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REVIEW ARTICLE

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Serum C-reactive protein in the prediction of cardiovascular diseases: Overview of the latest clinical studies and public health practice

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Cardiovascular disease is the most common cause of morbidity and mortality globally. Epidemiological studies using high-sensitivity assays for serum C-reactive protein have shown a consistent association between cardiovascular disease risk and serum C-reactive protein concentrations. C-reactive protein is a biomarker for inflammation, and has been established in clinical practice as an independent risk factor for cardiovascular disease events. There is evidence that serum C-reactive protein is an excellent biomarker of cardiovascular disease and is also an independent and strong predictor of adverse cardiovascular events. Further characterization of the impact and influence of lifestyle exposures and genetic variation on the C-reactive protein response to cardiovascular disease events may have implications for the therapeutic approaches to reduce cardiovascular disease events. This review summarizes the studies that have examined the association between serum C-reactive protein and the risk of cardiovascular disease. We also discuss the impact of independent factors and C-reactive protein genetic polymorphisms on baseline plasma C-reactive protein levels.

KEYWORDS
angiography, cardiovascular diseases (CVD), C-reactive protein (CRP), inflammatory biomarkers

1 | INTRODUCTION

Cardiovascular disease (CVD) comprises coronary artery disease (CAD), stroke, congestive heart failure, carotid artery disease, and peripheral artery disease (Nikpay et al., 2015). This disease is a common manifestation of atherosclerosis, which has now been established as a chronic inflammatory disorder (Kelly, Scanlan, McNally, Prichard, & Dodd, 2017; Nakou, Liberopoulos, Milionis, & Elisaf, 2008). CVD and the acute coronary syndrome (ACS) may be associated with complete or partial arterial thrombosis and atherosclerotic plaque rupture (Christiansen, 2017; Xu et al., 2008). CVD is the major cause of death, disability, and financial burden in most developed countries (Chandrashekara, 2014; Kelly et al., 2017).

Several clinical studies have identified a high correlation between C-reactive protein (CRP) levels and the severity of CAD in both men and women (Chandrashekara, 2014; Idicula, Brogger, Naess, Waje-Andreassen, & Thomassen, 2009; Williams et al., 2008). The sera of patients with acute *Streptococcus pneumonia* infection formed

Abbreviations: ACS, acute coronary syndrome; AHA, American Heart Association; BMI, high body mass index; CDC, Centers for Disease Control and Prevention; CI, confidence interval; CRP, C-reactive protein; CVD, cardiovascular disease; FHS, Framingham heart study; HDL, high-density lipoprotein; HR, hazard ratio; hs-CRP, high-sensitivity CRP; IMT, intima media thickness; JUPITER, intervention trial evaluating rosuvastatin; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; NHANES III, National Health and Nutrition Examination Survey; NOMAS, Northern Manhattan study; PAI-1, plasminogen activator inhibitor-1; PCI, percutaneous coronary intervention; PEACE, prevention of events with angiotensin-converting enzyme inhibition; PROVE IT-TIMI 22, pravastatin or atorvastatin evaluation and infection therapy-thrombolysis in myocardial infarction 22; RAH, resistant for arterial hypertension; SNPs, single-nucleotide polymorphisms; TNF-a, tumor necrosis factor-α.

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a precipitin with an extract from the streptococcal bacterium. The extract was later confirmed as Fraction C and, as a result of its reactivity with the C polysaccharide, the "substance" in the sera was named CRP (M. Kaur, 2017; Mirhafez et al., 2016). A decade later, Oswald Avery and his research team described CRP as an "acute-phase reactant" that was increased in the sera of patients suffering from the inflammation and myocarditis associated with rheumatic fever (Krams & Bäck, 2017). In 1950, other studies indicated that CRP concentrations consistently increased after myocardial necrosis and coronary ischemia (Krams & Bäck, 2017; Ridker, Rifai et al., 1998). Despite these early findings, it was not until the 1990s that interest in the relationship between CRP and CVD was revitalized. In the mid-1990s, immunoassays for CRP (high-sensitivity [hs]-CRP), with greater sensitivity than those previously used routinely, revealed that high serum CRP concentrations predict future CVD (M. Kaur, 2017; Ridker, Buring, Shih, Matias, & Hennekens, 1998; Ridker, Rifai et al., 1998).

CRP has been shown in several prospective, nested case–control studies to be associated with an increased risk of myocardial infarction (Christiansen, 2017; Ridker et al., 2000; Ridker, Rifai et al., 1998), stroke (Everett, Kurth, Buring, & Ridker, 2006; Idicula et al., 2009; Ridker, Buring et al., 1998), sudden death from cardiac causes, and peripheral arterial disease (Chandrashekara, 2014; Nakou et al., 2008; Tavakoly Sany et al., 2015). Although the results of these studies are consistent, there are limitations inherent in the design of nested case–control studies that make it difficult to assess the relative merit of CRP as a risk marker. In particular, population-based cut-off points for CRP remain uncertain, and reliable data describing receiver-operating-characteristic curves for CRP were not available (Alzalzalah, 2017; Koenig, Khuseyinova, Baumert, & Meisinger, 2008).

This review summarizes some of the latest data, which have examined the association of CRP variation with the risk of CVD events to refute or support the role of CRP in CVD as a marker or a causal factor. We also discuss the impact of CRP genetic polymorphisms on plasma CRP levels and associations with the risk of CVD events. This review also summarizes current studies that have examined the effect of several independent factors on plasma baseline CRP levels.

2 | CRP CHARACTERISTIC AND PRODUCTION

CRP belongs to the pentraxin family of calcium-dependent ligand-binding plasma proteins, composed of five identical nonglycosylated polypeptide subunits that has cyclic pentameric symmetry with a central core (Alzalzalah, 2017; Chandrashekara, 2014; Deban, Bottazzi, Garlanda, de la Torre, & Mantovani, 2009). Calcium atoms stabilize the integrity of the native pentamer and the structure of the protomer (Deban et al., 2009; Magen et al., 2008). These atoms are also essential for all physiological ligand binding by CRP. CRP may attach to low-density lipoprotein (LDL), and has been identified within the plaque, where it has been proposed to participate in the inflammatory atherogenic processes (Deban et al., 2009; Everett et al., 2006).

This biomarker has several interesting features. It is an acute-phase protein that has been found to be a marker for infection, increased in response to injury, systemic inflammation, and other inflammatory stimuli (Alzalzalah, 2017; Burke et al., 2002; Chandrashekara, 2014). The availability of hs-CRP assays has supported CRP as a strong biomarker in clinical practice because of its long half-life, stability, ease of assay, and reproducible results (M. Kaur, 2017; Shrivastava, Singh, Raizada, & Singh, 2015). CRP is predominantly synthesized in the liver in response to proinflammatory cytokines, especially interleukin IL-1, IL-6, and IL-17, and tumor necrosis factor (TNF)-α (Chandrashekara, 2014; Shrivastava et al., 2015). It is also produced by mature adipocytes and leukocytes a result of inflammatory stimulation by lipopolysaccharide and TNF-α (Bastard et al., 2006; Tsatsanis et al., 2005). CRP has the ability to enhance the production of chemoattractant and adhesion molecules in endothelial cells (ECs), including monocyte chemoattractant protein 1 (MCP-1) and soluble intracellular adhesion molecule-1 (Lawson & Wolf, 2009; Lespérance, Frasure-Smith, Théroux, & Irwin, 2004; Ren, Khera, de Lemos, Ayers, & Rohatgi, 2017). Studies have shown that nonhepatic cells (e.g., atherosclerotic plaques, neurons, monocytes, lymphocytes, and Kupffer cells) can produce CRP in very limited amounts (Chandrashekara, 2014). Similarly, CRP is synthesized by epithelial cells of both renal epithelium (Jabs et al., 2005) and the respiratory tract (Huang, Chen, Wu, Wei, & Guo, 2013; Jabs et al., 2005) under certain circumstances. Coronary artery smooth muscle cells also appear to produce CRP upon stimulation by inflammatory cytokines (Calabró, Willerson, & Yeh, 2003). Some studies have demonstrated that CRP is also produced at the site of the vessel wall and vulnerable plaque injured by percutaneous coronary intervention (PCI) to activate oligodeoxynucleotide-binding protein (Mac-1) and restenosis (Inoue et al., 2005; Meuwissen et al., 2006). These findings suggested that CRP levels may reach the maximum concentration in the plasma, reacting to different inflammatory stimuli during infection or tissue necrosis and decrease after the removal of inflammatory stimulus during an 18 hr half-life (Jain, Gautam, & Naseem, 2011; Tonstad & Cowan, 2009).

3 | SERUM CRP CONCENTRATIONS AND THEIR USE IN DISEASE STRATIFICATION

Surprisingly, in view of the range of the CRP response, speed, and sensitivity, subjects in the general clinical studies tend to have stable CRP levels, apart from occasional spikes, presumably related to systemic inflammation (Table 1; Schnell-Inderst et al., 2009; Shah et al., 2008). A large number of studies have shown that the median concentration of plasma CRP is 0.8 mg/L, the 90th centile is 3.0 mg/L, and the 99th centile is 10 mg/L in healthy young adults (Mega et al., 2006; Pepys & Hirschfield, 2003). In the

TABLE 1 Classification of serum CRP level based on recent clinical studies

Study	CRP classification (mg/L)	Results
Coronary artery disease (CAD)		
31 prospective cohorts (Shah et al., 2008)	Low risk: <1; moderate risk: 1–3; high risk: >3	Consistent association with CVD and CAD risk – CRP does not perform better than the Framingham risk equation – Limited information to predict the risk of CAD events
German Institute of Medical Documentation and Information (DIMDI) (Schnell-Inderst et al., 2009)	hs-CRP ranged from 0.7 to 2.47	– Independent association between hs-CRP and CVD events that fell within the range of 0.7–2.47. – For patients with medium CVD risk 5%–20% in 10 years), hs-CRP seems most likely to be clinically relevant to support the decision as to whether or not additional statin therapy should be initiated for primary prevention – Additional estimation of hs-CRP level increases the incremental predictive value of the risk prediction
253 ACS patients (Badran, Elnoamany, Khalil, & Eldin, 2013)	Group 1: <45 years old,6.1 ± 1.2; Group 2: 45–65 years, 8.4 ± 2.9; Group 3: ≥65 years,11.5 ± 3.2	– Young patients had different biochemical profiles and clinical, angiographic characteristics – Hs-CRP was positively correlated to the severity of CAD only in the older group – Hs-CRP peak levels did not correlate with angiographic observation in the young patients
Heart and soul study (Williams et al., 2008)	Hospitalized: >3; baseline: ≤3	– In stable CAD, elevated CRP levels predict hospitalization independent of baseline heart failure, heart failure, CHD severity, subsequent MI events, and medication use
PROVE IT (Mega et al., 2006)	hs-CRP levels < 2 mg/L	– Patients with hs-CRP levels lower than 2 mg/L had fewer recurrent events
PEACE (Williams et al., 2008)	hs-CRP > 1 mg/L	– hs CRP higher than 1 mg/L could be considered a significant predictor for adverse CVD events
1,444 patients in Brigham and Women's Hospital, Boston (Nakou et al., 2008)	Low: <1; moderate: 1–3; high: >3; mortality: >10	– In patients with ongoing ischemia, a preoperative CRP concentration more than 10 mg/L predicts mortality and morbidity after cardiac surgery – These preoperative CRP concentrations ≤3 are associated with increased long-term mortality (5-years) and extended hospital length of stay – Patients without ongoing ischemia undergoing coronary artery bypass grafting – In stable patients, prediction of mortality is unclear in lower values
Framingham heart study (Wilson et al., 2008)	Low: <1.00; moderate 1–2.99; high: ≥3.00 The mean CRP is 2.28 for women and 2.67 for men	– CRP level in plasma could be used most effectively to estimate the risk for initial CVD events in patients with an intermediate risk of CVD events – Offering moderate improvement in reclassification of risk
The women's health study (Ridker, Buring et al., 1998)	Mean (SD; mg/dl) Noncases: 2.8 (5.7); CAD cases: 3.3 (3.5)	– No association between cardiovascular disease and Lp-PLA2, although CRP was significantly associated with disease incidence
Hypertension		
Barzilai Medical Center (Magen et al., 2008)	Resistant for arterial hypertension (RAH): 6.9 ± 5.8; controlled (CAH): 4.2 ± 4.8	– RAH is associated with higher blood levels of complement C3 and CRP
767 hypertensives patients (Xu et al., 2008)	Case group ≥ 2.54; control group = 0.4	– In Mongolian patients, increased CRP concentration was associated with hypertension, insulin resistance, and cigarette smoking
Others (Cottone et al., 2006; Y.S. Lee, Ryu, Park, Kang, & Kim, 2005)	–	– In rural adults >50 years, hs-CRP variation is not a risk factor for hypertension – TNF-α and CRP are increased in endothelial activation and oxidative stress

(Continues)

TABLE 1 (Continued)

