Comparative Insights Into the Regulation of Inflammation: Levels and Predictors of Interleukin 6 and Interleukin 10 in Young Adults in the Philippines

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ABSTRACT Inflammation is a central part of innate immunity, but its role in anti-pathogen defenses has been overshadowed by recent interest in the contribution of inflammation to a wide range of chronic degenerative diseases. Current research on chronic inflammation is conducted primarily in affluent populations with low levels of infectious disease; comparative research in different ecological settings is needed to advance understandings of the causes and consequences of variation in the regulation of inflammation. This article investigates the levels and predictors of interleukin-6 (IL-6) and interleukin-10 (IL-10)—two cytokines important to the regulation of inflammation—in a large, population-based study in the Philippines. Concentrations of IL-6 and IL-10 were determined in $N = 1{,}569$ healthy young adults (20–22 years) in Metro Cebu, Philippines. IL-6 and IL-10 concentrations were positively correlated, and body mass index and symptoms of infectious disease were both associated with higher concentrations of IL-6 and IL-10. Median concentrations of IL-6 (1.0 pg/mL) and IL-10 (7.56 pg/mL) were substantially lower and higher, respectively, than levels reported for other populations based on a systematic review of prior research. This study contributes to a growing body of research in human ecological immunology, and suggests that there may be substantial population differences in the regulation of inflammation that has implications for the association between inflammation and disease. Am J Phys Anthropol 146:373–384, 2011.

Research in human ecological immunology has demonstrated the value of applying an adaptationist approach to understanding the development and function of the human immune system (McDade and Worthman, 1999; McDade, 2003; Muehlenbein and Bribiescas, 2005; Blackwell et al., 2010). The field-based, comparative perspective of human ecological immunology is important for documenting the range of variation in key immune processes, and for examining the contextual factors that shape this variation. We contribute to research in this area by investigating the levels and predictors of interleukin-6 (IL-6) and interleukin-10 (IL-10)—two cytokines critical to the regulation of inflammation—in healthy young adults in the Philippines.

Inflammation is a central part of innate immunity, and acute inflammation initiates a rapid, coordinated mobilization of non-specific cellular and biochemical defenses that promote pathogen clearance and healing (Kumar et al., 2004). Recently, inflammation's role in anti-pathogen defenses has been overshadowed by intense clinical and epidemiological interest in the contribution of inflammation to the pathophysiology of a wide range of chronic diseases (Festa et al., 2000; Pearson et al., 2003; Pickup, 2004). Elevated concentrations of C-reactive protein (CRP)—a prototypical acute phase protein—have been consistently associated with increased risk for cardiovascular disease (Ballou and Kushner, 1992; Libby et al., 2002), type II diabetes (Pradhan et al., 2001), late-life disability (Kuo et al., 2006), and mortality (Harris et al., 1999). While acute inflammation is typically viewed as an adaptive response to infection, this new line of inquiry suggests that chronic, low-grade activation of inflammatory pathways may have long-term, maladaptive consequences.

There are two important limitations to prior research in this area. First, most population-based studies have focused primarily on CRP as a biomarker of inflammation without attention to the upstream pathways that up- and downregulate inflammatory processes. IL-6 is a pro-inflammatory cytokine that is produced by endothe-

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lial cells, monocytes, macrophages, mast cells, and adipocytes, and is a primary determinant of CRP production and release (Yudkin et al., 1999a; Du Clos, 2000; Bermudez et al., 2002). While other cytokines are also involved in the activation of inflammation (e.g., Tumor necrosis factor (TNFα) IL-1β), IL-6 has received the most attention as a contributor to chronic degenerative diseases. Previous work has shown that individual correlations between concentrations of IL-6 and CRP are typically high (Esposito et al., 2003a) and elevated concentrations of IL-6 are associated with increased risk for cardiovascular disease and rheumatoid arthritis (Robak et al., 1998; Ridker et al., 2000b; Tziakas et al., 2003).

IL-10 is a cytokine secreted primarily by T and B lymphocytes, monocytes, and macrophages (Tedgui and Mallat, 2001), and it is a potent inhibitor of pro-inflammatory activity, including suppression of IL-6 production (Moore et al., 2001). Although relatively few studies have measured IL-10 in relation to health outcomes, lower concentrations of IL-10 have been associated with increased risk for metabolic syndrome (van Exel et al., 2002b; Esposito et al., 2003b; Choi et al., 2007), type 2 diabetes (van Exel et al., 2002b), stroke (van Exel et al., 2002a), and heart disease (Pradhan et al., 2001a; Tziakas et al., 2003). In sum, IL-10 and IL-6 appear to play counter-regulatory roles with respect to inflammation, and insufficient anti-inflammatory signaling may be an important, but relatively overlooked, mechanism through which inflammation contributes to chronic degenerative diseases.

A second limitation derives from the fact that current understandings of chronic inflammation and disease are based on research conducted primarily in relatively affluent western populations. These populations are typically characterized by low levels of infectious disease and high levels of caloric excess. Since the human immune system evolved in environments with marginal nutrition and substantially higher levels of microbial exposure, it is reasonable to suggest that over-nourished, "under-infected" western populations may not represent the most enlightening contexts in which to study inflammation (McDade, 2003; Gurven et al., 2008). Therefore research in different ecological settings, grounded by the adaptationist perspective of human ecological immunology, is needed to complement current biomedical research on the determinants of inflammation.

The Philippines represents such a setting. It is a lower-middle income nation undergoing significant economic, dietary, and lifestyle changes. Although rates of overweight/obesity, Cardiovasculor disease (CVD), and metabolic syndrome are relatively low, they are on the rise (Tanchoco et al., 2003; Pedro et al., 2007; Adair et al., 2011). At the same time, infectious disease accounts for more than 30% of all mortality in Southeast Asia, with pneumonia, diarrhea, and tuberculosis serving as major contributors (WHO, 2004). In the Philippines, respiratory infections rank beside ischemic heart disease as the top causes of mortality (WHO, 2006). This level of infectious disease exposure, in combination with recent trends toward increased body weight, is characteristic of many transitional populations globally and thus provides an interesting and important setting in which to investigate the dynamics of inflammation.

