Ther Adv Psychopharmacol
2020, Vol. 10: 1–13
DOI: 10.1177/2045125320973791

Early labor force exits in patients with treatment-resistant depression: an assessment of work years lost in a Danish nationwide register-based cohort study

Kathrine Bang Madsen, Liselotte Vogdrup Petersen, Oleguer Plana-Ripoll, Katherine L. Musliner, Jean-Christophe Philippe Debost, Frederikke Hordam Gronemann, Preben Bo Mortensen and Trine Munk-Olsen

Abstract

Background: Depression is one of the leading causes of premature workforce exit in many Western countries, but little is known about the extent to which treatment-resistance reduces number of work-years. We compared the risk of premature workforce exit among patients with treatment-resistant depression (TRD) relative to non-TRD patients and estimated work years lost (WYL) before scheduled retirement age.

Methods: The study population, identified in the Danish National Prescription Registry, included all individuals born and living in Denmark who redeemed their first antidepressant (AD) prescription for depression at age 18–60 years between 2005 and 2012. TRD was defined as failure to respond to at least two different treatment trials. Premature workforce exit was measured using disability pension records. We used Cox regression to estimate the hazard ratio (HR) for premature workforce exit in TRD relative to non-TRD patients, adjusting for calendar year, psychiatric and somatic comorbidity, and educational level. Differences in WYL in patients with TRD and all depression patients were estimated through a competing risks model.

Results: Out of the total sample of patients with depression ($N = 129{,}945$), 7478 (5.75%) were classified as having TRD. During follow up, 17% of patients with TRD and 8% of non-TRD patients received disability pension, resulting in a greater than three-fold larger risk of premature workforce exit [adjusted HR (aHR) 3.23 95% confidence interval (CI) 3.05–3.43]. The TRD group lost on average six work-years (95% CI 5.64–6.47) more than the total sample due to early labor force exit. The association between TRD and age at premature workforce exit was inversely U-shaped; the hazard rate of premature workforce exit for patients with TRD compared with non-TRD patients was highest in the age groups 31–35, 36–40, and 41–45 years.

Conclusion: Patients with TRD constitute a small group within depression patients, but contribute disproportionally to societal costs due to premature workforce exit at a young age.

Keywords: treatment-resistant depression, antidepressant treatment, work years lost, disability pension, labor force exit

Received: 26 June 2020; revised manuscript accepted: 20 October 2020.

Correspondence to:
Kathrine Bang Madsen
National Centre for Register-Based Research, Department of Economics and Business Economics, Aarhus University, Fuglesangs Allé 26, Building R, Aarhus V, 8210, Denmark; iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Aarhus, Denmark
kathrine.bang@econ.au.dk

Liselotte Vogdrup Petersen
Katherine L. Musliner
National Centre for Register-based Research, Department of Economics and Business Economics, Aarhus University, Aarhus, Denmark

iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark

Oleguer Plana-Ripoll
National Centre for Register-based Research, Department of Economics and Business Economics, Aarhus University, Aarhus, Denmark

Jean-Christophe Philippe Debost
National Centre for Register-based Research, Department of Economics and Business Economics, Aarhus University, Aarhus, Denmark

iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark

Department of Psychosis, Aarhus University Hospital Skejby, Denmark

Frederikke Hordam Gronemann
Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospitals, Copenhagen, Denmark

Introduction

Major depressive disorder (MDD) is associated with a substantial economic burden,[1,2] with costs corresponding to 1% of Europe's entire gross domestic product (GDP),[3] and $210 billion in the United States (US).[2] While depression in working-age adults generates direct costs in relation to outpatient care, hospitalization, and pharmacological treatment, the main cost drivers of the disorder are indirect expenses due to sick leave and early exit from the work force due to disability.[3,4] Previous studies estimate that mental health problems account for an average of one-third of all new disability pensions,[5] with common mental disorders such as anxiety and depression making up the largest proportion of claims for disability benefits.[6]

Preben Bo Mortensen
National Centre for Register-based Research, Department of Economics and Business Economics, Aarhus University, Aarhus, Denmark

iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark

CIRRAU - Centre for Integrated Register-Based Research, Aarhus University, Aarhus, Denmark

Trine Munk-Olsen
National Centre for Register-based Research, Department of Economics and Business Economics, Aarhus University, Aarhus, Denmark

iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark

Studies have reported that 17–22% of patients with depression are eventually granted a disability pension,[7–10] and the risk of obtaining a disability pension is 2–3 times higher in employees with severe depressive symptoms compared with the background population.[11,12] Years of work lost have, to our knowledge, not been estimated for individuals with depression, but one study showed that people who receive disability pension due to mood disorders lose around 15 years of work, assuming a scheduled retirement age of 67 years.[13]

Studies have shown that young age at depression onset, disease severity, duration and number of previous depression episodes, psychiatric and somatic comorbidity, as well as low educational level contribute to risk of early workforce exit.[7–10,14] This could suggest that individuals with treatment-resistant depression (TRD) are at particular high risk of early exit from the labor market.[15] TRD captures a severe form of depression characterized by lack of response to at least two sequential medication trials,[16,17] resulting in lengthy periods of untreated or insufficiently treated depressive symptoms and a higher risk of co-occurring medical and psychiatric conditions,[14,18] which could increase their risk of early work-force exit relative not only to the general population, but to other depression patients as well. Several studies using US commercial claims data have estimated that the costs of lost productivity specifically due to TRD is doubled compared with non-TRD controls.[19–21] Understanding the effect of TRD on loss of work productivity is essential in order to properly characterize the individual and societal consequences of this depression subtype. However, no studies to date have quantified the effect of TRD on premature workforce exit due to disability and the resulting excess years of work lost.

Here, we report the risk of premature workforce exit due to disability, and estimate differences in work years lost (WYL) in patients with TRD in a nationwide population-based study of patients initiating antidepressant (AD) treatment of depression.

