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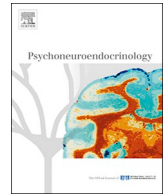
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## Herpes Simplex Virus Type 1 infection is associated with suicidal behavior and first registered psychiatric diagnosis in a healthy population

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### ABSTRACT

Increasing evidence shows that latent infections and inflammation is associated with cognitive and behavioral changes in humans. This case-control study investigates the association between Herpes Simplex Virus Type 1 (HSV-1) infection and C-reactive Protein (CRP) levels, and psychiatric disorders and suicidal behavior. Public health register data from 81,912 participants in the Danish Blood Donor Study, were reviewed to identify individuals registered with an ICD-10 code of any psychiatric diagnosis, or who had attempted or committed suicide. We found 1,504 psychiatric cases and 353 suicidal cases; for all cases, controls were frequency-matched by age and sex, resulting in 5,336 participants. Plasma samples were analyzed for IgG-class antibodies against HSV-1 and CRP. HSV-1 infection was associated with suicidal behavior (odds-ratio, 1.40; 95% confidence interval [CI] 1.11–1.77). Accounting for temporality, HSV-1 infection was associated with having first psychiatric disorder after the date of blood collection (incidence rate ratio, 1.44; 95% CI, 1.05–1.95). No association between CRP and psychiatric disorders or suicidal behavior was found. The finding that HSV-1 was associated with suicidal behavior and first psychiatric disorder indicates that infection may play a role in the etiology and pathogenesis of suicidal behavior and development of psychiatric disorders.

### 1. Introduction

Herpes Simplex Virus Type 1 (HSV-1), long considered largely innocuous, is now suspected of harmful effects on human cognition and

behavior, even in individuals without clinical apparent encephalitis (Becker, 1995; Dickerson et al., 2012; Schretlen et al., 2010; Yolken et al., 2011).

HSV-1 is neurotropic and predominantly replicates in the frontal

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and temporal regions of the brain, where it potentially could lead to cognitive impairments and memory alterations similar to those observed in individuals with schizophrenia (Pramod et al., 2013; Prasad et al., 2012). Latent neurotropic pathogens could contribute to cognitive impairments and behavioral changes (Dickerson et al., 2017; Duarte et al., 2019; Gale et al., 2016; Köhler-Forsberg et al., 2018; Pramod et al., 2013; Simanek et al., 2017).

Herpes viruses establish lifelong latent infections and may, during periods of reactivation, repeatedly induce an inflammatory response (Glaser and Kiecolt-Glaser, 1994). It is not known to what extent, or under which circumstances, inflammation, triggers psychiatric disease onset. Age, stress, co-existent infections, and genetic and environmental determinants of the immune response are potential reactivating factors (Daheshia et al., 1998; Jones, 2003; Taylor et al., 2002; Xiao et al., 2018). Psychiatric disease onset could be triggered by a chronic elevated inflammatory response or one or more severe inflammatory outbreaks throughout life. Reactivation of latent HSV-1 infection can lead to somatic symptoms (cold sores) months or years after the primary infection. We hypothesize that latent HSV-1 infections also produce inflammatory responses that influence brain tissue and potentially contribute to psychiatric disorders or suicidal behavior years or decades after the primary infection.

Elevated levels of the inflammatory biomarker C-reactive protein (CRP) is associated with psychiatric disorders (Wysokiński et al., 2015) including schizophrenia (Dickerson et al., 2007a), bipolar disorder (Dickerson et al., 2007b), depression (Ford and Erlinger, 2004), cognitive impairment (Yaffe et al., 2003), and suicide (Park and Kim, 2017). The effects of CRP may be additive with genetic risk factors for psychiatric disorders (Nimgaonkar et al., 2018). There is an additive effect of elevated levels of antibodies to HSV-1 and CRP on cognitive functioning in individuals with schizophrenia (Dickerson et al., 2012). Furthermore, HSV-1 infection and inflammation (the latter assessed by CRP levels) may both play a role in the etiology and pathogenesis of psychiatric disorders and suicidal behavior (Nelson and Demmler, 1997).

Even though a possible link between common infectious pathogens and inflammation, and the pathogenesis of psychiatric disorders and self-violence has been described, it remains challenging to firmly establish these associations. It needs to be elucidated whether these associations reflect causality, and underlying mechanisms need to be defined.

In the current study, we investigated the association between antibodies to HSV-1 and CRP levels in relation to psychiatric and suicidal outcomes in a large cohort of Danish blood donors. To provide indicators regarding causality, we accounted for temporality, with the exposure preceding the outcome of interest.

