Infections as Risk Factors for Suicide – a Nationwide Cohort Study

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Background:

Findings suggest that infections play a substantial role in the development of psychiatric disorders as well as in suicidal behavior. Still, large-scale studies are needed to investigate the impact of infection on the risk of suicide.

Methods:

We utilized the Danish nationwide registers to longitudinally investigate the associations between hospital contacts with infections and death by suicide. We followed individuals aged 15 years or older living in Denmark during 1980-2011 (N=7,221,578). Logistic regression analyses were adjusted for sex, age, calendar period, cohabitation status, socioeconomic status, and the Charlson Comorbidity Index.

Results:

A prior hospital contact with infection was linked to an elevated risk of suicide (incidence rate ratio, 1.42, 95% confidence interval [CI], 1.38 to 1.46), compared to those with no contacts. Dose-response associations were observed with the number of hospital contacts with different infections and days of treatment with infection. Individuals diagnosed with seven or more infections had a relative risk of 2.90 (95% CI, 2.14 to 3.93) when compared to those without while more than three months of hospital treatment with infection was associated with a relative risk of 2.38 (95% CI, 2.05 to 2.76). The risk of suicide was highest in timely proximity to last infection ($p<0.001$). The population attributable risk accounted for 10.1%.

Conclusions:

An increased risk of dying by suicide was found among people with hospital contacts with infections in both temporal and dose-response associations. This indicates a larger effect of infections on suicidal behavior than previously thought.

BACKGROUND

Infection is one of the most common causes of illness in the World[1] and it is increasingly recognized that infection and inflammation can play a critical role in psychiatric disorders[2–6] as well as in suicidal behavior.[7–10] While psychological predictors of suicide, such as psychiatric disorders and suicide attempts,[11] have been examined many times there is a dearth of longitudinal studies investigating the impact of biological factors, such as infection.

Certain infectious agents affect primarily the brain, others reach the brain from periphery, and yet others generate molecular mediators of inflammation that are crossing from periphery into the brain and thereby increase the risk of suicide;[12] examples of these are influenza B virus[13] and the parasite Toxoplasma gondii, which have been linked to suicidal behaviour.[14–17] Inflammation might also lead to dysregulation of neuroactive kynurenine pathway metabolites[18,19] where some of these have been found to be altered in the cerebrospinal fluid (CSF) and blood from patients with suicidal behavior.[20,21] Also, post mortem brain samples of patients that died by suicide have shown reduced microglial QUIN-immuno-reactivity[22] and increased mRNA levels of inflammatory cytokines.[23,24] Elevated levels of peripheral inflammatory markers, such as cytokines, have been found in the blood of suicide attempters and patients with high suicidal ideation.[25–27] However, most of the previous studies have been restricted by small sample size and cross-sectional study designs.[9,13,15,20–27]

Suicide is a major health problem worldwide.[28] The neurobiology of suicidal behavior is in rapid development, but still there is a need for large-scale studies to examine the role of infection in suicide. In the present study, we used the Danish nationwide registers to longitudinally investigated the associations between infectious diseases and the subsequent risk of dying by suicide. In order to address possible causality, we examined risk of suicide associated with number of hospital contacts with different infections, number of days in treatment with infection, and time since the last hospital contact with infection.

METHODS

Study population:

All individuals born in Denmark who were alive during the study period were included in our analyses. The cohort consisted of 7,221,578 individuals aged 15 years and older from Jan 1st 1980 and followed until death, emigration from Denmark, disappearance, or Dec 31st 2011, whichever came first. The Danish Civil Registration System contains complete and continuously updated administrative data on all residents living in Denmark.[29] A unique personal identification number assigned to each person enables accurate and complete linkage between various national registries. Data were taken from the following registers: the National Hospital Register,[30] the Psychiatric Central Research Register,[31] and the Cause of Death Register.[32] After 1995, contacts on outpatient visits and visits to emergency units were included in the registers. Diagnoses were recorded according to the diagnostic system of the *International Classification of Diseases, 8th revision* (ICD-8) until January 1, 1994, from when ICD-10 codes were used. All registers have full national coverage and information from the registers is anonymized when used for research. The project was approved by the Danish Data Protection Agency.

