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Prenatal Maternal Bereavement and Its Association With Intellectual Disability in the Offspring

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ABSTRACT

Objective: This study aimed to examine the association of a mother's loss of a close relative before or during pregnancy with intellectual disability (ID) in the offspring.

Methods: We performed a nationwide population-based cohort study based on Danish national registries. All live-born singletons born in Denmark during the 1978–2016 period (n = 2,216,601) were followed up starting from birth to 38 years of age. Log-linear Poisson regression was used to estimate the association between maternal bereavement (the death of an older child, a partner, or a parent 1 year before or during pregnancy) and the risk of ID in the offspring.

Results: Maternal bereavement during or before pregnancy was associated with an increased risk of ID (incidence rate ratio [IRR] = 1.15; 95% confidence interval [CI] = 1.04–1.28). The risk of ID was increased by 27% when maternal bereavement occurred during pregnancy (IRR = 1.27; 95% CI = 1.08–1.49). When stratifying on the child's sex, we also observed an increased risk of ID associated with maternal bereavement during pregnancy both for male (IRR = 1.25; 95% CI = 1.02–1.53) and for female (IRR = 1.31; 95% CI = 1.02–1.69), respectively. The IRRs for unnatural death of a relative were also elevated (IRR = 1.22; 95% CI = 0.91–1.64) in general, although the difference was not statistically significant.

Conclusions: Our findings suggest that prenatal stress due to maternal loss of a close relative may increase the risk of offspring's ID of both sexes, in particular when the loss happened during pregnancy.

Key words: prenatal stress, bereavement, intellectual disability, autism spectrum disorders.

INTRODUCTION

Intellectual disability (ID) is a generalized neurodevelopmental disorder characterized by significant impairments in intellectual functioning and in adaptive behavior (1,2). A meta-analysis including 52 studies reported that the prevalence of ID was 10.4/1000 persons, with the highest up to 26.1/1000 persons in urban slums/mixed rural-urban settings (3). The lifetime incidence rate was 1.8 per 10,000 person-years reported in a Danish study (4). Although genetic susceptibility is important (5,6), it has been suggested that the etiology of one-third to one-half of the cases is unknown (7,8). Given the long-term implications of ID for the affected individuals, the involved families, and society (9), further knowledge on ID's modifiable risk factors is necessary for disease prevention and management (10).

ASD = autism spectrum disorder, **CI** = confidence interval, **DNPR** = the Danish National Hospital Register, **ICD** = International Classification of Diseases, **ID** = intellectual disability, **IPW** = inverse probability of selection weighting, **IQ** = intelligence quotient, **IRR** = incidence rate ratio, **PCRR** = the Danish Psychiatric Central Research Register

SDC Supplemental Digital Content

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Maternal bereavement during pregnancy is associated with increased risks of several psychiatric disorders in the offspring (11), including attention-deficit/hyperactivity disorder, schizophrenia, and eating disorders (12–15), suggesting that prenatal stress could have a programming effect on brain development (16,17). A study based on the Danish Conscription Register found that the mother's loss of her partner during pregnancy was associated with lower intelligence quotient (IQ) scores at the age of 18 years in their male offspring (18). Because IQ is one of the main diagnostic criteria for ID, an association between maternal stress to bereavement during pregnancy and risk of ID in the offspring is plausible.

We aimed to examine the association between maternal bereavement by the death of a close relative 1 year before or during pregnancy and the risk of ID in the offspring. We hypothesized that the risk of ID after the prenatal stress may vary according to the timing of exposure (19), the mother's relationship to the deceased (20), the relative's cause of death (21), and sex of the child (22). We further investigated the importance of autism spectrum disorders (ASDs) in the association, as ASD co-occurs with more than 10% of ID cases (23).

METHODS

We performed a nationwide population-based cohort study using data from Danish national registries. The unique personal identification number allows for accurate individual-level record linkage across registries (24). The study was approved by the Danish Data Protection Agency (No. 2013-41-2569).

