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RUNNING HEAD: INCIDENCE OF MEDICALLY TREATED DEPRESSION

Incidence of medically treated depression in Denmark among individuals 15-44 years old: A comprehensive overview based on population registers

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Abstract

Objective: Examine the overall incidence of medically treated depression in Denmark among individuals 15-44 years old, and estimate the 5-year cumulative incidence of psychiatric hospital care among individuals treated first in non-hospital based care.

Methods: We followed all individuals born in Denmark between 1969 and 1998 from age 15 or 2006 (whichever came first) until first depression treatment; death; emigration; or December 31, 2013. Incidence rates were estimated using Poisson regression. Cumulative incidence of hospital care following treatment in non-hospital care was estimated using Kaplan-Meier curves.

Results: In this sample of 2,014,760 individuals, incidence rates of depression in non-hospital and hospital-based care in 2012-2013 were 6.6 (95% Confidence Interval: 6.5–6.7) per 1,000 person-years and 1.5 (95% CI: 1.5–1.6) per 1,000 person-years, respectively. Overall, 85-90% of first medical treatment for depression took place outside of psychiatric hospitals, but a quarter (26.3%) of individuals treated for depression received hospital care initially or within 5 years. Incidence of hospital care was higher in women and younger individuals.

Conclusions: Most medical treatment for depression in Denmark takes place in non-hospital settings. Women and younger individuals are more likely to receive hospital care both initially, and within 5 years after first antidepressant treatment.

Keywords: Depression, treatment, general practice, antidepressives, epidemiology

Significant Outcomes

- The overall incidence of medically treated depression in Denmark in 2012-2013 among individuals 15-44 years old ranged from 8.1 per 1,000 person-years to 10.1 per 1,000 person-years depending on the definition of non-hospital-treated depression, equivalent to a mean annual incidence of 0.8-1.0%.
- 85-90% of first medical treatment for depression takes place in non-hospital based settings
- One quarter (26.3%) of all medically treated depression cases received psychiatric hospital care for depression either initially, or within five years of their first antidepressant treatment.

Limitations

- Non-hospital treated depression was measured using antidepressant prescriptions with depression listed as the indication rather than diagnoses
- This study could not distinguish between non-hospital-based medical treated provided by general practitioners vs. private practicing psychiatrists

Data Availability Statement

The data that support the findings of this study are available from Statistics Denmark.

Restrictions apply to the availability of these data, which were used under license for this study. For information on accessing the data see www.dst.dk.

Introduction

Unipolar depression is a common and serious mental disorder, associated with substantial morbidity and mortality worldwide (1-4). Recommended treatments vary depending on the severity of symptoms, preferences of the patient and history of treatment response, and include pharmacological medications such as antidepressants; psychotherapy; and in rare cases electroconvulsive therapy (5, 6). While some individuals receive treatment from psychiatrists and other specialists, previous reports suggest that the majority of individuals who seek treatment for unipolar depression do so from general medical practitioners (GPs) (7, 8). Treatment setting is not static, however, and many individuals receive treatment in both primary and specialty care settings (9).

In Denmark, health care, including mental health care, is provided almost entirely through the public sector. As in many other countries, general medical care is provided by a GP who serves as a gatekeeper to specialty care, referring patients for specialty treatment when such care is deemed appropriate. Thus, individuals who seek treatment for unipolar depression usually begin the process by consulting their GP, who will either oversee their treatment personally or refer them for specialty care (10, 11). Decisions regarding treatment

plans and/or referrals are based in large part upon the severity of the symptoms and the age of the patient (12).