In prior research, we have reported exceptionally low concentrations of CRP among young adults in the Philippines compared with young adults in the US (McDade et al., 2009). In this article, we seek to build on these findings by investigating two cytokines centrally involved in pro- and anti-inflammatory processes. Specifically, the objectives of this analysis are threefold: (1) to report concentrations of IL-6 and IL-10 among healthy young adults in the Philippines, and to evaluate adiposity, infectious, and socioeconomic predictors of individual variation in IL-6 and IL-10; (2) to investigate patterns of association among IL-6, IL-10, and CRP; and (3) to compare IL-6 and IL-10 concentrations to prior studies in other populations. Based on our prior analysis of CRP, we hypothesized that concentrations of IL-6 would be lower and concentrations of IL-10 would be higher in the Philippines than in more affluent, industrialized populations. We also expected measures of adiposity and pathogen exposure to be significant predictors of inflammatory cytokine production. These analyses provide important comparative information for research on the regulation of inflammation, and contribute to a growing body of research in human ecological immunology.

METHODS

Participants and data collection

The Cebu Longitudinal Health and Nutrition Survey (CLHNS) began in 1983 with the recruitment of 3,327 pregnant women in Metro Cebu, which is among the largest and fastest growing metropolitan areas in the Philippines. For these women, 3,080 singleton infants were born between 1983 and 1984, representative of births in Metro Cebu for this period (Adair et al., 2010). The women and their children have been followed through multiple rounds of data collection since 1983. The data for the present analyses come from the 2005 survey, when all of the offspring of the original cohort were 20–22 years of age. Complete data were available for 1,598 participants. However, 29 women who were pregnant at the time of survey were excluded from the analyses resulting in a final sample of $N = 1{,}569$. Participants provided information on household demographics and income levels, environmental quality, and health behaviors in face-to-face interviews conducted in their homes. All data were collected under conditions of informed consent with institutional review board approval from the University of North Carolina, Chapel Hill.

We evaluated the degree to which the analytic sample differed from the original cohort as assessed when the study started in 1983. Compared to those lost to follow-up, participants remaining in the study were born to fathers with less formal education (mean (SE) difference = (0.54 (0.15) years; $P < 0.001$), to mothers with marginally less formal education (0.24 (0.13) years; $P < 0.10$), and into homes in slightly more rural communities ((2.05 (0.45); $P < 0.001$) points on 70-point urbanicity scale (Dahly and Adair, 2007)). Participants did not differ with respect to household income or assets at baseline. Attrition in the CLHNS is due primarily to factors related to out-migration rather than refusal to participate (Adair et al., 2010), and as a result, participants in the 2005 survey represent households that are less mobile compared with all participants in the original cohort.

Standard anthropometric techniques were used to measure body weight, height, waist circumference, and triceps, subscapular, and suprailiac skinfold thicknesses (Lohman et al., 1988). The body mass index (BMI) was calculated as the ratio of weight (kg)/height (m^2).

Following prior research in the Philippines and elsewhere (VanDerslice et al., 1994; Nurgalieva et al., 2002; Prado et al., 2003), we collected multiple proxy measures of the likelihood of exposure to infectious microbes, including household crowding (number of persons/number of rooms), type of toilet (no toilet, pit, flush/water sealed), and source of drinking water (bottled, piped municipal supply, closed well with pump, open sources: uncovered well, spring, river, rain). We also constructed a pathogen exposure scale based on five variables, each scored on a three point scale (0 = low exposure, 1 = moderate, 2 = high): cleanliness of the food preparation area, means of garbage disposal, presence of excrement near the house, level of garbage and excrement present in the neighborhood surrounding the household (McDade et al., 2009). In addition, at the time of blood collection, we asked participants whether they were currently experiencing any symptoms of infection, including runny nose, cough, fever, diarrhea, sore throat, as well as the more general categories of "flu," "cold," and "sinusitis". Responses were used to construct a summary variable indicating the presence or absence of any infectious symptoms at the time of blood collection.

Information on health behaviors of relevance to inflammation was collected during face-to-face interviews. Variables were constructed for smoking (none vs. $\geq$1 cigarette/day), alcohol consumption (never, occasionally, weekly, daily), and oral contraceptive use (yes/no). Measures of socioeconomic status included highest grade completed, household income, household assets, and home ownership. We also used a previously validated measure of the degree of urban development in the community in which participants lived (Dahly and Adair, 2007). This scale is based on population size and density, availability of communications (e.g., telephone, internet), transportation infrastructure, and presence of educational facilities, health services, and markets for food and other consumer goods. Higher scores (range 0–70) on the scale indicate a higher degree of urban development.

Analysis of IL-6 and IL-10

Blood samples were collected using EDTA-coated vacutainer tubes in the participants' homes in the morning after an overnight fast. Blood samples were kept in coolers on ice packs for no more than 2 h and were then centrifuged to separate plasma prior to freezing at -70°C. Samples were express shipped to Northwestern University on dry ice and stored frozen at -80°C until analysis. Samples were analyzed for CRP using a high sensitivity immunoturbidimetric method as previously described (McDade et al., 2009).

Concentrations of IL-6 and IL-10 were determined in the Laboratory for Human Biology Research at Northwestern University using a high sensitivity multiplex immunoassay protocol (HSCYTO-60SK, Millipore, Billerica, MA) on the Luminex platform (Luminex Corporation, Austin, TX). Briefly, samples were incubated with sets of polystyrene microspheres covalently coupled with capture antibodies specific for IL-6 and IL-10. Samples were then incubated with detection antibody labeled with a fluorescent reporter molecule. Data were acquired by running the samples through a modified flow cytometer that identifies and separates each set of microspheres, and quantifies the amount of bound analyte. The manufacturer-reported lower detection limits for IL-6 and IL-10 were 0.10 and 0.15 pg/mL, respectively, but for many samples we were able to estimate values for samples below these limits. Samples with undetectable concentrations were assigned a value of 0.0001 pg/mL. For IL-6, the between-assay percent coefficient of variation (%CV; SD/mean) for low and high control samples included with each assay was 14.7 and 12.4, respectively. For IL-10, the %CV for low and high controls was 15.4 and 11.6, respectively. All samples were analyzed in duplicate, with average within-assay %CVs of 13.3 for IL-6, and 14.1 for IL-10. These levels of analytic variation are comparable to, or lower than, previously reported applications of this method to multiplexed cytokine analysis (Prabhakar et al., 2002).

