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ORIGINAL PAPER

Risks of major mental disorders after parental death in children, adolescents, and young adults and the role of premorbid mental comorbidities: a population-based cohort study

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Abstract

Previous studies have shown an association between early parental death and the risk of subsequent major mental disorders (MMDs) among the bereaved children and adolescents; however, it is unclear whether this risk exists in young adults and in individuals with premorbid mental comorbidities. We aimed to explore differences between children, adolescents, and young adults in the risk of MMDs after parental death. We analyzed data from the Taiwan National Health Research Database. The index cohort was offspring (divided into four groups: aged < 6, 6–11, 12–17, and 18–29 years) whose parents had died. The control cohort was demographically matched offspring whose parents were still alive. Cox regression with adjustments for demographics was used to estimate the risk of subsequent MMDs between the index and control cohorts, including schizophrenia, bipolar disorder, and depressive disorder. We included 202,837 cases and 2,028,370 matched controls. As with the bereaved children and adolescents, the bereaved young adults had a significantly higher risk of schizophrenia (hazard ratio with 95% confidence interval: 5.63; 5.01–6.33), bipolar disorder (3.37; 2.96–3.84), and depressive disorder (2.78; 2.68–2.90) than the control cohort. The risk of MMDs was similar for maternal death and paternal death. Among premorbid mental comorbidities, bereaved individuals with premorbid substance use disorder were associated with the highest risk of schizophrenia (10.43; 8.57–12.71), bipolar disorder (12.93; 10.59–15.79), and depressive disorder (10.97; 10.22–11.78). Healthcare workers should be aware that young adults and individuals with premorbid mental comorbidities are at a higher risk of subsequent MMDs than those without premorbid mental comorbidities after parental death.

Keywords Parental death · Mental disorder · Children · Adolescent · Young adult

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Introduction

Around 140 million children worldwide suffered the death of either one or both parents in 2016, most of whom resided in low- or middle-income countries [1]. After parental loss, bereaved children may suffer from various stressful and unhealthy conditions which may affect their development, such as a lack of social system, loss of education, and unstable living situation [2, 3]. Previous reports have shown an association between parental death and a higher risk of prolonged grief, posttraumatic stress disorder, depression, anxiety, and behavior problems among bereaved children compared to controls [4, 5]. A national register-based study in Denmark reported that parental death during childhood was associated with a higher risk of self-harm behavior and violent criminality compared to those who parents were alive [6]. Specifically, low socioeconomic status, single status, and losing both parents may have contributed to the increased risk of suicide among the bereaved offspring.

Substantial evidence has suggested an increased risk of major mental disorders (MMDs) in children and adolescents after parental death. For example, an international case–control study reported that early parental death was associated with 1.54-fold greater odds of psychosis (including schizophrenia, schizoaffective disorder, and bipolar disorder) than the controls [7]. Another study indicated that offspring of parents who died by suicide had a higher risk of suicide attempts and depressive disorders than the controls [8]. An increased risk of depressive disorder was also observed in a nationwide population-based study [9]. In addition, a recent meta-analysis reported a positive association between the death of a parent before 18 years of age and the subsequent development of an anxiety, affective, or psychotic disorder [10]. Taken together, this evidence strongly supports the negative impact of parental death on the bereaved children and adolescents.

However, knowledge gaps still exist. First, pooled analysis of the association between parental death and subsequent MMDs is still inconclusive [10], suggesting that the association has a complicated etiology. Second, the sample sizes of previous studies have been limited [7–9], and few studies have identified the difference between maternal and paternal death using a population-based study [7]. Third, most studies have focused on parental death during childhood and adolescence, and few studies have addressed young adults [7, 11]. In addition, another population-based study found no association between parental death and lifetime mental disorders [12]. Therefore, the influence of parental death on the development of MMDs during early adulthood remains inconclusive. Fourth, to date, no studies have investigated the association between parental death and subsequent MMDs in individuals with premorbid mental disorders. To address these knowledge gaps, we aimed to conduct a population-based cohort study exploring the association between parental death and emergence of MMDs among bereaved offspring. In addition, we also aimed to identify the impact of premorbid mental comorbidities on this association. We hypothesized that parental death may be associated with increased risk of MMDs among bereaved offspring, and such risk may be associated with premorbid mental comorbidities.

