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Association of severe childhood infections with depression and intentional self-harm in adolescents and young adults

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ABSTRACT

Early-life infections have been linked with subsequent depression and self-harm. Examination of specific groups of infections and the role of familial factors may elucidate this observed relationship. We addressed these considerations in our investigations of the association of severe childhood infections with the risks of depression and self-harm in adolescence and early-adulthood. This population-based cohort study included all individuals born in Sweden between 1982 and 1996, with follow-up through 2013 (N = 1,506,070). Severe childhood infections were identified using inpatient and outpatient diagnoses from birth through age 12. Any infection as well as specific groups of infections were investigated. We examined diagnoses of depression and self-harm within inpatient and outpatient care and death by self-harm between ages 13 and 31. Cox proportional hazards regression models were used to estimate absolute risks, hazard ratios (HRs), and 95% CIs. When adjusting for sex and birth year, individuals exposed to any childhood infection demonstrated increased absolute risk differences for both outcomes (2.42% [95% CI, 0.41–4.43%] of being diagnosed with depression up until age 31, and 0.73% [−2.05% to 3.51%] of self-harm up until age 31) and increased relative risks (HR, 1.22 [1.20–1.24] for depression and HR, 1.29 [1.25–1.32] for self-harm). When controlling for unmeasured factors shared between family members by comparing discordant siblings, no strong association persisted. Our findings show that childhood infections may not be involved in the etiology of later depression and self-harm, and highlight the importance of identifying these genetic and environmental familial risk factors, which may serve as targets for interventions.

1. Introduction

Accumulating evidence suggests that infections, inflammatory response, and the immune system are associated with increased risks of depression (Benros et al., 2013; Köhler et al., 2017; Miller and Raison, 2016) and suicide (Lund-Sørensen et al., 2016; Brundin et al., 2017; Brundin et al., 2015; Hansen et al., 2019). While certain infectious agents reach the central nervous system directly (Okusaga et al., 2011; Yagmur et al., 2010; Zhang et al., 2012; Arling et al., 2009), others may affect the brain by altering the microbiome (Cryan and Dinan, 2012) or through innate immune system activation and inflammatory mediators (Setiawan et al., 2015; Dando et al., 2014). C-reactive protein, interleukin 6, and tumor necrosis factor are some of the inflammatory biomarkers which could cross the blood–brain barrier and potentially influence brain function. Their concentrations are often elevated in serum of patients with depression (Haapakoski et al., 2015; Dowlati et al., 2010), patients with high ratings of suicidal ideation (O'Donovan et al., 2013), and individuals who attempted suicide (Gabbay et al., 2009; Janelidze et al., 2011). Increased levels of interleukin 6 during childhood have been associated with higher risk of depression later in life (Khandaker et al., 2014). Additionally, PET imaging has revealed neuroinflammation in patients with depression (Setiawan et al., 2015; Richards et al., 2018; Setiawan et al., 2018; Holmes et al., 2018), while analyses of postmortem brain samples showed increased messenger RNA levels of inflammatory molecules in patients who died by suicide (Tonelli et al., 2008; Pandey et al., 2012). In addition to activation of the

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innate immune system and increased proinflammatory markers, multiple studies have reported that some patients with depression also display relative suppression of the adaptive immune system (Leday et al., 2018), which may potentially be linked to increased vulnerability for (re) infection in these individuals.

Exposure to infections during childhood could have a greater influence on depression and self-harm risks. As the central nervous system and the immune system continue to develop throughout childhood (de Graaf-Peters and Hadders-Algra, 2006; Holt and Jones, 2000), insults during this period could lead to disruptions in brain and immune system maturation, potentially impairing biological mechanisms involved in the etiology of depression and suicidal behavior (Du Preez et al., 2016). Moreover, because specific developmental processes occur at different ages during youth (de Graaf-Peters and Hadders-Algra, 2006), there might be sensitive time points throughout childhood at which infections could be more harmful.

Prior research has linked infections of the central nervous system during childhood with schizophrenia and other psychotic illnesses (Blomström et al., 2014; Khandaker et al., 2012). A Danish study of children and adolescents showed that treated infections were associated with a higher risk of subsequent affective disorders, including mania, bipolar disorder, and depression (Köhler-Forsberg et al., 2019). However, the specific association between infections and depression was not explored. Furthermore, the study investigated infection exposure at any point before adulthood, although infections during childhood may differ from the ones during adolescence in their effect on the developing body.

It is essential to examine whether a relationship between early-life infections and later depression and self-harm exists and, if it does, whether it is likely to be causal or if it could be explained by other mechanisms. For instance, there could be an increased vulnerability to infections among children who will later develop depression due to an underlying social or familial/genetic susceptibility to immune insults and/or subsequent inflammatory processes compared with the general population.

We investigated the association of severe childhood infections with later depression and self-harm, exploring the role of specific groups of infections, possible sensitive periods, and the effect of familial influences.

