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Association between early parental deprivation and cellular immune function among adults in rural Fujian, China.

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Abstract

This study investigated the role of childhood parental deprivation in the association between quality of life (QOL) and the Epstein–Barr virus (EBV) antibody titer, a marker of cellular immune functioning, using data from 734 adults living in seven communities in rural Fujian, China. Parental deprivation was defined if either of their parents had died, divorced, or left them for migratory work for more than 1 year before they turned (1) 16 years of age (childhood and adolescence), or (2) 3 years of age (early childhood). A mixed effects regression analysis with a random effects model revealed that parental deprivation during early childhood was positively associated with the EBV antibody titer (coefficient = 0.33, $p = 0.007$), whereas parental deprivation during the first 16 years was not. Further analysis incorporating an interaction term between QOL and parental deprivation revealed a significant interaction between QOL and

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Conflict of Interest

There is no conflict of interest to declare.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author (AY) upon reasonable request.

parental deprivation during early childhood; a significant association between QOL and the EBV antibody titer was found only among those who reported parental deprivation during early childhood. This study suggests that parental deprivation during the period of immune-system development may be linked with physiological responses to stressors later in life.

Keywords

Quality of Life; China; Family Relations; Biomarkers; Immune System Phenomena

1 | INTRODUCTION

Previous studies have suggested a link between the early-life environment and the development of the immune function (Weaver, 2009), and both physical (e.g., the in utero environment, nutritional status, microbial exposure) (MacGillivray & Kollmann, 2014) and social (e.g., poverty and adverse childhood experiences (ACEs)) (Danese & McEwen, 2012) environmental factors have been studied in this context. In general, living in an adverse environment may result in a weak immune system due to alterations in hypothalamic–pituitary–adrenal (HPA) axis functioning, which can lead to life-long dysregulation of reactions to stressors due to its regulation of cellular immunity (Gunnar & Quevedo, 2007). These findings are consistent with concepts originating in life history theory and ecological immunology (McDade, 2005).

To test the robustness of previous findings in other socio–ecological settings, we examined whether childhood parental deprivation, which is a form of neglect (Barlow et al., 2016), modified the association between psychological stress and cellular immune function in adults living in rural Chinese communities. We focused on parental deprivation as it can affect both the physical and psychological health of individuals (De Bellis, 2005). Additionally, as the number of left-behind children has been increasing in rural China, it is especially important to examine the impact of parental deprivation to increase our understanding of the impact of societal changes on the health of the population.

Therefore, this study examined whether individuals who experienced parental deprivation in their childhood tended to have worse cellular immune functioning; more specifically, following the lead of previous studies (McDade, 2001), we investigated whether cellular immune function, as measured by the Epstein–Barr virus (EBV) antibody titer, reacted to stressors differently in the presence of the third factor (i.e., parental deprivation in our study). The EBV is one of the ubiquitous herpes viruses that is regulated by the cell-mediated immune function and the EBV antibody titer has been used as an index of cellular immune functioning (Glaser et al., 1991).

2 | METHODS

2.1. | Field survey

A field survey was conducted in seven rural communities in Fujian, China, in August 2015 to collect information and dried blood spot samples for the measurement of the EBV antibody titer and C-reactive protein (CRP) concentration. All residents aged 18 years or

older who resided in the study communities were invited to participate in the survey. Sociodemographic data were obtained through the use of a questionnaire. The EBV antibody titer and CRP concentrations were analyzed by enzyme-linked immunosorbent assay (ELISA) based on the protocols developed by the Department of Anthropology at the University of Oregon (Eick, Urlacher, McDade, Kowal, & Snodgrass, 2016) and the Center for Studies in Demography and Ecology, University of Washington (Brindle, Fujita, Shofer, & O'Connor, 2010). Detailed information about the survey and measurement tools was provided previously (Yazawa et al., 2018).

2.2 | Parental deprivation

Parental deprivation was defined as the absence of either of the parents; more specifically, participants were asked if their parents had died, divorced, or left them for migratory work for more than 1 year before they turned (1) 16 years of age (childhood and adolescence) or (2) 3 years of age (early childhood). Although ACEs are usually defined as adverse experience that occurred before the age of 18 years (Boullier & Blair, 2018), we used 16 as cut-off given that people in rural China, particularly the current cohort, may have left home earlier (i.e., soon after they graduated from middle school).