Methods

Data source

The Taiwan National Health Research Database (NHIRD) consists of healthcare data, including demographic data, dates of clinical visits (outpatient visits and hospitalizations), and disease diagnoses, and covered over 99.7% of all Taiwanese residents at the end of 2010. The Taiwan NHIRD is audited and released by the National Health Research Institute for scientific and study purposes [13, 14]. Claims data of individuals included in the NHIRD are anonymized to maintain privacy. Using a unique personal identification number assigned to each resident in Taiwan, all of the information is linked together. Based on the methods of Chen et al. and Cheng et al., parent–child relationships were established [15, 16]. The diagnostic codes used are based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). The NHIRD has been used extensively in many epidemiologic studies in Taiwan [15–18]. This study protocol was reviewed and accepted by the Institutional Review Board of Taipei Veterans General Hospital (approval number: TPEVGH-IRB-2018–07-016AC). The requirement for patient consent was waived because the data used in this study were anonymized and derived wholly from a sizeable national database.

Inclusion criteria of children, adolescents, and young adults whose parents had died

We enrolled two parent–child cohorts, namely an index cohort and control cohort. We identified children aged < 6 years and aged between 7 and 11 years, adolescents aged between 12 and 17 years, and young adults aged between 18 and 29 years who lost any parent between 1996 and 2011 as the index cohort. The control cohort was randomly identified (1:10) on the basis of age, sex, income, and urbanization level. The outcomes of interest were new onset of schizophrenia (ICD-9-CM code: 295), bipolar disorder (ICD-9-CM codes: 296, except for 296.2, 296.3, 296.9, and 296.82), or depressive disorder (ICD-9-CM codes: 296.2,

296.3, 300.4, and 311) during the follow-up period (from the date of parental death to December 31, 2011, or death). These disorders were required to be diagnosed at least twice by board-certified psychiatrists based on their clinical judgment and diagnostic interviews. Parental mental disorders were assessed as a confounding factor, including schizophrenia, bipolar disorder, depressive disorder, alcohol use disorder (AUD), and substance use disorder (SUD). The premorbid mental disorders in the bereaved offspring included autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), anxiety disorder, AUD, and SUD. Evidence has suggested that premorbid mental conditions may be important risk factors of developing severe mental disorders later in life. For instance, early adolescent substance use was reported to be the risk factor for developing depression [19], and the link between ASD and schizophrenia was also identified [20]. The level of urbanization (level 1 to level 5; level 1: most urbanized region; level 5: least urbanized region) was also assessed [21].

Statistical analysis

For between-group comparisons, the F test was used for continuous variables and Pearson's χ^2 test for nominal variables, where appropriate. Cox regression analysis was performed to investigate the risk of subsequent MMDs between the index and control cohorts, with adjustments for age, sex, income, urbanization level, parental mental disorders, and offspring premorbid mental disorders. Hazard ratios (HRs) and 95% confidence intervals (CIs) were used to estimate the risk. Additional Cox regression analyses were performed for each age category (< 6 vs. 6–11 vs. 12–17 vs. 18–29 years), with adjustments for the same covariates. Finally, we examined the risk of MMDs after parental death between the offspring with premorbid mental disorders and the controls, with adjustments for age, sex, income, urbanization level, and parental mental disorders. A 2-tailed *P*-value of less than 0.05 was considered to be statistically significant. All data processing and statistical analyses were performed using SPSS version 17 software (SPSS Inc., Armonk, NY) and SAS version 9.1 software (SAS Institute, Cary, NC).

