Herpes Simplex Virus Type-1 Infection: Associations with Inflammation and Cognitive Aging in Relation to Schizophrenia

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Contents

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Abstract Most persons experience cognitive decline as they grow older. The term "cognitive aging," coined to describe milder varieties of cognitive decline, is likely to be due to multiple causes. Persistent or repeated infections of the central nervous system (whether subclinical or diagnosable) can cause damage to neurons directly or indirectly through inflammation resulting in incremental neuronal damage, thus eroding cognitive reserve. This possibility has not been considered widely. We evaluated the data linking persistent infection with herpes simplex virus type 1 (HSV-1) and cognitive aging by applying the Bradford Hill criteria. Despite inherent problems in establishing causal relations for chronic disorders, our analyses suggest plausible links. These studies are pertinent for patients with schizophrenia, who are particularly vulnerable due to disorder-related cognitive impairment. Further investigations are warranted to test a causal hypothesis, particularly prospective studies and intervention studies.

Keywords Bradford Hill criteria · Causality · Cognitive aging · Herpes virus · HSV-1 · Schizophrenia

1 Introduction

Cognitive dysfunction, whether mild or severe, extracts a heavy public health burden (Zhu et al. 2013). The type of cognitive dysfunction spans the continuum from mild changes to severe dementia. The Institute of Medicine recently published a report on "Cognitive Aging" to draw attention to incremental cognitive dysfunction that is noticeable as we age (Institute of Medicine 2015; Carbone et al. 2014). The cognitive dysfunction spans a spectrum of changes and severity. How and why the dysfunction occurs is a matter of conjecture, but it is reasonable to assume that it is multifactorial; in other words, no one cause needs be necessary or sufficient (Gould and Gottesman 2006). If mild cognitive impairment (MCI) or dementia occurs in even a minority of individuals with cognitive aging, the burden is likely to be much higher (Zhu et al. 2013; Paradise et al. 2015; Springate and Tremont 2013; Lin and Neumann 2013). Age-associated cognitive dysfunction will demand even more resources in the next decade, because the number of persons aged 60 years and older is expected to increase to 1.2 billion across the world by 2025 (http://www.who.int/ageing/en/index.html).

Numerous genetic factors have been associated with severe cognitive decline and dementias. While genetic factors certainly play a role in age-related cognitive decline, preventable and potentially treatable environmental factors need to be investigated too. We postulate that a portion of the risk could be contributed by chronic viral infections. Like cognitive aging, the prevalence of many viral infections increases with age (Smith and Robinson 2002). Furthermore, individuals with chronic infections perform less efficiently on cognitive tests compared with uninfected individuals in several cross-sectional studies, many of them focusing on herpes viruses (Aiello et al. 2006; Carbone et al. 2014; DeVaughn et al. 2015;

Barrientos et al. 2012; Bucks et al. 2008). Such infections have the potential to affect cognitive functions if they afflict the brain directly or indirectly. Mild or moderate levels of dysfunction in the cognitive domains of attention, working, and verbal memory were reported repeatedly among HSV-1 seropositive schizophrenia and bipolar patients and even healthy individuals in 19 studies (Dickerson et al. 2003a, 2004, 2012; Strandberg et al. 2003; Aiello et al. 2006; Prasad et al. 2012b; Schretlen et al. 2010; Prasad et al. 2011; Yolken et al. 2011; Gerber et al. 2012; Watson et al. 2013; Katan et al. 2013; Thomas et al. 2013; Tarter et al. 2014; Jonker et al. 2014; Wright et al. 2015; Fruchter et al. 2015; Nimgaonkar et al. 2016; Bhatia et al. 2017; Hamdani et al. 2017; Vanyukov et al. 2017). We and others have systematically investigated cognitive functions among individuals with chronic infections caused by herpes simplex virus type 1 (HSV-1) and explored whether such observations could explain a portion of cognitive aging (Watson et al. 2013; Thomas et al. 2013; Bhatia et al. 2016, 2017; Hamdani et al. 2017). Henceforth, for the sake of brevity, we refer to the putative association as HSV-1 – cognitive decline/dysfunction (HSVCD). In the following sections, we describe aspects of HSV-1 infections in humans relevant to a causal hypothesis, followed by possible mechanism for the HSVCD. In the final section, we evaluate the published HSV-1-related data in relation to Bradford Hill criteria, the current gold standard for investigating causal connections between chronic risk factors and noncommunicable human diseases. Our review includes cross-sectional and prospective studies relating HSV-1 infection to cognitive dysfunction, brain imaging studies, the effects of highly specific antiviral drugs on cognitive dysfunction, and efforts to model HSV-1 infections in vitro in human neuronal cells.

