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Increase in depression diagnoses and prescribed antidepressants among young girls. A national cohort study 2000–2013

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ABSTRACT
Aims: To analyse trends in depression diagnoses and antidepressant use according to age and gender.
Methods: Nationwide cohort study including all women and men of 10–49 years living in Denmark during 2000–2013. The Psychiatric Registry and Prescription Registry provided data on depression diagnoses and antidepressant medication, respectively. Incidence rates as well as 1-year prevalence rates were calculated.
Results: The incidence and 1-year prevalence rates of depression diagnoses increased during 2000–2013. The women/men rates were 2.0 for both 1-year prevalence of depressions diagnoses and antidepressant use. For adolescent girls, the absolute increase was 3 per 1000 for depression diagnoses and 8 per 1000 for first use of antidepressants, compared to boys who had an increase of 1.1 and 3 per 1000, respectively. Before puberty, boys and girls had almost the same incidence rates of both depression diagnoses and antidepressant use throughout the period. After puberty, girls had significantly higher incidence rates than boys, and experienced during the study period a steeper increase than boys. According to age, the girls/boys incidence rate ratio of a depression diagnosis increased from 0.8 in the 10–11 year age group to 2.7 at age 12–19 years and hereafter decreased with increasing age to 1.5 at age 45–49.
Conclusions: Depression diagnosed and first use of antidepressants increased more for girls of 12–19 years than for boys during 2000–2013, and the incidences were similar for girls and boys before puberty, but higher after puberty for girls.

Introduction
It is well known that the prevalence of depression is approximately twice as high in women as in men (1–7). The theories on this difference between women and men include different interacting factors that increase women’s risk of developing depression, such as hormonal factors (menarche, premenstrual syndrome, and hormonal contraception), socio-cultural factors (victimization, financially disadvantaged), and psychological factors (vulnerability to adverse life events and coping skills) (8–11). Another possible explanation is that women are better at asking for help than men, leading to more frequent treatment of women’s depressions. However, community surveys have confirmed the gender difference, also when confounding from help seeking is eliminated (6).

The increased prevalence of major depression disorder among women begins during adolescence and continues through menopause (12). Girls and boys were in 2008 found to be equally depressed before puberty, but more girls than boys were depressed by ages 13–15 (13). Kessler et al. (2) found, in 1993, a sex difference in prevalence of depression from 10 years of age, which persisted lifelong. According to a Danish study by Wesselhoeft et al. (14) from 2014, boys have a higher incidence of emotional disorders including depression before the age of 12, while the opposite is prevailing thereafter. A review from 2011 found that depressive disorders increase from childhood to adolescence and adulthood (15).

The lifetime prevalence rate of major depression is suggested to be ~10–20 per 100 individuals (16). Over the past decade, one of the controversial findings in the epidemiology of major depression has been whether the prevalence rates of depression are increasing, and whether it is occurring at a younger age. Despite methodological concerns about the reliability of lifetime major depression, studies across countries have reasonably consistently documented an increasing rate of major depression with an earlier age of onset (16–18). Due to the nationwide Danish registers it is possible to examine the trends in the incidence and prevalence of depression diagnoses and use of antidepressants over two decades and how it differs between gender and age groups. Thereby, we can get more knowledge about the aetiology of depression and the treatment of depression as well as sex differences in puberty. If girls are found more prone to depression than boys, particularly during puberty, this knowledge will be valuable in targeting prevention and treatment options; and will add to the understanding of potential...
underlying mechanisms such as endogenous hormones or behavioural changes during puberty, which differs between girls and boys.

The objective of this study was to analyse trends in the incidence and prevalence of depression diagnoses and use of antidepressants, according to age and gender through the period 2000–2013.

Materials and methods

Definition of study population

This study followed all women and men of 10–49 years old living in Denmark in the period 2000–2013, if they had no prior depression diagnoses or antidepressants use. Briefly, the cohort was identified in Statistics Denmark by the unique personal identification number given to all Danish citizens at birth or immigration. The personal identification number is used in all public registers, allowing reliable linkage of data between different registers.

