Chlamydia pneumoniae, Herpes Simplex Virus Type 1, and Cytomegalovirus and Incident Myocardial Infarction and Coronary Heart Disease Death in Older Adults

The Cardiovascular Health Study

David S. Siscovick, MD, MPH; Stephen M. Schwartz, PhD; Lawrence Corey, MD; J. Thomas Grayston, MD; Rhoda Ashley, PhD; San-Ping Wang, PhD; Bruce M. Psaty, MD, PhD; Russell P. Tracy, PhD; Lewis H. Kuller, MD, DrPH; Richard A. Kronmal, PhD

Background—Whether serological evidence of prior infection with Chlamydia pneumoniae, herpes simplex virus type 1 (HSV-1), and cytomegalovirus (CMV) is associated with myocardial infarction (MI) and coronary heart disease (CHD) death remains a source of controversy.

Methods and Results—We conducted a nested case-control study among participants in the Cardiovascular Health Study, a cohort study of persons aged ≥65 years. Cases experienced an incident MI and CHD death (n = 213). Control subjects were matched to cases by age, sex, clinic, year of enrollment, and month of blood draw (n = 405). Serum was analyzed for IgG antibodies to C pneumoniae, HSV-1, and CMV. After adjustment for other risk factors, the risk of MI and CHD death was associated with the presence of IgG antibodies to HSV-1 (odds ratio [OR] 2.0, 95% CI 1.1 to 3.6) but was not associated with the presence of IgG antibodies to either C pneumoniae (OR 1.1, 95% CI 0.7 to 1.8) or CMV (OR 1.2, 95% CI 0.7 to 1.9). Although there was little association with low to moderate C pneumoniae antibody titers (≤1:512), high-titer (1:1024) C pneumoniae antibody was associated with an increased risk (OR 2.2, 95% CI 1.1 to 4.4).

Conclusions—Among older adults, the presence of IgG antibodies to HSV-1 was associated with a 2-fold increase in the risk of incident MI and CHD death. For C pneumoniae, only high-titer IgG antibodies were associated with an increased risk of MI and CHD death. The presence of IgG antibodies to CMV was not associated with risk among the elderly.

(Circulation. 2000;102:2335-2340.)

Key Words: bacteria, viruses, myocardial infarction, coronary heart disease, aging

The role of viruses and other infectious agents, such as Chlamydia pneumoniae, in the development of atherosclerosis and incident myocardial infarction (MI) and coronary heart disease (CHD) death has long been an area of investigative interest.1–22 Animal/experimental, pathological, and cross-sectional seroepidemiological studies conducted among middle-aged populations provide some support for the hypothesis that infections with herpes simplex virus type 1 (HSV-1), cytomegalovirus (CMV), and C pneumoniae are associated with the development of atherosclerosis and CHD.5–16 However, recent reports from several prospective studies failed to demonstrate consistent associations between the presence of IgG antibodies to C pneumoniae, HSV-1, and CMV and incident MI.17–22 Given both the high prevalence of IgG antibodies to these agents and the high incidence of cardiovascular disease among older adults, it is particularly important to determine whether serological evidence of prior infection with these agents, assessed late in life, is associated with incident MI and CHD death. We examined this question in an ancillary study to the Cardiovascular Health Study (CHS), a cohort study of men and women aged ≥65 years.23

Methods

Overview

We conducted a nested case-control study within the CHS cohort.24–31 Cases (n = 213) were defined by the occurrence of an incident fatal or nonfatal MI (n = 167) or CHD death (n = 46) that...
occurred from 0.1 to 4.3 years after a blood draw. The median time
to event was 2.1 years (interquartile range 1.3 to 3.1 years. Approx-
imately 2 control subjects (n = 405) were individually matched to
each case (patient) by age, sex, field center, and date (year and
month) of blood draw. Sera from cases and control subjects were
tested for IgG antibodies to \textit{C pneumoniae}, HSV-1, and CMV.

\textbf{Setting}

Briefly, CHS is a prospective cohort study of 5888 men and women
\(\geq 65\) years old who were randomly selected from Medicare eligibility
lists in 4 communities: Forsyth County, NC; Sacramento County,
Calif; Washington County, Md; and Allegheny County, Pa. In 1989
through 1990, 5201 participants were recruited and examined; in
1992 to 1993, 687 additional black participants were recruited and
examined.

