

Increase in diagnosis of depressive disorders contributes to the increase in antidepressant use in adolescents

Skurtveit S, Bramness JG, Hjellvik V, Hartz I, Nesvåg R, Hauge LJ, Handal M. Increase in diagnosis of depressive disorders contributes to the increase in antidepressant use in adolescents.

Objective: To study if the observed increase in use of antidepressants (AD) among adolescents may be explained by higher incidence of depressive disorder diagnosis, increasing treatment of other mental disorders or more liberal prescribing practice.

Methods: We used three different study populations of girls and boys aged 13–17 years in Norway: 1) individuals who were diagnosed with depressive disorders in primary health care, 2) individuals who were diagnosed with depressive disorders in secondary health care; 3) individuals who were dispensed ADs as recorded in the prescription database. Dataset 2) and 3) were linked.

Results: Incidence of depressive disorders increased from 2010 to 2015 both in primary and secondary health care, especially in girls. One in four girls with incident depressive disorders was prescribed ADs and this proportion was stable over time. Among girls treated with ADs the proportion with a diagnosis where AD treatment is indicated increased from 61.1% to 66.0%. Furthermore, the proportion with moderate or severe episodes of major depressive disorders was stable and high, 72.9% in 2014.

Conclusion: The only issue studied that could explain increasing AD use in girls was increasing incidence of depressive disorders. Most adolescents with incident diagnosis of depressive disorders were not treated with ADs.

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Key words: anxiety; antidepressives; child and adolescent psychiatry; depression; obsessive compulsive disorder

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Significant outcomes

- Increasing incidence of depressive disorders may explain the increasing use of antidepressants (ADs) by adolescent girls in Norway.
- Most of the adolescents with incident depressive disorders were not treated with ADs.
- Most of the adolescents treated with ADs had been referred to secondary health care and diagnosed with mental disorders for which AD therapy is recommended in clinical guidelines.

Limitations

- The increase in incidence of diagnosed depressive disorders does not necessarily reflect a corresponding increase in depression in the population.
- We lack information about non-pharmacological treatments that should be given alone or in combination with drug-therapy.
- We did not have the possibility to link data from primary and secondary health care on an individual level to study the extent to which primary health care patients were referred to secondary health care.

Background

Recent studies have shown an increasing use of antidepressants (ADs) among adolescents in European countries and in the USA (1–8). In Norway, we have also seen a pronounced increase in the use of ADs between 2009 and 2016, particularly among 16- to 17-year-old girls (2, 3, 9). Data from The Norwegian Prescription Database (NorPD) has demonstrated that 1.1% of all 17-year-old boys and 3.0% of all 17-year-old girls filled a prescription for an AD in Norway in 2016 (9).

Several factors could explain an increasing use of ADs in adolescents, of which an increasing occurrence of depressive disorders in this age group is the most obvious candidate. Presently, we do not have data in Norway on trends of depression in the population. However, several studies have shown an increase in self-reported symptoms of depression among adolescents both in Norway and other countries (10, 11).

Changes in therapeutic practice could also contribute to the increase in AD use. In Norway, the selective serotonin reuptake inhibitor (SSRI) fluoxetine is recommended as first line treatment in moderate-to-severe depressive disorders if drug-therapy is considered necessary in minors. In 2009, the SSRI sertraline was approved for treatment of adolescent obsessive-compulsive disorders (OCD) (12). According to the Norwegian child and adolescent psychiatry guidelines SSRIs may be used to treat bulimia nervosa with episodes of binge eating and vomiting (13).

Treatment of adolescents with ADs has been controversial and there is an ongoing debate on potential beneficial vs. harmful effects. In a recently published systematic review and meta-analysis SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) showed significant but small benefits compared with placebo in treating common pediatric psychiatric disorders (14). At the same time, there have been reports of suicidal ideation and behaviour in young people using ADs (15). Increasing use of ADs by adolescents therefore warrants special attention.