Study	CRP classification (mg/L)	Results
Atherosclerosis		
302 autopsies of men and women (Burke et al., 2002)	Acute rupture 3.2 hs-CRP level; plaque erosion 2.9; stable plaque 2.5; controls 1.4	– CRP level significantly increased in patients with and without acute coronary thrombosis and with severe CVD – It correlates with numbers of thin-cap atheroma and immune histochemical staining intensity – hs-CRP levels were most closely associated with independent risk factors, namely, smoking, BMI, and age
(Nakou et al., 2008)	Low: <1 hs-CRP; average: 1–3; high: >3; >10 active inflammatory process	– Strong predictive association between future atherothrombotic events (stroke, peripheral arterial disease, and coronary events) and elevated hs-CRP concentration in plasma – hs-CRP is identified as an independent predictor of diabetes – hs-CRP concentration in plasma serum may predict health outcome after myocardial infraction
Ischemic stroke		
Bergen stroke study (Idicula et al., 2009)	Geometric average value: Men 3.1 Women 3.7	– CRP level is associated with long-term mortality and stroke severity when determined at least 24 hr after onset – CRP levels is considered an independent predictor of long-term mortality after ischemic stroke – A crude association was observed between poor short-term functional outcomes and elevated CRP levels, which is likely a secondary symptom for stroke severity – This association between elevated CRP levels and short-term functional outcomes was not significant after adjusting for confounding variables, such as stroke severity – Elevated CRP levels were not associated with CVD events
Women's health initiative observational study (R.C. Kaplan et al., 2008)	Median value (mg/dl) Case group: 3.6; control group: 2.6	– Multiple-biomarker panels could be useful to stratify an individual's risk of stroke – The importance of CRP for middle-aged populations may be higher than that in older adults
Northern Manhattan study (NOMAS; Elkind, Leon, Moon, Paik, & Sacco, 2009)	Median value for hs-CRP: Prestroke 2.2; poststroke 6.5; median 2.5 pre-MI to 13.5 post-MI	– Acutely hs-CRP concentration increases, and Lp-PLA2 mass and activity levels reduce after MI and stroke. – These variations show that estimations performed soon after MI and stroke may be less reliable for long-term risk stratification, and are not reflective of prestroke levels
Northern Manhattan study (NOMAS; Elkind et al., 2009)	hs-CRP > 3 mg/L: all-cause mortality and risk of MI	– Modestly associated with mortality and myocardial infarction – Population characteristics may affect the value of hs-CRP, such as age and other risk factors
15,632 initially healthy women who were followed for a 10-year period (Everett et al., 2006)	hs-CRP median control: 1.48; incident ischemic stroke: 2.85; incident CAD: 3.14	– hs-CRP was a more potent biomarker of future ischemic stroke than CAD, whereas Lipid levels were associated more closely with CAD than stroke – hs-CRP is associated more closely with ischemic stroke than CAD – Concomitant evaluation of hs-CRP levels and lipid levels may improve risk assessment for CAD and stroke
Other cardiovascular diseases (CVD)		
287 incipient in lupus nephritis patients in American College of Rheumatology (Shi et al., 2010)	Without LVH: 3.93 (1.48–9.48); with LVH: 8.03 (3.22–30.95)	– CRP levels were independently associated with left ventricular mass index (LVMI), suggesting that estimation of hs-CRP variation may provide practical clinical data to investigate (Lubrano & Balzan, 2015) left ventricular hypertrophy (LVH) in patient with lupus nephritis

(Continues)

TABLE 1 (Continued)

Study	CRP classification (mg/L)	Results
296 older African-American adults (Lewis, Aiello, Leurgans, Kelly, & Barnes, 2010)	Geometric average value (SD) 0.84 (5.52)	– Self-reported experiences of everyday discrimination are associated with higher CRP levels in older African-American adults. – Additional measurement needed to evaluate the CRP variations over time
National Health and Nutrition Examination Survey (NHANES) III (Simanek et al., 2011)	Low: 0.3; high: ≥0.3	– High CRP levels were associated with a significantly increased risk for both for all-cause and CVD-related mortality
PEACE (Ridker & Silvertown, 2008)	hsCRP, low risk: <1; moderate risk: 1–3; high risk: >3	– hs-CRP levels play an important direct role in atherothrombosis

Note: CAH, congenital adrenal hyperplasia; CHD, coronary heart disease; CRP, C-reactive protein; Lp-PLA2, lipoprotein-associated phospholipase A2; MI, myocardial infarction; PEACE, prevention of events with angiotensin-converting enzyme inhibition; PROVE IT, pravastatin or atorvastatin evaluation and infection therapy; SD, standard deviation; TNF-α, TNF-α tumor necrosis factor

acute-phase stimulus (e.g., acute inflammation) within 6 hr, plasma CRP levels increase from 50 μg/L to more than 500 mg/L within 48 hr, that is, 10,000-fold 26 (Pepys & Hirschfield, 2003; Shrivastava et al., 2015; Wilson et al., 2008). Importantly, acute-phase CRP values show no relationship to fasting state or diurnal patterns and have a long half-life. Subsequently, the plasma CRP levels return to very low reference values with the same speed (Shrivastava et al., 2015). In plasma, the half-life of CRP is around 19 hr and is constant under various conditions in sick and healthy people. Thus, the speed of production of CRP directly reflects the intensity of pathological process and it is the only factor that can be used to estimate CRP levels (Pepys & Hirschfield, 2003; Shrivastava et al., 2015).

The hs-CRP assay refers to a laboratory method that measures the concentration of CRP in serum at low levels (Cottone et al., 2006; Magen et al., 2008). Assays for hs-CRP identified automated and commercial CRP immunoassay systems with higher sensitivity than before, which is a new development in clinical practice (R.C. Kaplan et al., 2008; Y.S. Lee et al., 2005).

The classification of serum hs-CRP concentrations is as follows: <1 mg/L are defined as low-grade inflammation, which is a slight increase in the baseline concentration of CRP; levels between 1 and 3 mg/L are moderately increased; and individuals with CRP levels higher 3 mg/L and LDL cholesterol below 130 mg/dl are defined as being at high risk for future cardiovascular events (Elkind et al., 2009; Ridker & Silvertown, 2008). Values above 10 mg/L are considered clinically active inflammatory states, such as major trauma, chronic inflammatory diseases, and severe infection (Nakou et al., 2008; Shrivastava et al., 2015). These classifications help to explain why those with arthritis, periodontal disease, and other systemic inflammatory disorders all have a higher vascular risk.

4 | CLINICAL USE OF CRP

In recent years, attention has been focused on the clinical utility of serum CRP because of the following reasons (Figure 1):

- A large prospective study documented that elevated CRP is emerging as a clinical marker for many noncommunicable diseases (i.e., ischemic stroke, CAD, hypertension, insulin resistance, peripheral artery disease, and metabolic syndrome) because it is very stable in plasma or serum with very marginal fluctuations, it has assay characteristics that are useful for clinical use and more cost effective.
- It can be easily standardized, and measured with high sensitivity to yield the same results in frozen, stored, or fresh plasma, reflecting the stability of the protein (Brindle, Fujita, Shofer, & O'Connor, 2010; Shrivastava et al., 2015). In addition, clinical trials and epidemiological studies have found that there is no significant difference and diurnal variation in the distribution curve between women and men, and its

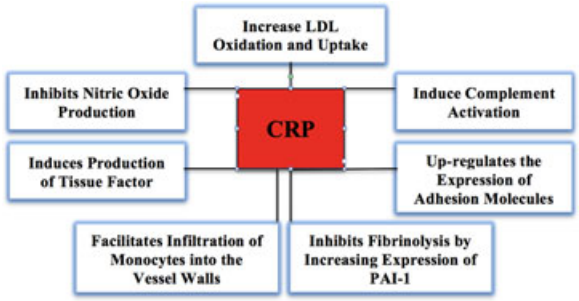

FIGURE 1 Representation of CRP-mediated effects on atherosclerosis and CHD. CRP, C-reactive protein; CVD, cardiovascular disease; LDL, low density lipoprotein, PAI, plasminogen activator inhibitor [Color figure can be viewed at wileyonlinelibrary.com]

serum concentrations are independent of ethnicity and age (Shrivastava et al., 2015; Xu et al., 2008).

- A large number of in vivo and vitro studies have found that serum CRP is a strong independent predictor of future CVD risk and events (Alzalzalah, 2017; Gupta, Gupta, Gupta, Arora, & Gupta, 2013). The attention focused on CRP reflects a strong correlation between elevated plasma levels of CRP and the risk of future atherothrombotic events (Chandrashekara, 2014; Wilson et al., 2008), including stroke (Elkind et al., 2009; Idicula et al., 2009), coronary events (Christiansen, 2017; Shah et al., 2008; Shrivastava et al., 2015), and peripheral arterial disease (Gupta et al., 2013; Inoue et al., 2005).
- Current knowledge suggests that serum hs-CRP could be useful to estimate the risk of plaque rupture (De Rosa et al., 2017; Hong et al., 2011) and the vulnerability of the atheromatous lesion (Libby, 2006; Zhong et al., 2015). In contrast, none of the other systemic markers of inflammation, such as upstream cytokine mediators, sensitive acute-phase proteins, negative acute-phase proteins, or cruder multifactorial measures, have such robust and desirable characteristics (Marks & Neill, 2007; Shrivastava et al., 2015).
- Recent studies have shown that plasma CRP concentrations predict the risk of the metabolic syndrome because components of the metabolic syndrome (i.e., central obesity, hypertension, low plasma concentrations of high-density lipoprotein (HDL), increased plasma triglyceride concentrations, and increased concentrations of blood glucose) correlate with increased plasma CRP concentrations (Hoogeveen et al., 2014; Shrivastava et al., 2015; Tully et al., 2015).
- Current studies suggested that exercise, weight loss, smoking cessation, diet, and diabetes control also reduce serum CRP levels (Church et al., 2010). Therefore, CRP levels could be used as an inflammation fitness score to assess improvement of CVD. Some medicines are associated with a reduction in serum CRP levels. These include statins, aspirin, thiazolidinediones, thienopyridines, and angiotensin (AT)-converting enzyme inhibitors (Ridker, Rifai et al., 1998; Shrivastava et al., 2015).
- Based on the considerable evidence of an expert panel assembled by the American Heart Association (AHA) termed CRP and the Centers for Disease Control and Prevention (CDC), serum CRP levels were considered useful nonspecific biochemical biomarkers of inflammation (Shrivastava et al., 2015; Tully et al., 2015), which contributes significantly to (a) screening of organic disease (Menees, Powell, Kurlander, Goel, & Chey, 2015; Tibble, Sigthorsson, Foster, Forgacs, & Bjarnason, 2002), (b) monitoring of the response to treatment of infection and inflammation (Menees et al., 2015; Simanek et al., 2011), and (c) detection of inter current infection (Tan et al.,).

5 | THE ROLE OF CRP IN CVD

Elevated levels of hs-CRP in plasma correlate with an increased risk of cardiovascular events (Menees et al., 2015). In agreement with this observation, the Canadian Cardiovascular Society, the National Academy of Clinical Biochemistry Laboratory Medicine, and the AHA (CDC/AHA) suggested that CRP plays a pivotal role in many aspects of CVD as described briefly below based on major clinical studies:

5.1 | Women's health study

The prospective data among apparently healthy middle-aged women showed that women with the highest baseline serum CRP levels had a seven fold increase in the risk of stroke or myocardial infraction (95% confidence interval [CI] 2.7–19.9; relative risk [RR] = 7.3; $p = 0.0001$) and a five fold increase in the risk of any CVD events (95% CI 2.3–10.1; RR = 4.8; $p = 0.0001$; Ansell, 2005; Peng, Dong, & Wang, 2016). These studies noted that serum CRP is a strong independent risk factor to predict the risk of CVD than models limited to usual factors since CRP is able to predict CVD events even among women with no readily apparent markers for CVD (Filiberto et al., 2013; Peng et al., 2016; Ridker, Buring et al., 1998).

It is also of interest that the risks of CVD associated with CRP levels were lower for men than women (Ebong et al., 2016; Shrivastava et al., 2015). This results reflect the effect modification by sex. Although this appears to be the main result for previous studies, this could be due to differences in the methods of blood collection and CRP assay techniques, which were different from those in previous studies (Ebong et al., 2016).

A prospective population-based study of apparently healthy postmenopausal women (n = 366) showed that hs-CRP was associated to LDL cholesterol (LDL-C) (Nakou et al., 2008) and concentrations might be a moderator of the contribution of hs-CRP to CVD events (Kamath, Xavier, Sigamani, & Pais, 2015). The Multi-Ethnic Study of Atherosclerosis from 2000 to 2012 showed that Loge hs-CRP was associated with cardiovascular risk in patients who had mean LDL-C concentrations equal to 130 mg/dl or higher (95% CI: 1.05, 1.60; hazard ratio [HR] = 1.29), but not in those with

LDL-C concentrations less than 130 mg/dl (CI: 0.74, 1.05; HR = 0.88, 95%; p for interaction = 0.003; Blaha et al., 2011; Meysamie et al., 2017).

A case–control study of postmenopausal women has indicated that serum hs-CRP is the strongest predictor of cardiovascular risk compared with homocysteine and other inflammatory markers, and baseline lipid levels (Liu et al., 2014; Morrow & Ridker, 2000). Also, hs-CRP was the strongest predictor of cardiovascular risk even in women with LDL cholesterol <130 mg/L (Kamath et al., 2015) and added prognostic information to the Framingham score (Kamath et al., 2015; Ridker, 2007).