Methods

Study population

From the Danish National Prescription Registry,[22] we identified all individuals born in Denmark who filled a prescription for an AD drug, Anatomical Therapeutic Chemical (ATC) code N06A, with the indication "for depression" or "for prevention of depression" (indication-codes 168 and 270) between the ages of 18 and 60 years in the calendar period from 1 January 2005 to 30 December 2012 ($N = 155{,}349$).

We applied a set of exclusion criteria in order to capture only the first-time AD users. A flowchart of the exclusion process is shown in Figure 1. First, individuals who filled a prescription before 2005 for a potential add-on medication for depression including lithium (N05AN01), risperidone (N05AX08), olanzapine (N05AH03), aripiprazole (N05AX12), and quetiapine (N05AH04) before their first AD prescription were excluded ($n = 375$). Second, each individual's information was linked to the Danish Psychiatric Central Research Register and the Danish National Patient Register,[23,24] and individuals were excluded if they, before their first filled AD prescription, had an in- or outpatient hospital contact with the following diagnoses: organic mental disorders (ICD-10: F00–09, ICD-8: 290.09, 290.10, 290.11, 290.18, 290.19, 292.x9, 293.x9, 294.x9, 309.x9), schizophrenia, schizotypal and delusional disorders (ICD-10: F20–29, ICD-8: 295.x9, 296.89, 297.x9, 298.29–298.99, 299.04, 299.05, 299.09, 301.83), or bipolar disorder (ICD-10: F30–31, ICD-8: 296.19, 296.39, 298.19) (available since 1969) ($n = 2367$). Third, patients with an in- or outpatient hospital contact with a diagnosis of a single or recurrent depressive episode (ICD-10: F32, F33, ICD-8: 296.09, 296.29, 298.09, 300.49) prior to their first prescription were excluded if the contact was more than 30 days before first prescription ($n = 3034$). If the admission occurred less than 30 days prior to their first prescription it was considered part of the initial episode and they were included in the sample, with follow up beginning on the date of their first AD prescription.

Also, we excluded individuals if their first treatment trial did not last for at least 4 weeks ($n = 12{,}328$) as these individuals did not take the medication long enough for its effectiveness to be evaluated. We used the unique identification number assigned to all individuals born or legally residing in Denmark (CPR), to link patient records from the Danish Civil Registration System and the Register of Employment Classification,[25,26] and excluded those who emigrated or retired before their first AD prescription ($n = 7300$). The final sample included 129,945 patients with depression.

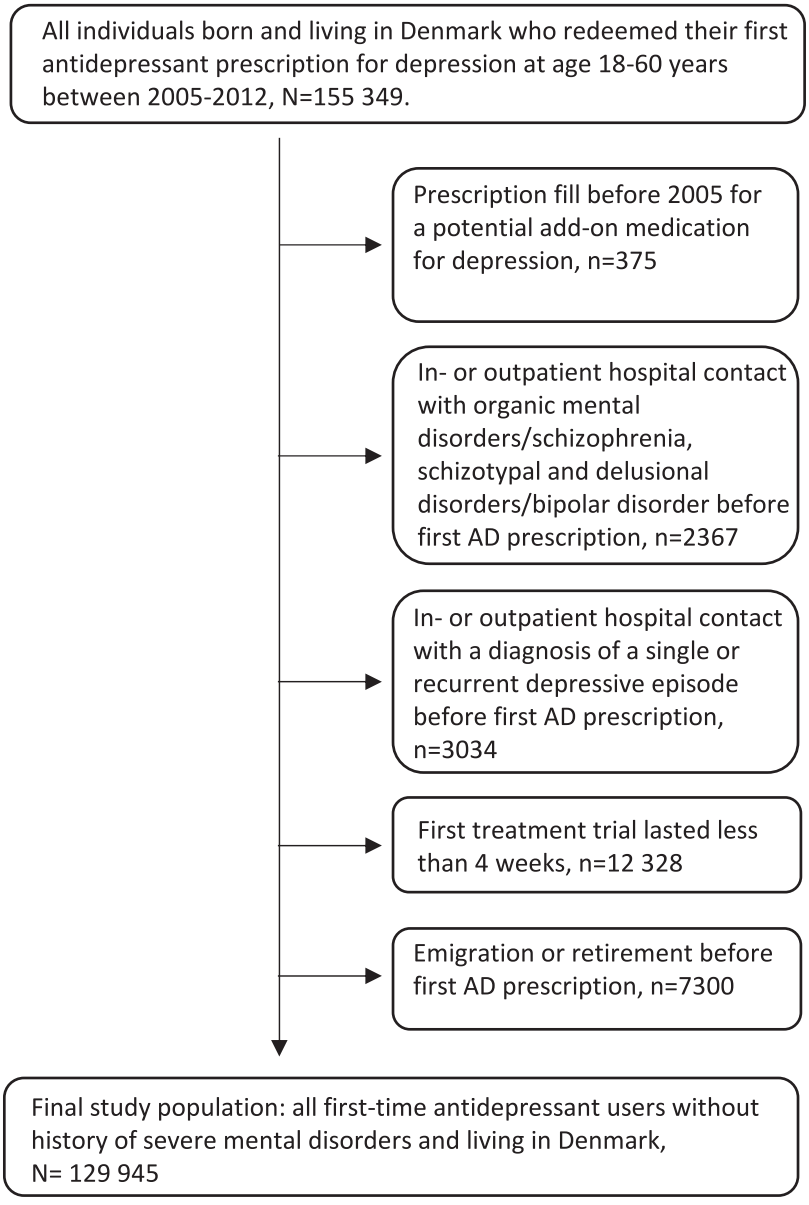

Figure 1. Flowchart of the exclusion procedure from the initial to the final study population.
AD, antidepressant.