All Norwegian citizens have a specific general practitioner (GP) who represents their primary level of public health care. If a patient needs treatment at a specialist level, the GP may refer him or her to a secondary health care facility, i.e. a hospital, out-patient clinic, or private specialist. Government-funded mental health clinics for children and adolescents are available throughout the country, serving the entire population. Mental health care for adolescents is free of charge. Diagnostic data from contacts with both primary and secondary

health care are reported to nationwide registries. All prescription drugs dispensed at pharmacies to out-patients are registered in the NorPD. Linkage of data across registries makes it possible to study drug use in different patient groups.

The aim of the present study was to investigate factors that may be related to the trend of increasing AD treatment of adolescents. Our research questions were as follows:

- Has there been an increase in the incidence of depressive disorders among adolescents in primary and secondary health care?
- Has AD treatment become more common in adolescents with incident diagnoses of depressive disorders?
- Has the severity of depressive disorders changed among AD users?
- Is it increasingly common to treat mental disorders other than depressive disorders with ADs?

Material and methods

The present study is based on data from the Primary Health Care Database (KUHR), the Norwegian Patient Registry (NPR), and the Norwegian Prescription Database (NorPD), all of which are nation-wide registries. Individual-level registry data from the NPR and the NorPD were linked using the unique (encrypted) personal identity number assigned to all individuals living in Norway. Individual-level data on consultations in primary care were available from KUHR, but could not be linked to data from the NPR and the NorPD.

Data sources

The primary health care database (KUHR). The KUHR is a Norwegian database for the control and reimbursement of health expenses in primary health care and contains data on claims for fee-for-service from 2006 and onwards, specifically from GPs as used in this study. For each patient-related contact, a claim for reimbursement is sent to the Norwegian Health Economics Administration. Only claims for reimbursement reflecting a face-to-face consultation with a GP in the period 2008–2015 were included in the present study. All claims contain an encrypted patient identifier, the date of consultation and one or more diagnoses according to the International Classification of Primary Care second version (ICPC-2) (16). Occurrence of depression was defined as a consultation with the ICPC-2 code P76.

The Norwegian patient registry. The NPR is an administrative database of records reported by

the secondary health care, i.e. all hospitals and out-patient clinics owned or financed by the government, including private child and adolescent psychiatrists. Thus, the NPR includes information on patients that have been referred by a GP because of a need for secondary health care. All referrals and registered contacts with secondary health care are included in the NPR. A registered contact in the NPR may thus indicate a more severe type of illness than a registered contact in KUHR. The NPR has included unique personal identification numbers since 2008, and consequently the registry contains nationwide individual-level secondary health care data from 2008 and onwards (17). In this study, we used data reported by hospital- and out-patient clinics and substance abuse treatment facilities in the period 2008–2015. Diagnoses in the NPR are coded according to the International Classification of Diseases, 10th revision (ICD-10). In the present study, diagnostic data were obtained for all mental disorders that may be treated with AD according to clinical guidelines for adults or adolescents. We identified depressive disorders as ICD-10 F32-34. We also studied more severe episodes of depressive disorders defined as moderate and severe episodes depressive disorders: F32.1-3 or F33.1-3. The following diagnoses were also identified:

Specific anxiety disorders: social phobias (F40.1), panic disorder (F41.0), generalized anxiety disorder (GAD) (F41.1), obsessive-compulsive disorder (OCD) (F42), post-traumatic stress disorder (PTSD) (F43.1), and bulimia nervosa (F50.2, F50.3).

The Norwegian prescription database. Data on dispensed ADs were drawn from the NorPD, which covers the entire Norwegian population (approximately 5.2 million inhabitants) (9). Since January 2004 all Norwegian pharmacies have been obliged to send data electronically to the Norwegian Institute of Public Health on all prescribed drugs (irrespective of reimbursement or not) dispensed to individuals in ambulatory care (18). Drugs administered to patients while in hospital are not reported to the NorPD. In the present study, we included the patients' unique (encrypted) identity number, gender, age, the date of dispensing, and generic drug information (Anatomical Therapeutic Chemical (ATC) code). Data on ADs (ATC code N06A) dispensed in 2009–2015 were included in the analyses. In the following, ADs dispensed, as recorded in the NorPD, are referred to as ADs used, even if

secondary non-compliance could constitute a problem (19).

