Trends in C-Reactive Protein Levels in United States Adults from 1999 to 2010

Short title: Trends in CRP in the US 1999-2010

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Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARA, aldosterone receptor antagonist; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CI, confidence interval; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HO-1, heme oxygenase-1; LDL, low-density lipoprotein; NHANES, National Health and Nutrition Examination Survey; SE standard error.

ABSTRACT

C-reactive protein (CRP) is a well-known biomarker of systemic inflammation and cardiovascular disease. We investigated the trends in prevalence of elevated CRP levels (>3.0 mg/L) in a general population of United States adults. Data from the 27,214 subjects aged ≥20 years in the National Health and Nutrition Examination Survey (NHANES) 1999-2010 were analyzed. After adjusting for age, sex, race/ethnicity, body mass index, and medications for lowering blood pressure, glucose and lipids, the prevalence of elevated CRP decreased significantly from 36.7% in 1999-2002 to 32.0% in 2007-2010, corresponding to a decrease in mean CRP level from 1.92 to 1.66 mg/L (both $P < 0.001$). The trend remained significant after additional adjustment for several traditional cardiovascular risk factors and use of different medications, including statins. However, the decreasing trends were attenuated after additional adjustment for total bilirubin ($P = 0.08$ and 0.02), which increased from 0.62 to 0.73 mg/dL over 12 years ($P < 0.001$). The decreasing trend of CRP levels is encouraging and may be related to the increase in total bilirubin levels. Such trends may be explained in part by the increasing use of some medications such as statins that can increase bilirubin levels and decrease CRP levels.

Key words: C-reactive protein; epidemiology; inflammation; population; risk factors

C-reactive protein (CRP) is a well-known non-specific biomarker of systemic inflammation, which appears to be linked to the development of cardiovascular diseases (1). Circulating levels are elevated in obesity, inflammation, insulin resistance, endothelial dysfunction, and subclinical atherosclerosis (2-4). Prospective studies have also demonstrated that elevated circulating CRP levels predict deterioration of glycaemia, incident cardiovascular disease, and mortality (5-13). CRP also adds prognostic information to that conveyed by the classical Framingham risk score for incident cardiovascular events (14).

Although the recently completed Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial has suggested that lowering CRP levels using a statin medication in asymptomatic subjects can reduce myocardial infarction, stroke and total mortality rate, even in subjects with elevated CRP levels but no hyperlipidemia (15, 16), the causal role of CRP in cardiovascular disease and related risk factors is still controversial (17). Nevertheless, the clinical utility of CRP as a biomarker to monitor the cardiovascular risk is well-recognized. A previous review has even suggested CRP level as a potential target for therapy (18). In this regard, a recent study has suggested the use of age and CRP level as a simple method to identify subjects at high cardiovascular risk (19). Moreover, the measurement of CRP has recently been recommended in all subjects with intermediate cardiovascular risk in Canada (20). Therefore, it is important to investigate CRP levels at a population level to identify the proportion of subjects at high risk of cardiovascular disease or related outcomes according to the measurement of CRP level. However, to the best of our knowledge, there is no report on recent trends in the prevalence of elevated CRP or mean CRP levels in a national survey study. Therefore, we investigated the 12-year trends in the prevalence of elevated CRP levels, as well as mean CRP level, in a general nationally representative non-institutionalized population of United States adults

during 1999-2010.

MATERIALS AND METHODS

Study subjects

The National Health and Nutrition Examination Survey (NHANES) 1999-2010 was conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention as a continuous cross-sectional survey of the health and nutritional status of the civilian, non-institutionalized United States population (21). In 1999, the survey became a continuous program and examined a nationally representative sample of about 5,000 persons each year. Data are released for every two-year cycle and the detailed measurement procedures and protocols have been described on its website (21). All participants gave informed consent and the study received approval from the Centers for Disease Control and Prevention Institutional Review Board. In NHANES 1999-2010, there were 30,752 subjects aged ≥20 years who were both interviewed and examined in the mobile examination center. After excluding pregnant women and subjects with missing data in CRP levels and body mass index, there were 27,214 subjects included in the analysis.

CRP measurement methods

CRP levels were measured by latex-enhanced nephelometry with a high sensitivity using a Dade Behring Nephelometer II Analyzer System (Dade Behring Diagnostics Inc, Somerville, NJ) in NHANES 1999-2010. The standards of the assays were prepared by Dade Behring Diagnostics and standardized against the WHO International Reference Preparation of CRP serum (21). The measurement was performed by the Immunology Division, Department of Laboratory Medicine, University of Washington Medical Center, and there were no changes to equipment, laboratory measurement methods, or laboratory site during the 12-year period

(21). The lowest reportable CRP level was approximately 0.2 mg/L (i.e. 0.02 mg/dL), which varied slightly with different calibrator lots. For CRP levels below the limit of detection (3.0% of all subjects in NHANES 1999-2012, 3.3% in 1999-2000, 3.1% in 2001-2002, 2.1% in 2003-2004, 2.5% in 2005-2006, 3.1% in 2007-2008, and 3.8% in 2009-2010), a level equal to the limit of detection divided by the square root of two was imputed. Two or three levels of quality controls were purchased from BioRad (Hercules, CA) or prepared in the laboratory. These quality controls with CRP levels spanning from the borderline and high range values were run for each test series. New controls were purchased or prepared in sufficient quantity to provide quality control for two years and were analyzed for at least 20 runs in parallel with the current controls. Data from these quality controls were then used to estimate any methodological imprecision and assess the magnitude of any time-associated trends. The coefficients of variation using different lots of CRP quality controls were all <10% in each of the 6 two-year survey periods. Details of sample collection, measurement procedures, quality control, and quality assurance have been described elsewhere (21). An elevated CRP level was defined as >3.0 mg/L (1).

Prescription medications

The use of prescription medications for lowering blood lipids, glucose, and blood pressure, as well as aspirin and clopidogrel, in the past month were assessed by questionnaires. Participants were asked whether they had taken or used any prescription medicine in the past month and showed the interviewer the medication containers and the exact name of all the products. If the container was unavailable, the interviewer asked the participants to verbally report this information. Details on the classification of the prescription medications can be found in Web Material. A participant, who took two or more different classes of medications for the same therapeutic use (lowering either blood lipids, glucose, or blood

pressure), either as a single combination pill or several different pills, was defined as receiving polytherapy.

Other variables of interest

Information on race/ethnicity, education, history of cardiovascular diseases, smoking, and alcohol consumption was obtained from self-reported questionnaires at baseline (21, 22). Ever smokers were defined as subjects who had smoked ≥100 cigarettes in their lives. Regular alcohol drinking was defined as consumption of any type of alcoholic beverage at least once a week in the past year. The estimated glomerular filtration rate (eGFR) was calculated using the modified prediction equation from the Modification of Diet in Renal Disease study (23). Albuminuria was defined as a urinary albumin-to-creatinine ratio ≥30 μg/mg (24). Total bilirubin levels were measured using a Hitachi Model 917 multichannel analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN) in 1999-2000 with both commercial and in-house quality controls covering the normal and abnormal levels. The levels were measured using a Beckman Synchron LX20 system in 2003-2007 and a Beckman UniCel® DxC800 Synchron (Beckman Coulter Inc, Fullerton, CA) in 2008-2010 with both commercial quality controls and blind quality control specimen from NHANES. In 2001-2002, these levels were measured using either a Hitachi Model 917 multichannel analyzer or a Beckman Synchron LX20 and the reported values were adjusted by regression equations to allow comparison across the two methods. Quality controls were run in each assay with coefficient of variation <10% in all the survey periods. Details on the laboratory measurement methods of other biochemical variables can be found in Web Appendix or elsewhere (21).

