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Sick leave due to mental disorders, morbidity and mortality: a prospective study of discordant twin pairs

Lisa Mather¹ · J. Narusyte¹ · A. Ropponen^{1,2} · G. Bergström^{3,4} · V. Blom^{1,5} · B. Helgadóttir¹ · P. Svedberg¹

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Abstract

Purpose To investigate if sick leave due to mental disorders increases the risk of morbidity measured by inpatient and specialized outpatient care, and mortality among women and men, independent of familial factors.

Methods An open cohort study of 4979 twin pairs discordant for sick leave due to mental disorders was conducted in 2005–2013. Twins were followed up in the cause of death and national patient registries until the end of study, emigration, death, and inpatient and specialized outpatient care. Conditional Cox proportional hazard regression, adjusting for the familial factors shared by the twins, was used to calculate hazard ratios (HR) with 95% confidence intervals (CI). In case of non-proportional hazards, time-varying covariates were used.

Results Sick leave due to mental disorders increased the risk for inpatient care among men (HR: 1.90, CI 1.66–2.17) and women (HR: 1.39, CI 1.27–1.51). For men, the risk of outpatient care was higher the first 2 years (HR: 2.08, CI 1.87–2.31), after which it was attenuated (HR: 1.32, CI 1.02–1.70). For women, the HR was 1.57 (CI 1.47–1.68) for the whole study time. There was an increased risk of death among men (HR: 2.91, CI 1.70–4.99), but not among women (HR: 0.84, CI 0.53–1.35).

Conclusions Sick leave due to mental disorders was a risk factor for mortality for men only, and increased the risk of inpatient and specialized outpatient care among both women and men, but the risks were higher for men when stratifying for sex.

Keywords Sick leave · Mental disorders · Mortality · Hospitalization · Ambulatory care · Twin study

Background

Mental disorders are a major public health problem worldwide [1], and the leading cause for work disability (sick leave and disability pension) in Europe [2]. In Sweden, levels of sick leave have fluctuated the last decades, with

sick leave being very high in 2005, then decreasing to lower levels in 2009 and is after that increasing again. The main diagnoses behind this increase are mental disorders, especially stress-related mental disorders [3]. While sick leave in general becomes more common with age, sick leave due to mental disorders is most common in a younger age group (30–39) [4]. Moreover, the gender differences are larger [5], prognosis are poorer for returning to work, and there is higher risk of a longer sick leave spell and disability pension compared with other diagnostic groups [6]. Since sick leave due to mental disorders represents an increasing proportion of sick leave, and hence is a common prescription in treatment of mental disorders, it is important to know the potential consequences both for the individuals and the health care system.

Sick leave due to mental disorders has been found to have a negative effect on future work life, such as a higher risk of unemployment and a lower income [7–9]. Sick leave has also been associated with a number of adverse health outcomes, such as poor self-rated health [10, 11] and early death [12]. Even though mental disorders are not

✉ Lisa Mather
lisa.mather@ki.se

¹ Division of Insurance Medicine, Department of Clinical Neuroscience, Karolinska Institutet, Berzelius väg 3, 171 77 Stockholm, Sweden

² Finnish Institute of Occupational Health, Helsinki, Finland

³ Unit of Intervention and Implementation Research for Worker Health, The Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

⁴ Department of Occupational and Public Health Sciences, Centre for Musculoskeletal Research, University of Gävle, Gävle, Sweden

⁵ The Swedish School of Sport and Health Sciences, Stockholm, Sweden

in themselves lethal, mental disorders increase the risk of death, both by external causes including suicide but also by natural causes [13]. Possible explanations for the excess mortality, that have been studied in psychiatric patients, are poorer physical health due to receiving a poorer quality of health care and adverse health behaviors [14–16]. Moreover, depression has been found to be a risk factor for cardiovascular disease, the main cause of death in Sweden [17, 18]. Studies of sick leave due to mental disorders have also shown increased risk of premature death [19–21] including suicide [22]. The risk of suicide was also higher in those on sick leave due to depression than those with depression that were not on sick leave [23]. Hence, some indications exist that severity of the depression or an adverse effect of the sick leave itself may also play a role in the association between sick leave and mortality. In a previous twin study, we found that the increased risk of subsequent sick leave, unemployment and disability pension was independent of familial factors [9]. Another twin study that investigated the influence of familial factors on the association between sick leave, all causes, and mortality found only minimal influence [24]. However, it has not previously been investigated whether there is also (1) a minimal influence of familial factors on sick leave due to mental disorders and/or (2) an effect of familial factors on the association between sick leave and morbidity.

