Archival Report

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Associations Between Mental Disorders in Donors and Matched Recipients of Hematopoietic Stem Cell Transplants: A Population-Based Cohort Study

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ABSTRACT

BACKGROUND: Immunological mechanisms have been implicated in the development of mental disorders, and interestingly, case reports have suggested that hematopoietic stem cell transplantation (HSCT) can both transmit and cure psychotic disorders by replacing immune progenitor cells.

METHODS: Using Danish registers, we followed patients who received HSCT from donors with a psychiatric diagnosis or psychotropic medication use. We assessed risk of incident mental disorders or psychotropic medication use compared with recipients with unaffected donors. We identified 464 donor-recipient pairs (51.3% male recipients). All donor-recipient pairs were related.

RESULTS: Receiving HSCT from a donor with a psychiatric history was not significantly associated with incident psychiatric diagnoses (hazard rate ratio [HRR] 2.79, 95% CI, 0.83–9.39; $p = .098$) or incident use of psychotropics (HRR 1.43, 95% CI, 0.91–2.24; $p = .118$). Subgroup analysis showed an increased risk of antipsychotic use, which remained significant after adjusting for confounders (HRR 4.73, 95% CI, 1.26–17.78; $p = .021$); however, this was based on a small number of cases. For depression and antidepressant use, data were available to perform a meta-analysis of our and one additional study, which showed no significant difference (HRR 1.24, 95%, CI 0.66–2.35).

CONCLUSIONS: Receiving HSCT from a donor with a psychiatric history did not affect risk of mental disorders. An increased risk of antipsychotic use was observed only in subgroup analyses; however, the exploratory nature of the study, the limited sample size, and family relationship between donors and recipients do not allow for causal conclusions, and external replication studies are warranted.

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It has been suggested that infections and immunological disturbances play a role in the pathophysiology of mental disorders. In recent decades, this hypothesis has gained support from descriptions of conditions such as autoimmune psychosis (1) and autoimmune obsessive-compulsive disorder (2), from meta-analyses showing effects of anti-inflammatory drugs in conditions such as depression (3) and psychosis (4), and epidemiological studies linking infections to subsequent risk of schizophrenia, depression, bipolar disorder, and other neuropsychiatric conditions (5,6).

Hematopoietic stem cell transplantation (HSCT) involves the infusion of stem cells derived from a donor (allogeneic HSCT) or from the patient (autologous HSCT) after myeloablative or nonmyeloablative conditioning regimens (7). The procedure thereby fully or partially replaces the immune cell population of the patient, which explains its curative potential in hematological malignancies. In the Danish context, the indications for HSCT and choice of donor have changed over time. Initially, the transplant program exclusively used related donors, but use of matched unrelated register donors was introduced in the 1990s. The donor population is currently approximately 20% related and 80% unrelated. Moreover, the use of nonmyeloablative transplants since 2000 has made it possible to transplant older patients with similar outcomes as younger patients (8). Indications for transplants were originally immune defects and bone marrow failure; currently, 90% of the patients have malignant diseases.

Experimentally, HSCT has been shown to affect behavior in a mouse model, indicative of a potential connection between HSCT and mental states (9). Clinically, remission of psychosis following HSCT from a healthy donor in a patient with treatment-resistant schizophrenia has been described in a case report (10), while another case report detailed the onset of chronic psychosis after HSCT from a sibling donor with schizophrenia (11). A recent epidemiological study on HSCTs in Sweden between 1977 and 2014 found an increased risk of depression in patients who received HSCT from a donor with depression, with a hazard ratio of 2.5 (95% CI, 1.3–5.1);

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however, the number of events was small (68 recipients were diagnosed with depression after HSCT), and the findings were nonsignificant after adjustment for relevant covariates, including family history of mental disorders (12) (hazard rate ratio [HRR] 1.89; 95% CI, 0.60–5.30). In the same study, the authors reported that none of the matched recipients of 16 donors with psychotic disorders were diagnosed with psychotic disorders after HSCT. The study was only based on hospital-recorded psychiatric diagnoses. To the best of our knowledge, no prior study has utilized a history of prescriptions for psychotropic medication as a proxy for mental disorders to increase the number of cases when investigating associations between mental disorders in donors and matched recipients of HSCT.