Statistical analysis

Data analysis was performed using the complex sampling function of SPSS version 20.0 (SPSS Inc, Chicago, IL). Data are expressed as mean or % (standard error [SE]). Variables with skewed distribution were expressed as geometric mean (95% confidence interval). Examination sampling weights were used in all analyses to adjust for non-response bias and the oversampling of blacks, Mexican Americans, and the elderly to obtain estimates representative of the United States Census civilian non-institutionalized population (21). Sampling errors were estimated using the primary sampling units and strata provided in the dataset. As serum triglycerides and low-density lipoprotein (LDL) cholesterol were measured only in subjects who were examined in the morning session and had fasted for 8-24 hours, separate fasting weights were used for the analysis of these variables. To obtain more reliable estimates, data from two survey cycles were combined together to produce estimates for each four-year period. To analyze the trends over time, multiple logistic or linear regression models were used, in which survey year (1999-2000, 2001-2002, 2003-2004, 2005-2006, 2007-2008, and 2009-2010) was included as an independent continuous variable. The *P* values for interaction were estimated by including each multiplicative interaction term in the regression models in full sample after adjusting for the main effects of the covariates. In a separate analysis, results were presented after excluding subjects with CRP levels >10 mg/L which may reflect acute inflammation (1). A two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

Table 1 shows the trends in clinical characteristics and cardiovascular risk factors from 1999-2002 to 2007-2010. During 1999-2010, there were significant increases in age, body mass index, education level, glycosylated hemoglobin, high-density lipoprotein (HDL)

cholesterol, eGFR, and total bilirubin, as well as the percentages of people that were non-smokers and regular alcohol drinkers (all adjusted $P < 0.05$). There were also significant decreases in total cholesterol, LDL cholesterol, triglycerides, blood pressure, alkaline phosphatase, aspartate aminotransferase, γ-glutamyltransferase, and the prevalence of albuminuria (all adjusted $P < 0.001$). Overall, 56.6 (SE 0.6) % of subjects reported the use of any prescription medication in the past month. Among them, 76.9 (0.6) % showed the interviewer all the medication containers, 7.4 (0.3) % showed some, but not all, containers, and 15.7 (0.5) % just verbally reported this information. As shown in Table 1, the use of medications for lowering blood pressure, glucose and lipids also increased significantly (all adjusted $P < 0.001$). Among different medications, the use of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), aldosterone receptor antagonists (ARAs), β-blockers, diuretics, metformin, thiazolidinediones, insulin, statins, nicotinic acid, and cholesterol adsorption inhibitor increased significantly.

Table 2 shows the clinical characteristics according to different CRP levels. As expected, CRP levels correlated positively with age, body mass index, glycosylated hemoglobin, total cholesterol, LDL cholesterol, triglycerides, systolic blood pressure, alkaline phosphatase, alanine aminotransferase and γ-glutamyltransferase, and correlated negatively with HDL cholesterol, eGFR and total bilirubin (all adjusted $P < 0.01$). Subjects with elevated CRP levels tended to be women, less educated, smokers, and were more likely to be non-Hispanic Black or Mexican American (all adjusted $P < 0.01$). The percentages of subjects with albuminuria and a history of previous diagnosis of cardiovascular disease were higher among subjects with elevated CRP levels (all adjusted $P < 0.01$). The percentage of subjects taking calcium channel blockers (CCBs), β-blockers, diuretics, thiazolidinediones, insulin, statins, and cholesterol adsorption inhibitor was also higher among subjects with elevated CRP levels

(all adjusted $P < 0.05$)

As shown in Table 3, the prevalence of elevated CRP decreased significantly from 36.7% in 1999-2002 to 32.0% in 2007-2010 (adjusted $P < 0.001$). This corresponded to a decrease in the mean CRP level from 1.92 to 1.66 mg/L (adjusted $P < 0.001$). The decreasing trend in CRP levels was significant over the 8-year period in both 1999-2006 and 2003-2010 (both adjusted $P < 0.01$). The decrease in the prevalence of elevated CRP or mean CRP level was significant in almost all subgroups by age (30-39, 40-49, 50-59, 60-69, 70-79, and ≥80 years), sex, race/ethnicity (non-Hispanic Whites, non-Hispanic Blacks, Mexican Americans, and others) and body mass index (<25.0, 25.0-29.9, and ≥30 kg/m^2). The change was not significant in those aged 20-29 years. The decrease in CRP levels was greater in subjects with higher age and non-Hispanic Whites (both *P* for interaction < 0.05, Table 3). In a separate analysis, similar trends were observed after excluding subjects with CRP levels >10 mg/L (Web Table 1). As shown in Web Table 2, subjects of higher age and non-Hispanic Whites tended to have larger increase in the use of any lipid lowering medication, especially statins, compared to subjects with lower age and other racial/ethnic groups (all *P* for interaction < 0.05).

As shown in Table 4, the decreases in the prevalence of elevated CRP and mean CRP level remained significant (both $P < 0.001$) after adjusting for age, sex, race/ethnicity, body mass index, and other characteristics that changed significantly over the 12-year period, but not total bilirubin. After further adjusting for total bilirubin levels, the decreasing trend in the prevalence of both elevated and mean CRP levels was attenuated ($P = 0.076$ and 0.024 respectively), although that of mean CRP level still remained significant. Similar trends were observed after excluding subjects with CRP levels >10 mg/L (Web Table 3).

Replacement of individual medications for lowering blood pressure, glucose, and lipids and their polytherapies by the use of any blood pressure, glucose, and lipid lowering medication in the adjustment models resulted in similar findings (Web Table 4). As statin medications were the most commonly used (Table 2), we investigated whether the change in CRP or total bilirubin levels was related to statin use. As shown in Web Table 5, the change in mean CRP level, but not total bilirubin level, was significantly larger in subjects taking statins (*P* for interaction = 0.005), although the difference in the change in prevalence of elevated CRP levels between subjects with and without taking statins did not reach statistical significance (*P* for interaction = 0.11). Among subjects who did not take aspirin, clopidogrel, or any medication for lowering blood pressure, glucose or lipids, the trends of decreasing CRP levels and increasing total bilirubin levels with time remained significant (all $P < 0.001$, Web Table 6).

DISCUSSION

This first report of the recent trend in CRP levels in a nationally representative population of United States adults shows a significant decreasing trend in CRP levels over a 12-year period. As CRP is a well-known non-specific biomarker of systemic inflammation, our study suggests that the decreasing trend could represent a significant improvement in the systemic inflammation status in US adults at the population level. Therefore, if the Cardiovascular Inflammation Reduction Trial (25) can show a direct effect of lowering CRP levels on the reduction of risk for myocardial infarction, stroke and cardiovascular death, we may expect a future reduction in CRP or systemic inflammation-related cardiovascular complications and mortality.

The reasons for the decreasing CRP levels with time are unclear. As shown in this and

earlier studies, elevated CRP levels are associated with other cardiovascular risk factors, such as aging, obesity, lower education level, smoking, history of cardiovascular disease, hyperglycemia, elevated blood pressure, dyslipidemia, renal dysfunction and liver damage. A recent NHANES study has shown no significant change in body mass index or obesity prevalence in the United States adults from 2003-2004 to 2009-2010 (26) while other NHANES studies have demonstrated an improvement in the control of hypertension, diabetes, and hypercholesterolemia among the United States adults (27-32). In our study, the decrease in the prevalence of elevated or mean CRP levels remained significant after adjusting for these potential confounding factors, suggesting that there may be some unidentified factors that may contribute to the observed decrease in CRP levels. However, the decreasing trend was attenuated substantially after additional adjustment for total bilirubin levels. Therefore, the decreasing trend in CRP levels over 12-year period could be related, at least partly, to the change in total bilirubin levels.

Bilirubin has antioxidant and anti-inflammatory properties and has been identified as a potential biomarker for cardiovascular risk (33). This may account for its inverse correlation with CRP levels (34). In our study, we found an increasing trend of the use of some BP, glucose, and lipid lowering medications over 12-year period. In this regard, lipid-lowering medications such as statins can reduce CRP levels (35). Moreover, statins have been shown to activate heme oxygenase-1 (HO-1), which may account for their anti-inflammatory and anti-proliferative effects (36). As HO-1 plays a role in the degradation of heme to biliverdin, carbon monoxide and ferritin, and biliverdin is converted to bilirubin by the enzyme biliverdin reductase (37), subjects taking statins may have higher total bilirubin levels (38). Therefore, total bilirubin levels may be used as a surrogate marker for the statin dosage.

Although the decreasing trend in CRP levels was significant in subjects with and without taking statins, the decrease in CRP levels was larger in subjects taking statins. Moreover, the percentage of subjects taking statins doubled from 8.4% to 16.0% over 12-year period. Therefore, the changes in total bilirubin and CRP levels could be explained at least in part by the increasing use of statins. Besides statins, other drugs such as aspirin, clopidogrel, ARBs, and ACEIs have also been reported in some studies to have CRP lowering effect in subjects at high cardiovascular risk (39-42). Their increasing uses could also contribute to the decreasing trend in CRP levels. Although the decreasing trend in CRP levels did not attenuate after additional adjustment for the use of different medications, the significant decrease in CRP levels with time in the full adjustment model could be due to some residual confounding effects and the lack of data on the dosage of each medication. Besides the increasing utilization of prescription medications, the improvement of cardiovascular risk profile such as education, smoking, lipids, blood pressure, renal function, and some liver function markers over the 12-year period may also contribute to the observed decreasing trend in CRP levels.

