Effects of Parental Severe Mental Disorders on All-Cause and Suicide Mortalities in Adolescents and Young Adults With Major Depressive Disorder

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Abstract

Background: Major depressive disorder (MDD) has been associated with both all-cause and suicide mortality in young adults. However, the effects of parental severe mental disorders (SMDs), such as schizophrenia, bipolar disorder, MDD, alcohol use disorder (AUD), and substance use disorder, on the risks of all-cause and suicide mortality in adolescents and young adults with MDD remain unclear.

Methods: We retrospectively evaluated the incidence of all-cause and suicide mortality (2001–2011) in 196,000 adolescents (age: 10–17 years) and young adults (age: 18–29 years) with MDD. We investigated associations between parental SMDs and all-cause and suicide mortality among patients with MDD using Cox regression analyses. In addition, we assessed the additive effects of paternal and maternal SMDs on the mortality risk of depressed offspring.

Results: Our findings revealed that all-cause mortality in offspring was associated with paternal AUD (hazard ratio [HR]: 1.66) as well as maternal schizophrenia (HR: 2.77), bipolar disorder (HR: 1.99), and MDD (HR: 1.25). Furthermore, suicide mortality in offspring was associated with maternal schizophrenia (HR: 4.36) and bipolar disorder (HR: 4.01). Notably, the risk of suicide mortality was the highest in offspring with paternal bipolar disorder and maternal MDD (HR: 7.31).

Conclusion: Parental SMDs such as schizophrenia, bipolar disorder, MDD, and AUD are associated with all-cause and suicide mortality in adolescents and young adults with MDD. Optimizing support systems and prioritizing early interventions for parental mental health problems may help reduce the risks of suicide and premature death in young patients with MDD.

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Major depressive disorder (MDD) among young people is a pressing concern; approximately 20% of all adolescents have a major depressive episode before reaching maturity.[1] Depression in young people can hinder the formation of positive social connections, increase the risk of social isolation, and lead to various physical health problems, such as metabolic syndrome.[2,3] Furthermore, depression during adolescence is strongly associated with unhealthy behaviors, including substance and alcohol abuse, and serves as a key predictor of recurrent depressive episodes in adulthood, as well as an elevated risk of suicide.[2,3]

A Swedish population-based cohort study involving 37,185 adolescents with a mean age of 16 years and diagnosed with MDD found that 360 individuals (1.0%) died during the follow-up period, representing a hazard ratio (HR) of 5.9 compared to the general population.[4] Of the deceased adolescents, 224 (62.2%) died by suicide, 93 (25.8%) died by other external causes, and 43 (12.0%) died by natural causes, indicating HRs of 14.6, 3.7, and 2.1, respectively, compared to the general population.[4] In Taiwan, data from the Ministry of Health and Welfare highlight that suicide and cardiovascular diseases rank as the second and fourth leading causes of death among individuals aged 15–24 years.[5] Alarmingly, the suicide rate among Taiwanese youth in this age group has more than doubled over 2 decades, rising from 4.0 per 100,000 in 2000 to 10.7 per 100,000 in 2022.[6] Psychiatric disorders are a major contributor to youth suicide, with a population-attributable fraction of

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Clinical Points

- Only a small proportion (0.4%) of depressed youth died during the follow-up period.
- The risk of parental severe mental disorders in offspring mortality was statistically significant but clinically small.
- Maternal schizophrenia was especially associated with the suicide death of their depressed offspring.
- Paternal bipolar disorder and maternal depression were associated with the highest suicide risk in their depressed offspring.

