in the prevalence of major depression. This may have led us to underestimate the prevalence of SSRI use among women with unhealthy lifestyles. Furthermore, as information on lifestyle factors was self-reported, it is possible that unhealthy lifestyles were underreported. It is possible that women who are depressed/using SSRIs may report lifestyle factors differently than other women and such a potential misclassification may affect our results.

Also, redeemed prescriptions may be an imperfect measure of actual drug intake and timing. This may have led to misclassification of some non-users as SSRI users due to non-compliance. While this would not explain our finding of a higher prevalence of current SSRI use among women with an unhealthy lifestyle, it could have led us to underestimate the association.

The results of this cross-sectional survey may be useful in quantifying the degree to which uncontrolled confounding by lifestyle factors may affect studies of SSRI use during pregnancy. However, it must be noted that women might alter their lifestyle in terms of alcohol use, smoking, and diet before or during pregnancy and thus the results may not be applicable for all pregnant women.

In conclusion, women with an unhealthy lifestyle were about 1.5-fold more likely to be current or former SSRI users than women with a healthier lifestyle.

Table 1. Distribution of selective serotonin reuptake inhibitor (SSRI) use in women aged 25-44 years according to lifestyle factors.

	Current use of SSRIs N (%)	Recent use of SSRIs N (%)	Former use of SSRIs N (%)	Never use of SSRIs N (%)	Total N (%)
Number of women	161 (3.8)	60 (1.4)	223 (5.3)	3,790 (89.5)	4,234 (100)
Median age and [range of	38.0 [25.4-44.9]	34.6 [25.3-44.9]	39.0 [25.3-44.9]	36.8 [25.1-44.9]	36.9 [25.1-44.9]

age]					
BMI					
<18.5	5 (5.1)	3 (3.1)	3 (3.1)	87 (88.8)	98 (100)
18.5-24.9	72 (3.0)	36 (1.5)	128 (5.2)	2,245 (90.5)	2,481 (100)
25.0-29.9	49 (4.9)	11 (1.1)	47 (4.7)	890 (89.3)	997 (100)
≥30.0	30 (5.3)	8 (1.4)	38 (6.8)	486 (86.5)	562 (100)
Missing	5 (5.2)	2 (2.1)	7 (7.3)	82 (85.4)	96 (100)
Smoking					
Current	44 (5.1)	20 (2.3)	67 (7.8)	725 (84.7)	856 (100)
Former	33 (3.2)	12 (1.2)	59 (5.5)	912 (89.8)	1,016 (100)
Never	82 (3.5)	27 (1.2)	95 (4.1)	2,136 (91.3)	2,340 (100)
Missing	2 (9.1)	1 (4.5)	2 (9.1)	17 (77.3)	22 (100)
Diet					
Unhealthy	26 (6.1)	12 (2.8)	24 (5.6)	366 (85.5)	428 (100)
Reasonable healthy	95 (3.5)	33 (1.2)	144 (5.3)	2,465 (90.1)	2,737 (100)
Healthy	38 (3.8)	14 (1.4)	48 (4.8)	895 (90.0)	995 (100)
Missing	2 (1.5)	59 (44.7)	7 (5.3)	64 (48.5)	132 (100)
Intake of alcohol					
More than seven drinks weekly	23 (6.3)	2 (0.5)	23 (6.3)	320 (87.0)	368 (100)
Seven drinks or less weekly	124 (3.5)	49 (1.4)	165 (4.7)	3,197 (90.4)	3,535 (100)
More than 14 drinks weekly	11 (10.6)	1 (1.0)	5 (4.8)	87 (83.7)	104 (100)
14 drinks or less weekly	136 (3.6)	50 (1.3)	183 (4.8)	3,430 (90.3)	3,799 (100)
Missing	14 (4.2)	9 (2.7)	35 (10.6)	273 (82.5)	331 (100)
Participation in regular physical activity					
Yes	77 (3.6)	24 (1.1)	102 (4.8)	1,935 (90.5)	2,138 (100)
No	83 (4.1)	35 (1.7)	119 (5.8)	1,803 (88.4)	2,040 (100)
Missing	1 (1.8)	1 (1.8)	2 (3.6)	52 (92.9)	56 (100)
Use of drugs other than SSRI					
Anti-diabetic drugs	1 (2.1)	2 (4.3)	4 (8.5)	40 (85.1)	47 (100)
Antiepileptic drugs	12 (15.2)	7 (8.9)	20 (25.3)	40 (50.6)	79 (100)

Antipsychotic drugs	30 (31.6)	3 (3.2)	32 (33.7)	30 (31.6)	95 (100)

Diet: Healthy (high amount of fruit, vegetables, fish, and low amount of saturated fat), reasonably healthy (median high amount of fruit, vegetables, fish, and saturated fat), or unhealthy diet (low amount of fruit, vegetables, fish, and high amount of saturated fat) .

Participation in regular physical exercise: Physical activity was asked as participation in leisure sports or other regular physical activity (yes/no) in the questionnaire.

Table 2. Prevalence ratios (PRs) and 95% confidence intervals (95% CIs) for use of selective serotonin reuptake inhibitors (SSRIs) in women aged 25-44 years, according to different lifestyle factors.