Data analysis

Analyses proceeded in three stages. First, we tested the hypothesis that adiposity, pathogen exposure, and health behaviors are significant predictors of cytokine levels by implementing a series of regression models with log-transformed IL-6 and IL-10 as dependent variables. We applied tobit regression models for censored data to account for non-normality in the distribution of IL-6 and IL-10 values. Even after log transformation, the distribution was left-censored due to the large number of observations with values below the lower detection limit of the cytokine assays. The application of ordinary least squares regression procedures would likely result in biased and unstable parameter estimates, whereas tobit regression takes into account the censored nature of the distribution to provide more reliable parameter estimates (Greene, 2000).

Measures of adiposity (waist circumference, BMI, and skinfold thickness), pathogen exposure (crowding, water source, toilet type, pathogen exposure scale, and presence of infectious symptoms), and health behaviors (smoking, alcohol consumption, and oral contraception) were considered in separate regression models as predictors of log-IL-6 and log-IL-10. Measures of socioeconomic status and urbanicity were also evaluated in an attempt to capture other unmeasured aspects of environmental quality and lifestyle that may be related to inflammation. Variables with $P < 0.10$ were retained and considered in a final model to evaluate their independent and combined contributions to explaining cytokine levels. All statistical analyses were conducted with Stata for Windows, version 10 (StataCorp, College Station, TX). Since episodes of acute inflammation may obscure assessment of chronic, low grade inflammatory activity in studies using samples collected at a single time point (Pearson et al., 2003), we conducted analyses for the entire sample, as well as analyses that excluded individuals reporting symptoms of infectious disease at the time of blood collection.

Second, bivariate associations between IL-6 and CRP, and between IL-10 and CRP, were evaluated to consider the degree to which each cytokine may be involved in the regulation of a key product of inflammation. We also investigated the bivariate association between IL-6 and IL-10 to evaluate the degree to which they may be playing counter-regulatory roles.

Third, descriptive analyses were used to investigate median levels of IL-6 and IL-10 in relation to previously reported values in other populations. We used electronic databases (Medline, Google Scholar) as well as bibliographies of past publications to conduct a comprehensive search for prior peer-reviewed publications containing

TABLE 1. Descriptive statistics for female and male participants

	Female (N = 703)	Male (N = 866)	Total (N = 1569)
Age (years)	20.9 (0.4)	20.9 (0.3)	20.9 (0.3)
Household income, weekly (pesos)	666.9 (1721.9)	571.9 (896.3)	614.5 (1331.5)
Highest grade of school completed	11.6 (3.3)	10.5 (3.9)	11.0 (3.6)
Currently in school	18.9	18.6	18.7
Urbanicity (0–70)	41.3 (13.2)	41.0 (13.7)	41.1 (13.5)
BMI (kg/m^2)	20.3 (3.2)	21.1 (3.1)	20.7 (3.2)
Waist circumference (cm)	68.0 (7.7)	72.2 (7.6)	70.3 (7.9)
Sum of skinfold thickness (mm)	62.1 (19.8)	37.8 (18.1)	48.7 (22.4)
Symptoms of infection (%)	15.1	13.6	14.3
Current smoker (%)	3.0	42.5	24.8
Oral contraceptive use (%)	3.7		
CRP (median, 25th, 75th percentile)	0.2 (0.1, 0.9)	0.3 (0.1, 0.9)	0.2 (0.1, 0.9)
IL-6 (median, 25th, 75th percentile)	0.97 (0.29, 3.01)	1.03 (0.26, 3.28)	1.00 (0.28, 3.21)
IL-10 (median, 25th, 75th percentile)	7.09 (2.71, 13.57)	7.88 (3.51, 15.15)	7.56 (3.09, 14.67)

Mean (SD) values are presented for continuous variables; % values are presented for categorical variables.

TABLE 2. Results of tobit regression models predicting log-transformed IL-6 (N = 1,569)

	Model 1		Model 2		Model 3		Model 4	
	B	SE	B	SE	B	SE	B	SE
Female	0.022	0.099	−0.013	0.098	0.032	0.099	0.060	0.100
BMI (kg/m^2)	0.039*	0.016					0.043**	0.015
Symptoms of infection (0, 1)			0.424**	0.139			0.431**	0.139
Oral contraception (0, 1)					−1.102**	0.396	−1.148**	0.394
Constant	−1.414***	0.334	−0.651***	0.069	−0.593***	0.066	−1.557***	0.334
Model P value	<0.05		<0.01		<0.05		<0.001	

†$P < 0.10$; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.
Models 1–3 consider gender as well as the separate associations of adiposity (model 1), pathogen exposure (model 2), and health behavior variables (model 3) shown in bivariate analyses to predict IL-6 at $P < 0.10$. Model 4 considers all variables simultaneously to evaluate their independence in predicting IL-6.

mean or median IL-6 or IL-10 concentrations from healthy individuals. In many cases an overall median or mean concentration was not provided; rather, values were presented for subgroups in a comparative study design. We report overall concentrations when available and concentrations for subgroups otherwise. For comparative purposes, we calculated weighted averages for IL-6 and IL-10 across these studies.

RESULTS

Predictors of IL-6 and IL-10

The young adults in this sample were lean, with low waist circumference compared to young adults in the US, and mean BMI values are at the low end of "normal" as defined by recent CDC guidelines (Okosun et al., 2004) (Table 1). Median IL-6 concentration for the entire sample was 1.00 pg/mL (interquartile range 0.28, 3.21). At the time of blood collection N = 224 individuals reported a symptom of infectious disease. With those individuals removed from the sample, median IL-6 was 0.95 pg/mL (0.24, 2.93). There was no evidence for any gender difference in IL-6 concentration.