To study whether risk of mental disorders can be transmitted through HSCT, we used the unique nationwide Danish registers to explore the association between psychiatric diagnoses and redeemed prescriptions of psychotropic medications in donors of HSCT and their matched recipients. Furthermore, we stratified the findings based on drug classes and diagnostic categories. We aimed to correct for confounding factors (including family history of mental disorders) to investigate whether potential associations may give clues to etiological factors contributing to the development of mental disorders.

METHODS AND MATERIALS

Data Sources and Setting

In Denmark, all inhabitants are given a unique 10-digit Central Person Registration (CPR) number at birth or at the time of immigration (13). We used the CPR number to link individuals in the following registers: the Danish National Prescription Registry, which contains complete information from all pharmacies in Denmark on redeemed prescriptions since 1995 (14); the Danish Psychiatric Central Research Register, which contains data on all inpatient and outpatient contacts with Danish psychiatric facilities since 1970 (15); the Danish National Patient Registry, which contains records of all inpatient, outpatient, and emergency department visits at Danish hospitals (16); and the Database for Integrated Labour Market Research, which contains data on most recent educational level completed, income level, and association with the job market (17). The HSCT register at the Copenhagen University Hospital was used to identify recipients and matched related donors of HSCT. The register contains nationwide data on adult allogeneic HSCTs from 1983 to 2014; from 2014 to 2021, a local register in Western Denmark was created, and the data therefore only covers Eastern Denmark (the Capital Region of Denmark and Region Zealand). Diagnostic information was based on ICD-8 from 1977 to 1993 and on ICD-10 from 1994. All register data were available until December 31, 2021. Treatment in Danish hospitals is free of charge for all residents.

Inclusion and Exclusion Criteria

The study population consisted of adult (≥18 years) patients who received allogeneic HSCT in Denmark between 1983 and 2021, both years included (nationwide data from 1983 to 2014; complete data from Eastern Denmark from 2015 to 2021), when the CPR number of both the donor and a matched recipient could be identified. This effectively excluded patients who received a transplant from an unrelated donor. We only included donors and recipients with a minimum of 3-year observation time in the registers to allow capture of exposure and outcome events. In the analysis pertaining to incident diagnosis of mental disorders, recipients with a psychiatric diagnosis prior to HSCT were excluded. In the analysis on incident use of psychotropics, recipients who had redeemed prescriptions for psychotropic medication prior to HSCT were excluded (for specific drug classes, only recipients with previous prescriptions of drugs in that specific class were excluded). In addition, individuals who received HSCT prior to 1998 were excluded from the analysis of medication use because the prescription registry only contains data from 1995 onward.

Exposure, Outcome, and Confounding Variables

In the analysis of psychiatric diagnoses, exposure was defined as having received HSCT from a donor with a registered psychiatric diagnosis prior to donation. The comparator group was recipients of HSCT from a donor without a registered psychiatric diagnosis prior to donation. The outcome was incident diagnosis with a mental disorder after HSCT in the recipient under the competing risk of censoring due to death, immigration, or end of follow-up. Psychiatric diagnosis was defined using ICD-10 codes F00–F99 or ICD-8 codes 290–315.

In the analysis of medication use, exposure was defined as receiving HSCT from a donor who had redeemed a prescription for a psychotropic medication prior to donation, whereas the comparator group received HSCT from a donor without a history of redeeming a prescription for psychotropic medication. The outcome was incident use (redeemed prescription) of any psychotropic medication in the recipient under the competing risk of censoring due to death, immigration, or end of follow-up.

