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C-reactive protein response to influenza vaccination predicts cardiovascular disease risk in the Philippines

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Abstract

Inflammation is associated with increased risk for chronic degenerative diseases, as well as age-related functional declines across many systems and tissues. Current understandings of inflammation, aging, and human health are based on studies conducted almost exclusively in high income nations that rely primarily on baseline measures of chronic inflammation. This analysis investigates the inflammatory response to vaccination as a predictor of cardiovascular disease (CVD) among older women in the Philippines, a lower-middle income nation with rising rates of overweight/obesity and relatively high burdens of infectious disease. Concentrations of C-reactive protein (CRP) were measured at baseline and 72 hours following influenza vaccination in 530 women (mean age = 55.2 years). Ankle-brachial index (ABI)—an indicator of peripheral arterial disease and broader CVD risk—was measured approximately three years later. The magnitude of CRP response to vaccination was positively associated with ABI, indicating that a larger inflammatory response predicts lower CVD risk. Baseline CRP was negatively associated with CRP response to vaccination, and was not associated with ABI independently of CRP response. These results suggest that research across ecological settings, and with more dynamic measures of inflammatory response and regulation, may yield important insights into the associations among inflammation, aging, and disease.

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Keywords

inflammation; ankle-brachial index; cardiovascular disease

Introduction

Chronic, low-grade, inflammation is an established risk factor for morbidity and mortality among older adults, and it is implicated in the pathophysiology of a wide range of chronic degenerative diseases of aging. C-reactive protein (CRP)—an acute phase protein and endpoint marker of systemic inflammation—predicts elevated risk for incident cardiovascular disease (CVD), late-life disability, dementia, and all-cause mortality (Harris et al. 1999, Pearson et al. 2003, Kuo et al. 2005, Kuo et al. 2006). Indeed, chronic inflammation has been proposed as a key driver of age-related functional declines across many systems and tissues—a process that has been labeled “inflammaging” (Franceschi and Campisi 2014).

Epidemiologic research on inflammation, aging, and health has been conducted almost exclusively in high income nations with low burdens of infectious disease. A broader, more global perspective may be important for at least two reasons. First, the vast majority of CVD cases now occur in low and middle income nations, and understanding the factors that contribute to CVD is a pressing global health challenge (Yusuf et al. 2001). Second, inflammation is an important component of innate immunity that provides protection against infectious disease, and infectious exposures early in development shape multiple aspects of immune function in adulthood, including pathways involved in the regulation of inflammation (McDade 2012, Rook et al. 2015). Therefore, it is important to consider whether current scientific understandings of links between inflammation and diseases of aging generalize to lower income, high infectious disease contexts.

The objective of this paper is to investigate the association between inflammation and cardiovascular disease among older women in the Philippines, a lower-middle income nation that exemplifies the global nutrition transition toward rising rates of overweight/obesity, CVD, and metabolic syndrome (Adair 2004). While rates of non-communicable diseases are on the rise in the Philippines, base rates of infectious diseases remain relatively high, leading to a double burden of morbidity and mortality that is common globally (Boutayeb 2006).

We use the Ankle-Brachial Index (ABI)—the ratio of systolic blood pressure measured at the ankle to systolic blood pressure measured at the brachial artery—as a measure of general CVD progression in both symptomatic and asymptomatic individuals (Aboyans et al. 2012). ABI is increasingly used to monitor peripheral atherosclerosis within and across populations, and lower ABI scores are associated with significantly elevated risk of subsequent coronary heart disease, stroke, cardiovascular mortality, and all-cause mortality (Heald et al. 2006). Several studies have documented negative, graded associations between CRP and ABI in older adults in the US and Europe (Wildman et al. 2005, Elias-Smale et al. 2007), consistent with the hypothesis that chronic inflammation contributes to the development of cardiovascular disease.

In addition to baseline measurement of CRP, we evaluate the CRP response to influenza vaccination as an additional predictor of CVD risk. Vaccination presents an opportunity to assess the inflammatory response to a mild, controlled stimulus, which may provide additional insight into individual differences in the regulation of inflammation of relevance to disease risk (Carty et al. 2006). In prior research, we have shown that influenza vaccination elicits a small, but significant increase in CRP among older adults in the Philippines, consistent with prior research in the US (Tsai et al. 2005) and the Netherlands (Posthouwer et al. 2004). In this analysis we test the hypothesis that CRP response to vaccination predicts CVD, independent of baseline CRP.