2. Methods

2.1. Data sources and study cohort

Data were obtained by linking several national Swedish registers through unique personal identity numbers (Ludvigsson et al., 2009). From the Medical Birth Register (Axelsson, 2003), we established a cohort of all children born in Sweden between 1982 and 1996, excluding still-births, individuals with severe congenital malformations, and children who died neonatally. We linked this information to the National Patient Register (NPR) (Ludvigsson et al., 2011; Sellgren et al., 2011; Ekholm et al., 2005), the Cause of Death Register (Brooke et al., 2017), the Total Population Register (Ludvigsson et al., 2016), the Multi-Generation Register (Ekbom, 2011), and the Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA) (Ludvigsson et al., 2019). We excluded 12,777 (0.8%) individuals who received a diagnosis of schizophrenia, schizoaffective disorders, bipolar disorder, or mania during the study period (see Supplementary Table A.1 for a complete list of *International Classification of Diseases,* ICD, codes). This was performed in an attempt to limit the sample to those who suffered from depression as the primary disorder rather than manifesting depressive symptoms as part of another mental illness. The resulting cohort consisted of 1,506,070 participants, with follow-up from birth until the occurrence of an outcome (i.e., depression or self-harm), death, emigration, or December 31, 2013, whichever occurred first, with the youngest cohort members censored at age 17 and the oldest at 31 years. This study was approved by the Regional Ethics Review Board in Stockholm, Sweden, necessitating no informed consent.

2.2. Assessment of severe infections

Patients with infections during childhood were identified from the NPR, using inpatient and outpatient diagnoses. Since no information from primary care was available, we likely captured the most serious cases, and therefore, refer to these conditions as severe infections. We investigated any infection as well as specific groups of infections (i.e., nervous system, gastrointestinal, genitourinary, respiratory, sepsis, skin) between ages 0 and 12, including the first-time diagnosis within each group of infections, irrespective of prior infection diagnoses. A complete list of all ICD codes is shown in the Supplementary Table A.2.

2.3. Assessment of depression and Self-Harm

Since depression is rarely diagnosed prior to early adolescence (Leone et al., 2021), we investigated depression with an onset during adolescence or early adulthood, which was defined has having received at least one inpatient or outpatient depression diagnosis from age 13 (*ICD*-9 codes 296B and 311; *ICD*-10 codes F32 and F33). Considering that the majority of psychiatric consultations for adult patients occurs in primary health care (~80%) (Sundquist et al., 2017), the use of inpatient/outpatient health registry data may limit the capture to the most severe depression cases among adult patients. Therefore, we conducted a sensitivity analysis in which we attempted to capture mild and moderate forms of depression managed in primary health care, by adding information on antidepressant prescriptions from the Swedish Prescribed Drug Register (Wettermark et al., 2007). This register was initiated in July 2005, and it contains information on prescribed and dispensed medicines classified according to the Anatomical Therapeutic Chemical (ATC) classification system. We included the first antidepressant prescription (ATC code: N06A) from age 13.

With respect to suicidal behavior, we identified all hospitalizations and specialist clinic contacts for intentional self-harm from age 13, as well as all deaths with self-harm as the primary cause (*ICD*-9 code E95; *ICD*-10 codes X60-X84 and X87.0).

2.4. Covariates

Attained age, sex, birth year, parental history of psychiatric illnesses (*ICD*-8: 290-315; *ICD*-9: 290-319; and *ICD*-10: F00-F99), and parental socioeconomic status (SES) were included as covariates. SES comprised information on highest parental educational level, parental unemployment and financial support from birth through age 18 of the child, as well as parental disposable income, which was divided into quartiles and calculated as the average between ages 9 and 11 of the child to account for year-to-year fluctuations.

2.5. Statistical analysis

We estimated absolute and relative risks of depression and self-harm from age 13 until the end of the follow-up. Absolute risks were calculated using the package stdReg (Sjölander, 2016). We computed cumulative incidences as the probability of receiving an outcome by attained age, while adjusting for sex and birth year. Absolute risk differences were calculated continuously throughout follow-up ages as the difference between children exposed and unexposed to infections. Relative risks were computed using Cox proportional hazards regression models with attained age as the underlying timescale (i.e., we compared individuals of the same age). We estimated hazard ratios (HRs) averaged over the entire duration of the follow-up for the outcome of interest, and

95% CIs. We adjusted for sex and birth year, performed sex-specific analyses, and used a robust (sandwich) estimator of standard errors, clustered by family, to account for non-independence between individuals in the same family (Williams, 2000).

When using Cox regression models, the assumption of proportional hazards between exposed and unexposed patients does not always hold (i.e., HRs may change over follow-up time). Since period-specific HRs have a built-in selection bias (Hernán, 2010), we explored how a consecutively increased follow-up time could influence the HRs. Thus, we allowed the follow-up time to increase by 1 year from age 13 to 31 (maximal follow-up time), and estimated time-updated HRs. To investigate whether temporal proximity between exposure and outcomes could influence the time-updated HRs, we performed a sensitivity analysis limiting the time of childhood infection between ages 0 and 8.

