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Gender-affirming treatment and mental health diagnoses in Danish transgender persons.

A nationwide register-based cohort study.

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Significance statement: The number of referrals for transgender care continues to increase and the main aim of gender affirming treatment is to improve mental health. We investigated longitudinal outcomes of diagnosis codes of mental and behavioral disorders and prescription of psychopharmacological agents in 3812 Danish transgender persons following their first diagnosis of transgender identity. We found that the odds ratio for mental health disorders was more than five times higher in transgender persons compared to controls at baseline. The risk for mental and behavioral disorders in transgender persons increased rapidly during the first year after the index date followed by a decreasing trend, but the odds ratio remained elevated throughout follow up, especially in transgender persons assigned male at birth.

Abstract

Objective: Gender affirming treatment aims to improve mental health. Our aim was to investigate longitudinal mental health outcomes in Danish transgender persons.

Methods: National register-based cohort study in Danish transgender persons with diagnosis code of "gender identity disorder" during the period 2000-2021. Five age-matched controls of the same sex at birth and five age-matched controls of the other sex at birth were included for each transgender person. The study outcomes were diagnosis codes of mental and behavioral disorders and/or prescription of psychopharmacological agents until June 2022.

Results: The cohort included 3812 transgender persons with median age (interquartile range) 19 (15; 24) years for persons assigned female at birth (AFAB, N=1993) and 23 (19; 33) years for persons assigned male at birth (AMAB, N=1819) and 38,120 controls. Follow up duration was up to 10 years with mean (standard deviation) 4.5 (4.3) years. In transgender persons AFAB compared to control women, the OR (95% confidence interval) for mental and behavioral disorders was 6.7 (5.5; 8.1) before the index date, 9.9 (8.4; 11.7) at one year, 5.8 (4.4; 7.7) at five years, and 3.4 (2.1; 7.5) at eight years follow up. In transgender persons AMAB compared to control men, corresponding ORs were 5.0 (4.0; 6.4), 11.3 (9.3; 13.7), 4.8 (3.5; 6.5), and 6.6 (4.2; 10.3) at eight years follow up (all $p < 0.001$).

Conclusion: The OR for mental health disorders was higher in transgender persons compared to controls and remained elevated throughout follow up, especially in transgender persons AMAB.

Introduction

The term transgender describes persons whose gender identity differs from the birth assigned sex (1). The proportion of transgender persons is estimated to be 0.6-1.1% in Europe (2, 3). Gender dysphoria is associated with two- to three-fold higher risk of mental illness including depression and anxiety compared with cisgender controls and prevalence of suicide attempts in transgender study populations approach 50% (4-6).

The aim of gender affirming care is to add to improving mental health (5, 7). Limited prospective studies on mental health outcomes are available in representative study cohorts of transgender persons (5, 8, 9). Prospective studies of up to two years duration documented decreased depression scores after initiation of gender affirming hormone treatment, whereas measures of anxiety were unchanged (9, 10). In a recent Swedish register based study (8), a health care visit due to mood and anxiety disorder was six times more likely in 2679 persons with gender incongruence diagnosis compared to the general population. Years since initiating of gender affirming hormone treatment was not related to likelihood of mental health treatment (adjusted odds ratio (OR) = 1.01, 95% confidence interval (CI) = 0.98, 1.03), whereas longer time since last gender-affirming surgery was associated with reduced mental health treatment (adjusted OR = 0.92, 95% CI = 0.87, 0.98) (8). The design of the study has been discussed (11) and the findings by Bränström *et al* remains to be reproduced in other national study cohorts.

The annual number of persons seeking health care due to gender identity related conditions continues to increase (2, 4). In Denmark, evaluation of gender dysphoria is highly specialized and takes place at three Danish Centers of Gender Identity (12). Danish transgender care follows international guidelines and initiation of gender affirming treatment is proceeded by psychological evaluation (1, 13). Gender affirming hormone treatment is most often initiated before gender affirming surgery (1, 13, 14).

The objective of this study was to investigate mental health outcomes after initiation of gender affirming care in Danish transgender persons.

Material and methods

The study was a register-based cohort study. In Denmark, a unique social security number (central person register, CPR) is issued to all citizens at birth or upon immigration to Denmark. The CPR individually enables linkage of data from all Danish health and social care registers (15, 16). The **National Patient Register** includes data on all somatic inpatient hospital contacts in Denmark since 1977, psychiatric inpatient hospital contacts in Denmark since 1995, and outpatient contacts since 1995 (17). The National Patient Register was used to extract ICD-10 diagnosis codes and dates for contacts. The **Civil Registration System** was established in 1968 and was used to extract data on sex, age, death date and emigration date (16). **The Danish Income Statistics Register** includes income of anyone economically active in Denmark (18). **The National Prescriptions Registry** contains complete record of Anatomic Therapeutic Chemical (ATC) code, date drug dispensed and number of drug packets for all prescriptions filled at Danish pharmacies issued by prescribers, general practitioners or specialists since 1995 (19).

Study population: Danish transgender persons were included according to national registers. We included persons aged 3 years or older with International Classification of Diseases (ICD-10) diagnosis code of transgender during 2000-2021 in the National Patient Register. The diagnosis codes F64-F649 (“transsexual, gender identity disorder”) were used from 2000 to 2017 (20) and the diagnosis codes DZ768E-DZ768E4 (“contact regarding gender identity condition”) were applied after 2017. Persons should have a valid Danish address at the time of inclusion. The index date was defined as the first date of transgender diagnosis within the study period.

Controls: Five age-matched controls of the same sex at birth and five age-matched controls of the other sex at birth were drawn for each transgender person from the Danish Civil registration system.

The controls were born in the same year and should be alive at the index date of their respective matched transgender person. The controls could not be included in the transgender group at the time of inclusion but were able to enter the transgender group later. Each control could only be included once. Controls were assigned the index date of their matched transgender person.

Assigned sex at birth in the transgender study cohort was determined as the earliest recorded CPR-encoded sex. Transgender persons were divided into persons AMAB (most often transgender women) and persons assigned female sex at birth (AFAB, most often transgender men). In Denmark, a citizen can apply for legal sex-change after the age of 18 years. Misclassification of assigned sex at birth could occur in persons immigrating to Denmark after sex-change abroad. Misclassification could also occur in individuals with transgender diagnosis or legal sex-change before year 2000. Therefore, persons with surgical codes of salpingo-oophorectomy and/or hysterectomy were defined as AFAB, persons with diagnosis codes of penis amputation and/or orchiectomy were defined as AMAB, which resulted in correction of assigned sex in 5 individuals (figure 1).

Definition of study parameters

The primary study outcome was mental and behavioral disorders diagnosed according to ICD-10 (primary and secondary diagnosis) or use of psychopharmacological agents.

Mental and behavioral disorders were defined by the ICD-10 codes F32-F33 (depression), F40-F41 (anxiety), X60-X84 (intentional self-harm), F10-F19 (psychoactive substance use), F20-F29 (psychotic disorders), F30-F31, and F34- F39 (bipolar and mood disorders) from hospital contacts.

Use of psychopharmacological agents was defined as more than one prescription and redemption of antidepressants (N06A), anxiolytics (N05B), or antipsychotics (N05A).

Results regarding the study outcomes on ICD10 diagnosis codes on mental and behavioral disorders and medicine prescriptions were presented as separate analyses instead of constructing a pooled study outcome.

Covariates

Age was calculated at the index date.

Personal income was extracted from the Income Statistics Register (18) in the calendar year of the index date (or the first calendar year prior to in case of missing income information) and included information on the available average income after tax and interest (included salary, retirement benefits, welfare payment, remuneration, company profits etc.). The income was categorized into tertiles (high, middle, low) within age groups with 5-7 years intervals.

Presence of medical morbidity (defined as Charlson comorbidity index ≥1) was defined from hospital diagnoses within five years before the index date. The Charlson comorbidity index is based on 19 medical conditions (21) and was calculated from the ICD-10 operationalization by Quan *et al*. *2005* (22)(23).

The event of gender affirming hormone treatment was defined as prescription followed by at least one purchase of feminizing and/or masculinizing treatment (7, 12-14) following the index date. The use of GAHT in Danish transgender persons until year 2018 has been published recently (13).

The event of gender affirming surgery was defined as surgical procedure codes for top or genital surgery, chondrolangyngoplasty and liposuction following the index date. According to Danish legislation, gender affirming surgery could only occur after the age of 18 years.