Methods

Participants and study design

The Cebu Longitudinal Health and Nutrition Survey (CLHNS) began in 1983 with the recruitment of 3327 pregnant women from randomly selected urban and rural neighborhoods (Adair et al. 2011). The present analyses focus on the subset of women who participated in the vaccination protocol in 2012, and who were subsequently assessed for ABI in 2015–16 (N=530). The 2012 Southern Hemisphere influenza vaccine was delivered through intramuscular injection, with blood samples collected immediately prior to vaccination, and again three days later (mean = 72.1 hours, range 71–74). Additional details on the vaccine protocol, and the measurement of CRP response, have been published previously (McDade et al. 2015). Briefly, CRP was quantified in dried blood spot (DBS) samples, using a previously validated high sensitivity enzyme immunoassay developed for DBS (McDade et al. 2004). Results were subsequently converted to plasma equivalent values, using a study-specific formula (McDade et al. 2015). The mean interval between vaccination and ABI measurement was 36.8 months, with a range of 31–41 months. All data were collected under conditions of informed consent with institutional review board approval from the University of North Carolina, Chapel Hill and the Office of Population Studies Foundation at the University of San Carlos, Cebu.

Measurement of ABI

Procedures for the measurement and calculation of ABI were based on the recent scientific statement from the American Heart Association (Aboyans et al. 2012). Trained technicians implemented measurements in health centers near participants' homes. Systolic blood pressure was measured twice at each ankle, and at the brachial artery in each arm, using the Doppler technique (Hadeco ES100V3 Bidop Arterial and Venous Doppler with Smart V-Link software) (Kuzawa et al. in press). The ABI was calculated as a prognostic marker, based on the ratio of systolic blood pressure measured at the ankle to that measured at the brachial artery, averaging the two measures for each limb and using the arm with the highest blood pressure measurement. Lower ABI indicates higher risk for cardiovascular events and mortality, with the exception of increased risk with ABI>1.4.

Data analysis

The distribution of CRP values was highly skewed at baseline and day 3, and values were log transformed (base 10) to normalize the distribution of errors. A variable representing the

CRP response to vaccination was calculated by subtracting the log₁₀ CRP concentration at baseline from the log₁₀ CRP concentration at day 3. A series of ordinary least squares regression models were implemented to test the hypotheses that ABI was significantly associated with CRP, and CRP response to vaccination. ABI was normally distributed, and modeled as a continuous dependent variable. Initial models considered the bivariate associations between ABI and baseline CRP and CRP response to vaccination, respectively. Subsequent models included potentially confounding variables, and a final model included both baseline CRP and CRP response to vaccination to determine their relative independence in predicting ABI. BMI and fat free mass were highly correlated (Pearson $R=0.74$), and we adjusted for fat free mass based on prior analyses indicating that it is a stronger predictor of ABI in this sample (Kuzawa et al., in press).

Potential confounders were measured in the 2012 survey, and included two measures of socioeconomic status: level of education (highest grade) and household assets (sum of items including ownership of air conditioner, refrigerator, TV, vehicle, and other material goods). Women were defined as smokers if they reported smoking at least one cigarette daily. Percent body fat was obtained with bioelectrical impedance (algorithms adjusted for Asian populations), which was used (along with weight) to calculate fat free mass (kg). Use of anti-inflammatory medication was based on self-report, and a summary variable was constructed based on the following MIMS sub-classes (MIMS Philippines, 2010): GIT regulators, antilululents, and anti-inflammatories; analgesics (non-opioid) and antipyretics; nonsteroidal anti-inflammatory drugs (NSAIDs); corticosteroid hormones. Use of cardiovascular medication was based on the following MIMS sub-classes: cardiac drugs, anti-anginal drugs, anti-hypertensives (e.g. diuretics, beta blockers), peripheral vasodilators and cerebral activators, vasoconstrictors, dyslipidaemic agents, haemostatics, anticoagulants, antiplatelets and fibrinolytics (thrombolytics), phlebitis and varicose preparations, haemorrhologicals, haematopoietic agents, and other cardiovascular drugs.

Acute inflammation in response to infection may confound, or obscure, associations between CRP and ABI. At the time of baseline blood collection, 7.2% of participants ($n=38$) reported one or more symptoms of infectious disease; as expected, these individuals had higher median CRP (1.8 vs. 1.2 mg/L; Wilcoxon rank-sum test $z = -2.72$, $p<0.01$), and were excluded. Similarly, CRP > 10 mg/L is widely used as an additional cut-off value to identify episodes of acute inflammation (4), and 6 additional participants with CRP > 10 mg/L were also removed, yielding a final sample size of $n=486$. Excluded participants did not differ from the rest of the sample in ABI, age, education, or household assets (all $p > 0.3$). They did, however, have marginally lower average BMI (24.1 vs. 25.3, $p=0.08$).

