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Adverse Life Events Increase Risk for Postpartum Psychiatric Episodes: A Population Based Epidemiologic Study

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Abstract: word count 250

Background: Trauma histories may increase risk of perinatal psychiatric episodes and other comorbidity. We designed an epidemiological population-based cohort study to explore if adverse childhood experiences (ACE) in girls increases risk of later postpartum psychiatric episodes. **Methods:** Using Danish registers, we identified women born in Denmark between January 1980 and December 1998, (129,439 childbirths). Exposure variables were ACE between age 0-15 including: (1) family disruption, (2) parental somatic illness, (3) parental labor market exclusion, (4) parental criminality, (5) parental death, (6) placement in out-of-home care, and (7).parental psychopathology excluding substance use disorders and (8) parental substance use disorder. The primary outcome was first occurrence of in- or outpatient contact 0-6 months (0-182 days) postpartum at a psychiatric treatment facility with any psychiatric diagnoses, ICD-10, F00-F99 (N=651). We conducted survival analyses using Cox proportional hazard regressions of postpartum psychiatric episodes. **Results:** Approximately 52% of the sample experienced ACE that significantly increased risk of any postpartum psychiatric diagnosis. Highest risks were observed among women who experienced out of home placement, hazard ratio (HR) 2.57 (95% CI: 1.90-3.48). Women experiencing 2 adverse life events had higher risks of postpartum psychiatric diagnosis HR: 1.88 (95% CI: 1.51-2.36), compared to those with 1 ACE, HR: 1.24 (95% CI: 1.03-1.49) and no ACE, HR: 1.00 (reference group). **Conclusions:** ACE primarily due to parental psychopathology and disability contributes to increased risk of postpartum psychiatric episodes; and greater numbers of ACE increases risk for postpartum psychiatric illness with an observed dose-response effect. Future work should explore genetic and environmental factors that increase risk and/or confer resilience.

Background: (word count of revised paper is 3321)

Adverse childhood experiences (ACE) are relatively common in the general population—more than half of adults report at least one adverse childhood event (Brown, Perera, Masho, Mezuk, & Cohen, 2015). ACE appears to play a vital role in the development of psychiatric morbidity in adulthood (Brown et al., 2015; Felitti et al., 1998), including major depression (MDD), post-traumatic stress disorder (PTSD), substance abuse disorders and others (Bergink et al., 2016; Brown et al., 2015; Chapman et al., 2004; Dahl et al., 2017; Edwards, Holden, Felitti, & Anda, 2003; Heim et al., 2002). Moreover, the number of early adverse events and MDD has a dose-response relationship (Dahl et al., 2017; Dunn, McLaughlin, Slopen, Rosand, & Smoller, 2013; Keyes et al., 2014) (Dahl et al., 2017) suggesting that the effect of ACE on depression risk in general is cumulative (Kessler et al., 2010). ACE is a critically important public health issue as negative events experienced in childhood or adolescence can confer an enduring deleterious effect on mental health across the entire lifespan (Gilman, Kawachi, Fitzmaurice, & Buka, 2003; Korkeila et al., 2005).

Women experience MDD at twice the rate of men across their lifetime including episodes of depression that occur outside of the perinatal period (Kessler, 2003; Pedersen et al., 2014; Seedat et al., 2009). However, women are particularly vulnerable to psychiatric illness in the postpartum period (Munk-Olsen, Laursen, Pedersen, Mors, & Mortensen, 2006; Munk-Olsen et al., 2016) for a range of postpartum psychiatric disorders including postpartum depression (PPD) and postpartum psychosis. Postpartum depression in particular has a prevalence of 10-15% across the world and greater prevalence in high risk populations of women (Gavin et al., 2005). ACE may be important risk factors for onset of depression during the perinatal period (Ansara, Cohen, Gallop, Kung, & Schei, 2005; Faisal-Cury, Menezes, d'Oliveira, Schraiber, & Lopes, 2013; Kendall-Tackett, 2007; Samantha Meltzer-Brody et al., 2013; Onoye, Goebert, Morland, Matsu, & Wright, 2009; Anna Plaza et al., 2012; Records & Rice, 2009; Robertson-Blackmore