## 2. Methods and materials

### 2.1. Study population and overall design

The overall study design has been described previously (Sølvsten Burgdorf et al., 2019). The Danish Blood Donor Study (DBDS) is an ongoing national large-scale prospective cohort of voluntary Danish blood donors recruited from blood donation centers across Denmark since 2010 (Burgdorf et al., 2017, 2016; Pedersen et al., 2012). We carried out a large-scale case-control study and a case-control study nested in the DBDS to account for temporality, i.e., the exposure should precede the outcome of interest. National registers for 81,912 individuals were reviewed to identify all cases registered with a psychiatric diagnosis (1971–2013), had attempted or committed suicide (1977–2011) or had been in a traffic accident (2008–2012). Cases with a traffic accident were used in a previous study of toxoplasmosis (Burgdorf et al., 2019). All cases were frequency matched by sex and age with suitable controls, resulting in 12,500 cases and controls. Plasma samples for cases and controls were randomized into three

batches and transferred to the Stanley Neurovirology Laboratory for analysis. Information on HSV-1 and CRP levels was available for two of the three batches, enabling us to study the effect of these on 1,504 psychiatric cases and 353 suicidal behavior cases, and their controls, in total 5,336 individuals.

At recruitment, oral and written informed consent was obtained from all participants and the study was carried out in accordance with the latest version of the Declaration of Helsinki. The Danish Data Protection Agency (2007-58-0015) and the Scientific Ethical Committee of the Central Denmark Region (M-20090237) approved the study.

### 2.2. Psychiatric diagnoses

The Danish Psychiatric Central Research Register (Mors et al., 2011) is a nationwide register with person-specific information on all admissions to Danish psychiatric inpatient facilities since 1969 and outpatient facilities since 1995. Psychiatric diagnoses are coded according to the International Classification of Diseases (ICD) - 8th Revision (WHO, 1965) between 1969 and 1993, inclusive; and 10th Revision (WHO, 1994) since 1994. Diagnosis of any psychiatric disorder (ICD-10: F00-F99 and eq. ICD-8) and subgroups including schizophrenia and related disorders (ICD-10: F20-F29 and eq. ICD-8 (Pedersen et al., 2014)), mood disorders (ICD10: F30-F39 and eq. ICD8) and neurotic, stress-related, and somatoform disorders (ICD-10: F40-F48 and eq. ICD-8) before 2014 was obtained. Information on parental history of any psychiatric diagnosis was obtained.

### 2.3. Attempting and committing suicide

Deliberate self-violence, such as attempting or committing suicide, was defined in agreement with the criteria set by the Danish National Patient Register (1977–2012), the Psychiatric Central Research Register (1969–2013) and the Danish Registers of Causes of Death (1970–2011), previously used in Danish register studies (Nordentoft, 2011). Only episodes registered after the age of 15 years were considered. Diagnoses are based on the ICD-8th Revision between 1977–1993 and ICD-10th Revision from 1994 onward.

### 2.4. Immunological assays

Plasma samples from cases and controls were analyzed at the Stanley Neurovirology Laboratory for specific enzyme-based immunoassays for immunoglobulin (IgG) class antibodies against HSV-1 and CRP, previously described (Dickerson et al., 2003). The raw IgG antibodies titer values were standardized across plates and the distribution of the standardized z-score was fitted with two normal distributions to determine the cut-off value for each batch and for each outcome of interest (Supplemental Figure S1 and S2). The cut-off was set to match the area under the tails in the two normal distributions, and a value above this cut-off was considered positive (or elevated).

### 2.5. Statistical methods

The associations between HSV-1 seropositivity or elevated CRP levels and the risk of psychiatric disorders or suicidal behavior were analyzed with a conditional logistic regression model on 5,336 individuals (1,504 psychiatric cases, 353 suicidal cases and 3,479 controls). By design, we controlled for sex, age at time of blood collection and adjusted for smoking and parental history of psychiatric disorder before time of blood collection as previously described (Pedersen et al., 2011). Additionally, we conducted an analysis where HSV-1 and CRP were mutually adjusted.

Odds ratios (ORs) and 95% likelihood ratio confidence intervals (95% CIs) were calculated, and a two-sided P-value of less than 0.05 was considered statistically significant. Statistical analyses were

performed using the PHREG procedure in SAS 9.3 (SAS Institute, Cary, North Carolina). Batch-specific estimates were calculated (Supplemental Figure S3 and S4).

The nested case–control study was conducted to account for temporality; i.e., the exposure should precede the outcome of interest to fulfill Hill’s causation criteria (Hill, 1965; Rothman et al., 2008). For each outcome of interest, only individuals with disease onset after the date of blood sampling were included. Conditional logistic regression for these cases and their time-, age-, and sex-matched controls were conducted. This method provides estimates that are informative about the risk of developing the outcomes of interest after exposure to HSV-1 or CRP levels; i.e., incidence-rate ratios (IRRs) (Pearce, 1993; Vandenbroucke and Pearce, 2012).