55.90%.[7] MDD accounts for the largest share at 29.08%, followed by schizophrenia (6.67%), substance and alcohol use disorders (5.61%), and bipolar disorder (4.57%).[7]

Increasing evidence has shown the MDD risk among offspring of parents with severe mental disorders (SMDs), namely, schizophrenia, bipolar disorder, MDD, alcohol use disorder (AUD), and substance use disorder (SUD).[8–11] Rasic et al[11] revealed that the relative rates of MDD in the offspring of parents with schizophrenia, those with bipolar disorder, and those with MDD were 1.31, 2.07, and 2.38, respectively, compared with the rate in the offspring of parents without any SMD. Similarly, Maher et al[12] identified strong associations between offspring MDD risk and parental AUD or SUD. Furthermore, a family history of psychiatric disorders not only heightens the risk of MDD but also increases suicide mortality in offspring.[13,14] For example, an analysis of family genetic risk scores (FGRSs) for SMDs in the Swedish general population (spanning 1932–2017) revealed that FGRSs for AUD and suicide attempts were strong predictors of suicide attempts, while FGRSs for schizophrenia, bipolar disorder, and suicide mortality were strong predictors of suicide mortality.[13] Across all SMDs, higher FGRSs correlated with younger ages at first suicide attempt and increased frequency of suicide attempts.[13] A Danish population-based study of 4,142 youth who died by suicide found a notable link between parental psychiatric history—particularly maternal hospitalization for psychiatric disorders—and increased youth suicide risk.[15]

The biopsychosocial risks of parental SMD can have a negative impact on offspring's mental health, including depression and suicide.[16] For example, children exposed to parents with SMDs were at a higher risk of experiencing violent victimization and engaging in suicidal behaviors later in life compared to those not exposed.[16] Youth aged 13–29 years reported higher mood symptoms and perceived lower social support from parents with mood disorders than those with parents without such conditions.[17] Notably, these findings are largely derived from studies conducted in Western countries. Whether they can be generalized to Asian populations, such as in Taiwan, remains an open question requiring further research and investigation.

Given that parental SMDs were strongly associated with offspring MDD risk and that they also had a negative impact on the clinical course of depression in offspring, we investigated the specific effects of parental SMDs on all-cause and suicide mortalities in offspring with MDD in Taiwan. We hypothesized that adolescents and young adults with MDD who were exposed to parental SMDs, namely, schizophrenia, bipolar disorder, MDD, AUD, and SUD, had increased likelihoods of all-cause and suicide mortality compared with those who were not exposed to parental SMDs.

METHODS

Data Source

The National Health Insurance Program, a mandated universal health insurance policy in place since 1995, provides complete medical care coverage to all residents of Taiwan. Upon formal application, the Taiwan National Health Research Institute audited and made the Taiwan National Health Insurance Research Database (NHIRD) available for scientific research, which includes medical records from more than 99.7% of Taiwan's population. The database includes comprehensive information on insured subjects, including demographic data, clinical visit dates, disease diagnoses, and prescriptions. The genealogy reconstruction (parent-child relationship) was based on the methods of Chen et al[18] and Cheng et al.[19] To protect individual privacy, the subjects' insurance claim information is anonymized. The diagnostic codes used were based on the *International Classification of Diseases, 9th Revision, Clinical Modification* (*ICD-9-CM*). In the present study, we used the NHIRD's mental disorder specialized data, which includes all psychiatric medical records of insured patients between 2000 and 2011. The NHIRD has been used in many Taiwanese epidemiologic studies.[20–23] This study protocol was reviewed and accepted by the Institutional Review Board of our hospital.

Study Population

The present study included adolescents aged between 10 and 17 years and young adults aged between 18 and 29 years who received a diagnosis of MDD (*ICD-9-CM* codes: 296.2, 296.3, 300.4, and 311) from a board-certified psychiatrist at least twice between 2001 and 2011. All patients were followed from enrollment (MDD diagnosis date) to the end of 2011 (average 7.89 ± 3.10 years) to identify all-cause mortality and suicide mortality. We separately assessed paternal and maternal SMDs, such as schizophrenia, bipolar disorder, MDD, AUD, and SUD. In addition, parents with SMDs often had psychiatric comorbidities, such as AUD and

SUD. We reported the AUD and SUD rates among parents with SMDs in Supplementary Table 1. We also examined personal psychiatric comorbidities such as autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), AUD, and SUD as confounding factors. All mental disorder diagnoses were given by board-certified psychiatrists at least twice, yielding improved diagnostic validity. We used income and urbanization levels to represent socioeconomic status. The level of urbanization (from level 1 to level 5; level 1: most urbanized region; level 5: least urbanized region) was also assessed for our study.[24]

Statistical Analysis

We used demographic analyses (percentage (%) or mean and standard deviation) for age, sex, income, level of urbanization, all-cause mortality rate, and suicide rate. We performed Cox regression analyses with the adjustment of demographic data (age, sex, income, level of urbanization) and personal psychiatric comorbidities (ASD, ADHD, AUD, and SUD) to investigate associations between parental SMDs and all-cause mortality, as well as suicide mortality among young patients with MDD.