Ethics

No approval is necessary from the local Ethics committee or Institutional Review Board on register studies according to Danish law. The study complied with the Helsinki declaration. The Data Protection Agency and Statistics Denmark approved the study with details published with OPEN ID: 939 https://open.rsyd.dk/OpenProjects/openProject.jsp?openNo=939&lang=da

Statistical analyses

Baseline characteristics in transgender persons were presented as frequencies for categorical variables and compared using chi-squared test. When estimating the incidence of study outcomes, subjects were considered at risk from the index date. The study population was followed until first occurrence of death, emigration, or end of study (31st December 2021), and for controls becoming cases until index date. The proportions of hospital contacts with psychiatric diagnoses and prescribed psychopharmacological agents were calculated within periods of years from the index date. The probability of hospital contacts with psychiatric diagnoses and prescribed psychopharmacological agents for cases compared with controls were calculated within periods of years from the index date using generalized estimating equations (GEE) with independent within-group correlation structure and binomial distribution. The probability of hospital contacts with psychiatric diagnoses and prescribed psychopharmacological agents for cases and controls over time were calculated within periods of years from the index date compared with two years prior to the index date using GEE with exchangeable within-group correlation structure and binomial distribution.

Sensitivity analysis:

In main analyses, ICD-10 diagnosis codes for mental and behavioral disorders could occur as primary or secondary diagnosis. However, transgender persons could have hospital contacts for somatic diseases where mental and behavioral disorders were not the primary reason for hospital contact. Transgender persons undergo psychological assessment prior to initiation of gender affirming hormone treatment, which can result in surveillance bias and over-diagnosis of mild mood/anxiety/substance abuse disorders in the transgender study population and mental health disorders could be under-reported in the control group. Therefore, we conducted a sensitivity analysis, allowing only primary diagnoses for mental and behavioral disorders as study outcome.

The primary study outcome included ICD-10 diagnosis codes for several mental and behavioral disorders. We investigated number of hospital contacts for suicide attempts (X60-X84) during follow up as a sensitivity analysis.

In Denmark, organization of gender affirming treatment differs between child and adolescent transgender persons and adult transgender persons. Therefore, we conducted a sensitivity analysis including only adult transgender persons aged at least 18 years old at time of their first diagnosis code of transgender.

Danish legislation was changed during the study period. In 2014, Denmark allowed legal sex-change independent of genital surgery and in 2015, the Danish national guideline was revised with focus on shortened evaluation period and wider access to gender affirming treatment. Therefore, we conducted a sensitivity analysis including only transgender persons with first diagnosis code of transgender from January 1st 2015 and onwards.

Data management and data analyses were conducted using Stata MP 17.0 through a remote virtual private network access to Statistics Denmark with analysts blinded to the personal identities of the study subjects.

Results

A flowchart of the Danish transgender population is shown in **Figure 1**. The transgender cohort included 3812 individuals, 1993 (52%) were AFAB and 1819 (48%) were AMAB.

Baseline: The median age (interquartile range) at the index date was 19 (15; 24) years in transgender persons AFAB and 23 (19; 33) years in AFAB individuals (**Table 1**). Medical morbidity (Charlson comorbidity index ≥1) was present five years before the index date in 4.4% persons AFAB and 4.3% persons AMAB. The number of persons with low tertile income was 46.7% in persons AFAB and 55.1% in persons AMAB.

Diagnosis codes for mental and behavioral disorders from five years before the index date is presented in **Table 1.** The frequency of any psychiatric diagnosis was 28.8% in transgender persons AFAB, 6.0% in control women and 4.1% in control men. In transgender persons AMAB, the prevalence was 24.6%, in control men 4.9% and in control women 6.9% (all $p<0.001$ vs. controls).

Prescription of psychopharmacological agents was present in 24.5% transgender persons AFAB and 24.0% in persons AMAB (all p<0.001 vs. controls).

Follow up: The follow up duration of the study cohort was up to 10 years with mean (SD) follow up duration of 4.5 (4.3) years; AFAB 3.6 (3.4) and AMAB 5.3 (4.8) years.

Psychiatric diagnoses: The proportion of persons with hospital contacts for psychiatric diagnoses in the study cohort from two years before the index date and until 10 years of follow up is presented in **Figure 2.** The proportion of transgender persons AFAB with psychiatric diagnoses was 13.6% before the index date, 27.2% one year after the index date, 16.2% after five years and 8.4% after eight years. In transgender persons AMAB, the corresponding proportions were 8.9%, 22.1%, 10.4% and 11.0%.

The OR for psychiatric diagnoses in transgender persons compared to controls is presented in **Appendix Figure 1**. In persons AFAB compared to control women, the ORs (95% CI) for mental and behavioral disorders were 6.7 (95% CI: 5.5; 8.1) before the index date, 9.9 (95% CI: 8.4; 11.7) at one year, 5.8 (95% CI: 4.4; 7.7) at five years, and 3.4 (95% CI: 2.1; 7.5) at eight years follow up. In persons AMAB compared to control men, the ORs for mental and behavioral disorders was 5.0 (95% CI: 4.0; 6.4) before the index date, 11.3 (95% CI: 9.3; 13.7) at one year, 4.8 (95% CI: 3.5; 6.5) at five years, and 6.6 (95% CI: 4.2; 10.3) at eight years follow up.

The OR for psychiatric diagnoses compared to the pre-index date is presented in **Figure 3**. In persons AFAB, the OR at one year was 2.4 (95% CI: 2.0; 2.8), at five years 1.6 (95% CI: 1.3; 2.0) and at eight years 1.1 (95% CI: 0.8; 1.5) compared to two years before baseline. In persons AMAB, the corresponding ORs were 3.0 (95% CI: 2.5; 3.6), 1.5 (95% CI: 1.2; 2.0) and 1.7 (95% CI: 1.3; 2.3).

Prescription of psychopharmacological agents: The proportion of transgender persons AFAB with prescription of psychopharmacological agents was 19.6% before the index date, 29.7% one year after the index date, 35.0% after five years and 39.0% after eight years, **Figure 2.** In

transgender persons AMAB, the corresponding proportions were 17.6%, 25.8%, 30.8% and 30.5%. The OR for prescription of psychopharmacological agents in transgender persons compared to controls is presented in **appendix Figure 1.** In persons AFAB compared to control women, the OR for prescription of psychopharmacological agents was 4.8 (95% CI: 4.1; 5.6) before the index date, 5.7 (95% CI: 5.0; 6.6) at one year, 4.4 (95% CI: 3.6; 5.4) at five years and 3.8 (95% CI: 2.9; 5.1) at eight years follow up. In transgender persons AMAB vs. control men, the corresponding ORs were 3.9 (95% CI: 3.3; 4.6), 5.0 (95% CI: 4.3; 5.8), 4.6 (95% CI: 3.7; 5.6), and 4.0 (95% CI: 3.1; 5.3). The OR for prescription of psychopharmacological agents compared to the pre-index date is presented in **Figure 3**. In persons AFAB, the OR at one year was 1.8 (95% CI: 1.6; 2.0), at five years 2.3 (95% CI: 2.0; 2.7) and at eight years 2.5 (95% CI: 2.1; 3.1) compared to two years before baseline. In persons AMAB, the corresponding ORs were 1.7 (95% CI: 1.5; 1.9), 2.1 (95% CI: 1.8; 2.4) and 1.8 (95% CI: 1.5; 2.2).

Gender affirming hormone therapy was prescribed in 2,089 transgender persons (1,046 AFAB and 1,043 AMAB). The average follow up duration from the index date to prescription of gender affirming hormone therapy was 1.8 (95% CI: 1.7; 1.9) years in persons AFAB and 1.2 (95% CI: 1.0; 1.3) years in persons AMAB. Statistical analyses were repeated with date for first prescription of gender affirming hormone therapy as the index date **(Appendix Figure 2).** In transgender persons AFAB, the OR for psychiatric diagnoses compared to two years before initiation of GAHT was 1.0 (95% CI: 0.8; 1.3) after one year, 1.1 (95% CI: 0.8; 1.5) at five years and 1.0 (95% CI: 0.6; 1.6) at eight years. In persons AMAB, the corresponding ORs were 1.5 (95% CI: 1.2; 2.0), 1.5 (95% CI: 1.1; 2.1) and 1.5 (95% CI: 1.0; 2.3). In transgender persons AFAB, the OR for prescription of psychopharmacological agents compared to before initiation of GAHT was 1.3 (95% CI: 1.1; 1.5) after one year, 2.0 (95% CI: 1.6; 2.5) at five years and 1.8 (95% CI: 1.4; 2.4) at eight years. In persons AMAB, the corresponding ORs were 1.3 (95% CI: 1.1; 1.5), 2.0 (95% CI: 1.6; 2.4) and 1.8 (95% CI: 1.4; 2.3).

Gender affirming surgery was performed in 752 transgender persons. Due to limited follow up duration after date of surgical procedures, the hypothesis that gender affirming surgery improved mental health in the study cohort could not be investigated (data not presented).

Sensitivity analysis:

Mental and behavioral disorders as primary diagnoses: Analyses were repeated where ICD-10 codes for mental and behavioral disorders should occur as primary diagnosis to be included as study outcome. The proportion of transgender persons AFAB with psychiatric diagnoses was 9.4% two years before the index date, 11.8% one year after the index date, and 11.8% after five years. In transgender persons AMAB, the corresponding proportions were 6.7%, 10.9%, and 7.8%. In transgender persons AFAB, the OR for psychiatric diagnoses compared to two years before the index date was 1.5 (95% CI: 1.2; 1.8) after one year and 1.7 (95% CI: 1.3; 2.1) at five years. In persons AMAB, the corresponding ORs were 1.9 (95% CI: 1.5; 2.3) and 1.4 (95% CI: 1.1; 1.9).