SSRI use	PRs comparing obese vs. non-obese women [95% CIs]	PRs comparing current smokers vs. non-current smokers [95% CIs]	PRs comparing alcohol intake above seven drinks weekly vs. alcohol intake of seven drinks or less weekly [95% CIs]	PRs comparing alcohol intake above 14 drinks weekly vs. alcohol intake of 14 drinks or less weekly [95% CIs]	PRs comparing unhealthy diet vs. healthy diet [95% CIs]	PRs comparing participation in regular activity vs. not participation in regular activity [95% CIs]
Never use	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Current use	1.5 [1.0 – 2.3]	1.6 [1.1 – 2.2]	1.8 [1.2 – 2.8]	2.9 [1.7 – 5.3]	1.7 [1.2 – 2.6]	0.9 [0.6 – 1.2]
Current/recent use	1.4 [1.0 – 2.0]	1.7 [1.3 – 2.2]	1.4 [0.9 – 2.1]	2.4 [1.4 – 4.1]	1.8 [1.3 – 2.6]	0.8 [0.6 – 1.0]
Former use	1.4 [1.0 – 1.9]	1.8 [1.3 – 2.3]	1.4 [0.9 – 2.1]	1.1 [0.5 – 2.6]	1.1 [0.8 – 1.7]	0.8 [0.6 – 1.0]

Current/recent use: In this group, we added recent use to current use. Current use was defined as women who redeemed at least one prescription within 90 days before and up to 30 days after completing the survey questionnaire. And recent use was defined as women who redeemed a prescription in the period from 365 until 91 days before completing the questionnaire.

Diet: Healthy (high amount of fruit, vegetables, fish, and low amount of saturated fat), reasonably healthy (median high amount of fruit, vegetables, fish, and saturated fat), or unhealthy diet (low amount of fruit, vegetables, fish, and high amount of saturated fat).

Participation in regular physical exercise: Physical activity was asked as participation in leisure sports or other regular physical activity (yes/no) in the questionnaire.

Acknowledgements: We wish to thank all the participants who helped us conduct this study by completing questionnaires.

Funding: This research was supported by the Clinical Epidemiology Research Foundation, Aarhus University Hospital, Denmark. The Department of Clinical Epidemiology, Aarhus University Hospital, receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of these studies have any relation to the present study.

Competing interests: None declared.

Data sharing statement: No additional data available.

REFERENCES

*1 Bennett HA, Einarson A, Taddio A, et al. Prevalence of depression during pregnancy; systematic review. Obstet Gynecol 2004;**103**:698-709.*

*2 Bennett HA, Einarson A, Taddio A, et al. Depression during Pregnancy: Overview of Clinical Factors. Clin Drug Investig 2004;**24**:157-179.*

*3 Zuckerman B, Amaro H, Baucher H, et al. Depressive symptoms during pregnancy: relationship to poor health behaviors. Am J Obstet gynecol 1989;**160**:1107-1111.*

*4 Lejoyeux M, Leon E, Rouillon F. Prevalence and risk factors of suicide and attempted suicide. Encephale 1994;**20**:495-503.*

*5 Bonari L, Pinto N, Ahn E, et al. Perinatal risks of untreated depression during pregnancy. Can J Psychiatry 2004;**49**:726-735.*

*6 Grote NK, Bridge JA, Gavin AR, et al. A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. Arch Gen Psychiatry 2010;**67**:1012-1024.*

*7 Cooper WO, Willy ME, Pont SJ, et al. Increasing use of antidepressants in pregnancy. Am J Obstet Gynecol 2007;**196**:544.e1-e5.*

*8 Andrade SE, Raebel MA, Brown J, et al. Use of antidepressant medications during pregnancy: a multisite study. Am J Obstet Gynecol 2008;**198**:194.e1-e5.*

9 Available at: http://www.sst.dk/Nyhedscenter/Nyheder/2007/nye_tal_20-07.aspx . Accesed 3/29 2013.

*10 Wen SW, Yang Q, Garner P, et al. Selective serotonin reuptake inhibitors and adverse pregnancy outcomes. Am J Obstet Gynecol 2006;**194**:961-966.*

*11 Lund N, Pedersen LH, Henriksen TB. Selective serotonin reuptake inhibitor exposure in utero and pregnancy outcomes. Arch Pediatr Adolesc Med 2009;**163**:949-954.*

*12 Reis M, Kallen B. Delivery outcome after maternal use of antidepressant drugs in pregnancy: an update using Swedish data. Psychol Med 2010;**40**:1723-1733.*

*13 Pedersen LH, Henriksen TB, Vestergaard M, et al. Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study. BMJ 2009;**339**:b3569.*

*14 Kieler H, Artama M, Engeland A, et al. Selective serotonin reuptake inhibitors during pregnancy and risk of persistent pulmonary hypertension in the newborn: population based cohort study from the five Nordic countries. BMJ 2012;**339**:d8012.*

15 Jimenez-Solem E, Andersen JT, Petersen M, et al. Exposure to selective serotonin reuptake inhibitors and the risk of congenital malformations: a nationwide cohort study. BMJ Open 2012;2:e001148

*16 Reis M, Kallen B. Combined use of selective serotonin reuptake inhibitors and sedatives/hypnotics during pregnancy: risk of relatively severe congenital malformations or cardiac defects: A register study. BMJ Open 2013;**3**.*

*17 Alwan S, Reefhuis J, Rasmussen SA, et al. Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth defects. N Engl J Med 2007;**356**:2684-2692.*

*18 Rogers JM. Tobacco and pregnancy: overview of exposures and effects. Birth Defects Res C embryo Today 2008;**84**:1-15.*

*19 Dennedy MC, Avalos G, O´Reilly MW, et al. The impact of maternal obesity on gestational outcomes. Ir Med J 2012;**105**:23-25.*

*20 Erickson AC, Arbour LT. Heavy smoking during pregnancy as a marker for other risk factors of adverse birth outcomes: a population-based study in British Columbia, Canada. BMC Public Health 2012;**12**:102.*

*21 Mateja WA, Nelson DB, Kroelinger CD, et al. The association between maternal alcohol use and smoking in early pregnancy and congenital cardiac defects. J Womens Health (Larchmt) 2012;**21**:26-34.*

