

# **Gender differences in the association between prescribed antidepressants and other prescribed drugs: a nationwide register-based study in Sweden**

Thunander Sundbom L, Hedborg K.

## **Abstract**

**Background:** People with depression are prescribed more drugs than people in general, partly due to comorbidity with other conditions. However, little research has been done on depression-related drug use from a gender perspective.

**Aim:** Examine gender differences in the association between antidepressants, other drugs, and polypharmacy.

**Methods:** Data on drugs dispensed October to December 2016 to all Swedish citizens aged 18-84 years were collected from the Swedish prescribed drug register. Logistic regression analyses were performed to examine gender differences in the associations between antidepressants and other drugs.

**Results:** For both men and women, associations were found between antidepressants and drugs for alimentary tract problems, respiratory problems, drugs for the blood, and drugs for the nervous system, analgesics, and polypharmacy. For many of the drugs, for example those for respiratory problems and analgesics, the association was stronger in women than in men. However, concerning drugs for the nervous system and polypharmacy, the association was stronger in men than in women. Furthermore, for women, but not men, associations were found for drugs for diabetes, musculoskeletal problems, dermatological problems, and systemic hormones.

**Conclusions:** Many of the associations between antidepressants and other drugs were found to be specific, or stronger, among women than among men. In some cases, however, the associations were stronger in men. Whether this indicates that men and women differ in comorbidity between depression and other conditions cannot be concluded based on this cross-sectional study. However, physicians should be aware that possible gender differences in comorbidity exist, and because comorbidity between depression and other conditions impairs the possibility of recovery, and decreases adherence, screening for depression could be valuable.

**Keywords:** Gender, Antidepressants, Prescribed drugs, Polypharmacy.

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## **Background and aim**

Depression, and hence the use of antidepressants, is common in the general population. The point prevalence of diagnosed depression is estimated to 5-8%, more common in women than in men. The prescription of antidepressants has even higher point prevalence, in Sweden approximately 9% (1-5). In general, people with depression are also prescribed drugs other than antidepressants more often than are those without depression (6, 7). The reason for this can partly be explained by comorbidity between depression and other conditions, mental as well as physical (8, 9). For example, in chronic diseases like diabetes, heart disease, and asthma, the prevalence of depression is above average (10-13). Moreover, there is a strong link between depression and medically inexplicable physical symptoms such as various pain conditions (e.g., fibromyalgia) and gastro intestinal symptoms (e.g., irritable bowel syndrome and non-ulcer dyspepsia) – problems that often lead to high health care utilization and consequently many prescribed drugs (14, 15). In addition, people with depression experience more severe symptoms and have more difficulty getting used to the symptoms of physical disease, probably increasing drug use additionally (16). Thus, physical disease is a risk factor for depression due to the burden of the physical disease and, vice versa, depression seems to be a risk factor for physical disease. This may have several causes. For instance, indirect depression-related effects, such as unhealthy lifestyle and poor adherence to medical recommendations, are considered important (17, 18). Moreover, depression and physical diseases sometimes share a common pathogenic mechanism or common genetic or environmental risk factors (19). Whether depression is primary or secondary to physical disease, or bidirectional, is difficult to determine. It is, however, likely that comorbidity impairs the possibility of recovery from the physical disease as well as from the depression (20).

In relation to some diseases, men and women seem to be mentally affected to different extents. Taking pain conditions as an example, depression has been found to be more common in women than in men (21). However, the connection between depression and other conditions, or the use of prescribed drugs for other conditions, in the general population has hardly been studied from a gender perspective. Moreover, although studies have consistently shown a higher use of health care services and drugs among women than among men (5, 22), and among depressed than among non-depressed individuals (6, 7), few studies have investigated the total depression-related drug usage among men and women. The use of multiple drugs (polypharmacy) is not uncomplicated, however, because it generates a greater risk for drug interactions and adverse drug reactions (23, 24). The aim of the present population-based study was to examine gender differences in the association between prescribed antidepressants and other prescribed drugs, different types of drugs as well as polypharmacy.

## **Methods**

The present cross-sectional study was based on all Swedish citizens aged 18-84 years who had dispensed at least one prescribed drug during the period October to December 2016. The study period of 3 months was based on the Swedish regulation that drugs can be dispensed for use during a 90-day period at most. Data on drugs dispensed were collected from the Swedish Prescribed Drug Register (SPDR), a national database established in 2005, regulated by the Swedish government and maintained by the National Board of Health and Welfare (5). The SPDR includes data on all dispensed prescriptions from the entire Swedish population (about 9.9 million inhabitants in 2016), and contains, in addition to the dispensed drugs, information on age, sex, and personal identification number (unique personal identifier given to all Swedish citizens/legal residents). All drugs in the SPDR are classified according to the anatomical therapeutic chemical (ATC) classification system (25). In the present