Suicide attempts: The number of hospital contacts for suicide attempts (X60-X84) during follow up was 510 (97 individuals) in persons AFAB and 198 (47 individuals) in persons AMAB, which made the study underpowered to investigate changes in hospital contacts over time.

Transgender persons aged ≥ 18 years at first referral: The study cohort included 2,670 transgender persons (1,174 AFAB, 1,496 AMAB) referred after the age of 18 years. In transgender persons AFAB, the OR for psychiatric diagnoses compared to two years before the index date was 1.5 (95% CI: 1.2; 1.9) after one year, 1.2 (95% CI: 0.8; 1.6) at five years and 1.1 (95% CI: 0.7; 1.7) at eight years. In persons AMAB, the corresponding ORs were 2.4 (95% CI: 1.8; 3.1), 1.3 (95% CI: 0.9; 1.8) and 1.5 (95% CI: 1.0; 2.3). In transgender persons AFAB, the OR for prescription of psychopharmacological agents compared to before the index date was 1.5 (95% CI: 1.3; 1.8) after one year, 1.5 (95% CI: 1.2; 1.9) at five years and 1.9 (95% CI: 1.4; 2.5) at eight years. In persons

AMAB, the corresponding ORs were 1.4 (95% CI: 1.1; 1.6), 1.8 (95% CI: 1.5; 2.2) and 1.5 (95% CI: 1.2; 1.9).

Transgender persons with first referral after January 1st 2015: The study cohort included 2,952 persons referred after January 1st 2015 (1,622 AFAB, 1,330 AMAB). In this study cohort, transgender persons AFAB had OR for psychiatric diagnoses compared to two years before the index date of 2.3 (95% CI: 2.0; 2.7) after one year and 2.2 (95% CI: 1.7; 2.8) at five years. In persons AMAB, the corresponding ORs were 2.7 (95% CI: 2.2; 3.3) and 2.3 (95% CI: 1.7; 3.2). In transgender persons AFAB, the OR for prescription of psychopharmacological agents compared to before the index date was 1.9 (95% CI: 1.7; 2.2) after one year and 2.7 (95% CI: 2.2; 3.3) at five years. In persons AMAB, the corresponding ORs were 1.8 (95% CI: 1.5; 2.1) and 2.9 (95% CI: 2.3; 3.6).

Discussion

In this register-based study, we investigated mental health outcomes from hospital contacts and prescribed medications in Danish transgender persons after contact to a national center of gender identity. The present dataset was unique as we could access hospital contacts for mental health diagnoses and use of psychopharmacological agents in a national study cohort of transgender persons in a longitudinal perspective. Our data showed that the risk for mental and behavioral disorders in transgender persons increased rapidly during the first year after the index followed by at decreasing trend. Furthermore, the OR for mental and behavioral disorders in transgender persons and controls remained elevated throughout follow up compared to two years before diagnosis, especially in transgender persons AMAB. The proportion of transgender persons with prescription of psychopharmacological agents increased from <20% at baseline to more than 30% who had prescriptions during follow up. Transgender persons attending transgender care after the year of 2015 showed similar findings compared to the whole study cohort. Furthermore, we found no evidence that inclusion of young and adolescent persons in the dataset affected our study results.

The present data add significant results to findings from a Swedish register based study (11) investigating ICD-10 diagnosis codes for mood (ICD-10 codes F30–F39) and anxiety (F40–F42) disorders, admission for suicide attempts (codes X60–X84) and prescription of antidepressant and anxiolytic medication (codes N06A and N05B) in transgender persons compared to controls. Of notice, the control population included the background population in Sweden, which implied a median age of 31.5 years in transgender persons compared to 40.7 years in controls, furthermore, transgender persons were not divided according to assigned gender at birth, and study outcomes had to occur in year 2015 to be included (11). In the present study, the ORs for all study outcomes of mental health were higher during follow up in transgender persons AFAB and AMAB compared to controls, which corresponded to findings by Bränström et al (11). We found that the OR for mental and behavioral disorders increased after the index date and then gradually decreased following one year after the index date in transgender persons AFAB compared to control women, whereas the ORs for mental and behavioral disorders reached a plateau in transgender persons AMAB. We conducted a sensitivity analysis including only the events where mental health disorders were coded as primary diagnosis. The 5-year results of these analyses were comparable to main analyses, but the initial rise in events of mental health diagnoses at 1 year disappeared. This finding supports that systematic psychological evaluation after referral to a center of gender identity will increase awareness of mental health disorders in transgender individuals. Interestingly, ORs for mental health outcomes in the present study were stable after initiation of gender affirming hormone treatment, without sign of decrease after the date for first prescription of gender affirming hormone. In accordance with this, Bränström et al (11) reported that years since initiation of hormone treatment were not significantly related to likelihood of mental health treatment (adjusted OR = 1.01, 95% CI = 0.98, 1.03). However, Bränström et al did not divide or stratify the study cohort according to masculinizing vs. feminizing treatment (11), which could have affected their study results. Time since last surgical treatment significantly reduced risk of mental health outcomes (adjusted OR = 0.92, 95% CI = 0.87, 0.97) (11) and the likelihood of being treated for mood or

anxiety disorder was reduced by 8% for each year since last gender-affirming surgery. In the present study, we did not have power to investigate changes in mental health after gender affirming surgery. The mean follow-up duration of the present study was 4.5 years, which resulted in limited number of performed surgical procedures. In Denmark, genital constructive surgery is performed at one center only, and at least 12 months hormone treatment and comprehensive multidisciplinary counseling is needed before the patient is registered on a waiting list for surgery (1, 24). The present study design therefore needs to be repeated with updated data extraction within the next 5-10 years to allow longer follow-up and investigate the hypothesis that gender affirmation surgery is associated with lower risk of mental health diagnoses in Danish transgender persons.

We observed that OR for psychiatric diagnoses before the index date was more than five in transgender persons compared to controls, the proportion of transgender persons with a diagnosis of mental and behavioral disorders was 26% and prescription of psychopharmacological agents before the index date was observed in 24%. These findings are in agreement with previous studies reporting significantly impaired mental health in transgender study populations before transgender care with prevalence of depression around 50% (9, 10, 25). The present transgender study cohort was defined by ICD-10 diagnosis code, which implied contact to a Danish center of gender identity, and supported that the present study cohort was comparable to other transgender study cohorts, which were included at centers of gender identity (9, 10, 25). We defined mental health outcomes by ICD-10 diagnosis codes and/or use of psychopharmacological agents. Treatment with antidepressants is only indicated in case of moderate or severe depression, whereas psychotherapy should be applied in patients with milder depressive symptoms (26). It is therefore possible that a considerable proportion of Danish transgender persons would have milder symptoms of depression without need for psychopharmacological agents, which could not be investigated in a register-based study design. Our finding of increasing risk of psychiatric diagnoses in transgender persons one year after the index date could seem an unexpected study result, however, psychological counselling

is advised before initiation of gender affirming treatment, which would result in higher awareness for diagnosis and treatment of mental health disorders in transgender persons attending a centre of gender identity and indicated a time of important life changes and social confrontation. For the same reason, we chose a time interval until two years before the index date for baseline reference in analyses of mental health outcomes during follow up. Interestingly, Tordoff et al (5) also described a transient impairment of mental health outcomes in the first several months of transgender care in 104 transgender and non-binary youth, which subsequently returned to baseline by 12 months. The authors suggested that delay in start of hormone medication could initially exacerbate mental health symptoms (5). Furthermore, delayed onset of mental health improvements associated with hormone treatment could lead to transient worsening of mental health (5). We found comparable mental health at baseline in transgender persons AFAB and transgender persons AMAB, but during follow up, mental health was more impaired in transgender persons AMAB compared to transgender persons AFAB. In accordance, feminizing hormone treatment did not improve mental health in adolescents to the same extent as masculinizing hormone treatment (10). Estrogen treatment is less potent than testosterone treatment regarding changes in body charachteristics and changes occur with longer onset (10, 14). Feminizing hormone treatment stimulates breast development, however the desired Tanner stage is not always obtained (27). Higher degree of minority stress has also been reported in transgender women compared to transgender men (28), which could be an additional explanation for lower mental health in persons AMAB during follow up. As recently reported, cyproterone acetate is the most prescribed androgen blocker in many European countries (4, 13). In the Nordic countries, cyproterone acetate is prescribed in >40% transgender women, whereas <10% are treated with spironolactone (12). Cyproterone acetate is a synthetic progesterone (progestin) and blocks the gonadal axis and potentially improves breast development (4). However, cyproterone acetate is associated with cardiovascular risk such as thromboembolism and hypertension (29, 30) and progestin use has been associated with deteriorated mental health (31, 32). Further studies on

mechanisms for difference in mental health outcomes between transgender women and transgender men are highly needed.