Results

Demographic and clinical characteristics

We included 202,837 bereaved individuals in the index cohort and 2,028,370 matched individuals in the control cohort, with a mean age of 20.41 (6.93) years (Table 1). Among them, 5797 (2.86%) of individuals in the parent-bereaved group and 16,114 (0.79%) of individuals in the control group developed a MMD. The average follow-up duration was 6.81 ± 3.47 years. Compared to the control cohort, the bereaved individuals had a significantly higher rate of MMDs, including schizophrenia (0.3% vs 0.1%, $p < 0.001$), bipolar disorder (0.3% vs 0.1%, $p < 0.001$), and depressive disorder (2.3% vs 0.7%, $p = 0.003$). The age at diagnosis of a MMD was younger in the index cohort than in the control cohort, including schizophrenia (25.68 vs 26.91 years, $p < 0.001$), bipolar disorder (25.49 vs 26.42 years, $p < 0.001$), and depressive disorder (25.74 vs 27.75 years, $p = 0.003$). Moreover, the bereaved individuals had a higher incidence of premorbid mental comorbidities than the control cohort, including ASD (0.128% vs 0.097%, $p < 0.001$), ADHD (0.7% vs 0.6%, $p < 0.001$), anxiety disorder (1.2% vs 0.7%, $p < 0.001$), SUD (0.6% vs 0.2%, $p < 0.001$), and AUD (0.5% vs 0.1%, $p < 0.001$). The bereaved individuals also had a higher rate of parental mental disorders, including schizophrenia (2.1% vs 0.7%, $p < 0.001$), bipolar disorder (1.7% vs 0.8%, $p < 0.001$), depressive disorder (5.0% vs 3.0%, $p = 0.003$), SUD (1.4% vs 0.9%, $p < 0.001$), and AUD (3.4% vs 1.2%, $p < 0.001$) than the controls.

Risk of subsequent MMDs after parental death, paternal death, and maternal death

After adjusting for confounding factors (i.e., age, sex, income, urbanization level, parental mental disorders, and offspring premorbid mental disorders), the index cohort had significantly higher risks of schizophrenia (reported as HR with 95% CI, 5.50; 4.98–6.07), bipolar disorder (3.39; 3.05–3.77), and depressive disorder (2.86; 2.77–2.96) than the control cohort. For the bereaved young adults (18–29 years), the risk remained significantly higher than in the controls for schizophrenia (5.63; 5.01–6.33), bipolar disorder (3.37; 2.96–3.84), and depressive disorder (2.78; 2.68–2.90). The other age categories showed similar risks for the three MMDs. The details of the characteristics are listed in Table 2.

The risks of developing MMDs after maternal death or paternal death are shown in Table 2. After adjusting for confounding factors, maternal death was significantly associated with higher risks of schizophrenia (4.87; 4.10–5.78), bipolar disorder (3.17; 2.63–3.82), and depressive disorder (2.78; 2.61–2.96) than the controls. The risks were similar after paternal death. After adjusting for confounding factors, paternal death was significantly associated with higher risks of schizophrenia (5.59; 5.02–6.21), bipolar disorder (3.34; 2.97–3.76), and depressive disorder (2.82; 2.72–2.93) than the controls (Table 3).

Table 1 Demographic characteristics and incidence of major mental disorders between bereaved and control cohorts

	Bereaved cohort ($n=202,837$)	Control cohort ($n=2,028,370$)	p-value
Age at parent's death/enrollment (years, SD)	20.41 (6.93)	20.41 (6.93)	0.911
< 6 years	8250 (4.1)		
6–11 years	20,385 (10.0)		
12–17 years	37,112 (18.3)		
18–29 years	137,090 (67.6)		
Male (n, %)	105,278 (51.9)	1,052,780 (51.9)	> 0.999
Bereaved parents (n, %)			
Father	155,642 (76.7)		
Mother	49,020 (24.2)		
Parental mental disorder (n, %)			
Schizophrenia	4220 (2.1)	14,081 (0.7)	< 0.001
Bipolar disorder	3504 (1.7)	16,091 (0.8)	< 0.001
Depressive disorder	10,213 (5.0)	60,340 (3.0)	< 0.001
Substance use disorder	2861 (1.4)	19,145 (0.9)	< 0.001
Alcohol use disorder	6966 (3.4)	24,752 (1.2)	< 0.001
Incidence of major mental disorders (n, %)			
Schizophrenia	699 (0.3)	1035 (0.1)	< 0.001
Age at diagnosis (years, SD)	25.68 (5.56)	26.91 (6.01)	< 0.001
Bipolar disorder	525 (0.3)	1182 (0.1)	< 0.001
Age at diagnosis (years, SD)	25.49 (5.70)	26.42 (6.10)	< 0.001
Depressive disorder	4573 (2.3)	13,897 (0.7)	0.003
Age at diagnosis (years, SD)	25.74 (5.53)	27.75 (5.81)	< 0.001
Premorbid mental comorbidities (n, %)			
ASD	260 (0.1)	1973 (0.1)	< 0.001
ADHD	1339 (0.7)	12,004 (0.6)	< 0.001
Anxiety disorder	2349 (1.2)	14,999 (0.7)	< 0.001
Substance use disorder	1227 (0.6)	3807 (0.2)	< 0.001
Alcohol use disorder	927 (0.5)	2553 (0.1)	< 0.001
Level of urbanization (n, %)			> 0.999
1 (most urbanized)	47,504 (23.4)	475,040 (23.4)	
2	66,087 (32.6)	660,870 (32.6)	
3	31,554 (15.6)	315,540 (15.6)	
4	22,844 (11.3)	228,440 (11.3)	
5 (most rural)	34,848 (17.1)	348,480 (17.1)	
Income-related insured amount (n, %)			> 0.999
≤ 19,100 NTD/month	33,141 (16.3)	331,410 (16.3)	
19,001 ~ 42,000 NTD/month	73,530 (36.3)	735,300 (36.3)	
> 42,000 NTD/month	96,166 (47.4)	961,660 (47.4)	

