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To assess, to control, to exclude: Effects of biobehavioral factors on circulating inflammatory markers ☆

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ABSTRACT

Behavioral scientists have increasingly included inflammatory biology as mechanisms in their investigation of psychosocial dynamics on the pathobiology of disease. However, a lack of standardization of inclusion and exclusion criteria and assessment of relevant control variables impacts the interpretation of these studies. The present paper reviews and discusses human biobehavioral factors that can affect the measurement of circulating markers of inflammation. Keywords relevant to inflammatory biology and biobehavioral factors were searched through PubMed. Age, sex, and hormonal status, socioeconomic status, ethnicity and race, body mass index, exercise, diet, caffeine, smoking, alcohol, sleep disruption, antidepressants, aspirin, and medications for cardiovascular disease are all reviewed. A tiered set of recommendations as to whether each variable should be assessed, controlled for, or used as an exclusion criteria is provided. These recommendations provide a framework for observational and intervention studies investigating linkages between psychosocial and behavioral factors and inflammation.

1. Introduction

Inflammation, as indexed by increases of circulating levels of C-reactive protein (CRP) and proinflammatory cytokines such as interleukin-6 (IL-6), is thought to influence the onset and course of a wide spectrum of diseases including cardiovascular disease, arthritis, type 2 diabetes, and certain cancers (Ferrucci et al., 1999). Further data show that elevated levels of IL-6 prospectively predict future disability, declines of health status, and mortality risk, particularly in older adults (Reuben et al., 2002; Volpato et al., 2001). Given substantial evidence that psychosocial factors such as depression, psychological stress, and social isolation increase cardiovascular morbidity and mortality, and hasten the onset and negatively impact the course of other inflammatory disorders, behavioral scientists have increasingly evaluated circulating levels of inflammatory markers in an effort to understand the signaling pathways by which these psychosocial dynamics impact the pathobiology of disease.

Part of the difficulty in evaluating changes in circulating levels of inflammatory markers in relation to psychosocial factors is that human populations display wide variability in a vast array of variables that are known to affect the production and expression of proinflammatory markers. Hence, reliable conclusions about the influence of biobehavioral processes on circulating markers of inflammation can be jeopardized when comparing different populations and/or different clinical settings without a common methodological framework.

However, standardization of inclusion and exclusion criteria and assessment of relevant control variables has provided a platform for the study of immunity in older adults, as well as prior psychoneuroimmunology studies of innate and cellular immunity. For example, the SENIEUR protocol identified a set of demographic and clinical criteria that guided the selection of relatively healthy participants for the study of the effects of aging on immunity in such a way that exogenous and endogenous influences on immunity were reduced to a minimum. Ultimately this standardized protocol influenced a generation of research that dissected the contribution of disease, as opposed to the impact

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of normal aging processes, on the immune system (Castle et al., 2001; Ligthart, 2001), which arguably could be generalized to other populations including those with medical comorbidities. Likewise Kiecolt-Glaser and Glaser (1988) identified a number of key behavioral factors that exert an influence on the measurement of cellular immunity, and discussed issues related to assessment in evaluation of psychosocial influences on measures of lymphocyte proliferation, natural killer cell activity, and antibodies to latent viruses. To our knowledge, no prior review has discussed the methodological issues relevant for the study of behavioral processes and inflammation in humans.

The goal of the present paper is to review and discuss human biobehavioral factors that can affect the measurement of circulating markers of inflammation. We chose to focus on select circulating inflammatory markers (e.g., interleukins (ILs) and tumor necrosis factor-α (TNF-α), their soluble receptors, and CRP) because of their broad use (and assay procedures) and well-established connections with clinical health outcomes afflicting a large proportion of studied populations. This review is primarily based on studies of non-medical adult populations, rather than those who have a particular medical disorder which might require assessment of certain behavioral factors at a much more detailed level. In the case of medications, antidepressants, statins, and antihypertensives are quite common, and empirical evidence for their effects on inflammatory markers typically comes from individuals with depression or existing cardiovascular disease. In an effort to guide biobehavioral research, key behavioral factors are identified for assessment consideration, with a tiered set of recommendations as to whether the variable should be assessed, controlled for, or used as an exclusion criteria, recognizing that clinical research effectively balances these methodological issues with cost and effort of assessment. Suggestions for assessment of these variables are also provided.

We are sensitive to the appropriate selection of control variables in biobehavioral research, due to the potential for "overfitting" regression models. Variables should be chosen for *a priori* reasons, and this paper may help investigators do just that. However, controlling for too many variables may lead to sample-specific results, limiting the replicability. Although it is beyond the scope of this manuscript, guidelines exist for choosing control variables in relationship to sample size, and some journals even require these guidelines to be followed (Babyak, 2004).