Population-level estimates of incidence are valuable tools for public health research and practice, because they provide an overview of the disease burden and impact. Population-level incidence rates of hospital care for psychiatric disorders in Denmark were previously estimated by Pedersen et al. (13), who found that the projected lifetime risk of hospital care for depression (single and recurrent) was 9% in males and 15.5% in females. Given past findings that most depression treatment takes place in primary care, it is reasonable to presume that the overall incidence of treated depression is far higher than estimates derived solely from hospital care would suggest. Skovlund et al. (14) examined incidence rates in Denmark of depression diagnoses and use of antidepressants, however antidepressants are often prescribed for conditions other than depression (15-17), so an antidepressant prescription on its own does not necessarily indicate an episode of depression. As such, a comprehensive overview of the incidence of medically treated depression in Denmark is still lacking.

Our main goal in this study is to provide a comprehensive estimate of the incidence of medically treated depression in Denmark by age and sex in both hospital and non-hospital based settings. Recognizing that the course of depression varies substantially between individuals (18, 19) and that treatment needs can vary over time, we also estimated the proportion of individuals treated first in non-hospital care who go on to receive psychiatric hospital care within 5 years, both for depression and for other psychiatric disorders.

Methods

Study design and population

We conducted a historical prospective cohort study using data from Danish nationwide registers. All citizens and legal residents are assigned a unique personal identifier number, which permits linkage of data between nationwide register databases. Using the Civil Registration system (20), we identified subjects aged 15 years and over who were born during 1969-1998 and who were still alive and residing in Denmark in 2006 (N=2,146,250). To ensure that we captured only incident (i.e. first-onset) cases of depression, we excluded persons with a previous diagnosis of unipolar depression (ICD-8 codes 296.09, 296.29, 298.09, 300.49; ICD-10 codes F32-F33) in a psychiatric hospital before 2006 (n=19,842) or their 15th birthday (n=1,674), as well as persons who redeemed any antidepressant prescription (Anatomical Therapeutic Chemical (ATC) codes N06A) before 2006 (n = 106,818) or their 15th birthday (n=3,156). After exclusion, 2,014,760 persons were included in the analysis.

Measures

Information on depression treated in non-hospital settings was extracted from the Danish National Prescription Registry (DNPreR) (21). This register includes ATC codes and dispensation dates for all prescriptions dispensed in community pharmacies since 1995, and treatment indication from April 2004 onwards. Since 2009, the majority of prescriptions are increasingly sent electronically from prescribers to pharmacies (22). When issuing an

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electronic prescription, an indication is required. The prescriber may select an indication code from a drop-down menu, or they can include the indication as free text, in which case no code is recorded (23). Due to substantial missing or unspecified indication codes in 2004-2005 (over 50%), we conducted our analyses using data from 2006-2013 during which time the proportion of missing or unspecified indications for antidepressants was roughly 26% (See Supplemental Materials).

We considered both broad and conservative definitions of non-hospital treated depression. For the broad definition, individuals were considered to have non-hospital treated depression if they redeemed at least one prescription for an antidepressant (ATC codes N06A) with the code '0000168' ('mod depression' [against depression]) listed as the indication. This code was by far the most common, recorded as the indication in 58.5% of all antidepressant prescriptions in 2012-2013 (See Supplemental Table 1). For the conservative definition, individuals were considered to have non-hospital treated depression if they redeemed at least two antidepressant prescriptions within 6 months of each other with depression listed as the indication. The dispensation date for the second antidepressant prescription was used as the onset date for conservatively defined non-hospital treated depression. Results from analyses using both broad and conservative definitions of non-hospital treated depression are included in the results section.

Information on hospital contacts for depression was obtained from the Danish Psychiatric Central Research Register (DPCRR) (24). This register includes information on inpatient psychiatric treatment from 1969 and outpatient and emergency treatment from 1995 onwards. Individuals were considered to have hospital treated depression if they received a

main or secondary diagnosis of single depressive episode or recurrent depression (ICD-10 codes F32-F33) in the DPCRR in 2006-2013.

The timing of first medically treated depression was defined as the day of the first (for broadly defined non-hospital treatment) or second (for conservatively defined non-hospital treatment) prescription redemption, or first inpatient, outpatient or emergency hospital contact for depression, whichever came first.