2.3. | Quality of life

A general question evaluating current quality of life (QOL) was drawn from the abbreviated version of the World Health Organization's Quality of Life questionnaire (WHOQOL-BREF) (World Health Organization, 1998) to evaluate QOL. Participants were asked "*How would you rate your quality of life?*"; responses were scored on a five-point Likert scale and then collapsed into two categories to identify those who were potentially stressed: "very poor" and "poor" were scored as 1, whereas "neither poor nor good," "good," and "very good" were scored as 0.

2.4. | Sociodemographic information

Marital status was analyzed in terms of three categories: partnered, unmarried and divorced/widowed. Educational attainment was divided into three categories: illiterate (cannot read or write) or has not graduated from elementary school (less than 6 years of schooling); graduated from elementary school (6 years of schooling); and junior high school or above (9 years of schooling or above). Self-rated health was assessed with the following question "*How satisfied are you with your health?*". "Very dissatisfied" or "dissatisfied" were scored as 1, whereas "neither satisfied nor dissatisfied," "satisfied," and "very satisfied" were scored as 0.

2.5. | Statistical analysis

After excluding those with missing information about socioeconomic variables and/or parental deprivation ($n = 33$), those who lacked blood samples ($n = 3$), and those with a serum-equivalent CRP concentration higher than 10 mg/L ($n = 27$; i.e., those with acute inflammation) (Libby & Ridker, 2004), the final sample size for the analysis was 734.

A mixed effects regression analysis with a random effects model to account for multiple individuals in each community were used to investigate the association between parental

deprivation during their first 16 years and EBV antibody titer in Model 1, whereas Model 2 included that during first 3 years. Models 3 and 4 included the interaction between parental deprivation during the first 16 and 3 years, respectively, and QOL. The models were adjusted for age, age-squared, sex, marital status, education and CRP concentration. Age-squared term was incorporated to account for non-linearity of the association between age and EBV antibody titer; marital status, education and CRP concentration were incorporated in the models as they might confound the association between parental deprivation and EBV antibody titer (Yazawa et al., 2018; Fagundes et al., 2012). We confirmed that there was no multicollinearity.

All statistical analyses were conducted using Stata 13.1 (StataCorp, College Station, TX, USA). The level of statistical significance was set at $p < 0.05$ (two-tailed).

2.6. | Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional and/or National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. The research protocol was officially approved by the appropriate sectors of the Chinese government. The field surveys were conducted after obtaining approval from the Ethics Committee for Medical Research at the University of Tokyo (No. 10515-(1)) and the Ethics Committee of the Institute of Tropical Medicine at Nagasaki University (No. 120910100).

3 | RESULTS

3.1 | Characteristics of study participants

The basic characteristics of the participants are shown in Table 1. Among the total population ($N = 734$), 25.6% and 6.7% experienced parental deprivation during their first 16 years and 3 years, respectively. The mean age was 58.9 years, and males accounted for 39% of the participants. The mean log-transformed EBV antibody titer was 4.9 ELISA units.

3.2 | Factors associated with EBV antibody titer

A mixed effects regression analysis with a random effects model (Table 2) revealed that parental deprivation during early childhood was positively associated with the EBV antibody titer (coefficient = 0.33, $p = 0.007$), whereas parental deprivation during the first 16 years was not significantly associated with the EBV antibody titer (coefficient = -0.014 , $p = 0.84$).

Further analysis incorporating the interaction term between QOL and parental deprivation revealed a significant interaction between QOL and parental deprivation during early childhood (coefficient = 0.61, $p = 0.043$). Specifically, whereas individuals without experience of parental deprivation had stable EBV antibody titers irrespective of their QOL, those who experienced parental deprivation in early childhood had increased EBV antibody titers when their QOL was worse (Figure 1).

4 | DISCUSSION

This study found that, in rural Fujian, China, lower QOL was associated with higher EBV antibody titers among those who experienced parental deprivation during early childhood (i.e., before the age of 3), whereas we did not find evidence of an association between QOL and the EBV antibody titer among those who did not experience parental deprivation. Such patterns were not observed when the period of parental deprivation was extended to cover all experiences before the age of 16 years. These findings suggest that parental deprivation early in life may have long-lasting effects on the immune function and that its impact might differ depending on the age at which such experiences occurred.