Study Population

We identified all live-born singletons born in Denmark during the 1978–2016 period (n = 2,673,760) and their family members in Denmark from the Danish Civil Registration System (25). Children with no information on sex (n = 3760) and those with missing or implausible gestational age (<154 or >315 days, n = 421,484) were excluded from the study. Children diagnosed with a chromosomal abnormality or fragile X chromosome (the *International Classification of Diseases, Eighth Revision* [*ICD-8*] codes 758.9, 759; *Tenth Revision* [*ICD-10*] codes Q90–Q99), or congenital malformations of the nervous system (*ICD-8* codes 740–743; *ICD-10* codes Q00–Q07) were also excluded (n = 31,915; eTable 1, Supplemental Digital Content, http://links.lww.com/PSYMED/A770). A total of 2,216,601 children were included in the final analysis. Cohort members were followed up from birth to the first diagnosis of ID, emigration, death, or end of follow-up (December 31, 2016), whichever came first.

Exposure

The cause and date of death were retrieved from the Danish Register of Cause of Death. We categorized children as the exposed if their mothers lost an older child, a spouse, or a parent 1 year before or during pregnancy. The remaining children were included in the unexposed cohort. Exposed children were further categorized into subgroups according to the following: a) the timing of bereavement (6–12 months before pregnancy, 0–6 months before pregnancy, during pregnancy [first, second, and third trimesters]); b) the relationship of their mother to the deceased (older child/spouse, parent); and c) the relative's cause of death (sudden or unnatural death, such as nonviolent death without a cause, accident due to traffic or poisoning, etc. [*ICD-8* codes 795, 800–807, 810–823, 825–999; *ICD-10* codes R95–R97, V01–V99, W00–X59, X60–Y89], and natural death [death by other causes]) (26–28).

Ascertainment of ID

Information on diagnosis of ID was obtained from the Danish National Hospital Register (DNPR) (29) and from the Danish Psychiatric Central Research Register (PCRR) (30). The DNPR included somatic inpatient contact from 1977 to 1994. Outpatient and emergency contacts have also been reported to the DNPR since 1995 (31). All mental hospitals and psychiatric departments were committed to reporting to the PCRR from 1970, which became an integrated part of the DNPR since 1995. Denmark used the *ICD-8* up to 1993, and *ICD-10* since 1994. We identified ID by any diagnosis with the codes 310–315 (*ICD-8*) and *ICD-10* codes of F70, F71, F72, F73, F78, and F79. We categorized cases of ID in four groups according to the severity of the disorder: a) borderline-mild ID (*ICD-8*: 310–311, *ICD-10*: F70), b) moderate ID (*ICD-8*: 312, *ICD-10*: F71), c) severe or profound ID (*ICD-8*: 313–314, *ICD-10*: F72–F73), and d) others or unspecified ID (*ICD-8*: 315, *ICD-10*: F78–F79). We also ascertained ASD by *ICD-8* codes of 29901–29903 or *ICD-10* codes of F840, F841, F845, F848, and F849 (eTable 1, Supplemental Digital Content, http://links.lww.com/PSYMED/A770).

Covariates

We adjusted for the following potential confounding factors: maternal age (<20, 20–24, 25–29, 30–34, ≥35 years), maternal education (<9, 10–14, ≥15 years, missing), maternal income quantiles, maternal country of origin (Nordic, others), maternal residence at childbirth (Copenhagen, Odense/Aarhus/Alborg, others), maternal smoking status (yes, no), and paternal age (<20, 20–24, 25–29, 30–34, ≥35 years, missing), parity (1, 2, ≥3), sex (male, female), birth year (1978–1987, 1988–1997, 1998–2007, 2008–2016), and parental history of psychiatric diseases (yes, no; *ICD-8* codes 290–315 and *ICD-10* codes F00–F99). Both maternal income and parental of psychiatric diseases were adjusted as time-very covariates in the model.

Statistical Analysis

χ^2 Test was applied to compare basic characteristics between the exposed and unexposed groups. We first estimated the incidence rate and overall incidence rate ratio (IRR) and 95% confidence interval (95% CI) for ID according to exposure using log-linear Poisson regression models having follow-up time as an offset, which is an approximation of Cox regression model and with time-saving property (32). We further performed analyses according to a) the timing of loss, b) the mother's relationship to the deceased, and c) the relative's cause of death. The potential sex specificity of the associations was estimated in the analyses stratified by sex.