Statistical Analysis

Individuals were followed from January 1st, 2006 or their 15th birthday, whichever came later, until the redemption of the first (or second, depending on the definition) antidepressant prescription for depression, their first hospital contact for depression, emigration, death, or December 31st, 2013, whichever came first. Individuals were at most 44 years old at the end of follow-up. Overall incidence rates of depression in 2006-2013, along with separate rates for hospital and non-hospital care, were calculated by dividing the number of cases by person-years at risk. Incidence rates were estimated using Poisson regression adjusted for sex (male/female) and age at onset (in years).

Secular trends in referral practices for GPs in Denmark are highly relevant for estimates of the incidence of depression. In 2008 and 2012, Danish regions expanded the referral criteria for psychological treatment for mild to moderate depression and anxiety, respectively. As this will have impacted the proportions of patients treated in primary vs. hospital care, we calculated incidence separately for the following periods: 2006-2007, 2008-2011, and 2012-

2013. The incidence rates by age and sex presented in the results section are from the most recent years (2012-2013).

The 5-year cumulative incidence of hospital treatment among individuals treated for depression in non-hospital care was estimated using Kaplan-Meier curves. Individuals treated for depression in non-hospital care were followed from the day of the first or second antidepressant prescription for depression until the first hospital contact for depression, emigration, death, or December 31st, 2013, whichever came first. In a separate analysis, we also calculated the 5-year cumulative incidence of hospital treatment for psychiatric disorders other than depression (ICD-10 codes F00-F99, excluding F32-F33) among individuals treated for depression in non-hospital care. Cumulative incidence estimates were stratified by sex (male/female) and age group (15-24, 25-34, and 35-44). Statistical analyses were performed using Stata 15.1 (StataCorp, College Station, TX, USA).

Results

Table 1 presents characteristics of the study population, which included 2,014,760 individuals aged 15-44 in 2006-2013, 51% of whom were male. The study population contributed 1.3×10^7 person-years at risk.

Incidence rate of medically treated depression

Mean follow-up time was 6.6 years ($SD=2.3$ years). The incidence rates for non-hospital and hospital-treated depression by age and sex are shown in Figure 1. Results presented in the figures pertain to the conservative definition of non-hospital treated depression.

Using the conservative definition of non-hospital care (two antidepressant prescriptions with depression listed as the indication filled within 6 months of each other), 125,886 individuals received treatment for depression during the analysis period. 106,837 (84.9%) were first treated in non-hospital care, and 19,049 (15.1%) were first treated in hospital. The overall sex and age-adjusted incidence rate of depression in 2012-2013 was 8.1 (95% CI: 8.0-8.2) per 1000 person-years, equivalent to a mean annual incidence of 0.8%. Sex-specific incidence rates were 6.0 (95% CI: 5.9-6.1) per 1000 person-years in males and 10.5 (95% CI: 10.3-10.7) per 1000 person-years in females. The incidence rates of depression in non-hospital and hospital care were 6.6 (95% CI: 6.5-6.7) and 1.5 (95% CI: 1.5-1.6) per 1,000 person years, respectively. As shown in Figure 1, individuals with onset at younger ages were more likely to receive their first depression treatment in a hospital setting.

Using the broad definition of medically treated depression in non-hospital care (one antidepressant prescription with depression listed as the indication), 162,889 individuals received treatment for depression during the study follow-up period: 146,889 (90%) in non-hospital settings and 16,086 (10%) in hospital settings. The overall incidence rate of medically treated depression was 10.1 (95% CI: 10.0-10.2) per 1,000 person-years, which is equivalent to a mean annual incidence rate of 1.0%. The sex-specific rates were 7.7 (95% CI: 7.6-7.8) per 1,000 person-years in males and 12.8 (95% CI: 12.6-13.0) per 1,000 person-years in females. The incidence rates of depression in non-hospital and hospital care were 8.8 (95% CI: 8.7-8.9) per 1,000 person-years and 1.3 (95% CI: 1.3-1.4) per 1,000 person-years, respectively.

