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Original article

# Does cytomegalovirus infection contribute to socioeconomic disparities in all-cause mortality?

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ABSTRACT

The social patterning of cytomegalovirus (CMV) and its implication in aging suggest that the virus may partially contribute to socioeconomic disparities in mortality. We used Cox regression and inverse odds ratio weighting to quantify the proportion of the association between socioeconomic status (SES) and all-cause mortality that was attributable to mediation by CMV seropositivity. Data were from the National Health and Nutrition Examination Survey (NHANES) III (1988–1994), with mortality follow-up through December 2011. SES was assessed as household income (income-to-poverty ratio ≤1.30; >1.30 to ≤1.85; >1.85 to ≤3.50; >3.50) and education (<high school; high school; >high school). We found strong associations between low SES and increased mortality: hazard ratio (HR) 1.80; 95% confidence interval (CI): 1.57, 2.06 comparing the lowest versus highest income groups and HR 1.29; 95% CI: 1.13, 1.48 comparing <high school versus >high school education. 65% of individuals were CMV seropositive, accounting for 6–15% of the SES-mortality associations. Age modified the associations between SES, CMV, and mortality, with CMV more strongly associated with mortality in older individuals. Our findings suggest that cytomegalovirus may partially contribute to persistent socioeconomic disparities in mortality, particularly among older individuals.



## 1. Introduction

In 2013, over 45 million Americans were living in poverty (DeNavas-Walt and Proctor, 2014) and 24.5 million of those over the age 25 had not completed high school (Census Bureau, 2013). Due to a complex and interrelated set of social, behavioral, and biological processes—both historical and contemporary—individuals with a lower socioeconomic status (SES) persistently suffer a disproportionate burden of premature mortality associated with a range of health conditions and have a lower overall life expectancy (Deaton, 2016; Chetty et al., 2016; Adler and Newman, 2002; Braveman et al., 2010; Meyer et al., 2013; Hummer and Hernandez, 2013; National Center for Health Statistics Health, 2011; Geronimus et al., 2011; Krueger et al., 2015; Muennig et al., 2010; Olshansky et al., 2012). While SES is clearly linked to mortality, the mechanisms underlying this disparity remain poorly understood.

One potential, yet under investigated, pathway through which socioeconomic disadvantage may "get under the skin" to impact mortality is through differential pathogen exposure across the life course. Prior studies have shown that low SES is associated with both seropositivity for (Bate et al., 2010; Cannon et al., 2010; Colugnati et al., 2007; Dowd et al., 2009a; Dowd et al., 2009b; Staras et al., 2006; Simanek et al., 2009) and immune control of (Dowd et al., 2008; Dowd and Aiello, 2009; Dowd et al., 2012) the herpesvirus cytomegalovirus (CMV), a pathogen that once acquired persists in a latent state but is capable of reactivation. A parallel body of evidence suggests that seropositivity to and reactivation of CMV may play a key role in long-term health outcomes. Indeed, the virus has been implicated in the etiology of numerous chronic disease outcomes including cardiovascular disease, cognitive and physical decline, depression and cancer (Simanek et al., 2009; Aiello et al., 2006; Harkins et al., 2002; Itzhaki et al., 2004; Liu et al.,

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2006; Samanta et al., 2003; Schmaltz et al., 2005; Sorlie et al., 2000; Simanek et al., 2014; Tarter et al., 2014). Moreover, in previous population-based studies by the authors as well as others, CMV seropositivity has been shown to predict all-cause mortality (Gkrania-Klotsas et al., 2013; Roberts et al., 2010; Simanek et al., 2011). The exact biological mechanisms by which CMV may impact health are still under investigation, but a growing body of evidence suggests that subclinical reactivation of the virus over the life course triggers clonal expansion of CMV-specific memory T-cells, ultimately contributing to overall age-related declines in immune function and increased levels of inflammation (Derhovanessian et al., 2011; Hadrup et al., 2006; Khan et al., 2002; Pawelec, 2013; Pawelec et al., 2009). The impact of CMV-driven immunosenescence may already be apparent in younger people and potentially accelerate as the individual ages (Turner et al., 2014). This is consistent with recent findings that CMV infection may enhance responses to influenza vaccination in young people but be detrimental in the elderly (Furman et al., 2015).

The social patterning of CMV and its implication in long-term health outcomes, including mortality, suggest that infection with the pathogen may partially contribute to socioeconomic disparities in mortality. While previous studies have identified CMV seropositivity as a key mediator of the association between SES and specific chronic disease outcomes (Simanek et al., 2009), to our knowledge, no studies have quantified the role of CMV as a mediator between SES and all-cause mortality at the population level. Using data from a nationally representative sample of US adults, we assessed whether two factors that influence socioeconomic status—household income and educational attainment—were associated with all-cause mortality, and moreover quantified the proportions of these associations that were attributable to mediation by CMV seropositivity. In addition, we examined whether the pathways linking socioeconomic status, CMV seropositivity, and mortality were modified by age.

