Web Appendix 1.

Women's Health and Aging Studies (WHAS) I and II details

WHAS I and II were sampled from the same sampling frame, the Health Care Financing Administration's Medicare eligibility lists for 12 contiguous zip code areas in Baltimore, Maryland. Besides disability status, eligibility criteria were identical for the two studies, except that a mini-mental state exam (MMSE) score (1) of 18 or higher was required for WHAS I and a score of 24 or higher was required for WHAS II. For WHAS I, an age-stratified random sample was drawn from 5,316 women who were eligible for screening, 4,137 were screened, 1,409 met study criteria, 1,002 agreed to participate in the study, and 786 participated in blood drawing. There were no major differences in sociodemographic or reported health characteristics between participants and those who declined to participate (2). Standardized questionnaires and physical examinations were administered in participants' homes at baseline and at 6 follow-up examinations conducted 6 months apart over a follow-up time of 3 years. For WHAS II, an age-stratified random sample was drawn from 3,541 women who were eligible for screening, 1,630 were screened, 880 met study criteria, 436 agreed to participate in the study, and 430 participated in blood drawing. Participants were more highly educated and reported more diseases than those who declined but did not differ significantly in disability characteristics (3). Standardized questionnaires and physical examinations were administered in the Johns Hopkins Functional Status Laboratory at baseline and at 6 follow-up examinations conducted 18 months apart, except for a 54-month interval between the second and third examinations, over a follow-up time of 12 years. For both cohorts, diagnoses of 17 major chronic diseases were adjudicated by physicians using ascertainment algorithms (2): diabetes mellitus, angina pectoris, myocardial infarction, congestive heart failure, peripheral arterial disease, stroke, Parkinson's disease, pulmonary disease, cancer, rheumatoid arthritis, osteoarthritis of the knee, hip, and hand, degenerative disc disease, spinal stenosis, osteoporosis, and hip fracture. In this study, diseases were considered present if classified as definite or probable by adjudication or as self-reported for non-adjudicated diagnoses.

Women who did and did not participate in blood drawing were not different by race, education, smoking history, or prevalence of diabetes, but were different by age (76.3 vs. 80.8 years, respectively; $P < 0.0001$) and prevalence of cardiovascular disease (51.3% vs. 61.4%, respectively; $P = 0.02$). However, any bias that could result from this would also require that the distribution of antibody-positive and negative women who did not participate in blood drawing be different from those who did participate. In this regard, it is possible to envision that those who did not participate, being older and more likely to have cardiovascular disease, might have a higher prevalence of antibody seropositivity and have a higher risk of mortality or incident frailty. If this were the case, our results would likely be biased conservatively toward the null, rather than overestimating the true association. Nevertheless, exclusion of these women should not affect the internal validity of our findings.

Web Appendix 2.

Additional details on CMV IgG measurement

The ELISA kit used in this study to measure serum CMV IgG included antigens from all parts of the virus replication cycle: early antigens, late antigens, nuclear antigen, cytoplasmic antigen, and structural and non-structural proteins. The preparation was derived from strain AD-169, cultured in MRC-5, a diploid cell line of human lung origin. Each specimen was tested in duplicate and the optical density was calibrated against four standard reference specimens to yield the quantitative IgG antibody concentration. Intra-assay coefficient of variation was 2.8%.

Web Appendix 3.

Definition and classification of frailty

Frailty was defined using a five-component measure that was originally proposed in the Cardiovascular Health Study (4) and subsequently validated in WHAS (5). The five components, each a binary criterion measured using standardized questions or protocols, consisted of:

1) Shrinking, defined as unintentional weight loss ≥ 10% since age 60 or body mass index (BMI) < 18.5 kg/m^2 (at baseline), or unintentional annual weight loss of ≥ 5% or BMI < 18.5 kg/m^2 (at follow-ups);

2) Exhaustion, defined as self report of having low usual energy level (≤ 3 on a 0–10 scale), feeling unusually tired in the previous month, or feeling unusually weak in the previous month;

3) Low energy expenditure, defined as being in the lowest quintile of energy expenditure measured using a six-item version of the Minnesota Leisure Time Activity Questionnaire (2) (walking, doing strenuous household chores, doing strenuous outdoor chores, dancing, bowling, regular exercise);

4) Slowness, defined as being in the lowest quintile of walking speed over a 4 m distance (assistance from a walking device, but not another person, allowed);

5) Weakness, defined as being in the lowest quintile of hand grip strength measured using a JAMAR handheld dynamometer (model BK-7498; Fred Sammons, Inc., Burr Ridge, IL) (best out of 3 attempts in the dominant hand).