Strengths and limitations. An important strength of the present study includes access to nationwide longitudinal data including all persons with contact to national centers of center identity in Denmark as ICD10 diagnosis codes of transgender are used in all contacts with national clinics. The study outcome was broad and included both ICD-10 diagnoses code of mental and behavioral disorders and use of psychopharmacological agents. Systematic psychological evaluation of transgender persons after referral could lead to surveillance bias, therefore baseline was defined as two years before the index date. We considered constructing a single pooled study outcome, but chose to present results of the study outcomes separately to ensure transparency of study results. Our finding of comparable changes in ICD10 diagnosis codes and medicine prescriptions in the transgender study cohort support valid study results. Furthermore, several sensitivity analyses were conducted. Events of suicide attempts and self-harm could be considered hard endpoints, but unfortunately, we did not have sufficient study power in the present dataset to detect changes in these endpoints. Our study results highlight the need for larger data set and longer follow up in transgender persons. Some limitations may apply to the present study. Transgender persons without hospital contact would not be included in the data set and persons who terminated transgender care before year 2000 are not included. Non-binary persons with no wish for gender affirming care at a center for gender identity would not be included in the dataset. Therefore, the study cohort represents a selected group of transgender persons. Use of gender affirming hormone treatment was defined by medicine prescriptions and self-prescribed hormone treatment by online purchase or through private contacts would not be included. Furthermore, transgender persons without prescription of gender affirming hormone prescription could be persons with shorter follow up (still undergoing initial psychological evaluation), non-binary persons with no wish for gender affirming hormone or could have contraindications for hormone treatment due to severe physical or mental illnes. The follow up

duration of the present study did not enable us to test possible reasons for not initiating gender affirming hormone treatment in the study cohort. Further studies regarding mental health in different sub-cohorts of transgender persons are highly relevant. Furthermore, gender affirmation surgery with insertion of breast implants is possible at Danish private clinics, which could leave some surgical breast augmentation procedures outside the dataset. Persons were divided according to assigned sex at birth, and misclassification of sex could occur in foreigners if they immigrated to Denmark after the date of legal sex-change. Therefore, persons AFAB included persons with surgical codes of salpingo-oophorectomy and/or hysterectomy and persons AMAB included persons with surgical codes of penis amputation and/or orchiectomy. Waiting time for gender affirming surgery resulted in limited follow-up duration after surgery and we did not have study power to detect mental health after gender affirmation surgery.

Conclusion: In the present study, mental health was stabilized during gender affirming care, but mental health was still impaired in transgender persons compared to age-matched controls.

Author contribution

Dorte Glintborg, Marianne Skovsager Andersen, Jens-Jakob Kjer Møller: Idea, design, writing manuscript

Jens-Jakob Kjer Møller: Data analysis

Øjvind Lidegaard, Guy T'Sjoen, Malene Hilden, Mie-Louise Julie Ørsted Larsen; Katrine Hass Rubin: Design, criticism of manuscript

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Table 1: Baseline characteristics of Danish transgender cohort and controls and diagnoses of mental and behavioral disorders and use of psychopharmacological before the index date.

	Transgender AFAB	Control Women	Control Men	Transgender AMAB	Control Men	Control Women
	N=1,993	N=9,965	N=9,965	N=1,819	N=9,095	N=9,095
Baseline						
Age, median (IQR)	19 (15;24)	19 (15;24)	19 (15;24)	23 (19;33)	23 (19;33)	23 (19;33)
Morbidity (yes)	88 (4.4%)	298 (4.0%)^{NS}	257 (3.6%)^{NS}	78 (4.3%)	311 (4.8%)^{NS}	340 (4.8%)^{NS}
Income low tertile	931 (46.7%)	3,456 (34.7%)	3,500 (35.1%)	1,003 (55.1%)	3,044 (33.5%)	3,152 (34.7%)
Income middle tertile	725 (36.4%)	3,607 (36.2%)	3,169 (31.8%)	513 (28.2%)	2,697 (29.7%)	3,272 (36.0%)
ICD-10						
Mental and behavioral disorders						
Depression (F32-F33)	290 (14.6%)	286 (2.9%)	110 (1.1%)	193 (10.6%)	126 (1.4%)	311 (3.4%)
Anxiety (F40-F41)	220 (11.0%)	189 (1.9%)	91 (0.9%)	117 (6.4%)	95 (1.0%)	189 (1.9%)
Psychoactive substance use (F10-F19)	83 (4.2%)	147 (1.5%)	184 (1.8%)	97 (5.3%)	217 (2.4%)	172 (1.9%)
Psychotic (F20-F29)	186 (9.3%)	87 (0.9%)	98 (1.0%)	147 (8.1%)	103 (1.1%)	89 (1.0%)
Bipolar and mood (F30-F31, F34-F39)	35 (1.8%)	31 (0.3%)	18 (0.2%)	29 (1.6%)	30 (0.3%)	47 (0.5%)
Intentional self-harm (X60-X84)	51 (2.6%)	47 (0.5%)	14 (0.1%)	21 (1.2%)	15 (0.2%)	53* (0.6%)
Any psychiatric diagnosis	**573 (28.8%)**	**599 (6.0%)**	**404 (4.1%)**	**447 (24.6%)**	**449 (4.9%)**	**630 (6.9%)**
ATC#						
Antidepressants (N06A)	412 (20.7%)	528 (5.3%)	306 (3.1%)	331 (18.2%)	422 (4.6%)	797 (8.8%)
Anxiolytics (N05B)	54 (2.7%)	85 (0.9%)	64 (0.6%)	60 (3.3%)	116 (1.3%)	221* (2.4%)
Antipsychotics (N05A)	193 (9.7%)	179 (1.8%)	164 (1.6%)	180 (9.9%)	199 (2.2%)	197 (2.2%)
Any psychopharmacological use	**489 (24.5%)**	**621 (6.2%)**	**433 (4.3%)**	**436 (24.0%)**	**576 (6.3%)**	**960 (10.6%)**

Baseline characteristics including morbidity, diagnoses of depression, and medication history five years before the index date.
Transgender cohort divided according to assigned gender at birth.
Morbidity defined as Charlson comorbidity index ≥1 five years before the index date
Statistical analyses performed in AFAB vs. control women, AFAB vs. control men, AMAB vs. control men, and in AMAB vs. control women
All P-values <0.001 except *: P<0.05, NS: P>0.05.
AFAB: Assigned female at birth, ATC: Anatomical Therapeutic Chemical Classification System, IQR: Interquartile range
#≥2 redemptions of medicine

Figure 1: Flowchart of study cohort

Figure 1: Flowchart of included study cohort.

AFAB: assigned female at birth, AMAB: Assigned male at birth.

Figure 2: Number and proportion of psychiatric diagnoses and use of psychopharmacological agents before and after the index date in transgender persons and controls

Legend Figure 2:

Number and proportion of psychiatric diagnoses (top panels) and use of psychopharmacological agents (lower panels) in transgender persons and controls before the index date and until 10 years of follow up.

Index date = date of first transgender (TG) diagnosis

TG AFAB: Transgender person assigned female at birth

TG AMAB: Transgender person assigned male at birth

Figure 3: Probability of psychiatric diagnoses and use of psychopharmacological agents in transgender persons and controls compared to before the index date