study, drugs were primarily divided into the anatomical main groups in the ATC system (Table 1). However, in some cases, subgroups were analysed separately, i.e. in main group A, diabetes (A10), and in main group N, analgesics (N01-N02) and antidepressants (N06A). The ATC groups P (Antiparasitic products, foremost preventive and over-the-counter (OTC) drugs) and V (Various, foremost diagnostic aids and antidotes) were excluded from the analyses. Those who had been dispensed at least one antidepressant (N06A) during the 3-month period studied were classified as users of antidepressants. The same classification of users was also applied to all the other ATC groups. Analyses of polypharmacy (defined as  $\geq 4$  types of drugs other than antidepressants, i.e. at least 5 drugs including antidepressants) (26) also concerned ATC groups. The ATC groups were counted once, even if drugs from the group were dispensed more than once.

### *Statistical analyses*

The study population was divided into men and women and users and non-users of different types of prescribed drugs (ATC groups). Chi-square tests (significance level  $p=0.05$ ) were performed to examine gender differences in the prevalence of antidepressants in the study population, as well as gender differences in the prevalence of antidepressants among those prescribed other types of drugs (different ATC groups as well as polypharmacy, Table 1). Logistic regression analyses (OR; 95% CI) were performed to examine the association between antidepressants and other types of prescribed drugs (different ATC groups as well as polypharmacy, Table 2) among men and women, adjusted for age as a potential confounder. The IBM SPSS Statistics for Windows (Version 22.0. Armonk, NY:IBM Corp.) was used to perform the analyses.

### *Ethical considerations*

The study fulfils research ethics requirements and was approved by the Regional Ethical Review Board in Uppsala, Sweden (Reg. no. 2016/235). Data were anonymized before the researchers were given access to it.

## **Results**

The study population included 3,884,468 individuals (42.6% men, and 57.4% women) and was relatively evenly distributed in terms of age (30.2% were 18-44 years of age, 34.1% 45-64 years, and 35.7% 65-84 years on October 1, 2016). In total, 15.3% of the study population dispensed at least one antidepressant during the 3-month period under study, more women (17.4%) than men (12.4%) ( $p<0.001$ ). In Table 1, the prevalence of antidepressants among men and women prescribed drugs from different ATC groups can be found. As can be seen, women were consistently prescribed antidepressants more often than men were in all ATC groups ( $p<0.001$ ).

In Table 2, the results from the logistic regression analyses can be found. Men and women showed somewhat different patterns regarding associations between antidepressants and other types of prescribed drugs. For both men and women, there were associations between antidepressants and drugs for alimentary tract problems, drugs for the blood, analgesics, drugs for the nervous system, drugs for respiratory problems, and polypharmacy. The association was stronger for women than for men concerning drugs for alimentary tract problems, drugs for the blood, analgesics, and drugs for respiratory problems. However, for drugs for the nervous system and polypharmacy, the association was the opposite, that is, stronger in men than in women. Further, for women, but not men, there were associations between antidepressants and drugs for diabetes, drugs for dermatological problems, systemic hormones, and drugs for musculoskeletal problems.

**Table 1** Prevalence of prescribed antidepressants among men and women prescribed other types of drugs (ATC classification)

ATC classification	Men		Women	
	Number*	Percentage proportions antidepressants	Number*	Percentage proportions antidepressants
A01-A09, A11-A16 Alimentary tract & metabolism	370,288	16.0	571,000	22.6
A10 Diabetes	202,191	10.1	137,865	18.2
B01-B06 Blood & blood forming organs	436,186	11.6	414,217	20.6
C01-C10 Cardiovascular system	812,718	9.7	775,499	16.7
D01-D10 Dermatologicals	171,916	11.3	218,242	17.7
G01-G04 Genito urinary systems & sex hormones	205,526	10.3	556,816	12.6
H01-H05 Systemic hormonal preparations	118,279	11.6	341,049	17.5
J01-J07 Antiinfectives for systemic use	198,677	8.8	343,245	14.8
L01-L04 Antineoplastic & immunomodulating agents	58,455	9.0	78,471	14.8
M01-M09 Musculo-skeletal system	217,227	10.5	290,797	19.2
N01-N02 Analgesics	276,973	16.1	465,350	23.8
N03-N05 + N07 Nervous system	306,577	30.7	465,438	36.9
R01-R07 Respiratory system	296,106	12.9	437,373	20.1
S01-S03 Sensory organs	123,560	9.2	173,574	15.7
Polypharmacy <sup>§</sup>	322,393	17.6	475,133	26.2

\*Number of individuals in study population prescribed at least one drug from respective ATC groups.

<sup>§</sup>Defined as  $\geq 4$  types of drugs other than antidepressants.

Chi-square tests comparing men and women;  $p < 0.001$  (all ATC groups and polypharmacy).