Psychotropic medication was defined as drugs with Anatomical Therapeutic Chemical codes N05 (antipsychotics, anxiolytics, hypnotics, and sedatives), N06 (antidepressants, psychostimulants, and antidementia drugs), and N07BB/N07BC (drugs used to treat alcohol or opioid dependence). Confounding variables included in the basic adjustment were sex, age, and year of HSCT. In the full adjustment, we also included relationship to donor (sibling/nonsibling), human leukocyte antigen match (identical/nonidentical), use of myeloablative treatment (yes/no), total body irradiation (yes/no), parental history of mental disorders (coded as none or any history of an ICD-10 diagnosis code of F00–F99 or ICD-8 code of 290–315), Charlson Comorbidity Index (0, 1, 2, 3, or ≥4 chronic disorders), the length of the hospital stay during which HSCT was performed (1–10, 11–20, 21–30, 31–40, 41–50, 51–100, or >100 days), educational level (elementary school, vocational training or high school, short- and long-cycle higher education), income (divided in quintiles), and work status (working, employed, retired, not in the workforce, or student).

Survival Analysis

A Cox proportional hazards model was used for survival analysis, and HRRs were reported as measures of relative risk. Calendar time after HSCT was used as the underlying time

scale. Time 0 was defined as the time of HSCT. We tested for proportional hazards by correlating the corresponding set of scaled Schoenfeld residuals against time for each covariate and the model globally. Crude analyses are reported, as well as models after basic adjustment and full adjustment. All confounding variables were fixed at the time of HSCT. Subgroup analyses were conducted on diagnoses (based on ICD-10 chapter, i.e., F0–F9) and 3-digit Anatomical Therapeutic Chemical codes. We conducted a sensitivity analysis in which organic mental disorders (e.g., delirium) defined as F00–F09 were excluded. Graphs were smoothed using a loess function. Because the study was exploratory in nature, we did not correct subgroup analyses for multiple testing. Two-tailed *p* values $<.05$ indicated statistical significance. Statistical analyses were conducted using R, version 4.2.2, with survival package version 3.4-0 (R Project for Statistical Computing).

Meta-Analysis

We conducted a post hoc meta-analysis of all available results using data from the current study and the previously published Swedish register-based study (12). Data (hazard ratios and CIs) were extracted for estimates related to the same patient population (based on diagnostic categories or medication use) and pooled using the inverse variance method. Between-study heterogeneity was estimated using restricted maximum-likelihood estimate for τ^2. All analyses were conducted using the *meta* package in R.

Ethics, Data Protection, and Reporting

All register-based information was anonymized for research purposes without requiring informed consent. The project was approved by the Danish Data Protection Agency. This study followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guideline. Counts <3 are considered microdata and cannot be reported according to Danish regulations.

RESULTS

We identified 2012 recipients of HSCT, 464 of whom had known donors with a CPR number that allowed for follow-up in the Danish registers. A total of 416 donor-recipient pairs remained after the exclusion criteria were applied (a minimum of 3 years of observation time for both recipient and donor). Cohort characteristics are detailed in Table 1. A large majority (91.6%) of donors and recipients were siblings. The frequency of transplants per year and the age of recipients both increased with time, while 180-day mortality after transplant decreased (Figures S1–S3). The assumption of proportional hazards was met for all models globally and for all covariates included in the models.

Association Between Mental Disorders in Donors and Recipients of HSCT

After exclusion of recipients with a recorded psychiatric diagnosis prior to HSCT, 393 donor-recipient pairs remained (Table 2). Follow-up time was shorter on average for the exposure group (mean 1820 days) than for the comparator group (mean 3099 days).

Table 1. Characteristics of the Total Study Cohort (*n* = 416 Donor-Recipient Pairs)