*22 Dawson DA, Grant BF, Stinson FS, et al. Psychopathology associated with drinking and alcohol use disorders in the college and general adult populations. Drug Alcohol Depend 2005;**77**:139-150.*

*23 Luppino FS, de Wit LM, Bouvy PF, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch Gen Psychiatry 2010;**67**:220-229.*

*24 Cheron-Launay M, Le Faou AL, Sevilla-Dedieu C, et al. Smoking and the consumption of antidepressants, anxiolytics and hypnotic drugs: results of a large, French epidemiological study in 2005. Addict Behav 2011;**36**:743-748.*

*25 Pedersen CB. The Danish Civil Registration System. Scand J Public Health 2011;**39**:22-25.*

*26 Edwards P, Roberts I, Clarke M, et al. Increasing response rates to postal questionnaires: systematic review. BMJ 2002;**324**:1183.*

27 Available at: http://apps.who.int/bmi/index.jsp?introPage=intro_3.html . Accessed 3/29 2013.

*28 Toft U, Kristoffersen LH,Lau C, et al. The Dietary Quality Score: validation and association with cardiovascular risk factors: the Inter99 study. Eur J Clin Nutr 2007;**61**:270-278.*

29 Available at: www.sst.dk/Sundhed%20og%20forebyggelse/Alkohol.aspx. Accessed 5/28 2013.

*30 Ehrenstein V, Antonsen S, Pedersen L. Existing data sources for clinical epidemiology: Aarhus University Prescription Database. Clin Epidemiol 2010;**2**:273-279.*

Use of selective serotonin reuptake inhibitors and lifestyle among women of childbearing age: A Danish cross-sectional survey

Kristina Laugesen[1], Ane Birgitte Telén Andersen[1], Mette Nørgaard[1], Rikke Beck Nielsen[1], Reimar Wernich Thomsen[1], Finn Breinholt Larsen[2], Henrik Toft Sørensen[1]

[1] Department of Clinical Epidemiology, Institute of Clinical Medicine, Aarhus University Hospital, 8200 Aarhus, Denmark

[2] Public Health and Quality Improvement, Central Denmark Region, 8200 Aarhus, Denmark

Corresponding author: Kristina Laugesen, Department of Clinical Epidemiology, Institute of Clinical Medicine, Aarhus University Hospital, Olof Palmes Allé 43-45, 8200 Aarhus N, Denmark. Phone: +4587168063; Fax: +4587167215; E-mail: kristina.laugesen@studmed.au.dk

Keywords: antidepressants, lifestyle, women, fertile

ABSTRACT

Objective To examine the use of selective serotonin reuptake inhibitors (SSRIs) among Danish women of childbearing age according to lifestyle factors.

Design Cross-sectional survey.

Setting The Central Denmark Region.

Participants 4,234 women (71.5% of the invited) aged 25-44 years who participated in a public health survey in 2006.

Outcome measures Prevalence and prevalence ratios (PRs) of current and former SSRI use among women characterized by selected lifestyle factors. We obtained information on SSRI use through linkage to the Aarhus University Prescription Database covering all pharmacies in the region.

Results Of 4,234 women in the study, 161 (3.8%) were current SSRI users, 60 (1.4%) were recent users, 223 (5.3%) were former users, and 3,790 (89.5%) were never users. Current use of SSRIs was more prevalent in obese women than in non-obese women (PR = 1.5, 95% CI: 1.0 to 2.3), in current smokers compared with non-current smokers (PR = 1.6, 95% CI: 1.1 to 2.2), in women who drank more than seven~~14~~ alcoholic drinks weekly compared with women who drank seven~~14~~ or fewer drinks weekly (PR = 1.8, 95% CI: 1.2 to 2.8), and in women with an unhealthy diet compared with women with a healthy diet (PR = 1.7, 95%: CI: 1.2 to 2.6). Prevalence of former use of SSRIs was similarly increased except in those with an unhealthy diet (PR= 1.1, 95% CI: 0.8 to 1.7). SSRI use did not differ according to participation in regular physical activity.

Conclusion Women with an unhealthy lifestyle were about 1.5-fold more likely to be current or former users of SSRIs than those with a healthy lifestyle. These findings may be useful for

quantitative assessment of the contribution of lifestyle factors to uncontrolled confounding in studies of SSRI use in pregnancy.

ARTICLE SUMMARY

Article focus

- To examine whether current and former use of SSRIs differ according to lifestyle factors among women of childbearing age.

Key messages

- Of 4,234 women aged 25-44 years participating in a public health survey, 161 (3.8%) were current SSRI users, 60 (1.4%) were recent users, and 223 (5.3%) were former users.
- Current and former use of SSRIs were at least 1.5-fold or more prevalent in women who were obese, who were current smokers, or who had a weekly alcohol intake above seven drinks ~~higher than recommended weekly alcohol intake~~, as compared with women with a healthier lifestyle. Current but not former use of SSRIs was more common in women with an unhealthy diet and in women with intake of alcohol of more than 14 drinks weekly. SSRI use did not differ much according to participation in regular physical activity.

Strengths and limitations of this study

- SSRI use was identified from a comprehensive population-based prescription database, thus eliminating recall bias. The high quality and completeness of data in this database has been documented. Detailed information on lifestyle factors was available from questionnaires.

- Because the study was based on volunteers in a health survey (participation rate of women of childbearing age = 71.5%), participants may have been more health conscious than non-participants.
- Filled prescriptions may not be an entirely perfect measure of actual drug intake and its timing and thus may have led to some misclassification of SSRI use.