2 The Nature of HSV-1 Infections

HSV-1 is a double-stranded DNA virus that causes human-specific infections. It initially infects mucosal surfaces. It migrates to sensory ganglia from the primary infection site, where it can lie dormant in a latent state for the lifetime of the host (Steiner et al. 2007). When latent, viral DNA assumes a circular form and exists without replication in the neuronal nucleus; it only produces relatively few untranslated viral transcripts that are not translated into viral proteins (Harkness et al. 2014; Steiner et al. 2007). Reactivation from latency can be induced by stress or immunosuppression (Steiner et al. 2007; Shimomura and Higaki 2011); reactivated virions migrate through sensory nerves to the original site of infection, where recurrent infection flares (Steiner et al. 2007). It is the reactivated state that causes acute lytic mucosal lesions. Viral particles are typically detectable at sites of reactivation and in mucosal fluids bathing the lytic mucosal lesions. Oral transmission of mucosal fluids from an infected individual is the typical route of primary infection, but transmission through sexual infection is an increasingly frequent form of primary infection, and infection of neonates during childbirth is thus a mounting public health concern (Kriebs 2008) (Fig. 1).

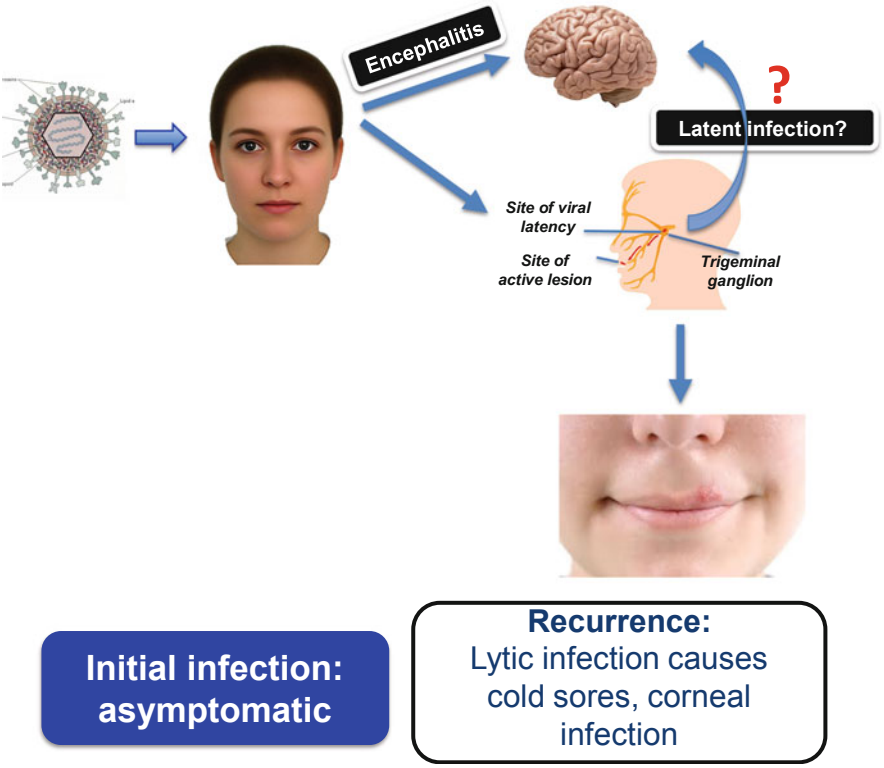

Fig. 1 Herpes simplex virus, type 1 (HSV-1) infection natural history and the human brain

More than 3.7 billion individuals aged 0–49 years are infected with HSV-1 worldwide, with rates exceeding 87% in Africa (Looker et al. 2015). The prevalence of HSV-1 seropositivity increases with age, being approximately 40% among US children/teens and 40–70% among adults less than 70 years of age (http://www.cdc.gov/nchs/nhanes.htm). The primary infection can be asymptomatic or it may be associated with mild fever. As noted above, HSV-1 causes recurrent mucosal infections, but the most damaging infections involve the eye and the brain. Approximately 500,000 persons have ocular HSV-1 infection across the world at any one time (Liesegang et al. 1989). Recurrent herpes stromal keratitis (HSK) can cause corneal scarring and blindness (Rowe et al. 2013). Ocular herpes is one of the chief causes of blindness worldwide, with a global incidence of approximately 1.5 million cases per year, and it is estimated that there are 40,000 new cases of visual impairment or blindness annually (Farooq and Shukla 2012). HSV-1 can also cause encephalitis, leading to death or severe residual cognitive impairment in survivors (Steiner et al. 2007). Thankfully, it is rare (~0.004%), and it typically occurs only in adults with compromised immune functions or increasingly in neonates.