It is noteworthy that a prospective study based on serum hs-CRP demonstrated that women with metabolic syndrome were at greater risk for cardiovascular events (Devaraj, Singh, & Jialal, 2009). Several epidemiological studies have concluded that obesity with metabolic syndrome seems to be associated with higher levels of CRP and probably increase CVD risk (Tully et al., 2015). From these findings, serum hs-CRP was shown to be the most significant predictor of the risk of cardiovascular events in future (J. Kaur, 2014; Naik, Balaji, Ganjayi, & Reddy, 2015).

Recent clinical studies examined the effects of hormone-replacement therapy (HRT) on markers of cardiovascular risk in postmenopausal women (Gooren, Wierckx, & Giltay, 2014). The estrogen replacement use increased hs-CRP by 38% at 3 years ($p = 0.002$) and 40% ($p = 0.01$) at 1 year (Gooren et al., 2014; Ouyang, Michos, & Karas, 2006). Also, an HRT-induced increase was observed in the median concentration of hs-CRP (54%) after 12 months of treatment with tibolone (Bowden et al., 2006). Moreover, significant changes in hs-CRP were associated with oral HRT after 3 months, whereas the hs-CRP concentration remained unchanged after 3 and 12 months of treatment with transdermal HRT (Chocano-Bedoya et al., 2014; Ouyang et al., 2006; Taşçı et al., 2014). This result may indicate that HRT may be promote CVD (Gooren et al., 2014). However, a recent meta-analysis concluded that HRT decreases the risk of CVD events in young postmenopausal women, whereas it increases, and then decreases risk over time in older women (Noyce, 2017).

5.2 | Coronary artery diseases

A recent study showed that serum CRP evaluation was useful for patients at intermediate risk of CAD compared with other markers since CRP could predict the risk of CAD in first cardiovascular events from 10% to nearly 20% within a period of 10 years (Lubrano & Balzan, 2015; Shi et al., 2010). Similarly, there is growing evidence that elevation of serum hs-CRP levels predicts a poor cardiovascular prognosis and clinical outcomes in ACS and may be used to identify high-risk patients for more aggressive management with statins and antiplatelet agents (Kelly et al., 2017; Nakou et al., 2008). Furthermore, higher serum hs-CRP concentrations were positively correlated with peripheral arterial disease independent of body mass index (BMI), waist circumference, smoking, serum total cholesterol, blood pressure, and other confounders (Christiansen, 2017; Syvänen, Korhonen, Jaatinen, Vahlberg, & Aarnio, 2011).

Recent studies reported that elevated hs-CRP level is an independent predictor of heart failure and long-term mortality (Christiansen, 2017; Zhang et al., 2017). Also, they introduced hs-CRP as a prognostic marker in patients with heart failure (Kamath et al., 2015; Zhang et al., 2017). Recently, higher mortality was found in patients with hs-CRP levels >3 mg/L (Shah et al., 2008). Similarity, the prevention of events with angiotensin-converting enzyme inhibition trial revealed that a higher serum hs-CRP concentration, even >1 mg/L, was associated with a higher risk of myocardial infarction, stroke, and cardiovascular death in patients with stable CAD (hs-CRP 1–3 mg/L: adjusted HR = 1.39; 95% CI 1.06–1.81; $p = 0.016$; hs-CRP >3 mg/L: adjusted HR = 1.52; 95% CI 1.15–2.02; $p = 0.003$; Nakou et al., 2008; Shah et al., 2008). Data from the Rotterdam Study based on a prospective population in women and men (>55 years old) showed a strong association between the incidence of heart failure and serum hs-CRP levels in men with the HR = 3.73 (95% CI 2.40–5.78) (Kardys et al., 2006; Lewis et al., 2010). Similarly, a prospective population-based study demonstrated an association between cardiovascular mortality and elevated hs-CRP levels (>3 mg/L) in a large group of middle-aged men ($n = 3{,}620$; Kamath et al., 2015; Shrivastava et al., 2015). Recent research suggests that the Reynolds Risk Score for men, which includes hs-CRP, has significantly better ability to predict the overall cardiovascular risk than traditional models (Kamath et al., 2015).

Data from the carotid atherosclerosis progression study revealed a significant association between serum hs-CRP levels and baseline carotid intima media thickness (IMT) in all carotid segments (Blaha et al., 2011; Burke et al., 2002). However, this association was no longer significant after controlling for cardiovascular risk factors, sex, and age (Kamath et al., 2015; M. Kaplan et al., 2014). Also, serum hs-CRP was not related to individual IMT progression. Also, the Cardiovascular Health Study has shown an insignificant association between any CRP gene polymorphism and carotid artery wall IMT (Lorenz, Karbstein, Markus, & Sitzer, 2007; Zhang et al., 2017). Recent studies revealed that increased hs-CRP levels in patients with acute ischemic stroke are significantly associated with an increased risk of recurrent stroke or other cardiovascular events (Kamath et al., 2015; Naik et al., 2015). Moreover, the proatherogenic actions of CRP were supported by its detection in atherosclerotic plaque and its binding to very-LDL and LDL (De Rosa et al., 2017; Shrivastava et al., 2015). Inflammatory mechanisms play a pivotal role in all stages of atherosclerosis (Lubrano & Balzan, 2015; Shrivastava et al., 2015). CRP could be involved in all stages by directly influencing the atherosclerotic process, such as apoptosis, complement activation, monocyte recruitment, vascular cell activation, thrombosis, and lipid accumulation (De Rosa et al., 2017; M. Kaplan et al., 2014). CRP is present in the atherosclerotic lesion specifically in the vascular intima, where it colocalizes with lipoproteins, monocyte-derived macrophages, and monocytes (M. Kaplan et al., 2014;

Nakou et al., 2008). CRP may play a role in many aspects of CVD and atherogenesis as explained briefly below:

- CRP increases macrophages' ability to make foam cells and enhances LDL uptake into macrophages (Meuwissen et al., 2006). Also, CRP binds the phosphocholine of oxidized LDL (Shrivastava et al., 2015).
- CRP directly facilitates and amplifies innate immunity by activation of the classical pathway of the complement system; this action has already been associated with the progression and initiation of CVD (Galkina & Ley, 2009).
- CRP has important antiatherogenic effects, such as expression of endothelial NO synthase (Gradinaru, Borsa, Ionescu, & Prada, 2015). These effects include decreased vasoconstriction, smooth muscle cell proliferation, and platelet aggregation (Gradinaru et al., 2015; Shrivastava et al., 2015).
- Activation of macrophages leads to secretion of a powerful procoagulant and tissue factor, which increase dissemination of intravascular coagulation and thrombosis in the inflammation process (Shrivastava et al., 2015).
- CRP can lead to the attraction of monocytes to the site of injury by upregulation of the expression of adhesion molecules in ECs (Pfützner, Schöndorf, Hanefeld, & Forst, 2010).
- CRP indirectly affects specific response of the immune system, during atherogenesis, by increasing of IL-12 from macrophages, with the subsequent induction of interferon gamma production and CD4+ T (mature T-helper cells) lymphocyte differentiation (Calabro, Golia, & Yeh, 2012).
- CRP increases the expression and activity of plasminogen activator inhibitor-1 (PAI-1); through this action, PAI-1 regulates fibrinolysis. High levels of PAI-1 decrease fibrinolysis and thus lead to atherogenesis (Cesari, Pahor, & Incalzi, 2010).

5.3 | Statin therapy

An Intervention Trial Evaluating Rosuvastatin (JUPITER) study showed that statin therapy (from 20 mg/day to 80 mg/day) is effective in the primary prevention of CVD events among patients with elevated hs-CRP levels (>2 mg/L) and below average concentrations of LDL cholesterol levels (<130 mg/dl; Nakou et al., 2008; Wong, 2009). In these clinical trials, unequivocal evidence of a reduction in cardiovascular mortality and morbidity was observed among patients who received rosuvastatin compared with those who received placebo. Also, the rates of CVD events RR were significantly increased in relation to the elevated hs-CRP levels at baseline (Kavsak et al., 2007; Yusuf et al., 2016).

Data from randomized-controlled trials have shown that statin therapy reduces hs-CRP levels significantly from baseline until 24 weeks (Kavsak et al., 2007; A.V. Khera et al., 2015; Nakou et al., 2008). In all trials, LDL cholesterol and total cholesterol were independently reduced, but the change in hs-CRP levels was unrelated to LDL-C (Albert, Danielson, Rifai, Ridker, & PRINCE Investigators, 2001; Taylor et al., 2013; van Wissen et al., 2002). Moreover, these results showed that all-cause mortality was decreased by statins therapy (odds ratio 0.86; 95% CI 0.79–0.94), as were coronary heart disease events (RR = 0.73; 95% CI 0.67–0.80), revascularization rates (RR = 0.62; 95% CI 0.54–0.72), and stroke rates (RR = 0.78; 95% CI 0.68–0.89) (Nakou et al., 2008). Available evidence demonstrated that statins therapy is likely to be a cost-effective approach to improve quality of life in people with CVD risk (Nakou et al., 2008; Pagidipati et al., 2017).

Data from the cholesterol and recurrent events trial have shown that serum hs-CRP levels may reflect infarct size and predict outcome after myocardial infarction. In randomized-controlled trials, patients with acute myocardial infarction were assigned to placebo or pravastatin (40 mg/day); those with elevated hs-CRP levels at baseline exhibited an increased risk of recurrent coronary events (RR = 1.77; $p = 0.02$; Kamath et al., 2015; Ong et al., 2015).

A prespecified analysis of the reversal of atherosclerosis with aggressive lipid lowering and the pravastatin or atorvastatin evaluation and infection therapy-thrombolysis in myocardial infarction 22 (PROVE IT-TIMI 22) studies demonstrated that lowering LDL-C levels and lowering hs-CRP levels in patients with CVD by intensive statin therapy (randomized to atorvastatin 80 mg/day vs. pravastatin 40 mg/day) attenuated the risk of cardiovascular events and atherosclerotic lesion progression (Nissen et al., 2005; Pagidipati et al., 2017). Specifically, PROVE IT revealed that the patients at the highest risk were those in whom both hs-CRP (≥2 mg/L) and LDL-C (≥70 mg/dl) concentrations were elevated despite statin therapy (Kostapanos & Elisaf, 2011). Patients whose hs-CRP concentration remained elevated (≥2 mg/L) but LDL-C was reduced to <70 (A.V. Khera et al., 2015) had the same recurrent event rates as those whose LDL was ≥70 mg/dl but hs-CRP levels were lowered to <2 mg/L. Patients with both low LDL cholesterol and hs-CRP concentrations had the lowest risk (Nakou et al., 2008; Ridker, Rifai et al., 1998).

Data from the myocardial ischemia reduction with aggressive cholesterol lowering studies have shown that the use of atorvastatin treatment with a high dose (80 mg/day) during 24–96 hr for non-Q-wave myocardial infarction or unstable angina was associated with a greater reduction in hs-CRP and ultimately ischemic events after 16 weeks in comparison with placebo (B.-K. Lee et al., 2016; Schwartz et al., 2001; Wong, 2009). Data from recent studies have showned a significant reduction in hs-CRP levels after statin treatment, which were inversely correlated with the rate of disease progression in patients with CAD (Pagidipati et al., 2017; Wong, 2009).

Rosuvastatin reduced hs-CRP to a greater extent compared with placebo, but rosuvastatin did not decrease the incidences of nonfatal stroke, nonfatal myocardial infractions, and cardiovascular deaths (Kjekshus et al., 2007; Nakou et al., 2008; Pagidipati et al., 2017). However, in the same trials, rosuvastatin significantly decreased the rate of cardiovascular hospitalizations and it did not decrease the primary outcome (Kjekshus et al., 2007; Nakou et al., 2008). These results may indicate no direct association between reduction of

hs-CRP by statin therapy and primary outcomes for patients with heart failure (Kjekshus et al., 2007)

5.4 | Angiography

PCI with stent implantation is a mainstay in the management of severe coronary artery atherosclerotic disease (Ahmed et al., 2016; Mincu, Jánosi, Vinereanu, Rassaf, & Totzeck, 2017). Indeed, PCI currently outperforms coronary artery bypass grafting, and the use of interventional procedures is projected to increase even more with the adoption of new-generation drug-eluting stents (Badran et al., 2013; Nazeminezhad et al., 2014; Wada et al., 2017). Several studies have examined the prognostic role of CRP levels after elective or emergent PCI with a positive prognostic impact (Almagor, Keren, & Banai, 2003; Gach et al., 2007; Zairis et al., 2002). On the other hand, other interventional studies failed to show a significant correlation between CRP levels and recurrent events or restenosis after elective or emergent PCI (Almagor et al., 2003; Bafadhel, Kishk, & Yousef, 2013; Youssef et al., 2012). Data from recent studies have shown a significant reduction in hs-CRP levels after statin treatment (Badran et al., 2013; Ding, Hu, Wu, & Tomlinson, 2015), which were inversely correlated with the rate of disease progression in patients with CAD (Almagor et al., 2003; Nakou et al., 2008; Wada et al., 2017).