Measures

A history of infection was defined as one or more diagnoses with infection listed in the National Hospital Register since 1977.[30] Infections were grouped as *any infection* and into subcategories including *type of infection*; i.e. bacterial, viral, and the remaining types of infections, as well as *site of infection*; i.e. sepsis, hepatitis, gastrointestinal, skin, respiratory, urological, genital, pregnancy-relate (among women), otitis media, central nervous system, and HIV/AIDS infections. All codes for included infectious diseases are listed as in previous studies.[2,3]

In addition, we assessed impact by *number of hospital contacts with different infections* (measured as different two-digit ICD-codes, for instance A40 and A41), *number of days in treatment with infection*

(measured as number of bed-days in hospital), and *time since last hospital contact with infections* (measured as days since discharge from hospitalization with infection).

Data on all psychiatric diagnoses were obtained from the Psychiatric Central Research Register[31] listing hospital contacts since 1968 and categorized as follows: affective disorders (ICD-8: 296, 298.09, 298.19, 300.49, 301.19, ICD-10: F30-F39) schizophrenia (ICD-8: 295, ICD-10: F20, F25) substance use disorders (ICD-8: 291, 303, 304, ICD-10: F10-F19) and the remaining types of psychiatric disorders except Y and Z –groups.

The outcome of interested was death by suicide; identified in the Cause of Death Register[32] as ICD-8: E950-E959 or ICD-10: X60-X84, Y87 or where the manner of death was listed as suicide.

Statistical analysis:

We used adjusted logistic regression models (Poisson regression) to calculate incidence rate ratios (IRRs) with 95% confidence intervals (CI). We measured the risk of suicide among individuals diagnosed with infection relative to individuals without infection. Risk estimates were obtained for different infection categories, including type of infection and site of infection, number of hospital contacts with different infections, number of days in treatment with infection, and time since last hospital contact with infections. In the basic model we adjusted for sex, age (14–year groups for 15 to 29 years, 19-year groups for 30 to 49 years, 14-year groups for 50 to 64, 14-year groups for 65 to 79 years, and ≥ 80 years), and calendar period (9-year groups from 1980 to 1989, 9-year groups from 1990 to 1999, and 11-year groups from 2000 to 2011). In the fully adjusted model we further adjusted for cohabitation status (cohabitation, no cohabitation), socioeconomic status (working, unemployed, disability pension, early retirement, student, and others), and the Charlson Comorbidity Index (none, 1+ chronic disorders).[33] To further investigate causality, we examined risk of suicide in relation to timing of infection and psychiatric disorders. We also

calculated the population attributable risk (PAR).[34] The formula for PAR; = (P_e (RR_e – 1)) / (1+P_e (RR_e – 1)), where P_e is the prevalence of exposure and RR_e is the relative risk of disease due to that exposure.

We conducted a sensitivity analysis by restricting the sample to persons born after 1962, for which complete lifetime follow-up on hospital contacts with infections from the age of 15 was available. In a second sensitivity analysis, the sample was restricted to persons with no previous psychiatric diagnosis.

RESULTS

The cohort consisted of 7,221,578 individuals observed for a total of 149,061,786 person-years. During the follow-up period, 809,384 (11,2%) individuals had a hospital contact with infection. A total of 32,683 suicides were observed over the follow-up period: of those 7,892 (24.1%) individuals had previously been diagnosed with an infection during a hospital contact.

In the fully adjusted model, the relative risk of suicide among individuals with any infection was 1.42 (95% CI, 1.38 to 1.46) when compared to individuals without infections. Except for pregnancy related and otitis media infections, all examined sites of infections were linked to increased risk of suicide; most pronounced for HIV/AIDS, hepatitis, respiratory, and sepsis (Table 1).

The risk of suicide increased in a dose-response relationship with the number of hospital contacts with different infections as illustrated in Figure 1. The highest incidence of suicide was found for seven or more hospital contacts with a relative risk of 2.90 (95% CI, 2.14 to 3.93) while individuals with one contact had a relative risk of 1.34 (95% CI, 1.30 to1.38) when compared to those with no contact. During the first 1-4 days in treatment with infection the relative risk was 1.46 (95% CI, 1.41 to 1.52) and after 94 days with treatment the risk was 2.38 (95% CI, 2.05 to 2.76) (Figure 2). Temporal proximity to the last hospital contact

with infection was linked to an elevated risk ($p<0.001$), with the strongest effect after one and two years when compared to those without infections (Figure 3).