## Discussion

Little research has been conducted on the relationship between depression and use of drugs for other conditions in the general population from a gender perspective. Therefore, the present large population-based study examining gender differences in the association between antidepressants and other types of drugs can contribute knowledge that is relevant to clinical practice and provides a basis for future studies on the topic. It is important to emphasize, however, that the cross-sectional design employed does not allow conclusions about causality to be drawn. Moreover, although the SPDR has the advantage of offering complete data on all dispensed drugs, it does not contain indications. Antidepressants, for example, sometimes have indications other than depression, e.g. neuropathic pain, anxiety disorders, and eating disorders, even though depression is still the main indication (27, 28). Dispensed drugs are often used as a proxy for disease (29), but because the indications for drug treatment are not fully known, the following discussion on conditions must be restricted to hypothetical considerations.

**Table 2** Association between prescribed antidepressants and other types of prescribed drugs (ATC classification) among men and women. Logistic regression (antidepressants vs. not antidepressants) adjusted for age

ATC classification	Men	Women
	OR (CI)	OR (CI)
A01-A09, A11-A16 Alimentary tract & metabolism	1.67 (1.65-1.69)	1.69 (1.67-1.70)
A10 Diabetes	0.88 (0.87-0.89)	1.10 (1.08-1.11)
B01-B06 Blood & blood forming organs	1.26 (1.24-1.28)	1.42 (1.40-1.43)
C01-C10 Cardiovascular system	0.77 (0.76-0.78)	0.99 (0.98-1.00)
D01-D10 Dermatologicals	0.87 (0.86-0.88)	1.03 (1.02-1.04)
G01-G04 Genito-urinary systems & sex hormones	0.95 (0.94-0.97)	0.60 (0.59-0.60)
H01-H05 Systemic hormonal preparations	1.00 (0.98-1.02)	1.03 (1.02-1.04)
J01-J07 Antiinfectives for systemic use	0.60 (0.59-0.61)	0.80 (0.79-0.80)
L01-L04 Antineoplastic & immunomodulating agents	0.75 (0.73-0.77)	0.83 (0.81-0.85)
M01-M09 Musculoskeletal system	0.80 (0.79-0.82)	1.16 (1.15-1.17)
N01-N02 Analgesics	1.55 (1.53-1.56)	1.74 (1.72-1.75)
N03-N05 + N07 Nervous system	5.06 (5.01-5.11)	4.47 (4.44-4.51)
R01-R07 Respiratory system	1.02 (1.01-1.03)	1.25 (1.24-1.26)
S01-S03 Sensory organs	0.77 (0.76-0.79)	0.90 (0.88-0.91)
Polypharmacy*	2.44 (2.42-2.47)	2.34 (2.32-2.36)

\*Defined as  $\geq 4$  types of drugs other than antidepressants.

OR= Odds Ratio, CI= 95 % Confidence Interval

The prevalence of antidepressants, in the total study population as well as in all the different ATC groups studied, was higher among women than among men during the 3-month period studied. The overall greater use of antidepressants among women compared to men is well-known (5, 30). However, whether this indicates that women are more depressed than men is hard to confirm. Given the more frequent health care contacts among women compared to men, and given that the diagnostic criteria are based on symptoms reported by women, women are more often diagnosed as having depression and thus more often prescribed antidepressants (31-33). Additionally, studies have shown that women are more likely than men are to receive a prescription when visiting health care services (34), which is important to bear in mind when interpreting our results. Moreover, factors other than gender affect diseases, health care utilization and drug use, factors such as educational level and socioeconomic status, which were not included in our study. Furthermore, depression is sometimes treated with, for example, psychotherapy and not antidepressants.

It has been found that people with depression, due to comorbidity with other conditions and the resultant great use of health care, use more drugs overall than do people without depression (6, 7, 35). In the present study, we found polypharmacy to be highly associated with antidepressants for men and women, with an even stronger association found in men. Medical comorbidity is probably an

important explanation for this association (8, 9). It is difficult to determine, however, whether depression causes conditions treated with various drugs or whether depression is a consequence of other conditions, as both casual pathways are likely. Polypharmacy is often used as an indicator of high morbidity, and the number of drugs may be a valuable proxy for burden of disease (29). The stronger association in men compared to women in our study may be interpreted as indicating that men with depression are more likely to have a high overall morbidity than women are. The association between polypharmacy and antidepressants could also be explained by adverse drug reactions that may be the cause of depression. Previous studies have found that women suffer from adverse drug reactions more often than men do (36), and adverse drug reactions may thus be an explanation for the association between antidepressants and polypharmacy, especially among women. Moreover, polypharmacy increases the risk of adverse drug reactions, such as drug interactions and non-adherence (37, 38), and the strong association between antidepressants and polypharmacy should be a serious cause for concern (39). That is, when prescribing and evaluating drug treatments, physicians need to be aware of the association between depression and polypharmacy. Worth noting is the fact that, in the present study, polypharmacy was based on ATC groups and not specific drugs classes. Thus, for many individuals in the study population, the number of drugs was probably considerably larger than the ATC groups assessed. In addition, the total drug use is certainly underestimated, as many people use medications other than prescribed drugs, such as OTC drugs, herbal remedies, drugs used in hospitals, and those purchased on the Internet. On the other hand, for a variety of reasons, a certain percentage of all dispensed drugs will never be used (i.e., non-adherence), resulting in an overestimation of drug use (40).