Twin studies take advantage of the natural experiment that there are two types of twins that share different amount of genetics but both types share environment to the same extent. Monozygotic (identical) twins share 100% of their segregating genes and dizygotic (fraternal) twins approximately 50%, and using a matched analysis of the discordant twin pairs, where one twin has sick leave due to mental disorder and the other does not, genetics and shared environment (familial factors) can be adjusted for. Moreover, analysis can be stratified on zygosity, and if the association is present in dizygotic but not monozygotic twins, genetics are likely involved in explaining the association, since monozygotic twins are more closely matched on genetics [25]. Previous twin studies have found that sick leave and disability pension due to mental disorders, as well as the disorders themselves, are influenced by genetic factors [26–30]. Further, the variation in life expectancy as well as self-rated health is influenced by genetic factors [31, 32]. Hence, by adjusting for familial factors we can investigate if the same factors that predispose to sick leave due to mental disorders also predispose to mortality and morbidity, and explain the associations.

The aim of this study was to investigate if sick leave due to mental disorders increases the risk of morbidity measured by inpatient and specialized outpatient care, and mortality among women and men, independent of familial factors.

Materials and methods

Sample

This study was register based and the source population was the Swedish Twin project Of Disability pension and Sickness absence (STODS). STODS contains 119,907 individual twins from the Swedish Twin Registry (STR) born in 1925–1990 and register data for these twins have been obtained from the following national registers using the personal identification number of the participants:

- MicroData for Analyses of Social insurance (MiDAS) register that contains dates and diagnoses for all sick leaves (from 2005) and disability pension spells reimbursed by the Swedish Social Insurance Agency (> 2 weeks).
- From Statistics Sweden the Longitudinal Integration Database for Health Insurance and Labor Market Studies Register (LISA by Swedish acronym) that contains socio-demographic variables.
- From the National Board of Health and Welfares, inpatient and specialized outpatient care registries that contain dates and diagnoses, and the causes of death register that contains dates and diagnoses for all deaths.

This was an open cohort study conducted between 1 January 2005 and 31 December 2013. In this study, only discordant twin pairs were included, i.e. pairs where one twin had a spell of sick leave due to a mental disorder starting in 2005–2013 and the other did not have sick leave due to a mental disorder during this time (Fig. 1). Only the first spell with a mental diagnosis was considered, and the start date was used as the starting point for follow-up for both twins in the pair until 2013. Twins that had sick leave in non-mental diagnoses were included, both among the cases and their co-twins. To be included in this study, both twins had to be alive, living in Sweden at the start of the follow-up, not be on disability pension and be between 18 and 64 years old (Fig. 1). The final sample contained 4979 discordant pairs that met inclusion criteria: 1145 were monozygotic, 1259 same sex dizygotic, 1782 opposite sex and 793 of unknown zygosity. The majority of the samples were women (59%) (Table 1). At baseline, 2.6% of the sample had long-term employment (> 180 days in the year), 133 (2.7%) of the cases and 128 (2.6%) among the co-twins. The majority of both the cases (50.4%) and co-twins (51.3%) had secondary education (Table 1).

Exposures

One binary variable was created; 1: having sick leave due to a mental diagnosis (ICD 10 codes F00-F99) and 0: not having sick leave due to a mental diagnosis.