Defining medical treatment episodes from recorded prescriptions

The duration of treatment trials was estimated based on the World Health Organization (WHO)'s defined daily dose (DDD) (volume in each pack) multiplied by number of packs per prescription fill if the individual had received 10 or fewer prescriptions. For episodes with more than 10 prescriptions, the median distance between fills was applied to calculate the duration of trials. To acknowledge that patients do not necessarily fill prescriptions at the exact time that they run out of medication, and to take stockpiling into account, we accumulated the amount of medication from prescriptions to calculate days in each continuous episode.[27] For the same reason, we allowed a grace period of 28 days between each prescription fill of the same ATC class at the fourth level [medication within the same category, e.g., selective serotonin reuptake inhibitors (SSRI)] – a method that has previously been applied by Reutfors *et al.*[28] Based on the above-mentioned information, treatment episodes were defined as continuous prescription fills with medication gaps no longer than 100 days. If medication gaps of more than 100 days

occurred, we assumed that the patient had stopped the treatment, and treatment after that was considered a new episode.

Definition of TRD (exposure)

TRD was defined *a priori* based on established definitions and on previous work from our group[16,29]; at least two shifts in treatment trials. Shifts had to occur within the same episode of continuous medical treatment within 2 years and were defined as: (I) Shift in medication class at the fourth ATC level, including augmentation (add-on medication with the following psychotropic drugs; lithium, risperidone, olanzapine, aripiprazole, and quetiapine) or combination (two different AD drug classes at the same time), (II) admission to in- or outpatient care with single or recurrent depressive episode (F32–33). Individuals were classified with TRD on the date that these criteria were met. The comparison sample consisted of individuals who had been prescribed AD medication and had a maximum of one shift in treatment trials (AD medication or hospital in- or outpatient contact with single or recurrent depressive episode) during the same episode within 2 years from first prescription.[29]

Premature workforce exit (outcome)

The main outcome of interest in this study was premature exit from the labor market, measured using information on receipt of disability pensions obtained from the Register of Employment Classification up until 31 December 2016.[26] In Denmark, an individual is eligible for disability pension if his or her ability to work is permanently impaired, and if the reduction is such that the person will not be able to become self-sufficient in income-generating work. Disability pension is granted by the municipal authorities and is a permanent public benefit. Only severe cases are awarded disability pension before the age of 40 years and if they can document that their ability to work cannot be improved by participating in relevant employment promotion programs.[30] In Denmark, individuals who pay into a state-run unemployment insurance for at least 30 years are eligible for voluntary early retirement at age 60, 7 years before the official retirement age of 67 for individuals born after 1953 and 65 for individuals born before 1953. In the current study, voluntary early retirement was considered a competing risk.

Covariates

Covariates were chosen *a priori* based on previous studies on the association between depression and early labor force exit.[7,31] We obtained information on psychiatric comorbidity from the Danish Psychiatric Central Research Registry. Psychiatric comorbidity was measured as in- or outpatient hospital contact before the date of first prescription of ADs with mental and behavioral disorders due to psychoactive substance abuse (ICD-10: F10–19, ICD-8: 291.x9, 294.39, 303.x9, 303.20, 303.28, 303.90), neurotic, stress-related, and somatoform disorders [ICD-10: F40–48, ICD-8: 300.x9 (excluding 300.49), 305.x9, 305.68, 307.99], eating disorders (ICD-10: F50, ICD-8: 305.60, 306.50, 306.58, 306.59), specific personality disorders [ICD-10; F60, ICD-8: 301.x9 (excluding 301.19), 301.80, 301.81, 301.82, 301.84], mental retardation (ICD-10: F70–79, ICD-8: 311.xx, 312.xx, 313.xx, 314.xx, 315.xx), pervasive developmental disorders (ICD-10: F84, ICD-8: 299.00, 299.01, 299.02, 299.03), and behavioral and emotional disorders with onset usually occurring in childhood and adolescence (ICD-10: F90–98, ICD-8: 306.x9, 308.0x).

A variable for somatic comorbidity (i.e., general medical conditions) prior to first AD prescription was constructed from diagnoses in the Danish National Patient Register according to the updated Charlson Comorbidity Index (uCCI).[24,32] Year of first AD prescription was obtained from the Danish National Prescription Registry and collapsed into the intervals 2005–2006, 2007–2008, 2009–2010, 2011–2012, to account for secular changes in AD prescription patterns.

Date of birth and sex were obtained from the Danish Civil Registration System and date of death from the Danish Register of Causes of Death.[25,33] Furthermore, highest educational level achieved as of the year of first AD prescription was obtained from the Danish Education Registers and categorized in three groups; low (primary and lower secondary school), medium (upper secondary school, short- and medium-cycle higher education), high (long-cycle higher education).[34]

Statistical analyses

Characteristics of TRD and non-TRD patients were summarized by the use of descriptive statistics and differences were tested with *t* tests and chi-square tests as appropriate.

Individuals were followed from the date of first prescription of AD medication until retirement (disability pension or voluntary early retirement), emigration, death, age 65 years, or 31 December 2016, whichever came first. End of follow up was set at age 65 years (scheduled age retirement for individuals born before 1953) because none of the individuals born after 1953 would have reached 67 years in 2016. Any individual who, after their first AD prescription and within 2 years, had a hospital contact with the ICD-10 diagnoses organic mental disorders, schizophrenia, schizotypal and delusional disorders, and bipolar disorders were censored on the date of admission. TRD was treated as a time-varying exposure with two categories: individuals with depression were unexposed to TRD, and exposed on the day when they fulfilled the requirements for the definition of TRD.

We compared the rate of disability pension between those with and without TRD using Cox proportional hazards regression models with age as the underlying time scale. Competing events (death and voluntary early retirement) were censored on the date these events occurred. Models were adjusted for birth year, year of first AD prescription, psychiatric and somatic comorbidity, and educational level to control for potential confounders and secular trends. The main assumption behind the Cox proportional hazards model is that the hazard ratio (HR) is constant over time (age in this case), that is the hazard rate of disability pension for the TRD group is proportional to that of the non-TRD group independent of age. When this assumption does not hold, the Cox model estimates can be interpreted as an average HR (aHR) over the entire follow-up period.[35] The proportionality between the rates of disability pension (the ratio of the hazard rates for the TRD and non-TRD group) was not constant over age, thus estimates were also calculated separately for specific age groups (18–20, 21–25, 26–30, 31–35, 36–40, 41–45, 46–50, 51–55, 56–60, 61–65 years).