Although assessing, controlling, and excluding variables is discussed, investigators may examine some variables as important components in a theoretical model. This may be either as a moderating variable that changes the relationship between the variables of interest (e.g., smoking magnifies the relationship between depression and inflammation), or as a mediating variable that explains the relationship between the variables of interest (e.g., the relationship between depression and inflammation might be partly explained by sleep disturbance (Irwin et al., 2006)).

We note that if investigators wish to examine some of these variables of interest as mediators, a key issue is the timing of assessment. Beyond the statistical criteria for mediation (Kraemer et al., 2001; MacKinnon et al., 2007), an important criterion is temporal precedence; that is, the mediating variables must be measured at some point after the independent variable and before the dependent variable. For instance, to establish that smoking explains/mediates the relationship between depression and inflammation, the smoking measures must be assessed sometime after depression is measured and before inflammatory markers are measured. However, it is beyond the scope of this paper to determine how to place these variables in investigators' theoretical and design frameworks.

2. Methods

2.1. Search strategy

Relevant articles were located with an online search of PubMed. Articles published through April 2008 were considered. Discussion among authors generated a list of key variables of importance for the present review. Keywords related to inflammatory biology were searched (Table 1, panel A). These terms were cross-referenced with keywords reflecting the variables of interest (Table 1, panel B). To ensure a comprehensive review of the literature, the reference sections of the generated articles were examined and relevant papers were then obtained. Reviewed papers were limited to studies published in peer-reviewed journals of adult human subjects and in English. Papers were chosen if they explicitly focused on the association between circulating proinflammatory cytokines (including CRP) and the variable of interest. The focus was on circulating cytokines, rather than stimulated production, because systemic inflammation has been associated with mortality outcomes, as well as a number of psychosocial factors. Circulating and stimulated cytokines reflect different processes, and may thus be influenced by different behavioral factors (i.e., conclusions for circulating levels may not apply to stimulated levels). An experimental study linking the variable of interest to a marker of inflammation was considered strong evidence of an influential factor, although findings from correlational and longitudinal studies were also considered. Studies that are reported have a total sample size greater than 50, unless explicitly stated. In the case of null findings, the present paper reports studies where the evidence suggests no difference; we can not comment on the possibility that studies have been conducted, found no difference, but did not publish a report. Only relationships (or their absence) that were found during the search of published findings were included in the present review.

3. Results

3.1. Age, sex, and hormonal status

Inflammatory biology is altered across the lifespan, and substantial evidence indicates that CRP (Hung et al., 2008; Worns et al., 2006; Ferrucci et al., 2005) and proinflammatory cytokines including IL-6, soluble IL-6 receptor (sIL-6r), TNF-α, soluble TNF receptor II (sTNFR-II), and interleukin-1 receptor antagonist (IL-1ra) increase with age in both men and women (Bruunsgaard et al., 2000; Ferrucci et al., 2005; Shurin et al., 2007). This relationship appears to be a fairly linear process; threshold age cut points for detecting increases are not evident. Importantly, these relationships between age and markers of inflammation have been found in epidemiologic studies (N = 1300–4000), with statistical control of confounding factors such as education, body mass index (BMI), physical activity, alcohol use and smoking status (Ferrucci et al., 2005; Hung et al., 2008).

In regards to sex and circulating markers of inflammation, several population-based studies have found that women show higher levels of CRP as compared to men, even controlling for BMI (Khera et al., 2005; Lakoski et al., 2006; Nazmi et al., 2008). One study has demonstrated no sex differences for CRP (Im et al., 2006); however this was a Japanese sample with very low CRP levels. In contrast, no consistent sex differences are reported for IL-6, sIL-6r, sTNF-RI, and sTNF-RII (López-Bermejo et al., 2007; Sadeghi et al., 2005), although the latter study was small (N = 46). In all of the studies cited, categorization of sex is based on biological characteristics (e.g., birth sex), and not on the gender displayed (Fishman et al., 1999).

Table 1
Keywords searched in PubMed.

Panel A: Keywords related to inflammatory markers
C-reactive protein, CRP
Interleukin-6, IL-6, sIL-6R, IL-1, IL-1β, IL-1RA
Inflammation, inflammatory
Tumor necrosis factor, TNF, sTNFR-II
Cytokines, cytokine levels
Circulating
Biomarkers
Panel B: Keywords related to variables of interest
Age, sex, gender, menstrual cycle, hormone replacement, oral contraceptive
Socioeconomic, education, income
Ethnicity, African American, Asian, Hispanic
Body mass index, BMI
Exercise, fitness
Diet, dietary, coffee, caffeine, nutrition
Tobacco, smoking, alcohol
Sleep, sleep deprivation, circadian rhythms
SSRI, selective serotonin reuptake inhibitor, Citalopram, Escitalopram, Fluoxetine, Paroxetine, Sertraline, Duloxetine
NSAID, aspirin, statin, antihypertensive, diuretic, angiotensin-converting enzyme inhibitor, β-blocker, calcium channel blocker, angiotensin receptor blocker

Table 2
Summary recommendations for each biobehavioral factor reviewed; however, caveats for each variable should be examined in the text. See text for discussion of each recommendation, with consideration that variables might be either controlled or excluded in part related to study design and explanatory model being evaluated (e.g., SSRI use).

