Published in final edited form as:
Brain Behav Immun. 2013 November ; 34: 177–179. doi:10.1016/j.bbi.2013.08.002.

Reply to Letter Re: Childhood adversity and cell-mediated immunity in young adulthood

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Dear Editor and BBI readership,

We appreciate the correspondence from Dowd and colleagues, which informed us and BBI readers that our study (Slopen et al., 2013) using data from the National Longitudinal Study of Adolescent Health (Add Health) included individuals who were Epstein Barr Virus (EBV) seronegative. We agree with Dowd and colleagues that (1) use of EBV antibodies as an indicator of stress-related reactivation of latent herpes virus applies only to seropositive individuals, and (2) studies of psychosocial stressors and reactivation of latent herpes virus should focus exclusively on seropositive individuals. In error, we assumed that seronegative individuals did not have valid entries for EBV antibody levels in the Add Health data; for this reason, all individuals with an EBV antibody value were eligible for inclusion (range: 18–1310 au/mL). As a result, as described by Dowd and colleagues, our findings reflect both risk for EBV seropositivity and antibody response to latent infection among seropositive individuals, which introduced error into our associations of interest.

We appreciate that Dowd and colleagues have estimated a seronegative cut-off (i.e., the lowest 10% of continuous survey-weighted EBV antibody values), based on recent estimates from NHANES (Dowd et al., 2013). The criterion for establishing seropositivity varies

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depending on the assay used to measure EBV antibody titers. Notably, the EBV threshold value used by Dowd and colleagues for Add Health data is much higher than a previously-reported threshold (McDade et al., 2000), which exemplifies the importance of disseminating seropositivity threshold values at the time of data release for public-use or contractual datasets like Add Health.

Although the seronegativity threshold for Add Health has not been officially released, we have prepared tables to estimate how our results change once EBV seronegative individuals (i.e., EBV antibody values in the bottom 10%) are excluded. Associations of socioeconomic position and child maltreatment with EBV antibody levels are attenuated once seronegative individuals are excluded, and several of the associations that were significant at $p < 0.05$ are no longer significant. Specifically, Table 3A shows that the pattern of significant associations for the indicators of socioeconomic position remain similar, with exceptions that the association between “some college” and elevated EBV titers dropped to marginal significance, and the middle parental occupational status category is no longer associated with elevated EBV titers. With regard to child maltreatment (see Table 4A), respondents who were first exposed to physical abuse at ages 3–5 years continue to have heightened EBV antibody levels both relative to those who were never abused ($p<.01$), and compared to those first exposed during ages 14–17 ($p < 0.05$). However, in contrast to our original results, models that only include seropositive individuals do not find that individuals reporting >10 occasions of sexual abuse had significantly higher EBV titers.

We thank the Editor for the opportunity to submit revised tables so that readers can observe how our results change once seronegative individuals are excluded. We have requested that these tables be linked to our original article.

References

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McDade TW, Stallings JF, Angold A, Costello EJ, Burleson M, Cacioppo JT, Glaser R, Worthman CM. Epstein–Barr virus antibodies in whole blood spots: a minimally invasive method for assessing an aspect of cell-mediated immunity. Psychosom. Med. 2000; 62:560–568. [PubMed: 10949102]

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Table 3A

Regression coefficients for the relationship between adolescent socioeconomic context and log EBV antibody titers (au/mL) in young adulthood among individuals seropositive for EBV (N = 11886).[a]