WYL were calculated using an adaptation of the life years lost method, which is used to estimate reduction in life expectancy (i.e., life years lost) in people experiencing a disease or condition. The technical details of this method have been published previously,[36] and a detailed tutorial on how to implement it is available.[37] In this study, we adapted the method to estimate WYL (instead of life years lost), which can be interpreted as the average period of reduced working life (compared with the scheduled age of retirement at 65 years). The differences in WYL between the TRD group and the entire sample (people experiencing depression) denote excess WYL, and is interpreted as the number of work-years that individuals with TRD lose in excess of that found in the total sample. The reason for which we compare those with TRD with the total sample, and not to the non-TRD, is that the number of WYL at a given age, for example 40 years, is estimated using hazard rates at ages 40 years and beyond. By choosing non-TRD as a comparison group, we would assume that someone who has not experienced TRD at age 40, would remain free of TRD until death. Total years of work lost were divided into years lost due to disability pension and other competing causes (death and voluntary early retirement) through a competing risks model. Results were stratified for each sex, and all estimates and confidence intervals (calculated using non-parametric bootstrap with 1000 simulations) were obtained using the "lillies" package.[37]

Statistical analyses were performed in Stata 15.1 (StataCorp, College Station, TX, USA) and in R (R Foundation for Statistical Computing, Vienna, Austria).

Results

The study included 129,945 patients who redeemed their first AD prescription at age 18–60 years between 2005 and 2012. Of the total population of individuals with depression, 7478 (5.75%) were classified as treatment-resistant. Descriptive data (Table 1) show that more than half of the population were women; 61% in the TRD group and 60% in the non-TRD group. Significantly more TRD patients (41%) had primary and lower secondary school as their highest completed education at the time of their first AD prescription compared with non-TRD patients (34%) ($p < 0.001$). Patients with TRD were significantly younger at first prescription, with a mean (SD) age of 35 (12) years compared with non-TRD patients [38 (12) years] ($p < 0.001$). Having one or more psychiatric comorbidities was more pronounced in the TRD group (15%) than in the non-TRD group (10%) ($p < 0.001$), and significantly more TRD patients had neurotic disorders (10% *versus* 6%), personality disorders (3% *versus* 2%), and behavioral and emotional disorders with early onset (1.5% *versus* 1.1%) ($p < 0.001$). The pattern of somatic comorbidity was similar in the two groups.

Table 1. Cohort characteristics for patients with and without treatment-resistant depression (TRD and non TRD) ($N = 129,945$).

	TRD	Non-TRD
	***n* = 7478 (5.75%)**	***n* = 122,467 (94.25%)**
	***n* (%)**	***n* (%)**
Sex		
Women	4535 (61)	73,083 (60)
Educational level the year of first prescription		
Low	3015 (41)	41,435 (34)
Medium	4122 (55)	73,292 (60)
High	284 (4)	6799 (6)
Missing	57	941
Year of first AD prescription		
2005–2006	1703 (23)	30,438 (25)
2007–2008	1861 (25)	31,215 (25)
2009–2010	2142 (28)	34,249 (28)
2011–2012	1772 (24)	26,565 (22)
Age at first AD prescription (years)		
18–29	3023 (41)	38,117 (31)
30–39	1811 (24)	31,264 (26)
40–49	1591 (21)	29,127 (24)
50–60	1051 (14)	23,959 (20)
Psychiatric comorbidity		
0	6384 (85)	110,430 (90)
1	880 (12)	9488 (8)
⩾2	214 (3)	2549 (2)
Mental and behavioral disorders due to psychoactive substance abuse	185 (2)	2551 (2)
Neurotic, stress-related, and somatoform disorders	763 (10)	7687 (6)
Eating disorders	57 (0.8)	805 (0.7)
Specific personality disorders	210 (3)	2261 (2)
Mental retardation	11 (0.2)	109 (0.1)
Pervasive developmental disorders	13 (0.2)	196 (0.2)
Behavioral and emotional disorders with onset usually occurring in childhood and adolescence	110 (1.5)	1377 (1.1)

(Continued)

Table 1. (Continued)

	TRD	Non-TRD
	***n* = 7478 (5.75%)**	***n* = 122,467 (94.25%)**
	***n* (%)**	***n* (%)**
Somatic comorbidity before first prescription—the uCCI		
0	6698 (90)	109,209 (89)
1	524 (7)	7591 (6)
2	190 (2)	4173 (4)
⩾3	66 (1)	1494 (1)
Work/life status		
Not retired and alive	5874 (79)	104,456 (85)
Disability pension	1256 (17)	9462 (8)
Voluntary early retirement	182 (2)	5926 (5)
Dead	166 (2)	2623 (2)
Year of disability pension award		
2005–2007	86 (7)	1007 (11)
2008–2010	448 (36)	3187 (34)
2011–2013	522 (41)	3816 (40)
2014–2016	200 (16)	1452 (15)

AD, antidepressant; TRD, treatment-resistant depression; uCCI, updated Charlson comorbidity index.

The cohort was observed over 926,859 person-years (TRD: 48,154 person-years), in which 10,718 patients (TRD: 1256) received a disability pension and 2789 patients died (TRD: 166). The proportion of patients in the TRD group who received a disability pension during follow up was larger than in the non-TRD (17% *versus* 8%, $p < 0.001$). Age at disability pension was lower in the TRD group [mean (SD) 46 years (10) *versus* 49 (10) years, $p < 0.001$], and this difference was more pronounced for women [mean (SD) 45 years (11) *versus* 49 (10) years, $p < 0.001$] than men [mean (SD) 47 years (10) *versus* 49 (10) years, $p < 0.001$].