INTRODUCTION

More than 10% of pregnant women experience depression.[1] In deciding to initiate antidepressant drug treatment in pregnant women, potential negative effects of untreated depression on the mother and fetus [2-6] must be weighed against the risk of adverse pregnancy outcomes associated with in utero exposure to antidepressant drugs.[2]

Selective serotonin reuptake inhibitors (SSRIs) constitute the most commonly used class of antidepressants. Use of these drugs has substantially increased [7,8] in recent years. In Denmark, 2.4% of all pregnant women were treated with SSRIs in 2006, compared with 0.3% in 1997.[9]

In a number of studies, SSRI use has been associated with adverse pregnancy outcomes including preterm birth, poor neonatal adaptation, low birth weight, persistent pulmonary hypertension, and cardiac malformations.[10-15]. One study reported an elevated risk of risk of cardiac malformations after prenatal exposure to SSRI, but concluded that this was due to unaccounted confounding.[15] However, other studies did not find such associations.[16,17] Studies investigating these associations often have lacked information on maternal lifestyle factors, such as smoking,[10] alcohol consumption,[12-14] and body mass index (BMI),[10,13,14]. Thus, they may have been biased by uncontrolled confounding, complicating interpretation of their results.

Unhealthy lifestyle choices during pregnancy, including smoking, alcohol consumption, and obesity, are known to be associated with increased risk of adverse pregnancy outcomes.[18-21] Still, few studies have investigated whether use of antidepressants differs according to lifestyle factors. Available studies have reported that depression and antidepressant use are more frequent among smokers, alcohol consumers, and obese people.[22-24] In the current study, we used data from a Danish public health survey to examine the relation between SSRI use and lifestyle among women of childbearing age.

METHODS

Study design

We conducted a cross-sectional study based on a 2006 public health survey administered in the Central Denmark region.

Setting

Denmark has 5.5 million inhabitants and is administratively divided into five regions. We conducted this study in one of these regions, the Central Denmark Region, with a population of about 1.2 million people. The Danish healthcare system provides tax-supported healthcare to all residents, guaranteeing free and unfettered access to primary and secondary care. Except for emergencies, general practitioners (GPs) are patients' initial contact with the health care system. GPs either treat the patients themselves or refer them to hospitals or specialists in the primary health care sector.

The unique 10-digit central personal registry number (CPR number) assigned to each Danish citizen at birth and to residents upon immigration [25] allows accurate and unambiguous linkage of all medical and administrative registries at the individual level in Denmark.

Study population

The study population was identified through the survey, "Hvordan har du det?"/ "How Are You?", a questionnaire-based public health study conducted by the Centre for Public Health (now Centre for Public Health and Quality Improvement), Central Denmark Region. In 2006, a random sample of 31,500 people, living in the region, was invited to participate in the study. Eligible participants,

identified through the Civil Registration System, were 25-79 years of age, residents of the Central Denmark Region, and Danish citizens with at least one parent born in Denmark. In total, 21,708 (69%) invited persons agreed to participate. A questionnaire and stamped return envelope was delivered by mail. In order to maximize participation [26], three reminders were sent to non-respondents. Those who agreed to participate completed a detailed questionnaire containing approximately 400 questions on self-rated health, occurrence of chronic diseases, socioeconomic factors, and lifestyle factors. The current study was based on a subsample of female respondents of childbearing age, defined as age 25-44 years. In this subsample, 4,234 (71.5 %) invited women agreed to participate.

The survey has been described in detail elsewhere (available in Danish: http://www.cfk.rm.dk/udgivelser/befolkningsundersøgelser).

Data on lifestyle factors

Lifestyle factors included in the study were BMI, participation in regular physical activity, diet, smoking status, and alcohol intake.

BMI was calculated as self-reported weight in kilograms divided by self-reported height in meters squared. BMI was categorized according to WHO criteria as underweight (BMI<18.5), normal weight (BMI 18.5-24.99), overweight (BMI 25-29.99), and obese (BMI ≥30).[27] Physical activity was in the questionnaire asked as participation in leisure sports or other regular physical activity (yes/no). To assess diet, this health survey used a score system developed by the Research Centre for Prevention and Health, the Capital Region of Denmark.[28] This included 30 different questions regarding intake of fruit, vegetables, fish, and fat. By the score system the responses were summarized into categories of healthy (high amount of fruit, vegetables, fish, and low amount of saturated fat), reasonably healthy (median high intake of fruit, vegetables, fish, and saturated fat),

or unhealthy diet (low amount of fruit, vegetables, fish, and high amount of saturated fat). Smoking status was categorized as never, former, and current (daily or occasional) tobacco smoking. Finally, alcohol use was in the questionnaire asked as how many drinks per week you drink. First, we categorized alcohol use according to the Danish Health and Medicine Authority's recommendations, *i.e.*, higher than recommended (> seven drinks weekly) or within recommended guidelines (≤ seven drinks weekly).[29] Second, we categorized alcohol in > 14 drinks weekly and ≤ 14 drinks weekly.

Data on SSRI and antiepileptic, anti-diabetics and antipsychotic use

In Denmark, antidepressants are available on prescription only. All pharmacies in the Central Denmark Region are equipped with a computerized accounting system that transmits data to the Danish Health Service for reimbursement of prescribed drugs. According to an agreement with Aarhus University, the National Health Service subdivision of the Central Denmark Region transfers individually identifiable prescription redemption data from the pharmacies to the Aarhus University Prescription Database (AUPD). The AUPD contains information on the CPR number of the patient, type of drug prescribed according to name and the Anatomic Therapeutic Chemical classification system (ATC), and date the prescription was redeemed.[30] Data are available from 1996 onwards. In Denmark, a prescription for SSRI generally lasts between 28 days and 100 days given that the daily use is one DDD. We classified current users of SSRIs (ATC code N06AB) as those who redeemed at least one prescription within 90 days before and up to 30 days after completing the survey questionnaire. We defined recent users as those who redeemed a SSRI prescription in the period from 365 until 91 days before completing the questionnaire. Former users were those who redeemed at least one SSRI prescription more than 365 days before completing the

questionnaire but had no prescriptions within 365 days before and up to 30 days after questionnaire completion. Never users were defined as women who never had a prescription for a SSRI.