5-year cumulative incidence of hospital care for depression among individuals treated for depression in non-hospital care

Using the conservative definition, the 5-year cumulative incidence of hospital care for depression among individuals treated for depression in a non-hospital setting was 12.1% (95% CI: 11.6-12.5%) in males and 13.9% (95% CI: 13.6-14.2%) in females. Using the broad definition, the 5-year cumulative incidence of hospital care for depression was 11.7% (95% CI: 11.4-12.0%) in males and 13.6% (95% CI: 13.4-13.9%) in females. Individuals treated for depression in non-hospital care between the ages of 15-24 were more likely to receive subsequent hospital care for depression regardless of sex (Figure 2).

5-year Cumulative incidence of hospital care for other psychiatric disorders among individuals treated for depression in non-hospital care

Using the conservative definition, the 5-year cumulative incidence of hospital care for a disorder other than depression among individuals treated for depression in non-hospital care was 12.7% (95% CI: 12.2-13.1%) in males and 11.8% (95% CI: 11.5-12.1%) in females.

Using the broad definition, the 5-year cumulative incidence of hospital care for a disorder other than depression was 16.8% (95% CI: 16.4-17.3%) in males and 15.0% (95% CI: 14.7-15.3%) in females. As with hospital care for depression, individuals 15-24 years old when first treated for depression in non-hospital care were more likely to receive subsequent hospital care for other psychiatric disorders, regardless of sex (Figure 3). Table 2 shows the main diagnoses besides unipolar depression received by individuals treated previously with

antidepressants in non-hospital care. Predictably, the most common diagnoses were anxiety disorders (males: cumulative incidence = 12.7%, 95% CI: 12.3-13.1; females: cumulative incidence = 13.5%, 95% CI: 13.2, 13.8).

Discussion

Our goals in this study were to estimate the population-level incidence of medically treated depression in Denmark among individuals aged 15-44 years, and to determine the proportion of individuals treated first in non-hospital settings who subsequently received hospital care for depression or other psychiatric disorders. Overall, the annual incidence rate of medically treated depression in the period from 2012-2013 was 8-10 per 1,000 person years, which is higher than most estimates from other countries based on diagnostic interviews (25-28). For example, The Swedish Lundby study estimated the annual incidence of depression (measured using in-person interviews) among individuals aged 15-39 from 1972-1997 to be 2.8 per 1,000 person years in men and 4.1 per 1,000 person years in women. This could indicate that depression is over-treated in Denmark, or that GPs in Denmark, like their American counterparts, prescribe antidepressants for less severe depression (29-31). However, some evidence suggests that the incidence of depression is increasing over calendar time (32). Thus, the possibilities that these differences do not reflect overprescribing so much as genuine changes in the incidence or detection of depression, or changes in diagnostic criteria or best practice guidelines, should not be ignored.

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Incidence of depression treated in non-hospital care was far larger than the incidence of depression treated in hospital care, which is consistent with patterns observed in other countries. Specifically, 85-90% of first depression treatment occurred in a non-hospital setting. Based on a conservative definition, 12.1% of males and 13.9% of females treated first in non-hospital care received hospital care for depression within 5 years, and 12.7% of males and 11.8% of females received hospital care for a different psychiatric disorder. This suggests that approximately one quarter (26.3%) of individuals treated for depression in Denmark receive care in a psychiatric hospital for depression within 5 years of their first treatment contact. When subsequent hospital care for other psychiatric disorders is also considered, over one third (35.5%) of individuals treated for depression in Denmark receive psychiatric hospital care within five years of their first treatment contact for depression.