Eight sensitivity analyses were performed to test the robustness of the main estimates. a) Because the etiology of ID might vary with its severity, we performed analyses with the outcome classified into four groups according to the severity of ID. b) We performed analyses stratified on follow-up years (0–3, 4–6, 7–17, >18 years) because children with a mild or moderate ID might receive a specific diagnosis until school age and more than half of children with severe ID could be identified in the first 3 years of life (33). c) Because some experts agree that the diagnostic criteria must be met by age 18 years, we also did a sensitivity analysis by limiting the age of follow-up to <18 years. d) We tested the impact of restricting the data to children who were born before 2009, thus including children with late diagnosis of ID (34). e) As it is reported that ASD and ID are biologically and clinically entangled (23,35), we performed a sensitivity analysis to estimate the risk of ID with ASD and ID without co-occurring ASD separately. f) We also performed analyses restricted to children born at term because preterm birth is a strong risk factor for ID (36). g) In addition, we used inverse probability of selection weighting (IPW) by including stillbirth to evaluate possible live-birth bias due to maternal stress or other risk factors for ID in offspring (37). The stillbirth information was retrieved from The Danish Medical Birth Register. These risk factors could lead to fetal loss such that naive analysis of data on live births could be misleading. IPW models for stillbirths included maternal age, maternal education, maternal income, maternal country of origin, maternal residence at childbirth, maternal smoking status, and paternal age, parity, birth year, and parental history of psychiatric diseases. h) We also performed multiple imputation using chained equations to account for missing data on covariates based on the assumption of missing at random. All covariates used in the main analysis were included in the model, and five complete data sets were created. Missing indicator method and complete case analysis were also performed for comparison.

TABLE 1. Baseline Characteristics of the Study Population According to Maternal Exposure to the Loss of a Close Relative the Year Before or During Pregnancy

Characteristics	Exposed (n = 54,669)	Unexposed (n = 2,161,932)
Sex of the index child		
Male	27,929 (51.1)	1,111,742 (51.4)
Female	26,740 (48.9)	1,050,190 (48.6)
Maternal age at childbirth, y		
<20	909 (1.7)	50,707 (2.3)
20–24	7964 (14.6)	381,175 (17.6)
25–29	18,020 (33.0)	792,554 (36.7)
30–34	17,714 (32.4)	647,025 (29.9)
≥35	10,062 (18.4)	290,471 (13.4)
Maternal smoking		
No	27,781 (71.6)	1,182,809 (77.6)
Yes	9497 (24.5)	288,990 (19.0)
Missing	1507 (3.9)	51,840 (3.4)
Maternal education, y		
≤9	15,929 (29.1)	561,072 (26.0)
10–14	23,404 (42.8)	932,876 (43.2)
≥15	14,997 (27.4)	621,001 (28.7)
Missing	339 (0.6)	46,983 (2.2)
Cohabitation with the partner		
No	25,688 (47.0)	981,658 (45.4)
Yes	28,981 (53.0)	1,179,428 (54.6)
Missing	—	846 (0)
Maternal residence		
Copenhagen	5456 (10.0)	254,128 (11.5)
Aarhus/Odense/Aalborg	6491 (11.9)	288,843 (13.0)
Other	42,722 (78.1)	1,673,630 (75.5)
Country of origin		
Nordic	52,629 (96.3)	1,905,860 (88.2)
Other country	2004 (3.7)	252,355 (11.7)
Missing	36 (0.1)	3717 (0.2)
Paternal age, y		
<20	235 (0.4)	13,121 (0.6)
20–24	4032 (7.4)	189,965 (8.8)
25–29	13,630 (24.9)	611,684 (28.3)
30–34	17,975 (32.9)	702,898 (32.5)
≥35	16,448 (30.1)	555,492 (25.7)
Missing	2349 (4.3)	88,772 (4.1)
Parity		
1	19,852 (36.3)	975,188 (45.1)
2	21,448 (39.2)	801,766 (37.1)
≥3	13,369 (24.5)	384,978 (17.8)
Low birth weight (<2500 g)		
No	51,316 (94.8)	2,027,498 (95.6)
Yes	2445 (4.5)	78,942 (3.7)
Missing	380 (0.7)	14,549 (0.7)
Preterm birth (<37 wk)		
No	51,639 (94.5)	2,060,207 (95.3)
Yes	3030 (5.5)	101,725 (4.7)
Parental history of psychiatric disorders		
No	42,733 (78.2)	1,734,545 (80.2)
Yes	11,936 (21.8)	427,387 (19.8)