Participants meeting three or more of these criteria were classified as frail; those meeting one or two as prefrail; and those meeting none as nonfrail.

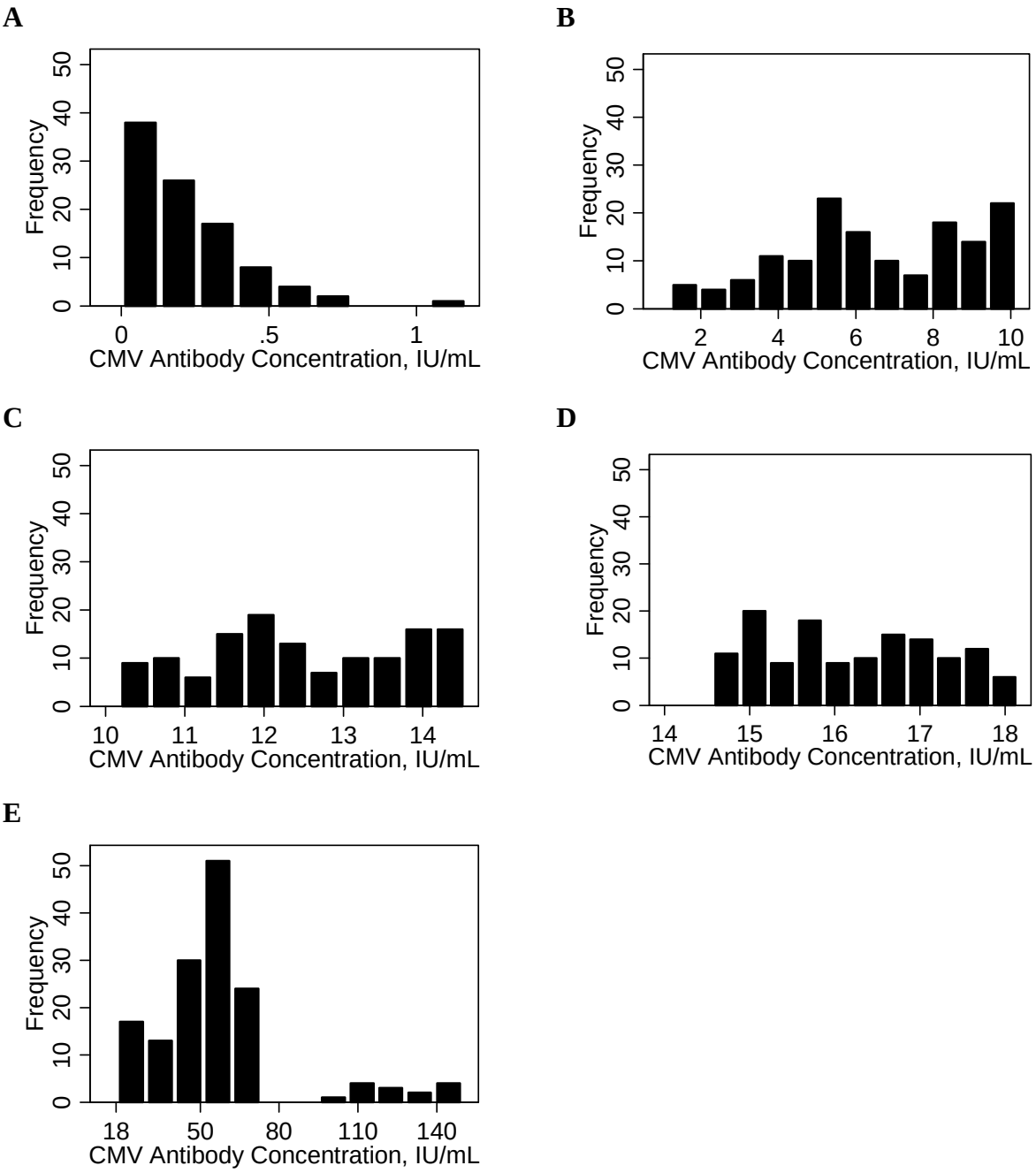
Web Appendix 4.