To investigate whether there are sensitive time periods throughout childhood during which infections could be more strongly associated with risks of depression/self-harm, we estimated HRs for several ages at infection (i.e., from birth through age 12, grouping infections in 1-year age bands). In these models, we compared individuals exposed to infections at each age (with and without adjustment for infections at any other time during childhood) to participants with no childhood infections.

Because the outpatient information in the NPR was introduced later (from 2001) compared with the inpatient information (since 1987), we performed a sensitivity analysis including only hospital contacts for infections, depression, and self-harm to compensate for the possible loss of early diagnoses within specialist clinics for the oldest individuals.

Finally, we evaluated the role of familial influences. First, we adjusted for parental psychiatric illnesses and SES using Cox regression. Then we conducted within-sibling analyses using stratified Cox regressions to adjust for unmeasured familial factors, thereby accounting for genetic and environmental risk factors shared by siblings; in these analyses, we excluded single-child families, and compared all full-siblings that were discordant for exposure to infections, while adjusting for sex and birth year (see Supplementary Methods A.1. for details on informative population).

All tests of statistical hypotheses were 2-sided and used a significance threshold of 0.05. Analyses were performed using R software, version 3.6.1 (R Foundation for Statistical Computing).

3. Results

3.1. Study population

The study population consisted of 1,506,070 individuals (48.7% female) born in Sweden between 1982 and 1996, with follow-up from birth through 2013. If no censoring occurred, age at the end of follow-up ranged between 17 and 31 years. In total, 338,251 individuals (22.5%; 44.7% female) had a hospital or outpatient contact for an infection between birth and age 12; 67,630 (4.5%; 63.3% female) participants received an inpatient or outpatient diagnosis of depression from age 13 to 31; 182,683 (12.1%; 62.7% female) received a depression diagnosis or an antidepressant prescription between ages 13 to 31 (Supplementary Table A.3); and 25,651 (1.7%; 64.6% female) were diagnosed with or died by intentional self-harm between ages 13 and 31. Details regarding the number of children exposed to each group of infections are given in Table 1. Information on hospital contacts is presented in the Supplementary Table A.4. Distributions of age at first ascertainment of exposures and outcomes are shown in the Supplementary Fig. A.1, A.2, and A.3.

3.2. Absolute risks

After accounting for demographic characteristics (age, sex, and birth year), severe infections from birth through age 12 were associated with increased absolute risks of receiving later diagnoses of depression (Fig. 1) and self-harm (Fig. 2). For example, when comparing individuals exposed to any childhood infection to the rest of the cohort, the absolute risk difference of being diagnosed with depression up until age 31 was 2.42% [95% CI, 0.41–4.43%]. This means that, if we had followed every participant until age 31, more than 36,000 additional individuals who experienced any early-life infection would be diagnosed with depression during adolescence or early adulthood, compared to the risk for depression in the general population. When including antidepressant prescriptions in the definition of depression, the absolute risk difference for individuals exposed to any childhood infection was considerably higher: 4.79% [95% CI, 3.89–5.68%] (Supplementary Fig. A.4). The absolute risk difference of self-harm following any childhood infection and up until age 31 was 0.73% [95% CI, −2.05% to 3.51%]. When investigating exposure to specific groups of infections during childhood and the risk of depression/self-harm, no major differences emerged. Sex-specific absolute risks are presented in the Supplementary Fig. A.5, A.6, and A.7.

Table 1
Number of individuals exposed and unexposed to childhood infections among the total cohort of 1,506,070 and among patients with depression or self-harm.

	Unexposed to Infection, No. (%)	Exposed to Infection, No. (%)	*P* value [a]
Any Infection			
Total cohort	1,167,819 (77.5)	338,251 (22.5)	NA
Depression	50,553 (4.3)	17,077 (5.0)	<0.001
Self-harm	18,946 (1.6)	6,705 (2.0)	<0.001
Nervous System Infections			
Total cohort	1,497,400 (99.4)	8,670 (0.6)	NA
Depression	67,194 (4.5)	436 (5.0)	0.02
Self-harm	25,478 (1.7)	173 (2.0)	0.04
Gastrointestinal Infections			
Total cohort	1,402,310 (93.1)	103,760 (6.9)	NA
Depression	62,063 (4.4)	5,567 (5.4)	<0.001
Self-harm	23,390 (1.7)	2,261 (2.2)	<0.001
Genitourinary Infections			
Total cohort	1,471,697 (97.7)	34,373 (2.3)	NA
Depression	65,662 (4.5)	1,968 (5.7)	<0.001
Self-harm	24,930 (1.7)	721 (2.1)	<0.001
Respiratory Infections			
Total cohort	1,298,494 (86.2)	207,576 (13.8)	NA
Depression	57,288 (4.4)	10,342 (5.0)	<0.001
Self-harm	21,551 (1.7)	4,100 (2.0)	<0.001
Sepsis			
Total cohort	1,501,063 (99.7)	5,007 (0.3)	NA
Depression	67,371 (4.5)	259 (5.2)	0.02
Self-harm	25,564 (1.7)	87 (1.7)	0.89
Skin Infections			
Total cohort	1,471,188 (97.7)	34,882 (2.3)	NA
Depression	65,982 (4.5)	1,648 (4.7)	0.03
Self-harm	24,995 (1.7)	656 (1.9)	0.01