Study population

We used three different study populations of individuals aged 13–17 years in Norway during 2008–2015 to answer the different research questions in our study:

- i) Primary health care population; individuals who were diagnosed with depressive disorders in KUHR at least once.
- ii) Secondary health care population; individuals who were diagnosed with depressive disorders in the NPR at least once.
- iii) AD-treated population; individuals who were dispensed ADs as recorded in NorPD at least once.

Analytical approach

- i) For each year in the period 2010–2015, we identified individuals with an incident diagnosis of depressive disorders in the primary or secondary health care population. A diagnosis was defined as incident in a given year if an individual had not been registered in KUHR or NPR, respectively, with such diagnosis any of the previous years back to January 1st 2008. The denominator in all of the incidence analyses, the population at risk, was the total number of inhabitants in Norway in the age group 13–17 years per July 1st in the actual year, as registered by Statistics Norway, minus the number of individuals who had received the diagnosis in the relevant database (KUHR or the NPR) at any time before the actual year.

To get an impression of changes in health care seeking behaviour we also calculated for each year the proportion of 13–17-year old girls in Norway who were in contact with the primary health care for any reason, and the number of contacts per individual.

In a sub-analysis, we explored the proportion of moderate and severe episodes of depressive disorders among all individuals with incident depressive disorders in NPR.

- ii) For the individuals with incident diagnoses of depressive disorders in the NPR in 2010–2014 we calculated the annual proportion who were dispensed an AD during the period 2 months before to 6 months after the date of the first diagnosis.
- iii) To explore to what extent AD users had diagnoses for which use of these drugs is

recommended, we first calculated the prevalence of depressive disorders in the NPR for all 13–17 year old AD-users in each of the years 2010 and 2014. Presence of depressive disorders was defined as at least one diagnosis of F32–F34 in the period 2 years before to one year after the first time an AD was dispensed the actual year. Among the AD-users not diagnosed with depressive disorders, the prevalence of anxiety disorder diagnoses (social phobia, panic disorder, GAD, OCD, or PTSD) in the same time interval was investigated. Among the remaining AD-users, who were neither diagnosed with depressive disorders nor with anxiety disorders, the prevalence of bulimia nervosa diagnoses was investigated. In a sub-analysis we also studied whether the proportion of adolescents with a moderate or severe episode of depressive disorder changed among the AD users.

Lastly, among all AD treated individuals, the prevalence of any mental, behavioural and neurodevelopmental disorders diagnosis in NPR (any F-diagnosis; F01-F99) during the entire study period (2008–2015) over time was investigated.

All the above analyses were done separately by gender. All analyses were performed using spss 22.0 for Windows.

Ethical considerations

The register-linkage was approved by The Regional Committee for Medical Research Ethics (2010/131) and by the Norwegian Data Protection Authority (10/00447-5).

Results

Incident diagnoses of depressive disorders among adolescents in primary and secondary health care

Roughly, the incidence curves for depressive disorders from primary and secondary health care follow each other closely over time in both girls and boys (Fig. 1). In girls, there was a marked increase in incident diagnosis of depressive disorders from 2010 to 2013, increasing from 7.3 to 12.4 per 1000 in primary health care, and from 5.9 to 11.5 per 1000 in secondary health care respectively. No further increase was observed between 2013 and 2015. In boys the incidence in 2010 was less than half the incidence in girls, and the relative increase in incidence in boys from 2010 to 2013 was less than half the relative increase in girls. In the total adolescent population, the incidence of depressive disorders in