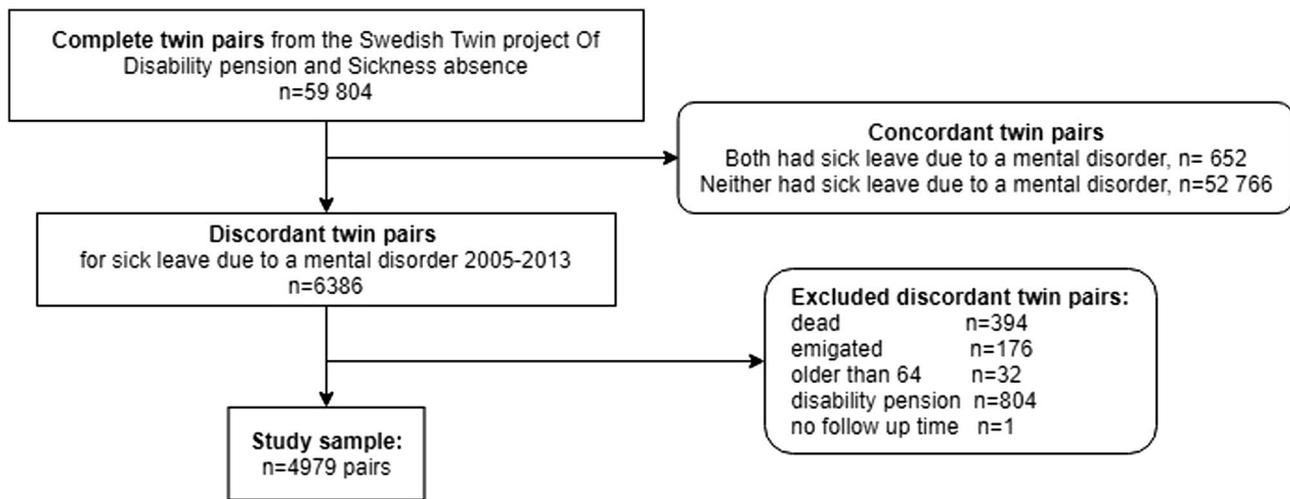


Fig. 1 Flow chart of the study sample

Table 1 Frequencies of outcomes and sex among cases and their co-twins

	Sick leave due to mental diagnosis, N=4979	Co-twins, N=4979
<i>Sex</i>		
Men	1594 (32.0)	2448 (49.2)
Women	3385 (68.0)	2531 (50.8)
<i>Education</i>		
Primary	571 (11.5)	614 (12.3)
Secondary	2507 (50.4)	2555 (51.3)
Higher education	1890 (38.0)	1789 (35.9)
Missing	11 (0.2)	21 (0.4)
<i>Inpatient care</i>		
Yes	1864 (37.4)	1260 (25.3)
No	3115 (62.6)	3719 (74.7)
<i>Outpatient care</i>		
Yes	3944 (79.2)	3311 (66.5)
No	1035 (20.8)	1668 (33.5)
<i>Died</i>		
Yes	69 (1.4)	58 (1.2)
No	4910 (98.6)	4921 (98.8)

Covariates

Sex was used as a dichotomous variable. Age was calculated as the year the spell of sick leave started minus the year of birth. For the co-twins, the year the twin started their spell was used. Zygosity was measured with the best available zygosity diagnosis from the STR, and for the majority of twins this was by a set of questions measuring twin pair similarity, included in survey studies conducted by the STR. This method has been validated against serological

and micro-satellite markers, and has been found to be 99% accurate in a subsample. When available, genetically tested zygosity was used [33, 34].

Outcomes

Mortality: the twins were followed up in the cause of death register for date of death, and cause of death was also used in descriptive analyses.

Morbidity: the date of the first inpatient and specialized outpatient care episode during follow-up was used. The presence of psychiatric inpatient and outpatient care during the years 2005–2013 was used for descriptive analyses.