Abbreviation: NA, not applicable.
[a] Significance testing of differences between exposed and unexposed individuals among the depression and the self-harm group, using the Pearson χ^2 test.

3.3. Relative risks

In the analysis adjusted for sex, and birth year, individuals exposed to any childhood infection had increased relative risks of both depression (HR, 1.22; 95% CI, 1.20–1.24) and self-harm (HR, 1.29; [1.25–1.32]) later in life. In particular, childhood sepsis was associated with the highest relative risk of depression (HR, 1.26; [1.11–1.42]), while gastrointestinal infections were associated with the highest HR of self-harm (HR, 1.32; [1.27–1.38]). Infection-specific and sex-specific

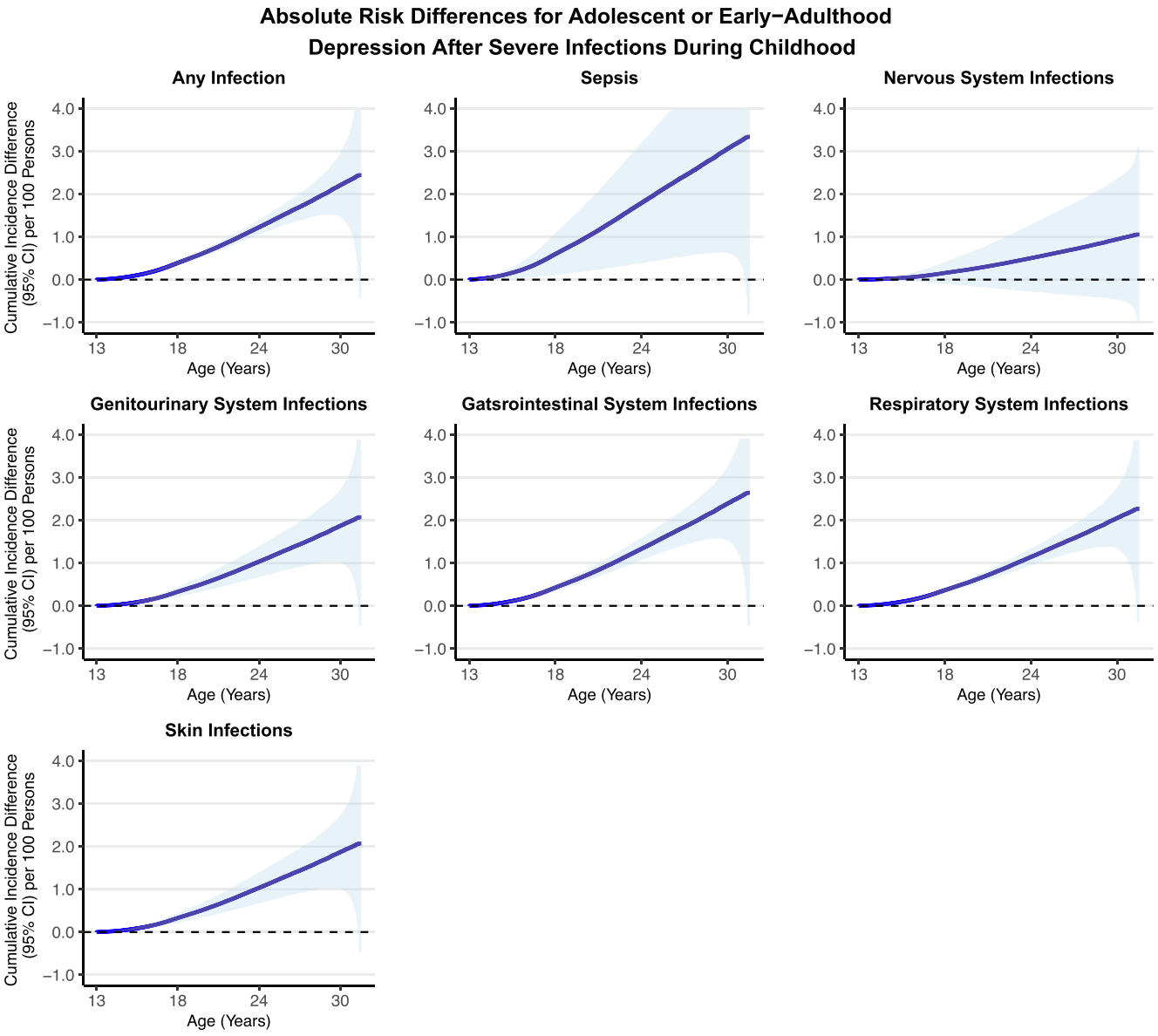

Fig. 1. Absolute risk differences for adolescent or early-adulthood depression after severe infections during childhood. Legend: Each panel shows the time-specific risk differences (calculated as the difference between cumulative incidences among children exposed and unexposed to severe infections) of depression from age 13 years up until age 31 years, following exposure to specific groups of infections during childhood. Some CIs are cut from the plots for visual purposes.