## 2. Methods

### 2.1. Study population

The data for the present study were from the National Health and Nutrition Examination Survey (NHANES) III (1988–1994), a population-based survey based on a multistage stratified probability sample. NHANES III was conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) and was designed to provide nationally representative estimates of the civilian noninstitutionalized US population. Full details on the NHANES III study design and response rates have been published previously (Anon, 1994).

Of the 39,994 individuals who participated in the NHANES III, all individuals who completed both the household interview and the physical examination (n = 30,818) were eligible for inclusion in the present analysis (see Fig. 1). To focus on adult socioeconomic status, we limited our analysis to individuals who were at least 25 years of age (n = 14,769), as has been done in prior studies (Dowd and Aiello, 2009). Fully adjusted models were further limited to those who had been tested for CMV and those who had complete information on household income and study covariates (n = 12,729). Four additional individuals had insufficient identifying data to confirm their mortality status in the National Death Index, resulting in a final sample size of 12,725.

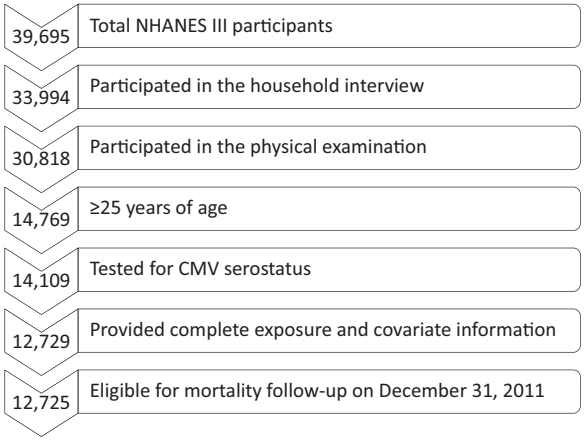


**Fig. 1.** Study Flow.

### 2.2. Measures

#### 2.2.1. Socioeconomic status

The primary exposure in the present study was socioeconomic status assessed as household income and educational attainment. Household income was measured by the income-to-poverty ratio (IPR), which was calculated by dividing total annual household income by the annual poverty threshold as determined by the US Census Bureau based on household size (for example, an IPR of 1.5 indicates that the family income is 1.5 times the poverty threshold). As prior studies strongly suggest that the income-mortality gradient is non-linear (Dowd et al., 2011), we created four categories for household income using the US Department of Agriculture's food assistance program's income eligibility cut-points for free (IPR $\leq$1.30) or reduced (IPR $\leq$1.85) school lunches as recommended in the NHANES III Analytic and Reporting Guidelines (National Center for Health Statistics, 1996): low (IPR $\leq$1.30), low-middle (IPR >1.30 to $\leq$1.85), middle (IPR >1.85 to $\leq$3.50), and high (IPR >3.50). Educational attainment was originally assessed as the number of years of completed education, which we categorized as: less than high school (0 to <12 years), high school (12 years), and more than high school (13+ years) based on recommended cut-points in the NHANES III guidelines (National Center for Health Statistics, 1996).

#### 2.2.2. Mortality status

To ascertain participants' mortality status, we linked the NHANES III interview, examination, and laboratory data to the Public-use Linked Mortality File, which includes vital statistics for survey participants 18 years of age and older from the date of survey participation through December 31, 2011 (National Center for Health Statistics, 2015). All NHANES III participants with sufficient identifying information to confirm their mortality status in the National Death Index were included in the Public-use Linked Mortality File. Full details on the linkage process have been described previously (National Center for Health Statistics, 2011).

#### 2.2.3. CMV serostatus

CMV serostatus (positive or negative) was the mediating pathway of interest. CMV specific immunoglobulin G (IgG) antibody levels were measured at the CDC in stored sera of NHANES III participants with an Enzyme Linked Immunosorbent Assay (ELISA) (Quest International, Inc., Miami FL). Sera with values near the ELISA cutoff were confirmed with a second ELISA assay (bioMerieux, Inc., Durham, NC). If results of the initial and confirmatory tests disagreed, an Immunofluorescence Assay (IFA) (Bion International, Inc.) was used and the result from this assay was taken as the final test result. This algorithm achieved 98% sensitivity and 99% specificity (Staras et al., 2006).

#### 2.2.4. Covariates

Potential confounders of the association between SES and mortality were assessed via a directed acyclic graph (Greenland et al.,