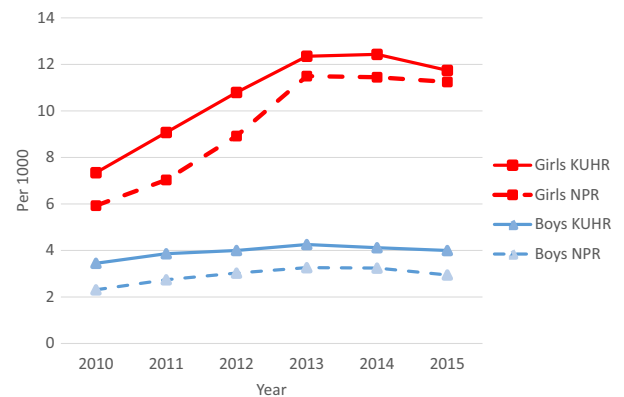


Fig. 1. Incidence of depressive disorders per 1000 inhabitants in girls and boys 13–17 years of age in Norway 2010–2015 as measured by primary health care contacts (Primary Health Care Database, KUHR) and secondary health care contacts (Norwegian Patient Registry, NPR). [Colour figure can be viewed at wileyonlinelibrary.com]

secondary health care increased from 4.1 to 6.9 per 1000 from 2010 to 2015. There were no changes in age distribution from 2010 to 2014. The highest incidence was seen for the oldest adolescents in both boys and girls.

Adolescents with a moderate or severe episode of depressive disorder constituted 52.6% of all adolescents with an incident diagnosis of depressive disorder in 2010, the proportion increased to 57.3% in 2015. There were only small differences between boys and girls; in 2015, 58.6% of boys and 52.7% of girls received these diagnoses as their first diagnosis.

Contact with primary health care for any reason

The proportion of girls who contacted primary health care for any reason at least once during a year increased from 64.4% in 2010 to 68.3% in 2014 (Table 1). The mean number of consultations increased from 2.6 per year in 2010 to 2.8 per year in 2015.

AD treatment in adolescents with an incident diagnosis of depressive disorders

Among adolescents who had an incident diagnosis of depressive disorder in secondary health care, about one in four were dispensed an AD during the period 2 months before to 6 months after the date of the first diagnosis (Fig. 2). This proportion was similar in boys and girls and stable over time. Figure 3 shows that the proportions of boys and girls with an incident diagnosis of depressive disorder in 2014 treated with ADs were higher with increasing age. This was most prominent for girls with 9.6% treated at age 13 and 29.5% at age 17.

Adolescent depression and antidepressant use

Table 1. Number and proportion of all 13–17 years old girls in Norway who were in contact with the primary health care every year for any reason 2010–2015

Year	Population Number	Girls with any consultation Number (%)	Number of consultations	
			Mean	Median
2010	1 55 348	99985 (64.4)	2.6	2
2011	1 55 316	103824 (66.8)	2.7	2
2012	1 55 567	103826 (66.7)	2.7	2
2013	1 55 745	104179 (66.9)	2.7	2
2014	1 54 383	105451 (68.3)	2.7	2
2015	1 53 181	104157 (68.0)	2.8	2

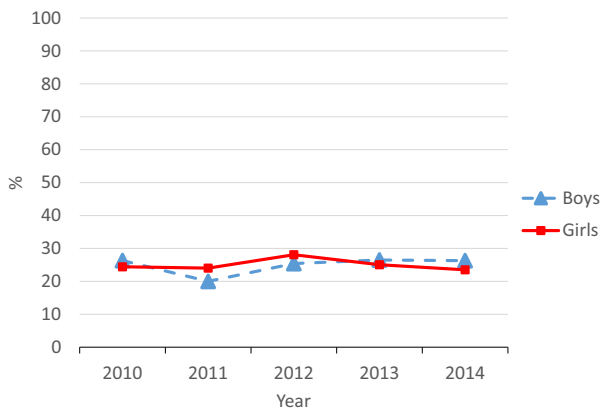


Fig. 2. Percentage of 13–17 years old Norwegian girls and boys with incident diagnoses of depressive disorders in 2010–2014 that were treated with antidepressants in the period 2 months before to 6 months after the first diagnosis. Data from the Norwegian Patient Registry (NPR) and the Norwegian Prescription Database (NorPD). [Colour figure can be viewed at wileyonlinelibrary.com]