risks are summarized in the Supplementary Table A.5 and A.6. When expanding the definition of depression to antidepressant prescriptions, all relative risks attenuated (Supplementary Table A.7).

We fitted a series of time-updated HRs for increasingly longer periods of follow-up to evaluate whether age-specific changes in HRs impacted the overall HR in the Cox regression models (Supplementary Fig. A.8 and A.9). In these analyses, all relative risks appeared to be robust throughout increasing follow-up time, with a slight increase observed between ages 13–15. To investigate whether this could be explained by temporal proximity between exposure and outcomes, we performed a sensitivity analysis limiting the time of childhood infection between ages 0 and 8. In this analysis, all HRs were similar, regardless of the follow-up duration (Supplementary Fig. A.10 and A.11).

When investigating potential sensitive time periods by grouping infections in 1-year age bands, no major differences between infections during early compared to late childhood emerged (Supplementary Fig. A.12 and A.13).

To account for the later initiation of the outpatient register in the NPR, we performed a sensitivity analysis only using hospitalizations. Overall, compared to the estimates from the previous models, the HRs for depression slightly increased while the risks of self-harm remained similar (Supplementary Table A.8 and A.9).

3.4. *Familial risk factors*

Fig. 3 shows the relative risks of depression and self-harm among individuals exposed to specific groups of infections during childhood, comparing estimates from three different models. Compared to the regression model adjusted for sex and birth year, in the model further adjusted for parental psychiatric illnesses and SES all risks decreased, but most remained statistically significant. Finally, estimates from a third model are reported: using a within-sibling analysis, we compared full-siblings differentially exposed to early-life infections while adjusting for sex and birth year. In this model, all associations were further