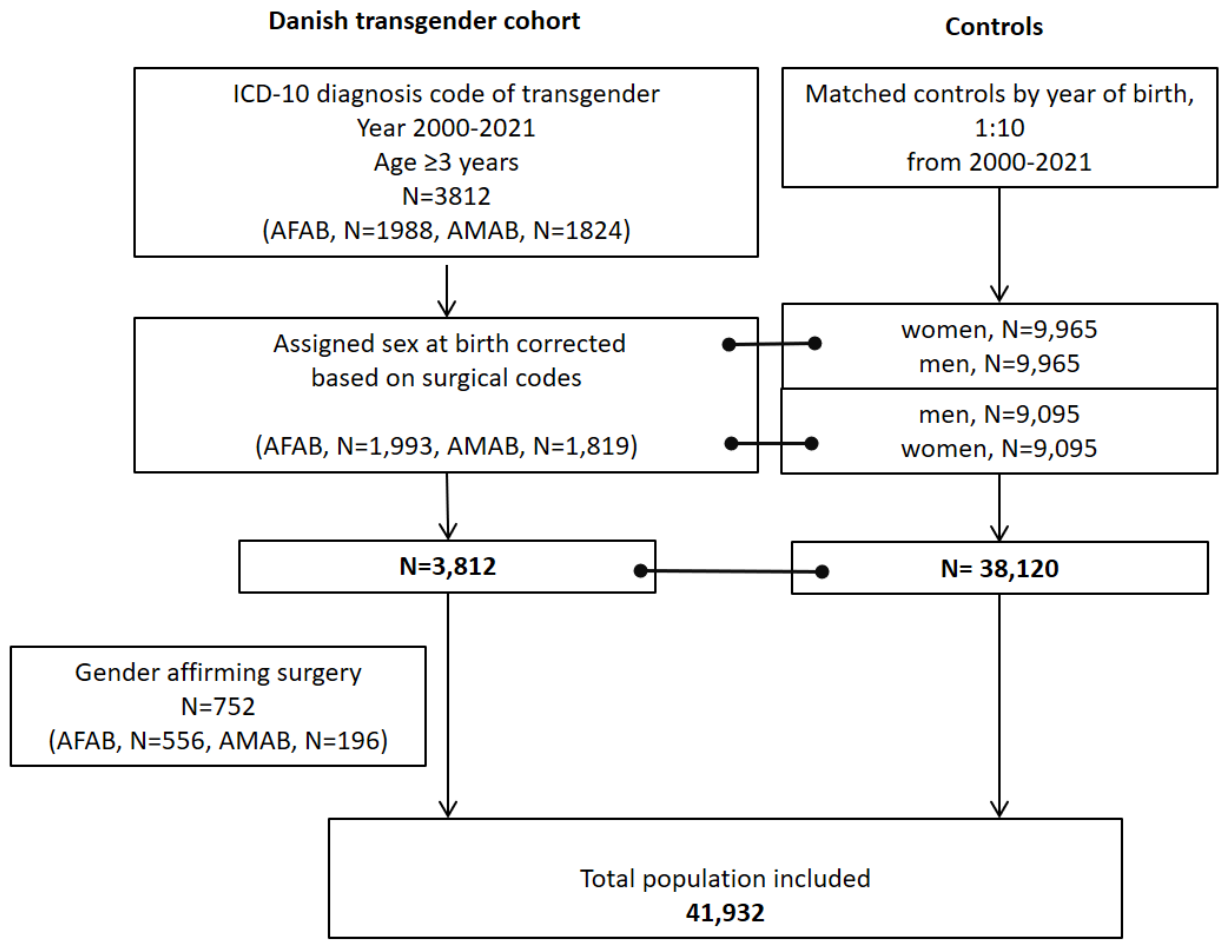
Legend figure 3:

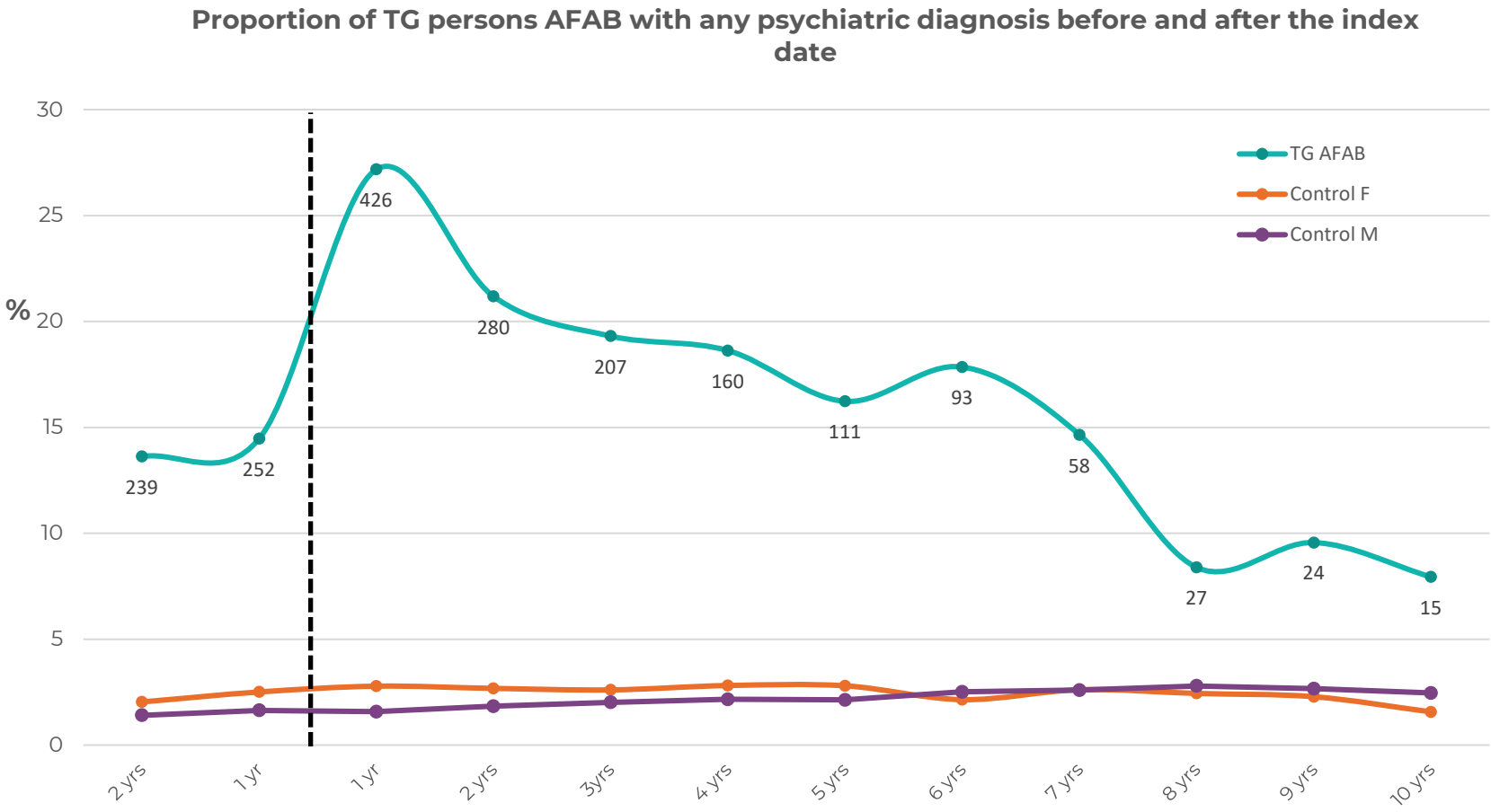
Odds ratio (interquartile range) for psychiatric diagnoses (top panels) and use of psychopharmacological agents (lower panels) in transgender persons and controls during follow up compared to two years before the index date.

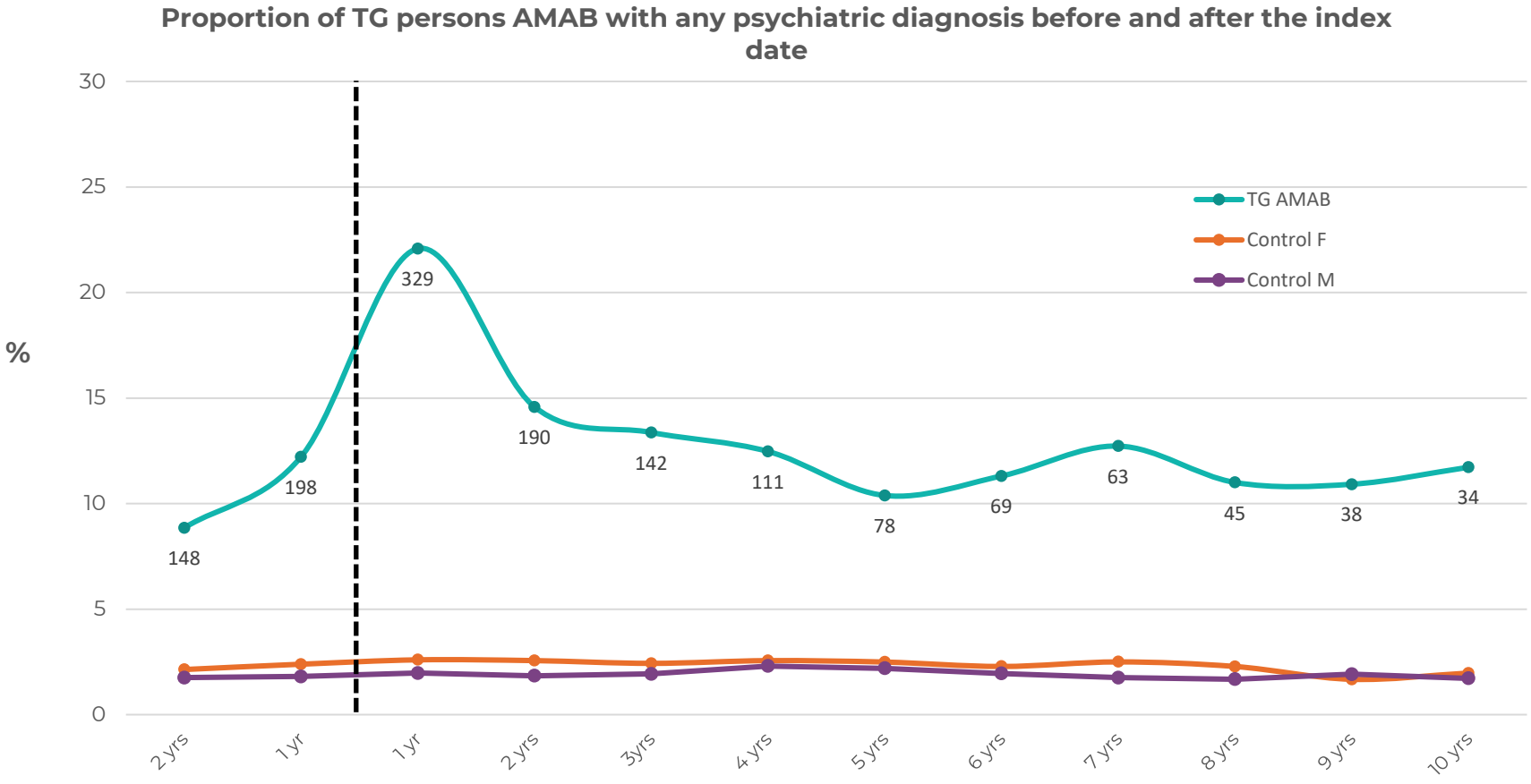
Index date = date of first transgender (TG) diagnosis