NHANES 1999-2010 is a continuous survey program and this provides a good opportunity to study trends in the prevalence of elevated CRP levels or mean CRP levels in the recent 12-year period from 1999-2000 to 2009-2010, especially since there were no changes to the equipment, laboratory measurement methods, or laboratory site (21). Our study has the strengths of the large sample size, good sampling design, and good quality control of the NHANES, allowing us to obtain nationally representative estimates. However, this study has several limitations. We could not exclude the possibility that the observed decreasing trend in CRP levels could be due to a downward assay drift as assay drift was monitored

within each survey period, but not across different survey periods. This could have exaggerated the CRP trend. Nevertheless, the observed trend remained significant if we excluded the first or last four-year period, suggesting that it was unlikely to be due to large drift at either end of the study period. As the sample size of this study is very large, the significances of the trends in some subgroups and some interaction terms could be misleading due to the very high power to detect very small differences/associations. Moreover, the lack of data on the dosage of the prescription medications and rheumatological conditions are also limitations of this study. .

CONCLUSION

There was a decreasing trend of CRP levels in the United States adults over 12-year study period, which may represent an improvement in systemic inflammation at the population level. This decrease in CRP levels may be related to an increase in total bilirubin levels in the same period. Such trends may be explained, at least in part, by increasing use of medications, such as statins, which have been shown to raise total bilirubin while decreasing CRP levels.

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Conflict of interest: Philip J. Barter has received honoraria from Abbott, AstraZeneca, Kowa, Merck, Novartis, Pfizer and Roche, and has been Advisory Board member for AstraZeneca, CSL, Lilly, Merck, Novartis, Pfizer and Roche. No potential conflicts of

interest relevant to this article were reported by other authors.

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Table 1. Trends in Clinical Characteristics in United States Adults, 1999-2010

Characteristics[a]	**1999-2002 (*n* = 8,074)**			**2003-2006 (*n* = 8,316)**			**2007-2010 (*n* = 10,824)**			***P* Value for Linear Time Trend**[b]
	% (SE)	**Mean (SE)**	**95% CI**	**% (SE)**	**Mean (SE)**	**95% CI**	**% (SE)**	**Mean (SE)**	**95% CI**	
Age, years		46.1 (0.3)			46.8 (0.5)			47.1 (0.3)		0.013
Women, %	51.0 (0.5)			50.9 (0.5)			51.3 (0.4)			0.76
Body mass index, kg/m^2		28.0 (0.1)			28.4 (0.1)			28.6 (0.1)		<0.001
Race/ethnicity, %										0.41
Non-Hispanic White	72.1 (1.8)			72.8 (2.1)			69.6 (2.5)			-
Non-Hispanic Black	10.1 (1.2)			10.8 (1.3)			10.5 (1.0)			-
Mexican American	7.0 (0.9)			7.7 (1.1)			8.4 (1.3)			-
Others	10.9 (1.7)			8.7 (0.7)			11.5 (1.3)			-
Education, %										0.003
<High school	21.5 (0.8)			17.6 (0.9)			19.5 (0.9)			-
High school diploma	25.7 (1.0)			26.0 (0.7)			24.0 (0.8)			-
>High school	52.8 (1.4)			56.4 (1.2)			56.5 (1.4)			-
Smoking, %										0.022
Never	50.3 (1.3)			49.9 (0.8)			53.9 (1.2)			-
Former	25.1 (0.9)			25.1 (0.6)			24.5 (0.7)			-

Current	24.5 (0.9)			25.0 (0.8)			21.6 (0.8)			-
Regular alcohol drinking, %	34.0 (1.7)			33.9 (1.3)			36.1 (1.3)			0.018
History of any cardiovascular disease, %	7.7 (0.4)			8.7 (0.5)			8.0 (0.5)			0.25
Glycosylated hemoglobin, %[c]		5.40	5.36, 5.44		5.43	5.40, 5.46		5.56	5.53, 5.59	<0.001
Total cholesterol, mg/dL[c]		198.9	197.2, 200.6		195.9	194.8, 196.9		192.4	191.3, 193.5	<0.001
HDL cholesterol, mg/dL		51.0 (0.4)			54.1 (0.3)			52.5 (0.3)		<0.001
LDL cholesterol, mg/dL[c,d]		118.2	116.4, 120.0		110.5	108.9, 112.2		111.0	109.7, 112.2	<0.001
Triglycerides, mg/dL[c,d]		121.2	117.6, 124.9		118.9	116.0, 121.9		109.8	107.3, 112.3	<0.001
Systolic blood pressure, mm Hg		123.1 (0.5)			122.6 (0.3)			120.7 (0.3)		<0.001
Diastolic blood pressure, mm Hg		72.6 (0.3)			70.7 (0.3)			70.1 (0.4)		<0.001
eGFR, mL/min/1.73m^2		86.4 (0.5)			86.1 (0.6)			88.6 (0.6)		<0.001
Albuminuria, %	10.4 (0.5)			9.7 (0.4)			9.0 (0.4)			<0.001
Alkaline phosphatase, U/L[c]		70.1	68.7, 71.4		65.3	64.5, 66.2		64.2	63.6, 64.9	<0.001
Alanine aminotransferase, U/L[c]		22.5	22.2, 22.8		23.1	22.8, 23.4		23.0	22.7, 23.3	0.46
Aspartate aminotransferase, U/L[c]		22.9	22.6, 23.1		24.0	23.8, 24.3		24.5	24.2, 24.8	<0.001
γ-glutamyltransferase, U/L[c]		23.3	22.8, 23.8		21.4	21.0, 22.0		21.9	21.3, 22.6	<0.001
Total bilirubin, mg/dL[c]		0.62	0.61, 0.63		0.70	0.69, 0.72		0.73	0.72, 0.74	<0.001

BP lowering medication, %				
ACEI	7.3 (0.3)	10.0 (0.5)	10.9 (0.4)	<0.001
ARB	2.9 (0.2)	4.7 (0.4)	6.6 (0.4)	<0.001
CCB	6.1 (0.4)	7.1 (0.4)	6.4 (0.3)	0.39
ARA	0.4 (0.1)	0.5 (0.1)	0.7 (0.1)	0.030
β-blockers	6.8 (0.4)	10.3 (0.5)	10.7 (0.5)	<0.001
Diuretics	9.3 (0.7)	11.6 (0.6)	12.0 (0.6)	0.015
Others	3.1 (0.3)	3.0 (0.2)	3.2 (0.2)	0.18
Any of the above	21.2 (0.9)	25.4 (0.9)	27.0 (0.8)	<0.001
Polytherapy	10.6 (0.6)	14.2 (0.7)	15.2 (0.6)	<0.001
Glucose lowering medication, %				
Metformin	2.3 (0.2)	3.7 (0.3)	4.9 (0.3)	<0.001
Sulfonylureas	2.8 (0.2)	3.1 (0.3)	3.1 (0.2)	0.42
Thiazolidinediones	0.7 (0.1)	2.0 (0.2)	1.5 (0.2)	0.001
Insulin	1.1 (0.1)	1.5 (0.1)	2.0 (0.2)	0.002
Others	0.2 (0.0)	0.1 (0.0)	1.0 (0.1)	<0.001
Any of the above	5.0 (0.3)	6.4 (0.3)	7.7 (0.4)	<0.001
Polytherapy	1.8 (0.2)	3.1 (0.3)	3.6 (0.3)	<0.001
Lipid lowering medication, %				

Statin	8.4 (0.4)	12.5 (0.6)	16.0 (0.5)	<0.001
Fibrate	1.0 (0.2)	1.2 (0.1)	1.5 (0.2)	0.10
Bile acid sequestrant	0.1 (0.0)	0.3 (0.1)	0.2 (0.1)[e]	0.59
Nicotinic acid	0.1 (0.0)	0.3 (0.1)	0.7 (0.1)	<0.001
Cholesterol adsorption inhibitor	0.0 (0.0)	1.2 (0.2)	2.1 (0.2)	<0.001
Others	0.1 (0.0)[e]	0.0 (0.0)[e]	0.0 (0.0)[e]	0.005
Any of the above	9.3 (0.5)	13.9 (0.7)	17.4 (0.5)	<0.001
Polytherapy	0.4 (0.1)	1.6 (0.2)	2.9 (0.2)	<0.001
Taking aspirin, %	0.6 (0.1)	0.5 (0.1)	1.4 (0.1)	<0.001
Taking clopidogrel, %	0.4 (0.1)	1.5 (0.2)	1.6 (0.2)	<0.001

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARA, aldosterone receptor antagonist; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CI, confidence interval; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SE, standard error.