Assess/describe
Menopausal status
Fitness level
Diet
Smoking history
Medication
Control
Age
Sex
Socioeconomic status
Ethnic and racial differences
Body mass index (or waist–hip ratio)
Alcohol use
Sleep quality, sleep habits
Aspirin, statin, antihypertensive use
SSRI use
Exclude
Acute exercise
Acute use of caffeine/excessive caffeine use
Acute smoking/current smokers
Alcohol dependence
Acute sleep deprivation or sleep disorders
SSRI use

Among women, various hormonal factors may impact immune processes, including stage of menstrual cycle, use of oral contraceptives (OC), menopausal status, and use of hormone replacement therapy (HRT). The evidence is mixed regarding the impact of such hormonal events on circulating markers of inflammation. For example, whereas many studies find no menstrual cycle-dependent changes in CRP, IL-6, sIL-6r, and TNF-α (Wunder et al., 2006; O'Brien et al., 2007; Al-Harthi et al., 2000; Willis et al., 2003; Abrahamsen et al., 2003; Salkeld et al., 2001), other studies find that IL-6 is higher (Souter et al., 2005) and CRP is lower (Jilma et al., 1997) during the follicular phase as compared to the luteal phase. All of these menstrual cycle studies are $N < 50$, however. In regards to OC use, no differences in IL-6 and TNF-α were found (Giraldo et al., 2008; Kluft et al., 2002; Souter et al., 2005; van Rooijen et al., 2006), although these studies were also quite small ($N = 35–68$). Other studies found increases of CRP in those taking OC (Hung et al., 2008) with $N > 4{,}000$. With respect to menopause, post-menopausal women have shown higher levels of CRP (Muzzio et al., 2007) but other interleukins have not shown a difference (Yasui et al., 2008). Finally, CRP increases with oral, but not transdermal HRT (Eilertsen et al., 2005; Hung et al., 2008; Lacut et al., 2003; Zegura et al., 2006). The effect of HRT treatment has been much more variable for IL-6, sIL-6r, and TNF-α (Straub et al., 2000; Abrahamsen et al., 2000; Vitale et al., 2005; Lacut et al., 2003; Zegura et al., 2006; Eilertsen et al., 2005).

Recommendations: Given substantial evidence linking age and markers of inflammation, information on age and sex should be routinely obtained. Further, in comparison studies between groups of participants, age should be matched and/or statistically controlled. Likewise, information on use of oral contraceptives, menopausal status and HRT should be obtained, when studies involve CRP. There is less support for the routine evaluation of menstrual cycle phase (Table 2).

3.2. Socioeconomic status

Socioeconomic status (SES), usually determined by education, occupation, income, wealth, neighborhood socioeconomic conditions, or combinations of these, has been consistently inversely associated with circulating levels of inflammatory markers. Of the inflammatory markers, CRP has been most frequently examined and low SES correlates with high circulating levels of CRP independent of demographic, biomedical (e.g., longstanding diseases and blood pressure) and biobehavioral (e.g., depression, perceived stress, smoking, drinking, exercise, and obesity) factors (Jousilahti et al., 2003; Lubbock et al., 2005; Owen et al., 2003; Panagiotakos et al., 2004; Prescott et al., 2007; Rosvall et al., 2007). However, it should be noted that other studies found that multivariable adjustment attenuates the association between SES and CRP to a substantially weaker level (Alley et al., 2006; Gimeno et al., 2007; Koster et al., 2006; Pollitt et al., 2007) or even to the null (Kivimaki et al., 2005; McDade et al., 2006; Rathmann et al., 2006). Of the covariates mentioned above, the most important ones are smoking, drinking, exercise, and obesity (see relevant sections below). These variables may act as mediating factors of the inverse association between SES and CRP.

Findings similar to CRP are reported for other inflammatory markers. For instance, low SES was associated with elevated levels of circulating IL-6, TNF-α, and IL-1ra (Gimeno et al., 2007; Koster et al., 2006; Steptoe et al., 2002) and again biobehavioral factors explained a considerable part of this inverse association. Overall, SES is a major correlate of the inflammatory state.