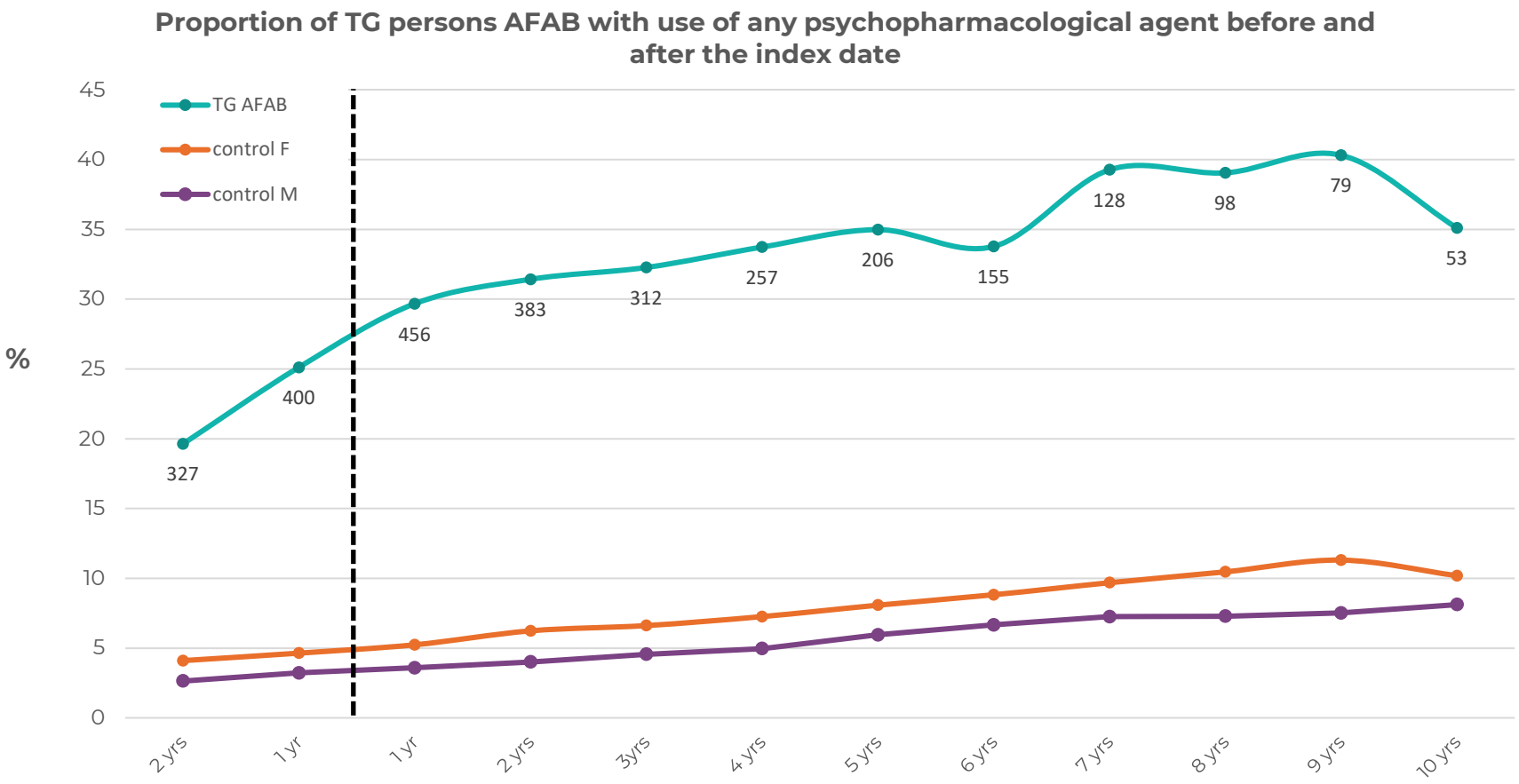
TG AFAB: Transgender person assigned female at birth

TG AMAB: Transgender person assigned male at birth

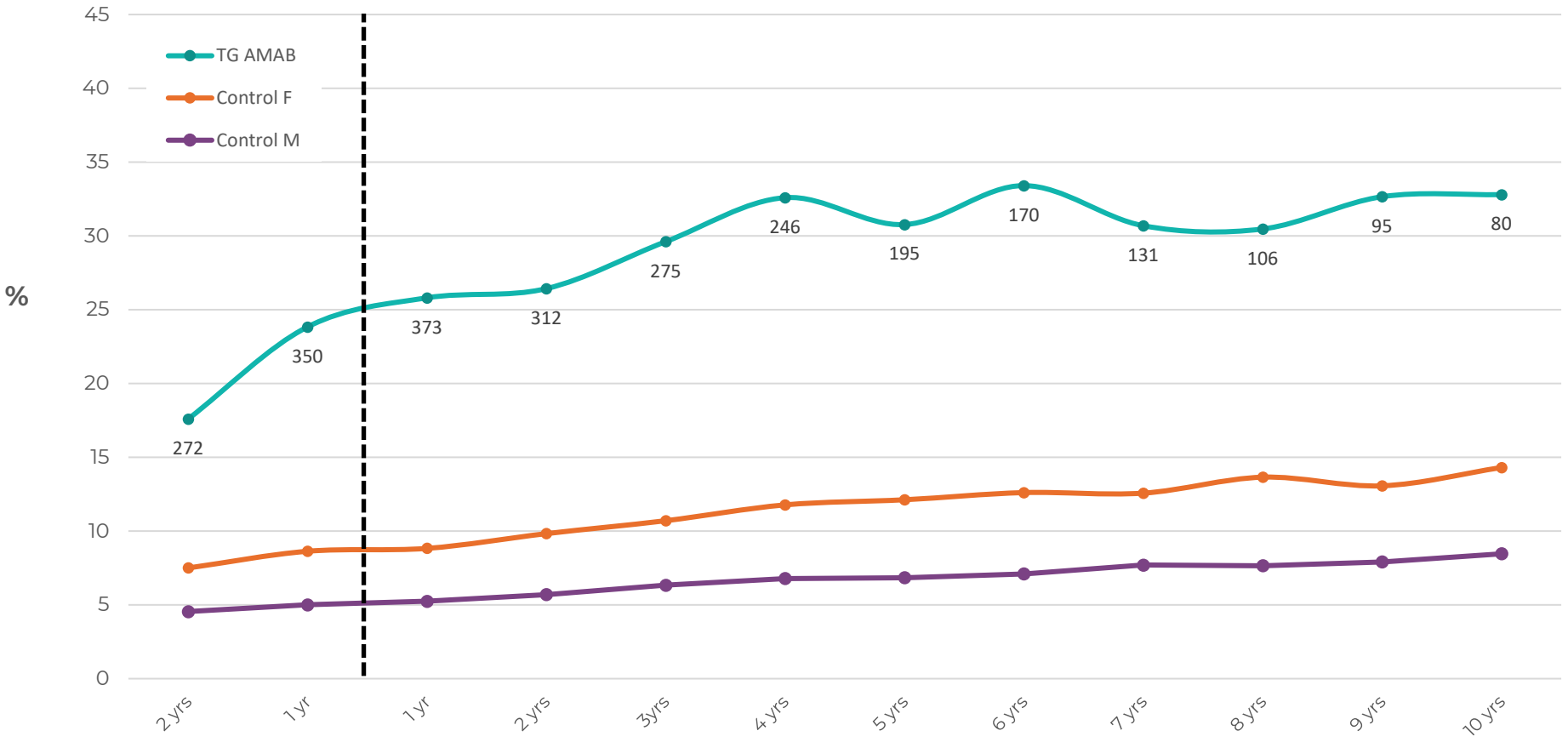

Danish transgender cohort
Controls
ICD-10 diagnosis code of transgender
Year 2000-2021
Age ≥3 years
N=3812
(AFAB, N=1988, AMAB, N=1824)
Matched controls by year of birth,
1:10
from 2000-2021
Assigned sex at birth corrected
based on surgical codes
(AFAB, N=1,993, AMAB, N=1,819)
women, N=9,965
men, N=9,965
men, N=9,095
women, N=9,095
N=3,812
N= 38,120
Gender affirming surgery
N=752
(AFAB, N=556, AMAB, N=196)
Total population included
41,932