Although a few studies have reported higher EBV antibody titers among those with ACEs, e.g., girls who experienced traumatic life events (McDade et al., 2000) and breast cancer survivors who experienced childhood adversity (Fagundes, Glaser, Malarkey, & Kiecolt-Glaser, 2013), this study found immune dysfunction only when people reported a low QOL (i.e., presumably due to exposure to more stressors). This may be explained by the stress amplification model, which is among the theories used to explain the greater psychological sensitivity to current stressors observed among people with ACEs (Rudolph & Flynn, 2007). The present results suggest that the immune function of people who have experienced parental deprivation may also become sensitive to subsequent stressors.

There are several possible mechanisms that may underlie this association. First, parental deprivation may have resulted in a lack of physical support, which is vital for the development of the immune system in early life (e.g., breast feeding). Given that most study participants were children soon after World War II, when the country was severely affected by famine, children who lacked parental care might have been at a higher risk of material deprivation as well. Second, parental deprivation may have put people at higher risk for insecure attachment. Attachment is defined as the affectional bond between primary caregivers and children that shapes the latter's relationships with other people, behavior, and coping skills used to respond to stressors throughout life (Bowlby, 1977). Insecure attachment has been shown to be associated with worse health outcomes, including higher EBV antibody titers among adults (Fagundes et al., 2014; Miller, Chen, & Parker, 2011).

In terms of the timing of the exposure, the present study indicated that earlier exposure (i.e., in the first 3 years) was detrimental to cellular immune functioning in adulthood, whereas that during the first 16 years was not associated with it. Our findings are consistent with those reported by Slopen, McLaughlin, Dunn, and Koenen (2013) showing that participants who experienced physical abuse when they were 3 to 5 years old showed significantly suppressed immune function compared to those exposed during ages 14 to 17 and those who were never abused. Given that there are marked changes in HPA axis activity during the first few years of life (Jansen, Beijers, Riksen-Walraven, & de Weerth, 2010), it is possible that earlier experiences of adversity have a more fundamental impact on immune development than do later experiences.

There are several limitations to our study. First, the cross-sectional nature of this study prevented us from making causal inferences. Second, although we used information on

quality of life, which was the best available in our dataset, to identify those who were potentially stressed, a direct measure of psychological stress (e.g., perceived stress scale (Cohen, Kamarck, & Mermelstein, 1983)) might have been more appropriate. Also, the single question of QOL might not have been fully captured the multifaceted nature of QOL. Third, information on other forms of ACEs (e.g., child abuse and poverty) was not available. As other ACEs also have substantial effects on the development of the immune system, the lack of such information limited our ability to understand all aspects of this issue. Fourth, our study sample might not have represented the rural population in Fujian; for example, those who did not participate in the study or those who were excluded due to missing information might have been biased in terms of socioeconomic status or parental deprivation. Fifth, data on relationships with alternative caregivers (e.g., grandmothers) were not available, which further limited our ability to interpret our data in terms of attachment theory given that individuals other than parents may have provided warm and responsive caregiving to those who experienced parental deprivation.

Data show that one in five children in China—about 61 million—are currently left behind by their parents who migrate for the purpose of work; this pattern is especially true in rural areas (The All-China Women's Federation's, 2013). Given that those with impaired immunity would be at higher risk for poor mental and physical health (Elwenspoek, Kuehn, Muller, & Turner, 2017), attention should be paid to the impact of parental deprivation on health to develop better public health strategies and prevent the further expansion of rural–urban inequalities in health.

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Figure 1.

Interaction effect of the relationship between QOL and early parental deprivation on EBV antibody titer.

*Log-transformed Epstein-Barr virus antibody titer scores of 4.3 and 5.5 correspond to the 25th and 75th percentile values, respectively.

Table 1.