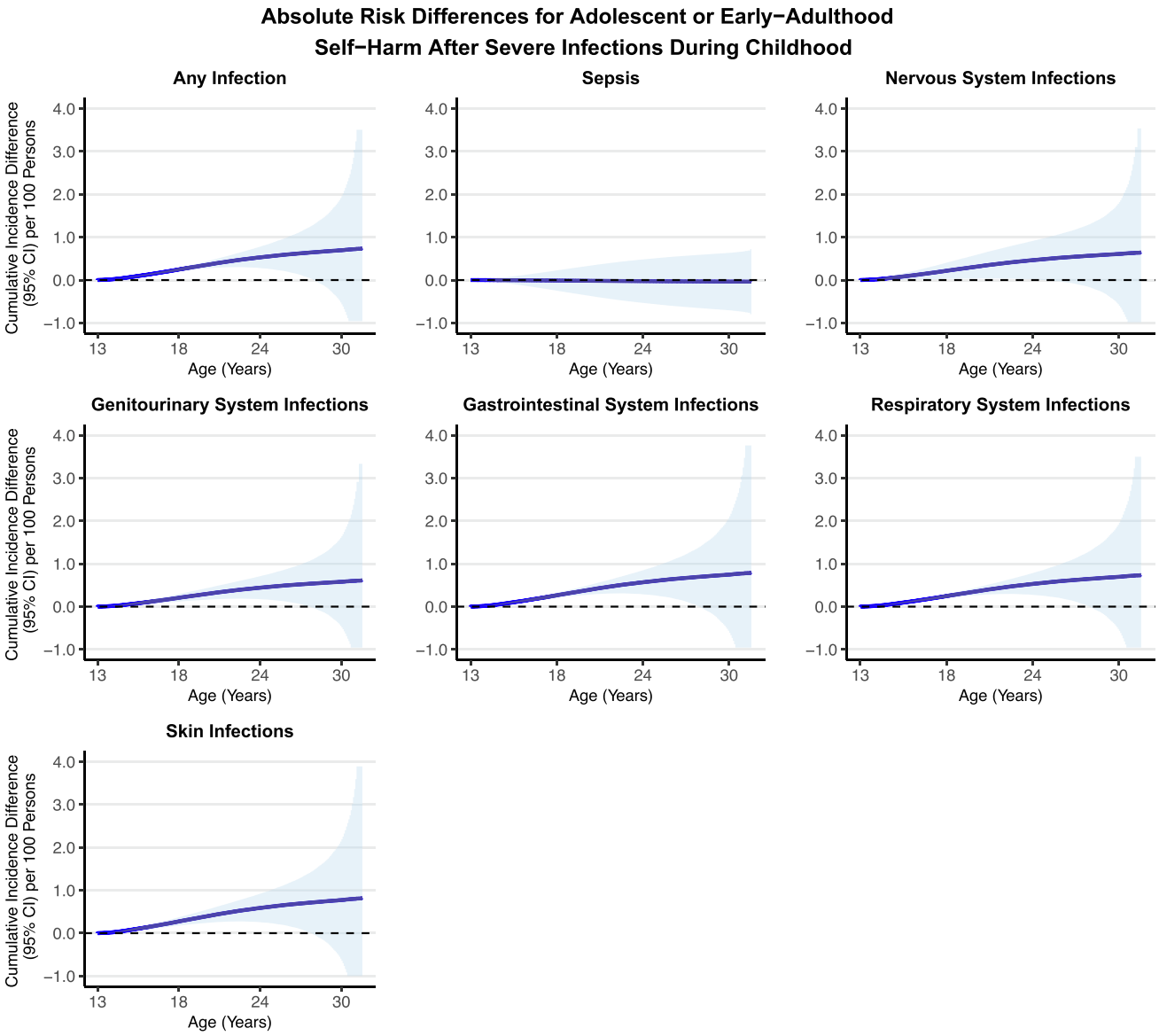

Fig. 2. Absolute risk differences for adolescent or early-adulthood self-harm after severe infections during childhood. Legend: Each panel shows the time-specific risk differences (calculated as the difference between cumulative incidences among children exposed and unexposed to severe infections) of self-harm from age 13 years up until age 31 years, following exposure to specific groups of infections during childhood. Some CIs are cut from the plots for visual purposes.

attenuated, mostly to non-significance, with the strongest association observed for gastrointestinal infections and self-harm (HR, 1.15; [1.04–1.27]).

4. Discussion

To our knowledge, this was the largest and most comprehensive study investigating the relationship between early-life infections and the risks of depression and self-harm during adolescence and early adulthood. In contrast with prior research exploring infections at any point before adulthood (Köhler-Forsberg et al., 2019; Goodwin, 2011), we exclusively focused on infections during childhood to explore exposures throughout early developmental years.

We observed increased absolute risks of depression and self-harm among participants exposed to early-life infections compared with the rest of the population. When investigating exposure to specific groups of infections, absolute risks were comparable, suggesting that infections across different organs and systems were similarly associated. In the sensitivity analysis including antidepressant prescriptions, all absolute risks considerably increased, reflecting the higher prevalence of depression cases when using this definition of depression.

When adjusting for demographic characteristics (age, sex, and birth year), increased relative risks of both outcomes following childhood infections were observed, with the strongest association found for gastrointestinal infections and self-harm. All relative risks attenuated when including antidepressants as a measure of depression, possibly reflecting the capture of less severe depression cases treated by physicians within primary health care.

We evaluated the estimates from the Cox regression models by calculating a series of average HRs for increasingly longer follow-up time. Our results showed that the associations between childhood infections and depression/self-harm did not vary substantially depending on how long we followed the cohort, except for a slight increase in early adolescence, possibly related to the temporal proximity of exposure and outcome and/or to an increased vulnerability to immune challenges during puberty. In fact, when limiting the time of infection between age 0 and 8 (i.e., removing the latest infections), we did not observe increased relative risks of depression/self-harm between ages 13 and 15.