A conclusive diagnosis of HSV-1 infection requires detection of the viral particles at reactivated sites or in mucosal fluids, but reactivation is unpredictable. Therefore, it is difficult to detect viral particles in the blood or saliva during the latent, persistent phases (Corstjens et al. 2012). Consequently, specific host-generated IgG antibodies in the serum (which can remain elevated for prolonged periods) are typically used as indirect indicators of infection with HSV-1.

HSV-1 can be effectively treated with nucleoside analogues such as valacyclovir (VAL) and its derivatives. Once these drugs are converted into their active forms by viral thymidine kinase, they can inhibit DNA polymerase and even terminate its activity (Kimberlin and Whitley 2007). Because the conversion into active metabolites can only occur in cells with actively replicating virions, the drugs are inactive in uninfected human cells and thus have relatively few side effects. Thus, VAL-like drugs are highly specific antiviral agents. On the other hand, the drugs are ineffective against the latent viral form. Thus, the antiviral drugs can abort productive infection but cannot eliminate virions from the human body. No effective vaccines have been found for HSV-1. Thus, HSV-1 infection is essentially incurable at present even though highly efficacious and specific antiviral drugs are available.

3 Plausible Mechanisms for Cognitive Aging Attributed to HSV-1

Acute encephalitis caused by HSV-1 is potentially lethal but can be alleviated if it is detected in time and is treated with VAL. Individuals who survive encephalitis can have severe, enduring cognitive impairment. A similar mechanism could operate in the absence of severe encephalitis. If subacute or latent HSV-1 infection occurs in the brain, it is possible that localized recrudescence could occur without detection or overt symptoms, yet it could potentially culminate in cognitive impairment. This possibility was presciently suggested by Becker over a decade ago (Becker 2002). He suggested that HSV-1 virions could infect the olfactory regions following nasal infection and thence track to the temporal or frontal cortical regions. Even if such infection does not occur in the brain, another possibility is indirect damage to the brain following repeated infection in the periphery, with the release of cytokines that can cross the blood brain barrier and thus impair neuronal function (Yarlagadda et al. 2009). Infection with other viruses, such as cytomegalovirus (CMV), herpes simplex virus, type 2 (HSV-2), and Epstein-Barr virus (EBV), may result in cognitive deterioration in older individuals, independent of age-related variables (Nimgaonkar et al. 2016). It should be noted that the majority of studies linking HSV-1 infections with cognitive dysfunction have been conducted among persons with schizophrenia, who have disorder-related cognitive dysfunction (Gur et al. 2007). It is plausible that HSV-1 infection acts additively or even interacts with such factors.

4 Bradford Hill Viewpoints for Etiological Links for Chronic Diseases

Early in the twentieth century, Koch enunciated criteria that he felt must be fulfilled before a putative risk factor could be accepted as an etiological agent for a human disease (Evans 1976). These "postulates" were articulated in the era when infectious agents were being linked putatively to specific infections. Koch required that the infectious agent be identified from infected tissues, be cultured in vitro, and be shown to cause the disease in question in animal models. Though Koch's postulates definitively linked many infectious agents to deadly diseases such as cholera, it is difficult to apply the postulates to many noninfectious diseases or to diseases caused by genetic mutations. It is particularly difficult to utilize them for infectious diseases of the central nervous system (CNS), because of difficulties in obtaining CNS tissues from live individuals. Therefore, it may be prudent to seek other types of evidence. In the wake of uncertainties about links between cigarette smoking and lung cancer, Sir Austin Bradford Hill articulated a set of nine "viewpoints" that could be evaluated to test for causal links (Hill 1965). Unlike Koch, who required that all his postulates must be fulfilled before etiological links could be accepted, Bradford Hill emphasized that his viewpoints should not be considered as hard-and-fast rules; rather he suggested them as guideposts that could be used to evaluate the body of evidence to enable consensus. The Bradford Hill viewpoints have been used extensively in the past 50 years. Recent advances in genetics, statistics, and toxicology enable more sophisticated analyses and tests of these viewpoints (Fedak et al. 2015). In the following sections, we evaluate each of the Bradford Hill viewpoints (criteria) in relation to persistent HSV-1 infection and cognitive dysfunction.