[a]Data are expressed as mean or % (SE). For variables with skewed distribution, data are expressed as geometric mean (95% CI).

[b]Adjusted for age, sex, race/ethnicity, and body mass index, where appropriate.

[c]Data were ln-transformed before analysis due to skewed distribution.

[d]Data were only available in a sub-sample of subjects that had fasted for 8-24 hours (*n* = 3,696, 3,639, and 4,858 in NHANES 1999-2002, 2003-2006, and 2007-2010 respectively).

[e]Estimates are unreliable due to coefficient of variation > 0.3.

Table 2. Clinical Characteristics According to CRP Levels in United States Adults, 1999-2010

Characteristics[a]	**CRP level (mg/L)**									***P* Value**
	<1.0			**1.0-3.0**			**>3.0**			**for**
	(*n* = 7,693)			**(*n* = 9,258)**			**(*n* = 10,263)**			**Linear**
	% (SE)	**Mean (SE)**	**95% CI**	**% (SE)**	**Mean (SE)**	**95% CI**	**% (SE)**	**Mean (SE)**	**95% CI**	**Trend**[b]
Age, years		43.0 (0.2)			47.9 (0.3)			49.0 (0.2)		<0.001
Women, %	45.1 (0.6)			46.6 (0.6)			60.9 (0.6)			<0.001
Body mass index, kg/m^2		25.0 (0.1)			28.1 (0.1)			31.7 (0.1)		<0.001
Race/ethnicity, %										<0.001
Non-Hispanic White	72.3 (1.2)			72.5 (1.4)			69.6 (1.5)			-
Non-Hispanic Black	8.9 (0.6)			9.5 (0.7)			12.9 (0.8)			-
Mexican American	7.0 (0.5)			7.8 (0.7)			8.2 (0.8)			-
Others	11.7 (0.8)			10.2 (0.9)			9.3 (0.8)			-
Education, %										<0.001
<High school	15.9 (0.6)			19.5 (0.7)			22.7 (0.6)			-
High school diploma	22.6 (0.6)			26.1 (0.7)			26.6 (0.6)			-
>High school	61.5 (1.0)			54.4 (1.0)			50.6 (0.8)			-
Smoking, %										<0.001
Never	55.3 (0.9)			50.5 (0.8)			48.7 (0.8)			-
Former	23.5 (0.6)			25.8 (0.7)			25.4 (0.6)			-

Current	21.2 (0.7)			23.7 (0.7)			25.9 (0.5)		-
Regular alcohol drinking, %	41.4 (1.1)			35.2 (1.0)			28.2 (0.9)		0.10
History of cardiovascular disease, %									
Congestive heart failure	1.2 (0.1)			1.8 (0.2)			3.6 (0.2)		<0.001
Coronary heart disease	2.3 (0.2)			3.6 (0.2)			4.3 (0.2)		0.024
Angina	1.8 (0.2)			2.4 (0.2)			3.6 (0.2)		0.11
Heart attack	2.4 (0.2)			3.3 (0.2)			4.5 (0.2)		0.005
Stroke	1.6 (0.2)			2.3 (0.2)			3.8 (0.3)		<0.001
Any of the above	5.3 (0.3)			7.9 (0.4)			11.0 (0.4)		<0.001
Glycosylated hemoglobin, %[c]		5.29	5.27, 5.31		5.45	5.43, 5.47		5.65	5.62, 5.67	<0.001
Total cholesterol, mg/dL[c]		188.3	187.3, 189.3		198.6	197.3, 200.0		199.4	198.3, 200.6	<0.001
HDL cholesterol, mg/dL		56.5 (0.3)			51.8 (0.2)			49.8 (0.2)		<0.001
LDL cholesterol, mg/dL[c,d]		107.6	106.3, 109.0		116.1	114.7, 117.5		115.1	113.5, 116.7	<0.001
Triglycerides, mg/dL[c,d]		95.9	94.0, 98.0		120.7	117.8, 123.6		133.0	130.1, 136.0	<0.001
Systolic blood pressure, mm Hg		118.4 (0.3)			122.7 (0.3)			124.9 (0.3)		<0.001
Diastolic blood pressure, mm Hg		70.1 (0.2)			71.5 (0.2)			71.5 (0.2)		0.16
eGFR, mL/min/1.73m^2		89.2 (0.4)			86.0 (0.4)			86.3 (0.4)		0.001
Albuminuria, %	6.4 (0.3)			9.3 (0.4)			13.0 (0.4)			<0.001

Alkaline phosphatase, U/L[c]		59.9	59.3, 60.4		66.5	65.9, 67.1	72.9	72.1, 73.6	<0.001
Alanine aminotransferase, U/L[c]		21.7	21.5, 22.0		23.8	23.5, 24.1	23.1	22.8, 23.4	0.009
Aspartate aminotransferase, U/L[c]		23.5	23.3, 23.7		24.3	24.1, 24.5	23.6	23.4, 23.9	0.063
γ-glutamyltransferase, U/L[c]		18.7	18.4, 19.1		22.7	22.2, 23.1	25.4	24.9, 25.9	<0.001
Total bilirubin, mg/dL[c]		0.75	0.74, 0.77		0.70	0.69, 0.71	0.62	0.61, 0.63	<0.001
Blood pressure lowering medication, %									
ACEI	6.4 (0.3)			9.7 (0.4)			12.1 (0.3)		0.69
ARB	3.4 (0.2)			4.3 (0.3)			6.6 (0.4)		0.54
CCB	3.6 (0.2)			6.3 (0.3)			9.5 (0.4)		<0.001
ARA	0.3 (0.1)			0.5 (0.1)			0.8 (0.1)		0.34
β-blockers	6.4 (0.4)			9.1 (0.4)			12.3 (0.5)		0.042
Diuretics	5.7 (0.3)			10.5 (0.5)			16.3 (0.5)		<0.001
Others	1.9 (0.2)			3.2 (0.2)			4.0 (0.2)		0.070
Any of the above	15.9 (0.6)			24.4 (0.6)			32.9 (0.7)		0.006
Polytherapy	8.0 (0.4)			12.8 (0.5)			18.9 (0.5)		0.001
Glucose lowering medication, %									
Metformin	2.2 (0.2)			3.4 (0.2)			5.3 (0.3)		0.53

Sulfonylureas	1.8 (0.2)	2.8 (0.2)	4.3 (0.2)	0.56
Thiazolidinediones	1.2 (0.1)	1.3 (0.2)	1.8 (0.1)	<0.001
Insulin	0.9 (0.1)	1.3 (0.2)	2.4 (0.2)	0.014
Others	0.3 (0.1)	0.4 (0.1)	0.6 (0.1)	0.89
Any of the above	3.9 (0.2)	5.8 (0.3)	9.4 (0.4)	0.32
Polytherapy	1.8 (0.2)	2.6 (0.2)	4.1 (0.3)	0.56
Lipid lowering medication, %				
Statin	10.7 (0.5)	13.7 (0.5)	12.8 (0.4)	<0.001
Fibrate	0.7 (0.1)	1.5 (0.2)	1.4 (0.1)	0.58
Bile acid sequestrant	0.1 (0.0)[e]	0.2 (0.1)	0.3 (0.1)	0.30
Nicotinic acid	0.4 (0.1)	0.4 (0.1)	0.4 (0.1)	0.60
Cholesterol adsorption inhibitor	1.0 (0.1)	1.4 (0.2)	1.1 (0.1)	0.04
Others	0.0 (0.0)[e]	0.0 (0.0)[e]	0.1 (0.0)[e]	0.097
Any of the above	11.3 (0.5)	15.3 (0.6)	14.3 (0.4)	<0.001
Polytherapy	1.5 (0.2)	1.8 (0.2)	1.7 (0.2)	0.052
Taking aspirin, %	0.6 (0.1)	0.9 (0.1)	1.1 (0.1)	0.66
Taking clopidogrel, %	0.9 (0.1)	1.1 (0.1)	1.5 (0.2)	0.27

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARA, aldosterone receptor antagonist; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CI, confidence interval; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein;

LDL, low-density lipoprotein; SE, standard error.