ASD, autism spectrum disorder; ADHD, Attention-deficit hyperactivity disorder; SD, standard deviation; NTD, new Taiwan dollar

Risk of subsequent MMDs after parental death across different premorbid mental comorbidities

Most of the premorbid mental comorbidities were associated with an increased risk of MMDs after parental death compared to the controls. The bereaved individuals with premorbid SUD were associated with the highest risks of schizophrenia (10.43; 8.57–12.71), bipolar disorder (12.93; 10.59–15.79), and depressive disorder (10.97; 10.22–11.78) after parental death, and those with premorbid AUD were associated with higher risks of schizophrenia (5.48; 4.39–6.84), bipolar disorder (10.02; 8.07–12.43), and depressive disorder (9.41; 8.73–10.16) than the controls. The other premorbid mental comorbidities were also associated with increased risks of the three MMDs compared to the controls, except for the association between ADHD and schizophrenia (Table 4).

Table 2 Cox regression analyses of subsequent major mental disorders after parental death

Age at parent's death	< 6 years	6–11 years	12–17 years	18–29 years	Total
Schizophrenia					
Control cohort (*n*, %)	7 (0.0)	82 (0.0)	214 (0.1)	732 (0.1)	1035 (0.1)
Bereaved cohort (*n*, %)	5 (0.1)	31 (0.2)	142 (0.4)	521 (0.4)	699 (0.3)
HR	**6.68**	**3.28**	**5.74**	**5.63**	**5.50**
95% CI	**2.02–22.11**	**2.15–4.99**	**4.62–7.14**	**5.01–6.33**	**4.98–6.07**
Bipolar disorder					
Control cohort (*n*, %)	19 (0.0)	90 (0.0)	282 (0.1)	791 (0.1)	1182 (0.1)
Bereaved cohort (*n*, %)	8 (0.1)	30 (0.1)	123 (0.3)	364 (0.3)	525 (0.3)
HR	**3.37**	**2.86**	**3.54**	**3.37**	**3.39**
95% CI	**1.42–8.00**	**1.88–4.36**	**2.84–4.41**	**2.96–3.84**	**3.05–3.77**
Depressive disorder					
Control cohort (*n*, %)	99 (0.1)	893 (0.4)	2464 (0.7)	10,441 (0.8)	13,897 (0.7)
Bereaved cohort (*n*, %)	33 (0.4)	236 (1.2)	899 (2.4)	3405 (2.5)	4573 (2.3)
HR	**3.19**	**2.45**	**3.26**	**2.78**	**2.86**
95% CI	**2.15–4.75**	**2.12–2.83**	**3.02–3.53**	**2.68–2.90**	**2.77–2.96**

Bold type means the statistical significance

HR, hazard ratio; CI, confidence interval

Table 3 Cox regression analyses of subsequent major mental disorders after parental death, stratified by fathers and mothers