Donors	Mean (SD) or *n* (%)
Age, Years	46.7 (14.3)
Male	214 (51.3%)
Psychiatric Diagnosis	
None	370 (88.9%)
Before donation	24 (5.8%)
After donation	22 (5.3%)
Psychotropic Medication	
None	225 (54.1%)
Before donation	101 (24.3%)
After donation	90 (21.6%)
Recipients	
Age, Years	46.0 (14.3)
Male	237 (57.0%)
BMI	24.8 (4.5)
Employed	309 (74.3%)
CCI Group 3+	117 (28.1%)
Died Before End of Follow-Up	209 (50.2%)
Days from HSCT to death	1473 (1998)
Year of HSCT	2007 (9.4)
Range	1983–2020
Psychiatric Diagnosis	
None	367 (88.2%)
Before HSCT	23 (5.5%)
After HSCT	26 (6.2%)
Psychotropic Medication Use	
None	136 (32.7%)
Before HSCT	151 (36.3%)
After HSCT	129 (31.0%)
≥1 Parent With Psych. Disorder	51 (12.3%)
Sibling of Donor	381 (91.6%)
Myeloablative HSCT	194 (46.6%)
Total Body Irradiation	319 (76.7%)
HLA Identical Match	384 (92.3%)

BMI, body mass index; CCI, Charlson Comorbidity Index; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; Psych., psychiatric.

Overall, risk of incident psychiatric diagnosis was not significantly higher in subjects who received a transplant from a donor with a history of a psychiatric diagnosis (HRR 2.79, 95% CI: 0.83–9.39, $p = .098$) (Figure 1). The number of events did not allow for subgroup analyses because there were <3 events in the exposure group in each diagnostic category. Excluding organic mental disorders (F00–F09) did not change the conclusion of the analysis, with the overall difference in risk of mental disorders remaining nonsignificant both before adjustment (HRR 3.32, 95% CI 0.97–11.35, $p = .056$) and after adjustment (Figure S4).

Association Between Psychotropic Medication Use in Donors and Recipients of HSCT

A total of 338 donor-recipient pairs remained after exclusion of HSCTs conducted before 1998. After exclusion of recipients with a history of psychotropic drug use prior to HSCT, 189

Table 2. Characteristics of HSCT Recipients by Analysis and Donor Status

Characteristic	Recipients Included in Analysis on Psychiatric Diagnoses			Recipients Included in Analysis on Psychotropic Medication Use		
	Donor Without Psychiatric Diagnosis, *n* = 371	Donor With Psychiatric Diagnosis, *n* = 22	Total (Analysis on Diagnoses), *n* = 393	Donor Without Medication History, *n* = 146	Donor With Medication History, *n* = 43	Total (Analysis on Medication), *n* = 189
Male	211 (56.9%)	11 (50.0%)	222 (56.5%)	92 (63.0%)	29 (67.4%)	121 (64.0%)
Age, Years	46.2 (14.3)	46.7 (14.3)	46.2 (14.2)	44.8 (15.1)	49.1 (15.3)	45.8 (15.2)
BMI	24.6 (4.3)	27.2 (6.4)	24.8 (4.5)	24.5 (3.8)	25.7 (4.7)	24.8 (4.1)
Year of HSCT	2006 (9.4)	2010 (8.2)	2006 (9.4)	2010 (6.1)	2011 (6.3)	2010 (6.1)
Days of Follow-Up	3099 (3262)	1820 (1825)	3027 (3210)	1549 (2050)	839 (1262)	1388 (1920)
Died Before End of Follow-Up	187 (50.4%)	12 (54.5%)	199 (50.6%)	55 (37.7%)	23 (53.5%)	78 (42.6%)
Cause of Death						
Recurrence of cancer	79 (21.3%)	6 (27.3%)	85 (21.6%)	25 (17.1%)	9 (20.9%)	34 (18.0%)
Graft-versus-host	19 (5.1%)	N/A[a]	N/A[a]	6 (4.1%)	6 (14.0%)	12 (6.3%)
Infection	24 (6.5%)	N/A[a]	N/A[a]	7 (4.8%)	4 (9.3%)	11 (5.8%)
Organ failure	18 (4.9%)	N/A[a]	N/A[a]	6 (4.1%)	N/A[a]	N/A[a]
Other	47 (12.7%)	N/A[a]	N/A[a]	11 (7.5%)	N/A[a]	N/A[a]
Indication for HSCT						
ALL	17 (4.6%)	N/A[a]	N/A[a]	5 (3.4%)	4 (9.3%)	9 (4.8%)
CLL	42 (11.4%)	N/A[a]	N/A[a]	13 (8.9%)	9 (20.9%)	21 (11.1%)
AML	139 (37.5%)	N/A[a]	N/A[a]	69 (47.2%)	13 (30.2%)	82 (43.4%)
CML	32 (8.6%)	N/A[a]	N/A[a]	3 (2.1%)	N/A[a]	N/A[a]
MDS	57 (15.4%)	5 (22.7%)	62 (15.8%)	25 (17.1%)	5 (14.0%)	30 (15.9%)
Hodgkin's lymphoma	9 (2.4%)	N/A[a]	N/A[a]	4 (2.7%)	3 (7.0%)	7 (3.7%)
Non-Hodgkin's lymphoma	24 (6.5%)	N/A[a]	N/A[a]	7 (4.8%)	3 (7.0%)	10 (5.3%)
Anemia	13 (3.5%)	N/A[a]	N/A[a]	9 (6.2%)	0 (0%)	9 (4.8%)
Myelomatosis	11 (3.0%)	N/A[a]	N/A[a]	3 (2.1%)	0 (0%)	3 (1.6%)
Other	27 (7.3%)	N/A[a]	N/A[a]	8 (5.8%)	N/A[a]	N/A[a]
Sibling of Donor	N/A (∼90%)[a]	N/A (∼90%)[a]	361 (91.9%)	142 (97.3%)	40 (93.0%)	182 (96.3%)
Myeloablative HSCT	170 (45.8%)	12 (54.5%)	182 (46.3%)	81 (55.5%)	18 (41.9%)	99 (52.4%)
Total Body Irradiation	287 (77.4%)	15 (68.2%)	302 (76.8%)	116 (79.5%)	33 (76.7%)	149 (78.8%)
CCI Group 3+	102 (27.5%)	9 (40.9%)	111 (28.2%)	32 (21.9%)	17 (39.5%)	49 (25.9%)
≥1 Parent With Psych. Disorder	44 (11.9%)	3 (13.6%)	47 (12.0%)	16 (11.0%)	6 (14.0%)	22 (11.6%)
Employed	284 (76.5%)	14 (63.6%)	298 (75.8%)	109 (74.7%)	29 (67.4%)	138 (73.0%)