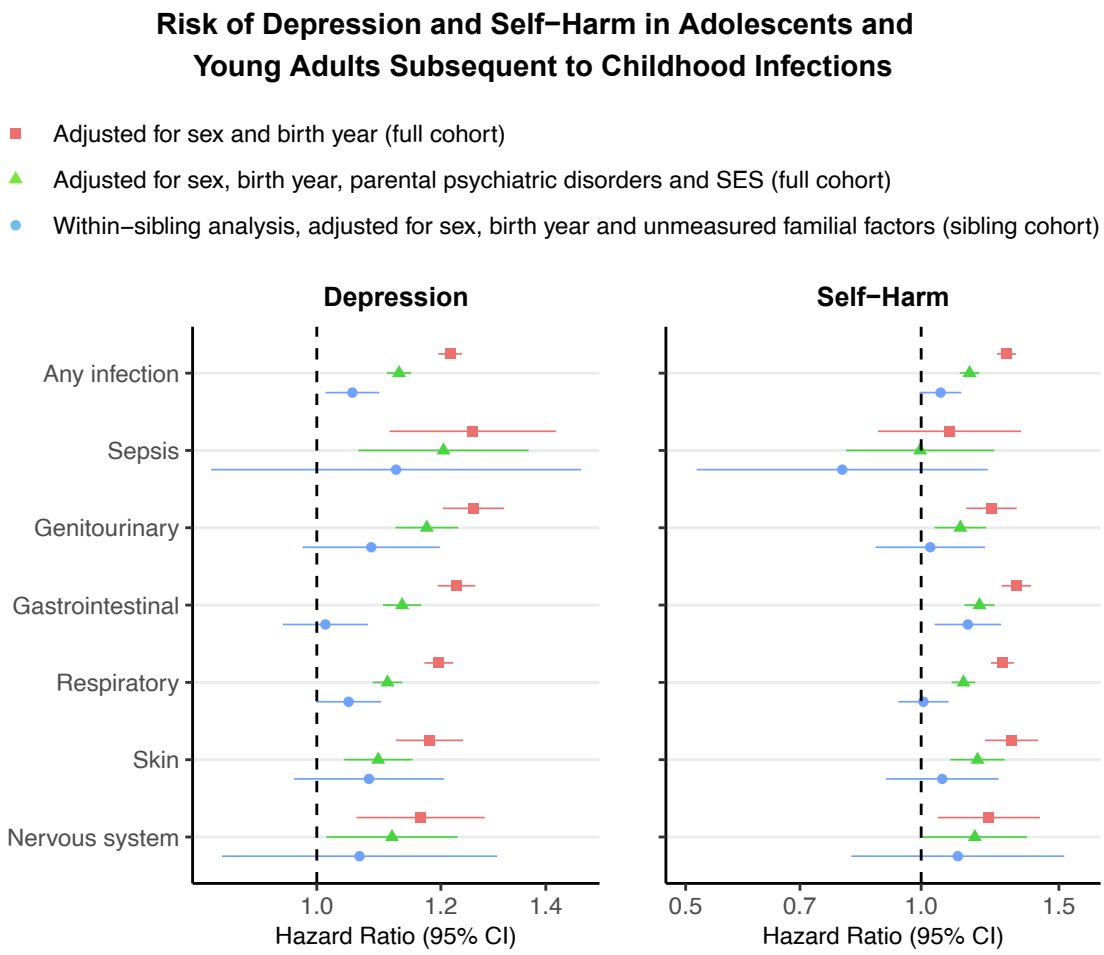

Fig. 3. Risk of depression and self-harm in adolescents and young adults subsequent to childhood infections. Legend: Relative risks of depression (left) and self-harm (right) between ages 13 and 31, following exposure to specific groups of infections during childhood. Hazard Ratios and 95% confidence intervals were estimated via Cox proportional hazards regression model with attained age as underlying timescale. Three models are compared: i) adjusted for birth year and sex (red squares), including the full cohort of 1,506,070 individuals; ii) further adjustment for parental psychiatric disorders and SES (green triangles), including the full cohort of 1,506,070 individuals; iii) within-sibling analysis adjusted for birth year and sex (blue circles), only including differentially exposed full-siblings (see Supplementary Methods A.1). The within-sibling design allows to adjust for unmeasured familial risk factors (i.e., genetic and environmental factors shared by siblings). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

To identify potential windows of vulnerability, we explored exposure to severe infections during 1-year periods from birth through age 12 and risk for later depression and self-harm. No strong evidence for sensitive periods emerged.

Because information for the oldest participants in our cohort was predominantly derived from hospital contacts, we performed a sensitivity analysis restricting the data to hospitalizations for infections, depression, and self-harm. In this analysis, relative risks of depression slightly increased, suggesting that mainly the most severe cases were captured. However, the HRs for self-harm remained similar to those including both inpatient and outpatient data. This is possibly explained by the fact that in our cohort, the majority of self-harm diagnoses were given within inpatient settings.

In the analyses adjusted for parental psychiatric illnesses and SES, all HRs were attenuated while mostly remaining statistically significant. This indicates that these measured parental factors could partially explain the observed associations by influencing risks of severe infections as well as later depression/self-harm, and substantiates previous research linking parental mood disorders and low SES to offspring's healthcare utilization (Dreyer et al., 2018), and poor physical and mental health (Leijdesdorff et al., 2017; Pierce et al., 2020; Mok et al., 2016; Hakulinen et al., 2020; Björkenstam et al., 2017; Hughes et al., 2017; Kivimäki et al., 2020). Several mechanisms could explain our findings. For example, it is possible that parents with low SES and/or psychiatric disorders are limited in their options to maintain a lifestyle that promotes good general health (Ridley et al., 2020), increasing the offspring risks for both severe childhood infections and later depression/self-harm. In addition, low parental SES has been linked with childhood adversity, which has harmful effects on physical and mental health of the offspring (Repetti et al., 2002). Thus, low parental SES may act as an indicator for several risk factors which, through biological and psychosocial mechanisms, could influence children's health outcomes (Jensen et al., 2017). Further research is needed to elucidate these complex pathways.