Covariates in multivariable models: definition and rationale for choice

In multivariable models, we controlled for the effects of participant factors that were highly likely to be confounders in, and for possible modifying effects they might have on, the relationship between CMV IgG antibody concentration and frailty or mortality: age, race, years of education, coverage by private medical insurance, history of smoking, cardiovascular disease, diabetes mellitus, and plasma IL-6 concentration. CMV infection is known to be associated with older age, female sex, being black or Mexican American, fewer years of education, birth outside of the U.S., medical insurance from a nonprivate source, lower household income, and larger family size, according to seroepidemiologic data from the National Health and Nutrition Examination Survey (NHANES) III (6). However, the associations with household income and family size could be accounted for by the other demographic factors in multivariable models (6). Data on country of birth were not collected in WHAS. Therefore, the sociodemographic variables included in our final models were age, race, completion of high school education, and coverage by private medical insurance, all of which have been reported to be associated with frailty (4, 7) and mortality (8, 9) or have scientific plausibility to be associated with these outcomes (10). CMV infection is associated with cardiovascular disease, including coronary atherosclerosis, myocardial infarction, congestive heart failure, carotid atherosclerosis, and stroke (11-17). Diabetes and cigarette smoking can also be potentially associated with CMV infection, frailty, and mortality (4, 18-23). IL-6 is a known effect modifier in the association between CMV infection and frailty (24) and cardiac mortality (25). Although cognitive decline is associated with both CMV infection and frailty (4, 26), MMSE, when added to the regression models, did not influence the effect estimates in an important way and was not included in the final model in order to avoid over-adjustment.

To avoid the assumption of linearity in the relationship between CMV IgG antibody concentration and prevalent frailty, incident frailty, and mortality, we categorized CMV IgG concentration (IU/mL) into five groups: a seronegative group and four additional groups according to quartiles of antibody concentration in the seropositive range. Frequency distributions of antibody concentration in each of the five groups are shown in Web Figure 1. Continuous variables consisted of age (years, centered around 70), cigarette smoking (pack-years), and plasma IL-6 concentration (pg/mL), the last of which, being highly skewed, was transformed by a natural logarithm. We did not transform cigarette smoking because, despite its skewed distribution, transformations did not improve model fit. Categorical variables consisted of self-identification as being white or black, completion of high school education (yes, no), coverage by private medical insurance (yes, no), presence of cardiovascular disease (yes, if presence of any of the following: angina, myocardial infarction, congestive heart failure, peripheral artery disease, or stroke; no, if absence of all of these entities), and presence of diabetes mellitus (yes, no).

Web Figure 1. Frequency distributions of cytomegalovirus antibody concentration for participants in the (A) seronegative range (≤1.20 IU/mL) and (B) first quartile (1.21–10.16 IU/mL), (C) second quartile (10.17–14.55 IU/mL), (D) third quartile (14.56–18.16 IU/mL), and (E) fourth quartile (18.17–150 IU/mL) of the seropositive range.

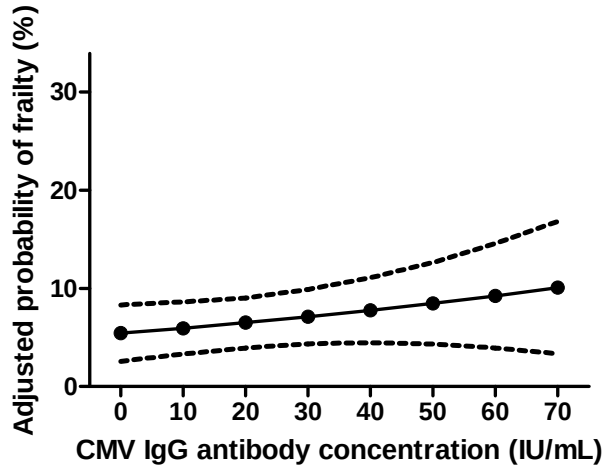


Web Appendix 5.