A history of psychiatric disorders was the variable associated with the highest risk of suicide with a relative risk of 8.38 (95% CI, 8.15 to 8.62) when compared to individuals without infections and psychiatric disorders. Individuals who were diagnosed with infection before a psychiatric disorder had a relative risk of 10.17 (95% CI, 9.65 to 10.71), which is higher than those, diagnosed with psychiatric disorders before infection that had a relative risk of 7.78 (95% CI, 7.40 to 8.18) in comparison to those with no diagnosis of infections and psychiatric disorders.

We found that the population attributable risk was 10.1%; implying that one in ten suicides could be prevented if infections were to be eliminated entirely provided the association was causal.

Sensitivity analysis

Complete lifetime follow-up on hospital contacts was obtained by restricting the cohort to those born after 1962. In this analysis, similar results were found; individuals with hospital contacts with infection had higher risks of suicide (incidence rate ratio, 1.40; 95% CI, 1.33 to 1.49) when compared to those without infections.

When we excluded individuals on the date of being diagnosed with schizophrenia or affective disorders, the result among those with infections remained elevated with a relative risk of 1.40 (95% CI, 1.36 to 1.44). Excluding individuals with substance use disorders also rendered significant effects; i.e. with a relative risk of 1.35 (95% CI, 1.36 to 1.39). Omitting individuals with any diagnosis of psychiatric disorders was linked to a relative risk of 1.31 (95% CI, 1.27 to 1.36).

DISCUSSION

To our knowledge, this is the largest study to date, to examine infections as a predictor of death by suicide. In this nationwide population-based cohort study, we find an association between hospital contacts for infections and an increased risk of suicide. A dose-response relation was found with respect to number of hospital contacts with different infections as well as days in treatment. Also, an increased risk was noted in relation to temporal proximity to last hospital contact with infection. All analyses were adjusted for chronic and physical comorbidity using the Charlson Comorbidity Index and adverse social factors including cohabitation status and socioeconomic status. These adjustments reduced the relative risk for suicide in most but not all infections, and the risk estimates were still significant in the fully adjusted model. Furthermore, the association between infections and suicide was supported in a cohort born after 1962 with complete lifetime follow-up on all registers.

As mentioned above, there are several potential causal links between infections and suicide. Our findings support the prevalent literature in this field where small-scale studies have linked infections, proinflammatory cytokines, and inflammatory metabolites with increased risk of suicidal behavior.[9,13,15,20–27] Also, infection with the parasite Toxoplasma gondii has been associated with suicide attempts.[14–17]

In this study, we find that all types of infections are linked to an elevated risk of suicide as well as most infectious sites. Only pregnancy-related and otitis media infections did seemingly not have an impact on suicide. While parenthood has a protective impact on suicide risks,[35] otitis media infection often occur early in life and generally has a lower systemic response, which could explain the lack of associations. Infectious sites such as sepsis infection, respiratory infections, and genital infections among others induce a more severe systemic response; this could support the hypothesis of a biological link to suicide.

The highest risks of suicide were found among individuals with hepatitis infection and HIV/AIDS infection. Hepatitis and HIV/AIDS infection is strongly linked to psychiatric disorders and substance use disorders. Patients, furthermore, report higher levels of suicide-related thoughts and behaviors than the general population.[36–38] Yet, after excluding individuals with psychiatric disorders, including substance use disorders, the risk estimate remained significant; implying that this could only explain parts of the association.

The association between infections and suicide could also be an epiphenomenon. The psychological impact of being hospitalized with a severe infection may increase the risk of suicide. Yet, we found that the risk remained more than seven years after the last hospital contact with infection while adjusting for chronic and somatic diseases. In addition, certain genetic variations in the susceptibility to infections may explain the association; exemplified in research investigating the microbiome-gut-brain axis and its effects on human behavior.[39] Also, treatment with antibiotics have impact on the human microbiom.[40]

Although psychiatric disorders, chronic and physical comorbidities, and self-harm seemingly are stronger predictors of suicide,[11] we found that infections accounted for a population attributable risk of nearly 10.1%. Obviously, infections are not always amenable as a direct basis for intervention. However, in terms of preventive measures, it may be both biologically and pragmatically meaningful to consider individuals with a recent history of severe infection; particularly HIV/AIDS infections, hepatitis infections, respiratory infections, and sepsis infections as potentially more suicide-prone immediately after their discharge from hospital. Our estimates of attributable risk of infections on risk of suicide do not exclude the possibility that genetic vulnerability factors for suicide exists. They do, however, suggest that both genetic factors and environmental factors such as infections are probably both risk factors for suicide.