et al., 2013; Rodríguez et al., 2010; Silverman & Loudon, 2010a, 2010b). Women who experience traumatic life events appear to have an increased risk of perinatal depression during pregnancy (antenatal depression), postpartum (PPD) or throughout the entire perinatal period (S. Meltzer-Brody et al., 2013; Meltzer-Brody et al., 2011; A. Plaza et al., 2012; Robertson-Blackmore et al., 2013). However, in some studies, history of trauma increased the risk of antenatal depression, but not PPD (Robertson-Blackmore et al., 2013), whereas in others, the risk of PPD was increased in women who experienced ACE (A. Plaza et al., 2012; Records & Rice, 2009).

Studying sensitive topics such as early life stress and mental health is challenging, and many of the prior studies referenced above had relatively small sample sizes or relied on self-reported data with possible recall bias, underreporting, misclassification and subsequent biased results. We designed an epidemiological population-based cohort study to explore if women experiencing early adverse life events during their childhood/adolescence are at risk of postpartum psychiatric episodes following childbirth. In particular, we focused on early adverse life events that mainly, but not exclusively, involved parental psychopathology and disability. Further, we assessed a range of disorders observed postpartum, including postpartum psychosis, depression and acute stress reactions specifically. Using information from nationally inclusive registers, the aims of this present work were to a) describe the associations between early childhood adversity and postpartum psychiatric episodes and b) to investigate the impact of number of events to assess for a dose-response effect on onset of postpartum psychiatric episodes.

Methods

Study design

We designed an epidemiological population-based cohort study to examine if girls experiencing adverse life events in childhood and adolescence are at increased risk of postpartum psychiatric episodes after they become mothers. For this purpose, 482,295 women born in Denmark to Danish-born parents between January 1980 and December 1998 were found. Of these, 387,763 did not give birth, 31 had their first child before age 15, and 9,421 were diagnosed with a psychiatric illness before having their first child. Among the remaining 85,080 women, we identified 129,439 childbirths between 1995 and 2012. The follow-up time started at time of childbirth and follow-up ended 182 days later, at date of first recorded postpartum mental disorder (any diagnoses between 0-182 days/6 months postpartum, at date of emigration, or date of death, whichever ever came first. Women who gave birth before age 15 years were excluded from the study. Childbirths with records of psychiatric diagnoses before the birth were also excluded from the study to ensure that postpartum psychiatric episodes were incident episodes (first-time psychiatric diagnoses).

Linkage of relevant population register data was ensured through a personal identification number assigned to all citizens in Denmark. For the present study, we linked each child to legal parents through The Central Registration System, a register that holds updated information on vital status, migration and links to family members. All diagnoses are recorded using ICD-8 codes until 1994, and ICD-10 codes from 1994 and onwards. For the present study the included information came from a range of data sources/population registers. Note, as various population registers were initiated at different time points, we defined our study population by including women born 1980 or later, to ensure as complete exposure information as possible.

Exposure definition: Early Adverse Life Events

We defined the main exposure variables as a panel of various early life events in children from 0 to 15 years. Using the Danish population registers, the selected various early adverse life

events were mainly those that involved parental psychopathology and disability and included the following: (1) family disruption, (2) parental somatic illness, (3) parental labor market exclusion, (4) parental criminality, (5) parental death, (6) placement in out-of-home care, and (7) parental psychopathology excluding substance use disorders and (8) parental substance use disorder as in previous studies from our group (Bergink et al., 2016; Dahl et al., 2017). For all identified adversities we used information on specific dates for each adversity and focused on the first record of any of the adversities/exposures in each child in the cohort.

Familial disruption was considered to be any other household composition than the cohort member living with both legal parents (Pedersen, 2011). Please note that records of other included adversities such as placement in out-of-home care, parental death, or parental imprisonment per definition meant that the individual cohort member was not sharing an address with both legal parents, and consequently these were not included in the definition of familial disruption in particular to avoid any misclassification.

The Charlson Comorbidity Index (CCI) composed the underlying basis for assessing **parental chronic somatic disorders** (Thygesen, Christiansen, Christensen, Lash, & Sorensen, 2011). Only diagnosis assigned point values according to the CCI were defined as an exposure. Furthermore, we excluded all parental psychiatric diagnoses used in the CCI since these were already encompassed in records of parental psychopathology. First registered admission as either in- or outpatient with any CCI diagnosis in The National Patient Register (Lyng, Sandegaard, & Rebolj, 2011) was regarded an exposure.