BMI, waist circumference, and skinfold thickness were highly correlated and were therefore considered separately in regression models predicting IL-6 to avoid problems associated with collinearity. Body mass index was the strongest predictor of the three variables, and was positively associated with IL-6 concentration (Table 2, model 1). Among the pathogen exposure variables, the presence of infectious disease symptoms at the time of blood collection was the only significant predictor, and was positively associated with IL-6 (Table 2, model 2). Measures of socioeconomic status and urbanicity were not significantly associated with IL-6. Among the health behaviors, oral contraceptive use among women was rare (N = 26), but was associated with significantly lower concentrations of IL-6 (Table 2, model 3).

Patterns of association were similar when BMI, infectious symptoms, and oral contraceptive use were considered simultaneously (Table 2, model 4), indicating that their associations with IL-6 were relatively independent. When individuals with current symptoms of infection were eliminated from the final model, the association between BMI and IL-6 strengthened (B = 0.057, SE = 0.017, P<0.001), while the association with oral contraceptive use was essentially the same (B = −1.143, SE = 0.429, P<0.01).

Median IL-10 concentration in the sample was 7.56 pg/mL (3.09, 14.67). When individuals with symptoms of infectious disease were removed, median IL-10 was lower at 7.38 pg/mL (2.88, 14.51). Concentrations of IL-10 were slightly, but not significantly, lower in females (7.09 pg/mL, 2.71, 13.57) than in males (7.88 pg/mL, 3.51, 15.15).

As with IL-6, BMI was positively associated with IL-10, and was the strongest predictor among the adiposity variables (Table 3, model 1). Infectious symptoms were also strongly and positively associated with IL-10 (Table 3, model 2). Oral contraceptive use was associated with lower IL-10, while urbanicity was negatively associated with IL-10. Formal schooling was marginally associated with higher IL-10. Coefficients were similar when these

TABLE 3. Results of tobit regression models predicting log-transformed IL-10 (N = 1,569)

	Model 1		Model 2		Model 3		Model 4	
	B	SE	*B*	SE	*B*	SE	*B*	SE
Female	−0.209**	0.076	−0.232**	0.075	−0.202**	0.076	−0.183*	0.076
BMI (kg/m^2)	0.024*	0.012					0.029*	0.012
Symptoms of infection (0, 1)			0.302**	0.107			0.300**	0.106
Oral contraception (0, 1)					−0.637*	0.298	−0.666*	0.297
Urbanicity (0–70)					−0.007**	0.003	−0.008**	0.003
Education (years)					0.161†	0.096	0.153	0.096
Constant	0.102	0.468	0.573***	0.052	0.885***	0.124	0.251	0.273
Model *P* value	<0.01		<0.001		<0.001		<0.001	

$^\dagger P < 0.10$; $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

Models 1–3 consider gender as well as the separate associations of adiposity (model 1), pathogen exposure (model 2), and health behavior variables (model 3) shown in bivariate analyses to predict IL-10 at $P < 0.10$. Model 4 considers all variables simultaneously to evaluate their independence in predicting IL-10.

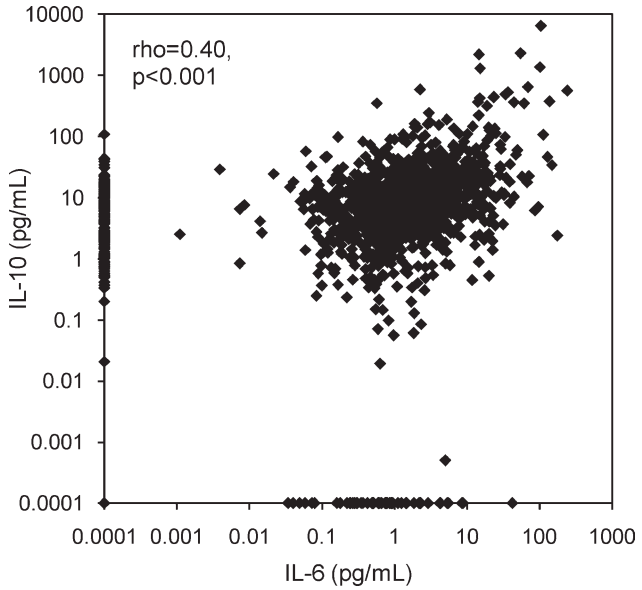

Fig. 1. Bivariate association between concentration of IL-6 and IL-10 in young adults in the Philippines (N = 1,569).

variables were considered simultaneously, suggesting independent associations with IL-10. Years of schooling were an exception, which was attenuated in the full model. When individuals with current symptoms of infection were eliminated from the final model, the association between BMI and IL-10 strengthened (B = 0.037, SE = 0.013, P<0.01), while associations with oral contraceptive use (B = −0.310, SE = 0.327, P = 0.3) and education were attenuated (B = 0.136, SE = 0.109, P = 0.2). The association with urbanicity remained essentially unchanged (B = −0.007, SE = 0.003, P<0.05).

Associations among IL-6, IL-10, and CRP

Concentrations of IL-6 and IL-10 were each positively associated with CRP. Spearman rank correlation indicates a moderately strong and significant association between IL-6 and CRP for the entire sample (rho = 0.26, P<0.001). The correlation was reduced when individuals with symptoms of infectious disease were removed (rho = 0.23, P<0.001), but was substantially higher in the subset of individuals with infectious symptoms at the time of blood collection (rho = 0.36, P<0.001).

The correlation between IL-10 and CRP was significant but relatively weak (rho = 0.10, P<0.001), and was similar in magnitude when individuals with symptoms of infectious disease were excluded (rho = 0.10, P<0.001), or considered separately (rho = 0.09, P = 0.17). Patterns of association between IL-6/IL-10 and CRP were very similar for males and females.