Strengths and limitations

Strengths of the study are the nationwide registers with individual level-data, which allowed for investigation of outcomes with low frequency, such as suicide. We adjusted for a range of time-varying covariates which allow us to generate more exact risk estimates. All data were collected prospectively with a follow-up period of 30 years. Also, there is full national coverage on all registers, given that there is free access and treatment in Danish hospitals and no loss to follow-up.

The present study has certain limitations. Firstly, data on infections were limited to hospital contacts for much of the period under study, and, therefore, milder infections that do not require hospital treatment were not included. Secondly, we cannot determine whether the hospital treatment for infection could explain some of the observed risks. The association between infections and suicide remained significant even after seven years since last hospital contact with infection, which minimizes the possibility that our findings were based on the hospital treatment. Thirdly, we did not have information on hospital contacts with infection before January, 1st 1977. However, a cohort born after 1962 with complete lifetime follow-up on all registers supported the association between infections and suicide. Finally, there is still a risk of residual confounding by variables which are not captured in the registers such as undiagnosed infections or psychiatric disorders. Likewise, although the suicide registration in Denmark is evaluated to be reliable; under-recordings cannot be excluded.

Conclusion

We found that infections are associated with an increased risk of dying by suicide after adjusting for a range of possible confounders. Our findings indicate that infections may play an important role in the pathophysiological mechanisms in suicidal behavior and might even be an independent risk factor for suicide. Attention and identification of patients with severe infections might be needed to lower suicidal outcomes and a viable path to reducing suicidal behavior. Still, further efforts are needed to clarify the exact mechanisms by which infection affect human behavior and risk of suicide.

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Table 1. Incidence Rate Ratios of Suicide According to Site and Type of Infection

		Basic adjustment model*	Fully adjusted model†
	N suicides	Incidence rate ratio (95% CI)	Incidence rate ratio (95% CI)
Any infection			
No	24,791	1.00	1.00
Yes	7,892	1.61 (1.56-1.65)	1.42 (1.38-1.46)
Type of infection			
Bacterial infections			
No	28,057	1.00	1.00
Yes	4,626	1.57 (1.52-1.62)	1.37 (1.33-1.42)
Viral infections			
No	31,653	1.00	1.00
Yes	1,030	1.45 (1.36-1.54)	1.26 (1.18-1.34)
Remaining types of infections			
No	31,109	1.00	1.00
Yes	1,574	1.68 (1.59-1.77)	1.40 (1.33-1.48)
Site of infection			
Sepsis infections			
No	32,429	1.00	1.00
Yes	254	2.17 (1.91-2.45)	1.51 (1.33-1.71)
Hepatitis infections			
No	32,456	1.00	1.00
Yes	227	3.61 (3.17-4.11)	2.12 (2.25-2.36)
Gastrointestinal infections			
No	31,299	1.00	1.00
Yes	1,384	1.21 (1.14-1.27)	1.18 (1.12-1.25)
Skin infections			
No	31,015	1.00	1.00
Yes	1,668	1.68 (1.60-1.76)	1.42 (1.35-1.49)
Respiratory infections			
No	29,801	1.00	1.00
Yes	2,882	1.86 [1.79-1.94]	1.54 (1.48-1.60)
Urological infections			
No	31,679	1.00	1.00
Yes	1,004	1.65 (1.55-1.76)	1.30 (1.22-1.39)
Genital infections			
No	31,960	1.00	1.00
Yes	723	1.53 (1.42-1.65)	1.43 (1.33-1.54)
Pregnancy-related infections			
No	21,593	1.00	1.00
Yes	275	0.80 (0.63-1.01)	0.86 (0.68-1.09)
Otitis media infections			
No	32,296	1.00	1.00
Yes	387	1.11 (1.00-1.23)	1.03 (0.93-1.14)
Central nervous system infections			
No	32,513	1.00	1.00
Yes	170	1.42 (1.22-1.65)	1.25 (1.08-1.46)
HIV/AIDS infections			
No	32,602	1.00	1.00
Yes	81	6.33 (5.09-7.88)	2.32 (1.86-2.89)

Figure 1. Incidence Rate Ratios of Suicide According to Number of Hospital Contacts with Different Infections