4.1 Strength

Bradford Hill suggested that the magnitude of the association between the suspected risk factor and the outcome of interest could be used as a gauge, provided potential confounding factors were taken into account. With regard to smoking and lung cancer, he wrote: "prospective inquiries into smoking have shown that the death rate from cancer of the lung in cigarette smokers is nine to ten times the rate in non-smokers and the rate in heavy cigarette smokers is twenty to thirty times as great." By using carefully matched cases and controls, he suggested that the substantial odds ratios provided a persuasive pointer implicating smoking in the etiology of lung cancer. With regard to HSV-1 infections and cognitive dysfunction, the estimated odds ratios are 1.25–3.2, i.e., in the small to medium effect size range (Prasad et al. 2012b). Our analyses indicate population attributable risks (PAR) between 15.2 and 59.3% (Prasad et al. 2012b), making this a potentially important public health hazard. Further, HSV-1, like many infections, is common among individuals with lower socioeconomic status (SES). Thus, HSV-1 infection could

serve as a proxy for low SES. Most of the cross-sectional studies have attempted to control for SES, though this is admittedly difficult; for example, respondents can provide misleading information regarding household income. Another concern – whether the cognitive dysfunction is a residuum of prior encephalitis – is unlikely, because acute encephalitis is so rare.

4.2 Consistency

Bradford Hill emphasized the importance of attempting replication not only from the viewpoint of scientific rigor but also because it provides more confidence in a causative link. He suggested that the association under scrutiny was unlikely to be due to chance if it could be detected at different sites, at different times, and using different study designs. He pointed out that such variation could serve as a check against factors that might not be obvious, such as disease severity. He also admonished against mistaking statistical significance for consistency. From the viewpoint of this guideline, HSVCD has been detected in 19 studies that were conducted in Europe, India, and the USA. The studies were conducted over a 25-year period. The majority of studies incorporated the conventional case-control design, while one study also included a family-based design (Watson et al. 2013). The association was investigated in healthy individuals, as well as clinic-based samples that included individuals with schizophrenia (SZ) and bipolar disorders (BD). Because a variety of cognitive tests were employed, there was variation in the cognitive domains that were associated, e.g., attention, immediate memory, language, verbal memory, and executive function. Most of the associations occurred with the cognitive domains of attention or the domains of working memory. As there is substantial correlation for performance in these domains, it is difficult to identify the domains with the primary association. In contrast, four groups of investigators did not report significantly impaired cognitive functions among seropositive individuals (Aiello et al. 2008; Barnes et al. 2014; Katan et al. 2013; Nimgaonkar et al. 2016). Some of these samples were larger than the samples in which a significant association was detected, e.g., (Nimgaonkar et al. 2016), and thus should have appropriate statistical power. The reasons for lack of replication are not obvious. It is notable all the studies with nonsignificant associations comprised individuals aged 60 or over (Aiello et al. 2008; Katan et al. 2013; Nimgaonkar et al. 2016). Thus, the HSVCD is largely consistent.

4.3 Specificity

Bradford Hill recognized that specificity is not a *sine qua non* for demonstrating etiology, though he pointed out that associations detected in specific situations or in groups of individuals were more likely to indicate causality. Pertinent to HSVCD, he

also recognized that the outcome of interest could have a multifactorial etiology. Moreover, the same etiological factor could have multiple effects. HSV-1 can infect the brain, causing encephalitis and many postencephalitic sequelae resembling those observed with HSVCD, thus lending credibility to HSVCD. Yet, the cognitive dysfunction predicted by HSVCD is also observed in relation to many other putative etiological agents, including herpes viruses such as cytomegalovirus (Wright et al. 2015; Dickerson et al. 2014; Shirts et al. 2008; Hamdani et al. 2017).