Concentrations of IL-6 and IL-10 were positively correlated across the entire range of measurement (see Fig. 1). Spearman rank correlation indicates a strong association between levels of IL-6 and IL-10 within individuals (rho = 0.40, P<0.001). The correlation was attenuated slightly when individuals with symptoms of infectious disease were removed (rho = 0.38, P<0.001), but was stronger in the subset of individuals with infectious symptoms at the time of blood collection (rho = 0.46, P<0.001).

Concentrations of IL-6 and IL-10 in comparison to other populations

Concentrations of IL-6 in the Philippines were low relative to previously reported values in other populations (Table 4). Of studies reporting medians, the weighted average IL-6 concentration was 1.91 pg/mL, with a range of 0.61–23.5. For studies reporting means, the weighted average IL-6 concentration was 2.83 pg/mL, and values ranged from a low of 0.39 to a high of 10.9. It should be emphasized that differences in study design complicate attempts to make valid comparisons of central tendency across populations. Figure 2 presents IL-6 results from Cebu in relation to the subset of prior studies in Table 4 likely to yield the most meaningful comparisons. Studies were included in Figure 2 if they reported median IL-6 concentrations, included healthy participants, did not focus exclusively on older adults (>60 years), and had a sample size of at least 25.

Only a handful of studies have investigated IL-10 concentrations in healthy adults (Table 5). Of the nine studies reporting median values, the weighted average IL-10 concentration was 3.17 pg/mL. Only one study in Italy (Galizia et al., 2002) reported median IL-10 concentrations higher than Cebu, with the other studies reporting substantially lower concentrations. Figure 3 compares results from Cebu with all prior studies reporting median IL-10 concentrations. Of the seven studies reporting IL-10 means, the weighted average IL-10 concentration was 8.64 pg/mL. For purposes of comparison, the mean IL-10 concentration in our Cebu sample was 25.48 pg/mL. Due to the high degree of skew in the distribution

TABLE 4. Prior research reporting concentrations of IL-6 (pg/mL) in healthy adults

Location	*N*	IL-6, median (IQR)	IL-6, mean (SD)	Age (years) mean (SD)	BMI (kg/m^2) mean (SD)	Sample characteristics	Reference
Bolivia	394		5.2 (9.0)		23.2 (2.9)	Healthy adults	(Vasunilashorn et al., 2010)
Canada	102	1.12 (0.77–1.6)		28.1 (5.5)	25.8 (4.5)	Healthy young adult males	(Cartier et al., 2009)
Canada	106	1.6 (1.09–2.28)		55.8 (6.7)	27.4 (3.9)	Healthy middle-aged males	(Cartier et al., 2009)
China	30	0.61 (0–4.42)		34 (8)		Healthy adults	(Wong et al., 2001)
France	8		0.39 (0.06)	42 (5)	20.6 (0.6)	Healthy adult females	(Bastard et al., 2000)
France	14		2.78 (0.30)	45 (4)	39.5 (1.1)	Healthy adult females (android obesity)	(Bastard et al., 2000)
India	50	12.56 (1.8–77.6)		45 (11)	22.5 (4.4)	Healthy adults	(Deepa et al., 2006)
India	40	7.15 (3.92–22.4)		38	23.3	Healthy adults (urban middle-class)	(Yudkin et al., 1999b)
India	28	23.5 (6.60–26.9)		35	22.3	Healthy adults (urban slum)	(Yudkin et al., 1999b)
India	43	2.50 (1.62–14.5)		28	18.7	Healthy adults (rural village)	(Yudkin et al., 1999b)
Ireland	29		0.56 (0.26)	31.0 (10.2)		Healthy white adults	(O'Donovan et al., 2010)
Italy	20		1.36 (0.6)	31 (1.7)	23.5 (0.8)	Healthy young adults	(Targher et al., 2001)
Italy	34		2.6 (1.3)	32 (7)		Healthy pre-menopausal women	(Cioffi et al., 2002)
Italy	48		10.9 (4.1)	54.8 (6)		Healthy post-menopausal women	(Cioffi et al., 2002)
Italy	20		2 (0.7)	35 (4)	24.2 (1.1)	Healthy young adults	(Esposito et al., 2002)
Italy	60	4.1 (2.0–9.0)		35 (5.1)	34.7 (2.4)	Healthy obese females (control diet)	(Esposito et al., 2003a)
Italy	60	4.3 (1.9–9.0)		34.2 (4.8)	35 (2.3)	Healthy obese females (intervention diet)	(Esposito et al., 2003a)
Japan	382		1.7 (1.99)	55.5	22.58 (2.96)	Healthy adults	(Coe et al., 2011)
Korea	312	1.1 (.5–1.9)		70 (5)	24.6 (3.1)	Healthy older adults	(Choi et al., 2007)
New Zealand	38	1.73 (0.93–2.67)		39 (5)		Healthy adult females (Asian Indian immigrants)	(Rush et al., 2007)
New Zealand	41	1.31 (0.8–2.24)		39 (5)		Healthy adult males (Asian Indian immigrants)	(Rush et al., 2007)
Poland	24	5.3 (0.5–16.6)	5.1 (3)			Healthy adults	(Robak et al., 1998)
Poland	51		1.7 (0.6)	51 (11)		Healthy middle-aged adults	(Wykretowicz et al., 2004)
Poland	28	4.4 (0.5–14.6)	4.49 (2.91)	63		Healthy adults	(Urbańska-Ryś et al., 2000)
Spain	132	6.4 (1–13.1)		40.5 (11)	25.4 (4)	Healthy white adult males	(Fernandez-Real et al., 2001)
Spain	96	5.8 (1.8–14)		37.5 (8.9)	24.6 (4.4)	Healthy white adult females	(Fernandez-Real et al., 2001)
USA	202	1.46 (1.04–2.28)		59.1 (8.8)	24.9 (3)	Healthy middle-aged males	(Ridker et al., 2000b)
USA	244	1.3 (1–2.03)		59.3	26.0	Healthy middle-aged females	(Ridker et al., 2000a)
USA	362	1.38 (0.91–2.05)		54.7	25.6	Healthy middle-aged females	(Pradhan et al., 2001)
USA	850	1.84 (1.31–2.83)		73.9 (2.9)	26.9 (3.7)	Healthy older white males	(Visser et al., 2002)
USA	494	2.06		73.5 (2.8)	27.1 (4.2)	Healthy older black males	(Visser et al., 2002)
USA	764	1.63		73.5 (2.8)	25.9 (4.5)	Healthy older white females	(Visser et al., 2002)
USA	638	1.92		73.3 (3)	29.4 (5.8)	Healthy older black females	(Visser et al., 2002)
USA	304	1.47 (1.05–2.15)		69 (6.6)	26.6 (4.48)	Healthy older females	(Pradhan et al., 2002)
USA	50		1.9 (0.22)	30.2 (10.1)		Healthy young adults	(Miller et al., 2003)
USA	176	0.913 (0.64–1.49)		44.7 (3.91)	25.5 (3.04)	Healthy white middle-aged males	(Haddy et al., 2003)
USA	179	0.807 (0.57–1.31)		43.1 (4.00)	24.1 (4.14)	Healthy white middle-aged females	(Haddy et al., 2003)
USA	224	0.78 (0.47–1.32)		16 (3.86)	20.1 (3.15)	Healthy white teenage males	(Haddy et al., 2003)
USA	212	0.78 (0.47–1.48)		15.9 (3.85)	20.4 (3.08)	Healthy white teenage females	(Haddy et al., 2003)
USA	11	0.7	0.74 (0.12)	38.0 (13.27)	24.4 (3.61)	Healthy adults	(Dhabhar et al., 2009)
USA	343		3.10	63.7	29.0	Healthy adults (low cumulative socioeconomic position)	(Loucks et al., 2010)
USA	553		2.88	58.8	28.5	Healthy adults (medium cumulative socioeconomic position)	(Loucks et al., 2010)
USA	617		2.69	57.9	27.7	Healthy adults (high cumulative socioeconomic position)	(Loucks et al., 2010)