Values are presented as mean (SD) or *n* (%).

ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; BMI, body mass index; CCI, Charlson Comorbidity Index; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; HSCT, hematopoietic stem cell transplantation; MDS, myelodysplatic syndrome; N/A, not available; Psych., psychiatric.

[a]Microdata with counts below 3 cannot be shown according to Danish laws. Approximate percentages may therefore be listed.

donor-recipient pairs remained (Table 2). Follow-up time was shorter for the exposure group (mean 839 days) than for the comparator group (mean 1549 days) on average, and a larger proportion of individuals in the exposure group (53.3% vs. 37.7%) died before the end of follow-up.

Overall, the risk of incident use of any psychotropic medication was not significantly higher for individuals who received stem cells from a donor with a history of psychotropic medication use (HRR 1.43, 95% CI 0.91–2.24, p = .118) (Figure 1). Figure 2 depicts the cumulative incidence of any psychotropic medication use for the exposure and comparator groups.

When stratifying results based on the classes of psychotropic medications that were redeemed by HSCT recipients, HSCT recipients who received stem cells from a donor with a redeemed prescription for antipsychotics had increased risk for subsequent antipsychotic use (HRR 4.61, 95% CI 1.59–13.38, p = .005). The association remained significant after basic adjustment (HRR 5.00, 95% CI 1.65–15.15, p = .004) and full adjustment (HRR 4.73, 95% CI 1.26–17.78, p = .021) (Figure 1). All patients who were prescribed antipsychotics redeemed their prescription >1 month after HSCT.

Excluding organic mental disorders (F00–F09) did not change the conclusion of the analysis (both primary and subgroup analyses), with no change in overall risk of psychotropic drug use either before adjustment (HRR 1.43, 95% CI 0.91–2.55, p = .124) or after adjustment Figure S4).