In the present study, we found gender differences in the association between antidepressants and many other types of prescribed drugs. For example, an association was found, especially strong in women, between antidepressants and drugs for alimentary tract problems. It is known that many gastrointestinal problems are related to depression (14, 15). Also, in depression it is common for physical symptoms to derive from the gastrointestinal system (10). The stronger association in women found in our study may be explained by a greater comorbidity in women. Nevertheless, many of the drugs prescribed for gastrointestinal problems can be bought OTC. Because women, as mentioned above, seek health care more frequently than men do, it is possible that women have these drugs prescribed whilst men use them without prescription. Furthermore, this ATC group also includes, in addition to drugs for gastrointestinal problems, anti-obesity drugs. Some previous studies have found women at increased risk for depression related to obesity, which may hypothetically be associated with the elevated importance of weight in the identities of women compared to men (41, 42).

In relation to different pain conditions, particularly chronic pain, there is a well-known association with depression (12, 43, 44). We found a strong association between antidepressants and prescribed analgesics, particularly in women. Other studies have found the same: Women seem to be more mentally affected by pain conditions than men are (45). We also found an association for women, but not men, concerning drugs for musculoskeletal problems (including anti-inflammatory drugs related to pain conditions) and systemic hormones (including corticosteroids, often used in pain conditions). Explanations for the strong association between depression and pain in women have been discussed in terms of gender differences in morbidity. Women are more often diagnosed with diseases related to pain, for example, rheumatic diseases and migraine (45). These conditions are often severe and chronic and, therefore, related to depression. Further, women seem to have a greater sensitization to pain compared to men, and differences in work, lifestyle, and stressors may also contribute to the gender differences (46, 47). Moreover, as discussed concerning drugs for gastrointestinal problems, because women seek health care more often than men do, they may also be more likely to have OTC

analgesics prescribed for them.

Previous research has shown an association between depression and diabetes, type 1 as well as type 2 (8, 48). However, few studies have focused on gender differences. One previous study found depression in diabetes to be associated with female gender (49), which corresponds with our study, where an association was found between antidepressants and drugs for diabetes in women, but not in men. Women, more than men, seem to have many concerns related to diabetes self-management in daily life, which may cause depression (49). Depression decreases adherence to treatment regimens, and in diabetes adherence is essential to complication prevention and mortality reduction (50, 51). Thus, physicians need to pay attention to depression in relation to diabetes and should perhaps consider screening for depression, especially in women. In previous studies, asthma and other obstructive respiratory diseases have also been found to be related to depression (52, 53). Just as for many of the other types of drugs studied, we found a stronger association with antidepressants in women than in men. The reason for this gender difference is unclear; it may be related to the symptoms of the disease or to the treatment (54). Previous studies have shown that women in particular reported that their asthma interfered with social activities, sleep, and life in general (55). Just as for diabetes, self-management and adherence are essential to treatment outcomes in obstructive respiratory diseases (56). Therefore, an awareness of depression in relation to respiratory diseases, especially in women, is of great importance, and just as for diabetes, screening for depression may be valuable.

For men as well as women, the association between antidepressants and other drugs for the nervous system was pronounced. Comorbidity between mental health problems is well-known and a cause of more severe symptoms (57). The conditions treated with drug classes included in this ATC group, such as anxiolytics, hypnotics, antipsychotics, antiepileptics, and drugs for Parkinson's disease, have all been found to be related to depression (57-60). A bit surprising, however, was the fact that, in our study, the association was stronger in men than in women. In other studies, comorbidity between depression and other mental health problems, such as anxiety disorders and sleeping disorders, has repeatedly been found to be more frequent in women (60, 61). One hypothetical interpretation could be that the men in our study had a higher prevalence of comorbid mental health problems than the women did. Further studies analysing the association between antidepressants and the specific drug classes in this ATC group could reveal some gender differences that we are unaware of today.

Dermatological problems seriously affect self-image, self-esteem, and the ability to form relationships with others, and in several studies, they have been found to be related to depression (62). Although often seen as insignificant in comparison to other diseases, the effect of dermatological problems on mental health is comparable to that of pain, diabetes, and asthma (63). In the present study, an association between dermatologicals and antidepressants was found for women but not for men. Other studies have also found women to be more mentally affected by dermatological diseases than men are (64). The gender difference would seem to be related to appearance, as symptoms from visible body parts, such as the face and hands, were more often related to mental health problems among women than among men (65). Women with dermatological diseases have also been found to experience great complications in their relations with others (66). Because dermatological problems greatly interfere with women's daily life, the association to depression is important to take seriously.