There is evidence that hs-CRP level is an independent predictor of the occurrence of restenosis after coronary artery stenting (Badran et al., 2013; Ding et al., 2015). Similarly, in patients with stable angina pectoris, elevated hs-CRP concentration after PCI could be a strong predictor for long-term adverse cardiac events. Moreover, there is evidence for a strong association between high preoperative hs-CRP concentration and long-term risk of cardiovascular events in patients who undergo coronary artery bypass grafting (Ansell, 2005; Badran et al., 2013; Ding et al., 2015; Wada et al., 2017)

5.5 | Functional genetic variants of CRP

The cardiovascular health study showed that polymorphisms in the CRP gene could be associated with CRP synthesis and CVD events (Shen & Ordovas, 2009). Twin and family studies revealed that the genetic variation impact 40% of the variance in plasma CRP levels (Chandrashekara, 2014; Schulz et al., 2016). Several tagging single-nucleotide polymorphisms (SNPs) were described to be associated with circulating CRP levels in plasma (Ancelin et al., 2015; Schulz et al., 2016). Data from the study of three cohorts, including the physicians' health study, the pravastatin inflammation/CRP evaluation trial, and women's health study, have shown that a set of CRP SNPs, including intron 1 SNP, rs1417938; two promoter SNPs, rs3091244 and rs3093059; exon 2 SNP and rs1800947; and two three prime untranslated region (3′-UTR) SNPs, rs1205 and rs1130864, were significantly associated with plasma CRP levels in all study cohorts (Shen & Ordovas, 2009; Vinayagamoorthy et al., 2014). This result in agreement with data from a large cohort study in African American and European American young adults. In this study, seven haplotype-tagging SNPs were evaluated, including rs3091244, rs309358, rs1800947, rs2808630, rs1417938, rs3093066, and rs1205, and a strong association was found between CRP levels and *CRP* haplotypes (Danila et al., 2015; Zhang et al., 2017). Also, other large-scale studies, including the National Health and Nutrition Examination Survey (NHANES III), the Framingham heart study (FHS), and the third National Health, reported strong associations between plasma CRP levels and CRP genotypes (Lawlor et al., 2008; Shen & Ordovas, 2009). Thus, it is seems that individuals carrying certain CRP alleles associated with higher CRP expressions are at a higher risk for CVD (Nimptsch et al., 2015; Schulz et al., 2016). Although data from experimental models and in vitro observations confirm the impact of functional genetic variants of CRP, their value as predictors for further CVD events is unclear (Schulz et al., 2016; Zhu, Liu, He, Sun, & Zhuo, 2013).

On the basis of epidemiological observations, the association between CRP functional genetic polymorphisms and CVD events might be affected by confounding and reverse causation, which may potentially bias the results of studies (Casas et al., 2006; Heikkilä, Ebrahim, & Lawlor, 2007). Recent developments in the genetic dissection provide new options and treatment strategies to determine the impact of the CRP genotype on disease development by taking advantage of the "Mendelian randomization" (Casas et al., 2006; Interleukin-6 Receptor Mendelian Randomisation Analysis Consortium, 2012). This method was used to gain insight into the true nature of associations between the CRP polymorphism and health outcomes (Figure 2). In this respect, several large-scale cohort studies have evaluated the effect of CRP SNPs on CRP concentrations in patients with CVD disease (Casas et al., 2006; Danila et al., 2015; Interleukin-6 Receptor Mendelian Randomisation Analysis Consortium, 2012).

On the basis of in vitro observations, a CRP concentration ≥5 mg/L and CRP SNP rs1800947 were independent risk factors for CVD events in patients of Caucasian origin from Central Germany (3-years of follow-up) (Chandrashekara, 2014). Similarity, in an Italian population, the SNP rs1800947 of the CRP gene led to a higher risk for CVD events after 2 years of follow-up (Danila et al., 2015). In a Russian population, CC genotype carriers of SNP rs1130864 experienced a higher CVD risk after 2 years of follow-up (Barsova et al., 2015). Results from the from large cohort study of CVD risk in African American and European American young adults detected four tag SNPs that were genotyped in a white (European American)

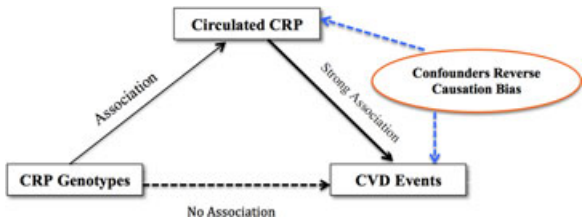

FIGURE 2 Casual association of circulating CRP levels, CRP genetic variants with CVD events. CRP, C-reactive protein; CVD, cardiovascular disease [Color figure can be viewed at wileyonlinelibrary.com]

population and a black (African American) population, aged 65 years or older (Casas et al., 2006; Zhang et al., 2017). The 790T and 1919T tag SNPs were associated with elevated hs-CRP concentrations in black and white participants, respectively. The 2667C allele was associated with lower CRP concentrations in white participants, whereas the 3872A allele was associated with lower CRP concentrations in both participants (Lange et al., 2006; Vinayagamoorthy et al., 2014). The 1919T allele was significantly associated with an increased risk of stroke and CVD mortality in the white population, whereas the 790T allele was associated with a four fold increased risk of myocardial infarction in black participants. The 2667C and 3872A alleles were associated with a decreased risk of CVD mortality in older adults (Danila et al., 2015; Lange et al., 2006). However, the results were controversial as other cohorts, including the NHANES III and the FHS, showed no or little association between the CRP genotype and the risk of CVD events (Cupples et al., 2007; McManus et al., 2013). Moreover, using the same approach, others found that although CRP concentrations in plasma are associated with a common CRP polymorphism, there was no association with the CVD events and genotype (Danila et al., 2015; Lange et al., 2006; Mahmood, Levy, Vasan, & Wang, 2014; Tsao & Vasan, 2015).

Several factors influence the interpretation of these results, such as the proportion of variability of CRP levels (CRP locus), RR of CVD disease, small sample sizes, sex, age, and stages of disease (Elliott et al., 2009; Osman, L'Allier, Elgharib, & Tardif, 2006). In summary, considerable evidence has shown a significant association between the baseline plasma CRP levels and CRP polymorphisms; however, the genetic association with the risk of CVD outcomes is equivocal despite the fact that CRP levels are a strong independent predictor of CVD (Elliott et al., 2009; Lange et al., 2006; Vinayagamoorthy et al., 2014). In this respect, further studies are needed to provide compelling evidence to evaluate the casual association of circulating CRP levels and CRP genetic variants with CVD events.

6 | CRP AND LIFESTYLE RISK FACTORS

Recent clinical evidence identified several lifestyle risk factors that affect CRP levels in plasma as described briefly below:

6.1 | Overweight and obesity

High BMI is significantly correlated with high CRP levels in the plasma. Also, overweight and obese individuals have higher CRP concentrations compared with normal-weight or lean individuals (Shen & Ordovas, 2009). Increased levels of hs-CRP are linked to BMI, insulin, homeostatic model assessment, and intact proinsulin (Onuma et al., 2016; Park, Park, & Yu, 2005). The relationship between BMI and CRP was more powerful than the relationship between any other continual variable involving measured lipid risk factors and age with CRP (Houde et al., 2015; Ishii et al., 2013). This correlation was stronger in women in comparison with men (Houde et al., 2015). Otsuka et al. (2008) showed that there is a relatively moderate relationship between hs-CRP and HDL-C, thyroglobulin (TG), and BMI (Ishii et al., 2013). In a study carried out by Rana et al. (2007), changes in plasma CRP showed a positive association with waist circumference and BMI in both men and women. Recent studies showed that obesity, a low-grade inflammation state, results from the release of chemokines, cytokines, and hormone-like factors (Nehete, Magden, Nehete, Hanley, & Abee, 2014; Ramos-Nino, 2013). Enhanced adipose mass is linked to increases in inflammatory molecules, such as CRP, IL-6, TNF, resistin, migration inhibitory factor, serum amyloid A, and inducible nitric oxide synthase (Luo et al., 2016; Ramos-Nino, 2013; Yang et al., 2017). Adipose tissue produces approximately 25% of the total circulating IL-6. In obese individuals, adipose tissue is developed by increasing the number of macrophages, which is the most important source of increase in the circulating inflammatory molecules in obesity (Bleau, Karelis, St-Pierre, & Lamontagne, 2015; Haneklaus & O'Neill, 2015).

6.2 | Physical activity

Physical inactivity is highly associated with increased concentrations of inflammatory markers and with CAD risk. Evidence has recently indicated a relationship between a decrease in physical activity and an increased CAD risk in males (20%) and females (36%; Shen & Ordovas, 2009). In some epidemiological studies, health evaluations of elderly men and women, athletes, and middle-aged men have shown an inverse relation between CRP and physical activities (Kasapis & Thompson, 2005; Loprinzi, 2015). Unfortunately, different statements were reported about a lifestyle practices (e.g., exercise). In fact, the data are usually classified in different ways without any standardized methodology. For instance, the effect of physical activity level in one study may be categorized as moderate, but as light in a different study. Moreover, self-reported physical activity differs from measured physical fitness. On the other hand, the presence of subgroups in a broader class also makes it difficult for investigators to interpret the data (Kasapis & Thompson, 2005; Loprinzi, 2015). For example, physical activity can be classified into relaxing time and professional activity. Furthermore, even the types of physical activity (e.g., resistance or flexibility training, and aerobic exercise) differ from each other. On the other hand, the CRP concentration was lower in physically active people than in those who were physically inactive and among alcohol drinkers than nondrinkers (Kasapis & Thompson, 2005; Plaisance & Grandjean, 2006).

6.3 | Diabetes

One of the other remarkable features of hs-CRP (especially in high levels) is its strong and independent correlation with type II diabetes (Asemi, Zare, Shakeri, Sabihi, & Esmaillzadeh, 2013; Schernthaner et al., 2017). Increased levels of hs-CRP are a significant predictor for the future diagnosis of metabolic syndrome and type II diabetes and remain effective even after considering smoking, family history of diabetes mellitus, BMI, and other factors (Gurven et al., 2016; Martín-Timón, Sevillano-Collantes, Segura-Galindo, & del Cañizo-Gómez, 2014). Moreover, it has been indicated that there is an involvement of high

hs-CRP with cardiovascular morbidity and mortality in people with these diseases (Gurven et al., 2016; Martín-Timón et al., 2014).

In a diabetes study conducted in Mexico city, it was shown that baseline hs-CRP is considerably correlated with the progression of the metabolic syndrome. It was also shown that the CRP concentration in women, smokers, and people with diabetes was higher than that in men, nonsmokers, and those without diabetes, respectively (Fonseca & Izar, 2016; Schernthaner et al., 2017). In addition to being an independent predictor (in its low-level increases) of future cardiovascular events, CRP can predict diabetes incidence and hypertension risk (Bowden et al., 2006; Gurven et al., 2016; Schernthaner et al., 2017).

6.4 | Tobacco use

Considerable clinical evidence has shown that smoking is associated with increased levels of IL-6, TNF-α, and CRP. Based on a large population-based study, there is an independent and strong dose–response relationship between cigarette smoking and CRP (Wendling et al., 2016, 2017). In fact, cigarette smoking is associated with elevated values of CRP (Wendling et al., 2016). However, CRP has been reported to be significantly elevated 10–19 years after smoking cessation, which suggests a continuing low-grade inflammatory response in former smokers (Tonstad & Cowan, 2009). Also, most of the other (noninflammatory) smoking-induced changes are reversible after giving up smoking. According to categorical variables, elevated baseline CRP was related to the status of smoking as ex-smokers and recent smokers had higher CRP compared with the nonsmokers (Tonstad & Cowan, 2009; Wendling et al., 2017).

6.5 | Alcohol

In recent years, an association between CRP concentrations with alcohol consumption has been proven. It has been shown that moderate consumption of alcohol is associated with reduced CRP levels (Albert, Glynn, & Ridker, 2003; Imhof et al., 2001). In a study, Albert et al. (2003) reported the median CRP values to be 2.60 mg/L and 1.6 mg/L in those consuming less than one drink per month and those consuming 5–7 drinks per week, respectively. Furthermore, a slight increase in CRP (1.8 mg/L) was observed in those consuming more than two drinks daily. On the other hand, the CRP concentration was lower in physically active people than in those who were physically inactive, and among alcohol drinkers than nondrinkers (Albert et al., 2003; Shivappa et al., 2014).

6.6 | Racial/ethnic

Socioeconomic and racial/ethnic factors strongly influence CVD outcomes and risk factors. CRP level is associated with cardiovascular risk, and knowledge about its distribution in the population may help direct preventive efforts. In 2003, the AHA/CDC panel recommended a significant need to study ethnic differences in CRP concentrations (Doran, Zhu, & Muennig, 2013; Nazmi & Victora, 2007). Based on population-based studies, most white individuals had the lowest CRP concentrations, but African-Americans, South Asians, and Hispanics showed the highest concentrations (Fonseca & Izar, 2016; Ford et al., 2003; Nazmi & Victora, 2007). The level of CRP in African-Americans was higher than that in white individuals (median, 3.0 vs. 2.3 mg/L; $p < 0.001$), whereas white women, African American women, and black men, all had higher CRP levels in comparison with white men, and the highest levels were observed among black women. Furthermore, the reviews showed that the range of hs-CRP differs in various ethnicities and groups (Nazmi & Victora, 2007; Uchino et al., 2016).