TABLE 4. Continued

Location	*N*	IL-6, median (IQR)	IL-6, mean (SD)	Age (years) mean (SD)	BMI (kg/m^2) mean (SD)	Sample characteristics	Reference
USA	976		2.79 (2.3)	58.4	29.1	Healthy white adults	(Coe et al., 2011)
USA	233		4.16 (3.7)	53.6	32.9	Healthy black adults	(Coe et al., 2011)
USA	9		3.4 (0.8)	34.3 (8.9)	25.8	Healthy adults	(Alesci et al., 2005)
USA	944	1.5 (0.9–2.5)		45.7 (3.4)	27 (6.4)	Healthy middle-aged white females	(Gruenewald et al., 2009)
USA	857	2.2 (1.3–3.4)		44.7 (3.9)	31.4 (7.3)	Healthy middle-aged black females	(Gruenewald et al., 2009)
USA	868	1.5 (0.9–2.4)		45.7 (3.4)	28.5 (6)	Healthy middle-aged white males	(Gruenewald et al., 2009)
USA	597	1.9 (1.1–3.0)		44.6 (3.7)		Healthy middle-aged black males	(Gruenewald et al., 2009)
USA	1744		3.6 (2.85)	62 (10)	27.6 (5.8)	Healthy older adult females	(Loucks et al., 2006)
USA	1487		3.95 (3.26)	62 (10)	28.8 (4.5)	Healthy older adult males	(Loucks et al., 2006)
USA	1028		2.8 (2.8)	58 (11.6)	29.2 (6)	Healthy older adults	(Morozink et al., 2010)
USA	3044	1.83 (1.27–2.79)		74.2 (2.8)	27.4 (2.9)	Healthy older black and white adults	(Koster et al., 2006)
USA	822		2.73 (2.81)	58.7 (11.7)	29.1 (6.0)	Healthy white adults	(Slopen et al., 2010)
USA	177		4.11 (3.45)	54.2 (10.7)	33.4 (8.9)	Healthy black adults	(Slopen et al., 2010)
USA	104	2.1 (1.8–2.3)		53.8	29.6 (0.5)	Healthy middle-aged males (Mediterranean diet score: 0–3)	(Dai et al., 2008)
USA	70	1.9 (1.6–2.2)		54.3	29.5 (0.6)	Healthy middle-aged males (Mediterranean diet score:4)	(Dai et al., 2008)
USA	81	1.8 (1.6–2.1)		54.5	29.5 (0.5)	Healthy middle-aged males (Mediterranean diet score:5)	(Dai et al., 2008)
USA	90	1.5 (1.3–1.7)		54.8	28.5 (0.5)	Healthy middle-aged males (Mediterranean diet score: 6–9)	(Dai et al., 2008)
USA	58		2.6 (1.5)	30 (7)	32.5 (6.5)	Healthy Pima Indian adults	(Vozarova et al., 2001)
USA	400		0.93	54.5 (6.6)	24.4 (3.9)	Healthy middle-aged females	(Sesso et al., 2007)
UK	1520		2 (1.48)	59.9 (5.7)	26.2 (4.2)	Healthy adults (low positive affect)	(Steptoe et al., 2008)
UK	675		1.84 (1.22)	59.8 (5.6)	26.1 (4.2)	Healthy adults (moderate positive affect)	(Steptoe et al., 2008)
UK	678		1.71 (1.03)	61.8 (5.7)	26.3 (3.9)	Healthy adults (high positive affect)	(Steptoe et al., 2008)
UK	48		1.15 (0.62)	52.5 (2.6)	25.7 (2.9)	Healthy middle-aged males (high SES)	(Steptoe et al., 2002)
UK	40		1.40 (0.67)	51.1 (2.3)	25.7 (4.3)	Healthy middle-aged females (high SES)	(Steptoe et al., 2002)
UK	42		1.26 (0.82)	51.8 (2.4)	25.9 (4.1)	Healthy middle-aged males (intermediate SES)	(Steptoe et al., 2002)
UK	35		1.04 (0.57)	52.5 (2.9)	25.0 (3.9)	Healthy middle-aged females (intermediate SES)	(Steptoe et al., 2002)
UK	35		1.17 (0.72)	53.7 (2.8)	25.7 (3.2)	Healthy middle-aged males (low SES)	(Steptoe et al., 2002)
UK	30		1.66 (1.2)	52.1 (2.8)	25.4 (4.1)	Healthy middle-aged females (low SES)	(Steptoe et al., 2002)
UK	107	2.19 (1.18–4.40)		59 (10.9)	25.9 (4.5)	Healthy middle-aged white adults	(Yudkin et al., 1999a)
UK	96		0.6 (0.1)	23.7 (0.5)	24 (0.3)	Healthy young adult males	(Miles et al., 2008)
UK	31		0.8 (0.1)	53.6 (1)	26.8 (0.5)	Healthy middle-aged males	(Miles et al., 2008)
UK	35		1.4 (0.2)	64.7 (0.8)	28.2 (0.8)	Healthy older males	(Miles et al., 2008)
UK	17		1.54 (0.5)	46.1 (6.2)	26.1 (2.5)	Healthy middle-aged males (high SES)	(Brydon et al., 2004)
UK	21		1.24 (0.8)	39.7 (6.7)	25.2 (2.7)	Healthy middle-aged males (low SES)	(Brydon et al., 2004)