[a]Data are expressed as mean or % (SE). For variables with skewed distribution, data are expressed as geometric mean (95% CI).

[b]Adjusted for age, sex, race/ethnicity, body mass index and survey period, where appropriate.

[c]Data were ln-transformed before analysis due to skewed distribution.

[d]Data were only available in a sub-sample of subjects that had fasted for 8-24 hours (*n* = 3,367, 4,195, and 4,631 for subjects with CRP levels of <1.0, 1.0-3.0 and >3.0 mg/L, respectively).

[e]Estimates are unreliable due to coefficient of variation >0.3.

Table 3. Prevalence of Elevated CRP and Geometric Mean CRP Levels in United States Adults, 1999-2010[a]

	1999-2002 (*n* = 8,074)			2003-2006 (*n* = 8,316)			2007-2010 (*n* = 10,824)			Change, 1999-2002 to 2007-2010	*P* Value for 12-year Linear Trend	*P* Value for Interaction
	% (SE)[b]	Mean[b]	95% CI[b]	% (SE)[b]	Mean[b]	95% CI[b]	% (SE)[b]	Mean[b]	95% CI[b]			
Overall												
Elevated CRP, %	36.7 (0.8)			35.2 (0.8)**			32.0 (0.6)***			-4.7	<0.001	
CRP level, mg/L		1.92	1.82, 2.02		1.87**	1.77, 1.97		1.66***	1.58, 1.74	-0.26	<0.001	
Age, years												
20-29 (*n* = 4,378)												
Elevated CRP, %	25.2 (1.5)			27.6 (1.4)			26.7 (1.4)			1.5	0.92	<0.001
CRP level, mg/L		1.26	1.15, 1.38		1.29	1.19, 1.40		1.28**	1.16, 1.40	0.02	0.12	<0.001
30-39 (*n* = 4,471)												

Elevated CRP, %	32.7 (1.1)			31.1 (1.5)			30.2 (1.1)			-2.5	0.001
CRP level, mg/L		1.64	1.52, 1.78		1.61*	1.49, 1.73		1.47**	1.36, 1.59	-0.17	<0.001
40-49 (*n* = 4,863)											
Elevated CRP, %	35.5 (1.6)			37.7 (1.6)			31.6 (1.5)**			-3.9	0.003
CRP level, mg/L		1.84	1.65, 2.06		2.02	1.86, 2.21		1.70**	1.55, 1.86	-0.15	0.004
50-59 (*n* = 3,975)											
Elevated CRP, %	43.4 (1.7)			37.1 (2.0)***			33.2 (1.4)			-10.2	<0.001
CRP level, mg/L		2.39	2.19, 2.61		2.04***	1.86, 2.24		1.76**	1.62, 1.90	-0.63	<0.001
60-69 (*n* = 4,402)											
Elevated CRP, %	47.2 (2.0)			42.4 (1.7)*			36.6 (1.4)*			-10.6	<0.001
CRP level, mg/L		2.75	2.57, 2.96		2.54*	2.38, 2.71		2.03**	1.88, 2.20	-0.72	<0.001
70-79 (*n* = 3,145)											

Elevated CRP, %	45.2 (1.9)			39.0 (1.8)*			38.4 (1.5)			-6.8	0.001	
CRP level, mg/L		2.78	2.57, 3.01		2.29**	2.10, 2.50		2.16	2.02, 2.32	-0.62	<0.001	
≥80 (*n* = 1,980)												
Elevated CRP, %	45.2 (2.4)			38.0 (1.6)			34.8 (3.0)			-10.4	0.033	
CRP level, mg/L		2.76	2.46, 3.10		2.39	2.19, 2.60		1.99*	1.76, 2.24	-0.77	0.012	
Sex												
Men (*n* = 13,605)												
Elevated CRP, %	28.7 (1.0)			28.6 (1.0)			25.8 (0.7)**			-2.9	<0.001	0.16
CRP level, mg/L		1.58	1.49, 1.68		1.59	1.50, 1.68		1.43***	1.35, 1.51	-0.15	<0.001	0.23
Women (*n* = 13,609)												
Elevated CRP, %	44.5 (1.0)			41.5 (1.2)***			38.0 (0.7)***			-6.5	<0.001	
CRP level, mg/L		2.31	2.16, 2.48		2.19**	2.04, 2.34		1.91***	1.81, 2.02	-0.40	<0.001	

Race/ethnicity											
Non-Hispanic White (*n* = 13,551)											
Elevated CRP, %	36.1 (1.0)			33.9 (1.0)**			31.1 (0.9)**			-4.9	<0.001	0.007
CRP level, mg/L		1.89	1.78, 2.01		1.83**	1.72, 1.94		1.62***	1.52, 1.73	-0.27	<0.001	0.004
Non-Hispanic Black (*n* = 5,210)											
Elevated CRP, %	42.2 (1.5)			43.4 (1.2)			41.9 (1.3)			-0.3	0.14	
CRP level, mg/L		2.26	2.02, 2.52		2.34	2.17, 2.53		2.13*	1.96, 2.31	-0.13	0.004	
Mexican American (*n* = 5,522)											
Elevated CRP, %	36.2 (1.3)			38.1 (1.8)			36.0 (2.1)*			-0.2	0.017	
CRP level, mg/L		1.87	1.70, 2.05		2.02	1.80, 2.27		2.01	1.79, 2.25	0.14	0.14	
Other (*n* = 2,931)											
Elevated CRP, %	36.3 (1.7)			32.7 (2.4)			25.6 (1.8)***			-10.7	<0.001	

CRP level, mg/L		1.85	1.63, 2.09		1.58*	1.38, 1.81		1.30***	1.18, 1.44	-0.54	<0.001	
Body mass index, kg/m^2												
<25.0 (*n* = 8,185)												
Elevated CRP, %	20.0 (0.8)			18.0 (0.9)**			15.0 (0.7)**			-5.0	<0.001	0.035
CRP level, mg/L		1.06	0.98, 1.14		1.00*	0.93, 1.08		0.86***	0.80, 0.92	-0.20	<0.001	0.061
25.0-29.9 (*n* = 9,557)												
Elevated CRP, %	33.5 (1.1)			30.4 (0.8)**			25.3 (1.0)**			-8.1	<0.001	
CRP level, mg/L		1.90	1.80, 2.01		1.79*	1.71, 1.87		1.49***	1.41, 1.58	-0.41	<0.001	
≥30.0 (*n* = 9,472)												
Elevated CRP, %	59.6 (1.4)			56.7 (1.3)			53.8 (0.7)*			-5.8	0.001	
CRP level, mg/L		3.84	3.62, 4.07		3.59	3.42, 3.77		3.30**	3.19, 3.42	-0.53	<0.001	

Abbreviations: CI, confidence interval; CRP, C-reactive protein; SE, standard error.

*$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ for the 8-year linear trend compared to the previous four-year cycle (i.e. 2003-2006 vs 1999-2002 or 2007-2010 vs 2003-2006).

[a]All *P* values were adjusted for age, sex (except sex-specific estimates), race/ethnicity (except race/ethnicity-specific estimates), body mass index, blood pressure lowering medication, glucose lowering medication, and lipid lowering medication. CRP values were ln-transformed when assessing the trend in mean CRP values. For the subgroups by age and body mass index, categorical subgroup variable, instead of the continuous level, was used in the adjustment model when assessing the *P* value for interaction.

[b]Data are expressed as % (SE) for elevated CRP. For continuous CRP level, data are expressed as geometric mean (95% CI) due to skewed distribution.

Table 4. Association of Survey Year With Elevated CRP or Geometric Mean Level in United States Adults, 1999-2010[a]

Model[b]	Elevated CRP (>3.0 mg/L)			ln CRP (mg/L)		
	Odds ratio	95% CI	*P* Value	Regression coefficient	95% CI	*P* Value
Unadjusted	0.95	0.93, 0.97	<0.001	-0.039	-0.058, -0.021	<0.001
1	0.92	0.90, 0.94	<0.001	-0.057	-0.071, -0.043	<0.001
2	0.92	0.90, 0.94	<0.001	-0.053	-0.066, -0.040	<0.001
3	0.95	0.93, 0.97	<0.001	-0.029	-0.042, -0.015	<0.001
4	0.95	0.93, 0.98	<0.001	-0.027	-0.040, -0.013	<0.001
5	0.95	0.93, 0.98	<0.001	-0.026	-0.040, -0.013	<0.001
6	0.98	0.95, 1.00	0.076	-0.016	-0.030, -0.002	0.024

Abbreviations: CI, confidence interval; CRP, C-reactive protein.