We further defined use of anti-diabetic (ATC code A10), antiepileptic (ATC code N03), and antipsychotic (ATC code N05A) drugs as ever having redeemed a prescription on these drugs before filling in the questionnaire.

STATISTICAL ANALYSES

We computed the prevalence of SSRI use (current, former, recent and never use) according to the available lifestyle factors and according to use of anti-diabetic, antiepileptic, and antipsychotic drugs . We then calculated prevalence ratios (PRs) and 95% confidence intervals (CIs) by the Clopper-Pearson exact method for current SSRI use and former SSRI use, comparing obese (BMI ≥ 30) to non-obese women (BMI < 30), current smokers to non-current smokers (never and former smokers), women with alcohol intake of more than seven drinks weekly ~~recommended alcohol use~~ to women with alcohol intake of seven drinks or less weekly~~who used alcohol within the recommended amount~~, women with alcohol intake of more than 14 drinks to women with alcohol intake of 14 drinks or less weekly, women with an unhealthy diet to women with a healthy diet (healthy and reasonably healthy), and women who participated in regular physical activity to women who did not. Women with missing data were excluded from the analyses.

In a sensitivity analysis, we added recent SSRI users to the group of current users and estimated PRs for current/recent use with 95% CIs associated with lifestyle factors. This analysis was undertaken to investigate whether potential misclassification between current and recent users could have affected our estimates.

All statistical analyses were conducted using Stata software (Release 12, StataCorp LP). The study was approved by the Danish Data Protection Agency (Record no. 2009-41-3866).

RESULTS

In total, 4,234 women (71.5% of those invited) aged 25 - 44 years participated in the survey. Of these, 161 (3.8%) were current SSRI users, 223 (1.4%) were former users, 60 (5.3%) were recent users, and 3,790 (89.5%) were never users. We investigated the number of pregnant women in our study population as the number of women who gave birth up to nine month after filling in the questionnaire. In total, we identified 232 pregnant women. Among these, 3 (1.3%) were current users, 3 (1.3%) were recent users, and 11(4.7%) were former users. The small number of pregnant women in our study population did not allow us to examine the relation between use of SSRI and lifestyle factors in pregnancy. Table 1 shows the distribution of SSRI use (current, recent, former, and never use) according to lifestyle factors and use of anti-diabetic, antiepileptic, and antipsychotic drugs.

Table 2 shows PRs for current, current/recent, and former use of SSRIs according to the lifestyle factors. Obese women had a higher prevalence of current SSRI use than non-obese women (PR = 1.5, 95% CI: 1.0 to 2.3). Current smokers had a higher prevalence of current SSRI use than non-current smokers (PR = 1.6, 95% CI: 1.1 to 2.2). Women with an intake of alcohol of more than seven drinks weekly ~~higher than recommended weekly alcohol intake~~ had a higher prevalence of current SSRI use than women whose weekly alcohol intake was seven drinks or less ~~within the recommendations~~ (PR = 1.8, 95% CI: 1.2 to 2.8). Using 14 drinks per week as level for overuse, the PR increased (PR = 2.9 , 95% CI: 1.7 to 5.3). Women with an unhealthy diet had a higher prevalence of current SSRI use than women with a healthy diet (PR= 1.7, 95% CI: 1.2 to 2.6). Women who participated in regular physical activity and women, who did not participate in regular

physical activity had a similar prevalence of current SSRI use. The prevalence of former SSRI use by lifestyle factors followed the same pattern as current use. The only exception was unhealthy diet (PR = 1.1, 95% CI: 0.8 to1.7) and alcohol intake of more than 14 drinks weekly (PR = 1.1, 95% CI: 0.5 to 2.6).

In the sensitivity analysis, which added recent users to the group of current users, the PRs for SSRI use were very similar to those in the main analysis (Table 2).

DISCUSSION

In our study, women with unhealthy lifestyles were more often current or former users of SSRIs compared with women with healthier lifestyles. However, the prevalence of current and former SSRI use among women not participating in regular physical activity was similar to that among women who participated in regular physical activity. Current but not former use of SSRIs was more common in women with an unhealthy diet and an alcohol intake of more than 14 drinks weekly.

Our study contributes to knowledge of how use of SSRIs differs according to lifestyle choices among women of childbearing age.

Our study differs from earlier studies [22-24] by focusing on women of childbearing age. Therefore, our findings are applicable for assessing potential confounding in studies of birth outcomes in women using SSRIs.

However, our findings are in line with the previous findings in populations consisting of both men and women, thus underlining the reliability of our results. A French questionnaire-based public health survey including 10,252 men and women over age 18 years found that both non-smokers and former smokers had 30% lower risk of being prescribed an antidepressant than current smokers.[24] An American study including 43,093 men and women found that abusers of alcohol had an increased risk of major depression compared with lifetime abstainers [OR = 2.1 (95% CI: 1.3 to 3.4)

for young adults not attending college and OR = 1.3 (95% CI: 1.0 to 1.6) for adults over age 30, respectively].[22] Also, a meta-analysis including in total 58,745 men and women found that obese persons were at increased risk of developing depression over time [pooled OR = 1.55 (95% CI: 1.23 to 2.01)].[23]

We identified use of SSRIs from a comprehensive population-based prescription database thus eliminating recall bias. This database is considered complete regarding SSRIs, as SSRIs are available by prescription only and therefore not sold as over-the-counter drugs.[30] Furthermore, our use of questionnaires permitted collection of detailed information on the selected lifestyle factors.