	β (Standard error)			
	Model 1	**Model 2**	**Model 3**	**Model 4**
Sex				
Female	0.12 (0.01)***	0.12 (0.01)***	0.12 (0.01)***	0.12 (0.01)***
Male	–	–	–	–
Age	0.01 (0.00)**	0.01 (0.00)**	0.01 (0.00)**	0.01 (0.00)**
Race				
Black	0.16 (0.02)***	0.16 (0.02)***	0.16 (0.02)***	0.16 (0.02)***
Asian	−0.04 (0.04)	−0.04 (0.04)	−0.04 (0.04)	−0.05 (0.04)
Hispanic	0.04 (0.03)	0.04 (0.03)	0.03 (0.03)	0.03 (0.03)
Multi-racial, native American, other	0.05 (0.03)	0.05 (0.03)	0.05 (0.03)	0.05 (0.03)
White	–		–	
Smoker in home, Wave 1				
Missing	0.01 (0.02)	0.01 (0.02)	0.02 (0.03)	0.00 (0.02)
Yes	0.04 (0.02)**	0.03 (0.02)*	0.04 (0.02)*	0.03 (0.02)*
No				
Parent education				
Parent did not attend or uncertain		0.00 (0.05)		
Less than high school		0.03 (0.03)		
High school/GED/vocational high school		0.07 (0.02)**		
Some voc. or tech. post-sec.		0.03 (0.03)		
Some college		0.05 (0.02)~		
College		0.04 (0.03)		
>College degree		–		
Family income, Wave 1				
Missing			0.02 (0.03)	
<$20,000			0.04 (0.02)~	
$20,001–$40,000			0.06 (0.02)*	
$40,001–$60,000			0.01 (0.02)	
>$60,000			–	
Parent occupation, Wave 1				
Missing				0.04 (0.03)
Service/construction/ military				0.05 (0.02)**
Technical/sales/office worker				0.03 (0.02)
Professional/manager				–
R^2	0.03	0.03	0.03	0.03

[a] All models are weighted and take into account complex sample design. Beta-coefficients are based on linear regression models predicting log-transformed EBV antibody titers. Seronegative individuals excluded from sample (estimated as bottom 10% of sample).

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.0001$.

~ $p < 0.10$.

Table 4A

Regression coefficients for the relationship between frequency of abuse and timing of 1st onset of abuse and log EBV antibody titers (au/mL) in young adulthood among individuals seropositive for EBV.[a,b,c]

	Physical abuse β (Standard error)				Sexual abuse β (Standard error)			
	Model 1a	**Model 2a**	**Model 3a**	**Model 4a**	**Model 1b**	**Model 2b**	**Model 3b**	**Model 4b**
	***N* = 11,838**	***N* = 11,838**	***N* = 11,680**	***N* = 2072**	***N* = 11,854**	***N* = 11,854**	***N* = 11,832**	***N* = 607**
Any abuse	0.02 (0.02)				−0.01 (0.03)			
Frequency								
1–2 times		0.04 (0.03)				−0.04 (0.04)		
3–10 times		−0.01 (0.03)				0.01 (0.04)		
>10 times		0.02 (0.03)				0.05 (0.05)		
None		–				–		
Timing of 1st abuse								
Infancy (0–2 years)			−0.04 (0.11)				0.11 (0.11)	
Preschool (3–5 years)			0.12 (0.04)**				0.01 (0.06)	
Latency (6–8 years)			−0.04 (0.04)				−0.06 (0.05)	
Pre-pubertal (9–10 years)			0.01 (0.05)				−0.02 (0.07)	
Pubertal (11–13 years)			0.05 (0.04)				0.08 (0.07)	
Adolescent (14–17 years)			0.03 (0.03)				−0.14 (0.08)	
Never abused			–				–	
Timing of 1st abuse among exposed								
Infancy (0–2 years)				−0.05 (0.11)				0.24 (0.15)
Preschool (3–5 years)				0.09 (0.04)*				0.16 (0.10)
Latency (6–8 years)				−0.05 (0.05)				0.09 (0.11)
Pre-pubertal (9–10 years)				−0.02 (0.06)				0.13 (0.10)
Pubertal (11–13 years)				0.02 (0.05)				0.22 (0.11)~
Adolescent (14–17 years)				–				–
R^2	0.03	0.03	0.03	0.04	0.03	0.03	0.03	0.07

[a]Beta-coefficients are based on linear regression models predicting log-transformed EBV antibody titers. All models are weighted, take into account complex sample design, and are adjusted for age, race, smoker in household at Wave 1, parental education, and parent occupation status at Wave 1. Seronegative individuals excluded from sample (estimated as bottom 10% of sample).

[b] Sample sizes vary slightly across models due to missing data on reports of physical and sexual abuse, and age at first onset of abuse. The sample sizes decrease in Model 3 because 158 respondents who reported physical abuse and 22 respondents who reported sexual abuse did not provide an age at first occurrence. In Model 4, the sample sizes reflect only individuals who reported abuse and provided an age at first occurrence.

[c] R^2 values reflect the full model (i.e., coefficients presented in the table, and covariates listed in Footnote a).

* $p < 0.05$.

** $p < 0.01$.

~ $p < 0.10$.