[a]Multiple logistics or linear regression was used with elevated CRP or ln CRP as the dependent variable. Data are presented as odds ratio (95% CI) for elevated CRP or regression coefficient (95% CI) for ln CRP level per each two-year cycle increase.

[b]Model 1 was adjusted for age, sex, race/ethnicity, and body mass index; model 2, further adjusted for education, smoking and regular alcohol drinking; model 3, further adjusted for glycosylated hemoglobin, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, estimated glomerular filtration rate, albuminuria, alkaline phosphatase, aspartate aminotransferase, and γ-glutamyltransferase; model 4, further adjusted for angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone receptor antagonists, β-blockers, diuretics, metformin, thiazolidinediones, insulin, “others” category of glucose lowering medications, statins, nicotinic acid, cholesterol adsorption inhibitor, “others”

category of lipid lowering medications, aspirin, and clopidogrel; model 5, further adjusted for blood pressure lowering polytherapy, glucose lowering polytherapy, and lipid lowering polytherapy; model 6 was further adjusted for total bilirubin.

Web Appendix

MATERIALS AND METHODS

Prescription medications

The usage of prescription medications for lowering blood lipids, glucose, and blood pressure as well as aspirin and clopidogrel in the past month was assessed by questionnaires. Participants were asked whether they had taken or used any prescription medicine in the past month and showed the interviewer the medication containers and the exact name of all the products. If the container was unavailable, the interviewer asked the participants to verbally report this information. Lipid lowering medications were classified into statins, fibrates, bile acid sequestrants, nicotinic acids, cholesterol adsorption inhibitor (i.e. ezetimibe), and others (including probucol and other unspecified medications). Blood pressure lowering medications were classified into angiotensin-converting enzyme inhibitors, angiotensin receptor blockers (ARBs), β-blockers, calcium channel blockers (CCBs), diuretics, aldosterone receptor antagonists, and others (including α-blockers, other antiadrenergic drugs, direct vasodilators, direct renin inhibitors and other unspecified anti-hypertensive medications). Glucose lowering medications were classified into metformin, sulfonylureas, thiazolidinediones, insulin, and others (including α-glucosidase inhibitors, amylin analogs, dipeptidyl peptidase 4 inhibitors, incretin mimetics, meglitinides, and other unspecific anti-diabetic medications). A participant can report the use of more than one medication, either as a single combination pill or several different pills. In this case, the participant was only counted once for any medication use category, and once within each class of medications. For example, a subject who reported the uses of “niacin/simvastatin”, “pravastatin”, “amlodipine, valsartan and hydrochlorothiazide”, and “metformin/pioglitazone” in the past month was only counted once for each of the classes,

nicotinic acid, statins, CCBs, ARBs, diuretics, metformin, and thiazolidinediones. A participant, who took two or more different classes of medications for the same therapeutic use (lowering either blood lipids, glucose, or blood pressure), either as a single combination pill or several different pills, was defined as receiving polytherapy.

Laboratory measurement

Serum high-density lipoprotein cholesterol, total cholesterol, and triglycerides were measured with a Hitachi Model 704 multichannel analyzer in 1999-2004, a Roche Hitachi 717 (Roche Diagnostics, Indianapolis, IN) in 2005, both Roche Hitachi 717 and 912 (Roche Diagnostics, Indianapolis, IN) in 2006, and a Roche Modular P chemistry analyzer (Roche Diagnostics, Indianapolis, IN) in 2007-2010. Low-density lipoprotein cholesterol was calculated using the Friedewald equation.

Glycosylated hemoglobin was determined by high performance liquid chromatography using a Primus CLC330 or a Primus CLC385 (Primus Corporation, Kansas City, MO) in 1999-2004, a Tosoh A1c 2.2 Plus Glycohemoglobin Analyzer (Tosoh Medics Inc, San Francisco, CA) in 2005-2006, and an A1c G7 HPLC Glycohemoglobin Analyzer (Tosoh Medics Inc, San Francisco, CA) in 2007-2010. Serum creatinine, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, and total bilirubin levels were measured as the routine laboratory blood parameters using a Hitachi Model 917 multichannel analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN) in 1999-2000, a Beckman Synchron LX20 system in 2003-2007 and a Beckman UniCel® DxC800 Synchron (Beckman Coulter Inc, Fullerton, CA) in 2008-2010. In 2001-2002, these levels were measured using either a Hitachi Model 917 multichannel analyzer or a Beckman Synchron LX20. The reported values have been adjusted by regression equations

to allow comparison across the two methods. Correction for serum creatinine data in 1999-2000 and 2005-2006 was performed according to the NHANES recommendations before calculating the estimated glomerular filtration rate.

Urinary creatinine was determined colorimetrically by the Jaffé rate reaction in a Beckman Synchron CX3 Clinical Analyzer (Beckman Instruments, Brea, CA) in 1999-2006, and a Roche/Hitachi Modular P Chemistry Analyzer (Roche Diagnostics, Indianapolis, IN) in 2007-2010. Data on urinary creatinine were adjusted using regression equations so that values from two different measurements could be combined and compared. Urinary albumin was measured with a solid-phase fluorescent immunoassay using a Sequoia-Turner Digital Model 450 fluorometer (Mountain View, CA) in 1999-2010.

Web Table 1. Prevalence of Elevated CRP and Geometric Mean CRP Levels in United States Adults, 1999-2010, After Excluding Subjects With CRP Levels >10 mg/L[a]

	1999-2002 (*n* = 7,217)			2003-2006 (*n* = 7,419)			2007-2010 (*n* = 9,757)			Change, 1999-2002 to 2007-2010	*P* Value for 12-year Linear Trend[b]	*P* Value for Interaction[b]
	% (SE)[b]	Mean[b]	95% CI	% (SE)[b]	Mean[b]	95% CI	% (SE)[b]	Mean[b]	95% CI			
Overall												
Elevated CRP, %	30.1 (0.7)			28.2 (0.8)**			25.7 (0.5)***			-4.4	<0.001	
CRP level, mg/L		1.52	1.45, 1.59		1.47***	1.40, 1.53		1.33***	1.28, 1.39	-0.19	<0.001	
Age, years												
20-29 (*n* = 4,040)												
Elevated CRP, %	20.6 (1.5)			21.6 (1.5)			20.7 (1.3)			0.0	0.90	0.006
CRP level, mg/L		1.06	0.98, 1.15		1.04	0.96, 1.12		1.02	0.93, 1.13	-0.04	0.10	<0.001
30-39 (*n* = 4,075)												

Elevated CRP, %	26.7 (1.1)			24.7 (1.5)*			24.5 (1.2)			-2.1	0.005
CRP level, mg/L		1.33	1.23, 1.44		1.29	1.20, 1.39		1.21**	1.11, 1.32	-0.12	<0.001
40-49 (*n* = 4,363)											
Elevated CRP, %	28.9 (1.5)			29.9 (1.5)			24.6 (1.3)			-4.3	0.014
CRP level, mg/L		1.47	1.34, 1.62		1.55	1.45, 1.65		1.34*	1.24, 1.44	-0.14	0.006
50-59 (*n* = 3,519)											
Elevated CRP, %	36.2 (1.7)			30.4 (2.0)**			27.1 (1.2)			-9.2	<0.001
CRP level, mg/L		1.87	1.74, 2.01		1.62**	1.49, 1.77		1.43**	1.35, 1.51	-0.44	<0.001
60-69 (*n* = 3,837)											
Elevated CRP, %	39.1 (1.9)			34.3 (1.7)*			30.2 (1.3)			-8.9	<0.001
CRP level, mg/L		2.08	1.96, 2.21		1.94**	1.81, 2.08		1.63***	1.53, 1.73	-0.45	<0.001
70-79 (*n* = 2,799)											
Elevated CRP, %	37.7 (2.1)			32.1 (1.9)			31.8 (1.5)			-5.9	0.007
CRP level, mg/L		2.13	2.00, 2.28		1.81***	1.70, 1.92		1.72*	1.63, 1.82	-0.41	<0.001