Meta-Analysis

In the previous Swedish study by Ekström *et al.*, only data on depression was available because no events were recorded in their exposure groups for bipolar disorder and psychosis (12). In the current study, estimates were available for

Group	Donor without psychiatric history (events/n)	Donor with psychiatric history (events/n)	HRR, unadjusted (95 % CI)	HRR, basic adj. (95 % CI)	HRR, full adj. (95 % CI)
Any mental disorder	23/371	3/22	2.79 (0.83 to 9.39)	2.70 (0.78 to 9.37)	3.50 (0.85 to 14.44)
Any psychotropics	78/146	26/43	1.43 (0.91 to 2.24)	1.50 (0.92 to 2.44)	1.40 (0.81 to 2.40)
Antipsychotics	24/306	4/14	4.61 (1.59 to 13.38)	5.00 (1.65 to 15.15)	4.73 (1.26 to 17.78)
Anxiolytics	43/232	12/39	1.96 (1.03 to 3.72)	1.84 (0.95 to 3.57)	1.63 (0.79 to 3.36)
Hypnotics	99/221	13/29	1.35 (0.76 to 2.42)	1.49 (0.80 to 2.78)	1.44 (0.73 to 2.82)
Antidepressants	54/227	9/42	1.09 (0.54 to 2.21)	1.06 (0.51 to 2.18)	0.96 (0.43 to 2.17)

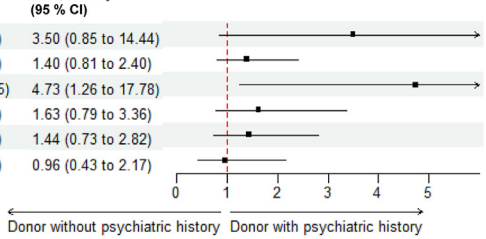

Figure 1. Forest plots of hazard rate ratios (HRRs) for incident mental disorders and psychotropic medication use. Forest plot of HRRs estimated by Cox regression models of the risk of incident diagnosis with a mental disorder or incident use of psychotropic medication for the exposure group (receiving hematopoietic stem cell transplantation [HSCT] from a donor with a history of a psychiatric diagnosis or psychotropic medication use) and control group (receiving HSCT from a donor without a psychiatric history). Estimates shown unadjusted, after basic adjustment (sex, age, and year of HSCT), and after full adjustment (basic + human leukocyte antigen match, total body irradiation, sibling of donor, length of hospital stay for HSCT, parental history of mental disorders, income, educational level, and work status). The forest plot shows the fully adjusted estimates. Note that numbers vary across medication subgroups because individuals were excluded based on use of psychotropic drugs prior to HSCT only for that given class of drugs. For example, a recipient who received an antidepressant prior to HSCT was excluded from the analysis on antidepressant use and the analysis on use of any psychotropics but was included in remaining subgroup analyses.

antidepressant use. Pooling these estimates showed no significant association between receiving HSCT transplants from a donor with a history of a depression diagnosis or antidepressant use (HRR 1.24, 95 % CI 0.66–2.35) (Figure 3) and subsequent risk of depression or incident use of antidepressants for the recipient.

DISCUSSION

In this register-based cohort study, we investigated the association between mental disorders and redeemed prescriptions for psychotropic medications in donors and matched recipients of HSCTs. We did not find a significant association overall between a diagnosis of mental disorders in donors and recipients or use of psychotropic medications; however, we did detect an increased risk of use of antipsychotics among individuals who received stem cells from donors with a history of antipsychotic use. This finding remained significant after adjusting for considered covariates, including parental history of mental disorders. However, the general limitations and exploratory nature of the study do not allow for conclusions about causal relationships between variables to be drawn based on subgroup analyses, and external replication studies are warranted.