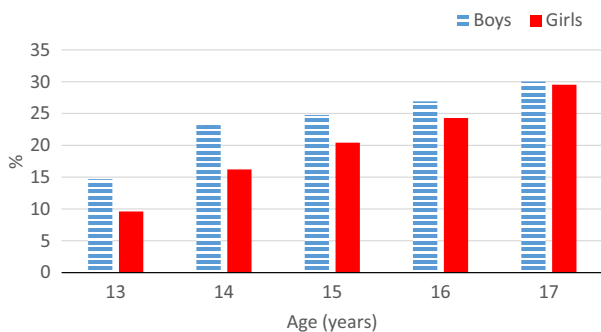


Fig. 3. Percentage of Norwegian 13–17 years old girls and boys with incident diagnoses of depressive disorders in 2014 that were treated with antidepressants in the period 2 months before to 6 months after the first diagnosis according to age. Data from the Norwegian Patient Registry (NPR) and the Norwegian Prescription Database (NorPD). [Colour figure can be viewed at wileyonlinelibrary.com]

This pattern was stable from 2010 to 2014 (data not shown).

Of the adolescents with an incident diagnosis of depressive disorder in 2014, 48.6% and 47.0% of boys and girls, respectively, also had

Table 2. Diagnoses in the Norwegian Patient Register given to 13–17 old antidepressant (AD) users registered in the Norwegian Prescription Database in 2010 and 2014

	2010		2014	
	Boys	Girls	Boys	Girls
Users of ADs, Number	830	1294	973	1975
Users of ADs receiving diagnoses in the period 2 years before to 1 year after the actual year				
Depression, Number (%)	258 (31.1)	580 (44.8)	317 (32.6)	998 (50.5)
Anxiety (without depression), Number (%)	161 (19.4)	196 (15.1)	209 (21.5)	297 (15.3)
Bulimia nervosa (without depression and/or anxiety), Number (%)	0	14 (1.1)	<5	8 (0.4)

Depression (ICD-10: F32-F34).

Anxiety (F40.1 or F41.0 or F41.1 or F42 or F43.1).

Bulimia nervosa (F50.2 or F50.3).

another ICD-10 mental disorder diagnosis during the period from 2 months before to 6 months after the date of the first depressive disorder diagnoses. The proportion of AD use was higher among those with a comorbid mental disorder in both boys and girls. In boys, 32.8% of those with a comorbidity was treated with AD compared with 20.1% in those without comorbidity. In girls, the corresponding proportions were 30.5% and 17.3%.

Irrespective of treatment with ADs or not, around 90% of the adolescents with an incident diagnosis of depressive disorder continued to be in contact with ambulatory psychiatric specialist health care during the first year after their incident depressive disorder diagnosis (data not shown).

Mental disorders in secondary health care in AD treated adolescents in 2010 and 2014

Of all adolescent girls in Norway who were dispensed ADs in 2010, 44.8% were diagnosed with depressive disorders in secondary health care in the period 2 years before to 1 year after the AD was dispensed (Table 2). This proportion increased to 50.5% in 2014. The increase was less pronounced in boys. The prevalence of anxiety disorders in adolescents who did not receive a diagnosis of depressive disorders, was very similar in 2010 and 2014; 15.1% and 15.3% in girls and 19.4% and 21.5% in boys (Table 2). Among the anxiety disorders social phobia and OCD were the dominating diagnoses among the adolescents (boys and girls) both in 2010 and in 2014. Furthermore, for girls we did observe an increase from 2010 to 2014 in the proportion of PTSD diagnosis from 11.7% to 20.5%.

The prevalence of bulimia nervosa without depressive disorders and/or anxiety was very small (<2%). In total 61.1% of girls who received ADs in 2010 had either a depressive disorder, one of the specified anxiety disorders or bulimia nervosa. This proportion increased to 66.0% in 2014.

Among patients treated with ADs and diagnosed with depressive disorders the severity of depressive disorders was stable; the proportion with moderate or severe episode of depressive disorder was 74.8% in 2010 and 75.3% in 2014. The proportion was higher in boys (82.5%) than in girls (72.9%) in 2014. Overall, around 90% of the AD users, both in 2010 and 2014, were diagnosed with at least one mental or behavioural disorder diagnosis in the secondary health care in 2008–2015.