6.7 | Diet

There are data demonstrating that diets are positively associated with high saturated and trans-fatty acids and biomarkers of inflammation, such as CRP (Shen & Ordovas, 2009). Also, recent studies have shown that a high omega 6/omega 3 ratio accelerates cardiovascular and inflammatory diseases, and increased levels of omega 3 fatty acids exert inhibitory effects (Shivappa et al., 2014). Many interventions that are known to decrease cardiovascular risk are linked to lower levels of CRP; specifically, weight loss, physical activity, diet, and giving up smoking all result in declined vascular risk and reduced levels of CRP (Kasapis & Thompson, 2005; Loprinzi, 2015).

6.8 | Sex

Blacks and females had higher levels of CRP, and this correlation was greater in women in comparison with men. The level of CRP in black individuals was higher than that in white individuals (median, 3.0 vs. 2.3 mg/L; $p < 0.001$) and the CRP level of women was higher than that in men (median, 3.3 vs. 1.8 mg/L; $p < .001$; Doran et al., 2013; A. Khera et al., 2005). The relationship between obesity, IL-6, and CRP was related more to the blood pressure in women; however, this was not observed in smokers (A. Khera et al., 2005; Peng et al., 2016). In women with cardiovascular events, levels of CRP have been found to be higher compared with control subjects (Doran et al., 2013).

6.9 | Cancer development

CVD and cancer are the two leading causes of chronic disease and death worldwide (Hashimoto, 2016; Heikkilä et al., 2009). These diseases have various possible delicate interactions and similarities, including similar risk factors, supporting a shared biology for which there is emerging evidence (Koene, Prizment, Anne Blaes, & Konety, 2017). The extensive overlap in disease prevention and risk factors for cancer and CVD shows that both diseases have some common basic molecular networks or pathways. In developed countries, environmental and lifestyle risk factors have been associated with four most common malignancies (lung, colorectal, breast, and prostate cancer; Koene et al., 2017; Nöthlings, Ford, Kröger, & Boeing, 2010). The World Health Organization reported that more than 30% of incidences of CVD and cancer deaths could be prevented by following a healthy lifestyle, including a healthy diet, no smoking, physical activity >3.5 hr weekly, and BMI < 3.5 (WHO,

2015). Furthermore, the results from the large number of epidemiologic studies demonstrate that controlling CVD risk factors can help reduce the risk of incident cancer over time (Koene et al., 2017; Nöthlings et al., 2010; Rasmussen-Torvik et al., 2013). Thus, understanding the delicate interaction between cancer and CVD in different populations may lead to earlier detection, better prevention, and a safer treatment strategy.

Chronic inflammation appears to be major a unifying biological mechanism in the pathogenesis and progression of both CVD and cancer, and occurs in common conditions, such as hyperglycemia, obesity, diabetes, hypertriglyceridemia, and hypertension (Heikkilä et al., 2009; Koene et al., 2017), and this may, in part, demonstrate why cancer and CVD share several risk factors. Recently, accumulating evidence has reported that chronic inflammation is associated with the severity and progression of many cancers, and may also play a causal role in carcinogenesis and malignant transformation of cells (Nelson et al., 2013). Considerable circumstantial and factual evidence has shown that inflammation-associated oxidative damage is linked to carcinogenesis by inactivating mutations in tumor-suppressor genes and modifying posttranslational in proteins involved in apoptotic control or DNA repair (Heikkilä et al., 2009). Similarly, inflammatory enzymes, transcription factors, and cytokines promote the proliferation and growth of cancer cells, and inhibit apoptosis. In addition, the activation of inflammatory pathways could promote vascular permeability, angiogenesis, and cell motility, therefore facilitating progression of many tumors (Koene et al., 2017; Zhu et al., 2013).

Therefore, recently, a large number of studies have focused on circulating biomarkers of inflammation to predict tumor recurrence and treatment response. They demonstrated that the presence of a systemic inflammatory response, as evidenced by an elevated IL-6 levels and an elevated CRP level, is associated with an increased risk of prevalent cancer, including lung, breast, ovarian cancers, and possibly colorectal, but unrelated to prostate cancer risk (Hashimoto, 2016; Heikkilä et al., 2009).

Several investigations have reported that these cancer cells produce CRP, and it stimulates the differentiation and growth of some malignant cells. Similarly, population-based investigations have indicated that patients with cancer tend to have higher circulating CRP concentrations than healthy individuals (Heikkilä et al., 2009). However, it is still unclear whether circulating CRP concentrations play causal roles in malignancy because CRP is a nonspecific marker of many diseases, and the biological processes involved in the malignant development in different organs may be different (Heikkilä et al., 2009; Koene et al., 2017). Therefore, individual association studies need to examine the causal role of CRP as inflammation biomarkers with different cancer types to provide robust biological evidence for a causal relationship.

7 | CONCLUSIONS

CVD is the leading cause of disability and death in humans, and is increasing in incidence rapidly in the developing world. Recent observation suggests that the CAD process is characterized by increasing levels of biomarkers of inflammation. Many clinical studies have focused on CRP variations in the plasma to improve global cardiovascular risk prediction.

These studies showed that CRP is not only an excellent biomarker or mediator of atherosclerosis and CVD but it also independently and strongly predicts adverse cardiovascular events, including ischemic stroke, myocardial infarction, and sudden cardiac death, in individuals. The commercial availability of CRP can lead to the development of high-sensitivity screening for this marker as it is reliable, reproducible, and simple, and can be applied as a clinical guide for the management, prognosis, and diagnosis of CVD.

The reported impact of *CRP* gene polymorphisms on CVD events provides some support for strong epidemiological associations between CRP and CVD events. However, these associations might be affected by confounding or reverse causation. On the basis of the Mendelian randomization method, the confounding impacts of environmental exposure might be overcome since the associations between specific gene polymorphisms and CVD events are not commonly susceptible to confounding and reverse causation.

Lifestyle factors also affect the variation in CRP levels, and there is support for the notion that lifestyle factors may interact to define this complex trait. Therefore, further characterization of the interaction and influence of lifestyle factors and genetic variations on the CRP response to CVD events may have major implications for the development of more therapeutic approaches and personalized preventive to reduce CVD events.

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CONFLICTS OF INTEREST

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REFERENCES

Ahmed, M., Chowdhury, N. A., Rahman, A., Rahman, M., Amin, M. G., Jannat, S., & Mollah, R. I. (2016). Elevated plasma high sensitivity C-reactive protein (hs-CRP) level is a predictor of periprocedural myocardial injury during percutaneous coronary intervention (PCI). *Bangladesh Heart Journal*, *30*(1), 5–12.

Albert, M. A., Danielson, E., Rifai, N., & Ridker, P. M. (2001). Effect of statin therapy on C-reactive protein levels: The pravastatin inflammation/

CRP evaluation (PRINCE): A randomized trial and cohort study. *Journal of the American Medical Association*, *286*(1), 64–70.

Albert, M. A., Glynn, R. J., & Ridker, P. M. (2003). Alcohol consumption and plasma concentration of C-reactive protein. *Circulation*, *107*(3), 443–447.

Almagor, M., Keren, A., & Banai, S. (2003). Increased C-reactive protein level after coronary stent implantation in patients with stable coronary artery disease. *American Heart Journal*, *145*(2), 248–253.

Alzalzalah, A. (2017). C-reactive protein as a biomarker of oral health and risk of cardiovascular disease in healthy and CV disease subjects, Baltimore: University of Maryland.

Ancelin, M. L., Farré, A., Carrière, I., Ritchie, K., Chaudieu, I., & Ryan, J. (2015). C-reactive protein gene variants: Independent association with late-life depression and circulating protein levels. *Translational Psychiatry*, *5*(1), e499.

Ansell, B. J. (2005). C-reactive protein: A new tool for cardiovascular disease risk prediction: With self-assessment test. *Resident and Staff Physician*, *51*(11), 10.

Asemi, Z., Zare, Z., Shakeri, H., Sabihi, S., & Esmaillzadeh, A. (2013). Effect of multispecies probiotic supplements on metabolic profiles, hs-CRP, and oxidative stress in patients with type 2 diabetes. *Annals of Nutrition and Metabolism*, *63*(1–2), 1–9.

Badran, H., Elnoamany, M. F., Khalil, T., & Eldin, E. M. (2013). Age-related alteration of risk profile, inflammatory response, and angiographic findings in patients with acute coronary syndrome. *European Journal of Heart Failure*, *12*, S80.

Bafadhel, T., Kishk, Y., & Yousef, A. (2013). Prognostic significance of high sensitivity C-reactive protein in patients with angina pectoris underwent percutaneous coronary intervention. *Journal of the Saudi Heart Association*, *25*(2), 168.

Barsova, R. M., Lvovs, D., Titov, B. V., Matveeva, N. A., Shakhnovich, R. M., Sukhinina, T. S., … Favorova, O. O. (2015). Variants of the coagulation and inflammation genes are replicably associated with myocardial infarction and epistatically interact in Russians. *PLoS One*, *10*(12), e0144190.

Bastard, J. -P., Maachi, M., Lagathu, C., Kim, M. J., Caron, M., Vidal, H., … Feve, B. (2006). Recent advances in the relationship between obesity, inflammation, and insulin resistance. *European Cytokine Network*, *17*(1), 4–12.

Blaha, M. J., Rivera, J. J., Budoff, M. J., Blankstein, R., Agatston, A., O'Leary, D. H., … Szklo, M. (2011). Association between obesity, hsCRP ≥2 mg/L, and subclinical atherosclerosis: Implications of JUPITER from the multi-ethnic study of atherosclerosis (MESA). *Arteriosclerosis, Thrombosis, and Vascular Biology*, *31*(6), 1430.

Bleau, C., Karelis, A. D., St-Pierre, D. H., & Lamontagne, L. (2015). Crosstalk between intestinal microbiota, adipose tissue and skeletal muscle as an early event in systemic low-grade inflammation and the development of obesity and diabetes. *Diabetes/Metabolism Research and Reviews*, *31*(6), 545–561.

Bowden, D. W., Lohman, K., Hsu, F. C., Langefeld, C. D., Carr, J. J., Lenchik, L., … Herrington, D. M. (2006). Hormone replacement therapy is associated with increased C-reactive protein in women with Type 2 diabetes in the Diabetes Heart Study. *Diabetic Medicine*, *23*(7), 763–767.

Brindle, E., Fujita, M., Shofer, J., & O'Connor, K. A. (2010). Serum, plasma, and dried blood spot high-sensitivity C-reactive protein enzyme immunoassay for population research. *Journal of Immunological Methods*, *362*(1), 112–120.

Burke, A. P., Tracy, R. P., Kolodgie, F., Malcom, G. T., Zieske, A., Kutys, R., … Virmani, R. (2002). Elevated C-reactive protein values and atherosclerosis in sudden coronary death. *Circulation*, *105*(17), 2019–2023.

Calabro, P., Golia, E., & Yeh, E. T. (2012). Role of C-reactive protein in acute myocardial infarction and stroke: Possible therapeutic approaches. *Current Pharmaceutical Biotechnology*, *13*(1), 4–16.

Calabró, P., Willerson, James T., & Yeh, Edward T. H., (2003). Inflammatory cytokines stimulated C-reactive protein production by human coronary artery smooth muscle cells. *Circulation*, *108*(16), 1930–1932.

Casas, J. P., Shah, T., Cooper, J., Hawe, E., McMahon, A. D., Gaffney, D., … Hingorani, A. D. (2006). Insight into the nature of the CRP–coronary event association using Mendelian randomization. *International Journal of Epidemiology*, *35*(4), 922–931.

Cesari, M., Pahor, M., & Incalzi, R. A. (2010). Plasminogen activator inhibitor-1 (PAI-1): A key factor linking fibrinolysis and age-related subclinical and clinical conditions. *Cardiovascular Therapeutics*, *28*, e72–e91.

Chandrashekara, S. (2014). C-reactive protein: An inflammatory marker with specific role in physiology, pathology, and diagnosis. *Internet Journal of Rheumatology and Clinical Immunology*, *2*(S1), 105–121.

Chocano-Bedoya, P. O., Mirzaei, F., O'Reilly, E. J., Lucas, M., Okereke, O. I., Hu, F. B., … Ascherio, A. (2014). C-reactive protein, interleukin-6, soluble tumor necrosis factor α receptor 2 and incident clinical depression. *Journal of Affective Disorders*, *163*, 25–32.

Christiansen, M. K. (2017). Early-onset Coronary Artery Disease Clinical and Hereditary Aspects. *Danish Medical Journal*, *64*(9), pii: B5406

Church, T. S., Earnest, C. P., Thompson, A. M., Priest, E. L., Rodarte, R. Q., Saunders, T., … Blair, S. N. (2010). Exercise without weight loss does not reduce C-reactive protein: The INFLAME study. *Medicine and Science in Sports and Exercise*, *42*(4), 708–716.

Cottone, S., Mule, G., Nardi, E., Vadala, A., Guarneri, M., Briolotta, C., … Cerasola, G. (2006). Relation of C-reactive protein to oxidative stress and to endothelial activation in essential hypertension. *American Journal of Hypertension*, *19*(3), 313–318.

Cupples, L. A., Arruda, H. T., Benjamin, E. J., D'Agostino, R. B., Demissie, S., DeStefano, A. L., … Atwood, L. D. (2007). The Framingham Heart Study 100K SNP genome-wide association study resource: Overview of 17 phenotype working group reports. *BMC Medical Genetics*, *8*(1), S1.