	Schizophrenia	Bipolar disorder	Depressive disorder
Control cohort (*n*, %)	1035 (0.1)	1182 (0.1)	13,897 (0.7)
Bereaved cohort (mother death) (*n*, %)	159 (0.3)	128 (0.3)	1147 (2.3)
HR	**4.87**	**3.17**	**2.78**
95% CI	**4.10–5.78**	**2.63–3.82**	**2.61–2.96**
Control cohort (*n*, %)	1035 (0.1)	1182 (0.1)	13,897 (0.7)
Bereave cohort (father death) (*n*, %)	549 (0.4)	405 (0.3)	3488 (2.2)
HR	**5.59**	**3.34**	**2.82**
95% CI	**5.02–6.21**	**2.97–3.76**	**2.72–2.93**

Bold type means the statistical significance

HR, hazard ratio; CI, confidence interval

Table 4 Premorbid mental comorbidities and risks of subsequent major mental disorders after parental death

	HR (95% CI)		
	Schizophrenia	Bipolar disorder	Depressive disorder
Autism spectrum disorder	**5.56 (3.80–8.12)**	**3.94 (2.55–6.10)**	**1.31 (1.01–1.69)**
Attention deficit hyperactivity disorder	1.16 (0.80–1.69)	**4.32 (3.21–5.81)**	**3.86 (3.44–4.34)**
Anxiety disorder	**7.41 (6.06–9.06)**	**4.04 (3.24–5.03)**	**4.58 (4.24–4.95)**
Substance use disorder	**10.43 (8.57–12.71)**	**12.93 (10.59–15.79)**	**10.97 (10.22–11.78)**
Alcohol use disorder	**5.48 (4.39–6.84)**	**10.02 (8.07–12.43)**	**9.41 (8.73–10.16)**

Bold type means the statistical significance

HR, hazard ratio; CI, confidence interval

Discussion

Main findings of the current study

Our results show the important role of parental death in the mental health of their offspring, even during early adulthood. Compared with the controls whose parents were still alive, the bereaved individuals had a 5.50-fold higher risk of schizophrenia, 3.39-fold higher risk of bipolar disorder, and 2.86-fold higher risk of depressive disorder after parental death. The increased risks were observed across all categories of offspring age, including young adults. In addition, both paternal and maternal death were associated with increased risks of MMDs. Importantly, premorbid mental comorbidities (i.e., ASD, ADHD, anxiety disorder, SUD, and AUD) were associated with an increased risk of developing MMDs among the bereaved offspring, and in particular premorbid SUD was associated with a 10.43-fold higher risk of schizophrenia, 12.93-fold higher risk of bipolar disorder, and 10.97-fold higher risk of depressive disorder. Taken together, our study findings suggest that parental death could be considered a risk factor for MMDs, even in young adults.

Association between parental death and subsequent MMDs in young adults

The associations between parental death and the development of schizophrenia, bipolar disorder, and depressive disorder are comparable with previous studies [11, 22, 23]. The association between parental death and MMDs may result from complicated and multidimensional etiologies. Most previous studies addressing parental bereavement have focused on individuals younger than 18 years of age [7, 9, 11, 22], and our study further suggests that parental death in offspring aged between 18 and 29 years was also associated with a higher risk of subsequent MMDs. Although seldom studies addressed the effect of parental death during young adulthood on the development of MMDs [9], one study reported an association between complicated grief and parental death in offspring during adulthood [24]. Differences in the etiology of the association between parental death and MMDs may exist between parental deaths during different timing, resulting in different impacts on the onset of MMDs. Several studies have discussed the factors associated with the impact of parental death during childhood and adolescence. Parental death often has a critical impact on multiple dimensions of a child's life by precipitating environmental factors associated with psychological challenges, including residential moves, school transfers, reduced economical support, burden for family members, and disturbances to family dynamics [25, 26]. A systematic review discussing traumatic experiences in early childhood reported the unique role of psychological trauma during preschool age when examining the impact of childhood adversity on developmental trajectories [27]. Our study further implies that parental death during young adulthood should be considered a risk factor for MMDs, and further studies on the etiology of this risk with regard to biological or environmental factors are warranted. On the other hand, we also found that both paternal and maternal deaths were related to subsequent MMDs. This finding is consistent with previous studies, demonstrating the effect of paternal and maternal death on the risk of mental disorders [7, 11]. However, further studies are needed to explore differences in the effect of paternal and maternal death on the risk of subsequent mental disorders.