Results

Participants ranged in age between 44 and 75 years, with a mean age of 55.2 (Table 1). Consistent with previous analyses of this dataset (Kuzawa et al. under review), mean ABI in the sample was 1.07 (SD = 0.08), with the following distribution across categories of PAD: 88.1% of participants at low risk (ABI > 1.0), 10.0% at moderate risk (ABI > 0.90 and ≤ 1.0), and 1.9% with PAD (ABI ≤ 0.90) (Aboyans et al. 2012). No participants had ABI >

1.40. ABI was therefore modeled as a continuous variable, with lower score indicating higher CVD progression.

Baseline CRP was negatively, but weakly, associated with ABI ($B = -0.014$, Pearson $R = -0.076$; $p=0.10$). After adjustment for potentially confounding variables, higher CRP was significantly associated with lower ABI (Table 2), consistent with the hypothesis that chronic inflammation contributes to the development of PAD. Smoking—although infrequent in this sample—predicted lower ABI, as did the use of anti-inflammatory medications. As shown previously in this sample (Kuzawa et al. under review), fat free mass was positively associated with ABI.

We next considered whether the CRP response to vaccination predicted ABI, above and beyond baseline CRP. Consistent with prior analyses in this sample (McDade et al. 2015), influenza vaccination resulted in a mild, but significant, increase in CRP: Median CRP was 1.56 mg/L three days following vaccination, compared with the baseline median of 1.16 mg/L (Wilcoxon rank-sum test $z=7.62$, $p<0.0001$). The magnitude of the CRP response to vaccination was negatively associated with baseline CRP (Pearson $R = -0.340$, $p < 0.0001$): The largest responses were evident in women with the lowest CRP at the time of vaccination.

CRP response to vaccination was positively associated with ABI (Pearson $R = 0.144$, $p < 0.01$), indicating that a larger inflammatory response was associated with lower CVD risk. When considered in conjunction with baseline CRP, CRP response to vaccination was a strong and independent predictor of ABI, and the association between ABI and baseline CRP was no longer statistically significant (Table 2). Adjusting for potential confounding variables produced similar results. Figure 1 presents the positive association between ABI and the magnitude of CRP response to vaccination.

Although individuals with symptoms of infection were excluded from the analysis, it is likely that subclinical infections, not reported by participants, were present for a subset of the sample at the time of blood collection. The negative association between baseline CRP and response to vaccination could be interpreted in this light: If an acute phase response to subclinical infection is in process at baseline, then CRP concentrations can be expected to drop as the response resolves, thereby obscuring the CRP response to vaccination. This situation makes it more difficult to disentangle the independent roles that chronic inflammation vs. the inflammatory response to vaccination may play in predicting ABI.

To address this issue, we re-ran the fully adjusted model predicting ABI with more stringent criteria for excluding individuals with possible subclinical infection at baseline. A consistent pattern of results would increase our confidence in concluding that the inflammatory response to vaccination is an independent predictor of cardiovascular disease risk. Alternatively, attenuated results would suggest that our initial findings were at least partially driven by processes that increased CRP prior to vaccination in a subset of participants. In addition to removing participants reporting infectious symptoms, as before, we restricted the analysis to individuals with $CRP < 3$ mg/L at baseline based on prior analyses in this sample indicating that this was an important inflection point in the association between baseline

CRP and the CRP response to vaccination (McDade et al. 2015). The association between ABI and CRP response to vaccination was stronger in this subsample ($B=0.038$, $SE=0.014$, $p<0.01$, $n=403$). Additional models with more stringent cut-off values yielded similar results (CRP<2 mg/L: $B=0.041$, $SE=0.015$, $p<0.01$, $n=343$; CRP<1 mg/L: $B=0.037$, $SE=0.014$, $p<0.05$, $n=210$).

Discussion

In this analysis we investigated whether inflammation predicts CVD risk in older women in the Philippines. A large body of research in high income nations indicates that chronic inflammation contributes to the pathophysiology of diseases of aging. Our results add to emerging evidence that these associations may differ across ecological settings, and they suggest that more dynamic measures of inflammatory response and regulation may yield important insights into the associations among inflammation, aging, and disease.