Danila, M. I., Westfall, A. O., Raman, K., Chen, L., Reynolds, R. J., Hughes, L. B., … Bridges, S. L. (2015). The role of genetic variants in CRP in radiographic severity in African Americans with early and established rheumatoid arthritis. *Genes and Immunity*, *16*(7), 446–451.

De Rosa, R., Vasa-Nicotera, M., Leistner, D. M., Reis, S. M., Thome, C. E., Boeckel, J. -N., … Zeiher, A. M. (2017). Coronary atherosclerotic plaque characteristics and cardiovascular risk factors—Insights from an optical coherence tomography study. *Circulation Journal*, *81*, 1165–1173.

Deban, L., Bottazzi, B., Garlanda, C., de la Torre, Y. M., & Mantovani, A. (2009). Pentraxins: Multifunctional proteins at the interface of innate immunity and inflammation. *Biofactors*, *35*(2), 138–145.

Devaraj, S., Singh, U., & Jialal, I. (2009). Human C-reactive protein and the metabolic syndrome. *Current Opinion in Lipidology*, *20*(3), 182–189.

Ding, C., Hu, M., Wu, Y. -J., & Tomlinson, B. (2015). Achievement of specified lipid and high-sensitivity C-reactive protein levels with two statins in Chinese patients with hypercholesterolaemia. *Lipids in Health and Disease*, *14*(1), 107.

Doran, B., Zhu, W., & Muennig, P. (2013). Gender differences in cardiovascular mortality by C-reactive protein level in the United States: Evidence from the National Health and Nutrition Examination Survey III. *American Heart Journal*, *166*(1), 45–51.

Ebong, I. A., Schreiner, P., Lewis, C. E., Appiah, D., Ghelani, A., & Wellons, M. (2016). The association between high-sensitivity C-reactive protein and hypertension in women of the CARDIA study. *Menopause*, *23*(6), 662–668.

Elkind, M. S. V., Leon, V., Moon, Y. P., Paik, M. C., & Sacco, R. L. (2009). High-sensitivity C-reactive protein and lipoprotein-associated phospholipase A2 stability before and after stroke and myocardial infarction. *Stroke*, *40*(10), 3233–3237.

Elliott, P., Chambers, J. C., Zhang, W., Clarke, R., Hopewell, J. C., Peden, J. F., … Bennett, D. (2009). Genetic loci associated with

C-reactive protein levels and risk of coronary heart disease. *Journal of the American Medical Association*, *302*(1), 37–48.

Everett, B. M., Kurth, T., Buring, J. E., & Ridker, P. M. (2006). The relative strength of C-reactive protein and lipid levels as determinants of ischemic stroke compared with coronary heart disease in women. *Journal of the American College of Cardiology*, *48*(11), 2235–2242.

Filiberto, A. C., Mumford, S. L., Pollack, A. Z., Zhang, C., Yeung, E. H., Perkins, N. J., … Schisterman, E. F. (2013). Habitual dietary isoflavone intake is associated with decreased C-reactive protein concentrations among healthy premenopausal women. *The Journal of Nutrition*, *143*(6), 900–906.

Fonseca, F. A., & Izar, M. C. (2016). High-sensitivity C-reactive protein and cardiovascular disease across countries and ethnicities. *Clinics*, *71*(4), 235–242.

Ford, E. S., Giles, W. H., Myers, G. L., Rifai, N., Ridker, P. M., & Mannino, D. M. (2003). C-reactive protein concentration distribution among US children and young adults: Findings from the National Health and Nutrition Examination Survey, 1999–2000. *Clinical Chemistry*, *49*(8), 1353–1357.

Gach, O., Legrand, V., Biessaux, Y., Chapelle, J. P., Vanbelle, S., & Pierard, L. A. (2007). Long-term prognostic significance of high-sensitivity C-reactive protein before and after coronary angioplasty in patients with stable angina pectoris. *The American Journal of Cardiology*, *99*(1), 31–35.

Galkina, E., & Ley, K. (2009). Immune and inflammatory mechanisms of atherosclerosis. *Annual Review of Immunology*, *27*, 165–197.

Gooren, L. J., Wierckx, K., & Giltay, E. J. (2014). Cardiovascular disease in transsexual persons treated with cross-sex hormones: Reversal of the traditional sex difference in cardiovascular disease pattern. *European Journal of Endocrinology*, *170*(6), 809–819.

Gradinaru, D., Borsa, C., Ionescu, C., & Prada, G. I. (2015). Oxidized LDL and NO synthesis—Biomarkers of endothelial dysfunction and ageing. *Mechanisms of Ageing and Development*, *151*, 101–113.

Gupta, S., Gupta, V. K., Gupta, R., Arora, S., & Gupta, V. (2013). Relationship of high-sensitive C-reactive protein with cardiovascular risk factors, clinical presentation and angiographic profile in patients with acute coronary syndrome: An Indian perspective. *Indian Heart Journal*, *65*(3), 359–365.

Gurven, M. D., Trumble, B. C., Stieglitz, J., Blackwell, A. D., Michalik, D. E., Finch, C. E., & Kaplan, H. S. (2016). Cardiovascular disease and type 2 diabetes in evolutionary perspective: A critical role for helminths? *Evolution, Medicine, and Public Health*, *2016*(1), 338–357.

Haneklaus, M., & O'Neill, L. A. J. (2015). NLRP3 at the interface of metabolism and inflammation. *Immunological Reviews*, *265*(1), 53–62.

Hashimoto, N. (2016). Evaluation of the relationship between C-reactive protein and prostate cancer. *Clinical Oncology (Royal College of Radiologists)*, *1*, 1005.

Heikkilä, K., Ebrahim, S., & Lawlor, D. A. (2007). A systematic review of the association between circulating concentrations of C reactive protein and cancer. *Journal of Epidemiology & Community Health*, *61*(9), 824–833.

Heikkilä, K., Harris, R., Lowe, G., Rumley, A., Yarnell, J., Gallacher, J., … Lawlor, D. A. (2009). Associations of circulating C-reactive protein and interleukin-6 with cancer risk: Findings from two prospective cohorts and a meta-analysis. *Cancer Causes & Control*, *20*(1), 15–26.

Hong, Y. J., Jeong, M. H., Choi, Y. H., Cho, S. H., Hwang, S. H., Ko, J. S., … Kang, J. C. (2011). Relation between high-sensitivity C-reactive protein and coronary plaque components in patients with acute coronary syndrome: Virtual histology-intravascular ultrasound analysis. *Korean Circulation Journal*, *41*(8), 440–446.

Hoogeveen, R. C., Gaubatz, J. W., Sun, W., Dodge, R. C., Crosby, J. R., Jiang, J., Boerwinkle, E. (2014). Small dense low-density lipoproteincholesterol concentrations predict risk for coronary heart disease. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *34*(2), 1069–1077.

Houde, A. -A., Légaré, C., Biron, S., Lescelleur, O., Biertho, L., Marceau, S., … Bouchard, L. (2015). Leptin and adiponectin DNA methylation levels in adipose tissues and blood cells are associated with BMI, waist girth and LDL-cholesterol levels in severely obese men and women. *BMC Medical Genetics*, *16*(1), 29.

Huang, Y., Chen, R., Wu, T., Wei, X., & Guo, A. (2013). Association between point-of-care CRP testing and antibiotic prescribing in respiratory tract infections: A systematic review and meta-analysis of primary care studies. *British Journal of General Practice*, *63*(616), e787–e794.

Idicula, T. T., Brogger, J., Naess, H., Waje-Andreassen, U., & Thomassen, L. (2009). Admission C–reactive protein after acute ischemic stroke is associated with stroke severity and mortality: The'Bergen stroke study'. *BMC Neurology*, *9*(1), 18.

Imhof, A., Froehlich, M., Brenner, H., Boeing, H., Pepys, M. B., & Koenig, W. (2001). Effect of alcohol consumption on systemic markers of inflammation. *The Lancet*, *357*(9258), 763–767.

Inoue, T., Kato, T., Uchida, T., Sakuma, M., Nakajima, A., Shibazaki, M., … Node, K. (2005). Local release of C-reactive protein from vulnerable plaque or coronary arterial wall injured by stenting. *Journal of the American College of Cardiology*, *46*(2), 239–245.

Interleukin-6 Receptor Mendelian Randomisation Analysis Consortium (2012). The interleukin-6 receptor as a target for prevention of coronary heart disease: A mendelian randomisation analysis. *The Lancet*, *379*(9822), 1214–1224.

Ishii, S., Cauley, J. A., Greendale, G. A., Crandall, C. J., Danielson, M. E., Ouchi, Y., & Karlamangla, A. S. (2013). C-reactive protein, bone strength, and nine-year fracture risk: Data from the Study of Women's Health Across the Nation (SWAN). *Journal of Bone and Mineral Research*, *28*(7), 1688–1698.

Jabs, W. J., Busse, M., Kruger, S., Jocham, D., Steinhoff, J., & Doehn, C. (2005). Expression of C-reactive protein by renal cell carcinomas and unaffected surrounding renal tissue. *Kidney International*, *68*(5), 2103–2110.

Jain, S., Gautam, V., & Naseem, S. (2011). Acute-phase proteins: As diagnostic tool. *Journal of Pharmacy and BioAllied Sciences*, *3*(1), 118.

Kamath, D. Y., Xavier, D., Sigamani, A., & Pais, P. (2015). High sensitivity C-reactive protein (hsCRP) & cardiovascular disease: An Indian perspective. *The Indian Journal of Medical Research*, *142*(3), 261–268.

Kaplan, M., Hamoud, S., Tendler, Y., Meilin, E., Lazarovitch, A., Nitecki, S., & Hayek, T. (2014). A significant correlation between C-reactive protein levels in blood monocytes derived macrophages versus content in carotid atherosclerotic lesions. *Journal of Inflammation*, *11*(1), 7.

Kaplan, R. C., McGinn, A. P., Baird, A. E., Hendrix, S. L., Kooperberg, C., Lynch, J., … Wassertheil-Smoller, S. (2008). Inflammation and hemostasis biomarkers for predicting stroke in postmenopausal women: The Women's Health Initiative Observational Study. *Journal of Stroke and Cerebrovascular Diseases*, *17*(6), 344–355.

Kardys, I., Knetsch, A. M., Bleumink, G. S., Deckers, J. W., Hofman, A., Stricker, B. H. C., & Witteman, J. C. M. (2006). C-reactive protein and risk of heart failure. The Rotterdam Study. *American Heart Journal*, *152*(3), 514–520.

Kasapis, C., & Thompson, P. D. (2005). The effects of physical activity on serum C-reactive protein and inflammatory markers: A systematic review. *Journal of the American College of Cardiology*, *45*(10), 1563–1569.

Kaur, J. (2014). A comprehensive review on metabolic syndrome. *Cardiology Research and Practice*, *2014*, 943162.

Kaur, M. (2017). C-reactive protein: A prognostic indicator. *International Journal of Applied and Basic Medical Research*, *7*, 2.

Kavsak, P. A., MacRae, A. R., Newman, A. M., Lustig, V., Palomaki, G. E., Ko, D. T., … Jaffe, A. S. (2007). Elevated C-reactive protein in acute coronary syndrome presentation is an independent predictor of long-term mortality and heart failure. *Clinical Biochemistry*, *40*(5), 326–329.

Kelly, B., Scanlan, E., McNally, S., Prichard, R., & Dodd, J. (2017). Breast arterial calcification on screening mammography can predict clinically significant coronary artery disease (CAD) in the BreastCheck screening cohort. *European Journal of Surgical Oncology*, *43*(5), S2.

Khera, A., McGuire, D. K., Murphy, S. A., Stanek, H. G., Das, S. R., Vongpatanasin, W., … de Lemos, J. A. (2005). Race and gender differences in C-reactive protein levels. *Journal of the American College of Cardiology*, *46*(3), 464–469.

Khera, A. V., Qamar, A., Murphy, S. A., Cannon, C. P., Sabatine, M. S., & Rader, D. J. (2015). On-statin resistin, leptin, and risk of recurrent coronary events after hospitalization for an acute coronary syndrome (from the pravastatin or atorvastatin evaluation and infection therapy-thrombolysis in myocardial infarction 22 study). *The American Journal of Cardiology*, *116*(5), 694–698.

Kjekshus, J., Apetrei, E., Barrios, V., Böhm, M., Cleland, J. G. F., Cornel, J. H., … Wikstrand, J. (2007). Rosuvastatin in older patients with systolic heart failure. *New England Journal of Medicine*, *357*(22), 2248–2261.

Koene, R. J., Prizment, Anna E. , Anne Blaes, M. S., & Konety, S. H. (2017). Evaluation of the relationship between C-reactive protein and prostate cancer. *Circulation*, *133*(11), 1104–1114.

Koenig, W., Khuseyinova, N., Baumert, J., & Meisinger, C. (2008). Prospective study of high-sensitivity C-reactive protein as a determinant of mortality: Results from the MONICA/KORA Augsburg Cohort Study, 1984–1998. *Clinical Chemistry*, *54*(2), 335–342.

Kostapanos, M. S., & Elisaf, M. S. (2011). JUPITER and satellites: Clinical implications of the JUPITER study and its secondary analyses. *World Journal of Cardiology*, *3*(7), 207.

Krams, R., & Bäck, M. (2017). ESC textbook of vascular biology. Oxford University Press.