Unexpectedly, drugs related to the cardiovascular system were not associated with use of antidepressants in the present study, although there is a well-known bi-directional association between depression and heart disease (13, 67). Depression in relation to cardiovascular diseases seems to be

under-recognized (68), however – and as our results indicate, also under-treated. Nevertheless, we found an association, stronger in women than in men, between antidepressants and drugs related to the blood (e.g., anticoagulants). These drugs are often used in cardiovascular diseases, and our result may indicate that men, in particular, are under-treated for depression in relation to cardiovascular diseases. Depression has been found to be associated with increased morbidity and death rates in coronary heart diseases (69), and is therefore important to consider. Screening for depression in relation to cardiovascular diseases, just as for other diseases discussed, could be valuable, particularly in men.

## Conclusions

This large population-based study found that antidepressants were often associated with other types of prescribed drugs, as well as polypharmacy. Many of these associations were found to be specific, or stronger, among women than among men, for example drugs for respiratory diseases, pain conditions, dermatological conditions, and diabetes. However, in some cases, for example in polypharmacy, the association was stronger in men than in women. Whether this indicates that men and women differ in comorbidity between depression and other conditions cannot be determined on the basis of the present cross-sectional study. However, the study does contribute knowledge that is important for clinical practice and that can serve as a basis for future studies on the topic aimed at establishing a causal relationship. Comorbidity between depression and other conditions impairs the possibility of recovery, and decrease adherence to medical recommendations and polypharmacy are associated with adverse drug reactions and other risks that may cause depression. Therefore, physicians should be aware that possible gender differences in comorbidity exist and that, in relation to some diseases, screening for depression could be of great value.

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## References

1. Alonso J, Angermeyer MC, Bernert S, Bruffaerts R, Brugha TS, Bryson H, et al. Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta psychiatrica Scandinavica Supplementum*. 2004 (420):21-7. PubMed PMID: 15128384.
2. Alonso J, Angermeyer MC, Bernert S, Bruffaerts R, Brugha TS, Bryson H, et al. Psychotropic drug utilization in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta psychiatrica Scandinavica Supplementum*. 2004 (420):55-64. PubMed PMID: 15128388.
3. Kessler RC, Aguilar-Gaxiola S, Alonso J, Chatterji S, Lee S, Ormel J, et al. The global burden of mental disorders: an update from the WHO World Mental Health (WMH) surveys. *Epidemiologia e psichiatria sociale*. 2009 Jan-Mar;18(1):23-33. PubMed PMID: 19378696. Pubmed Central PMCID: 3039289.
4. Lejtzén N, Sundquist J, Sundquist K, Li X. Depression and anxiety in Swedish primary health care: prevalence, incidence, and risk factors. *European Archives of Psychiatry and Clinical Neuroscience*. 2014 Apr;264(3):235-45. PubMed PMID: 23828500.
5. The National Board of Health and Welfare. Stockholm: The National Board of Health and Welfare. Official statistics of Sweden. Statistics-Health and Medical Care. Pharmaceuticals-statistics for 2016. 2016.
6. Paaren A, von Knorring L, Jonsson U, Bohman H, Olsson G, von Knorring AL. Drug prescriptions of adults with adolescent depression in a community sample. *Pharmacoepidemiology and Drug Safety*. 2012 Feb;21(2):130-6. PubMed PMID: 21523852.
7. Schmitz N, Kruse J. The relationship between mental disorders and medical service utilization in a