The reason that we adjusted for personal psychiatric comorbidities in the regression models was because we attempted to clarify an independent effect of parental SMDs on offspring mortality. We further assessed the additive effects of parental SMDs on the likelihood of all-cause mortality and suicide, compared to those not exposed to both paternal and maternal SMDs. We treated the offspring of both parents without SMDs as a reference group in the analyses on the additive effects of parental SMDs. We examined the remaining 35 conditions of parental mental disorders, such as paternal schizophrenia and maternal depression, paternal AUD and maternal schizophrenia, with the offspring mortality risk. In addition, if a parent had two diagnoses, such as schizophrenia and SUD, this parent was analyzed twice for the separate additive effect on offspring mortality. A 2-tailed *P* value of less than .05 was considered statistically significant. We performed all data processing and statistical analyses using the Statistical Package for Social Science (SPSS) version 17 software (SPSS Inc) and the Statistical Analysis Software (SAS) version 9.1 (SAS Institute, Cary, NC).

RESULTS

In all, 196,000 adolescents and young adults with MDD were included in the present study, with an average age of 22.42 ± 4.43 years and a female predominance (58.2%) (Table 1). Table 1 shows the prevalence of parental and maternal SMDs, respectively. Specifically, the prevalence of paternal schizophrenia was 0.5% (n = 904), paternal bipolar disorder with 0.7% (n = 1,362), paternal MDD with 4.7% (n = 9,211), paternal AUD with 1.7% (n = 3,304), and paternal SUD with 1.2% (n = 2,394) (Table 1). The prevalence of maternal SMDs was 0.7% (n = 1,394) in schizophrenia, 1.2% (n = 2,270) in bipolar disorder, 9.1% in MDD (n = 17,764), 0.8% (n = 1,563) in AUD, and 0.9% (n = 1,735) in SUD (Table 1). In addition, 19,009 (9.7%) adolescent and young adult probands with MDD were comorbid with SUD, 12,512 (6.4%) with AUD, 7,100 (3.6%) with ADHD, and 1,524 (0.8%) with ASD (Table 1). Supplementary Table 2 reported the sample sizes of the subgroups stratified by parental SMDs.

The Cox regression analyses with adjustment of demographic data and personal psychiatric disorders demonstrated associations of all-cause mortality with paternal AUD (HR: 1.66, 95% confidence interval [CI],

Table 1.

Demographic and Clinical Characteristics of Adolescents and Young Adults With MDD (n = 196,000)

Age at depression diagnosis, y, mean (SD)	22.42 (4.43)
Male, n (%)	80,839 (41.2)
Paternal SMD, n (%)	
Schizophrenia	904 (0.5)
BD	1,362 (0.7)
MDD	9,211 (4.7)
AUD	3,304 (1.7)
SUD	2,394 (1.2)
Maternal SMD, n (%)	
Schizophrenia	1,394 (0.7)
BD	2,270 (1.2)
MDD	17,764 (9.1)
AUD	1,563 (0.8)
SUD	1,735 (0.9)
Personal comorbidities, n (%)	
ASD	1,524 (0.8)
ADHD	7,100 (3.6)
AUD	12,512 (6.4)
SUD	19,009 (9.7)
Level of urbanization, n (%)	
1 (most urbanized)	54,003 (27.6)
2	64,551 (32.9)
3	26,137 (13.4)
4	18,879 (9.6)
5 (most rural)	32,430 (16.5)
Income-related insured amount, n (%)	
≤19,100 NTD/month	34,073 (17.4)
19,001∼42,000 NTD/month	67,465 (34.4)
>42,000 NTD/month	94,462 (48.2)
All-cause mortality, n (%)	867 (0.4)
Average mortality age, y, mean (SD)	27.60 (4.63)
Suicide mortality, n (%)	142 (0.1)
Average suicide age, y, mean (SD)	27.90 (4.42)
Average follow-up years, y, mean (SD)	7.89 (3.10)