Proportion of TG persons AFAB with any psychiatric diagnosis before and after the index date
%
30
25
20
15
10
5
0
TG AFAB
Control F
Control M
239
252
426
280
207
160
111
93
58
27
24
15
2 yrs
1 yr
1 yr
2 yrs
3yrs
4 yrs
5 yrs
6 yrs
7 yrs
8 yrs
9 yrs
10 yrs

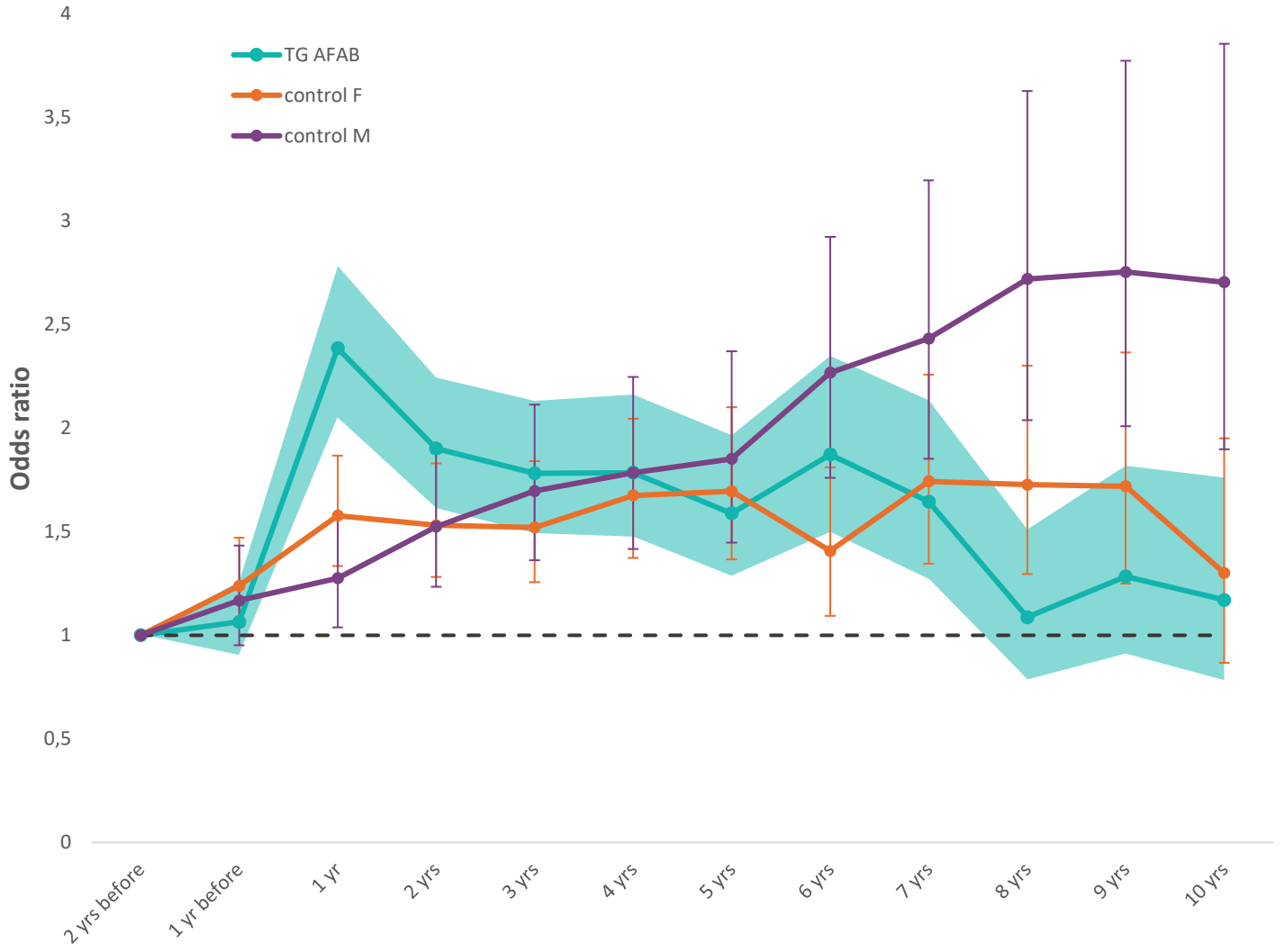

Proportion of TG persons AMAB with any psychiatric diagnosis before and after the index date
%
30
25
20
15
10
5
0
TG AMAB
Control F
Control M
148
198
329
190
142
111
78
69
63
45
38
34
2 yrs
1 yr
1 yr
2 yrs
3yrs
4 yrs
5 yrs
6 yrs
7 yrs
8 yrs
9 yrs
10 yrs

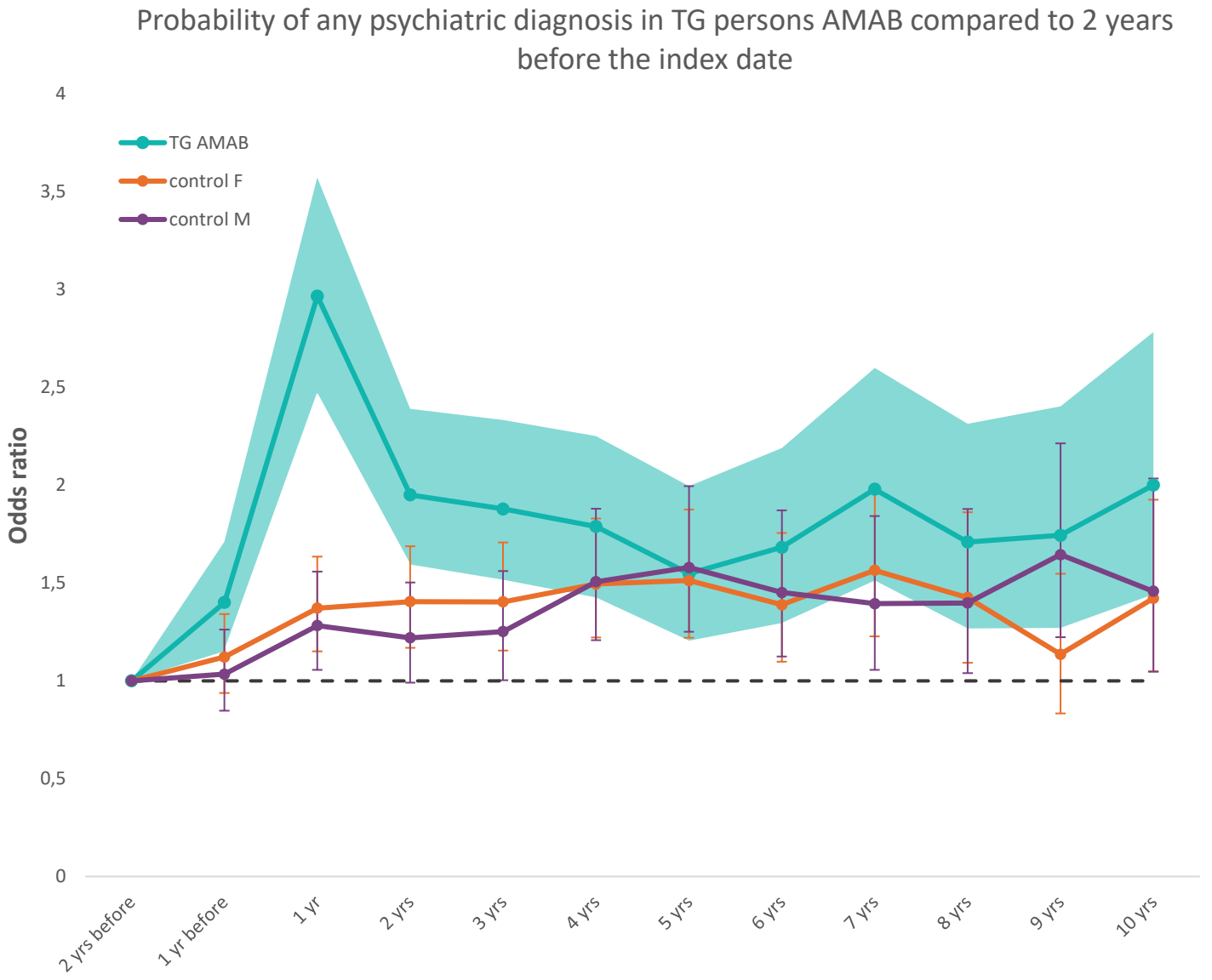

Proportion of TG persons AFAB with use of any psychopharmacological agent before and after the index date
%
45
40
35
30
25
20
15
10
5
0
TG AFAB
control F
control M
327
400
456
383
312
257
206
155
128
98
79
53
2 yrs
1 yr
1 yr
2 yrs
3yrs
4 yrs
5 yrs
6 yrs
7 yrs
8 yrs
9 yrs
10 yrs