- representative community sample. *Social Psychiatry and Psychiatric Epidemiology*. 2002 Aug;37(8):380-6. PubMed PMID: 12195545.
8. Katon W, Ciechanowski P. Impact of major depression on chronic medical illness. *Journal of Psychosomatic Research*. 2002 Oct;53(4):859-63. PubMed PMID: 12377294.
  9. Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *Lancet*. 2007 Sep 08;370(9590):851-8. PubMed PMID: 17826170.
  10. Sobel RM, Markov D. The impact of anxiety and mood disorders on physical disease: the worried not-so-well. *Current Psychiatry Reports*. 2005 Jun;7(3):206-12. PubMed PMID: 15935135.
  11. Stordal E, Bjelland I, Dahl AA, Mykletun A. Anxiety and depression in individuals with somatic health problems. The Nord-Trøndelag Health Study (HUNT). *Scandinavian Journal of Primary Health Care*. 2003 Sep;21(3):136-41. PubMed PMID: 14531503.
  12. Demyttenaere K, Bruffaerts R, Lee S, Posada-Villa J, Kovess V, Angermeyer MC, et al. Mental disorders among persons with chronic back or neck pain: results from the World Mental Health Surveys. *Pain*. 2007 Jun;129(3):332-42. PubMed PMID: 17350169.
  13. Ormel J, Von Korff M, Burger H, Scott K, Demyttenaere K, Huang YQ, et al. Mental disorders among persons with heart disease - results from World Mental Health surveys. *General hospital psychiatry*. 2007 Jul-Aug;29(4):325-34. PubMed PMID: 17591509. Pubmed Central PMCID: 2048744.
  14. Henningsen P, Zimmermann T, Sattel H. Medically unexplained physical symptoms, anxiety, and depression: a meta-analytic review. *Psychosomatic Medicine*. 2003 Jul-Aug;65(4):528-33. PubMed PMID: 12883101.
  15. Van Oudenhove L, Aziz Q. The role of psychosocial factors and psychiatric disorders in functional dyspepsia. *Nature Reviews Gastroenterology & Hepatology*. 2013 Mar;10(3):158-67. PubMed PMID: 23358396.
  16. Katon W, Lin EH, Kroenke K. The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. *General Hospital Psychiatry*. 2007 Mar-Apr;29(2):147-55. PubMed PMID: 17336664.
  17. Bonnet F, Irving K, Terra JL, Nony P, Berthezene F, Moulin P. Anxiety and depression are associated with unhealthy lifestyle in patients at risk of cardiovascular disease. *Atherosclerosis*. 2005 Feb;178(2):339-44. PubMed PMID: 15694943.
  18. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Archives of Internal Medicine*. 2000 Jul 24;160(14):2101-7. PubMed PMID: 10904452.
  19. Konsman JP, Parnet P, Dantzer R. Cytokine-induced sickness behaviour: mechanisms and implications. *Trends in Neurosciences*. 2002 Mar;25(3):154-9. PubMed PMID: 11852148.
  20. Gerrits MM, van Oppen P, van Marwijk HW, van der Horst H, Penninx BW. The impact of chronic somatic diseases on the course of depressive and anxiety disorders. *Psychotherapy and Psychosomatics*. 2013;82(1):64-6. PubMed PMID: 23147409.
  21. Bingefors K, Isacson D. Epidemiology, co-morbidity, and impact on health-related quality of life of self-reported headache and musculoskeletal pain--a gender perspective. *European Journal of Pain*. 2004 Oct;8(5):435-50. PubMed PMID: 15324775.
  22. Loikas D, Wettermark B, von Euler M, Bergman U, Schenck-Gustafsson K. Differences in drug utilisation between men and women: a cross-sectional analysis of all dispensed drugs in Sweden. *BMJ open*. 2013;3(5). PubMed PMID: 23645921. Pubmed Central PMCID: 3646185.
  23. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. *Expert opinion on drug safety*. 2014 Jan;13(1):57-65. PubMed PMID: 24073682. Pubmed Central PMCID: 3864987.
  24. Colley CA, Lucas LM. Polypharmacy: the cure becomes the disease. *Journal of General Internal Medicine*. 1993 May;8(5):278-83. PubMed PMID: 8505690.
  25. WHO. Guidelines for ATC classification and DDD assignment. WHO Collaborating Centre for Drug Statistics Methodology, Oslo. www.whocno. 2005.
  26. Mortazavi SS, Shati M, Keshtkar A, Malakouti SK, Bazargan M, Assari S. Defining polypharmacy in the elderly: a systematic review protocol. *BMJ open*. 2016;6(3):e010989. PubMed PMID: 27013600. Pubmed Central PMCID: 4809106.