Lange, L. A., Carlson, C. S., Hindorff, L. A., Lange, E. M., Walston, J., Durda, J. P., … Reiner, A. P. (2006). Association of polymorphisms in the CRP gene with circulating C-reactive protein levels and cardiovascular events. *Journal of the American Medical Association*, *296*(22), 2703–2711.

Lawlor, D. A., Harbord, R. M., Timpson, N. J., Lowe, G. D. O., Rumley, A., Gaunt, T. R., … Smith, G. D. (2008). The association of C-reactive protein and CRP genotype with coronary heart disease: Findings from five studies with 4,610 cases amongst 18,637 participants. *PLoS One*, *3*(8), e3011.

Lawson, C., & Wolf, S. (2009). ICAM-1 signaling in endothelial cells. *Pharmacological Reports*, *61*(1), 22–32.

Lee, B. -K., Koo, B. -K., Nam, C. -W., Doh, J.-H., Chung, W.-Y., Cho, B.-R., & Fearon, W. F. (2016). Does pre-treatment with high dose atorvastatin prevent microvascular dysfunction after percutaneous coronary intervention in patients with acute coronary syndrome? *Korean Circulation Journal*, *46*(4), 472–480.

Lee, Y. S., Ryu, S. Y., Park, J., Kang, M. G., & Kim, K. S. (2005). The association of high sensitivity C-reactive protein (hsCRP) with hypertension in some rural residents. *Journal of Preventive Medicine and Public Health*, *38*(3), 325–329.

Lespérance, F., Frasure-Smith, N., Théroux, P., & Irwin, M. (2004). The association between major depression and levels of soluble intercellular adhesion molecule 1, interleukin-6, and C-reactive protein in patients with recent acute coronary syndromes. *American Journal of Psychiatry*, *161*(2), 271–277.

Lewis, T. T., Aiello, A. E., Leurgans, S., Kelly, J., & Barnes, L. L. (2010). Self-reported experiences of everyday discrimination are associated with elevated C-reactive protein levels in older African-American adults. *Brain, Behavior, and Immunity*, *24*(3), 438–443.

Libby, P. (2006). Inflammation and cardiovascular disease mechanisms. *The American Journal of Clinical Nutrition*, *83*(2), 456S–460S.

Liu, Z. M., Ho, S. C., Chen, Y. M., Ho, S., To, K., Tomlinson, B., & Woo, J. (2014). Whole soy, but not purified daidzein, had a favorable effect on improvement of cardiovascular risks: A 6-month randomized, double-blind, and placebo-controlled trial in equol-producing postmenopausal women. *Molecular Nutrition & Food Research*, *58*(4), 709–717.

Loprinzi, P. D. (2015). Dose–response association of moderate-to-vigorous physical activity with cardiovascular biomarkers and all-cause mortality: Considerations by individual sports, exercise and recreational physical activities. *Preventive Medicine*, *81*, 73–77.

Lorenz, M. W., Karbstein, P., Markus, H. S., & Sitzer, M. (2007). High-sensitivity C-reactive protein is not associated with carotid intima-media progression. *Stroke*, *38*(6), 1774–1779.

Lubrano, V., & Balzan, S. (2015). Consolidated and emerging inflammatory markers in coronary artery disease. *World Journal of Experimental Medicine*, *5*(1), 21.

Luo, M., Luo, P., Zhang, Z., Payne, K., Watson, S., Wu, H., … Cai, L. (2016). Zinc delays the progression of obesity-related glomerulopathy in mice via down-regulating P38 MAPK-mediated inflammation. *Obesity*, *24*(6), 1244–1256.

Magen, E., Mishal, J., Paskin, J., Glick, Z., Yosefy, C., Kidon, M., & Schlesinger, M. (2008). Resistant arterial hypertension is associated with higher blood levels of complement C3 and C-reactive protein. *The Journal of Clinical Hypertension*, *10*(9), 677–683.

Mahmood, S. S., Levy, D., Vasan, R. S., & Wang, T. J. (2014). The Framingham Heart Study and the epidemiology of cardiovascular disease: A historical perspective. *The Lancet*, *383*(9921), 999–1008.

Marks, A. R., & Neill, U. S. (2007). Science in medicine: The JCI textbook of molecular medicine. Burlington, MA: Jones & Bartlett Learning.

Martín-Timón, I., Sevillano-Collantes, C., Segura-Galindo, A., & del Cañizo-Gómez, F. J. (2014). Type 2 diabetes and cardiovascular disease: Have all risk factors the same strength? *World Journal of Diabetes*, *5*(4), 444.

McManus, D. D., Beaulieu, L. M., Mick, E., Tanriverdi, K., Larson, M. G., Keaney, J. F., … Freedman, J. E. (2013). Relationship among circulating inflammatory proteins, platelet gene expression, and cardiovascular risk significance. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *33*(11), 2666–2673.

Mega, J. L., Morrow, D. A., Cannon, C. P., Murphy, S., Cairns, R., Ridker, P. M., & Braunwald, E. (2006). Cholesterol, C-reactive protein, and cerebrovascular events following intensive and moderate statin therapy. *Journal of Thrombosis and Thrombolysis*, *22*(1), 71–76.

Menees, S. B., Powell, C., Kurlander, J., Goel, A., & Chey, W. D. (2015). A meta-analysis of the utility of C-reactive protein, erythrocyte sedimentation rate, fecal calprotectin, and fecal lactoferrin to exclude inflammatory bowel disease in adults with IBS. *The American Journal of Gastroenterology*, *110*(3), 444–454.

Meuwissen, M., Van der Wal, A., Niessen, H., Koch, K., De Winter, R., Van der Loos, C., … Becker, A. (2006). Colocalisation of intraplaque C reactive protein, complement, oxidised low density lipoprotein, and macrophages in stable and unstable angina and acute myocardial infarction. *Journal of Clinical Pathology*, *59*(2), 196–201.

Meysamie, A., Ghodsi, S., Ghalehtaki, R., Esteghamati, A., Asgari, F., & Gouya, M. M. (2017). Distributions of high-sensitivity C-reactive protein, total cholesterol-HDL ratio and 10-year cardiovascular risk: National Population-Based Study. *Acta Medica Iranica*, *55*(4), 218–227.

Mincu, R. -I., Jánosi, R. A., Vinereanu, D., Rassaf, T., & Totzeck, M. (2017). Preprocedural C-reactive protein predicts outcomes after primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction a systematic meta-analysis. *Scientific Reports*, *7*.

Mirhafez, S. R., Tajfard, M., Avan, A., Pasdar, A., Nedaeinia, R., Aghasizade, M., … Ghayour-Mobarhan, M. (2016). Association between serum cytokine concentrations and the presence of hypertriglyceridemia. *Clinical Biochemistry*, *49*(10–11), 750–755.

Morrow, D. A., & Ridker, P. M. (2000). C-reactive protein, inflammation, and coronary risk. *Medical Clinics of North America*, *84*(1), 149–161.

Naik, S. R., Balaji, M., Ganjayi, M. S., & Reddy, P. A. (2015). Effect of metabolic parameters and hs-CRP levels on cardiac autonomic function in patients with metabolic syndrome. *Indian Journal of Medical Research and Pharmaceutical Sciences*, *2*, 55–61.

Nakou, E., Liberopoulos, E., Milionis, H., & Elisaf, M. (2008). The role of C-reactive protein in atherosclerotic cardiovascular disease: An overview. *Current Vascular Pharmacology*, *6*(4), 258–270.

Nazeminezhad, R., Tajfard, M., Latiff, L. A., Mouhebati, M., Esmaeily, H., Ferns, G. A. A., … Rahimi, H. R. (2014). Dietary intake of patients with angiographically defined coronary artery disease and that of healthy controls in Iran. *European Journal of Clinical Nutrition*, *68*(1), 109–113.

Nazmi, A., & Victora, C. G. (2007). Socioeconomic and racial/ethnic differentials of C-reactive protein levels: A systematic review of population-based studies. *BMC Public Health*, *7*(1), 212.

Nehete, P., Magden, E. R., Nehete, B., Hanley, P. W., & Abee, C. R. (2014). Obesity related alterations in plasma cytokines and metabolic hormones in chimpanzees. *International Journal of Inflammation*, *2014*, 856749.

Nelson, E. R., Wardell, S. E., Jasper, J. S., Park, S., Suchindran, S., Howe, M. K., … McDonnell, D. P. (2013). 27-Hydroxycholesterol links hypercholesterolemia and breast cancer pathophysiology. *Science*, *342*(6162), 1094–1098.

Nikpay, M., Goel, A., Won, H. -H., Hall, L. M., Willenborg, C., Kanoni, S., … Farrall, M. (2015). A comprehensive 1000 Genomes-based genome-wide association meta-analysis of coronary artery disease. *Nature Genetics*, *47*(10), 1121–1130.

Nimptsch, K., Aleksandrova, K., Boeing, H., Janke, J., Lee, Y. A., Jenab, M., … Pischon, T. (2015). Association of CRP genetic variants with blood concentrations of C-reactive protein and colorectal cancer risk. *International Journal of Cancer*, *136*(5), 1181–1192.

Ning, H., Van Horn, L., Shay, C. M., & Lloyd-Jones, D. M. (2014). Associations of dietary fiber intake with long-term predicted cardiovascular disease risk and C-reactive protein levels (from the National Health and Nutrition Examination Survey Data [2005–2010]). *The American Journal of Cardiology*, *113*(2), 287–291.

Nissen, S. E., Tuzcu, E. M., Schoenhagen, P., Crowe, T., Sasiela, W. J., Tsai, J., … Ganz, P. (2005). Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. *New England Journal of Medicine*, *352*(1), 29–38.

Nöthlings, U., Ford, E. S., Kröger, J., & Boeing, H. (2010). Lifestyle factors and mortality among adults with diabetes: Findings from the European Prospective Investigation into Cancer and Nutrition–Potsdam study. *Journal of Diabetes*, *2*(2), 112–117.

Noyce, P. (2017). Establishing the risk related to hormone replacement therapy and cardiovascular disease in women. *Management*, *12*, 17.

Ong, P., Carro, A., Athanasiadis, A., Borgulya, G., Schäufele, T., Ratge, D., … Kaski, J. C. (2015). Acetylcholine-induced coronary spasm in patients with unobstructed coronary arteries is associated with elevated concentrations of soluble CD40 ligand and high-sensitivity C-reactive protein. *Coronary Artery Disease*, *26*(2), 126–132.

Onuma, H., Tabara, Y., Kawamura, R., Ohashi, J., Takata, Y., Ohyagi, Y., … Osawa, H. (2016). The DNA methylation of single nucleotide polymorphism (SNP)-420 in RETN is associated with hs-CRP and BMI in the general Japanese Population, USA: American Diabetes Association.

Osman, R., L'Allier, P. L., Elgharib, N., & Tardif, J. -C. (2006). Critical appraisal of C-reactive protein throughout the spectrum of cardiovascular disease. *Vascular Health and Risk Management*, *2*(3), 221–237.

Otsuka, T., Kawada, T., Katsumata, M., Ibuki, C., & Kusama, Y. (2008). High-sensitivity C-reactive protein is associated with the risk of coronary heart disease as estimated by the Framingham Risk Score in middle-aged Japanese men. *International Journal of Cardiology*, *129*(2), 245–250.

Ouyang, P., Michos, E. D., & Karas, R. H. (2006). Hormone replacement therapy and the cardiovascular system: Lessons learned and unanswered questions. *Journal of the American College of Cardiology*, *47*(9), 1741–1753.

Pagidipati, N. J., Navar, A. M., Mulder, H., Sniderman, A. D., Peterson, E. D., & Pencina, M. J. (2017). Comparison of recommended eligibility for primary prevention statin therapy based on the US preventive services task force recommendations vs the ACC/AHA guidelines. *Journal of the American Medical Association*, *317*(15), 1563–1567.

Park, H. S., Park, J. Y., & Yu, R. (2005). Relationship of obesity and visceral adiposity with serum concentrations of CRP, TNF-α and IL-6. *Diabetes Research and Clinical Practice*, *69*(1), 29–35.

Peng, Y., Dong, B., & Wang, Z. (2016). Overall and gender-specific associations between C-reactive protein and stroke occurrence: A Cross-sectional Study in US. *Journal of Stroke*, *18*(3), 355–357.

Pepys, M. B., & Hirschfield, G. M. (2003). C-reactive protein: A critical update. *Journal of Clinical Investigation*, *111*(12), 1805–1812.

Pfützner, A., Schöndorf, T., Hanefeld, M., & Forst, T. (2010). High-sensitivity C-reactive protein predicts cardiovascular risk in diabetic and nondiabetic patients: Effects of insulin-sensitizing treatment with pioglitazone. *Journal of Diabetes Science and Technology*, *4*(3), 706–716.

Plaisance, E. P., & Grandjean, P. W. (2006). Physical activity and high-sensitivity C-reactive protein. *Sports Medicine*, *36*(5), 443–458.

Ramos-Nino, M. E. (2013). The role of chronic inflammation in obesity-associated cancers. *ISRN Oncology*, *2013*.

Rana, J. S., Boekholdt, S. M., Ridker, P. M., Jukema, J. W., Luben, R., Bingham, S. A., … Khaw, K.-T. (2007). Differential leucocyte count and the risk of future coronary artery disease in healthy men and women: the EPIC–Norfolk Prospective Population Study. *Journal of Internal Medicine*, *262*(6), 678–689.