Using data from the register on Integrated Database for Labour Market Research (IDA) (Petersson, Baadsgaard, & Thygesen, 2011) we assessed **parental labour market exclusion**. Exposure was first record of the parent being excluded from the workforce. Note

our definition only included variables indicating a permanent exclusion from the work force, which mainly were records of disability pension.

Parental imprisonment was assessed through The National Crime Register held by Statistics Denmark. Unconditional sentences according to The Danish Penal Law, the Law on Psychedelic Drugs, the Offensive Weapons Act, and the Law on Drink Driving was included as an exposure of adversity.

Records on **parental death**, including both natural and unnatural cause of death were obtained through The Danish Civil Registration System(Pedersen, 2011).

Records on placements in **out-of-home care** during upbringing were obtained through the register on Support for Marginalized Children and Adolescents, and included information on placement among others in family foster care, network foster family, 24-hour care centre, and boarding schools.

Parental psychopathology was defined as a parent's first registered admission as an in- or outpatient with any psychiatric diagnosis (ICD-8: 290-315; ICD-10: F00-F99) in The Psychiatric Central Research Register(Mors, Perto, & Mortensen, 2011) Further subgroups were defined to explore possible effects of substance use specifically: Parental psychopathology excluding substance use (ICD-8: 291.x9, 294.39, 303.x9, 303.20, 303.28, 303.90, 304.x9, ICD-10: F10-F19, and substance use as a separate category.

Outcome definition: Postpartum psychiatric disorders

The outcome of interest in this study was first occurrence of an in- or outpatient contact 0-6 months (0-182 days) postpartum at a psychiatric treatment facility with any psychiatric diagnoses, ICD-8 290-315 or ICD-10 F00-F99. We further examined subtypes of postpartum

psychiatric disorder based on three groups: postpartum depression (ICD-10: F32-F33 excluding F32.3), postpartum psychosis (ICD-10: F20, F23, F25, F28-F31, and F32.3) and postpartum acute stress reaction (ICD-10: F43). Data on diagnoses were obtained through The Danish Psychiatric Central Research Register²².

Statistical Analyses

We conducted survival analyses using Cox proportional hazard regression and estimated the main outcome measure with hazard ratios (HRs). Time since childbirth was treated as the underlying time axis, and all estimates were adjusted for age as a time-dependent variable in five-year intervals and birth number (1st birth, 2nd or higher birth). Further adjustments were made for clustering (individual women giving birth multiple times during the study period). We also examined the association of early adverse life event by subtype of postpartum psychiatric disorder based on three groups: postpartum depression, postpartum psychosis and postpartum acute stress reaction. For all analyses the reference group was mothers not exposed to any of the defined early life events during upbringing. To evaluate the effect of an increasing number of different adversities on disease risk, cohort members were grouped according to number of adversities experienced. Each adversity was assessed at first date of the adversity of interest and the analyses of numbers of adversities subsequently described the effect of experiencing 0, 1, 2 or 3+ different adversities until age 15. To present absolute risks of postpartum psychiatric episodes, we calculated cumulative incidences for disease onset for number of early life adversities by competing risk regression with death as the competing event. All analyses were conducted using Stata statistical software, version 13 (StataCorp)²⁵.

Results:

Using the Danish population registers, we examined all women who were born in Denmark from 1980 to 1998 and gave birth in Denmark between January 1995 and December 2012.

There were 129,439 childbirths by 85,080 women (Table 1), and the mean age at birth of first child for these women was 23.95 (SD=3.51).

More than half of the entire study sample (~52%) experienced some form of an early adverse life event, mainly in the form of parental psychopathology and disability. The types of childhood adverse life events and risk for any type of postpartum psychiatric disorders are presented in Table 2. The greatest risks for any type of postpartum psychiatric episodes were observed with history of placement in out-of-home-care (HR=2.57; 95% CI: 1.90-3.48), parental psychopathology excluding substance abuse (HR=1.90; CI: 1.44-2.50), parental labor market exclusion (HR=1.63; 95% CI 1.26-2.10, and parental somatic illness (HR=1.56; 95% CI 1.26-1.94).