### 3. Results

A total of 5336 cases and controls were enrolled in this study. The distribution of cases and controls (non-exclusive) are shown in Table 1. Overall, 1504 individuals (853 women) were registered with a psychiatric disorder and 353 individuals (193 women) had attempted or committed suicide. The average age at blood donation was 37.6 years (Supplemental Figure S5) and 50.9% had serological evidence of HSV-1 infection and 46.5% had elevated CRP levels.

Attempting or committing suicide was associated with HSV-1 (OR, 1.40; 95%CI, 1.11–1.77) (Table 1). Considering only the 10 cases who for the first time attempted or committed suicide after the date of blood collection, no association between HSV-1 and subsequent suicide or suicide attempts was observed (IRR, 0.78; 95%CI, 0.21–2.98).

Accounting for temporality (considering only individuals diagnosed after the date of blood collection) HSV-1 was associated with developing any psychiatric disorder (IRR, 1.45; 95% CI, 1.06–2.00) (Table 1).

No associations between CRP levels and psychiatric disorders or suicidal behavior were found (Table 1).

### 4. Discussion

This large-scale seroepidemiological case–control study is the first to show an association between HSV-1 infection and the risk of attempting or committing suicide in an otherwise healthy population. This finding indicates that HSV-1 infection may be a contributing factor for suicidal behavior. Moreover, we found that HSV-1 infection could be a contributing causal factor for development of any psychiatric disorder, as we show that infection with HSV-1 occurred prior first registered psychiatric diagnosis. Our results are in agreement with and supports the findings that primary HSV-1 infection, in some individuals, may decade after lead to neural damage that promote or contribute to neurodegenerative disorders (Duarte et al., 2019).

The consequences of latent infection may significantly differ depending on its timing, the stages of brain development; and the site of entrance, localization, and distribution in the brain. These factors may result in varying degrees of lifelong changes in behavior and cognition (Yolken and Torrey, 2008). Antibody titers reflect pathogen infection, but they provide little information about the timing, localization, distribution or duration of the infection. HSV-1 antibody titers accurately reflect the presence of central nervous system HSV-1 infection in post-mortem studies of humans and rodents (Hill et al., 2008). Because of the repeated cycles of reactivation, viral titers generally remain elevated throughout life. In individuals who do not experience repeated cycles of reactivations, antibody titers tend to decline over time. Antibody titers reflect exposure as well as host-related factors; such as genetic variations affecting immune responses and may in some individuals lead to lower antibody titers. Latent HSV-1 infection or genetic variations affecting the immune responses could result in a reduced association between HSV-1 infection and cognitive dysfunction (Prasad et al., 2012).

**Table 1**  
The association between HSV-1 infection or CRP levels with psychiatric disorders and suicidal behavior.

	Odds ratios				Incidence rate ratios (IRRs) <sup>a</sup>			
	Case N (HSV-1 neg/pos)	Control N (HSV-1 neg/pos)	HSV-1	CRP	Case N (HSV-1 neg/pos)	Control N (HSV-1 neg/pos)	HSV-1	CRP
Any Psychiatric disorder (F00-F99)	1,504 (724/780)	3,665 (1,836/1,829)	1.03 (0.91;1.17)	1.06 (0.93;1.20)	181 (103/78)	2,945 (1,619/1,326)	1.44 (1.05;1.98)	0.82 (0.60;1.13)
Neurotic, stress-related, and somatoform disorders (F40-F48)	820 (376/444)	3,720 (1,865/1,855)	1.08 (0.92;1.27)	1.09 (0.93;1.27)	119 (56/63)	2,992 (1,509/1,483)	1.19 (0.81;1.75)	0.84 (0.57;1.23)
Mood disorders (F30-F39)	389 (197/192)	3,758 (1,880/1,878)	0.98 (0.79;1.22)	1.05 (0.85;1.31)	76 (36/40)	3,030 (1,524/1,506)	1.32 (0.82;2.14)	0.89 (0.55;1.43)
Schizophrenia and related disorders (F20-F29)	81 (38/43)	3,791 (1,891/1,900)	1.15 (0.72;1.84)	0.94 (0.59;1.49)	14 (9/5)	3,056 (1,676/1,381)	1.78 (0.60; 5.23)	0.79 (0.25; 2.52)
Attempting or committing suicide	353(139/214)	3,763 (1,879/1,884)	1.40 (1.11;1.77)	1.19 (0.95;1.50)	10 (5/5)	3,034 (1,521/1,513)	0.78 (0.21;2.98)	-

Adjusted for sex and age due to design and parental history of psychiatric disorder and smoking.