Continued on next page

All analyses were conducted using the SAS 9.4 software package (SAS Institute Inc, Cary, North Carolina). Statistical significance was set at $p < .05$, and all tests were two-tailed.

RESULTS

Of the 2,216,601 children in our study, 54,669 (2.5%) were born to mothers who experienced prenatal stress due to loss of a close relative the year before or during pregnancy; 7758 children were born to mothers who lost an older child, 46,265 to mothers who lost a parent, and 646 to mothers who lost her partner. The baseline characteristics of the exposed cohort and the unexposed are presented in Table 1. Exposed children were more likely to have an older parent and a higher birth order than their unexposed counterparts.

A total of 11,919 children were diagnosed with ID by the end of the follow-up; the incidence rate of ID was 2.9 per 10,000 person-years during follow-up of up to 38 years. With respect to specific subtypes of ID, we identified 4801 (40.3%) cases of borderline-mild ID, 1227 (10.3%) cases of moderate ID, 389 (3.3%) cases of severe or profound ID, and 5502 (46.2%) cases of other or unspecified ID.

Overall, maternal loss of a close relative before childbirth was associated with a 15% increased ID risk (IRR = 1.15; 95% CI = 1.04–1.28) in the offspring. Maternal loss of a close family member during pregnancy seemed to be more strongly associated with ID in the offspring (IRR = 1.27; 95% CI = 1.08–1.49) than the loss in other periods within the exposure time window. We did not observe a substantial change of the association of stress and ID by the mother's relationship to the deceased or the cause of death (Table 2).

Table 3 presents the associations between maternal loss of bereavement the year before or during pregnancy and the risks of ID in offspring by sex. A diagnosis of ID was more common in male offspring (n = 7391) than among female offspring (n = 4528). The overall IRRs of ID are 1.17 (95% CI = 1.02–1.33) for male offspring and 1.12 (95% CI = 0.95–1.33) for female offspring. When restricting the timing of bereavement to "during pregnancy," we observed a relatively high increased risk of ID associated with maternal bereavement during pregnancy for both male (IRR = 1.25; 95% CI = 1.02–1.53) and female (IRR = 1.31; 95% CI = 1.02–1.69), respectively. When categorizing the outcome according to the severity of ID, we observed a higher risk of both borderline-mild ID (IRR = 1.22; 95% CI = 1.05–1.43) and severe-profound ID (IRR = 1.56; 95% CI = 0.93–2.62), respectively (Table 4).

We did not observe an obvious time trend according to the follow-up years (birth to 3 years: IRR = 0.98, 95% CI = 0.78–1.22; 4–6 years: IRR = 1.23, 95% CI = 0.96–1.56; 7–17 years: IRR = 1.14, 95% CI = 0.97–1.35; ≥18 years: IRR = 1.12, 95% CI = 0.87–1.43; eTable 2, Supplemental Digital Content, http://links.lww.com/PSYMED/A770). When we defined the end of

TABLE 2. Risk of Intellectual Disability According to Maternal Exposure to Death of a Close Relative the Year Before or During Pregnancy