The fact that the vast majority of first depression treatment occurred outside of psychiatric hospitals is consistent with the structure of Denmark's health care system, in which GPs serve as the gatekeepers to specialty care. Only around 10% of individuals presenting with depression were immediately referred for hospital treatment. These individuals likely represent those patients with the highest functional impairment, or the greatest risk for suicide (10, 12). In addition to clinician judgment, patient preferences may contribute to this pattern: patients may prefer medication management from their GP due to stigma or negative attitudes towards mental illness (33). The fact that women were more likely than men to be referred for hospital care is consistent with this, as women have more positive attitudes towards mental health treatment seeking (34, 35). In contrast, individuals treated in non-hospital care who were subsequently referred for hospital care may represent the

group of depression patients who proved treatment resistant. It is common practice among Danish GPs to refer patients for hospital care if they have failed to respond to one or two antidepressant trials (10).

It is notable that the proportion of individuals with subsequent hospital contacts for other psychiatric disorders was almost as large as the proportion with subsequent contacts for depression. Some conversions may be due to greater diagnostic precision among hospital-based psychiatrists. However, this also likely reflects the high degree of comorbidity among psychiatric conditions (36), and the fact that many individuals with disorders such as bipolar disorder or schizophrenia experience unipolar depression first (37, 38). Interestingly, diagnostic instability was higher in males than in females. This supports previous findings that men are more likely to convert from depression to schizophrenia (37), and suggests that this pattern may also hold true for other disorders.

The incidence of hospital-based care for depression decreased with age, both within the general population and among individuals initially treated in non-hospital care. This is likely attributable in large part to current treatment guidelines, which state that GPs must not prescribe antidepressants to patients younger than 18, and that antidepressant treatment for patients 18-24 must be supervised by a psychiatrist, the majority of whom operate out of psychiatric hospitals (12). However, this pattern may also reflect age-based differences in severity, course and comorbidity: early-onset depression is associated with greater severity, suicidality, chronicity and recurrence risk (39-41), as well as risk for progression to schizophrenia (37). Therefore individuals first diagnosed at an earlier age may have greater need for hospital-based care both immediately and in subsequent years.

Strengths and Limitations

The results of this study should be interpreted in light of several limitations. First, our measure of non-hospital treated depression relied on records of redeemed antidepressant medications with depression listed as the indication. Information on medication indications was collected not for research purposes but as part of routine clinical practice. To our knowledge this variable has not been validated, so it is unclear to what extent this measure is subject to bias or error. Furthermore, a substantial proportion (26%) of antidepressant prescriptions are missing an indication code, or have 'unspecified' listed as the indication, therefore these results likely underestimate the true incidence of depression treated in non-hospital based care. Second, as the oldest individuals in our sample were only 44 years old at censoring, our estimates do not represent the incidence of medically treated depression across the lifespan. Third, we were not able to distinguish between antidepressant prescriptions issued by GPs vs. private practicing psychiatrists. However, the number of private practicing psychiatrists in Denmark is small. In 2012 there were only 141 private practicing psychiatrists vs. 3,578 GPs (42, 43). Therefore, it is reasonable to assume that the majority of non-hospital treatment for depression takes place in primary care.

Our study also has notable strengths. The registers record information for the entire population of Denmark, and as such they provide an unparalleled opportunity to investigate the nationwide incidence of medically treated depression. To some extent these estimates are sure to be specific to Denmark, reflecting the policies and practices of the Danish medical community as well as the preferences and behavioral patterns of the Danish people. However, these results are also useful for understanding the incidence of treated depression at a transnational level: The gatekeeper model of primary care is common,

meaning these results are likely generalizable to other countries with similar healthcare systems. Additionally, Denmark has a generous welfare system that includes free medical care and few barriers to treatment. As such, these results reflect to some degree the treatment patterns that might be expected under circumstances of near-universal access.