4.4 Temporality

Bradford Hill pointed out that the putative etiological agent must predate the outcome of interest. This requirement is a sine qua non for postulating a cause and effect relationship. As noted earlier, it is difficult to detect HSV-1 virions in serum or saliva; they are only detected locally in lytic lesions. Though HSV-1 virions are detectable in the cerebrospinal fluid (CSF) during acute encephalitis, they are not detectable in CSF during persistent, quiescent infection. Therefore, we have to rely on antibody titers as a sensitive and specific mark of prior infection. Even so, antibody titers do not indicate the timing of infection. Hence, temporality would be difficult to test unless prospective cohorts of birth populations were conducted. Instead, many investigators have conducted prospective studies in adults, following up individuals who were seronegative and seropositive at study entry and simultaneously evaluating changes in cognitive functions. Four studies have reported significantly worse cognitive function over time when participants seropositive at baseline were followed over 1–2 years and their temporal profile was compared with participants who were HSV-1 seronegative at study entry (Strandberg et al. 2003; Prasad et al. 2012b; Fruchter et al. 2015; Bhatia et al. 2017). No cognitive decline was associated with HSV-1 in three studies of older individuals (Nimgaonkar et al. 2016; Aiello et al. 2008; Barnes et al. 2014). However, temporal cognitive improvement was reported after acute encephalitis in one study (Hokkanen and Launes 1997). Thus, longitudinal follow-up studies of older individuals – similar to the pattern observed in cross-sectional studies – do not support HSVCD. Thus, temporality, an important tenet for Bradford Hill, is not observed consistently for HSVCD.

4.5 Biological Gradient

A linear relationship between the exposure to the risk factor or the “dose” of the risk factor and the outcome of interest provides persuasive evidence supporting causality, though the absence of such a relationship need not disprove causality. Bradford Hill cited the example of increased risk of lung cancer being related to the quantity of cigarettes consumed in support of this contention. This guideline is difficult to examine with regard to viral infection, as the “dose” of initial infection, the extent

of replication, and the residual infection are clearly impossible to quantify in the clinical research setting. Still, it has been reported that memory functions and executive functioning are associated with level of HSV1 exposure (Jonker et al. 2014). Though antibodies to HSV-1 are used routinely as a proxy for viral exposure, the antibody titers fluctuate with time and thus cannot be used to estimate "dosage" of exposure.

4.6 Plausibility

Bradford Hill suggested biological plausibility for the putative etiological link as another viewpoint, but he recognized that it depends on the level of knowledge available – and its unpredictable dependence on future scientific advances. In the case of HSV-1, the natural history of infection provides strong plausible links. It is well known that HSV-1 can infect the brain, causing acute encephalitis. Survivors of encephalitis are very likely to suffer from residual, lifetime cognitive impairment (Hokkanen and Launes 2007). The pertinent question is whether subacute (recurrent) encephalitis can occur and whether it is associated with cognitive impairment. Though replicating HSV-1 virions have not been detected in brains of humans, sans acute encephalitis, several studies have documented the presence of viral DNA among postmortem brain tissues from individuals who died from causes other than HSV-1 encephalitis (Baringer and Pisani 1994; Karatas et al. 2008; Hill et al. 2008). Thus, a plausible biological explanation is available for HSVCD.

4.7 Coherence

This viewpoint is related to plausibility. Bradford Hill suggested that the interpretation of cause-effect relationships should not conflict with what is known while recognizing that an absence of "coherence" should not be viewed as evidence against causality. With regard to smoking and lung cancer, Bradford Hill cited epidemiologic data relating to temporal changes in the incidence of smoking and lung cancer, as well as gender differences in the prevalence of both variables. Both sets of data are "coherent" with the proposed links between smoking and lung cancer. In the case of HSVCD, it may be instructive to draw on several brain imaging studies. All published studies of structural brain MRI scans have detected reduced gray matter volume in temporal-frontal brain regions among individuals without a history of encephalitis (Prasad et al. 2007, 2011; Schretlen et al. 2010; Pandurangi et al. 1994). While these cross-sectional studies are susceptible to some of the confounds discussed above with regard to the cross-sectional studies relating HSV-1 exposure to cognitive impairment, it is remarkable that the brain regions with significant differences among HSV-1-exposed and HSV-1-nonexposed individuals coincide with the regions predominantly affected in acute encephalitis due to HSV-1.

Furthermore, progressive cognitive impairments and gray matter loss were also reported among HSV-1 seropositive individuals with SZ, but not among seropositive nonpsychotic control individuals (Prasad et al. 2011).