Data sources for outcomes

The Danish Psychiatric Central Research Registry includes in- and out-patients at all psychiatric departments in Denmark from 1995 (19). All women and men of 10–49 years old who had a primary discharge depression diagnosis in the range F32–F33.9 according to the International Classification of Diseases, 10th revision were assessed. The Danish Prescription Registry covers all redeemed prescriptions of antidepressants from Danish pharmacies, including 98.7% of all antidepressants used in Denmark (20). All medical products in this register are defined according to the World Health Organization Anatomic Therapeutic Chemical Classification System (21). Antidepressants with code N06A were included in the study, except N06AX12, which is prescribed for smoking cessation (Supplementary Appendix Table 1S). All redeemed prescriptions in Denmark are by law registered as part of the national healthcare reimbursement scheme. All prescriptions recorded in The Registry of Medicinal Product Statistics have been redeemed and paid for. Several factors support a high data quality, and, for individuals with permanent residence in Denmark, loss to follow-up is unlikely (22,23). Information is recorded prospectively and transferred by bar codes from the pharmacies, including detailed information on the drug redeemed, which eliminates recall bias (24,25).

Definition of outcome

Sex-specific incidence rates were calculated as first ever depression diagnosis in the study period, stratified by year and divided by the size of the population at risk in the given year, and expressed as rates per 1000 persons. Sex-specific incidence rates of first ever use of antidepressants were calculated the same way and expressed per 100 persons. We applied 5-year age groups, except for the two lowest age strata, to further describe sex difference before, during, and after puberty. The sex specific 1-year prevalence rates were calculated as number of unique persons registered with a depression diagnoses in a given year, divided by the size of the population and multiplied by 1000. All rates were given with 95% confidence limits. The 1-year prevalence rates for antidepressant use were calculated the same way, but multiplied by 100 to get the rate per 100 persons.

Ethical approval

The databases were available through Statistic Denmark, and approval was obtained from the Danish Data Protection Agency (license: 2011–41–6361). According to the Danish Research Ethics Committee Law (§ 8, section 3), ethical approval is not required for registry-based studies in Denmark.

Results

The study covered 40 165 630 person-years of observation of all women and men of 10–49 years old living in Denmark during the study period 2000–2013.

Trends in incidence through the period 2000–2013

Incident depression diagnoses increased for both women and men from 2000–2010, and remained at the high level through 2013. The rate ratio of depression diagnoses in women-to-men ranged between 1.7–1.9 in the same period (Figure 1, upper, and Supplementary Appendix Table 2S). A first use of antidepressants increased for both women and men until 2010, and decreased thereafter significantly, reaching the level of year 2000 in 2013 in both women and men. The rate ratio of women-to-men ranged between 1.5–1.6 (Figure 1, lower, and Supplementary Appendix Table 3S).

Adolescence

Trends during 2000–2013 in first ever depression diagnoses and first use of antidepressants among adolescent girls and boys of 15–19 years compared to the 10–49 year average are illustrated in Figure 2. From 2000–2013, the absolute increase among adolescent girls of 3 per 1000 for depression diagnoses and 8 per 1000 in first use of antidepressants were significantly higher than the increase among boys of 1.1 per 1000 and 3 per 1000, respectively. The ‘girls-to-boys’ ratio in depression diagnoses was unchanged through the period, with means of 2.5 and 2.3, respectively, for first use of antidepressants (Supplementary Appendix Tables 2S and 3S).

Puberty

Figure 3 shows the trends in first depression diagnoses and first use of antidepressants for boys and girls in the age groups 10–11 and 12–14 years. For the age group 10–11 years, boys and girls had almost the same incidence rates of a first depression diagnosis though the period, with a mean ‘girls-to-boys’ ratio of 0.9. For the age group 12–14 years,
girls had significantly higher incidence rates of a first depression diagnosis than boys, with a mean ‘girls-to-boys’ ratio of 2.9 (Supplementary Appendix Table 2S).