≥80 (*n* = 1,760)											
Elevated CRP, %	37.4 (2.7)			31.0 (1.5)			27.2 (3.1)			-10.3	0.024
CRP level, mg/L		2.11	1.89, 2.34		1.87	1.75, 2.00		1.52*	1.35, 1.71	-0.59	0.002
Sex											
Men (*n* = 12,614)											
Elevated CRP, %	24.0 (0.9)			23.8 (0.9)			21.1 (0.6)			-2.9	<0.001	0.27
CRP level, mg/L		1.34	1.27, 1.42		1.34	1.28, 1.41		1.21***	1.16, 1.27	-0.13	<0.001	0.36
Women (*n* = 11,779)											
Elevated CRP, %	36.3 (1.0)			32.7 (1.1)***			30.2 (0.7)			-6.1	<0.001	
CRP level, mg/L		1.73	1.62, 1.85		1.60**	1.51, 1.70		1.46***	1.38, 1.54	-0.27	<0.001	
Race/ethnicity											
Non-Hispanic White (*n* = 12,292)											

Elevated CRP, %	29.9 (0.9)			27.3 (0.9)**			25.0 (0.8)			-4.8	<0.001	0.022
CRP level, mg/L		1.53	1.44, 1.62		1.45**	1.38, 1.53		1.31***	1.24, 1.39	-0.21	<0.001	0.026
Non-Hispanic Black (*n* = 4,461)												
Elevated CRP, %	32.3 (1.5)			33.1 (1.1)			33.0 (1.1)			-0.7	0.38	
CRP level, mg/L		1.56	1.44, 1.70		1.63	1.52, 1.76		1.54*	1.45, 1.62	-0.03	0.009	
Mexican American (*n* = 4,962)												
Elevated CRP, %	30.1 (1.2)			31.1 (1.4)			29.0 (1.9)			-1.1	0.004	
CRP level, mg/L		1.50	1.38, 1.63		1.57	1.44, 1.70		1.61	1.45, 1.78	0.11	0.083	
Other (*n* = 2,678)												
Elevated CRP, %	29.6 (1.7)			27.5 (2.4)			20.8 (1.5)			-8.8	<0.001	
CRP level, mg/L		1.46	1.30, 1.63		1.32	1.17, 1.50		1.11***	1.01, 1.21	-0.35	<0.001	
Body mass index,												

kg/m^2												
<25.0 (*n* = 7,714)												
Elevated CRP, %	15.9 (0.8)			13.7 (0.9)*			11.7 (0.6)			-4.2	<0.001	0.054
CRP level, mg/L		0.91	0.85, 0.98		0.85*	0.79, 0.92		0.76***	0.71, 0.81	-0.16	<0.001	0.12
25.0-29.9 (*n* = 8,890)												
Elevated CRP, %	28.4 (1.0)			25.6 (0.8)**			21.3 (1.0)			-7.1	<0.001	
CRP level, mg/L		1.60	1.52, 1.68		1.52*	1.47, 1.57		1.31***	1.24, 1.38	-0.29	<0.001	
≥30.0 (*n* = 7,789)												
Elevated CRP, %	51.0 (1.5)			47.4 (1.4)			44.9 (0.8)			-6.1	0.002	
CRP level, mg/L		2.79	2.67, 2.92		2.58	2.46, 2.71		2.42***	2.35, 2.48	-0.38	<0.001	

Abbreviations: CI, confidence interval; CRP, C-reactive protein; SE, standard error.

*$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ for the 8-year linear trend compared to the previous four-year cycle (i.e. 2003-2006 vs 1999-2002 or 2007-2010 vs 2003-2006).

[a]All *P* values were adjusted for age, sex (except sex-specific estimates), race/ethnicity (except race/ethnicity-specific estimates), body mass index, blood pressure lowering medication, glucose lowering medication, and lipid lowering medication. CRP values were ln-transformed when assessing

the trend in mean CRP values. For the subgroups by age and body mass index, categorical subgroup variable, instead of the continuous level, was used in the adjustment model when assessing the *P* value for interaction.

[b]Data are expressed as % (SE) for elevated CRP. For continuous CRP level, data are expressed as geometric mean (95% CI) due to skewed distribution.

Web Table 2. Medication Use Pattern by Age and Race/ethnicity in United States Adults, 1999-2010[a]

	Overall 1999-2010	**1999-2002**	**2003-2006**	**2007-2010**	**Change, 1999-2002 to 2007-2010**	***P* Value for Linear Time Trend**	***P* Value for Interaction[b]**
Any blood pressure lowering medication, %							
Age, years							
20-39 (*n* = 8,848)	3.7 (0.2)	3.1 (0.4)	3.7 (0.5)	4.2 (0.4)	1.1	0.21	0.14
40-59 (*n* = 8,830)	23.7 (0.7)	21.2 (1.3)	24.3 (1.0)	25.4 (1.1)	4.2	0.18	
≥60 (*n* = 9,516)	60.1 (0.8)	53.2 (1.4)	62.1 (1.3)	63.8 (1.4)	10.5	<0.001	
Race/ethnicity							
Non-Hispanic White (*n* = 13,547)	26.7 (0.6)	22.9 (1.0)	27.5 (1.1)	29.6 (1.1)	6.6	0.001	0.62
Non-Hispanic Black (*n* = 5,200)	28.1 (0.7)	25.1 (1.3)	28.8 (1.2)	30.1 (1.3)	5.0	0.11	
Mexican American (*n* = 5,520)	11.3 (0.8)	8.5 (0.8)	10.4 (1.4)	14.1 (1.4)	5.6	0.016	
Other (*n* = 2,927)	16.8 (0.9)	14.6 (1.2)	17.3 (2.2)	18.3 (1.1)	3.7	0.073	
Any glucose lowering medication, %							
Age, years							
20-39 (*n* = 8,848)	1.4 (0.1)	1.1 (0.2)	1.6 (0.2)	1.5 (0.2)	0.4	0.14	0.92

40-59 (*n* = 8,830)	6.3 (0.3)	5.1 (0.5)	6.3 (0.5)	7.5 (0.6)	2.4	0.021	
≥60 (*n* = 9,516)	14.7 (0.5)	11.9 (0.6)	14.3 (0.8)	17.2 (1.0)	5.3	0.001	
Race/ethnicity							
Non-Hispanic White (*n* = 13,547)	5.8 (0.3)	4.3 (0.4)	5.9 (0.4)	7.1 (0.6)	2.8	0.002	0.73
Non-Hispanic Black (*n* = 5,200)	9.6 (0.4)	7.9 (0.8)	9.1 (0.6)	11.6 (0.8)	3.7	0.012	
Mexican American (*n* = 5,520)	6.5 (0.4)	5.2 (0.5)	6.4 (0.5)	7.6 (0.8)	2.4	0.14	
Other (*n* = 2,927)	7.6 (0.6)	7.1 (1.1)	7.8 (1.3)	7.8 (0.9)	0.7	0.38	
Any lipid lowering medication, %							
Age, years							
20-39 (*n* = 8,848)	1.1 (0.1)	0.7 (0.2)	0.9 (0.2)	1.6 (0.3)	0.9	0.002	0.010
40-59 (*n* = 8,830)	13.1 (0.5)	9.9 (0.8)	13.4 (1.0)	15.5 (0.8)	5.6	0.001	
≥60 (*n* = 9,516)	35.0 (0.6)	23.4 (1.0)	35.4 (1.0)	44.1 (0.8)	20.7	<0.001	
Race/ethnicity							
Non-Hispanic White (*n* = 13,547)	15.6 (0.4)	10.9 (0.6)	15.6 (0.8)	19.9 (0.7)	9.0	<0.001	0.007
Non-Hispanic Black (*n* = 5,200)	9.8 (0.5)	5.1 (0.5)	10.4 (0.7)	13.3 (0.8)	8.2	<0.001	