27. Mercier A, Auger-Aubin I, Lebeau JP, Schuers M, Boulet P, Hermil JL, et al. Evidence of prescription of antidepressants for non-psychiatric conditions in primary care: an analysis of guidelines and systematic reviews. *BMC Family Practice*. 2013;14:55. PubMed PMID: 23641784. Pubmed Central PMCID: 3648410.
28. Mojtabai R, Olfson M. Proportion of antidepressants prescribed without a psychiatric diagnosis is growing. *Health Affairs*. 2011 Aug;30(8):1434-42. PubMed PMID: 21821561.
29. Brilleman SL, Salisbury C. Comparing measures of multimorbidity to predict outcomes in primary care: a cross sectional study. *Family Practice*. 2013 Apr;30(2):172-8. PubMed PMID: 23045354. Pubmed Central PMCID: 3604888.
30. Boyd A, Van de Velde S, Pivette M, Ten Have M, Florescu S, O'Neill S, et al. Gender differences in psychotropic use across Europe: Results from a large cross-sectional, population-based study. *European Psychiatry : Journal of the Association of European Psychiatrists*. 2015 Sep;30(6):778-88. PubMed PMID: 26052073.
31. Owens GM. Gender differences in health care expenditures, resource utilization, and quality of care. *Journal of Managed Care Pharmacy : JMCP*. 2008 Apr;14(3 Suppl):2-6. PubMed PMID: 18439060.
32. Kovess-Masfety V, Boyd A, van de Velde S, de Graaf R, Vilagut G, Haro JM, et al. Are there gender differences in service use for mental disorders across countries in the European Union? Results from the EU-World Mental Health survey. *Journal of Epidemiology and Community Health*. 2014 Jul;68(7):649-56. PubMed PMID: 24616352.
33. Hirshbein LD. Science, gender, and the emergence of depression in American psychiatry, 1952-1980. *Journal of the History of Medicine and Allied Sciences*. 2006 Apr;61(2):187-216. PubMed PMID: 16397200.
34. Skoog J, Midlov P, Beckman A, Sundquist J, Halling A. Drugs prescribed by general practitioners according to age, gender and socioeconomic status after adjustment for multimorbidity level. *BMC Family Practice*. 2014;15:183. PubMed PMID: 25421269. Pubmed Central PMCID: 4246463.
35. Nordstrom A, Bodlund O. Every third patient in primary care suffers from depression, anxiety or alcohol problems. *Nordic Journal of Psychiatry*. 2008;62(3):250-5. PubMed PMID: 18609025.
36. Tran C, Knowles SR, Liu BA, Shear NH. Gender differences in adverse drug reactions. *Journal of Clinical Pharmacology*. 1998 Nov;38(11):1003-9. PubMed PMID: 9824780.
37. Johnell K, Klarin I. The relationship between number of drugs and potential drug-drug interactions in the elderly: a study of over 600,000 elderly patients from the Swedish Prescribed Drug Register. *Drug Safety*. 2007;30(10):911-8. PubMed PMID: 17867728.
38. Mjorndal T, Boman MD, Hagg S, Backstrom M, Wiholm BE, Wahlin A, et al. Adverse drug reactions as a cause for admissions to a department of internal medicine. *Pharmacoepidemiology and Drug Safety*. 2002 Jan-Feb;11(1):65-72. PubMed PMID: 11998554.
39. Aronson JK. Polypharmacy, appropriate and inappropriate. *The British Journal of General Practice : the journal of the Royal College of General Practitioners*. 2006 Jul;56(528):484-5. PubMed PMID: 16834872. Pubmed Central PMCID: 1872056.
40. DiMatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. *Medical Care*. 2004 Mar;42(3):200-9. PubMed PMID: 15076819.
41. Barry D, Pietrzak RH, Petry NM. Gender differences in associations between body mass index and DSM-IV mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Annals of Epidemiology*. 2008 Jun;18(6):458-66. PubMed PMID: 18329894. Pubmed Central PMCID: 2504706.
42. Grover VP, Keel PK, Mitchell JP. Gender differences in implicit weight identity. *The International Journal of Eating Disorders*. 2003 Jul;34(1):125-35. PubMed PMID: 12772177.
43. McWilliams LA, Cox BJ, Enns MW. Mood and anxiety disorders associated with chronic pain: an examination in a nationally representative sample. *Pain*. 2003 Nov;106(1-2):127-33. PubMed PMID: 14581119.
44. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. *Archives of Internal Medicine*. 2003 Nov 10;163(20):2433-45. PubMed PMID: 14609780.
45. Munce SE, Stewart DE. Gender differences in depression and chronic pain conditions in a national epidemiologic survey. *Psychosomatics*. 2007 Sep-Oct;48(5):394-9. PubMed PMID: 17878497.
46. Fillingim RB. Sex, gender, and pain: women and men really are different. *Current Review of Pain*.