Patients with TRD had a more than three-fold higher risk of being on disability pension during follow up compared with depressed patients without treatment-resistance (aHR: 3.23, 95% CI 3.05; 3.43). This difference was particularly pronounced for women (aHR for women: 3.60, 95% CI 3.33; 3.89 and aHR for men: 2.78, 95% CI 2.54; 3.06) (Table 2).

The association between TRD and age at receiving disability pension was inversely U-shaped; the rate of disability pension for patients with TRD compared with non-TRD patients increased with age, and was highest in the age groups 31–35, 36–40 and 41–45 years, and decreased thereafter (Figure 2).

Work years lost

On average, TRD patients lost 12.37 years of work before the age of 65 years, while the total sample of patients with depression lost 6.56 years due to all causes. In relation to disability pension, TRD patients lost 10.61 years of work while the total sample lost 4.55 years, resulting in an excess

Table 2. aHR reflecting risk of disability pension for patients with TRD compared with non-TRD.

	All		Men		Women	
	aHR (95% CI)*	aHR (95% CI)**	aHR (95% CI)*	aHR (95% CI)**	aHR (95% CI)*	aHR (95% CI)**
Disability pension	3.33 (3.14; 3.54)	3.23 (3.05; 3.43)	2.91 (2.65; 3.19)	2.78 (2.54; 3.06)	3.71 (3.43; 4.00)	3.60 (3.33; 3.89)

*Adjusted for birth year and year of first AD prescription.
**Adjusted for birth year, year of first AD prescription, educational level, psychiatric comorbidities, number of psychiatric comorbidities, and somatic comorbidity (uCCI).
AD, antidepressant; aHR, adjusted hazard ratio; CI, confidence interval; TRD, treatment-resistant depression; uCCI, updated Charlson comorbidity index.

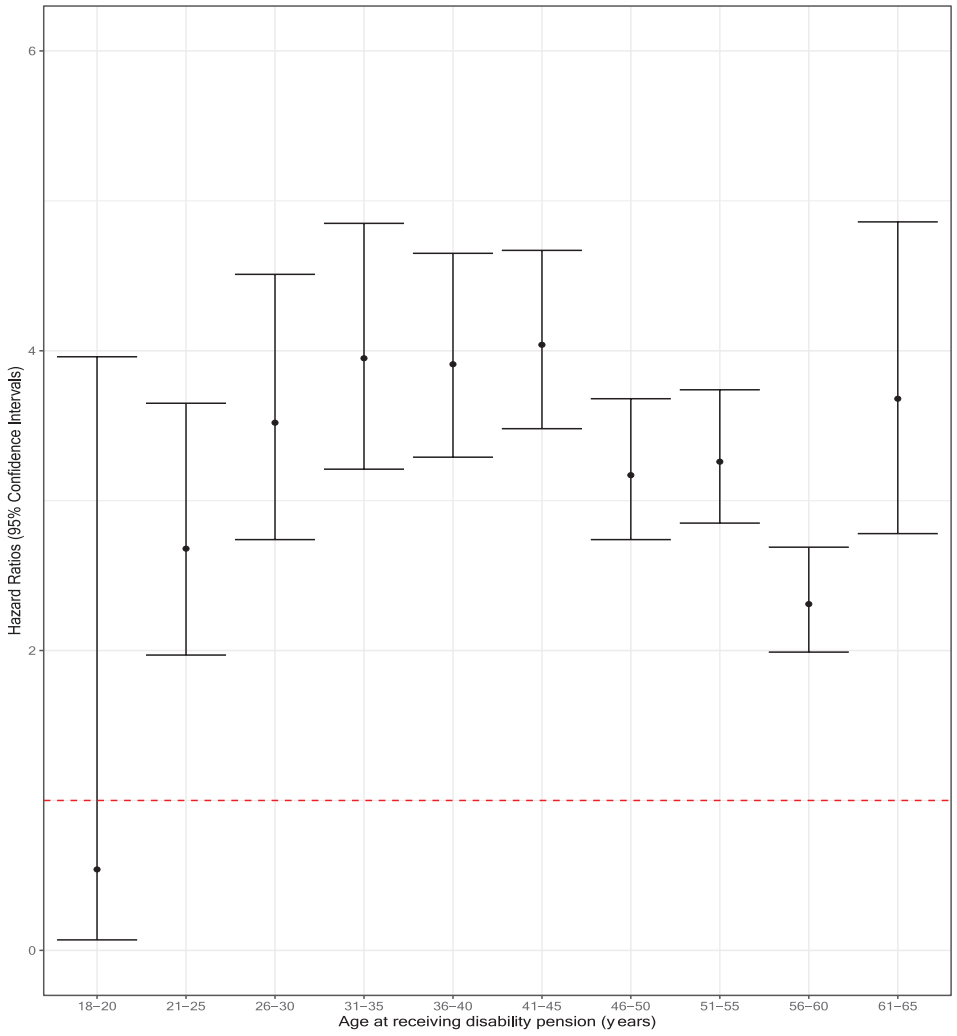

Figure 2. Risk of disability pension for patients with TRD compared with non-TRD split in age-groups at age of receiving disability pension.
TRD, treatment-resistant depression

WYL of 6.06 years (95% CI: 5.64; 6.47). Again, this difference was more pronounced for women [who, on average, lost 6.90 years (95% CI: 6.33; 7.46) in excess of all women with depression] compared with men [4.96 years (95% CI: 4.31; 5.59)]. The total sample of patients with depression had, to a greater extent, retired early voluntarily, thus, the excess WYL due to voluntary

early retirement was negative (−0.46 95% CI: −0.52; −0.40) (Table 3).