Maternal Bereavement	No. Cases	Incidence Rate (Per 10,000)	Crude IRR (95% CI)	Adjusted[a] IRR (95% CI)
Unexposed	11,555	2.9	1.00 (ref)	1.00 (ref)
Exposed	364	3.5	**1.22 (1.10–1.35)**	**1.15 (1.04–1.28)**
By type of deceased relative				
Child/spouse	68	3.7	**1.33 (1.05–1.69)**	1.12 (0.88–1.42)
Parents	296	3.5	**1.20 (1.06–1.34)**	**1.16 (1.03–1.30)**
By time of exposure				
6–12 mo before pregnancy	156	3.3	1.14 (0.97–1.33)	1.07 (0.91–1.26)
0–6 mo before pregnancy	54	3.3	1.16 (0.89–1.52)	1.09 (0.83–1.42)
During pregnancy	154	3.9	**1.33 (1.13–1.55)**	**1.27 (1.08–1.49)**
1st trimester	44	3.8	1.30 (0.97–1.75)	1.25 (0.93–1.68)
2nd trimester	59	3.9	1.35 (1.05–1.75)	1.27 (0.99–1.65)
3rd trimester	51	3.9	1.35 (1.02–1.77)	1.29 (0.98–1.70)
By cause of the relative's death				
Sudden, unnatural death	45	4.0	**1.47 (1.09–1.96)**	1.22 (0.91–1.64)
Natural death	319	3.4	**1.19 (1.06–1.33)**	**1.14 (1.02–1.28)**

IRR = incidence rate ratio; CI = confidence interval; ref = reference value.

Values in boldface are significant.

[a] Adjusted for parental age, parental history of psychiatric disorders, maternal cohabitation with her partner, maternal education, maternal income, maternal smoking, maternal country of origin, parity, sex, and birth year of the index child.

the follow-up to <18 years of age, the risk of ID is almost the same as that in the main analysis (overall IRR = 1.15; 95% CI = 1.02–1.29; eTable 3, Supplemental Digital Content, http://links.lww.com/PSYMED/A770). When restricting the data to children who were born before 2009, the estimates are similar to the main analysis (eTable 4, Supplemental Digital Content, http://links.lww.

TABLE 3. Sex-Specific Risks of Intellectual Disability as Related to Maternal Exposure to Death of a Close Relative the Year Before or During Pregnancy

	Male		Female	
Maternal Bereavement	No. Cases (IR, Per 10,000)	Adjusted[a] IRR (95% CI)	No. Cases (IR, Per 10,000)	Adjusted[a] IRR (95% CI)
Unexposed	7164 (3.5)	1.00 (ref)	4391 (2.3)	1.00 (ref)
Exposed	**227 (4.3)**	**1.17 (1.02–1.33)**	137 (2.7)	1.12 (0.95–1.33)
By relative type				
Child/spouse	45 (4.9)	1.23 (0.92–1.65)	23 (2.5)	0.94 (0.63–1.42)
Parents	182 (4.2)	1.15 (0.99–1.34)	114 (2.7)	1.17 (0.97–1.41)
By time window				
6–12 mo prior	99 (4.1)	1.10 (0.91–1.35)	57 (2.4)	1.02 (0.79–1.32)
0–6 mo prior	35 (4.3)	1.16 (0.83–1.62)	19 (2.4)	0.97 (0.62–1.53)
During	**93 (4.6)**	**1.25 (1.02–1.53)**	**61 (3.1)**	**1.31 (1.02–1.69)**
1st trimester	**32 (5.4)**	**1.50 (1.06–2.12)**	12 (2.1)	0.87 (0.49–1.53)
2nd trimester	35 (4.6)	1.22 (0.88–1.71)	24 (3.2)	1.35 (0.90–2.01)
3rd trimester	26 (3.8)	1.06 (0.72–1.55)	**25 (3.9)**	**1.68 (1.13–2.49)**
By death cause				
Sudden, unnatural death	30 (5.3)	1.34 (0.94–1.92)	15 (2.7)	1.03 (0.62–1.71)
Natural death	197 (4.2)	1.15 (0.99–1.32)	122 (2.7)	1.14 (0.95–1.36)

IRR = incidence rate ratio; CI = confidence interval; ref = reference value.

Values in boldface are significant.