Analysis

Follow-up started at the first date of sick leave with a mental diagnosis for both the case and their co-twin. Follow-up was censored for emigration (defined as missing in the LISA register for 2 years in a row—follow-up to the 31st of December the year before), the respective outcomes and the analyses with inpatient and specialized outpatient care as outcomes were also censored for death. Since LISA data for 2013 were not available, emigration is not considered that year. Conditional cox proportional hazard models were fitted, both for the whole sample and stratified on sex and zygosity. The stratified cox models were in addition to 95% CI also fitted with 84% CI to assess differences between groups as per Payton et al. [35]. The post-estimation proportional hazards test was used to test for proportional hazards. In cases where the hazards were not proportional, follow-up times were split using the tv function in STATA IC 12 and the time point for the split was chosen based on hazards curves. Moreover, the AIC and BIC values were used to select the best fitting

models, in cases where the proportional hazards assumption was not met.

Results

Descriptive analyses

The mean age in the sample was 42 years (standard deviation 11.6). Comorbidity was common in this sample, among the cases 2388 (48.0%) had sick leave due to another diagnosis sometime between 2005 and 2013, and the corresponding number for the co-twins was 1882 (37.8%). The difference was statistically significant ($\chi^2 = 104.97$, $df = 1$, $p < 0.01$). Out of the co-twins, 50 (1.0%) had psychiatric inpatient care sometime between 2005 and 2013; among the cases, the corresponding number was 500 (10.0%). The difference was statistically significant ($\chi^2 = 389.71$, $df = 1$, $p < 0.01$). Among the cases, 1598 (32.1%) had specialized psychiatric outpatient care in 2005–2013, and among the controls the corresponding number was 374 (7.5%). The difference was statistically significant ($\chi^2 = 947.324$, $df = 1$, $p < 0.01$).

The main diagnosis of the sick leave spells (exposure) differed among men and women ($\chi^2 = 389.97$, $p < 0.001$). Among the 1594 men that had sick leave due to a mental disorder, 575 (36.1%) had depression, 166 (10.4%) had anxiety, 619 (38.8%) had stress-related disorder, and 234 (14.7%) had another mental disorder. Among the 3385 women, the corresponding numbers were depression: 1063 (31.4%), anxiety: 387 (11.4%), stress: 1685 (49.8%), other: 250 (7.4%). There was also a difference in educational attainment between men and women, with a larger proportion of women having

higher education and a larger proportion of men having only primary education (Table 1) ($\chi^2 = 134.55$, $df = 3$, $p < 0.001$), but no statistically significant sex difference in long-term unemployment at baseline ($\chi^2 = 3.7$, $df = 1$, $p > 0.05$).

Mortality

There were 127 deaths during follow-up, 48 women and 79 men, and the difference was statistically significant ($\chi^2 = 24.92$, $df = 1$, $p < 0.001$). Among the co-twins, the most common cause of death was neoplasms (ICD C00-D48) 30 (51.7%), followed by diseases of the circulatory system (ICD I00-I99) 12 (20.7%). Among the cases, the most common cause of death was external causes (V01-Y98) 24 (34.8%) followed by neoplasms (ICD C00-D48) 23 (33.3%). The difference in cause of death between cases and co-twins was not statistically significant ($\chi^2 = 6.75$, $df = 9$, $p = 0.053$); however, it was between women and men ($\chi^2 = 26.58$, $df = 9$, $p < 0.01$). Out of the external causes, the majority (19) were men.

The average follow-up time was 4.8 years. Hazards were proportional ($p = 0.11$). In the whole sample, there was no significant association between sick leave due to mental disorders and death (Table 2). However, when stratifying the analyses for sex, for men, those with sick leave due to mental disorders had a 2.91 times higher risk of death compared to their co-twin. For women, the HR was not significant. The 84% CI did not overlap, CI 1.98–4.28 for men and 0.60–1.18 for women. The hazard ratios (HR) were lower among monozygotic compared to dizygotic male twin pairs so genetic factors may be involved in the association; however,

Table 2 Hazard ratios for death, and inpatient and outpatient care with 95% confidence intervals, for the whole sample and stratified on sex and zygosity