WYL were estimated as an average at each age from 18 to 65 years, but an example is shown for the specific age of 30 years in Figure 3. Among those alive and not retired at age 30 years, less than 10% in the TRD group are expected to be alive and not retired at age 65 years, while this is the case for more than 20% in the total sample. Expected remaining work-years at age 30 years was estimated as the area under the conditional survival curve until age 65 years and was about 20 years for patients with TRD compared with 27 years among all patients with depression (Figure 3).

Discussion

To our knowledge, this is the first study to investigate the risk of premature exit from the workforce and estimate the reduction in work-years in patients with and without TRD. In our study, 6% of patients with depression met criteria for TRD, and having TRD was associated with a significant and substantial risk of leaving the labor force prematurely. Men and women with TRD had about a three-fold higher risk of premature workforce exit in comparison with non-TRD patients. Correspondingly, men and women with TRD had a shortened work-life of 5.1 and 6.4 years, respectively, in excess of the total sample of men and women with depression. We found a higher risk of premature workforce exit in women with TRD than in men, and, correspondingly, more WYL. This could be explained by the fact that women with TRD were, on average, younger than men when they began receiving a disability pension (44 years *versus* 46 years).

Prior evidence shows that, in general, individuals with mental disorders qualify for disability pensions at significantly younger ages than individuals with somatic conditions.[5,7,13] Our findings confirm these results, suggesting depression is a costly and debilitating disease, and, for some patients, can result in an impaired ability to work and an early and permanent exit from the labor market.[31,38] However, our results add to the current evidence that both the personal and the societal burdens of depression are much greater among patients who do not respond to treatment. In our study, 17% of the patients with TRD and 8% of the non-TRD received a disability pension during follow up, and most did so early in their

Table 3. WYL due to early retirement or death in patients with and without TRD.

	All				Men				Women			
	TRD	Total sample	Excess WYL	95% CI	TRD	Total sample	Excess WYL	95% CI	TRD	Total sample	Excess WYL	95% CI
All causes	12.37	6.56	5.81	5.42; 6.19	11.61	6.55	5.06	4.50; 5.65	12.91	6.52	6.39	5.88; 6.91
Disability pension	10.61	4.55	6.06	5.64; 6.47	9.28	4.33	4.96	4.31; 5.59	11.57	4.67	6.90	6.33; 7.46
Scheduled early retirement	0.45	0.91	−0.46	−0.52; −0.40	0.45	0.72	−0.27	−0.36; −0.17	0.47	1.08	−0.62	−0.70; −0.52
Death	1.32	1.10	0.21	−0.01; 0.43	1.88	1.51	0.37	0.01; 0.78	0.87	0.76	0.11	−0.12; 0.33

CI, confidence interval; TRD, treatment-resistant depression; WYL, work years lost.

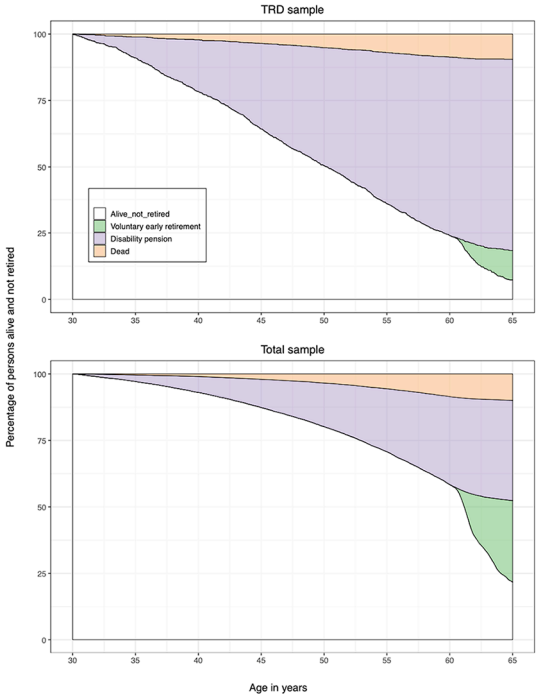

Figure 3. Stacked cause-specific cumulative incidences for disability pension, voluntary early retirement, and death for patients with TRD and the total sample, who were alive and not retired at age 30 years and followed until age 65 years.
TRD, treatment-resistant depression

work-life, resulting in a substantial number of WYL.

For society at large, early labor force exit and the resulting high number of WYL leads to both an enormous burden in economic spending on disability benefits, and additionally to lost tax payments and lost productivity.[38] Not surprisingly, research has shown that the indirect costs of depression, public benefit payment, and loss of production, by far exceeds the direct costs for hospitalization, outpatient care, and medication, and that it can be attributed mainly to those who are treatment resistant.[3,21] It is worth noting that only 6% of patients with depression met our stringent criteria for TRD. Nevertheless, they accounted for a disproportionate amount of productivity loss, which is a great challenge for any welfare state.

Lost productivity has devastating consequences not just for society, but also for the individual.[39] Since it is very unlikely for individuals with disability pension to return to the labor market, retirement at a young age may, in part, explain the markedly reduced lifetime income often reported for individuals with depression.[5,38,40] Adding to this, low income may have an adverse impact on the entire family. For instance, growing up poor or with unemployed parents play a significant role in children's development of cognitive and social-emotional skills, exemplified by high rates of academic failure and mental health problems among youth.[41–43] Also, early labor market exit may lead to marginalization from social life, because employment maintains a connection with the community and is vital for self-esteem, for creating a social identity, and for belonging in social networks.[38,39] Also, premature exit from the labor market has been linked to worsened health behavior, increased mortality, and even an increased risk of suicide, especially when awarded at a young age.[44–47]

The major strength of our study was the use of nationwide register data collected systematically and consistently, allowing for an extended follow up and without any attrition. In addition, our study included all patients with depression who were prescribed ADs during 2005–2012, including those who were treated only in primary care. The inclusion of primary care patients increases the generalizability to the broader population of individuals with depression, since the vast majority of patients with depression are identified and first treated in primary care.[48,49]

This study has several limitations. When using redeemed prescriptions to define TRD, there is inevitably a risk of misclassification. The lack of clinical information about adherence to treatment, as well as the dose of ADs taken by the patient, made it impossible to evaluate the reasons for shifts in medical treatment. We evaluated the definition of TRD in a previous study restricting in various ways, but results remained the same.[29] Thus, although we cannot know the exact reason each patient switched medications, we can be sure that this definition captures a group of patients with both increased mortality and risk of leaving the labor force early,[29] which could reflect a difference in the underlying severity of the disorder. Of course, there is also the possibility that the definition of TRD may be confounded by an increased duration of depressive symptoms that have not been managed appropriately, since increased symptom duration correlates with inadequate treatment response. Besides, we do not know the diagnosis registered on the disability

pension application. It could be depression, but could also be other medical conditions associated with depression or AD drug use, and is a potential source of confounding.