Finally, although not necessarily a limitation, it is worth noting that estimates of treated depression underestimate the true incidence of depressive disorders because not all individuals who meet the criteria for depression receive treatment. A study by Thornicroft and colleagues using data from the World Mental Health Surveys showed that 65% of individuals in high income countries who met DSM-IV criteria for 12-month major depressive disorder perceived that they needed treatment, and of these, 78% had contact with a service provider within the past 12 months (44). There can also be significant delays in treatment seeking. A study by Wang and colleagues also from the World Mental Health Surveys found that while most (89-99%) individuals meeting criteria for depression in northern European countries received treatment eventually, the median delay was 1-3 years (45). This suggests that while most individuals with depression in Denmark will likely receive treatment, the onset of treatment does not necessarily correspond with the onset of symptoms.

Conclusion

In conclusion, the vast majority (85-90%) of individuals 15-44 years old medically treated for first depression in Denmark receive treatment in a non-hospital setting. Among those treated first outside hospitals, 11-14% subsequently received medical treatment for depression in a hospital-based setting within 5 years, and an additional 12-13% received

hospital treatment for a different psychiatric disorder. Individuals with onset of depression at younger ages are more likely to be referred for hospital care for their first period of treatment, and subsequently during the 5-year period following initial antidepressant use, which is consistent with present guidelines. Future research may focus on further examination of patient trajectories and the efficacy of treatment guidelines.

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Table 1. Characteristics of study population

Characteristics	Male (N=1,036,587)	Female (N=978,173)	All (N=2,014,760)
Age at the start of follow-up (years)			
15–24	625,112 (60.3)	592,610 (60.6)	1,217,722 (60.4)
25–34	342,288 (33.0)	321,500 (32.9)	663,788 (33.0)
35–44	69,187 (6.7)	64,063 (6.5)	133,250 (6.6)
Birth place			
Capital or capital suburb	221,248 (21.4)	204,515 (20.9)	425,763 (21.1)
Provincial city or town	402,352 (38.8)	370,047 (37.8)	772,399 (38.4)
Rural areas	412,987 (39.8)	403,611 (41.3)	816,598 (40.5)
Calendar year of birth			
1969–1975	248,662 (24.0)	232,747 (23.8)	481,409 (23.9)
1976–1980	162,813 (15.7)	152,816 (15.6)	315,629 (15.7)
1981–1985	154,191 (14.9)	145,075 (14.8)	299,266 (14.8)
1986–1990	176,369 (17.0)	168,168 (17.2)	344,537 (17.1)
1991–1998	294,552 (28.4)	279,367 (28.6)	573,919 (28.5)

Table 2 Cumulative incidence (95% confidence interval) of hospital care for other psychiatric disorders besides depression among individuals treated for depression first in non-hospital based care

ICD-10 diagnostic category	Male	Female
Organic mental disorders (F00-F09)	0.6 (0.5-0.7)	0.3 (0.2-0.3)
Mental and behavioral disorders due to psychoactive substance use (F10-F19)	4.7 (4.5-5.0)	1.3 (1.2-1.4)
Schizophrenia, schizotypal and delusional disorders (F20-F29)	5.2 (4.9-5.5)	2.6 (2.5-2.7)
Mood disorders other than unipolar depression (F30-31, F34-F39)	2.1 (1.9-2.3)	1.9 (1.8-2.1)
Neurotic, stress-related and somatoform disorders (F40-F49)	12.7 (12.3-13.1)	13.5 (13.2-13.8)
Behavioral syndromes associated with physiological disturbances and physical factors (F50-F59)	0.3 (0.2-0.4)	1.8 (1.7-1.9)
Disorders of adult personality and behavior (F60-F69)	3.9 (3.6-4.1)	7.0 (6.8-7.3)
Mental retardation (F70-F79)	0.5 (0.4-0.6)	0.4 (0.4-0.5)
Disorders of psychological development (F80-F89)	1.1 (1.0-1.2)	0.5 (0.4-0.5)
Behavioral and emotional disorders with onset occurring in childhood and adolescence (F90-F99)	3.7 (3.5-4.0)	2.1 (2.0-2.3)

Note: These estimates include admissions with depression (ICD-10 codes F32-F33) as a secondary diagnosis. Diagnostic categories are not mutually exclusive, meaning individuals can be included in multiple diagnostic categories if they are treated in a psychiatric hospital on more than one occasion and receive different diagnoses.