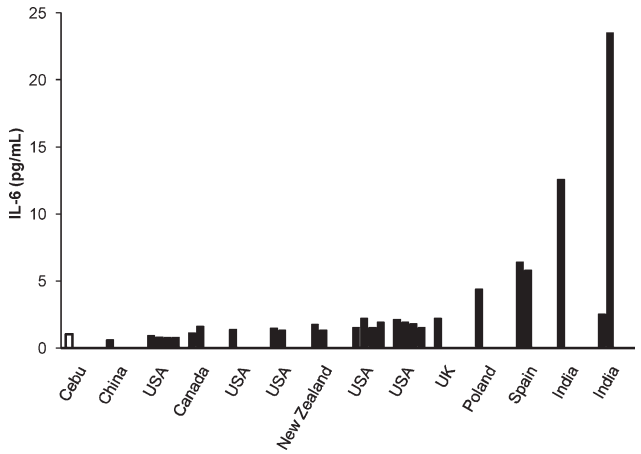

Fig. 2. Median IL-6 concentration in Cebu in comparison with prior studies reporting median values for healthy adults, middle-age and younger, with a sample size of $N > 25$. References for the included studies can be found in Table 4.

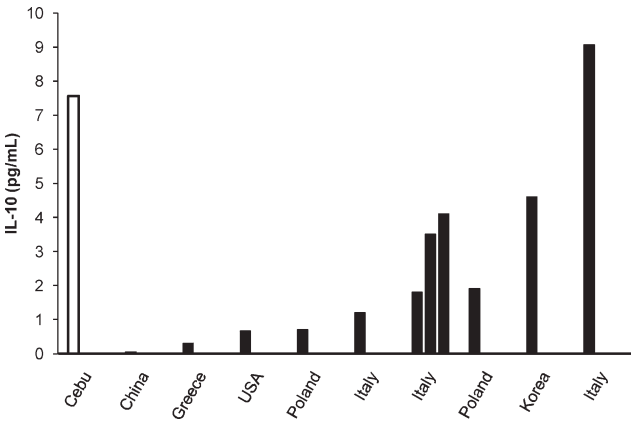

Fig. 3. Median IL-10 concentration in Cebu in comparison with prior studies reporting median values for healthy adults. References for the included studies can be found in Table 5.

of IL-10, median values better represent the central tendency in our dataset.

It is important to note that prior research has demonstrated substantial variation in cytokine concentrations across assay methods (Eishal and McCoy, 2006). The vast majority of the studies listed in Tables 4 and 5 applied enzyme-linked immunosorbent assay (ELISA) methods using reagents supplied by R&D Systems. In a recent, direct comparison of results produced by R&D Systems ELISA and the high sensitivity multiplex immunoassay protocol applied in our study, concentrations of IL-6 were found to be significantly lower when samples were analyzed with the R&D ELISA protocol (Dossus et al., 2009). Differences in assay methods are therefore not likely to account for the low concentrations of IL-6 in our sample. Similar comparisons have not been reported for IL-10, and we therefore cannot eliminate assay method as a contributor to the high IL-10 in our sample.

DISCUSSION

In this study, we investigated concentrations of IL-6 and IL-10 in healthy young adults in the Philippines to advance comparative research on the regulation of inflammation. Our study is among the largest analyses to date of these important inflammatory cytokines, and we find lower concentrations of IL-6, and substantially elevated concentrations of IL-10, in comparison to prior research. These results suggest the possibility of substantial population differences in the regulation of the inflammation, and point toward productive directions for future research.

Although concentrations of IL-6 in Cebu are among the lowest on record, patterns of association between IL-6 and other variables are similar to prior research in other settings. IL-6 is positively correlated with CRP, as expected given the well-established, potent effect of IL-6 on hepatic production of CRP (Castell et al., 1989; Harris et al., 1999; Friedman and Herd, 2010). Similarly, symptoms of infectious disease predict elevated IL-6, likely reflecting acute pro-inflammatory cytokine production by monocytes and other activated immune cells in response to pathogenic challenge. Finally, BMI is positively associated with IL-6, despite the relatively low levels of overweight/obesity and the restricted range of BMI variation in our sample. Adipose tissue is an important source of circulating IL-6, and prior research in post-nutrition transition populations with higher rates of overweight/obesity reports similar associations between adiposity and inflammation (Bermudez et al., 2002; Esposito et al., 2003a; Howren et al., 2009).

Relatively few studies have taken a population-based approach to investigating the correlates of IL-10, and our study is the largest reported analysis of this key anti-inflammatory cytokine. Concentrations in the Philippines stand out as high in comparison to prior studies in other populations. As with IL-6, IL-10 is positively—although weakly—correlated with CRP. It is also positively associated with BMI and symptoms of infectious disease.