The findings by specific subtype of postpartum psychiatric illness were similar to those observed for the overall group of any type of postpartum psychiatric disorder (Table 2). For example, a history of placement in out-of-home-care was associated with the greatest risk for both developing postpartum depression HR=2.15; 95% CI: 1.27-3.64, and postpartum acute stress reaction HR= 3.02; 95% CI: 1.89-4.81. Adverse life history of parental psychopathology excluding substance abuse was associated with the second greatest risk for the subtypes of postpartum depression HR=1.67; CI: 1.06-2.65, and postpartum acute stress HR=1.72; 95% CI: 1.08-2.76. Across all studied adversities, we did not observe an increased risk of postpartum psychosis.

In addition, we also mutually adjusted results for early life adversity and subsequent risk of postpartum psychiatric episodes. These results are presented in Table 3, and take into account the potential correlation of individual effects of the single adversities, adjusted for any additional effects of correlated adversities. As expected all results were attenuated when compared to the effect sizes presented in Table 2, which suggests at least some of the adversities are correlated.

We also observed a cumulative effect (ranging from 0.4% to 0.8%) whereby the number of childhood adverse events was associated with increased risk of postpartum psychiatric episodes jointly with a threshold effect (Figure 1). Women who experienced two adverse life events had the greatest risk for onset of overall postpartum psychiatric episodes (HR=1.88; 95% CI 1.51-2.36) as well as by subtype of postpartum psychiatric disorder for both postpartum depression (HR= 2.02; 95% CI=1.44-2.83) and postpartum acute stress reaction (HR=1.92; 95% CI=1.33-2.77, Table 2). This risk was markedly higher than having zero or one adverse life event for overall postpartum psychiatric episodes (HR=1.24; 95% CI 1.03-1.49), which was also observed by subtype of disorder.

Discussion:

In the Danish population-based registers, we examined if girls experiencing adverse life events in childhood and adolescence due to parental psychopathology and disability are at increased risk of postpartum psychiatric episodes following childbirth. To our knowledge, this study is the largest to date that has examined this question, and our findings suggest significant associations between various childhood adverse life events and the development of postpartum psychiatric episodes.

Our findings demonstrated that a greater number of early adverse life events is associated with increased risk of postpartum episodes with an observed dose-response effect, from 0 to 1 and 2 records of adversities, which has been shown for MDD in general, but rarely for postpartum psychiatric episodes (Perry et al., 2016). This finding was observed for any type of postpartum psychiatric as a group and by subtype of disorder, except for 3 or more adversities, which may be due to limited statistical power based on few observations. Our findings also demonstrate that some of the adversities are correlated, since our results were attenuated when comparing to the effect sizes presented in Table 2 versus the mutually adjusted results in Table 3.

Nonetheless, we did observe a persistent effect of ACE on risk of postpartum psychiatric episodes with a dose-response effect and believe this is the first paper to report on this finding in perinatal mood disorders using a large population based cohort. The negative experience of sustaining multiple adverse life events throughout childhood could result in multiple biologic changes by increasing allostatic load, or the cumulative stress on the body that is a sum of lifetime stress exposure(Geronimus, Hicken, Keene, & Bound, 2006). Possible explanations for this could be lasting alterations of the hypothalamic pituitary adrenal stress axis reactivity(Wilkinson & Goodyer, 2011), and other biologic changes including epigenetic modification(Perroud et al., 2011), persistent alterations in transcriptional control of stress-responsive pathways(Schwaiger et al., 2016), and shortened telomere length(Vincent et al., 2017).