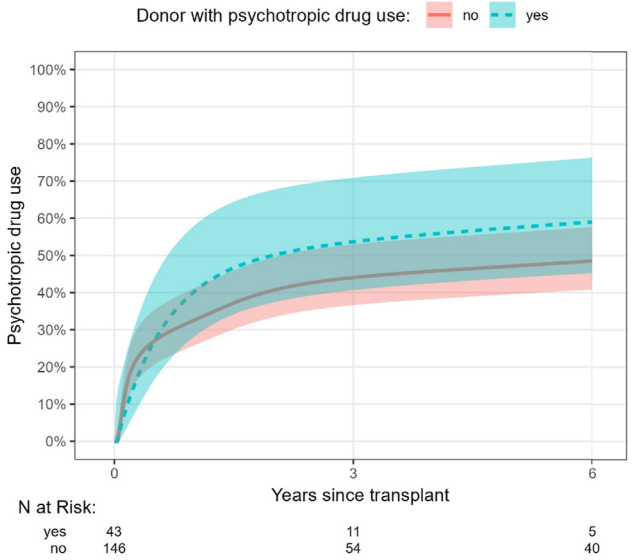

Figure 2. Cumulative incidence of psychotropic medication use among recipients of hematopoietic stem cell transplantation (HSCT). Aalen-Johansen plot of the cumulative incidence of psychotropic medication use for the exposure and comparator group under the competing risk of death or censoring. Shaded areas indicate 95% confidence intervals.

Conceptually, the study is based on the hypothesis that immune-related processes may contribute to the development of mental disorders and symptoms. The transfer of HSCs from donor to recipient represents a pseudo-experimental setting in which the immune system of the recipient is partially or fully replaced by that of the donor. Therefore, immune-related factors that might have contributed to the risk of mental disorders in the donor could be transmitted to the recipient. Overall, the current study does not provide evidence that mental disorders or liability to redeem psychotropic medications can be transmitted through HSCT. However, an increased risk of antipsychotic use was detected in the current study, although based on a relatively small number of cases and with notable uncertainty in the estimated HRR. It is worth noting that the age of the study population was well above what is normally associated with first-episode psychosis. Furthermore, the only 2 published case reports on mental disorders and HSCT detailed patient histories of developing chronic psychosis after HSCT from a donor with schizophrenia and, conversely, achieving remission of treatment-resistant schizophrenia after HSCT from a healthy donor (10,11). While the data from case reports and the current study do not provide causal evidence, the findings suggest that factors transmitted through HSCT may impact the development of psychotic disorders.

The only previous study that investigated a similar hypothesis used Swedish registers to probe whether having a confirmed psychiatric diagnosis in a hospital setting among donors was associated with increased risk of psychiatric diagnosis among recipients after HSCT (12). The study did find

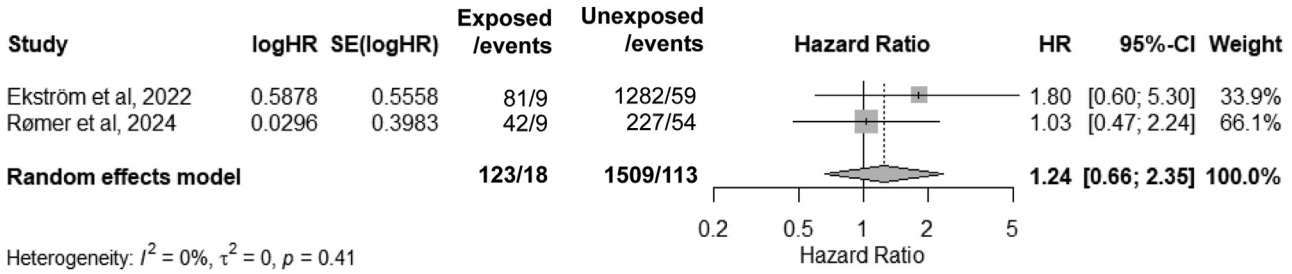

Figure 3. Meta-analysis: association between depression in donors and recipients of hematopoietic stem cell transplantation (HSCT). Forest plot based on a meta-analysis of results from the current study and one previously published study [Ekström *et al.* (12)]. Note that estimates from Ekström *et al.* are based on risk of new-onset diagnosis of depression after receiving stem cells from a donor with depression, while estimates from Rømer *et al.* are based on risk of prescription of antidepressants after receiving stem cells from a donor with a history of antidepressant use. HR, hazard ratio.

an association between depression in donors and recipients; however, the association was nonsignificant after correcting for family history of mental disorders. Consistent with these findings, no overall significant association between diagnoses of mental disorders in donors and recipients was observed in the current study. It should be considered that both the previous Swedish study and the current study involved small cohorts of patients, and weaker associations may be detectable if samples sizes are increased.