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ASD = autism spectrum disorder, AUD = alcohol use disorder, BD = bipolar disorder, MDD = major depressive disorder, NTD = new Taiwan dollars, SMD = severe mental disorder, SUD = substance use disorder.

1.06–2.59), maternal schizophrenia (2.77, 1.77–4.34), maternal bipolar disorder (1.99, 1.24–3.20), and maternal MDD (1.25, 1.00–1.56) among their offspring with MDD (Table 2). Furthermore, maternal schizophrenia (HR: 4.36, 95% CI: 1.78–10.73) and bipolar disorder (4.01, 1.64–9.84) were particularly associated with suicide among young patients with MDD (Table 2).

Tables 3 and 4 show the additive effects of paternal and maternal SMDs on all-cause mortality and suicide. The risk of all-cause death was highest for individuals whose father had schizophrenia and whose mother also had schizophrenia (HR: 21.58, 95% CI, 5.35–86.99), followed by the risk of all-cause death for children whose father had AUD and whose mother had schizophrenia (13.11, 3.26–52.72; Table 3). Furthermore, the additive effect (HR: 7.31, 95% CI, 1.02–52.60) of paternal bipolar disorder and maternal MDD exhibited the highest suicide risk among offspring with MDD (Table 4).

Table 2.

Cox Regression Models for Associations Between Parental SMD and All-Cause and Suicide Mortality in Offspring[a]

	All-cause mortality		Suicide mortality	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Paternal SMD				
Schizophrenia	1.22 (0.54–2.75)	.641	1.13 (0.15–8.51)	.907
BD	1.53 (0.82–2.84)	.185	1.59 (0.37–6.92)	.535
MDD	0.95 (0.68–1.32)	.755	1.03 (0.48–2.25)	.931
AUD	**1.66 (1.06–2.59)**	**.027**	1.30 (0.43–3.97)	.642
SUD	0.76 (0.40–1.42)	.387	1.24 (0.35–4.34)	.741
Maternal SMD				
Schizophrenia	**2.77 (1.77–4.34)**	**<.001**	**4.36 (1.78–10.73)**	**.001**
BD	**1.99 (1.24–3.20)**	**.005**	**4.01 (1.64–9.84)**	**.002**
MDD	**1.25 (1.00–1.56)**	**.048**	1.15 (0.65–2.05)	.627
AUD	0.68 (0.32–1.46)	.327	NA	–
SUD	0.72 (0.35–1.47)	.362	NA	–

[a]Adjusting for age, sex, income, level of urbanization, and personal comorbidities. Bold type indicates statistical significance.

Abbreviations: AUD = alcohol use disorder, BD = bipolar disorder, HR = hazard ratio, MDD = major depressive disorder, NA = not available, SMD = severe mental disorder, SUD = substance use disorder.

DISCUSSION

To the best of our knowledge, this nationwide study is the first to investigate how a parental SMD affects mortality in offspring with MDD. We found that paternal SUD and maternal MDD increased the risk of all-cause mortality in offspring with MDD. Multiple interconnected factors contribute to this increased risk of mortality. The offspring of parents with SUD or depression may encounter elevated levels of stress, trauma, and adversity during their developmental years.[25,26] Prolonged exposure to these stressors can disrupt the body's stress response systems, increasing the risks of mental (ie, depression) and physical health problems (ie, cardiovascular risk).[27] Furthermore, living in a family where SUD is common or depression is untreated may influence young depressed patients' health behaviors, making them more susceptible to SUD, self-harm, and unhealthy coping behaviors, all of which can worsen their mental and physical health and increase their mortality risk.[28]