For 68,351 childbirths in the entire cohort and more than half of the study population the mothers giving birth had records of at least one childhood adversity during childhood and adolescence, demonstrating the high prevalence of early adverse life events in the general population. Among these 651 women subsequently developed a postpartum psychiatric episode, which confirms previous findings that childhood adversity is a risk factor for postpartum psychiatric illness(A. Plaza et al., 2012; Records & Rice, 2009). Since the experience of childhood adversity is unfortunately relatively common, a history of a childhood adversity has a low positive predictive value for the later onset of a postpartum psychiatric episode. Before our findings and those from previous work identifying risk factors for postpartum psychiatric disorders can be translated into any routine clinical practice recommendations for screening purposes, we need to increase our understanding of why some women develop psychiatric illness following childbirth, whereas others do not. Current knowledge suggests a two-hit model whereby underlying genetic vulnerability in combination with environmental stressors triggers the onset of psychiatric illness(Lesse, Rether, Groger,

Braun, & Bock, 2016). Future work that integrates epidemiological and genetic risk will lead to greater clarification of etiology, nosology and risk status that may in the future lead to meaningful prediction tools for application in clinical settings.

In particular, our results indicate that parental psychopathology and disability have a significant contribution on whether a woman will develop a postpartum psychiatric episode. This is likely due to both the genetic loading that comes from having a parent with mental illness, in addition to the environmental exposure associated from living with a parent with psychopathology and disability. Thus, parental history of onset of psychopathology following childbirth supports the genetic hypothesis for psychiatric illness in general. But, it is also consistent with recent work demonstrating increased heritability of perinatal mood disorders in particular (Viktorin et al., 2016). Consequently, the growing literature on using polygenic risk scores to construct a diathesis-stress model are of great interest to increasing our understanding the vulnerability or risk of developing depression or other psychiatric disorders. For example, recent work demonstrates an extra risk for individuals with combined genetic vulnerability and high number of reported personal life stressors beyond what would be expected from the additive contributions of these factors to the liability for depression, supporting the multiplicative diathesis–stress model for depression in general. Further, this work suggests that the underlying causes of depression may differ for men versus women. (Colodro-Conde et al., 2017). Therefore, while parental psychopathology serves as marker for a genetic vulnerability to psychiatric disorders and depression in general, it is, also an important marker of environmental stress for the individual girl who likely was raised in a more stressful environment. In addition, women may have increased vulnerability for depression in general due to genetic risk. Therefore, future work will need to tease apart these contributions and will require both robust genetic and environmental data to examine polygenic risk in postpartum psychiatric disorders.

As for all studies, our results should be considered in the light of the following limitations: First, our study does not include childhood adverse life events of sexual and physical abuse as the numbers of reported cases in the Danish registers were too small to include and there are specific restrictions under Danish law, to report results only when no individuals can be recognized. Second, as we have described, the adverse events identified using the Danish registers are primarily those associated with parental psychopathology and disability. Third, The register data does not allow for determination of precise timing of when any particular adversity may have negatively influenced the lives of the individual children. Fourth, we had limited power to explore differences of all specific types of postpartum psychiatric episodes; specifically for postpartum psychosis, which has been shown to have distinctly lower prevalence but is relatively rare and is often considered part of a bipolar spectrum (Bergink et al., 2012; Di Florio et al., 2013). Our definition of postpartum psychiatric episodes was based on records of in- or outpatient hospital psychiatric treatment by a specialist. Primary care visits were not included in this analysis. Therefore, our results may not directly translate to milder forms of postpartum psychiatric episodes, including e.g. mild to moderate episodes of postpartum depression that would have initially presented to a primary care provider. It is important to note that the prevalence of postpartum episodes in register based data is markedly less than reported in general prevalence studies of postpartum women using patient self-report forms such as the Edinburgh Postnatal Depression Scale (EPDS) (Cox, Holden, & Sagovsky, 1987). Fifth, we did not examine comorbidity with posttraumatic stress disorder. However, in contrast to the limitations mentioned above, our study is the biggest to date on this topic, and does not rely on self-report of adverse life events but rather is population register-based information, thereby limiting bias and confounding.

Conclusion: The experience of childhood adverse life events primarily due to parental psychopathology and disability contributes to increased risk for onset of postpartum psychiatric

episodes. Further, the experience of greater numbers of adverse events increases the risk for postpartum psychiatric illness with an observed dose-response effect. Future work in the area of early adverse life events and postpartum psychiatric episodes should focus on the interaction between genetic and environmental factors that increase risk and/or confer resilience.