Basic characteristics of the participants (N = 734)

	Total	Parental deprivation during the first 16 years		Parental deprivation during the first 3 years	
		Yes (n=188)	No (n=546)	Yes (n=49)	No (n=685)
Age (in years), mean [SD]	58.9 [12.9]	65.6 [11.8]	56.6 [12.4]	68.6 [10.5]	58.2 [12.7]
Sex (male), n (%)	286 (39.0)	85 (44.7)	202 (37.0)	19 (38.8)	267 (39.0)
Marital status, n (%)					
Unmarried	27 (3.6.8)	5 (2.7)	22 (4.0)	3 (6.2)	24 (3.5)
Partnered	596 (81.2)	135 (71.8)	461 (84.4)	30 (61.2)	566 (82.6)
Divorced or widowed	111 (15.1)	48 (25.5)	63 (11.5)	16 (32.7)	95 (13.9)
Education, n (%)					
Illiterate	271 (36.9)	88 (46.8)	183 (33.5)	29 (59.2)	242 (35.3)
Less than elementary school	292 (39.8)	73 (38.8)	219 (40.1)	16 (32.7)	276 (40.3)
Junior high school or high school	171 (23.3)	27 (14.4)	144 (26.4)	4 (8.2)	167 (24.4)
QOL (Bad)	96 (13.1)	32 (17.0)	64 (11.7)	10 (20.5)	86 (12.6)
Self-rated health (Bad)	181 (24.7)	49 (26.1)	132 (24.2)	14 (28.6)	167 (24.4)
Log-EBV antibody titer (ELISA unit), mean [SD]	4.9 [0.83]	5.0 [0.87]	4.9 [0.82]	5.3 [0.94]	4.9 [0.82]
Log-CRP concentration (mg/L), mean [SD]	-0.32 [1.1]	-0.19 [1.2]	-0.36 [1.1]	-0.088 [1.2]	-0.34 [1.1]

SD: standard deviation; CRP: C-reactive protein; EBV: Epstein-Barr virus; ELISA: Enzyme-linked immunosorbent assay

Table 2.

Association between parental deprivation and EBV antibody titer (N = 734)

	Model 1	Model 2	Model 3	Model 4
Parental deprivation during first 16 years	-0.026 (-0.17, 0.12)		-0.035 (-0.19, 0.12)	
Parental deprivation during first 3 years		0.32** (0.081, 0.56)		0.20 (-0.066, 0.47)
Overall QOL (ref. Good)	-0.041 (-0.23, 0.15)	-0.051 (-0.24, 0.14)	-0.059 (-0.28, 0.16)	-0.11 (-0.31, 0.082)
Parental deprivation during first 16 years × Overall QOL			0.058 (-0.32, 0.43)	
Parental deprivation during first 3 years × Overall QOL				0.61* (0.014, 1.2)
Age (in years)	-0.14 (-0.49, 0.22)	-0.025 (-0.061, 0.011)	-0.027 (-0.063, 0.0096)	-0.025 (-0.060, 0.011)
Age squared	2.8×10^{-4} (-2.6×10^{-5} , 5.9×10^{-4})	2.6×10^{-4} (-4.8×10^{-5} , 5.6×10^{-4})	2.8×10^{-4} (-2.4×10^{-5} , 5.9×10^{-4})	2.5×10^{-4} (-5.1×10^{-5} , 5.6×10^{-4})
Sex	0.11 (-0.020, 0.24)	0.11 (-0.025, 0.24)	0.11 (-0.021, 0.24)	0.11 (-0.026, 0.24)
Marital status (ref. Partnered)				
Unmarried	-0.14 (-0.49, 0.22)	-0.16 (-0.51, 0.19)	-0.14 (-0.49, 0.22)	-0.14 (-0.49, 0.21)
Divorced or widowed	8.6×10^{-4} (-0.18, 0.19)	-0.010 (-0.19, 0.17)	-0.0016 (-0.19, 0.18)	-0.0097 (-0.19, 0.17)
Education (ref. Illiterate)				
Less than elementary school	-0.14 (-0.28, 0.0060)	-0.13 (-0.28, 0.011)	-0.14 (-0.28, 0.0076)	-0.13 (-0.28, 0.0099)
Junior high school or more	-0.13 (-0.31, 0.061)	-0.12 (-0.31, 0.067)	-0.13 (-0.31, 0.061)	-0.13 (-0.32, 0.057)
General health (ref. Good)	0.14 (-0.0018, 0.29)	0.15 (-3.8×10^{-5} , 0.29)	0.14 (-0.0023, 0.29)	0.15* (0.0069, 0.30)
CRP concentration (log-transformed)	0.049 (-0.0067, 0.11)	0.048 (-0.0077, 0.10)	0.049 (-0.0069, 0.10)	0.050 (-0.0054, 0.11)

Correlation coefficients and 95% confidence intervals are shown.

A random effects model was used to account for multiple individuals in each community.

** : p < 0.01;

* : p < 0.05