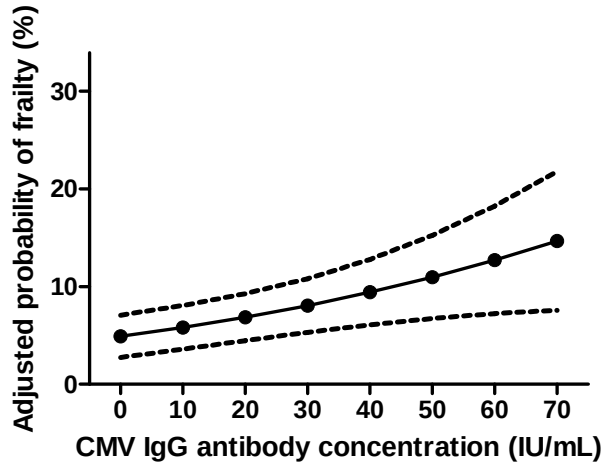
Web Figure 2. Predicted probabilities of frailty at incremental levels of cytomegalovirus IgG antibody concentration, at three different plasma interleukin-6 concentrations.

Predicted probabilities of frailty at incremental levels of serum CMV IgG antibody concentration are shown at three plasma IL-6 concentrations: the midpoints of the (A) first tertile (1.62 pg/mL), (B) second tertile (2.69 pg/mL), and (C) third tertile (4.81 pg/mL). Probabilities of frailty were predicted from a multinomial regression model, modeling CMV as a continuous variable, adjusting for age, race, high school education, coverage by private medical insurance, pack-years of smoking, cardiovascular disease (angina, myocardial infarction, congestive heart failure, peripheral artery disease, or stroke), and diabetes mellitus, and modeling for effect modification by plasma IL-6 concentration. Variables other than CMV and IL-6 were set to their mean values, after centering. Dotted lines delineate the point-wise 95% CI. CMV, cytomegalovirus; IgG, immunoglobulin G.

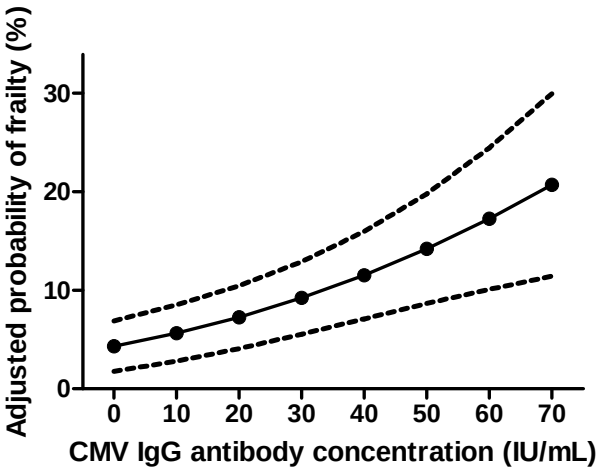
A



B



C


Adjusted probability of frailty (%)
30
20
10
0
0
10
20
30
40
50
60
70
CMV IgG antibody concentration (IU/mL)

Web Appendix 6.

Web Table 1. Causes of Death by Cytomegalovirus IgG Antibody Concentration, Women's Health and Aging Studies I and II, Baltimore, Maryland, 1992–2002.

CMV IgG Antibody Concentration (IU/mL)	Cause of Death	No. of Participants	Percentage Among Participants in Antibody Concentration Category (%)
≤1.20	CVD, including MI	2	28.6
	Cancer	1	14.3
	Infection, urinary tract	1	14.3
	Respiratory disease, excluding infection	1	14.3
	Unknown	2	28.6
1.21–10.16	CVD, including MI	7	38.9
	Cancer	2	11.1
	Gastrointestinal	1	5.6
	Psychiatric	1	5.6
	Respiratory, excluding infection	3	16.7
	Sensory organ	1	5.6
	Stroke	1	5.6
	Unknown	2	11.1
10.17–14.55	CVD, including MI	6	35.3
	Cancer	4	23.5
	Gastrointestinal	2	11.8
	Infection, lung	1	5.9
	Infection, wound	1	5.9
	Respiratory, excluding infection	1	5.9
	Stroke	1	5.9
	Unknown	1	5.9
14.56–18.16	CVD, including MI	2	14.3
	Cancer	3	21.4
	Dementia	1	7.1
	Diabetes	1	7.1
	Infection, bone	1	7.1
	Infection, lung	1	7.1
	Respiratory, excluding infection	3	21.4
	Stroke	1	7.1
	Unknown	1	7.1
18.17–150	CVD, including MI	10	28.6
	Cancer	7	20.0
	Dementia	1	2.9
	Diabetes	1	2.9
	Infection, lung	1	2.9
	Joint	1	2.9
	Respiratory, excluding infection	4	11.4
	Renal	2	5.7
	Stroke	4	11.4
	Unknown	4	11.4