There were too few depression cases in the current study to allow for subgroup analysis with depression as an outcome. Unlike the Swedish study, our study also defined exposure and outcome based on redeemed prescriptions for psychotropic medication, which has the advantage of capturing psychiatric cases treated in the primary care sector, as these are included in prescription registers, whereas registers of diagnoses are limited to secondary-level care. Therefore, we pooled data on new-onset diagnosis of depression from the Swedish study and prescription of antidepressants from our study. While the 2 groups did not directly correspond, this approach allowed for meta-analysis of the available results. However, the analysis confirmed the overall findings and did not show an association between donors and recipients. No systematic review was conducted to identify other data sources.

The current study has several limitations that are important to consider. For both analyses, the duration of follow-up in the exposure group was shorter than that in the comparator group (Table 2), which may have contributed to the overall null findings because events (prescriptions/diagnoses) cannot be captured after death or administrative censoring. We did not find any obvious explanations for the differences in follow-up time between the outcome and exposure groups. In general, hematological malignancies—the diseases for which HSCT are most often used—have high mortality rates, which may contribute to an underestimation of the association between exposure and outcome. Furthermore, approximately 90% of donors and recipients are siblings and therefore share an average of 50% of their genetic makeup. Exposures known to affect risk of mental disorders, such as childhood home environment, are also shared between siblings. Therefore, the donors and recipients cannot be considered independent of each other because these environmental and genetic confounders likely contribute to any detected association. Another limitation is that the use of psychotropic medication is only a proxy/marker for underlying mental disorders. Many classes of psychotropic medications, including antipsychotics such as quetiapine, are used to treat sleep disorders or other nonspecific conditions, which may not be classified as mental disorders as such. In addition, the Danish National Prescription Registry only contains information about out-of-hospital medication, and information on psychotropic drugs prescribed during hospitalization was not captured. Several types of medications were assayed, but because the study was exploratory and tests were considered individual [following (18)], we did not correct for multiplicity of testing, which should caution against overly confident interpretations of the results. Finally, it would have been of interest to compare the disease trajectories (e.g., number of hospitalizations and redeemed prescriptions) of patients with mental disorders who received HSCT from healthy donors. However, the small number of HSCT recipients with a prior diagnosis of a mental disorder (n = 23) did not allow for meaningful analysis.

The limitations of the study limit the extent to which the findings can be used to claim any causal effects between exposure and outcome. Therefore, the findings are primarily of theoretical interest when investigating the etiologies of mental disorders, and they do not currently have clinical implications such as, e.g., the exclusion of donors with a history of antipsychotic use as donors in HSCTs. Likewise, it is important to note that the number of cases included in the study was small, and the absolute risk of psychiatric disorders after HSCT was not assessed.

Conclusions

Overall, the current study did not find an association between history of mental disorder or psychotropic medication use in HSCT donors and recipients of HSCT. In subgroup analyses, an association between use of antipsychotics in donors and recipients was detected and remained significant after adjustment for confounding factors. This could suggest that immunological factors transmitted through HSCT contribute to the development of psychotic disorders. However, the study is limited by a small sample size, varying follow-up times, and potential genetic and environmental confounders. International studies using larger databases and unrelated donor-recipient pairs could allow for further exploration and for investigations of a more causal nature.

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TBR and MEB conceived and designed the study. HS collected the data. RHBC and TBR conducted the statistical analysis. TBR drafted the manuscript. All authors edited and approved the manuscript.

All presented data are available to Danish researchers after approval of access from the data accessor authorities.

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