We further observed that the rate of suicide mortality was higher in young patients with MDD whose mothers had schizophrenia or bipolar disorder than in those whose parents did not have any SMD. Evidence suggests that mental illnesses such as schizophrenia, bipolar disorder, and depression have a genetic component. The offspring of parents with mental illnesses may be more likely to develop depression and other mood disorders.[29,30] This genetic susceptibility can manifest as a severe and resistant form of depression, increasing the risk of engaging in suicidal behaviors.[31] In a household where the mother has schizophrenia or bipolar disorder, children may have high stress levels and receive inadequate mental support. Adverse childhood experiences accelerate the onset of depression and increase the risks of suicidal thoughts and behaviors.[32] A family in which the parents had schizophrenia or bipolar disorder may face additional psychosocial stressors, such as economic instability, social isolation, and challenges in maintaining relationships. These stressors can exacerbate depression and lead to hopelessness and despair, thereby increasing the risk of suicide in young patients with depression. Furthermore, maternal mental disability can lead to a delay in diagnosis and treatment in the affected child.[33] Insufficient support and interventions for young patients with depression can result in prolonged periods of untreated or undertreated depression, ultimately increasing the risk of suicide. As previously mentioned, the biopsychosocial risks associated with parental SMDs negatively impacted the mental and physical health of their depressed offspring.[16]

Finally, young patients with MDD who had mothers with schizophrenia and fathers with either schizophrenia (22-fold increase) or AUD (13-fold) had a significantly higher risk of all-cause mortality than did those of parents without SMDs (Table 3). Furthermore, young patients with MDD who had mothers with MDD and fathers with bipolar disorder had a 7-fold higher risk of suicide mortality (Table 4). Notably, the sample sizes of the subgroups with both parents having an SMD were small (Table 4), which might have limited the generalizability of our findings. Few studies have investigated the combined effects of parental mental health conditions on the risks of all-cause and suicide mortalities in offspring with depression.

The strength of our study is its use of a nationwide data set, which includes data on adolescents and young

Table 3.

All-Cause Mortality (HR and 95% CI) in Adolescents and Young Adults With MDD[a]

	Paternal SMD					
Maternal SMD	**Schizophrenia**	**BD**	**MDD**	**AUD**	**SUD**	**None**
Schizophrenia	**21.58 (5.35–86.99)[b]**	NA	2.49 (0.35–17.73)	**13.11 (3.26–52.72)[b]**	NA	**2.53 (1.56–4.10)[b]**
BD	NA	NA	1.56 (0.22–11.08)	4.95 (0.70–35.23)	NA	**2.00 (1.23–3.23)[c]**
MDD	2.20 (0.31–15.68)	2.42 (0.60–9.69)	0.95 (0.43–2.13)	1.70 (0.55–5.28)	2.15 (0.69–2.70)	**1.26 (1.00–1.58)[d]**
AUD	NA	NA	2.78 (0.39–19.80)	NA	6.59 (0.93–46.94)	0.83 (0.38–1.88)
SUD	NA	NA	NA	NA	NA	1.07 (0.53–2.15)
None	0.84 (0.27–2.60)	1.88 (0.97–3.62)	1.10 (0.79–1.54)	1.55 (0.98–2.45)	0.88 (0.44–1.77)	1 (ref)

[a]Bold type indicates statistical significance.
[b]$P < .001$.
[c]$P = .005$.
[d]$P = .050$.
Abbreviations: AUD = alcohol use disorder, BD = bipolar disorder, HR = hazard ratio, MDD = major depressive disorder, NA = not available, SMD = severe mental disorder, SUD = substance use disorder.

Table 4.