Abbreviations: CMV, cytomegalovirus; IgG, immunoglobulin G; CVD, cardiovascular disease; MI, myocardial infarction.

Web Appendix 7.

Web Table 2. Adjusted Hazard Ratios[a] for Incident Frailty by Cytomegalovirus IgG Antibody Concentration, Effect-Modified by Interlukin-6 Concentration, Women's Health and Aging Studies I and II, Baltimore, Maryland, 1992–2002.

	CMV IgG Antibody Concentration (IU/mL)[b]								
Plasma IL-6	≤1.20	1.21–10.16		10.17–14.55		14.56–18.16		18.17–150	
Concentration[c]	HR	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
1st Tertile	1.00	2.35	0.82, 6.75	1.12	0.33, 3.77	0.58	0.13, 2.58	1.66	0.54, 5.05
2nd Tertile	1.00	1.94	0.75, 4.99	1.48	0.54, 4.08	1.10	0.37, 3.32	2.31	0.90, 5.92
3rd Tertile	1.00	1.55	0.41, 5.91	2.05	0.55, 7.62	2.28	0.64, 8.15	3.32	0.94, 11.75

Abbreviations: CMV, cytomegalovirus; IgG, immunoglobulin G; IL-6, interleukin-6; HR, hazard ratio; CI, confidence interval.

[a] Hazard ratios were derived from a Cox proportional hazards model, adjusting for age, race, high school education, coverage by private medical insurance, pack-years of smoking, cardiovascular disease (angina, myocardial infarction, congestive heart failure, peripheral artery disease, or stroke), and diabetes mellitus, and modeling for effect modification by plasma IL-6 concentration. Comparisons were made against participants whose CMV IgG antibody concentration was ≤ 1.20 IU/mL.

[b] Baseline CMV IgG antibody concentration > 1.20 IU/mL was considered seropositive, reflecting prior CMV infection.

[c] Plasma IL-6 concentration was modeled as a continuous variable. Hazard ratios were derived by setting IL-6 to the midpoints (medians) of each indicated tertile, the values of which were 1.62, 2.69, and 4.81 pg/mL, respectively.

Web Table 3. Adjusted Hazard Ratios for Mortality by Cytomegalovirus IgG Antibody Concentration, Effect-Modified by Interlukin-6 Concentration, Women's Health and Aging Studies I and II, Baltimore, Maryland, 1992–2002.

	CMV IgG Antibody Concentration (IU/mL)[b]								
Plasma IL-6	≤1.20	1.21–10.16		10.17–14.55		14.56–18.16		18.17–150	
Concentration	HR	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
1st Tertile	1.00	1.72	0.51, 5.81	0.80	0.20, 3.25	1.00	0.28, 3.51	1.44	0.46, 4.56
2nd Tertile	1.00	2.03	0.82, 5.02	1.69	0.63, 4.58	1.36	0.53, 3.53	2.65	1.09, 6.41
3rd Tertile	1.00	2.46	0.52, 11.69	3.95	0.91, 17.16	1.95	0.43, 8.79	5.18	1.24, 21.62

Abbreviations: CMV, cytomegalovirus; IgG, immunoglobulin G; IL-6, interleukin-6; HR, hazard ratio; CI, confidence interval.

[a] Hazard ratios were derived from a Cox proportional hazards model, adjusting for age, race, high school education, coverage by private medical insurance, pack-years of smoking, cardiovascular disease (angina, myocardial infarction, congestive heart failure, peripheral artery disease, or stroke), and diabetes mellitus, and modeling for effect modification by plasma IL-6 concentration. Comparisons were made against participants whose CMV IgG antibody concentration was ≤ 1.20 IU/mL.