- 2000;4(1):24-30. PubMed PMID: 10998712.
47. Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley JL, 3rd. Sex, gender, and pain: a review of recent clinical and experimental findings. *The Journal of pain : official journal of the American Pain Society*. 2009 May;10(5):447-85. PubMed PMID: 19411059. Pubmed Central PMCID: 2677686.
48. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care*. 2001 Jun;24(6):1069-78. PubMed PMID: 11375373.
49. Trento M, Trevisan M, Raballo M, Passera P, Charrier L, Cavallo F, et al. Depression, anxiety, cognitive impairment and their association with clinical and demographic variables in people with type 2 diabetes: a 4-year prospective study. *Journal of Endocrinological investigation*. 2014 Jan;37(1):79-85. PubMed PMID: 24464454.
50. Gonzalez JS, Peyrot M, McCarl LA, Collins EM, Serpa L, Mimiaga MJ, et al. Depression and diabetes treatment nonadherence: a meta-analysis. *Diabetes Care*. 2008 Dec;31(12):2398-403. PubMed PMID: 19033420. Pubmed Central PMCID: 2584202.
51. Lin EH, Katon W, Von Korff M, Rutter C, Simon GE, Oliver M, et al. Relationship of depression and diabetes self-care, medication adherence, and preventive care. *Diabetes Care*. 2004 Sep;27(9):2154-60. PubMed PMID: 15333477.
52. Gao YH, Zhao HS, Zhang FR, Gao Y, Shen P, Chen RC, et al. The Relationship between Depression and Asthma: A Meta-Analysis of Prospective Studies. *PloS One*. 2015;10(7):e0132424. PubMed PMID: 26197472. Pubmed Central PMCID: 4510436.
53. Goodwin RD, Jacobi F, Thefeld W. Mental disorders and asthma in the community. *Archives of General Psychiatry*. 2003 Nov;60(11):1125-30. PubMed PMID: 14609888.
54. Belloch A, Perpina M, Martinez-Moragon E, de Diego A, Martinez-Frances M. Gender differences in health-related quality of life among patients with asthma. *The Journal of Asthma : official journal of the Association for the Care of Asthma*. 2003 Dec;40(8):945-53. PubMed PMID: 14736095.
55. Sundberg R, Toren K, Franklin KA, Gislason T, Omenaas E, Svanes C, et al. Asthma in men and women: treatment adherence, anxiety, and quality of sleep. *Respiratory Medicine*. 2010 Mar;104(3):337-44. PubMed PMID: 19910178.
56. Cluley S, Cochrane GM. Psychological disorder in asthma is associated with poor control and poor adherence to inhaled steroids. *Respiratory Medicine*. 2001 Jan;95(1):37-9. PubMed PMID: 11207015.
57. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*. 2005 Jun;62(6):617-27. PubMed PMID: 15939839. Pubmed Central PMCID: 2847357.
58. Reijnders JS, Ehrt U, Weber WE, Aarsland D, Leentjens AF. A systematic review of prevalence studies of depression in Parkinson's disease. *Movement Disorders : official journal of the Movement Disorder Society*. 2008 Jan 30;23(2):183-9; quiz 313. PubMed PMID: 17987654.
59. Kanner AM. Depression in epilepsy: prevalence, clinical semiology, pathogenic mechanisms, and treatment. *Biological Psychiatry*. 2003 Aug 01;54(3):388-98. PubMed PMID: 12893113.
60. Murphy JM, Horton NJ, Laird NM, Monson RR, Sobol AM, Leighton AH. Anxiety and depression: a 40-year perspective on relationships regarding prevalence, distribution, and comorbidity. *Acta Psychiatrica Scandinavica*. 2004 May;109(5):355-75. PubMed PMID: 15049772.
61. McLean CP, Asnaani A, Litz BT, Hofmann SG. Gender differences in anxiety disorders: prevalence, course of illness, comorbidity and burden of illness. *Journal of Psychiatric Research*. 2011 Aug;45(8):1027-35. PubMed PMID: 21439576. Pubmed Central PMCID: 3135672.
62. Barankin B, DeKoven J. Psychosocial effect of common skin diseases. *Canadian Family Physician Medecin de famille canadien*. 2002 Apr;48:712-6. PubMed PMID: 12046366. Pubmed Central PMCID: 2214020.
63. Mallon E, Newton JN, Klassen A, Stewart-Brown SL, Ryan TJ, Finlay AY. The quality of life in acne: a comparison with general medical conditions using generic questionnaires. *The British Journal of Dermatology*. 1999 Apr;140(4):672-6. PubMed PMID: 10233319.
64. Zachariae R, Zachariae C, Ibsen HH, Mortensen JT, Wulf HC. Psychological symptoms and quality of life of dermatology outpatients and hospitalized dermatology patients. *Acta Dermato-Venereologica*. 2004;84(3):205-12. PubMed PMID: 15202837.

65. Picardi A, Abeni D, Melchi CF, Puddu P, Pasquini P. Psychiatric morbidity in dermatological outpatients: an issue to be recognized. *The British Journal of Dermatology*. 2000 Nov;143(5):983-91. PubMed PMID: 11069507.
66. Ginsburg IH. The psychosocial impact of skin disease. An overview. *Dermatologic Clinics*. 1996 Jul;14(3):473-84. PubMed PMID: 8818557.
67. Van der Kooy K, van Hout H, Marwijk H, Marten H, Stehouwer C, Beekman A. Depression and the risk for cardiovascular diseases: systematic review and meta analysis. *International Journal of Geriatric Psychiatry*. 2007 Jul;22(7):613-26. PubMed PMID: 17236251.
68. Larsen KK. Depression following myocardial infarction--an overseen complication with prognostic importance. *Danish Medical Journal*. 2013 Aug;60(8):B4689. PubMed PMID: 23905572.
69. Carney RM, Freedland KE. Depression, mortality, and medical morbidity in patients with coronary heart disease. *Biological Psychiatry*. 2003 Aug 01;54(3):241-7. PubMed PMID: 12893100.