Finally, we conducted a full-sibling analysis. Because siblings share a higher amount of genetic and environmental factors than unrelated individuals, comparing siblings discordant for the exposure allows for adjustment of these shared, unmeasured factors (Merlo et al., 2010; Lahey and D'Onofrio, 2010). In this analysis, all relative risks were considerably attenuated and no strong association persisted, suggesting that familial influences may almost fully explain the associations between severe childhood infections and later depression/self-harm. Several explanations are possible. First, there could be a genetic liability for both poor mental health and immune dysregulation (e.g., dysfunction of innate and/or adaptive immune system), which could modify the body's ability to react to stressors (e.g., infections) and

increase the risk of depression/self-harm. For instance, compared to the general population, individuals with such underlying genetic predisposition may experience an enhanced proinflammatory activation of the peripheral innate immune system following infections, as well as an increased risk to develop depression/self-harm. Another hypothesis is that early-life infections may be an index of a dysfunctional adaptive immune system, reflecting an underlying vulnerability to (re)infections, of which reactive heightened inflammation may represent only an epiphenomenon. The genetic hypothesis is supported by studies highlighting the probable involvement of immune-related genes in the liability to depressive disorder and suicidality (Wray et al., 2018; Network et al., 2015; Kokkosis and Tsirka, 2020; Kappelmann et al., 2020). Second, immune dysregulation is associated with some but not all depressive symptoms, and only a subgroup of patients with depression exhibit an increased number of inflammatory markers. Evidence of symptom-specificity was also supported by recent genetic-informative studies, which reported association and coheritability between inflammation and certain symptoms of depression (Milaneschi et al., 2017; Badini et al., 2020; Kappelmann et al., 2021; Milaneschi et al., 2021). Therefore, investigating depressive disorder as one homogeneous outcome may have limited our ability to detect the association between childhood infection and later depression in a subgroup of the population. Examination of individual depression symptoms is an essential next step to better understand the role of infections, inflammatory response, and the immune system. Third, these unmeasured familial factors could partially represent residual confounding from parental psychiatric illnesses and SES, particularly since we were unable to capture parental psychiatric disorders diagnosed within primary care or those who never sought clinical care. Finally, it is possible that temporal proximity between exposure and outcome influences these associations. In this respect, the time lag between exposure during childhood and depression/self-harm onset during adolescence or early adulthood could weaken these associations.

4.1. Limitations

Despite several strengths, such as the large population-based sample, longitudinal data, comprehensive Swedish register information, and the application of sibling analysis, it is important to acknowledge several limitations. Given that our ascertainment of infections, depression, and self-harm was restricted to hospital-based and specialist outpatient diagnoses, we may have mainly captured severe cases for both exposures and outcomes, limiting the generalizability of the findings. We attempted to identify patients with mild or moderate depression managed within primary health care by including information on antidepressant prescriptions. However, studies show that less than 60% of antidepressant prescriptions are indicated for depression, while an increasing proportion is indicated for anxiety disorders, personality disorders, insomnia, pain, and panic disorders (Sundquist et al., 2017; Noordam et al., 2015; Wong et al., 2016). Therefore, this approach could have led to misclassification of some depression cases. Moreover, the Swedish Prescribed Register was initiated in July 2005, leading to a possible loss of early prescriptions for the oldest individuals in our cohort.

In the analysis of survival data, ignoring competing events such as death may lead to biased estimates of the cumulative incidence risks (i.e., absolute risks). However, since the present study was conducted on a young population (with less than 0.7% mortality during follow-up), the impact of death as a competing risk may have been minimal. Receiving a diagnosis of bipolar disorder may also represent a competing event, as it might prevent individuals from being diagnosed with depression. Nevertheless, these patients were excluded from our analyses at the initial cohort selection process.

In sibling comparison studies, estimates could be biased by non-shared confounders if discordant siblings are less similar with regard to such confounders than to the exposure. Additionally, the design assumes no carryover effects across the siblings, and sibling analyses are more sensitive to measurement error in exposure and outcome, which could lead to inappropriate attenuation of the associations (Frisell et al., 2012).

5. Conclusions

Associations between childhood infections and later depression or self-harm were largely influenced by familial factors. That is, genetic and/or environmental factors shared within families appear to be common causes of both childhood infections and later depression or self-harm. It is essential for future research to identify these familial factors as they may represent suitable targets for public health interventions aimed at improving both mental and physical health.

6. Role of the funding source

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7. Data availability

The authors are not permitted to share the data used in this study. However, researchers can access the data through application to the Swedish National Board of Health and Welfare (Socialstyrelsen) and to Statistics Sweden (Statistiska centralbyrån).

Declaration of Competing Interest

Ms. Leone is an employee of Johnson & Johnson. Dr. D'Onofrio reports grants from Swedish Research Council during the conduct of the study. Dr. Larsson has served as a speaker for Medice, Evolan Pharma and Shire/Takeda and has received research grants from Shire/Takeda, all outside the submitted work. Dr. Leval is an employee of and owns stock in Johnson & Johnson.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2021.10.004.

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