[b] Baseline CMV IgG antibody concentration > 1.20 IU/mL was considered seropositive, reflecting prior CMV infection.

[c] Plasma IL-6 concentration was modeled as a continuous variable. Hazard ratios were derived by setting IL-6 to the midpoints (medians) of each indicated tertile, the values of which were 1.62, 2.69, and 4.81 pg/mL, respectively.

Web Appendix 8.

Sensitivity analysis: Adopting three alternative categorization schemes for CMV antibody concentration

Web Table 4. Incident Frailty and Mortality Rates by Cytomegalovirus IgG Antibody Concentration, Women's Health and Aging Studies I and II, Baltimore, Maryland, 1992–2002.

		CMV IgG Antibody Concentration (IU/mL)[a]			
Incident Frailty (3 Years)	All participants	≤1.20	1.21–11.93	11.95–16.82	16.83–150
No. at risk	482	73	151	128	130
No. of events	80	7	29	16	28
Incidence (95% CI) per 1000 person-years	60.1 (48.3, 75.6)	29.6 (14.3, 71.9)	68.1 (47.8, 100.2)	45.6 (27.5, 81.2)	84.6 (59.3, 124.9)
Unadjusted hazard ratio (95% CI)		1.0	2.32 (1.00, 5.39)	1.58 (0.62, 4.00)	3.01 (1.28, 7.05)
Adjusted hazard ratio*[b] (95% CI)		1.0	2.00 (0.81, 4.93)	1.11 (0.40, 3.02)	2.04 (0.81, 5.16)
All-Cause Mortality (5 Years)					
No. at risk	635	92	188	168	187
No. of events	91	7	26	20	38
Incidence (95% CI) per 1000 person-years	28.0 (22.7, 35.0)	14.0 (6.7, 34.2)	26.2 (17.9, 39.6)	23.1 (14.6, 38.7)	42.3 (30.6, 59.8)
Unadjusted hazard ratio (95% CI)		1.0	1.87 (0.79, 4.42)	1.65 (0.67, 4.08)	3.04 (1.32, 7.02)
Adjusted hazard ratio**[b] (95% CI)		1.0	2.10 (0.91, 4.83)	1.55 (0.63, 3.80)	2.33 (1.03, 5.30)

Abbreviations: CMV, cytomegalovirus; IgG, immunoglobulin G; CI, confidence interval.

* $P = 0.38$; ** $P = 0.12$ (P by likelihood ratio test)

[a] Baseline CMV IgG antibody concentration > 1.20 IU/mL was considered seropositive, reflecting prior CMV infection.

[b] Hazard ratios were derived from Cox proportional hazards models, adjusting for age, race, high school education, coverage by private medical insurance, pack-years of smoking, cardiovascular disease (angina, myocardial infarction, congestive heart failure, peripheral artery disease, or stroke), diabetes mellitus, and plasma interleukin-6 concentration. Comparisons were made against participants whose CMV IgG antibody concentration was ≤ 1.20 IU/mL.

Web Table 5. Incident Frailty and Mortality Rates by Cytomegalovirus IgG Antibody Concentration, Women's Health and Aging Studies I and II, Baltimore, Maryland, 1992–2002.

		CMV IgG Antibody Concentration (IU/mL)[a]			
Incident Frailty (3 Years)	All participants	≤1.20	1.21–29.99	30–69.99	70–150
No. at risk	482	73	322	76	11
No. of events	80	7	53	17	3
Incidence (95% CI) per 1000 person-years	60.1 (48.3, 75.6)	29.6 (14.3, 71.9)	60.2 (46.1, 80.1)	84.3 (53.3, 141.4)	117.2 (39.5, 505.8)
Unadjusted hazard ratio (95% CI)		1.0	2.05 (0.91, 4.62)	3.12 (1.26, 7.73)	4.79 (1.14, 20.21)
Adjusted hazard ratio*[b] (95% CI)		1.0	1.63 (0.68, 3.93)	2.11 (0.78, 5.66)	2.42 (0.56, 10.37)
All-Cause Mortality (5 Years)					
No. at risk	635	92	415	106	22
No. of events	91	7	52	24	8
Incidence (95% CI) per 1000 person-years	28.0 (22.7, 35.0)	14.0 (6.7, 34.2)	24.0 (18.2, 32.4)	50.3 (33.7, 77.9)	71.7 (36.2, 153.7)
Unadjusted hazard ratio (95% CI)		1.0	1.72 (0.76, 3.89)	3.61 (1.51, 8.65)	5.27 (1.84, 15.13)
Adjusted hazard ratio**[b] (95% CI)		1.0	1.71 (0.77, 3.80)	2.72 (1.15, 6.40)	3.73 (1.26, 11.08)

Abbreviations: CMV, cytomegalovirus; IgG, immunoglobulin G; CI, confidence interval.