Figure 1. Incidence rate of treated depression in 2012–2013 by sex and age

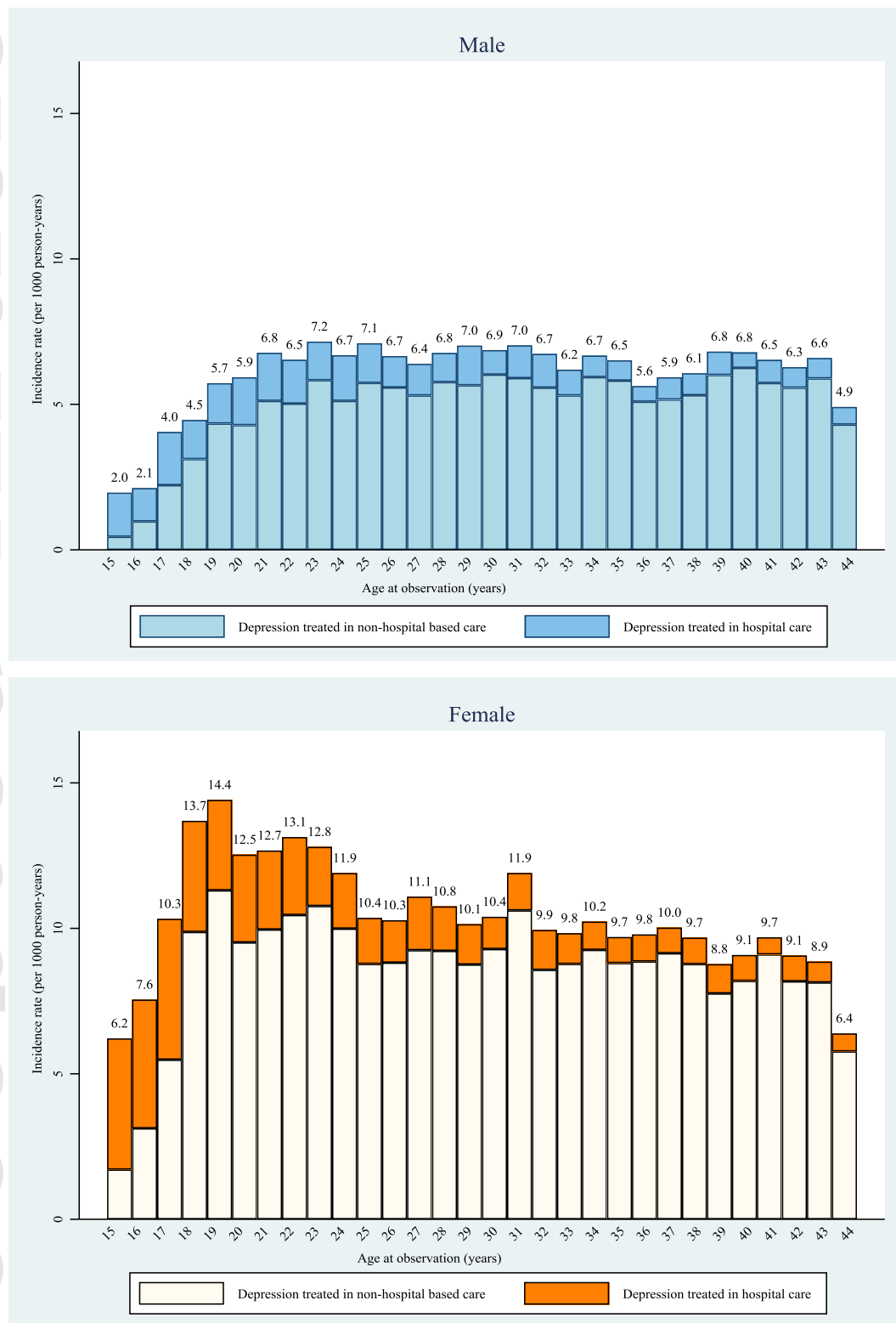


Figure 2. Cumulative incidence of depression treated in hospital care among individuals treated for depression first in non-hospital settings, according to sex and age (N=106,837)