For boys and girls aged 10–11 years, incidence of a first use of antidepressants was similar throughout the study period. For the age group 12–14 years, girls had a steeper increase in first use of antidepressants than boys; peaking in 2010, after which both gender experienced decreasing incidence rates of a first antidepressant use (Figure 3, lower).

Incidence rates according to age

The average incidence rate of depression diagnoses and first use of antidepressants according to age are illustrated in Figure 4.

Incident depression diagnoses in girls increased from 0.27 [0.22–0.32] per 1000 among 10–11 years of age to 1.93 [1.79–2.07] among girls of 12–14 years of age, peaking at 4.50 [4.30–4.63] at 15–19 years of age. Thereafter, the incidence rate decreased with increasing age. Among boys and men, the increase was less steep, reaching a maximum of 2.23 [2.11–2.34] at 20–24 years of age, and thereafter decreasing slightly with increasing age. The girls/boys rate ratio was below 1 at age 10–11 years, and increased to 2.7 at age 12–14 years and age 15–19 years. Thereafter, decreasing with increasing age (Figure 4, and Supplementary Appendix Table 4S).

Similarly, the incidence of a first use of antidepressants increased steeper in young women than in young men. The ‘girls-to-boys’ rate ratio increased from 0.8 in age group 10–11 years to 2.0 in age group 12–14 years, and peaked at 2.3 in the 15–19-year age group. Thereafter, the rate ratio decreased to 1.6 at 20–24 years, and went flat at 1.4–1.5 from 25 years (Figure 4 and Supplementary Appendix Table 4S).

Trends in prevalence through the period 2000–2013

The 1-year prevalence rate of a depression discharge diagnosis and use of antidepressants in 2000–2013 among women and men of 10–49 years old is illustrated in Figure 5. For all women of 10–49 years old, the prevalence rate increased...
from 2.34 [2.26–2.42] per 1000 women in 2000 to 4.38 [4.27–4.49] in 2008, and was thereafter stable. For men of 10–49 years of age, the prevalence rate increased from 1.28 [1.23–1.34] per 1000 men in 2000 to 2.29 [2.21–2.36] in 2013.

The prevalence rate of users of antidepressants among women of 10–49 years of age rose from 4.1% [95% CI = 4.08–4.15] in 2000 to 8.9% [8.84–8.93] in 2010, ending at 8.1% [8.03–8.12] in 2013, and among men from 2.4% [3.34–2.39] in 2000 to 4.9% [4.89–4.96] in 2010, ending on 4.5% [4.46–4.53] in 2013. The rate ratio of women over men was between 1.7–1.8 throughout the study period (Figure 5).

**Prevalence in different age groups**

For year 2013, the 1-year prevalence rate of depression diagnoses and users of antidepressants according to age are illustrated in Supplementary Appendix Figure 1(S). For age group 10–11 years, the rate of depression diagnoses was 0.50 per 1000 for girls and 0.56 per 1000 for boys. For age group 12–14 the rate increased to 2.8 per 1000 for girls and to 1.0 per 1000 for boys. The rate for girls peaked among adolescents aged 15–19 years, at 6.2 per 1000 and for boys at 2.8 per 1000 at age 20–24 years. The 1-year prevalence rate of users of antidepressants increased with increasing age for both women and men (Supplementary Appendix Figure 1S).

**Discussion**

We found a steeper increase in incidence of depression diagnoses as well as in a first use of antidepressants among young girls of 12–19 years compared to boys. Girls were found to have a similar incidence of depression before puberty compared to boys, but a significantly higher incidence after puberty. For all ages we found an increase in incident depression in the entire period, for incident antidepressants use we found an increase until 2010 and hereafter a decrease.

The steeper increase that we see for girls by time compared to boys is not necessarily only explained by an increase in morbidity. Girls might be more willing to ask for help than boys, and perhaps more by time. An earlier onset of puberty may be associated with an increased risk of depressive disorders. Possible explanations for the increase in
morbidity could be an increase in the many demands young women feel, making them more vulnerable to stress (24).