Previously, we reported that influenza vaccination elicited a mild increase in CRP in this cohort of women in the Philippines, consistent with prior research using vaccination as an *in vivo* model for investigating the regulation of inflammation (McDade et al. 2015). Further, we hypothesized that the combination of low baseline CRP and robust increases in response to challenge may represent a tightly regulated system that is optimal for health: Infectious threats are met with acute increases in inflammatory activity, while risk for tissue damage, degeneration, and chronic disease is minimized by low levels of chronic activation. Our analysis of ABI provides important support for this hypothesis by linking inflammatory response with chronic disease: Lower baseline CRP is associated with a larger CRP response to vaccination, and a larger CRP response to vaccination predicts reduced CVD progression.

Convergent evidence in support of this relationship comes from recent studies of inflammation, aging, and disease in non-affluent, lower income settings. For example, substantially lower concentrations of CRP among adults, and an attenuated pattern of increase with age, have been reported in Ghana, Ecuador, and Indonesia in comparison with the US (McDade 2012, Eriksson et al. 2013, Wiria et al. 2013). Similarly, two studies conducted in settings with high burdens of infection (rural Bolivia, rural Ghana) report no association between baseline measures of inflammation and CVD risk or progression (Gurven et al. 2009, Koopman et al. 2012). Lastly, a study in rural Ecuador used repeat measures of CRP to distinguish acute from baseline levels of inflammatory activity, and found no evidence for chronic low-grade inflammation in this high infectious disease environment (McDade et al. 2012). The origins of these population-level differences in inflammation are not clear, but may trace to ecological differences in the intensity and diversity of microbial exposures in infancy and early childhood that play important roles in the development of immunoregulatory pathways (McDade 2012, Rook et al. 2015).

These findings point toward a more complicated pattern of association among inflammation, aging, and disease than has emerged from research on inflammaging in high income, post-epidemiologic transition settings. Methodologically, they suggest that more dynamic measures of inflammation, across a wide range of ecological settings, are needed to advance our understanding of how, and where, inflammation contributes to diseases of aging.

Multiple measures of inflammatory markers over time, vaccine response protocols, and in vitro cell culture systems are examples of protocols that complement common epidemiological approaches drawing on single measures of baseline activity. Conceptually, it may be important to distinguish acute from chronic inflammation, and to recognize that high concentrations of inflammatory markers are not always pathological, and may in fact be salutary if they indicate a responsive, tightly regulated system.

A limitation of this study is the use of a single measure of CVD, as well as the implementation of a single post-vaccination CRP measure. Future follow-up surveys will provide additional measures of morbidity, as well as mortality, in this cohort. Prior studies investigating the inflammatory response to vaccination have collected samples 24–72 hours following vaccination, typically with a single follow up sample, but collecting multiple samples over time would provide additional information on the pattern of response. Lastly, the exclusive focus on women limits generalizability, although the community-based sample enhances external validity, and the Philippines context provides an important opportunity for comparison with studies conducted in high income settings.

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Figure 1.
Bivariate association between ABI score and CRP response to influenza vaccination.
Magnitude of CRP response is calculated as $\log\text{CRP}_{\text{day 3}} - \log\text{CRP}_{\text{day 0}}$, and results exclude participants with symptoms of infectious disease or $\text{CRP} > 10 \text{ mg/L}$ at baseline.

Table 1.

Baseline characteristics for study participants (N=530).

Age (years)	55.2 ± 5.8 (44–75)
Education (highest grade)	6.9 ± 3.1 (0–17)
Household assets (# items)	5.2 ± 1.6 (0–11)
Body mass index (kg/m ²)	25.2 ± 4.6 (14.2–42.9)
Daily smoker (%)	7.4
Anti-inflammatory medication (%)	5.3
Cardiovascular medication (%)	15.7

Note. Values are mean ± standard deviation for continuous variables (range).

Table 2.

Results of least squares regression models predicting ABI (n=486).

	Model 1		Model 2		Model 3	
	B	95% CI	B	95% CI	B	95% CI
CRP, baseline	-0.018 *	-0.034, -0.001	-0.005	-0.023, 0.012	-0.010	-0.027, 0.008
CRP response			0.037 **	0.011, 0.063	0.033 *	0.008, 0.059
Age	0.000	-0.001, 0.001			0.000	-0.001, 0.001
Fat free mass	0.002 *	0.000, 0.004			0.002 *	0.000, 0.004
Education	-0.001	-0.003, 0.001			-0.001	-0.003, 0.001
Assets	0.001	-0.004, 0.005			0.001	-0.004, 0.005
Daily smoker	-0.033 *	-0.060, -0.006			-0.031 *	-0.058, -0.005
Anti-inflammatory medication	-0.009	-0.042, 0.024			-0.009	-0.042, 0.024
Cardiovascular medication	-0.033 **	-0.053, -0.014			-0.034 **	-0.054, -0.015

*
p<0.05**
p<0.01