[a] Adjusted for parental age, parental history of psychiatric disorders, maternal cohabitation with her partner, maternal education, maternal income, maternal smoking, maternal country of origin, parity, and birth year of the index child.

TABLE 4. Risk of Different Severity Levels of Intellectual Disability According to Maternal Exposure to Death of a Close Relative the Year Before or During Pregnancy

Severity of ID	Unexposed (*n*/IR, Per 10,000)	Exposed (*n*/IR, Per 10,000)	Crude IRR (95% CI)	Adjusted[a] IRR (95% CI)
Borderline-mild ID	4636 (1.2)	165 (1.6)	1.33 (1.14–1.55)	**1.22 (1.05–1.43)**
Moderate ID	1201 (0.3)	26 (0.3)	0.80 (0.51–1.13)	0.76 (0.52–1.13)
Severe-profound ID	374 (0.1)	15 (0.1)	1.51 (0.90–2.52)	1.56 (0.93–2.62)

ID = intellectual disability; IRR = incidence rate ratio; CI = confidence interval.

Values in boldface are significant.

[a] Adjusted for parental age, parental history of psychiatric disorders, maternal cohabitation with her partner, maternal education, maternal income, maternal smoking, maternal country of origin, parity, sex, and birth year of the index child.

com/PSYMED/A770). The estimates for maternal bereavement were statistically significant both for ID without ASD (IRR = 1.31; 95% CI = 1.03–1.67) and for ID co-occurring with ASD (IRR = 1.12; 95% CI = 1.00–1.26; eTable 5, Supplemental Digital Content, http://links.lww.com/PSYMED/A770). Analyses restricting to term-born children found that the estimates were similar to those observed in the main analysis (eTable 6, Supplemental Digital Content, http://links.lww.com/PSYMED/A770). When restricting the analysis to children without a parental history of psychiatric disorders, the estimates also did not change substantially (IRR = 1.18; 95% CI = 1.04–1.35; eTable 7, Supplemental Digital Content, http://links.lww.com/PSYMED/A770). In our evaluation of live-birth bias, the IPW approach yielded almost identical results as the primary analyses (eTable 8, Supplemental Digital Content, http://links.lww.com/PSYMED/A770). In the sensitivity analysis using multiple imputation approach for missing data, the findings were similar to those in the main analysis (eTable 9, Supplemental Digital Content, http://links.lww.com/PSYMED/A770).

DISCUSSION

In this large population-based cohort study, we observed that prenatal stress after maternal bereavement was associated with an increased risk of ID in offspring of both sexes, and the association was mainly driven by the bereavement events happened during pregnancy. We also observed increased risks of borderline-mild and severe-profound ID among children whose mothers lost a close relative 1 year before or during pregnancy. In addition, the association of ID with maternal bereavement was independent of the concurrence of ASD. However, there was no substantial change of the association of prenatal stress after bereavement with ID by the mother's relationship to the deceased or the cause of death.

An experimental animal study showed that stressful events during pregnancy could lead to nonreversible and long-lasting structural effects in the offspring (38). Spiers et al. (39) also reported that most brain epigenetic changes occur early in fetal development and are stable throughout life. The developmental and behavioral abnormalities in prenatally stressed offspring could occur through sensitization of the fetal brain by maternal stress hormones to the action of glucocorticoid and corticotropin-releasing hormone and to neurotransmitters affected by them (40). However, empirical research on the effect of prenatal stress on ID has been limited. Previous studies have shown that exposure to prenatal stress after maternal bereavement or postnatal stress after bereavement in childhood might be associated with an increased overall risk of psychiatric illness in offspring (12–14,19). Based on nationwide data with up to 38 years of follow-up, we observed an association between prenatal exposure to maternal bereavement and an increased risk of ID offspring, which might mostly be attributed to the exposure during pregnancy.