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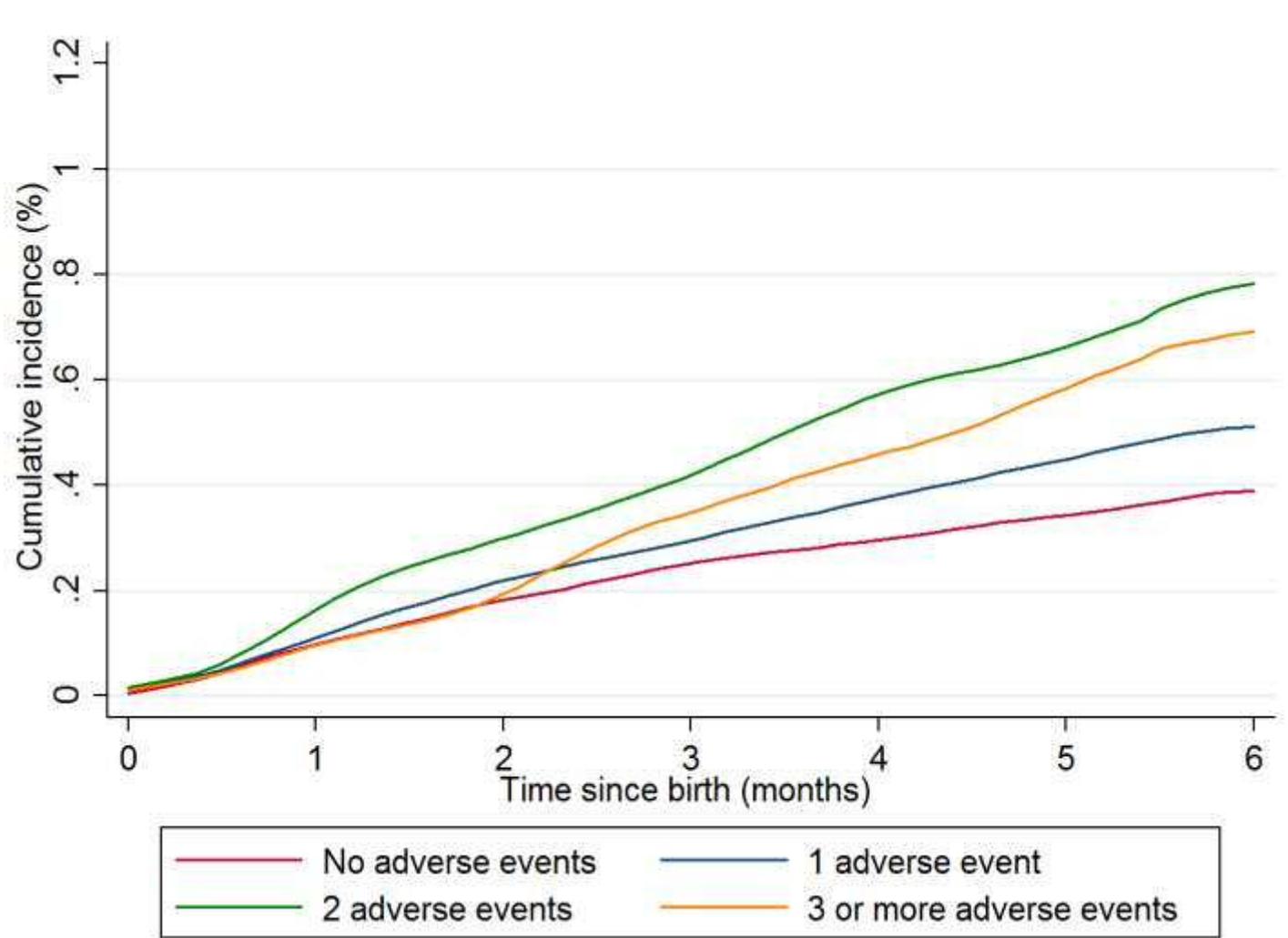
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Figure 1. Cumulative incidence of any postpartum psychiatric diagnosis by number of different adversities experienced at age 0-15 years.



Cumulative incidence calculated using competing risk regression with death as competing event.

Table 2. Hazard ratios (HR) and 95% confidence intervals (CI) for postpartum psychiatric episodes for each type of adversity.