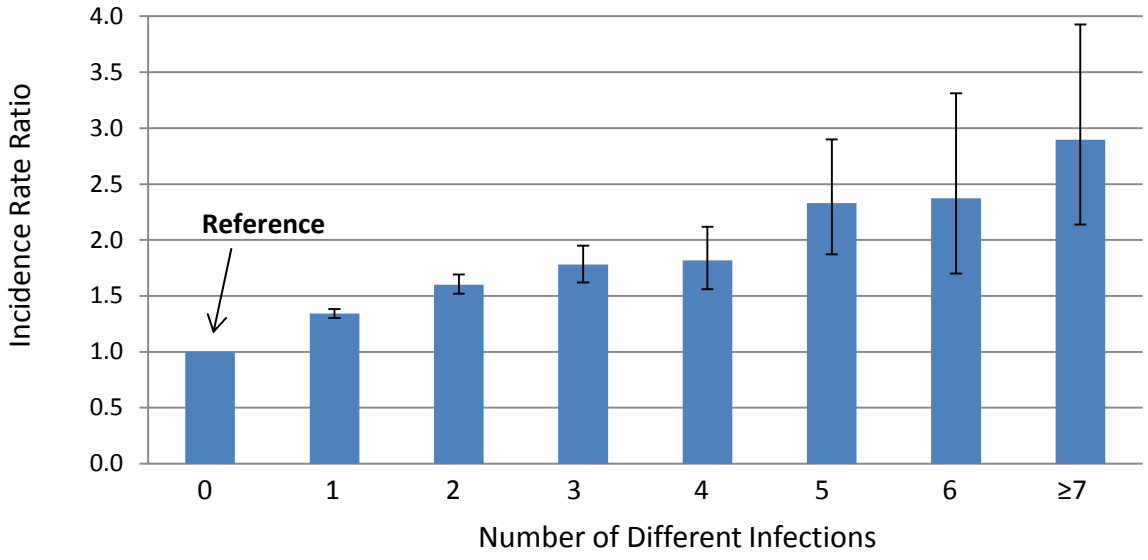

Figure 2. Incidence Rate Ratios of Suicide According to Number of Days in Treatment with Infection

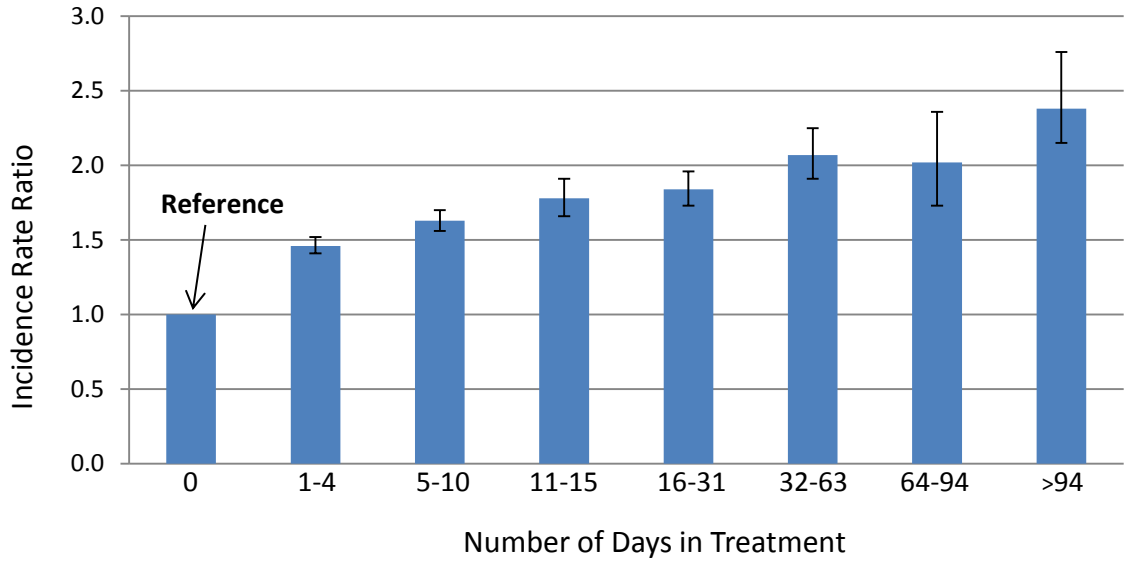

Figure 3. Incidence Rate Ratio According to Time Since Last Treatment with Infection