Our results contribute to the theory that the difference in risk of depression between women and men is influenced by puberty, with its biological and social changes (8,9). Like Wesselhoeft et al. (14), we found higher incidence rates of depression diagnoses in girls compared to boys above the age of 12 years, and, like Wijlaars et al. (26), we found a similar incidence in boys and girls of depression and first use of antidepressants use before puberty; and an increased incidence for girls compared to boys after puberty.

Our study appears to be the first to reveal that the rate of depression diagnoses as well as first use of antidepressants has increased substantially among girls during puberty and adolescence in recent decades. A Danish study by Mohr Jensen and Steinhausen (27) in 2016, based on incident depression diagnoses like ours, showed an increase in depression from the period 2000–2010, which was particularly pronounced in young adulthood. This study did, however, not assess age and sex differences.

The decrease in a first use of antidepressants from 2010–2013 is likely to be caused by a media criticism in 2010 of doctors’ prescription practice in Denmark, rather than being due to a real change in morbidity. At the same time, the Danish Health Board pointed out that prescription of antidepressants to children and adolescents is a specialist task (28). That is supported by our data, demonstrating a rather stable increase in the number of persons diagnosed with depression throughout the period, contrasting the decline in a first use of antidepressants after 2010. The decline in antidepressant treatment from 2010 may also imply that some patients with depression are now not treated. One could speculate as to whether or not this decline in antidepressants treatment was followed by an increase in the use of cognitive therapy.

Data from psychiatric hospitals cover the more severe spectrum of depression. According to our data, ~95% of depressions in women and men are diagnosed and treated by general practitioners or specialists in psychiatry working in private clinics (23).

**Strengths and limitations**

Among the strengths of this study were, first, the primarily non-selected inclusion of all women and men living in
Denmark aged 10–49 years followed through a 14-year period with no loss to follow-up, providing a study population of 40 million person-years.

Another strength was the fact that information on depression diagnoses comes from all psychiatric departments in Denmark, including both in- and out-patients, and information on antidepressant use was obtained through bar codes, eliminating recall bias.

It is possible that physicians are more observant of the onset of depressive symptoms among patients to whom they already have given another psychiatric diagnosis (detection bias). Nevertheless, it is unlikely that such bias can explain the increased rate of depression diagnoses at a psychiatric hospital, as these diagnoses reflect the more severe depressive disorders that will be evident, regardless of clinical attention.

Although first use of antidepressants was calculated in the current study as a proxy for the treatment of depression, it must be taken into consideration that not all depressed are treated with antidepressants, as some will get cogitative therapy alone (29), and that antidepressants are prescribed for treatment of other conditions than depression such as anxiety disorders. According to studies on representative populations by Henriksson et al. (30) from 2003 and Patten et al. (31) from 2007, depression is the main indication (~80%) for the prescription of selective serotonin re-uptake inhibitors, while only 20–30% of the old antidepressants are used for treatment of depression. It is not possible in these studies to see if this percentage differs between adolescents and adults (30,31).

The study is limited to only include depression diagnoses from persons who attended a psychiatric hospital or were treated with antidepressants; persons treated with cognitive therapy in private practice were, therefore, not included.

**Conclusion**

Over the last decade, a significantly higher increase of both first depression diagnoses and first use of antidepressants was found among Danish girls and young women aged...
12–19 years, compared to boys and men of the same age. Before puberty, boys and girls seemed equally depressed; while after puberty girls were found to have a 2–3-fold higher incidence rate of depression than boys.

Clinicians and psychiatrists should be aware of this increased incidence and prevalence of depression diagnoses and use of antidepressants among young girls. Efforts should be made to find out why girls and young women apparently are more prone to depression than boys.

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Disclosure statement

Øjvind Lidegaard has within the last 3 years received honoraria for speeches in pharmaco epidemiological issues, and Lars Vedel Kessing has been a consultant for Lundbeck and has received honoraria for this work. Charlotte Wessel Skovlund and Lina Steinrud Mørch report no conflicts of interest.

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C. W. SKOVLUND ET AL.