4.8 Experiment

Bradford Hill recommended that experimental manipulation of the risk factor ought to provide valid tests of the putative hypothesis. This is not feasible for HSV-1, as effective vaccines are currently not available. On the other hand, randomized, controlled trials (RCTs) could provide relevant information, as could systematic reviews of such trials. As noted earlier, efficacious antiviral drugs, comprising acyclovir (ACV) and its prodrug valacyclovir (VAL), are widely available for treating HSV-1 infections. These drugs effectively halt the replicating stage and can be used prophylactically to reduce reactivation (Miserocchi et al. 2007; Acyclovir for the prevention of recurrent herpes simplex virus eye disease. Herpetic Eye Disease Study Group 1998; Wilhelmus et al. 1998), but they do not affect the latent state. Dickerson and colleagues initially reported improvement of psychotic symptoms following treatment with valacyclovir (VAL, an antiviral drug for HSV-1 infection) among individuals with SZ who were seropositive for cytomegalovirus (CMV) in a non-blinded study (Dickerson et al. 2003b), but the improvement could not be detected in randomized controlled trial (RCT) (Dickerson et al. 2009). Earlier, DeLisi and colleagues tested acyclovir in eight patients with schizophrenia and did not detect significant improvement (DeLisi et al. 1987). However, these studies were conducted among individuals with chronic SZ, and seropositivity for HSV-1 was not assessed. In contrast, our initial RCT indicated beneficial effects of adjunctive VAL over placebo among early-course HSV-1 seropositive SZ patients (Prasad et al. 2012a). A subsequent, larger RCT also detected improvement in two cognitive domains, although the cognitive domains in which improvement differed from the earlier RCT (Bhatia et al. 2017). A systematic review of these studies may provide worthwhile information, though it may be difficult to "harmonize" the differing sets of cognitive variables used in these treatment studies. Another caveat is the lack of efficacy of currently available antivirals against latent HSV-1 infection. If the cognitive impairment accrues from recurring cycles of latency and reactivation in small regions of the brain or it stems from immunological reactions to the infection (e.g., release of cytokines that can cross the blood-brain barrier to cause neuronal damage (Yarlagadda et al. 2009)), then the RCTs would not test the causal links rigorously.

4.9 Analogy

Bradford Hill suggested that persuasive evidence of a causal relationship between another agent and a specific disease could be marshalled to garner support for the agent of interest, even if the evidence was weaker. In the case of HSV-1, links between infection and cognitive impairment have been suggested for cytomegalovirus (CMV), although the evidence is also inconclusive (Shirts et al. 2008; Nimgaonkar et al. 2016). Stronger evidence has emerged for cognitive impairment even among individuals treated effectively for human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) (Watkins and Treisman 2015; Shirts et al. 2008). Thus, analogy, an admittedly weaker viewpoint, can still be marshalled in support of the HSVCD hypothesis.

5 Discussion

Based on these analyses, six out of nine Bradford Hill criteria for causation are fulfilled for HSVCD, thus linking chronic, asymptomatic HSV-1 infection to cognitive dysfunction *sans* encephalitis (Prasad et al. 2012b). A major proportion of the relevant studies have been conducted among patients with schizophrenia, though the associations have also been reported among otherwise healthy individuals. On balance, the accumulating evidence continues to incriminate HSV-1, though it is by no means unequivocal. The main criticism of the HSVCD hypothesis is that infective virions have not been identified in human brain tissues in the absence of acute encephalitis. Arguably, another unidentified coincidental infection or even low socioeconomic status could explain the observed cross-sectional associations.

Suggestions for future studies. More convincing evidence will only come from additional treatment trials, as well as cohort-based longitudinal studies. Furthermore, other modern advances could be marshalled to examine the HSVCD (Fedak et al. 2015). For example, large archival data, including datasets with DNA sequences from postmortem tissues, could be examined for the presence of HSV-1 sequences. Cognitive dysfunction related to persistent HSV-1 infection has been detected among otherwise healthy individuals, as well as persons with schizophrenia. It is uncertain whether the effect size of the associations is greater among the latter group, though an interaction between HSV-1 exposure and psychiatric diagnosis has not been reported. Still this question needs to be addressed further.

6 Conclusions

Our work suggests plausible causal links with enormous public health consequences, based on fulfillment of a majority of Bradford Hill viewpoints. In our view, the bulk of evidence points to moderate to strong evidence for causality. We recommend specific additional studies to test the hypothesis further.

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