Mexican American (*n* = 5,520)	6.2 (0.6)	2.8 (0.3)	5.2 (0.6)	9.7 (1.1)	6.9	<0.001	
Other (*n* = 2,927)	10.1 (0.7)	6.8 (1.0)	11.6 (1.6)	11.7 (0.9)	4.8	<0.001	
Statins, %							
Age, years							
20-39 (*n* = 8,848)	0.9 (0.1)	0.5 (0.1)	0.8 (0.2)	1.4 (0.3)	0.9	<0.001	0.036
40-59 (*n* = 8,830)	11.7 (0.5)	8.7 (0.7)	11.8 (0.9)	14.2 (0.7)	5.5	<0.001	
≥60 (*n* = 9,516)	32.3 (0.5)	21.8 (0.9)	32.3 (0.9)	40.7 (0.8)	18.9	<0.001	
Race/ethnicity							
Non-Hispanic White (*n* = 13,547)	14.2 (0.4)	9.9 (0.6)	14.0 (0.7)	18.3 (0.6)	8.4	<0.001	0.004
Non-Hispanic Black (*n* = 5,200)	9.1 (0.5)	4.5 (0.4)	9.5 (0.7)	12.6 (0.7)	8.1	<0.001	
Mexican American (*n* = 5,520)	5.6 (0.5)	2.4 (0.3)	4.7 (0.5)	8.7 (1.0)	6.3	<0.001	
Other (*n* = 2,927)	8.7 (0.6)	5.6 (0.8)	10.0 (1.4)	10.5 (0.9)	4.8	<0.001	

[a]Data are expressed as % (standard error). All *P* values were adjusted for age, sex (except sex-specific estimates), race/ethnicity (except race/ethnicity-specific estimates), and body mass index.

[b]For the subgroups by age, categorical subgroup variable, instead of the continuous level, was used in the adjustment model when assessing the *P* value for interaction.

Web Table 3. Association of Survey Year With Elevated CRP or Geometric Mean Level in United States Adults, 1999-2010, After Excluding Subjects With CRP Levels >10 mg/L[a]

Model[b]	Elevated CRP (>3.0 mg/L)			ln CRP (mg/L)		
	Odds ratio	95% CI	*P* Value	Regression coefficient	95% CI	*P* Value
Unadjusted	0.95	0.93, 0.97	<0.001	-0.035	-0.051, -0.019	<0.001
1	0.92	0.90, 0.94	<0.001	-0.051	-0.063, -0.039	<0.001
2	0.92	0.90, 0.94	<0.001	-0.048	-0.059, -0.037	<0.001
3	0.95	0.92, 0.97	<0.001	-0.028	-0.039, -0.016	<0.001
4	0.95	0.93, 0.98	<0.001	-0.026	-0.037, -0.014	<0.001
5	0.95	0.93, 0.98	<0.001	-0.026	-0.037, -0.014	<0.001
6	0.97	0.95, 1.00	0.030	-0.018	-0.030, -0.006	0.005

Abbreviations: CI, confidence interval; CRP, C-reactive protein.

[a]Multiple logistics or linear regression was used with elevated CRP or ln CRP as the dependent variable. Data are presented as odds ratio (95% CI) for elevated CRP or regression coefficient (95% CI) for ln CRP level per each two-year cycle increase.

[b]Model 1 was adjusted for age, sex, race/ethnicity, and body mass index; model 2, further adjusted for education, smoking and regular alcohol drinking; model 3, further adjusted for glycosylated hemoglobin, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, estimated glomerular filtration rate, albuminuria, alkaline phosphatase, aspartate aminotransferase, and γ-glutamyltransferase; model 4, further adjusted for angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone receptor antagonists, β-blockers, diuretics, metformin,

thiazolidinediones, insulin, “others” category of glucose lowering medications, statins, nicotinic acid, cholesterol adsorption inhibitor, “others” category of lipid lowering medications, aspirin, and clopidogrel; model 5, further adjusted for blood pressure lowering polytherapy, glucose lowering polytherapy, and lipid lowering polytherapy; model 6, further adjusted for total bilirubin.

Web Table 4. Alternative Regression Models for the Association of Survey Year With Elevated CRP or Geometric Mean Level in United States Adults, 1999-2010[a]

Model[b]	Elevated CRP (>3.0 mg/L)			ln CRP (mg/L)		
	Odds ratio	95% CI	*P* Value	Regression coefficient	95% CI	*P* Value
1	0.95	0.93, 0.98	<0.001	-0.027	-0.041, -0.014	<0.001
2	0.98	0.95, 1.00	0.062	-0.017	-0.031, -0.003	0.016

Abbreviations: CI, confidence interval; CRP, C-reactive protein.

[a]Multiple logistics or linear regression was used with elevated CRP or ln CRP as the dependent variable. Data are presented as odds ratio (95% CI) for elevated CRP or regression coefficient (95% CI) for ln CRP level per each two-year cycle increase.

[b]Model 1 was adjusted for age, sex, race/ethnicity, body mass index, education, smoking, regular alcohol drinking, glycosylated hemoglobin, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, estimated glomerular filtration rate, albuminuria, alkaline phosphatase, aspartate aminotransferase, γ-glutamyltransferase, any blood pressure lowering medication, any glucose lowering medication, any lipid lowering medication, aspirin, and clopidogrel; model 2, further adjusted for total bilirubin.

Web Table 5. Prevalence of Elevated CRP Levels, Geometric Mean CRP Levels, and Mean Total Bilirubin Levels in United States Adults According to Statin Use, 1999-2010

	1999-2002			2003-2006			2007-2010			Change, 1999-2002 to 2007-2010	*P* Value for Linear Time Trend[b]	*P* Value for Interaction[b]
	% (SE)[a]	Mean[a]	95% CI	% (SE)[a]	Mean[a]	95% CI	% (SE)[a]	Mean[a]	95% CI			
Elevated CRP, %												
Without statins (*n* = 23,215)	36.5 (0.8)			34.9 (0.9)			31.8 (0.7)			-4.6	<0.001	0.11
With statins (*n* = 3,979)	39.4 (2.7)			36.6 (1.9)			33.1 (1.3)			-6.3	<0.001	
CRP level, mg/L												
Without statins (*n* = 23,215)		1.89	1.79, 1.99		1.82	1.72, 1.93		1.63	1.55, 1.72	-0.25	<0.001	0.005
With statins (*n* = 3,979)		2.33	2.02, 2.67		2.21	2.06, 2.37		1.80	1.65, 1.96	-0.53	<0.001	
Total bilirubin,												

mg/dL									
Without statins (*n* = 23,048)	0.62	0.60, 0.63	0.70	0.69, 0.72	0.73	0.72, 0.74	0.11	<0.001	0.92
With statins (*n* = 3,946)	0.62	1.72, 1.93	0.71	0.70, 0.73	0.74	0.72, 0.76	0.12	<0.001	

Abbreviations: CI, confidence interval; CRP, C-reactive protein; SE, standard error.

[a]Data are expressed as % (SE) for elevated CRP. For continuous CRP and total bilirubin levels, data are expressed as geometric mean (95% CI) due to skewed distribution.

[b]CRP and total bilirubin values were ln-transformed when assessing the trend in geometric mean values. All *P* values were adjusted for age, sex, race/ethnicity, body mass index, blood pressure lowering medication and glucose lowering medication.

Web Table 6. Prevalence of Elevated CRP Levels, Geometric Mean CRP Levels, and Mean Total Bilirubin Levels in United States Adults Without Taking Aspirin, Clopidogrel, or any Medication for Lowering Blood Pressure, Glucose or Lipids, 1999-2010 (*n* = 17,495)

	1999-2002			2003-2006			2007-2010			Change, 1999-2002 to 2007-2010	*P* Value for Linear Time Trend[b]
	% (SE)[a]	Mean[a]	95% CI	% (SE)[a]	Mean[a]	95% CI	% (SE)[a]	Mean[a]	95% CI		
Elevated CRP, %	32.3 (0.8)			31.2 (0.9)			28.4 (0.8)			-3.9	<0.001
CRP level, mg/L		1.64	1.55, 1.75		1.60	1.51, 1.70		1.45	1.36, 1.54	-0.20	<0.001
Total bilirubin, mg/dL		0.62	0.61, 0.64		0.71	0.69, 0.72		0.73	0.72, 0.74	0.11	<0.001

Abbreviations: CI, confidence interval; CRP, C-reactive protein; SE, standard error.

[a]Data are expressed as % (SE) for elevated CRP. For continuous CRP and total bilirubin levels, data are expressed as geometric mean (95% CI) due to skewed distribution.

[b]CRP and total bilirubin values were ln-transformed when assessing the trend in geometric mean values. All *P* values were adjusted for age, sex, race/ethnicity, body mass index, blood pressure lowering medication, glucose lowering medication, and lipid lowering medication.