* $P = 0.11$; ** $P = 0.005$ (P by likelihood ratio test)

[a] Baseline CMV IgG antibody concentration > 1.20 IU/mL was considered seropositive, reflecting prior CMV infection.

[b] Hazard ratios were derived from Cox proportional hazards models, adjusting for age, race, high school education, coverage by private medical insurance, pack-years of smoking, cardiovascular disease (angina, myocardial infarction, congestive heart failure, peripheral artery disease, or stroke), diabetes mellitus, and plasma interleukin-6 concentration. Comparisons were made against participants whose CMV IgG antibody concentration was ≤ 1.20 IU/mL.

Web Table 6. Incident Frailty and Mortality Rates by Cytomegalovirus IgG Antibody Concentration, Women's Health and Aging Studies I and II, Baltimore, Maryland, 1992–2002.

		CMV Serpositivity[a]	
Incident Frailty (3 Years)	All participants	Negative	Positive
No. at risk	482	73	409
No. of events	80	7	73
Incidence (95% CI) per 1000 person-years	60.1 (48.3, 75.6)	29.6 (14.3, 71.9)	65.7 (52.3, 83.5)
Unadjusted hazard ratio (95% CI)		1.0	2.28 (1.03, 5.05)
Adjusted hazard ratio*[b] (95% CI)		1.0	1.73 (0.73, 4.13)
All-Cause Mortality (5 Years)			
No. at risk	635	92	543
No. of events	91	7	84
Incidence (95% CI) per 1000 person-years	28.0 (22.7, 35.0)	14.0 (6.7, 34.2)	30.5 (24.4, 38.4)
Unadjusted hazard ratio (95% CI)		1.0	2.18 (0.98, 4.85)
Adjusted hazard ratio**[b] (95% CI)		1.0	2.03 (0.93, 4.40)

Abbreviations: CMV, cytomegalovirus; IgG, immunoglobulin G; CI, confidence interval.

* $P = 0.17$; ** $P = 0.07$ (P by likelihood ratio test)

[a] Baseline CMV IgG antibody concentration > 1.20 IU/mL was considered seropositive, reflecting prior CMV infection.

[b] Hazard ratios were derived from Cox proportional hazards models, adjusting for age, race, high school education, coverage by private medical insurance, pack-years of smoking, cardiovascular disease (angina, myocardial infarction, congestive heart failure, peripheral artery disease, or stroke), diabetes mellitus, and plasma interleukin-6 concentration. Comparisons were made against participants whose CMV IgG antibody concentration was ≤ 1.20 IU/mL.