\textbf{Baseline Examination}

The baseline examination, which was conducted in 1989 to 1990,
consisted of standard questionnaires that were used to assess risk
factors and medical history\textsuperscript{23,24} and a clinic examination that in-
cluded seated blood pressure, anthropometric measures, venipunc-
ture, resting ECG, spirometry, ankle-arm systolic blood pressure
index, and carotid sonography.\textsuperscript{25–29} Fasting serum glucose, plasma
lipids and lipoproteins, serum fibrinogen, C-reactive protein, and
white blood cell count were measured. During an examination in
1992 to 1993, the baseline examination described here was repeated
for the initial (1989 to 1990) cohort and was conducted for the first
time for the supplemental black (1992 to 1993) cohort.

\textbf{Follow-Up and Classification of Events}

Details of the follow-up for events are described elsewhere.\textsuperscript{31} All
participants were contacted every 6 months, and the contacts
alternated between a telephone interview and an in-clinic examina-
tion. At each 6-month contact, participants were asked about
vascular events and all hospitalizations. Discharge summaries
and diagnoses were obtained for all hospitalizations. For all potential
vascular events, additional information, including cardiac
diagnoses were obtained for all hospitalizations. For all potential
vascular events, additional information, including cardiac
enzyme and serial ECGs, was collected from the medical records.
The algorithms for classification of MI and definite fatal CHD are
described elsewhere.\textsuperscript{31}

\textbf{Selection of Cases and Control Subjects}

The cases and matched control subjects were selected for this
ancillary study in 2 phases, on the basis of the first available serum
specimen, with each phase defined according to the source of the
blood specimen used to test for antibodies. For the first phase, the
source of the blood specimen was the baseline CHS examination
(1989 to 1990), and we selected all cases of incident MI or CHD
death that occurred during the initial 5.5 years of follow-up after the
baseline examination. For the second phase, the source of the blood
specimen was the 1992 to 1993 clinical examination, and we selected
all cases of incident MI or CHD death that occurred during 3.5 years
of follow-up among participants in that examination and whose
events had not already been selected in the first phase. From each
phase, we excluded a participant if he or she had a prior history of
MI that predated the blood draw. Incident MI or CHD deaths
that were the consequence of a procedure, such as surgery or
angioplasty, were not included.

\textbf{Serological Evidence of Prior Infection}

Sera obtained at baseline or at the 1992 to 1993 clinic examinations
were shipped to the University of Washington (Seattle) for testing.
The samples were batch-analyzed with case-control pairs retained
in random order within the same batch. The laboratories were blinded
to case-control status of the paired sera.

IgG antibody to \textit{C pneumoniae} was measured with a microimmu-
nofluorescence antibody test.\textsuperscript{32} Sera were screened for a positive
antibody response at a dilution of 1:8, and those with a positive
response were further tested at dilutions of 1:8, 1:16, 1:32, 1:64, and
1:1024. Based on an earlier report,\textsuperscript{14} an IgG antibody titer of at least
1:8 was considered diagnostic of past \textit{C pneumoniae} infection
a priori. Prior duplicate testing demonstrated that the percent
agreement with a cut point of 1:8 as a positive antibody response was
100%.

IgG antibody to HSV-1 was assessed with a Western blot test.
Because HSV titers are not associated with reactivation of latent
HSV or with clinical disease,\textsuperscript{33,34} we focused on the presence or
absence of antibody to HSV-1 and did not measure antibody titers.
The methods and criteria for assay of the presence of HSV-1
antibody have been described in detail elsewhere.\textsuperscript{34} The assay
discriminates between HSV-1 and HSV-2.

Antibody to CMV was assessed with a passive latex agglutination
assay (CMVScan; Becton Dickinson). This test has been shown to be
both sensitive and specific compared directly with other test formats
for CMV antibody.\textsuperscript{35,36} Because of variation in end point titers
between runs, the result of considerable run-to-run variability in the
performance of the test for the antigen, we focused on the presence
or absence of antibody to CMV, rather than on CMV antibody titers.