Suicide Mortality (HR and 95% CI) in Adolescents and Young Adults With MDD[a]

	Paternal SMD					
Maternal SMD	**Schizophrenia**	**BD**	**MDD**	**AUD**	**SUD**	**None**
Schizophrenia	NA	NA	NA	NA	NA	**4.38 (1.78–10.82)[b]**
BD	NA	NA	NA	NA	NA	**3.56 (1.45–8.76)[c]**
MDD	NA	**7.31 (1.02–52.60)[d]**	0.95 (0.13–6.86)	NA	NA	1.02 (0.55–1.89)
AUD	NA	NA	NA	NA	NA	NA
SUD	NA	NA	NA	NA	NA	NA
None	1.63 (0.23–1.69)	1.29 (0.18–9.23)	1.34 (0.62–2.87)	1.86 (0.68–5.05)	1.83 (0.58–5.77)	1 (ref)

[a]Bold type indicates statistical significance.
[b]$P = .001$.
[c]$P = .006$.
[d]$P = .048$.
Abbreviations: AUD = alcohol use disorder, BD = bipolar disorder, HR = hazard ratio, MDD = major depressive disorder, NA = not available, SMD = severe mental disorder, SUD = substance use disorder.

adults with MDD and their parents with mental illnesses. Furthermore, psychiatric disorders were diagnosed by board-certified psychiatrists. However, this study has several limitations. First, some subgroups had small sample sizes; for example, paternal schizophrenia and maternal bipolar disorder were recorded for only 9 young patients with MDD (Supplementary Table 2). The small sample size might have limited the statistical power of our findings, and thus our findings should be interpreted with caution. Second, the genetic basis for psychiatric disorders varies across ethnicities.[34] Because we focused on Taiwanese individuals, additional research is required to ascertain the applicability of our findings to other ethnic groups. Third, our cohort was tracked for only 11 years; thus, we might have missed late-onset parental SMDs. Fourth, a new-onset or recurrent MDD cannot be exactly defined in the register database. Further investigation would be required to determine whether the effect of parental SMDs on offspring mortality differs between new-onset and recurrent MDD. Fifth, parental suicide attempt data were not available in the NHIRD. It was difficult for us to assess how these factors affected the study's results due to a lack of data. Sixth, we changed the P value for the additive effects of parental SMDs on mortality from .05 to .05/35 (.0014) as a result of the multiple comparison correction. The findings of associations between maternal schizophrenia only and offspring all-cause and suicide mortalities remained significant. The results of associations between maternal schizophrenia plus paternal schizophrenia, or AUD, and offspring all-cause mortality were also still significant. Our findings echoed Stenager and Qin's[15] results that maternal hospitalization for a psychiatric disorder was particularly related to youth suicide risk. Seventh, the NHIRD does not include information on covariates such as lifestyles, education levels, or environmental factors; the lack of data limited our ability to estimate the effects of these factors on the study outcomes. Finally, although our study suggested the impact (HRs ranged from 1.25 to 4.36) of parental SMDs on offspring mortality, the all-cause and suicide mortality rates were low (0.4% and 0.1%, respectively) among youth with MDD. Only a very small proportion of depressed youth who had parents with SMDs died

during the follow-up. The statistical significance of the impact of parental SMDs on offspring mortality reminded public health officers and clinicians to pay attention to the physical and mental health of the offspring of parents with SMDs.

In conclusion, adolescents and young adults with MDD do not uncommonly have parents with SMDs. Certain types of parental SMDs are associated with increased risks of all-cause and suicide mortality in offspring with MDD. Specifically, paternal SUD and maternal schizophrenia, as well as MDD, have been shown to increase the risk of all-cause mortality in offspring with MDD. Additionally, maternal schizophrenia and maternal bipolar disorder are linked to a heightened risk of suicide among offspring with MDD. Further investigation is necessary to determine whether timely diagnosis and optimal intervention of parental mental health problems may reduce the risks of all-cause and suicide mortalities in offspring with MDD. Additionally, clinicians and mental health providers should develop a new therapeutic model that targets both parents with SMDs and offspring with MDD.

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Supplementary Material

Article Title: Appetite Hormone Regulation Biotypes of Major Affective Disorders in Proinflammatory Cytokines and Executive Function

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

1. **Figure 1** GLMs for Estimated Appetite Hormone Levels Between the Control and Patient Groups
2. **Figure 2** GLMs for Estimated Proinflammatory Cytokine Levels and Executive Function Between the Control and Patient Groups

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