Rasmussen-Torvik, L. J., Shay, C. M., Abramson, J. G., Friedrich, C. A., Nettleton, J. A., Prizment, A. E., & Folsom, A. R. (2013). Ideal cardiovascular health is inversely associated with incident cancer: The Atherosclerosis Risk In Communities study. *Circulation*, *113*, 001183–001275.

Ren, H.-Y., Khera, A., de Lemos, J. A., Ayers, C. R., & Rohatgi, A. (2017). Soluble endothelial cell-selective adhesion molecule and incident cardiovascular events in a multi-ethnic population. *American Heart Journal*, *191*, 55–61.

Ridker, P. M. (2007). C-reactive protein and the prediction of cardiovascular events among those at intermediate risk. *Journal of the American College of Cardiology*, *49*(21), 2129–2138.

Ridker, P. M., Buring, J. E., Shih, J., Matias, M., & Hennekens, C. H. (1998). Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. *Circulation*, *98*(8), 731–733.

Ridker, P. M., Rifai, N., Pfeffer, M., Sacks, F., Lepage, S., & Braunwald, E. (2000). Elevation of tumor necrosis factor-α and increased risk of recurrent coronary events after myocardial infarction. *Circulation*, *101*(18), 2149–2153.

Ridker, P. M., Rifai, N., Pfeffer, M. A., Sacks, F. M., Moye, L. A., Goldman, S., … Braunwald, E. (1998). Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. *Circulation*, *98*(9), 839–844.

Ridker, P. M., & Silvertown, J. D. (2008). Inflammation, C-reactive protein, and atherothrombosis. *Journal of Periodontology*, *79*(8S), 1544–1551.

Schernthaner, G., Jarvis, S., Lotan, C., Prázný, M., Wanner, C., & Wascher, T. (2017). Advances in the management of cardiovascular risk for patients with type 2 diabetes: Perspectives from the Academy for Cardiovascular Risk, Outcomes and Safety Studies in Type 2 diabetes. *Therapeutics and Clinical Risk Management*, *13*, 69–79.

Schnell-Inderst, P., Schwarzer, R., Göhler, A., Grandi, N., Grabein, K., Stollenwerk, B., … Siebert, U. (2009). Prognostic value, clinical effectiveness and cost-effectiveness of high sensitivity C-reactive protein as a marker in primary prevention of major cardiac events. *GMS Health Technology Assessment*, *5*

Schulz, S., Lüdike, H., Lierath, M., Schlitt, A., Werdan, K., Hofmann, B., … Reichert, S. (2016). C-reactive protein levels and genetic variants of CRP as prognostic markers for combined cardiovascular endpoint (cardiovascular death, death from stroke, myocardial infarction, and stroke/TIA). *Cytokine*, *88*, 71–76.

Schwartz, G. G., Olsson, A. G., Ezekowitz, M. D., Ganz, P., Oliver, M. F., Waters, D., … Stern, T. (2001). Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: The MIRACL study: A randomized controlled trial. *Journal of the American Medical Association*, *285*(13), 1711–1718.

Shah, T., Casas, J. P., Cooper, J. A., Tzoulaki, I., Sofat, R., McCormack, V., … Hingorani, A. D. (2008). Critical appraisal of CRP measurement for the prediction of coronary heart disease events: New data and systematic review of 31 prospective cohorts. *International Journal of Epidemiology*, *38*(1), 217–231.

Shen, J., & Ordovas, J. M. (2009). Impact of genetic and environmental factors on hsCRP concentrations and response to therapeutic agents. *Clinical Chemistry*, *55*(2), 256–264.

Shi, B., Ni, Z., Cai, H., Zhang, M., Mou, S., Wang, Q., … Qian, J. (2010). High-sensitivity C-reactive protein: An independent risk factor for left ventricular hypertrophy in patients with lupus nephritis. *BioMed Research International*, *2010*, 2010–2015.

Shivappa, N., Steck, S. E., Hurley, T. G., Hussey, J. R., Ma, Y., Ockene, I. S., … Hébert, J. R. (2014). A population-based dietary inflammatory index predicts levels of C-reactive protein in the Seasonal Variation of Blood Cholesterol Study (SEASONS). *Public Health Nutrition*, *17*(8), 1825–1833.

Shrivastava, A. K., Singh, H. V., Raizada, A., & Singh, S. K. (2015). C-reactive protein, inflammation and coronary heart disease. *The Egyptian Heart Journal*, *67*(2), 89–97.

Simanek, A. M., Dowd, J. B., Pawelec, G., Melzer, D., Dutta, A., & Aiello, A. E. (2011). Seropositivity to cytomegalovirus, inflammation, all-cause and cardiovascular disease-related mortality in the United States. *PLoS One*, *6*(2), e16103.

Stewart, S. H., Mainous, A. G., & Gilbert, G. (2002). Relation between alcohol consumption and C-reactive protein levels in the adult US population. *The Journal of the American Board of Family Practice*, *15*(6), 437–442.

Syvänen, K., Korhonen, P., Jaatinen, P., Vahlberg, T., & Aarnio, P. (2011). High-sensitivity C-reactive protein and ankle brachial index in a Finnish cardiovascular risk population. *International Journal of Angiology*, *20*(1), 43–48.

Tan, D. H., Szadkowski, L., Raboud, J., Yi, T. J., Shannon, B., Kaul, R., Walmsley, S. (2015). Effect of intercurrent infections and vaccinations on immune and inflammatory biomarkers among human immunodeficiency virus-infected adults on suppressive antiretroviral therapy. Oxford University Press. Open Forum Infection Disease. 2(2): ofv036.

Taşçı, T., Şükür, Y. E., Özmen, B., Atabekoğlu, C. S., Cengiz, S. D., Koçbulut, E., … Sönmezer, M. (2014). Effects of transdermal and oral hormone replacement therapies on monocyte chemoattractant protein-1 levels: A randomized clinical trial. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, *176*, 50–54.

Tavakoly Sany, S. B., Hashim, R., Salleh, A., Rezayi, M., Karlen, D. J., Razavizadeh, B. B. M., & Abouzari-Lotf, E. (2015). Dioxin risk assessment: Mechanisms of action and possible toxicity in human health. *Environmental Science and Pollution Research*, *22*(24), 19434–19450.

Taylor, F., Huffman, M. D., Macedo, A. F., Moore, T. H., Burke, M., Davey Smith, G., … Ebrahim, S. (2013). Statins for the primary prevention of cardiovascular disease. *The Cochrane Library*.

Tibble, J. A., Sigthorsson, G., Foster, R., Forgacs, I., & Bjarnason, I. (2002). Use of surrogate markers of inflammation and Rome criteria to distinguish organic from nonorganic intestinal disease. *Gastroenterology*, *123*(2), 450–460.

Tonstad, S., & Cowan, J. L. (2009). C-reactive protein as a predictor of disease in smokers and former smokers: A review. *International Journal of Clinical Practice*, *63*(11), 1634–1641.

Tsao, C. W., & Vasan, R. S. (2015). Cohort profile: The Framingham Heart Study (FHS): Overview of milestones in cardiovascular epidemiology. *International Journal of Epidemiology*, *44*(6), 1800–1813.

Tsatsanis, C., Zacharioudaki, V., Androulidaki, A., Dermitzaki, E., Charalampopoulos, I., Minas, V., … Margioris, A. N. (2005). Adiponectin induces TNF-α and IL-6 in macrophages and promotes tolerance to itself and other pro-inflammatory stimuli. *Biochemical and Biophysical Research Communications*, *335*(4), 1254–1263.

Tully, P. J., Baumeister, H., Bengel, J., Jenkins, A., Januszewski, A., Martin, S., & Wittert, G. A. (2015). The longitudinal association between inflammation and incident depressive symptoms in men: The effects of hs-CRP are independent of abdominal obesity and metabolic disturbances. *Physiology & Behavior*, *139*, 328–335.

Uchino, B. N., Ruiz, J. M., Smith, T. W., Smyth, J. M., Taylor, D. J., Allison, M., & Ahn, C. (2016). Ethnic/racial differences in the association between social support and levels of C-reactive proteins in the North Texas Heart Study. *Psychophysiology*, *53*(1), 64–70.

van Wissen, S., Trip, M. D., Smilde, T. J., de Graaf, J., Stalenhoef, A. F. H., & Kastelein, J. J. P. (2002). Differential hs-CRP reduction in patients with familial hypercholesterolemia treated with aggressive or conventional statin therapy. *Atherosclerosis*, *165*(2), 361–366.

Vinayagamoorthy, N., Hu, H.-J., Yim, S.-H., Jung, S.-H., Jo, J., Jee, S. H., & Chung, Y.-J. (2014). New variants including ARG1 polymorphisms associated with C-reactive protein levels identified by genome-wide association and pathway analysis. *PLoS One*, *9*(4), e95866.

Wada, H., Dohi, T., Miyauchi, K., Doi, S., Naito, R., Konishi, H., … Daida, H. (2017). Independent and combined effects of serum albumin and C-reactive protein on long-term outcomes of patients undergoing percutaneous coronary intervention. *Circulation Journal*, *81*, 1293–1300.

Wendling, D., Guillot, X., Gossec, L., Prati, C., Saraux, A., & Dougados, M. (2016). THU0375 ASDAS-based remission was less frequent than BASDAI-based remission, and both were related To CRP and smoking in early axial spondyloarthritis, The Desir Cohort. *Annals of the Rheumatic Diseases*, *75*(2), 323–329.

Wendling, D., Guillot, X., Gossec, L., Prati, C., Saraux, A., & Dougados, M. (2017). Remission is related to CRP and smoking in early axial spondyloarthritis, The DESIR cohort. *Joint, Bone, Spine*, *84*(4), 473–476.

WHO. 2015. Cancer. World Health Organization. Retrieved from http://www.who.int/mediacentre/factsheets/fs297/en/.

Williams, E. S., Shah, S. J., Ali, S., Na, B. Y., Schiller, N. B., & Whooley, M. A. (2008). C-reactive protein, diastolic dysfunction, and risk of heart failure in patients with coronary disease: Heart and Soul Study. *European Journal of Heart Failure*, *10*(1), 63–69.

Wilson, P. W. F., Pencina, M., Jacques, P., Selhub, J., D'agostino, R., & O'donnell, C. J. (2008). C-reactive protein and reclassification of cardiovascular risk in the Framingham Heart Study. *Circulation: Cardiovascular Quality and Outcomes*, *1*(2), 92–97.

Wong, N. D. (2009). Justification for the use of statins in primary prevention: An intervention trial evaluating rosuvastatin (the JUPITER trial). *Current Cardiovascular Risk Reports*, *3*(2), 83–85.

Xu, T., Ju, Z., Tong, W., Hu, W., Liu, Y., Zhao, L., & Zhang, Y. (2008). Relationship of C-reactive protein with hypertension and interactions between increased C-reactive protein and other risk factors on hypertension in Mongolian people, China. *Circulation Journal*, *72*(8), 1324–1328.

Yang, P., Xiao, Y., Luo, X., Zhao, Y., Zhao, L., Wang, Y., … Chen, Y. (2017). Inflammatory stress promotes the development of obesity-related chronic kidney disease via CD36 in mice. *Journal of Lipid Research*, *58*, 1417–1427.

Youssef, A. A., Kishk, Y. T., Abdelhafez, H. A., Bafadhl, T. A., Tsui, P. T., Lau, C. L., Sattwika, K. A. (2012). Prognostic significance of high sensitivity C-reactive protein before and after percutaneous coronary intervention in patients with angina pectoris. *The Medical Journal of Cairo University*, *24*(4), 299–302.

Yusuf, S., Bosch, J., Dagenais, G., Zhu, J., Xavier, D., Liu, L., … Lonn, E. (2016). Cholesterol lowering in intermediate-risk persons without cardiovascular disease. *New England Journal of Medicine*, *374*(21), 2021–2031.

Zairis, M. N., Ambrose, J. A., Manousakis, S. J., Stefanidis, A. S., Papadaki, O. A., Bilianou, H. I., … Foussas, S. G. (2002). The impact of plasma levels of C-reactive protein, lipoprotein (a) and homocysteine on the long-term prognosis after successful coronary stenting: The Global Evaluation of New Events and Restenosis After Stent Implantation Study. *Journal of the American College of Cardiology*, *40*(8), 1375–1382.

Zhang, L., Li, S., Li, J., Sang, X., Zakir, R., Liu, J., & Li, Z. (2017). High-sensitivity C-reactive protein (hs-CRP) gene polymorphisms (rs1205 and rs2794520) associated with hs-CRP serum levels in periodontitis-associated chronic kidney disease patients from Uyghur adults. *International Journal of Clinical and Experimental Pathology*, *10*(3), 3939–3948.

Zhong, Z. X., Li, B., Li, C. R., Zhang, Q. F., Liu, Z. D., Zhang, P. F., … Wen, F. L. (2015). Role of chemokines in promoting instability of coronary atherosclerotic plaques and the underlying molecular mechanism. *Brazilian Journal of Medical and Biological Research*, *48*(2), 161–166.

Zhu, Y., Liu, T., He, H., Sun, Y., & Zhuo, F. (2013). C-reactive protein gene polymorphisms and myocardial infarction risk: A meta-analysis and meta-regression. *Genetic Testing and Molecular Biomarkers*, *17*(12), 873–880.

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