\textbf{TABLE 1. Characteristics of Patients With MI/CHD Death and
Control Subjects}

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (n=213)</th>
<th>Control Subjects (n=405)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>74.3±6.2</td>
<td>73.6±5.5</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>63.9</td>
<td>63.2</td>
</tr>
<tr>
<td>White, %</td>
<td>85.5</td>
<td>88.6</td>
</tr>
<tr>
<td>Education, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12, %</td>
<td>38.0</td>
<td>29.0</td>
</tr>
<tr>
<td>12–16, %</td>
<td>30.1</td>
<td>35.6</td>
</tr>
<tr>
<td>17+, %</td>
<td>31.9</td>
<td>35.4</td>
</tr>
<tr>
<td>Cigarette smoking, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>11.9</td>
<td>11.8</td>
</tr>
<tr>
<td>Former</td>
<td>48.6</td>
<td>44.3</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.2±4.4</td>
<td>26.7±4.5</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>25.2</td>
<td>14.1</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>50.2</td>
<td>40.7</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>142.3±21.9</td>
<td>136.6±21.7</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>116.3±40.0</td>
<td>109.9±32.2</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>143.7±79.4</td>
<td>131.8±65.9</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>51.1±14.8</td>
<td>53.1±14.2</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>123.8±34.7</td>
<td>123±36.1</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>331.3±64.2</td>
<td>324.7±67.6</td>
</tr>
<tr>
<td>WBC, ×10(^3)</td>
<td>6.74±1.9</td>
<td>6.20±1.7</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>3.2±3.6</td>
<td>3.5±6.5</td>
</tr>
<tr>
<td>Albumin, mg/dL</td>
<td>4.0±0.3</td>
<td>4.0±0.3</td>
</tr>
<tr>
<td>FEV(_1)</td>
<td>2.05±0.7</td>
<td>2.24±0.7</td>
</tr>
<tr>
<td>Energy expenditure, kcal/wk</td>
<td>1534.8±1918.2</td>
<td>1715.0±2005.9</td>
</tr>
<tr>
<td>Self-assessed health status, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good or excellent</td>
<td>31.0</td>
<td>42.8</td>
</tr>
<tr>
<td>Fair</td>
<td>42.3</td>
<td>36.9</td>
</tr>
<tr>
<td>Aspirin use,* %</td>
<td>34.5</td>
<td>36.0</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; CRP, C-reactive protein.
* = \(\geq 2\) d in 2 wk before blood draw.
Values are mean±SD.
Statistical Analysis

We used conditional logistic regression, and we estimated the odds ratio (OR) and 95% CIs associated with serological evidence of prior infection, as reflected by the presence of IgG antibodies. Separate multivariate models were used to examine the association between each infection and incident MI and CHD death. We also examined the associations with prior infection when the 3 agents were considered simultaneously in the same logistic model. For C pneumoniae, we also examined the associations of antibody titers with incident MI and CHD death. In addition, we explored whether the time to event influenced the risk associated with either the presence (for HSV-1 and CMV) or titer (for C pneumoniae) of IgG antibody.

To determine whether the association between antibodies and incident MI and CHD death was modified by other factors, we estimated the relative risk in both the presence and absence of other risk factors, markers of chronic inflammation, and measures of subclinical atherosclerotic disease. All probability values represent 2-sided tests.

Results

The cases and control subjects were similar with respect to age (mean 74 years) and sex (63% were men) (Table 1). Diabetes, hypertension, and former cigarette smoking were more common among the cases, and higher educational attainment and good or excellent self-assessed health were more common among the control subjects. Mean systolic blood pressure and serum glucose, triglyceride, and fibrinogen levels were higher, and mean HDL cholesterol, FEV1, and energy expended in leisure-time physical activity were lower among the cases than the control subjects. The mean body mass index (BMI), LDL cholesterol, C-reactive protein, and serum albumin levels were similar among the cases and control subjects.