References for Web Appendix

1. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12(3):189-98.
2. Fried LP, Kasper JD, Guralnik JM, et al. The Women's Health and Aging Study: An introduction. In: Guralnik JM, Fried LP, Simonsick EM, et al., eds. *The Women's Health and Aging Study: Health and Social Characteristics of Old Women with Disability (NIH Publication no 95-4009)*. Bethesda, MD: National Institute on Aging, 1995:1-8.
3. Fried LP, Bandeen-Roche K, Chaves PH, et al. Preclinical mobility disability predicts incident mobility disability in older women. *J Gerontol A Biol Sci Med Sci* 2000;55(1):M43-52.
4. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *The journals of gerontology Series A, Biological sciences and medical sciences* 2001;56(3):M146.
5. Bandeen-Roche K, Xue QL, Ferrucci L, et al. Phenotype of frailty: characterization in the women's health and aging studies. *JGerontolA BiolSciMedSci* 2006;61(3):262.
6. Staras SA, Dollard SC, Radford KW, et al. Seroprevalence of cytomegalovirus infection in the United States, 1988-1994. *ClinInfectDis* 2006;43(9):1143.
7. Woods NF, LaCroix AZ, Gray SL, et al. Frailty: emergence and consequences in women aged 65 and older in the Women's Health Initiative Observational Study. *JAmGeriatrSoc* 2005;53(8):1321.
8. Lantz PM, House JS, Lepkowski JM, et al. Socioeconomic factors, health behaviors, and mortality: results from a nationally representative prospective study of US adults. *Jama* 1998;279(21):1703-8.
9. McWilliams JM, Zaslavsky AM, Meara E, et al. Health insurance coverage and mortality among the near-elderly. *Health Aff (Millwood)* 2004;23(4):223-33.
10. Baker DW, Sudano JJ, Albert JM, et al. Lack of health insurance and decline in overall health in late middle age. *N Engl J Med* 2001;345(15):1106-12.
11. Blum A, Giladi M, Weinberg M, et al. High anti-cytomegalovirus (CMV) IgG antibody titer is associated with coronary artery disease and may predict post-coronary balloon angioplasty restenosis. *Am J Cardiol* 1998;81(7):866-8.
12. Newman AB, Gottdiener JS, McBurnie MA, et al. Associations of subclinical cardiovascular disease with frailty. *JGerontolA BiolSciMedSci* 2001;56(3):M158.
13. Sorlie PD, Nieto FJ, Adam E, et al. A prospective study of cytomegalovirus, herpes simplex virus 1, and coronary heart disease: the atherosclerosis risk in communities (ARIC) study. *Arch Intern Med* 2000;160(13):2027-32.
14. Nieto FJ, Adam E, Sorlie P, et al. Cohort study of cytomegalovirus infection as a risk factor for carotid intimal-medial thickening, a measure of subclinical atherosclerosis. *Circulation* 1996;94(5):922-7.
15. Gattone M, Iacoviello L, Colombo M, et al. Chlamydia pneumoniae and cytomegalovirus seropositivity, inflammatory markers, and the risk of myocardial infarction at a young age. *Am Heart J* 2001;142(4):633-40.
16. Simanek AM, Dowd JB, Aiello AE. Persistent pathogens linking socioeconomic position and cardiovascular disease in the US. *Int J Epidemiol* 2009;38(3):775-87.

17. Adam E, Melnick JL, Probtsfield JL, et al. High levels of cytomegalovirus antibody in patients requiring vascular surgery for atherosclerosis. *Lancet* 1987;2(8554):291-3.
18. Pak CY, Eun HM, McArthur RG, et al. Association of cytomegalovirus infection with autoimmune type 1 diabetes. *Lancet* 1988;2(8601):1-4.
19. Roberts BW, Cech I. Association of type 2 diabetes mellitus and seroprevalence for cytomegalovirus. *South Med J* 2005;98(7):686-92.
20. Blum A, Peleg A, Weinberg M. Anti-cytomegalovirus (CMV) IgG antibody titer in patients with risk factors to atherosclerosis. *Clin Exp Med* 2003;3(3):157-60.
21. Hubbard RE, Searle SD, Mitnitski A, et al. Effect of smoking on the accumulation of deficits, frailty and survival in older adults: a secondary analysis from the Canadian Study of Health and Aging. *J Nutr Health Aging* 2009;13(5):468-72.
22. Kenfield SA, Stampfer MJ, Rosner BA, et al. Smoking and smoking cessation in relation to mortality in women. *Jama* 2008;299(17):2037-47.
23. Roper NA, Bilous RW, Kelly WF, et al. Excess mortality in a population with diabetes and the impact of material deprivation: longitudinal, population based study. *Bmj* 2001;322(7299):1389-93.
24. Schmaltz HN, Fried LP, Xue QL, et al. Chronic cytomegalovirus infection and inflammation are associated with prevalent frailty in community-dwelling older women. *J Am Geriatr Soc* 2005;53(5):747-54.
25. Blankenberg S, Rupprecht HJ, Bickel C, et al. Cytomegalovirus infection with interleukin-6 response predicts cardiac mortality in patients with coronary artery disease. *Circulation* 2001;103(24):2915-21.
26. Aiello AE, Haan M, Blythe L, et al. The influence of latent viral infection on rate of cognitive decline over 4 years. *J Am Geriatr Soc* 2006;54(7):1046-54.