Reply to Mendy

To the Editor—We thank Mendy for highlighting the importance of appropriate control of covariates including visual impairment, child’s education level and stroke, when examining the association between herpesviruses and cognitive impairment [1]. As noted, herpes simplex virus type 1 (HSV-1) enters latency in the trigeminal ganglion but can travel along facial nerves to the eye and cause ocular diseases such as conjunctivitis and herpes keratitis, severe cases of which may lead to scarring of the cornea and subsequent vision impairment, including blindness [2]. Similarly, cytomegalovirus (CMV) can infect the eye, causing CMV retinitis, which, although primarily observed in immunocompromised populations, can also lead to blindness [3]. Mendy, therefore, draws attention to one biological mechanism by which herpesviruses may lead to poorer performance on visually based cognitive tasks [1]. The National Health and Nutrition Examination Survey (NHANES) III asked all participants whether they had “trouble seeing with one or both eyes, even when wearing glasses or contact lenses,” and asked adults whether they had “total blindness in one or both eyes.” Among those tested for HSV-1 and cognition, the weighted proportion reporting visual impairment among children and middle-aged adults was 13.3% and 10.8%, respectively, and the weighted proportion reporting blindness among middle-aged adults was <1.0%.

HSV-1 but not CMV seropositivity was significantly associated with visual impairment among children in our sample (odds ratio, 1.69 [95% confidence interval (CI), 1.03–2.76]), after controlling for age, sex, race/ethnicity, poverty income ratio (PIR), family education level, country of origin, and smoking exposure. While there was no association between visual impairment and reading score, visual impairment remained significantly associated with block design score (β, −0.62 [95% CI, −1.22 to −0.02]), after adjusting for age, sex, race/ethnicity, PIR, family education level, country of origin, smoking exposure, and HSV-1 seropositivity. After additional adjustment for visual impairment, the associations between HSV-1 seropositivity and reading and block design scores were only slightly attenuated (i.e., β, −0.67 [95% CI, −1.17 to −0.16] and −0.78 [95% CI, −1.25 to −0.31], respectively) and remained statistically significant. Among middle-aged adults, CMV and HSV-1 seropositivity were not significantly associated with visual impairment, nor was visual impairment significantly associated with serial digit substitution test (SDST) impairment in fully adjusted models. In addition, there was no association between HSV-1 or CMV seropositivity and blindness, nor was blindness associated with SDST impairment among middle-aged adults. Moreover, there was no substantial attenuation of the association between HSV-1 or
CMV seropositivity and SDST impairment after additionally controlling for visual impairment or blindness. Our findings suggest, therefore, that herpesviruses likely negatively impact reading, spatial reasoning, and coding speed via mechanisms beyond infection-related visual impairment. Importantly, even if the impact of herpesviruses on cognitive test performance was mediated solely by visual impairment, herpesvirus infections could still result in the same adverse consequences across the lifecourse, such as poorer grades, lower educational attainment, and decreased social mobility.

Mendy also suggested that, beyond controlling for education level of head of household and PIR, we should control for child’s education level in our analyses [1]. However, since children in our sample had not completed their education, age is directly correlated with grade level; thus, additionally controlling for child’s education level would introduce substantial colinearity into our models. In auxiliary analyses, we did not observe a statistically significant association between HSV-1 or CMV seropositivity and repeating a grade because of academic failure in fully adjusted models among children in our sample. Most importantly, if herpesviruses are causally related to impaired cognition in childhood, lower educational attainment for age would be considered a potentially important consequence of infection-related cognitive deficits and not a confounder of the association between herpesviruses and cognitive impairment among children. Taken together, we consider controlling for child’s education level to be inappropriate in our analyses.

Finally, Mendy emphasized the importance of controlling for stroke in the examination of the association between herpesviruses and cognitive impairment among adults [1]. As noted elsewhere, cognitive impairment is a well-established sequel of stroke [4–5]. Importantly, several recent studies have implicated numerous persistent pathogens, including herpesviruses, in the etiology of stroke [6–8]; thus, history of stroke may represent an important mediating pathway by which herpesviruses influence cognitive impairment. In NHANES III, adult participants were asked, “Has a doctor ever told you that you had a stroke?” Among adults included in our analytic sample, the weighted population proportion reporting history of stroke was very low (<1.0% for middle-aged adults and <6.0% for older adults). Moreover, stroke history was not significantly associated with any measures of cognitive impairment among adults in our fully adjusted models. Furthermore, adjustment for stroke history resulted in no substantial attenuation of the association between HSV-1 or CMV seropositivity and SDST impairment or serial digit learning test total score among middle-aged adults and slightly increased the effect estimate for the association between HSV-1 and immediate memory impairment among adults ≥60 years of age (odds ratio, 3.28 [95% CI, 1.68–6.42]). Although we cannot rule out that cerebrovascular disease is a relevant mediating pathway by which herpesviruses influence cognition, these findings suggest that HSV-1 and CMV may impact cognitive impairment among US adults via biological mechanisms other than stroke. Overall, future studies that examine the longitudinal association between herpesviruses, beginning in childhood, and a wide range of cognitive measures (both visually and not visually based) across the lifecourse and that elucidate the biological pathways by which herpesviruses impact different domains of cognition are warranted.

Notes

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