Table 2 shows the prevalence of IgG antibodies to HSV-1, CMV, and C pneumoniae among cases and control subjects and the adjusted odds ratios. As expected, the prevalence of IgG antibodies was 82% to HSV-1, 84% to CMV, and 83% to C pneumoniae among control subjects. After adjustment for the matching factors (age, sex, clinic, month, and year of blood draw) and for cigarette smoking, diabetes, hypertension, HDL cholesterol, BMI, physical activity, and years of education, the presence of IgG antibodies to HSV-1 was associated with an increased risk of MI and CHD death (for HSV-1, OR 2.0, 95% CI 1.1–3.6), but the presence of IgG antibodies to C pneumoniae and CMV was not associated with an increased risk of MI and CHD death (for C pneumoniae, OR 1.1, 95% CI 0.7–1.8; for CMV, OR 1.2, 95% CI 0.7–1.9). The findings were altered only slightly both after inclusion of the 3 agents in a single conditional logistic regression model and after exclusion of CHD deaths.

For C pneumoniae, there was little evidence of an association between IgG antibody titers of ≤1:512, but the prevalence of an IgG antibody titer of 1:1024 was higher among

### Table 2. IgG Antibodies to C pneumoniae, HSV-1, and CMV and Risk of MI and CHD Death

<table>
<thead>
<tr>
<th>Agent</th>
<th>Patients (n=213)*</th>
<th>Control Subjects (n=405)*</th>
<th>OR (95% CI)†</th>
<th>OR (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>C pneumoniae§</td>
<td>84.0</td>
<td>82.7</td>
<td>1.1 (0.7–1.8)</td>
<td>1.1 (0.7–1.8)</td>
</tr>
<tr>
<td>HSV-1</td>
<td>89.6</td>
<td>82.2</td>
<td>1.9 (1.1–3.2)</td>
<td>2.0 (1.1–3.6)</td>
</tr>
<tr>
<td>CMV</td>
<td>86.3</td>
<td>84.1</td>
<td>1.2 (0.7–1.9)</td>
<td>1.2 (0.7–1.9)</td>
</tr>
</tbody>
</table>

*Serological data were available for ≥1 agent for 213 patients and 405 control subjects. For C pneumoniae, serology data were available for 212 patients and 404 control subjects. For HSV-1, serology data were available for 211 patients and 381 control subjects, and for CMV, serology data were available for 212 patients and 402 control subjects.

†Adjusted for matching factors (age, sex, clinic, month, and year of blood draw).

‡Adjusted for matching factors, cigarette smoking (ever, never), diabetes mellitus (yes, no), hypertension (yes, no), HDL cholesterol (continuous), BMI (continuous), kilocalories expended in physical activity per week (continuous), and years of education (<12, 12–16, 17+).

§Titers 1:8.

|| IgG antibody present.

### Table 3. C pneumoniae Titer and Risk of MI/CHD Death

<table>
<thead>
<tr>
<th>C pneumoniae Titer</th>
<th>Patients (n=212)</th>
<th>Control Subjects (n=404)</th>
<th>OR* (95% CI)</th>
<th>OR† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>16.0</td>
<td>17.3</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>8–64</td>
<td>22.7</td>
<td>22.5</td>
<td>1.1 (0.6–1.9)</td>
<td>1.2 (0.7–2.1)</td>
</tr>
<tr>
<td>128–256</td>
<td>32.5</td>
<td>34.7</td>
<td>1.1 (0.6–1.8)</td>
<td>0.9 (0.5–1.6)</td>
</tr>
<tr>
<td>512</td>
<td>13.7</td>
<td>16.8</td>
<td>0.9 (0.5–1.7)</td>
<td>0.9 (0.5–1.8)</td>
</tr>
<tr>
<td>1024</td>
<td>15.1</td>
<td>8.7</td>
<td>2.1 (1.1–4.1)</td>
<td>2.2 (1.1–4.4)</td>
</tr>
</tbody>
</table>

*Adjusted for matching factors.

†Adjusted for matching factors plus cigarette smoking, diabetes, hypertension, HDL cholesterol, BMI, energy expenditure, and years of education.
TABLE 4.  Risk of MI/CHD* Death Associated With IgG Antibodies, According to Time to Event