Finally, Denmark has a strong welfare state, which grants pensions to its citizens at a rate that is somewhat higher than in many other countries. These observations affect the generalizability of the results to other countries with different welfare systems. However, note that, in the current study, we use the information on disability pension as a proxy measure for premature workforce exit, and the implications for patients with TRD can hence be considered transnational. Danish guidelines state that disability pension should not be issued to people below the age of 40 years except for very severe cases where the person's ability to work cannot be improved. Nevertheless, our results show that the risk of receiving disability pension is highest for patients with TRD aged 31–45 years, which means that these patients would likely have exited the workforce even if living in another country.

The consequences of depression are large both for society and the individual, but they are not at all equally distributed across depression patients. Although patients with TRD constitute a smaller group within depression patients generally, they contribute disproportionally to the societal costs of depression with increased risk of premature labor force exit and the resulting WYL.

Acknowledgements

Kathrine Bang Madsen and Trine Munk-Olsen carried out this work as part of the MOOD STRATIFICATION- EU project 754740.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Ethical statement

According to Danish law, informed consent is not required for register-based studies. The Danish Data Protection Agency and the Danish Health Data Authority approved the current study. All data were de-identified and not recognizable at an individual level.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Kathrine Bang Madsen receives funding from the European Union's Horizon 2020 research program under the grant agreement No 754740 "Moodstratification". Oleguer Plana-Ripoll receives funding from the European Union's Horizon 2020 research and innovation program under the Marie Sklodowska-Curie grant agreement No 837180 and the Danish National Research Foundation (Niels Bohr Professorship to Prof. John J. McGrath). Katherine L. Musliner receives funding from the Lundbeck Foundation, Grant #R303-2018-3551. Jean-Christophe Philippe Debost receives funding from the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH) (Grant number R155-2014-1724); the Danish Council for Independent Research (Grant number 8020-00013). Trine Munk-Olsen receives funding from The Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH (grant R155-2014-1724).

ORCID iD

Kathrine Bang Madsen https://orcid.org/0000-0002-0103-5534

References

1. Gustavsson A, Svensson M, Jacobi F, *et al.* Cost of disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol* 2011; 21: 718–779.
2. Greenberg PE, Fournier A-A, Sisitsky T, *et al.* The economic burden of adults with major depressive disorder in the United States (2005 and 2010). *J Clin Psychiatry* 2015; 76: 155–162.
3. Sobocki P, Jonsson B, Angst J, *et al.* Cost of depression in Europe. *J Ment Health Policy Econ* 2006; 9: 87–98.
4. Sobocki P, Lekander I, Borgstrom F, *et al.* The economic burden of depression in Sweden from 1997 to 2005. *Eur Psychiatry* 2007; 22: 146–152.
5. OECD. Sickness, disability and work: breaking the barriers [Internet]. OECD, https://www.oecd-ilibrary.org/social-issues-migration-health/sickness-disability-and-work-breaking-the-barriers_9789264088856-en (2010, accessed 14 November 2019).
6. Harvey SB, Henderson M, Lelliott P, *et al.* Mental health and employment: much work still to be done. *Br J Psychiatry* 2009; 194: 201–203.
7. Mittendorfer-Rutz E, Harkanen T, Tiihonen J, *et al.* Association of socio-demographic factors, sick-leave and health care patterns with the risk

of being granted a disability pension among psychiatric outpatients with depression. *PLoS One* 2014; 9: e99869.