A series of animal studies by Mueller and Bale (41,42) also indicated that prenatal stress on offspring long-term outcomes might be temporal specific and sex dependent, including cognitive abilities and stress-coping strategies. It is interesting to observe that maternal bereavement during the first trimester was associated with an increased risk of ID in male offspring. This is supported by previous studies that indicated that women carrying male fetuses had higher levels of salivary cortisol initially and across the trimesters compared with women carrying female fetuses (43,44). We also observed that bereavement during the third trimester was associated with an increased risk of ID in female offspring in the present study. However, our current data failed to observe an overall sex-specific effects in relation to exposure because of a rare outcome, as suggested by others (41,42).

According to the diagnostic criteria for ID (2), children with mild ID (IQ <70) were likely to be with learning difficulties in school but were able to work and maintain good social relationships (adaptive behavior), whereas children with severe or profound ID were not only with lower IQ (<35) but also with impairments of adaptive functioning. A previous study based on data from the Danish Conscription Register reported that men prenatally exposed to the death of their father had a lower IQ at the age of 18 years than their unexposed counterparts (18). For the first time, we showed that maternal bereavement during pregnancy was associated with an overall increased risk of ID, including borderline-mild and severe-profound ID, although some estimates were not statistically significant because of the limited cases. In addition, a systematic review showed that approximately 10% of children with ID show or develop symptoms of autism (45). In the study, we observed overall increased risks of ID in children both with ASD and without ASD, whose mothers lost a close relative during pregnancy. All of the aforementioned results indicated that maternal bereavement was associated with both IQ and adaptive function impairment.

It has been shown that loss of a child or the partner, or unnatural death might be more stressful than loss of parents or siblings and led to poorer mental and physical health consequences (12,46). We did observe higher crude rates associated with these two types of exposures, but the estimates became not statistically significant after adjustment of covariates, possibly because of limited statistical power as indicated by the wide confidence intervals. Future studies are needed to confirm these findings.

Our study has several methodological strengths. First, the use of nationwide registries makes selection bias and loss to follow-up unlikely in our study. There are few missing data on all variables included in our study (<4%). A live-birth selection bias analysis, using available information on stillbirths, also provides reassurance that restricting our sample to live-births was unlikely to substantially affect the observed associations. Second, the death of a close family member may be regarded as a rather objective source of stress that is likely to induce stress for most individuals, irrespective of coping abilities; our identification of exposure to bereavement through nationwide registers reduces the risk of systematic measurement errors, including recall bias. Third, the comprehensive data on sociodemographic variables and health-related covariates and the large sample size allowed us to adjust for a number of potential confounders. Last but not least, as a previous study indicated that a late of diagnosis (age at diagnosis >20 years) was frequent (24%), and with 10% of them being older than 40 years (34), a 38-year-long follow-up could guarantee most of cases were identified in the study.

Our findings should also be interpreted with caution because our study has several limitations. Although we tried to identify cases of ID using both the DNPR and the PCRR, it is possible that some mild cases were not be identified. Second, the diagnostic process varied during the follow-up. For example, *ICD-8* has a code to identify borderline mental retardation, whereas *ICD-10* has no code for this disorder. However, the adjustment for calendar periods did not affect our results. Third, although this study is nationwide with large sample size, because of the rarity of the exposure and outcome, the statistical power was limited in some subanalyses as indicated by broader confidence intervals. Fourth, we did not have access to other sources of stress and thereby could not take them into consideration, for example, job loss, divorce, and so on. Fifth, our research outcome of ID was based on the hospital diagnosis of ICD code and no specific information related to diagnostic criteria of adaptive behavior was available in the register system. However, our results on the association of ID with ASD or without ASD or different severity of ID after maternal bereavement indicated that prenatal stress might impair both IQ and adaptive behavior.

CONCLUSIONS

In conclusion, our findings suggest that prenatal stress due to maternal loss of a close relative may increase the risk of ID for both sexes of offspring, in particular when the loss happened during pregnancy.

Author Contribution: J.L. and Y.Y. had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. X.S., Y.Y., and J.L. made a substantial contribution to the conception or design of the work; X.S. and Y.Y. performed the statistical analysis; X.S. and L.M. drafted the work; all the other coauthors made a contribution to the interpretation of data for the work; all authors revised the manuscript critically for important intellectual content and approved the final version of the manuscript to be published.

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