Discussion

There was an increase in the incidence of depressive disorders in 13–17-year-olds in both primary, and secondary health care services in Norway during 2010–2015, especially among girls. Use of ADs by adolescents with a new diagnosis of depressive disorders was, however, stable at about 1 in 4 during the observation period. Thus, the increased incidence in depressive disorders can presumably explain the increased use of ADs reported in adolescents.

The incidence rates of depressive disorders were quite similar in primary and secondary health care services, and the incidence curves changed in parallel over time. This indicates that most adolescents who were diagnosed with depressive disorders in primary health care were referred to secondary health care, where the incidence rate in girls almost doubled from 2010 to 2013. The incidence rate leveled out from 2013 and onwards. Increase in occurrence of depressive disorders among adolescents has also been reported in several other studies from Nordic countries (20, 21).

Our study reveals that around 1.2–1.7% of Norwegian adolescent girls and 0.3–0.4% of the boys were diagnosed with depressive disorders for the first time in 2015. It is, however, not straightforward to compare incidence rates across studies due to methodological differences such as use of different diagnostic manuals, differences in study populations and study periods, differences in organization and availability of health care services and/or level of health care services studied. In a study from Denmark, using the Danish Psychiatric Central Research Registry, the incidence rate of major depressive disorders in 2010 was reported to be 223.3 per 100 000 person years in 13–18 year

olds (21). This is markedly lower than the incidence rate in the NPR in our study in 2010 (406 per 100 000 for the total adolescent population). One factor that could contribute to higher prevalence in Norway was that the definition of depression disorders in our study was somewhat broader than what was used in the Danish study.

The reason for the observed increase in diagnoses of depressive disorders in girls is not clear, but several factors may have contributed. The most obvious explanation is that the occurrence of depressive disorders/depression in the general population might have increased. This is difficult to investigate and no Norwegian population based data are available. However, several health surveys indicate an increase in depressive symptoms among adolescents in Norway and other countries (22, 23). Another explanation could be that the public knowledge about, and attention to, psychiatric morbidity has increased, and that the stigma associated with having a psychiatric disorder has decreased. These factors may in turn have led to increased contact with the health services. Both the present study and the above-mentioned Danish study (21) showed an increase over time in the proportion of adolescents that were in contact with health services. Increased availability of mental health services may be part of the explanation (24). Possibly doctors also have become more aware of the occurrence of depressive disorders among adolescents. Thus, the increase in depressive disorders could partly be explained by an underdiagnosing of these disorders in previous years.

In Norway (25) and in other countries (26, 27), there was a downward trend in the use of ADs in children and adolescents after questions were raised in 2004 about the effectiveness (28) and increased suicidality of SSRIs (29) in this age group. The decrease in use of ADs was followed by worries that it might lead to under-treatment and even increased suicidality (26, 30, 31). Increased use of ADs after the dip in 2004–7 could thus indicate a return to a more normal situation (32). A previous study from Norway (2), however, showed that the increase in use of ADs did not only return to the 2004 level (around 2010), but increased further. The current study shows that the increase in AD use in 2010–2013 was paralleled by a similar increase in incident depressive disorders.

A steep increase both in AD use and in incident depressive disorders was observed, especially among adolescent girls. Only a weak increase was observed in boys. This is in line with previous studies that have separately studied either diagnosed or self-reported depression or prescription of ADs (1, 2, 7, 21).