Our study also has limitations. The study was cross-sectional and based on responses of women who volunteered to participate in a health survey. Because participants in such surveys might be more health conscious than non-participants, our cohort may not be representative of lifestyle choices in the general population. Survey participation was 69% overall and 71.5% among women aged 25 - 44 years. It is possible that non-participants may have differed from participants not only in lifestyle but also in the prevalence of major depression. This may have led us to underestimate the prevalence of SSRI use among women with unhealthy lifestyles. Furthermore, as information on lifestyle factors was self-reported, it is possible that unhealthy lifestyles were underreported. It is possible that women who are depressed/using SSRIs may report lifestyle factors differently than other women and such a potential misclassification may affect our results.

Also, redeemed prescriptions may be an imperfect measure of actual drug intake and timing. This may have led to misclassification of some non-users as SSRI users due to non-compliance. While

this would not explain our finding of a higher prevalence of current SSRI use among women with an unhealthy lifestyle, it could have led us to underestimate the association.

The results of this cross-sectional survey may be useful in quantifying the degree to which uncontrolled confounding by lifestyle factors may affect studies of SSRI use during pregnancy. However, it must be noted that women might alter their lifestyle in terms of alcohol use, smoking, and diet before or during pregnancy and thus the results may not be applicable for all pregnant women.

In conclusion, women with an unhealthy lifestyle were about 1.5-fold more likely to be current or former SSRI users than women with a healthier lifestyle. ~~These results may be useful in quantifying the degree to which uncontrolled confounding by lifestyle factors may affect studies of SSRI use during pregnancy.~~

Table 1. Distribution of selective serotonin reuptake inhibitor (SSRI) use in women aged 25-44 years according to lifestyle factors.

	Current use of SSRIs N (%)	Recent use of SSRIs N (%)	Former use of SSRIs N (%)	Never use of SSRIs N (%)	Total N (%)
Number of women	161 (3.8)	60 (1.4)	223 (5.3)	3,790 (89.5)	4,234 (100)
Median age and [range of age]	38.0 [25.4-44.9]	34.6 [25.3-44.9]	39.0 [25.3-44.9]	36.8 [25.1-44.9]	36.9 [25.1-44.9]
BMI					
<18.5	5 (5.1)	3 (3.1)	3 (3.1)	87 (88.8)	98 (100)
18.5-24.9	72 (3.0)	36 (1.5)	128 (5.2)	2,245 (90.5)	2,481 (100)
25.0-29.9	49 (4.9)	11 (1.1)	47 (4.7)	890 (89.3)	997 (100)
≥30.0	30 (5.3)	8 (1.4)	38 (6.8)	486 (86.5)	562 (100)
Missing	5 (5.2)	2 (2.1)	7 (7.3)	82 (85.4)	96 (100)
Smoking					
Current	44 (5.1)	20 (2.3)	67 (7.8)	725 (84.7)	856 (100)
Former	33 (3.2)	12 (1.2)	59 (5.5)	912 (89.8)	1,016 (100)
Never	82 (3.5)	27 (1.2)	95 (4.1)	2,136 (91.3)	2,340 (100)
Missing	2 (9.1)	1 (4.5)	2 (9.1)	17 (77.3)	22 (100)
Diet					
Unhealthy	26 (6.1)	12 (2.8)	24 (5.6)	366 (85.5)	428 (100)
Reasonable healthy	95 (3.5)	33 (1.2)	144 (5.3)	2,465 (90.1)	2,737 (100)
Healthy	38 (3.8)	14 (1.4)	48 (4.8)	895 (90.0)	995 (100)
Missing	2 (1.5)	59 (44.7)	7 (5.3)	64 (48.5)	132 (100)
Intake of alcohol					
More than seven drinks weekly	23 (6.3)	2 (0.5)	23 (6.3)	320 (87.0)	368 (100)
Seven drinks or less weekly	124 (3.5)	49 (1.4)	165 (4.7)	3,197 (90.4)	3,535 (100)
More than 14 drinks weekly	11 (10.6)	1 (1.0)	5 (4.8)	87 (83.7)	104 (100)
14 drinks or less weekly	136 (3.6)	50 (1.3)	183 (4.8)	3,430 (90.3)	3,799 (100)
Missing	14 (4.2)	9 (2.7)	35 (10.6)	273 (82.5)	331 (100)
Participation in regular					

physical activity					
Yes	77 (3.6)	24 (1.1)	102 (4.8)	1,935 (90.5)	2,138 (100)
No	83 (4.1)	35 (1.7)	119 (5.8)	1,803 (88.4)	2,040 (100)
Missing	1 (1.8)	1 (1.8)	2 (3.6)	52 (92.9)	56 (100)
Use of drugs other than SSRI					
Anti-diabetic drugs	1 (2.1)	2 (4.3)	4 (8.5)	40 (85.1)	47 (100)
Antiepileptic drugs	12 (15.2)	7 (8.9)	20 (25.3)	40 (50.6)	79 (100)
Antipsychotic drugs	30 (31.6)	3 (3.2)	32 (33.7)	30 (31.6)	95 (100)

Diet: Healthy (high amount of fruit, vegetables, fish, and low amount of saturated fat), reasonably healthy (median high amount of fruit, vegetables, fish, and saturated fat), or unhealthy diet (low amount of fruit, vegetables, fish, and high amount of saturated fat) .

Participation in regular physical exercise: Physical activity was asked as participation in leisure sports or other regular physical activity (yes/no) in the questionnaire.

Table 2. Prevalence ratios (PRs) and 95% confidence intervals (95% CIs) for use of selective serotonin reuptake inhibitors (SSRIs) in women aged 25-44 years, according to different lifestyle factors.