<sup>a</sup>bold indicates a likelihood ratio based 95% p-value < 0.05.

N, number of cases or controls; HSV-1 neg, HSV-1 seronegative individuals; HSV-1 pos, HSV-1 seropositive individuals.

\* Incidence rate ratios considering only cases with first outcome of interest after the date of blood collection.

Lifelong latent infections may, during repeated cycles of latency and reactivation, over time lead to a decrease in cortical gray matter with consequent cognitive impairment, thus participating in the pathological processes of severe psychiatric disorders such as schizophrenia and bipolar disorder (Prasad et al., 2011, 2007). A causal relationship between serological evidence of HSV-1 infection and memory deficits has only been well studied in individuals with schizophrenia (Dickerson et al., 2012, 2004; Prasad et al., 2012; Schretlen et al., 2010; Shirts et al., 2008; Yolken et al., 2011). HSV-1 infection and elevated CRP levels are associated with the severity of cognitive impairment in schizophrenia. In addition, an additive effect of inflammation (assessed by circulating CRP level) and history of HSV-1 infection on immediate memory is found. These findings indicate that infection and inflammation may play a major role in the cognitive deficits associated with schizophrenia (Dickerson et al., 2012). In this study, we found that HSV-1 infection was associated with having any psychiatric disorder, but only in individuals registered with first psychiatric disorder after the date of blood collection and – the infection occurred prior first registered psychiatric diagnosis. As a marker of general inflammation CRP levels was analyzed, but no association between CRP levels and psychiatric disorders or suicidal behavior were found. We cannot rule out that reactivation of latent HSV-1 infection may induce a local neuroinflammatory response in the brain that potential could invoke severe cognitive dysfunctions associated with psychiatric disorders or suicidal behavior.

There may exist a window of opportunity for treating HSV-1 infections prior to the time they lead to irreversible damage to key cortical networks leading to development of cognitive deficits. Irreversible damage to key cortical networks could not be ameliorated by antiviral therapies (Breier et al., 2018). Therefore, treating individuals before they develop irreversible cortical network damage may be a more effective treatment than treating individuals who already developed irreversible damage leading to psychiatric disorders (Breier et al., 2018; Prasad et al., 2013).

The strength of our study is that it is based on a large, nationwide population tested for HSV-1 and CRP levels, and that we were able to account for temporality (i.e., whether the pathogen exposure precedes the outcome), smoking and parental history of psychiatric disorders. A limitation of this study is that we could not determine the etiological relationship between HSV-1 infection and CRP levels; nor directly prove a causal relationship between HSV-1 or CRP and suicidal tendency. We assessed past HSV-1 exposure and current CRP status; this may be problematic, as the timeframes differ.

Moreover, only IgG levels of HSV-1, indicator of lifelong HSV-1 infection, was analyzed. IgM levels of HSV-1, indicator of primary infection or reactivation of the virus, was not analyzed. We were not able to control for socioeconomic factors, which may influence probability of pathogen infection, psychiatric disorders or suicidal behavior. Moreover, behavioral changes due to psychiatric disorders may lead to higher risk of contracting infectious diseases, including HSV-1. In addition, we were only able to control for current smoking status but not factors like diet and allergies that might also influence CRP levels. We cannot rule out the possibility that these factors account for part or all of the observed effect. The generalizability to other settings may be limited, since the study population comprises of voluntary blood donors who are healthier than the general population; older blood donors in particular represent a highly selected group of individuals (the healthy donor effect) (Rigas et al., 2017). These factors can also influence the probability of pathogen infection, psychiatric disorders or suicidal behavior.

For future studies, our cohort holds some unique advantages for studying development of psychiatric disorders and suicidal behavior. What is exceptional is that we have a large numbers of consecutive samples per individual, to explore change in inflammatory markers in infected and non-infected individual prior to disease onset or suicidal behavior.

In conclusion, this largest to date seroepidemiology study is the first to show that HSV-1 infection may be a risk factor for self-directed violence in the form of attempting or committing suicide, in an otherwise healthy population. Interesting, we also showed that HSV-1 infection occurred prior first registered psychiatric diagnosis. Targeting HSV-1 infection may potential provide novel diagnostic and therapeutic approaches. Treating HSV-1 infection prior to the time they lead to suicidal behavior or psychiatric disorders may be more effective than treating individuals who already have developed suicidal behavior or psychiatric disorders, thus supporting a causal relationship.

Declaration of Competing Interest

None.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.psyneuen.2019.06.015>.

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