	Conditional cox all	DZ opposite sex	DZ same sex	MZ
<i>Death</i>				
All	1.19 (0.93–1.53)	0.74 (0.49–1.12)	1.45 (0.84–2.53)	1.73 (1.00–2.97)
Men	2.91 (1.70–4.99)		3.67 (1.30–10.38)	1.67 (0.80–3.49)
Women	0.84 (0.53–1.35)		0.63 (0.28–1.41)	1.80 (0.81–4.02)
<i>Inpatient care</i>				
First 2 years	1.89 (1.75–2.05)	2.67 (2.30–3.11)	1.64 (1.40–1.92)	1.32 (1.14–1.53)
After 2 years	1.49 (1.36–1.64)	1.65 (1.40–1.93)	1.34 (1.12–1.60)	1.46 (1.20–1.77)
Men	1.90 (1.66–2.17)		1.96 (1.58–2.42)	1.46 (1.17–1.83)
Women	1.39 (1.27–1.51)		1.32 (1.15–1.52)	1.34 (1.17–1.53)
<i>Outpatient care</i>				
First 2 years	1.94 (1.85–2.04)	2.27 (2.08–2.48)	1.87 (1.70–2.06)	1.66 (1.51–1.83)
After 2 years	1.27 (1.12–1.44)	1.50 (1.22–1.85)	0.93 (0.74–1.17)	1.73 (1.29–2.33)
Men first 2 years	2.08 (1.87–2.31)		2.58 (2.13–3.12)	1.74 (1.47–2.07)
Men after 2 years	1.32 (1.02–1.70)		0.97 (0.67–1.39)	2.45 (1.43–4.20)
Women	1.57 (1.47–1.68)		1.51 (1.36–1.68)	1.61 (1.44–1.80)

DZ dizygotic, MZ monozygotic

Bold value represents Statistically significant HR

power was low in the stratified analyses and the 85% CI overlapped, 1.74–7.73 for DZ and 0.98–2.83 for MZ. When running the analyses for men without the external causes of death included, HR was 2.50 (1.33–4.70).

Inpatient care

During follow-up, 3124 persons had inpatient care, 2092 women and 1032 men. Out of the 1864 cases that had inpatient care during follow-up, 390 were in psychiatric care (first inpatient care visit). Among the co-twins, 1260 had inpatient care and out of those 30 were in psychiatric care (first inpatient care visit).

The average follow-up time was 3.6 years. Hazards were not proportional in the whole sample, so a 2-year tvf cutoff was used ($p < 0.01$); however, hazards were proportional among women ($p = 0.50$) and men ($p = 0.06$) separately, and the AIC and BIC values were lower for the models without a tvf for women and men separately. Among men, those with sick leave due to mental disorders had 1.90 times higher risk of inpatient care compared to their co-twin. Among women, the risk was 1.39 times higher. Both among women and men, the hazard ratios were similar among monozygotic and dizygotic twins (Table 2).

Outpatient care

The majority of the sample, 7255 individuals, had outpatient care during follow-up, 4522 women and 2733 men. Out of the 3944 cases that had outpatient care, 905 were psychiatric care (first outpatient care visit). Among the 3311 co-twins, 115 were in psychiatric care (first outpatient care visit).

The average follow-up time was 1.8 years. Hazards were proportional for women ($p = 0.10$), but not for men ($p = 0.04$) and not for the sample as a whole ($p < 0.01$), so a 2-year tvf cutoff was used. Among women, those with sick leave due to a mental disorder were 1.57 times more likely to have inpatient care compared to their co-twin, and the HR did not differ between monozygotic and dizygotic twins (Table 2). Among men, the risk was 2.08 times higher for the case, compared to the co-twin the first 2 years. When stratifying on zygosity, the risk was lower among monozygotic twins than dizygotic twins and after 2 years the risk was attenuated (Table 2).

Discussion

In this prospective open cohort study, we found that sick leave due to mental disorders increased the risk of death among men, after adjustment for familial factors. Moreover, we found that sick leave due to mental disorders increased

the risk of inpatient and outpatient care both among women and men, and to a larger degree for men.