SSRI use	PRs comparing obese vs. non-obese women [95% CIs]	PRs comparing current smokers vs. non-current smokers [95% CIs]	PRs comparing alcohol intake above seven drinks weekly vs. alcohol intake of seven drinks or less weekly [95% CIs]	PRs comparing alcohol intake above 14 drinks weekly vs. alcohol intake of 14 drinks or less weekly [95% CIs]	PRs comparing unhealthy diet vs. healthy diet [95% CIs]	PRs comparing participation in regular activity vs. not participation in regular activity [95% CIs]
Never use	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Current use	1.5 [1.0 – 2.3]	1.6 [1.1 – 2.2]	1.8 [1.2 – 2.8]	2.9 [1.7 – 5.3]	1.7 [1.2 – 2.6]	0.9 [0.6 – 1.2]
Current/recent use	1.4 [1.0 – 2.0]	1.7 [1.3 – 2.2]	1.4 [0.9 – 2.1]	2.4 [1.4 – 4.1]	1.8 [1.3 – 2.6]	0.8 [0.6 – 1.0]
Former use	1.4 [1.0 – 1.9]	1.8 [1.3 – 2.3]	1.4 [0.9 – 2.1]	1.1 [0.5 – 2.6]	1.1 [0.8 – 1.7]	0.8 [0.6 – 1.0]

Current/recent use: In this group, we added recent use to current use. Current use was defined as women who redeemed at least one prescription within 90 days before and up to 30 days after completing the survey questionnaire. And recent use was defined as women who redeemed a prescription in the period from 365 until 91 days before completing the questionnaire.

Diet: Healthy (high amount of fruit, vegetables, fish, and low amount of saturated fat), reasonably healthy (median high amount of fruit, vegetables, fish, and saturated fat), or unhealthy diet (low amount of fruit, vegetables, fish, and high amount of saturated fat).

Participation in regular physical exercise: Physical activity was asked as participation in leisure sports or other regular physical activity (yes/no) in the questionnaire.

Acknowledgements: We wish to thank all the participants who helped us conduct this study by completing questionnaires.

Funding: This research was supported by the Clinical Epidemiology Research Foundation, Aarhus University Hospital, Denmark. The Department of Clinical Epidemiology, Aarhus University Hospital, receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of these studies have any relation to the present study.

Competing interests: None declared.

Data sharing statement: No additional data available.

REFERENCES

*1 Bennett HA, Einarson A, Taddio A, et al. Prevalence of depression during pregnancy; systematic review. Obstet Gynecol 2004;**103**:698-709.*

*2 Bennett HA, Einarson A, Taddio A, et al. Depression during Pregnancy: Overview of Clinical Factors. Clin Drug Investig 2004;**24**:157-179.*

*3 Zuckerman B, Amaro H, Baucher H, et al. Depressive symptoms during pregnancy: relationship to poor health behaviors. Am J Obstet gynecol 1989;**160**:1107-1111.*

*4 Lejoyeux M, Leon E, Rouillon F. Prevalence and risk factors of suicide and attempted suicide. Encephale 1994;**20**:495-503.*

*5 Bonari L, Pinto N, Ahn E, et al. Perinatal risks of untreated depression during pregnancy. Can J Psychiatry 2004;**49**:726-735.*

*6 Grote NK, Bridge JA, Gavin AR, et al. A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. Arch Gen Psychiatry 2010;**67**:1012-1024.*

*7 Cooper WO, Willy ME, Pont SJ, et al. Increasing use of antidepressants in pregnancy. Am J Obstet Gynecol 2007;**196**:544.e1-e5.*

*8 Andrade SE, Raebel MA, Brown J, et al. Use of antidepressant medications during pregnancy: a multisite study. Am J Obstet Gynecol 2008;**198**:194.e1-e5.*

9 Available at: http://www.sst.dk/Nyhedscenter/Nyheder/2007/nye_tal_20-07.aspx . Accesed 3/29 2013.

*10 Wen SW, Yang Q, Garner P, et al. Selective serotonin reuptake inhibitors and adverse pregnancy outcomes. Am J Obstet Gynecol 2006;**194**:961-966.*

*11 Lund N, Pedersen LH, Henriksen TB. Selective serotonin reuptake inhibitor exposure in utero and pregnancy outcomes. Arch Pediatr Adolesc Med 2009;**163**:949-954.*

*12 Reis M, Kallen B. Delivery outcome after maternal use of antidepressant drugs in pregnancy: an update using Swedish data. Psychol Med 2010;**40**:1723-1733.*

*13 Pedersen LH, Henriksen TB, Vestergaard M, et al. Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study. BMJ 2009;**339**:b3569.*

*14 Kieler H, Artama M, Engeland A, et al. Selective serotonin reuptake inhibitors during pregnancy and risk of persistent pulmonary hypertension in the newborn: population based cohort study from the five Nordic countries. BMJ 2012;**339**:d8012.*

15 Jimenez-Solem E, Andersen JT, Petersen M, et al. Exposure to selective serotonin reuptake inhibitors and the risk of congenital malformations: a nationwide cohort study. BMJ Open 2012;2:e001148

*16 Reis M, Kallen B. Combined use of selective serotonin reuptake inhibitors and sedatives/hypnotics during pregnancy: risk of relatively severe congenital malformations or cardiac defects: A register study. BMJ Open 2013;**3**.*

*17 Alwan S, Reefhuis J, Rasmussen SA, et al. Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth defects. N Engl J Med 2007;**356**:2684-2692.*

*18 Rogers JM. Tobacco and pregnancy: overview of exposures and effects. Birth Defects Res C embryo Today 2008;**84**:1-15.*