While this pattern of results may appear inconsistent with IL-10's putative role as an anti-inflammatory cytokine, it is important to note that the counter-regulatory activity of IL-10 may only be necessary when pro-inflammatory pathways are activated. The strong and positive correlation between IL-10 and IL-6—particularly among individuals with active infections—supports this interpretation, and is consistent with prior research reporting positive associations between IL-10 and IL-6 (Urbánska-Rýs et al., 2000; Dhabhar et al., 2009). The low concentrations of IL-6 and/or high IL-10 in Cebu may reflect a balance of pro- to anti-inflammatory signaling that differs significantly from other populations, perhaps explaining the exceptionally low concentrations of CRP in the Philippines (McDade et al., 2009, 2010).

The origin of this inflammatory phenotype is not clear, and likely reflects ecological, developmental, and/or genetic factors that influence inflammation. For example, micronutrients common in the Filipino diet may reduce pro-inflammatory cytokine production (Barber et al., 1999; Walston et al., 2006), and similar dietary differences have been proposed as a partial explain for low concentrations of IL-6 in Japanese adults compared to adults in the US (Coe et al., 2011). In addition, we have suggested that low CRP concentrations among Filipino adults may trace back to relatively high levels of microbial exposure in infancy (McDade et al., 2010), consistent with a wider body of research on the

TABLE 5. Prior research reporting concentrations of IL-10 (pg/mL) in healthy adults

Location	N	IL-10, median (IQR)	IL-10, mean (SD)	Age (years), mean (SD)	BMI (kg/m^2), mean (SD)	Sample characteristics	Reference
China	30	0.05 (0–4.26)		34 (8)		Healthy adults	(Wong et al., 2001)
Greece	16	0.3 (0.01–1.1)		54 (5)		Healthy middle-aged adults	(Tziakas et al., 2003)
Italy	50	1.2 (0.7–2.9)		35.9 (4.9)	23.8 (1.2)	Healthy young females	(Esposito et al., 2003b)
Italy	34		13.5 (8)	32 (7)		Healthy pre-menopausal females	(Cioffi et al., 2002)
Italy	48		16 (6.6)	54.8 (6)		Healthy post-menopausal females	(Cioffi et al., 2002)
Italy	25	9.07 (7.4–12)	9.26 (1.5)			Healthy adults	(Galizia et al., 2002)
Italy	20	4.1 (3.5–4.8)		46 (11)	25.2 (2.2)	Healthy adult females	(Manigrasso et al., 2005)
Italy	20	3.5 (2.9–4.3)		49 (11)	33.4 (2.6)	Healthy adult females (gynoid obesity)	(Manigrasso et al., 2005)
Italy	64	1.8 (1.2–3.3)		49 (14)	37.1 (5.3)	Healthy adult females (android obesity)	(Manigrasso et al., 2005)
Japan	11		1.1 (0.6)	45		Healthy adults	(Kakumu et al., 1997)
Korea	312	4.6 (3.9–5.5)		70 (5)	24.6 (3.1)	Healthy older adults	(Choi et al., 2007)
Poland	51		9 (3.0)	51 (11)		Healthy middle-aged adults	(Wykretowicz et al., 2004)
Poland	30		0.92 (0.17)	42.5 (8.2)	24.7 (2.9)	Healthy middle-aged adults	(Myśliwska et al., 2005)
Poland	93	0.7 (0.6–1.0)		28.1 (8.4)	26.1 (4.8)	Healthy young adults	(Straczkowski et al., 2005)
Poland	28	1.9 (0.9–21.5)	3.23 (3.97)	63		Healthy adults	(Urbańska-Ryś et al., 2000)
USA	11	0.67	0.83 (0.19)	38 (13.3)	24.4 (3.6)	Healthy adults	(Dhabhar et al., 2009)

"hygiene" or "old friends" hypothesis (Rook and Stanford, 1998; Yazdanbakhsh et al., 2002; Radon et al., 2004; Rook, 2010). Similar exposures early in development may also shape the balance of pro- and anti-inflammatory signaling in Cebu. Lastly, several polymorphisms are known to influence production of IL-6 and IL-10 (Fishman et al., 1998; Gibson et al., 2001), although we have recently shown that genetic differences cannot explain population differences in CRP concentration (Curocichin et al., under review). Each of these factors represents promising areas for future research into population variation in the regulation of inflammation.

The long-term health implications of our findings are not known, but to the extent that inflammation contributes to the pathophysiology of cardiovascular, metabolic, or atopic/autoimmune diseases, low IL-6 and high IL-10 may represent a favorable balance of pro- vs. anti-inflammatory signaling. In a recent study of obesity and the metabolic syndrome, concentrations of IL-6 and IL-10 were elevated in obese women compared to non-obese controls (Esposito et al., 2003b). However, obese women with symptoms of the metabolic syndrome had lower levels of IL-10—levels that were indistinguishable from non-obese women. This pattern suggests that the metabolic syndrome may be characterized by dysregulated inflammation, in which an important anti-inflammatory signal is absent. Similarly, in a prospective study of patients with acute coronary syndromes, baseline IL-10 concentration was a significant predictor of death or myocardial infarction during 6 months of follow-up, but only in conjunction with baseline CRP: 6.8% of patients with high CRP and high IL-10 experienced an adverse outcome, compared to 21.8% of patients with high CRP but low IL-10 (Heeschen et al., 2003). These findings implicate uncontrolled inflammation, rather than inflammation in general, in adverse health outcomes, and suggest that additional research on IL-10 may be a particularly promising direction for future investigation.

Limitations of our study include the use of a single IL-6 and IL-10 measure, which makes it more difficult to differentiate acute episodes of inflammation from chronic, low-grade inflammatory activity. We also do not evaluate other cytokines (e.g., IL-1β, TNFα) which play important roles in the regulation of inflammation and should be considered in subsequent comparative research. In addition, differences in sampling strategy, study design, and assay methodology make comparisons with prior studies difficult, and conclusions drawn from such comparisons should be considered tentative. We hope the findings reported here will motivate future research into population differences in the regulation of inflammation and their genetic, ecological, and developmental antecedents.

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