A study of the French GAZEL cohort found higher risk of death for both women and men with sick leave due to mental disorders compared with those with no mental sick leave. However, they found the risk was somewhat higher among men, compared to women [21]. A study of the whole Swedish working-age population found that mental sick leave in 2005 increased the risk of death both among women and men, the two following years, where the reference group was those without sick leave [19]. The fact that an increased risk was found for women in the whole population but not among the discordant twin pairs in this study point to that the higher risk of death among women with sick leave found in these other studies is explained by familial factors. This indicates that it is the familial predisposition to a mental disorder (that is shared with the twin) that is causing the increased risk of premature death and not the sick leave due to that disorder. In fact, sick leave seems to be protective against premature death in women, but this was not statistically significant. However, in men familial factors do not seem to have a big influence, but instead it seems that the sick leave due to a mental disorder increases the risk of mortality regardless of familial predisposition.

A possible reason for the differences between men and women in risk of mortality, and inpatient and outpatient care is that men and women tend to differ in help-seeking behavior. Women tend to have a more positive attitude to seeking help for their mental health problems [36] and have been found to more often have received treatment for psychiatric problems than men [37]. According to the Swedish National Board of Health and Welfare, sick leave is also a part of healthcare and treatment [38]. Hence, once the men seek help and get granted sick leave, their disorders may be more advanced and, therefore, they have a poorer prognosis, while the women who seek help in time may respond better to treatment, including sick leave, since previous research has shown that having a longer duration of untreated mental illness is associated with worse outcomes [39].

A possible explanation for the higher risk of death in men could be that men have higher rates of death by suicide [22]. Death from external causes represented a third of the deaths among those with sick leave due to mental disorders mostly among men in this study. However, the association between sick leave due to mental disorders and mortality was still present in the analyses that excluded deaths due to external causes. Since the association was weaker among monozygotic than dizygotic twins, genetic factors seem to explain some of the increased risk of death among men, though the power was limited.

We found that approximately a third of those with sick leave due to mental disorders received specialized psychiatric outpatient care during the follow-up time, meaning

that two-thirds were treated in primary health care for their psychiatric health problems. Treatment of mental health conditions in primary care is common, and a previous study has found that more than half of those that were granted disability pension due to a common mental disorder had not received specialized outpatient care [40]. Comorbidity with somatic conditions was common as almost half of those with sick leave due to mental diagnosis also had sick leave in other diagnoses during the study years and this is in line with previous research [41]. The types of mental disorders that were the main diagnosis for the sick leave differed somewhat between men and women. The fact that men had a higher risk than women for both inpatient and specialized outpatient care is possibly due to the types and severity of the mental disorders. Women had more stress-related mental disorders, and men had more “other” mental disorders including schizophrenia, bipolar disorder and drug/alcohol addictions.

Strengths of this study include the use of register data with minimal loss of follow-up and no recall bias. Moreover, the STR is population based making the results generalizable. Previous studies have shown that sick leave and disability pension due to mental disorders in the twin cohort are comparable to the general population [42, 43]. However, there are some weaknesses that should be noted, for example, due to availability of diagnoses in the MiDAS registry only being available from 2005; the follow-up time was only 8 years maximum, which leads to limited power in the analyses with death as an outcome. We opted to use an open cohort design that collects cases as they occurred. This means we had a larger study population; however, this type of design has no set baseline. Hence, we could not do an analysis of the whole sample to compare the co-twin analysis. However, a previous study using the Swedish twin register showed similar results as analysis of the whole Swedish population in the analysis of sick leave in general as a risk factor for mortality [16, 21]. Moreover, since register data were used, we only had access to inpatient and specialized outpatient care, and could not include cases with self-reported measures of health. Those treated in primary care were not possible to include due to the non-existence of such a register currently.

In conclusion, after controlling for familial factors by matching, sick leave due to mental disorders was a risk factor for mortality for men only, and increased the risk of inpatient and specialized outpatient care among both women and men; however, the risks were higher for men.

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Author contributions PS originated the idea. LM analyzed the data in consultation with PS, JN, AR, VB, GB and BH. LM wrote the first and subsequent drafts of the manuscript, with important intellectual input from all the co-authors. All authors contributed in designing the study and to the interpretation of the results as well as to the writing and approval of the final version of the article.

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