<table>
<thead>
<tr>
<th>Time to Event</th>
<th>Positive Serology or Titer, %</th>
<th>OR† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Control Subjects</td>
</tr>
<tr>
<td>C pneumoniae IgG+</td>
<td>(n=212)</td>
<td>(n=404)</td>
</tr>
<tr>
<td>&lt;2.1 y</td>
<td>85.6</td>
<td>81.5</td>
</tr>
<tr>
<td>2.1 + y</td>
<td>82.4</td>
<td>83.7</td>
</tr>
<tr>
<td>C pneumoniae titer = 1:1024</td>
<td>(n=212)</td>
<td>(n=404)</td>
</tr>
<tr>
<td>&lt;2.1 y</td>
<td>14.4</td>
<td>6.7</td>
</tr>
<tr>
<td>2.1 + y</td>
<td>15.7</td>
<td>10.5</td>
</tr>
<tr>
<td>HSV-1 IgG+</td>
<td>(n=211)</td>
<td>(n=381)</td>
</tr>
<tr>
<td>&lt;2.1 y</td>
<td>88.5</td>
<td>81.5</td>
</tr>
<tr>
<td>2.1 + y</td>
<td>90.7</td>
<td>82.7</td>
</tr>
<tr>
<td>CMV IgG+</td>
<td>(n=212)</td>
<td>(n=402)</td>
</tr>
<tr>
<td>&lt;2.1 y</td>
<td>85.7</td>
<td>84.5</td>
</tr>
<tr>
<td>2.1 + y</td>
<td>86.9</td>
<td>83.7</td>
</tr>
</tbody>
</table>

*Associated with C pneumoniae titer (+/− and 1:1024 vs <1:1024); HSV-1 (+/−), and CMV (+/−).
†Adjusted for matching factors and cigarette smoking, diabetes, hypertension, HDL cholesterol, BMI, energy expenditure, and years of education.
‡P for interaction with time to event: for C pneumoniae IgG+, 0.183; for C pneumoniae titer (1:1024), 0.045; for HSV-1 IgG+, 0.733; for CMV IgG+, 0.868.

cases (15.1%) than among control subjects (8.7%) (Table 3). After adjustment for other risk factors, the presence of a C pneumoniae titer of 1:1024 was associated with a 2-fold increase in risk compared with the absence of IgG antibodies (OR 2.2, 95% CI 1.1 to 4.4). There also was some evidence that the risk associated with high-titer IgG antibodies for C pneumoniae varied according to the time to event (Table 4). When we stratified the data by the median time to event of 2.1 years, the increased risk of MI and CHD death associated with a high C pneumoniae titer was restricted to early events (for early events, OR 4.2, 95% CI 1.7 to 10.7; for later events, OR 1.3, 95% CI 0.7 to 2.7; P for interaction = 0.045). In contrast, there was little evidence that the risk associated with the presence of HSV-1 antibodies was greater for early than for late events (P for interaction = 0.733) and that the presence of CMV antibody was associated with either early or late events.

There was little evidence that the presence of other risk factors, markers of chronic inflammation (serum fibrinogen, C-reactive protein, white blood cell count, and albumin), and subclinical atherosclerosis (common carotid artery intimal-medial thickness, ankle-arm systolic blood pressure index, and Cardiac Infarction Injury Score) were important modifi-
cations of the association between HSV-1 with MI and CHD death. There also was little evidence that these other clinical characteristics modified the risk of MI and CHD death associated with either antibodies to C pneumoniae or CMV.

In addition, the association of HSV-1 antibodies and MI and CHD death was altered only slightly when we included terms that represented markers of inflammation and subclinical vascular disease in the multivariate models.

Discussion

Among older adults, the presence of antibodies to HSV-1, measured late in life, was associated with a 2-fold increase in the risk of MI and CHD death overall. In contrast, the presence of IgG antibodies to C pneumoniae and CMV was not associated with incident MI or CHD death. However, there was some evidence that high-titer C pneumoniae antibody was associated with an increased risk, and the association of high titer with risk was particularly large for events that occurred within the first 2.1 years after the blood draw. Multivariate adjustment for other factors that might bias the associations and potential mediators altered the findings only slightly.

Several limitations must be considered in interpretation of these findings. We used the presence of IgG antibodies (and for C pneumoniae, IgG titer) measured on a single occasion late in life to characterize prior infection. Other clinical characteristics not considered in our analyses might have biased the observed associations, and we may have had inadequate statistical power to detect an 80% to 90% increase in the risk of MI or CHD death associated with the presence of prior infection with C pneumoniae and CMV. In addition, the findings from this study may not be generalizable to young and middle-aged adults.