A common claim regarding the increased use of ADs in adolescents is that doctors too easily treat psychiatric problems in adolescents with drugs. Our finding that only 1 in 4 patients with a newly diagnosed depressive disorder were treated with ADs, and that this level of AD use was stable over time, argues against this claim. Also, the fact that most of the adolescents who received ADs had been in contact with secondary health care and were recorded with diagnoses for which AD therapy is approved, indicates that adolescents with depressive disorders are taken seriously by their GPs, and that AD treatment is not taken lightly. The low prevalence of AD treatment among the adolescents with depressive disorders indicates that over-treatment of depression with ADs is unlikely. This is also supported by the finding that the oldest adolescents and the ones with most comorbid disorders were more frequently treated. Parallel, the proportion of AD-treated adolescents with a diagnosis approved as an indication for AD treatment increased from 2010 to 2015, also indicating improvement in quality of treatment. Guidelines recommend AD therapy to be given in combination with non-pharmacological treatment in adolescents, and emphasize that AD use should be monitored closely regarding effect and side-effects after initiation (13). The results indicate that almost all adolescents with newly diagnosed depressive disorders continued to be in contact with secondary health care one year after the diagnosis independent of AD treatment or not.

In 2000 and 2009, respectively, the SSRIs fluoxetine and sertraline were approved for use in children and adolescents in Norway, and since then, they have been included in national guidelines for treatment of severe cases of depressive disorders (fluoxetine) and OCD (sertraline) (13). Our study documents that already in 2010 a high proportion of adolescent AD drug users were diagnosed with depressive disorders and anxiety disorders including OCD.

Methodological considerations

The use of national registries eliminates recall bias and minimizes selection bias. Another major strength is the linkage of data from the NPR and the NorPD on an individual level, using the encrypted unique personal identification number.

The NPR has individual level data from 2008. Because of the shorter available history with registry data in 2010 than in 2015, there might have been some more cases in 2010 that were not truly incident cases. However, out of the incident 13–17 year old patients in 2015 (i.e. those who had

a depression diagnosis in 2015, but not in 2013 or 2014), only 1% had a depression diagnosis in 2008–2012.

Only children or adolescents with moderate and severe episodes of depressive disorders should receive AD treatment according to the Norwegian Medical Association's guidelines for child and adolescent psychiatry (13). We could have restricted our diagnostic groups to these depression diagnoses. However, since we studied only the first depression diagnosis and we know that the severity of depression might change over time, we included all depression diagnoses in our main analysis.

A weakness of the current study is that we did not have the possibility to link individual-level data from primary health care to data from secondary health care. This would have made it possible to confirm that the parallel and similar level of depression diagnoses were a result of referral of patients from one level of care to the other. Another putative limitation to the generalizability of the findings is lack of formal validity testing of mental disorder diagnoses set by GPs or in the secondary health care.

We have no information about drugs administered to hospitalized adolescents. However, in Norway, very few adolescents are institutionalized for long periods, and rarely for depressive or anxiety disorders, so we do not expect this lack of information to substantially influence the estimates of incidence.

Overall, this study shows that most of the increase in use of ADs in the adolescent population can be explained by an increase in incident diagnoses of depressive disorders. This again might partly be caused by an actual increase in occurrence of depressive disorders among adolescents in the general population, but it could partly also be explained by increased awareness and acceptance of the depressive disorders in the population, and/or by more help-seeking behaviour. Earlier detection with the possibility of earlier treatment might result in a better prognosis indicating that the increased incidence of depression diagnoses might not necessarily be negative (22). The proportion of moderate and severe depression increased among those diagnosed, which may indicate that more adolescents in need of treatment got in contact with the health care system during the study period.

The low proportion of adolescents with depressive disorders that received AD treatment is an argument against the often proposed claim of pharmacological over-treatment of this patient group by the GPs. In addition, it seems that the AD treatment to a large degree was appropriate

since a large part of the adolescents received appropriate diagnosis, and most of those who got treatment because of depression disorders had more severe episodes of depression. The indication that GPs seem to refer nearly all these patients to secondary health care also supports the argument.

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Authors' contributions

SS had the idea and contributed to the design of the study, performed the analysis and contributed to interpretation of the data, and drafted the manuscript. JGB contributed to the interpretation of the data, and drafted part of the manuscript. VH, IH, RN contributed to the interpretation of the data and revised the manuscript critically. LJH performed the analysis of KUHR data, contributed to interpretation of the data and revised the manuscript critically. MH had the idea, contributed to the design of the study, interpretation of the data, and drafted the manuscript. All authors have read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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