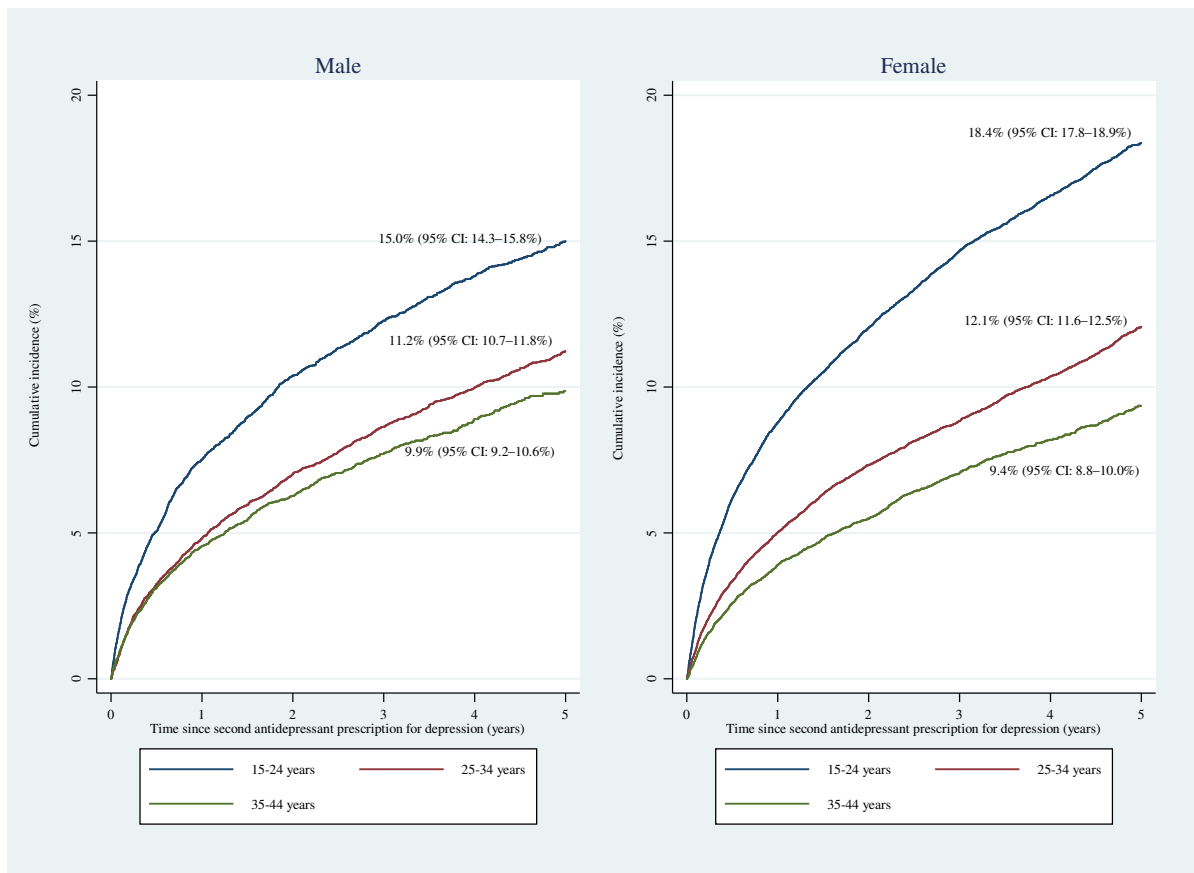


Figure 3. Cumulative incidence of hospital treatment for other psychiatric disorders excluding depression among individuals treated for depression first in non-hospital settings, according to sex and age (N=106,837)