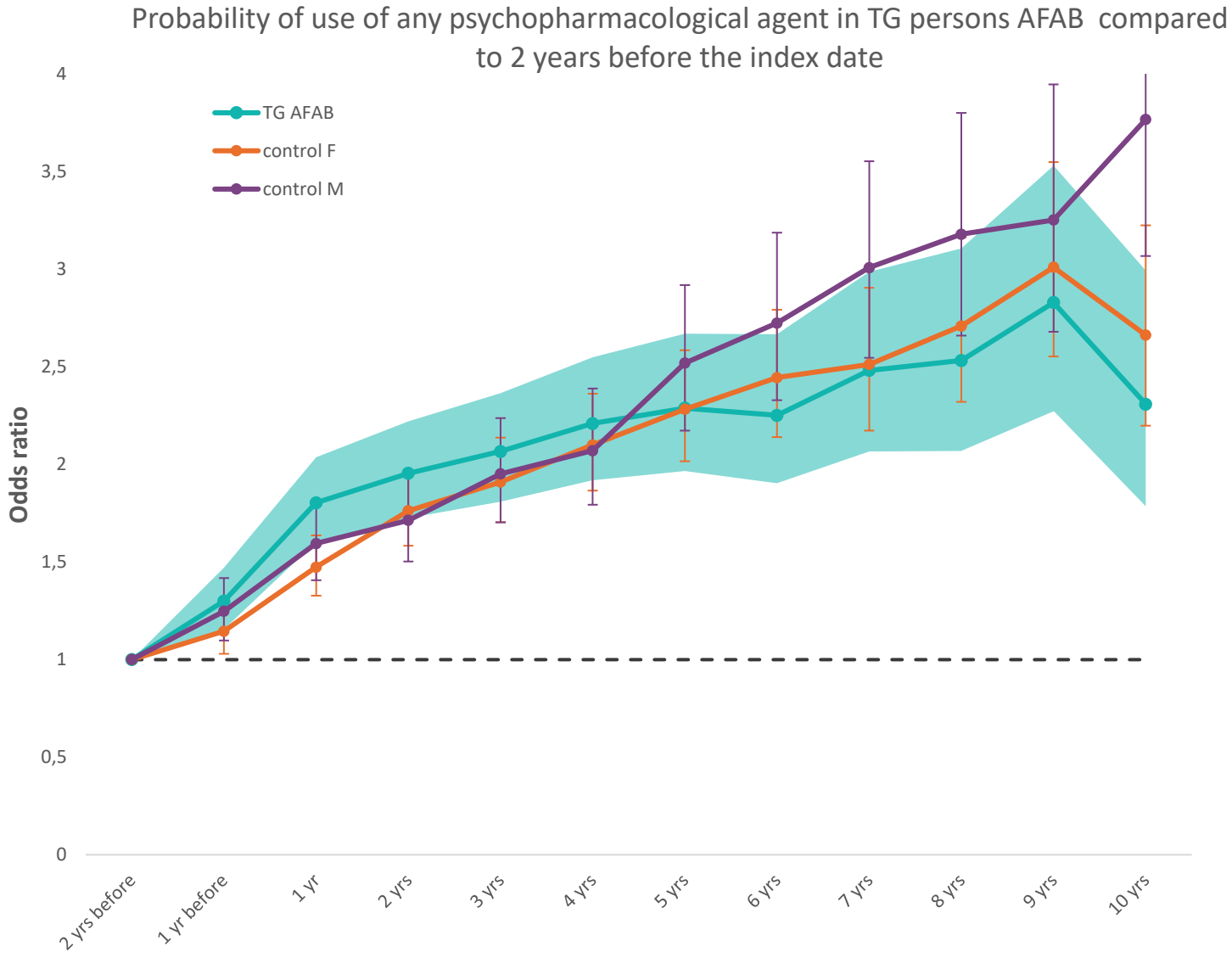
Proportion of TG persons AMAB with use of any psychopharmacological agent before and after the index date

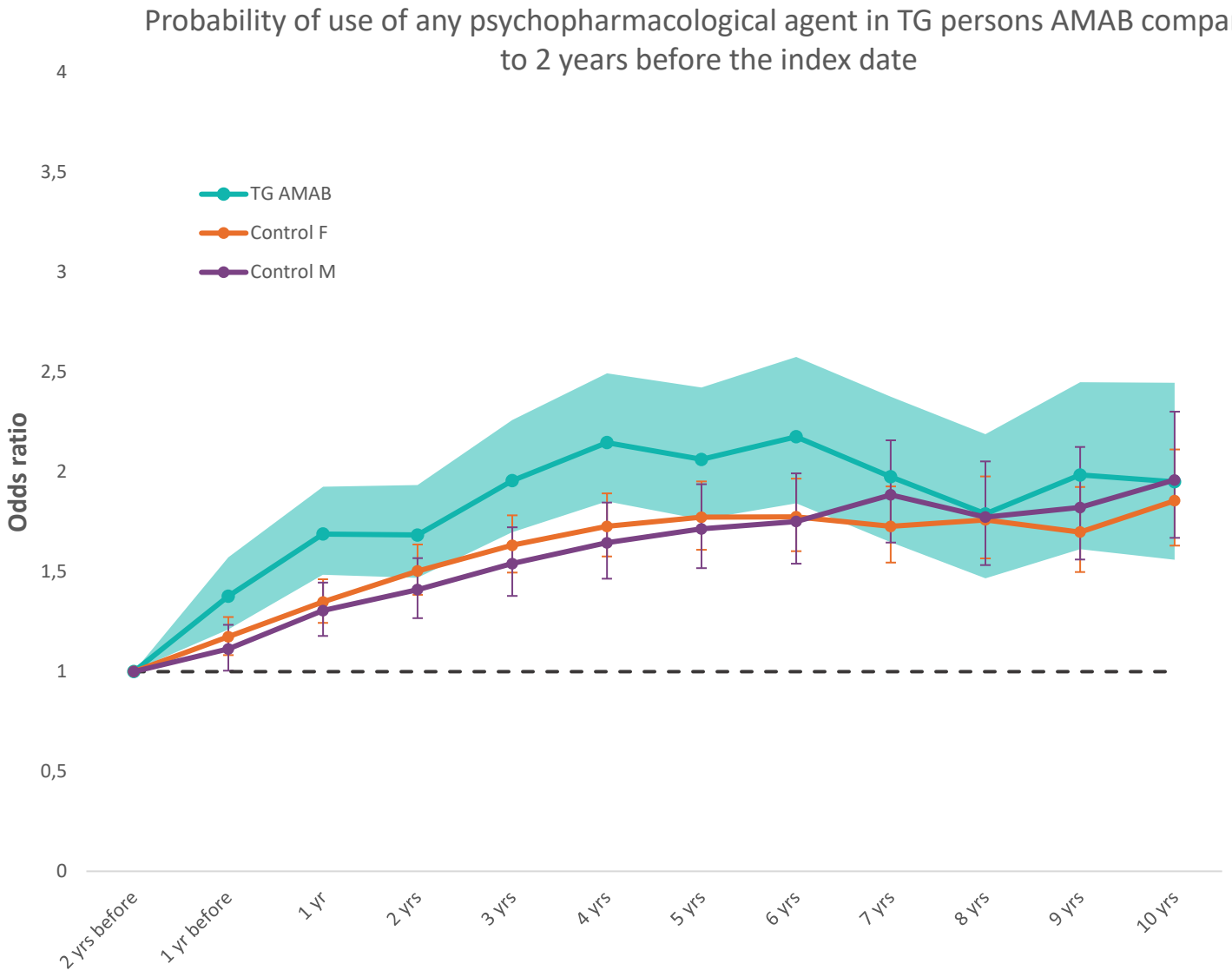


Probability of any psychiatric diagnosis in TG persons AFAB compared to 2 years before the index date




Probability of any psychiatric diagnosis in TG persons AMAB compared to 2 years before the index date
TG AMAB
control F
control M
Odds ratio
4
3,5
3
2,5
2
1,5
1
0,5
0
2 yrs before
1 yr before
1 yr
2 yrs
3 yrs
4 yrs
5 yrs
6 yrs
7 yrs
8 yrs
9 yrs
10 yrs


Probability of use of any psychopharmacological agent in TG persons AFAB compared to 2 years before the index date
TG AFAB
control F
control M
Odds ratio
4
3,5
3
2,5
2
1,5
1
0,5
0
2 yrs before
1 yr before
1 yr
2 yrs
3 yrs
4 yrs
5 yrs
6 yrs
7 yrs
8 yrs
9 yrs
10 yrs


Probability of use of any psychopharmacological agent in TG persons AMAB compared to 2 years before the index date
Odds ratio
4
3,5
3
2,5
2
1,5
1
0,5
0
TG AMAB
Control F
Control M
2 yrs before
1 yr before
1 yr
2 yrs
3 yrs
4 yrs
5 yrs
6 yrs
7 yrs
8 yrs
9 yrs
10 yrs