To our knowledge, this is the first prospective report of an association of recent, high-titer C pneumoniae antibodies with the risk of incident MI and CHD death among elderly persons. These preliminary findings suggest that high-titer C pneumoniae antibodies were associated with an increased risk, particularly for events that occurred during the initial 2.1 years after the blood draw. Of note, in a nested case-control study of incident CHD among the middle-aged persons followed for 3 years in the Atherosclerotic Risk in Communities Study, the prevalence of high-titer antibodies (both 1:512 and 1:1024) was higher among patients with CHD than among control subjects. Whether recently measured high-titer antibodies to C pneumoniae are more likely to reflect the etiologically relevant aspect of exposure to this agent, such as chronic infection or reinfection, rather than merely past infection remains unknown.

The data suggest a possible association between HSV-1 seropositivity and incident MI and CHD death among older adults. Although a similar association of HSV-1 antibodies with incident MI and CHD death was reported recently from the Helsinki Heart Study, an association between HSV-1 antibodies and incident MI and stroke was not observed in several prospective studies. Whether differences in study design or in the populations studied, such as the prevalence of other risk factors, account for the differences in findings remains unknown. In contrast, the absence of an association with CMV antibodies in this report is consistent with the findings from other prospective studies.

This epidemiological study does not provide information about the potential mechanisms for the association of HSV-1 and acute cardiac events. One hypothesis relates to the potential reactivation of HSV-1 in autonomic nerves that innervate the coronary arteries, subsequent endothelial injury, and the initiation of an acute thrombotic event. HSV-1 reactivation is more frequent and more severe among persons who are immunocompromised; older persons are more likely to be immunocompromised; endothelial cells can be infected with HSV-1; and infection results in cell death and a
leukocytoclastic vasculitis-like picture, including the conversion of the endothelial surface from antithrombotic to prothrombotic.\textsuperscript{37–40} Furthermore, mural thrombi have been described in the coronary arteries of chickens infected with Marek’s disease virus.\textsuperscript{5} Given the role of plaque disruption and the formation of occlusive thrombi in the occurrence of MI and CHD death, it is possible that reactivation of HSV-1 may result in endothelial injury that may increase the risk of thrombosis in the setting of atherosclerotic coronary disease. Unfortunately, because HSV-1 reactivation is not associated with consistent alterations in IgM, IgA, or IgG subclass antibody responses or in quantitative changes in HSV-1–specific antibodies, in this epidemiological study, we could not directly address this hypothesis.

This report is the first to examine the associations of IgG antibodies to \textit{C pneumoniae}, HSV-1, and CMV, measured late in life, with incident MI and CHD death among older adults. The finding of a possible association of the presence of antibody to HSV-1, assessed latter in life, with incident MI and CHD among older adults is of potential importance, given the high incidence of CHD and the high prevalence of IgG antibody to HSV-1 among older adults. In addition, the association of recent high-titer IgG antibodies to \textit{C pneumoniae} with the risk of acute cardiac events among older adults must be confirmed in other studies. Several large-scale secondary prevention trials that examine the effect of macrodide antibiotic therapy for \textit{C pneumoniae} among patients with known coronary heart disease are now in progress, but these trials have not targeted older persons with high-titer IgG antibodies. Additional clinical trials should be considered to determine more fully the potential clinical and public health implications of the associations reported herein.

### Appendix

**Participating Institutions and Principal Staff**


### Acknowledgments

This work was supported by an NHLBI Shannon Award (R55-HL-46900) and by contracts NO1-HC-87079, NO1-HC-87080, NO1-HC-87081, NO1-HC-87082, NO1-HC-87083, NO1-HC-87084, NO1-HC-87085, NO1-HC-87086, and AI-30731.

### References


Chlamydia pneumoniae, Herpes Simplex Virus Type 1, and Cytomegalovirus and Incident Myocardial Infarction and Coronary Heart Disease Death in Older Adults: The Cardiovascular Health Study

David S. Siscovick, Stephen M. Schwartz, Lawrence Corey, J. Thomas Grayston, Rhoda Ashley, San-Ping Wang, Bruce M. Psaty, Russell P. Tracy, Lewis H. Kuller and Richard A. Kronmal

Circulation. 2000;102:2335-2340
doi: 10.1161/01.CIR.102.19.2335

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/102/19/2335

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/