*19 Dennedy MC, Avalos G, O´Reilly MW, et al. The impact of maternal obesity on gestational outcomes. Ir Med J 2012;**105**:23-25.*

*20 Erickson AC, Arbour LT. Heavy smoking during pregnancy as a marker for other risk factors of adverse birth outcomes: a population-based study in British Columbia, Canada. BMC Public Health 2012;**12**:102.*

*21 Mateja WA, Nelson DB, Kroelinger CD, et al. The association between maternal alcohol use and smoking in early pregnancy and congenital cardiac defects. J Womens Health (Larchmt) 2012;**21**:26-34.*

*22 Dawson DA, Grant BF, Stinson FS, et al. Psychopathology associated with drinking and alcohol use disorders in the college and general adult populations. Drug Alcohol Depend 2005;**77**:139-150.*

*23 Luppino FS, de Wit LM, Bouvy PF, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch Gen Psychiatry 2010;**67**:220-229.*

*24 Cheron-Launay M, Le Faou AL, Sevilla-Dedieu C, et al. Smoking and the consumption of antidepressants, anxiolytics and hypnotic drugs: results of a large, French epidemiological study in 2005. Addict Behav 2011;**36**:743-748.*

*25 Pedersen CB. The Danish Civil Registration System. Scand J Public Health 2011;**39**:22-25.*

*26 Edwards P, Roberts I, Clarke M, et al. Increasing response rates to postal questionnaires: systematic review. BMJ 2002;**324**:1183.*

27 Available at: http://apps.who.int/bmi/index.jsp?introPage=intro_3.html . Accessed 3/29 2013.

28 Toft U, Kristoffersen LH,Lau C, et al. The Dietary Quality Score: validation and association with cardiovascular risk factors: the Inter99 study. Eur J Clin Nutr 2007;**61**:270-278.

29 Available at: www.sst.dk/Sundhed%20og%20forebyggelse/Alkohol.aspx. Accessed 5/28 2013.

30 Ehrenstein V, Antonsen S, Pedersen L. Existing data sources for clinical epidemiology: Aarhus University Prescription Database. Clin Epidemiol 2010;**2**:273-279.

Table x. Prevalence ratios (PRs) and 95% confidence intervals (95% CIs) for use of selective serotonin reuptake inhibitors (SSRIs) in women aged 25-44 years, according to different lifestyle factors and stratified on age (25-34 and 35-44 years of age).

SSRI use	PRs comparing obese vs. non-obese women [95% CIs]	PRs comparing current smokers vs. non-current smokers [95% CIs]	PRs comparing alcohol intake above seven drinks weekly vs. alcohol intake of seven drinks or less weekly [95% CIs]	PRs comparing alcohol intake above 14 drinks weekly vs. alcohol intake of 14 drinks or less weekly [95% CIs]	PRs comparing unhealthy diet vs. healthy diet [95% CIs]	PRs comparing participation in regular activity vs. not participation in regular activity [95% CIs]
25-44 years of age						
Never use	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Current use	1.5 [1.0 – 2.3]	1.6 [1.1 – 2.2]	1.8 [1.2 – 2.8]	2.9 [1.7 – 5.3]	1.7 [1.2 – 2.6]	0.9 [0.6 – 1.2]
Current/recent use	1.4 [1.0 – 2.0]	1.7 [1.3 – 2.2]	1.4 [0.9 – 2.1]	2.4 [1.4 – 4.1]	1.8 [1.3 – 2.6]	0.8 [0.6 – 1.0]
Former use	1.4 [1.0 – 1.9]	1.8 [1.3 – 2.3]	1.4 [0.9 – 2.1]	1.1 [0.5 – 2.6]	1.1 [0.8 – 1.7]	0.8 [0.6 – 1.0]
25-34 years of age						
Never use	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Current use	1.2 [0.6- – 2.5]	2.3 [1.3 – 4.0]	2.0 [0.9 – 4.6]	5.8 [2.0 – 16.6]	3.0 [1.7 – 5.4]	0.8 [0.5 – 1.4]
Current/recent use	1.3 [0.7 – 2.2]	2.1 [1.4 – 3.3]	1.4 [0.7 – 3.1]	4.9 [1.9 – 11.1]	2.8 [1.8 – 4.4]	0.8 [0.5– 1.1]
Former use	1.1[0.6 – 2.0]	2.2 [1.4 – 3.5]	1.6 [0.8 – 3.5]	1.5 [0.2 – 10.1]	0.9 [0.4 – 1.9]	0.8 [0.5 – 1.2]
35-44 years of age						
Never use	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Current use	1.7 [1.1 – 2.7]	1.3 [0.8 – 2.0]	1.7 [1.0 – 2.7]	2.3 [1.2 – 4.6]	1.2 [0.7 – 2.1]	0.9 [0.6 – 1.3]
Current/recent use	1.5 [1.0 – 2.3]	1.4 [1.0 – 2.1]	1.4 [0.9 – 2.3]	1.9 [1.0 – 3.7]	1.3 [0.8 – 2.1]	0.8 [0.6 – 1.1]
Former use	1.6 [1.1 – 2.4]	1.5 [1.1 – 2.2]	1.2 [0.8 – 2.1]	1.0 [0.4 – 2.6]	1.3 [0.8 – 2.1]	0.8 [0.6 – 1.1]

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6,7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7,8,9
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	7,8,9
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7,8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	9
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	10
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10,14
		(b) Indicate number of participants with missing data for each variable of interest	14
Outcome data	15*	Report numbers of outcome events or summary measures	10, 14
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	16
		(*b*) Report category boundaries when continuous variables were categorized	7, 8, 14
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9, 16
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
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	12, 13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11, 12
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
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	17

*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.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.