	Any postpartum psychiatric diagnosis	Postpartum depression	Postpartum psychosis	Postpartum acute stress reaction
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Exposure to adverse event				
Family disruption	1.44 (1.21-1.72)	1.34 (1.02-1.77)	0.99 (0.41-2.37)	1.42 (1.06-1.90)
Parental somatic illness	1.56 (1.26-1.94)	1.54 (1.10-2.17)	1.00 (0.35-2.86)	1.51 (1.05-2.17)
Parental labor market exclusion	1.63 (1.26-2.10)	1.27 (0.81-1.98)	1.56 (0.52-4.63)	1.60 (1.05-2.42)
Parental criminality	1.43 (1.07-1.90)	1.14 (0.70-1.87)	0.37 (0.05-2.85)	1.38 (0.86-2.22)
Parental death	1.25 (0.82-1.93)	0.95 (0.44-2.06)	N/A	1.34 (0.67-2.67)
Placement in out-of-home care	2.57 (1.90-3.48)	2.15 (1.27-3.64)	1.48 (0.31-7.12)	3.02 (1.89-4.81)
Parental psychopathology excl. SUD	1.90 (1.44-2.50)	1.67 (1.06-2.65)	0.91 (0.20-4.10)	1.72 (1.08-2.76)
Parental substance use disorder	1.47 (0.97-2.21)	1.46 (0.76-2.82)	N/A	1.04 (0.48-2.26)
Number of adverse events				
0	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
1	1.24 (1.03-1.49)	1.26 (0.95-1.67)	0.84 (0.35-2.05)	1.25 (0.92-1.71)
2	1.88 (1.51-2.36)	2.02 (1.44-2.83)	1.49 (0.53-4.17)	1.92 (1.33-2.77)
3 or more	1.62 (1.23-2.12)	1.00 (0.59-1.71)	0.72 (0.16-3.32)	1.51 (0.97-2.37)

The comparison group is persons who were not exposed to any adversity. Adjusted for time since childbirth, age in five-year intervals and birth number (1st birth, 2nd or higher birth).

Out of the 651 postpartum psychiatric diagnoses, 122 were diagnosed with disorders not included in the three postpartum subcategories.

For postpartum psychosis there were too few exposed cases in four of the adversity categories to reliably estimate hazard ratios.

Table 3. Hazard ratios (HR) and 95% confidence intervals (CI) with mutually adjusted results for early life adversity and risk of postpartum psychiatric episodes

	Any postpartum psychiatric diagnosis	Postpartum depression	Postpartum psychosis	Postpartum acute stress reaction
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Exposure to adverse event				
Family disruption	1.23 (1.05-1.44)	1.14 (0.89-1.48)	0.98 (0.43-2.23)	1.20 (0.92-1.56)
Parental somatic illness	1.26 (1.03-1.55)	1.38 (0.99-1.91)	1.04 (0.35-3.06)	1.19 (0.84-1.66)
Parental labor market exclusion	1.10 (0.86-1.41)	0.87 (0.56-1.36)	1.98 (0.70-5.63)	1.09 (0.73-1.63)
Parental criminality	0.99 (0.74-1.32)	0.83 (0.49-1.38)	0.36 (0.05-2.37)	0.95 (0.58-1.54)
Parental death	0.82 (0.53-1.26)	0.64 (0.30-1.39)	N/A	0.89 (0.44-1.79)
Placement in out-of-home care	1.94 (1.42-2.63)	1.82 (1.05-3.15)	1.94 (0.45-8.35)	2.49 (1.54-4.03)
Parental psychopathology excl. SUD	1.41 (1.05-1.89)	1.33 (0.79-2.23)	1.11 (0.26-4.67)	1.32 (0.82-2.13)
Parental substance use disorder	0.76 (0.48-1.20)	0.95 (0.44-2.09)	N/A	0.52 (0.23-1.20)

The comparison group is persons who were not exposed to any adversity. The results are mutually adjusted and adjusted for time since childbirth, age in five-year intervals and birth number (1st birth, 2nd or higher birth).

Out of the 651 postpartum psychiatric diagnoses, 122 were diagnosed with disorders not included in the three postpartum subcategories.

For postpartum psychosis there were too few exposed cases in four of the adversity categories to reliably estimate hazard ratios.