Effect of premorbid mental comorbidities

Another novel finding of the current study is the effect of premorbid mental comorbidities on the association between parental death and subsequent MMDs. The comorbidities between MMDs and other mental disorders have been investigated, such as between neurodevelopmental disorders and MMDs [28, 29]. In addition, the comorbidity between ASD and multiple mental disorders has been shown to have complicated etiologies [30], and the relationships between ADHD and bipolar disorder or schizophrenia are intertwined [31, 32]. Genetic studies have shown that neurodevelopmental disorders and MMDs share biological etiologies, such as genomic copy number variants [31, 33]. Moreover, several studies have reported high comorbidity between SUD and MMDs, including schizophrenia [34], depression [35], and bipolar disorder [36]. A previous study also demonstrated that shared genetic determinants for schizophrenia and SUD may make patients vulnerable to substance use [37]. To the best of our knowledge, no previous study has explored the effect of comorbidity with SUD on the development of MMDs after parental death. However, a previous study demonstrated that parental separation had the strongest impact on the risk of substance abuse or dependence [38]. This may suggest the intertwined interaction between SUD and parenting dysfunction due to parental loss. On the other hand, subjects with mental comorbidities may have maladaptive coping strategies to stressful events. A previous study demonstrated that individuals with mental illness were associated with a higher level of coping styles in disengagement and externalization of distress [39]. Moreover, subjects with anxiety or mood disorder have been shown to demonstrate poorer coping skills in facing the coronavirus disease 2019 pandemic than those without

mental comorbidities (40). Taken together, we hypothesize that shared etiologies between premorbid mental comorbidities and MMDs may make increase the vulnerability of individuals, resulting in the emergence of MMDs. However, this hypothesis needs to be tested with prospective cohort studies regarding the biological or environmental factors. In addition, further mediation or moderation analysis is also required to clarify the intertwined relationships between premorbid mental comorbidities, parental death, and MMDs.

Limitations

Several limitations of the current study should be addressed. First, due to the limitation of the research protocol approved by the Institutional Review Board, subjects older than 30 years when their parents died were not included, and therefore we could not identify the effect of parental death in subjects in this age group. Second, due to limitations of the NHIRD, interactions between premorbid mental comorbidities, parental death, and subsequent MMDs could not be clearly identified with mediation or moderation analysis. In addition, the cause of parental death cannot be identified. Third, the severity of MMD was not identified due to the limitation of database, and the generalizability of our result should be noticed for a single population. Finally, although we adjusted for parental mental disorders and premorbid mental comorbidities in the risk of MMDs after parental death, residual confounding factors may still exist in our study. However, this naturalistic observation may reflect clinical practice in the real world.

Conclusions

In the present study, we identified an association between parental death and subsequent MMDs. Our results fill the knowledge gap of previous studies and showed that this association was still significant for offspring who were in early adulthood (18–29 years) when their parents died. In addition, we also found a significant risk of MMDs after parental death among individuals with premorbid mental comorbidities compared with those without premorbid mental comorbidities. These findings may highlight the importance of timely assessments and interventions for individuals after parental death. Furthermore, those with premorbid mental comorbidities should be especially monitored due to the higher risk of MMDs after parental death. Further neurobiological investigations are warranted to better clarify the etiology behind the association of parental death and subsequent MMDs among their offspring.

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Author contributions Drs MHC, YMB, and CSL designed the study. Drs DJL, MHC, CSL wrote the draft; Drs DJL, SJT, CMC, TPS, and TJC performed the literature review and revised the manuscript; Dr MHC performed the statistical analysis; all authors reviewed the final manuscript and agreed with its publication.

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Declarations

Conflict of interest All authors have no financial relationships relevant to this article to disclose, and all authors declare that they have no conflicts of interest.

Ethical standards This study protocol was reviewed and accepted by the Institutional Review Board of Taipei Veterans General Hospital (approval number: TPEVGH-IRB-2018-07-016AC). The requirement for patient consent was waived because the data used in this study were anonymized and derived wholly from a sizeable national database.

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