8. Sorvaniemi M, Helenius H and Salokangas RKR. Factors associated with being granted a pension among psychiatric outpatients with major depression. *J Affect Disord* 2003; 75: 43–48.
9. Rytsala HJ, Melartin TK, Leskela US, *et al.* Predictors of long-term work disability in major depressive disorder: a prospective study. *Acta Psychiatr Scand* 2007; 115: 206–213.
10. Holma IAK, Holma KM, Melartin TK, *et al.* A 5-year prospective study of predictors for disability pension among patients with major depressive disorder. *Acta Psychiatr Scand* 2012; 125: 325–334.
11. Bultmann U, Christensen KB, Burr H, *et al.* Severe depressive symptoms as predictor of disability pension: a 10-year follow-up study in Denmark. *Eur J Public Health* 2008; 18: 232–234.
12. Lassemo E, Sandanger I, Nygard JF, *et al.* Predicting disability pension—depression as hazard: a 10 year population-based cohort study in Norway. *Int J Methods Psychiatr Res* 2016; 25: 12–21.
13. Knudsen AK, Overland S, Hotopf M, *et al.* Lost working years due to mental disorders: an analysis of the Norwegian disability pension registry. *PLoS One* 2012; 7: e42567.
14. Madsen KB, Momen NC, Vogdrup Petersen L, *et al.* Bidirectional associations between treatment-resistant depression and general medical conditions. *Manuscr Prep* 2020.
15. Kautzky A, Dold M, Bartova L, *et al.* Clinical factors predicting treatment resistant depression: affirmative results from the European multicenter study. *Acta Psychiatr Scand* 2019; 139: 78–88.
16. Conway CR, George MS and Sackeim HA. Toward an evidence-based, operational definition of treatment-resistant depression: when enough is enough. *JAMA Psychiatry* 2017; 74: 9–10.
17. Gaynes BN, Lux L, Gartlehner G, *et al.* Defining treatment-resistant depression. *Depress Anxiety*. Epub ahead of print 22 October 2019. DOI: 10.1002/da.22968.
18. Kubitz N, Mehra M, Potluri RC, *et al.* Characterization of treatment resistant depression episodes in a cohort of patients from a US commercial claims database. *PLoS One* 2013; 8: e76882.
19. Ivanova JI, Birnbaum HG, Kidolezi Y, *et al.* Direct and indirect costs of employees with treatment-resistant and non-treatment-resistant major depressive disorder. *Curr Med Res Opin* 2010; 26: 2475–2484.
20. Corey-Lisle PK, Birnbaum HG, Greenberg PE, *et al.* Identification of a claims data "signature" and economic consequences for treatment-resistant depression. *J Clin Psychiatry* 2002; 63: 717–726.
21. Amos TB, Tandon N, Lefebvre P, *et al.* Direct and indirect cost burden and change of employment status in treatment-resistant depression: a matched-cohort study using a US commercial claims database. *J Clin Psychiatry* 2018; 79: 17m11725.
22. Kildemoes HW, Sorensen HT and Hallas J. The Danish National Prescription Registry. *Scand J Public Health* 2011; 39(7 Suppl.): 38–41.
23. Mors O, Perto GP and Mortensen PB. The Danish Psychiatric Central Research Register. *Scand J Public Health* 2011; 39(7 Suppl.): 54–57.
24. Lynge E, Sandegaard JL and Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011; 39(7 Suppl.): 30–33.
25. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011; 39(7 Suppl.): 22–25.
26. Petersson F, Baadsgaard M and Thygesen LC. Danish registers on personal labour market affiliation. *Scand J Public Health* 2011; 39(7 Suppl.): 95–98.
27. Tanskanen A, Taipale H, Koponen M, *et al.* From prescriptions to drug use periods—things to notice. *BMC Res Notes* 2014; 7: 796.
28. Reutfors J, Andersson TM-L, Brenner P, *et al.* Mortality in treatment-resistant unipolar depression: a register-based cohort study in Sweden. *J Affect Disord* 2018; 238: 674–679.
29. Bang Madsen K, Plana-Ripoll O, Musliner KL, *et al.* Cause-specific life years lost in individuals with treatment-resistant depression: a nationwide register-based cohort study. In press.
30. The Danish Social Pensions Act. Legislative Decree no. 1239 October 13, 2016.
31. Rudolph KE and Eaton WW. Previous anxiety and depression as risk factors for early labour force exit. *J Epidemiol Community Health* 2016; 70: 390–395.
32. Quan H, Li B, Couris CM, *et al.* Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol* 2011; 173: 676–682.

33. Helweg-Larsen K. The Danish Register of causes of death. *Scand J Public Health* 2011; 39(7 Suppl.): 26–29.

34. Jensen VM and Rasmussen AW. Danish Education Registers. *Scand J Public Health* 2011; 39(7 Suppl.): 91–94.

35. Xu R and O'Quigley J. Estimating average regression effect under non-proportional hazards. *Biostatistics* 2000; 1: 423–439.

36. Andersen PK. Life years lost among patients with a given disease. *Stat Med* 2017; 36: 3573–3582.

37. Plana-Ripoll O, Canudas-Romo V, Weye N, *et al.* lillies: an R package for the estimation of excess Life Years Lost among patients with a given disease or condition. *PLoS One* 2020; 15: e0228073.

38. Schofield DJ, Shrestha RN, Percival R, *et al.* The personal and national costs of mental health conditions: impacts on income, taxes, government support payments due to lost labour force participation. *BMC Psychiatry* 2011; 11: 72.

39. Knapp M. Hidden costs of mental illness. *Br J Psychiatry* 2003; 183: 477–478.

40. Hakulinen C, Musliner KL and Agerbo E. Bipolar disorder and depression in early adulthood and long-term employment, income, and educational attainment: a nationwide cohort study of 2,390,127 individuals. *Depress Anxiety* 2019; 36: 1080–1088.

41. Dearing E. Psychological costs of growing up poor. *Ann N Y Acad Sci* 2008; 1136: 324–332.

42. Pedersen CR and Madsen M. Parents' labour market participation as a predictor of children's health and wellbeing: a comparative study in five Nordic countries. *J Epidemiol Community Health* 2002; 56: 861–867.

43. Hakulinen C, Webb RT, Pedersen CB, *et al.* Association between parental income during childhood and risk of schizophrenia later in life. *JAMA Psychiatry* 2019; 77: 17–24.

44. Hewitt S and Graff-Iversen S. Risk factors for cardiovascular diseases and diabetes in disability pensioners aged 40–42 years: a cross-sectional study in Norway. *Scand J Public Health* 2009; 37: 280–286.

45. Wallman T, Wedel H, Johansson S, *et al.* The prognosis for individuals on disability retirement. An 18-year mortality follow-up study of 6887 men and women sampled from the general population. *BMC Public Health* 2006; 6: 103.

46. Schneider B, Grebner K, Schnabel A, *et al.* Impact of employment status and work-related factors on risk of completed suicide. A case-control psychological autopsy study. *Psychiatry Res* 2011; 190: 265–270.

47. Rahman SG, Alexanderson K, Jokinen J, *et al.* Disability pension due to common mental disorders and subsequent suicidal behaviour: a population-based prospective cohort study. *BMJ Open* 2016; 6: e010152.

48. Musliner KL, Liu X, Gasse C, *et al.* Incidence of medically treated depression in Denmark among individuals 15–44 years old: a comprehensive overview based on population registers. *Acta Psychiatr Scand* 2019; 139: 548–557.

49. Ohayon MM, Priest RG, Guilleminault C, *et al.* The prevalence of depressive disorders in the United Kingdom. *Biol Psychiatry* 1999; 45: 300–307.