Additionally, two particular aspects of this relationship are worth mentioning. First, the association between SES and inflammatory markers seems stable over time. A large prospective study reported that relative differences by SES remained unchanged, despite overall substantial increases of CRP and IL-6 over a decade at every stratum of SES (Gimeno et al., 2007). Second, the association between SES and CRP appears particularly strong at very high levels of CRP. A cross-sectional survey of the US population found that the association between poverty and CRP was significant only at very high levels of CRP (>10 mg/L) and this remained significant even after controlling for acute illness, chronic conditions and behavioral risk factors (Alley et al., 2006). Researchers often exclude those participants with levels of CRP higher than 10 mg/L as these levels may be clinically indicative of infections (Pearson et al., 2003). However, this approach may lead to a loss of valuable information and should be further scrutinized based on empirical data.

Recommendations: There is a stable association between low SES and higher levels of inflammatory markers. Therefore, in biobehavioral research involving inflammatory markers, SES should be eval-

uated and considered as a main variable or a control covariate. Regarding the measurement of SES, it has been suggested that various measures of SES are related to measures of health outcome through different causal pathways (Taylor et al., 1997). Thus, it has been recommended that measures of SES be selected in the context of plausible explanatory pathways (Braveman et al., 2005). However, if the constraints of available resources do not allow researchers to measure more than a single parameter of SES and there is no *a priori* hypothesis favoring a particular parameter, education is perhaps the measure of choice for the following reasons. First, although there has been no formal study comparing different SES variables for their association with the inflammatory endpoints, in three studies presenting data on at least two different SES variables and CRP (Kivimaki et al., 2005; Koster et al., 2006; Lubbock et al., 2005), a higher statistical significance was observed for education compared to income, occupation or assets. Second, there is some evidence that education has the strongest and most consistent correlation with cardiovascular risk factors (Winkleby et al., 1992). Third, education is a widely used and easily assessed measure (Table 2).

3.3. Ethnic and racial differences

Large-scale epidemiologic investigations have examined the impact of ethnicity and race on CRP and proinflammatory cytokines, with findings obtained from the SWAN study (Kelley-Hedgepeth et al., 2008; Matthews et al., 2005), the Dallas Heart Study (Khera et al., 2005), NHANES III and IV (Abramson et al., 2002; Alley et al., 2006), Chicago Health, Aging and Social Relations Study (McDade et al., 2006) and the MESA study (Lakoski et al., 2006). Together, these studies have consistently demonstrated that African Americans and Hispanics have higher CRP levels than white Americans. Additionally, LaMonte et al. (2005) noted that Native Americans have higher CRP levels than white Americans. Importantly, most studies statistically controlled for the effects of relevant covariates, including age, sex, SES, BMI, or tobacco use, estrogen usage, statins, physical activity, and diet (Anand et al., 2005; Forouhi et al., 2001; Kelley-Hedgepeth et al., 2008; Khera et al., 2005; Matthews et al., 2005; Pollitt et al., 2007). Only one study, to our knowledge, found no difference when examining CRP levels between African Americans, Hispanics, and white Americans (i.e., NHANES 1999–2002 (Meng et al., 2007)).

Among Asian participants, CRP levels differ based on their national origin. Several studies demonstrate that South Asians have higher levels of CRP than white Americans (Anand et al., 2004; Dotsenko et al., 2007; Forouhi and Sattar, 2006; Forouhi et al., 2001; Lear et al., 2003). In contrast, Chinese and Japanese individuals consistently have the lowest CRP levels compared to Caucasian Americans and other ethnic groups (Anand et al., 2004; Kelley-Hedgepeth et al., 2008; Lakoski et al., 2006; Matthews et al., 2005).

Fewer studies have examined ethnic differences in relation to proinflammatory cytokines; however, the pattern is similar to the findings for CRP. African Americans show higher IL-6 levels than white Americans (Kiecolt-Glaser et al., 2003; Mills et al., 2007; Walston et al., 2007). Additionally, Ho and colleagues (2005) reported that Mexican Americans have higher levels of TNF-α and lower sTNFR than white Americans. To our knowledge, no published study has examined whether proinflammatory cytokine levels in Asians differ from other ethnic or racial groups.

Several caveats should be noted in ethnic and racial differences for CRP. Importantly, gender may influence differences across ethnic groups. Forouhi and colleagues (2001) found that South Asian women had nearly double the CRP levels of European women; however, there was no difference between South Asian and European men. Similarly, Danner and colleagues (2003) found an interaction between race and gender on CRP levels. African Americans had the highest CRP levels in this sample, followed by Mexican Americans and then white Americans. However, when examining CRP in men and women separately, they found no difference in CRP levels between African American and Mexican American women.

In addition to gender, BMI may also interact with ethnic differences for CRP levels (Kelley-Hedgepeth et al., 2008). For example, Kelley and colleagues reported that the strength of associations between ethnicity and CRP concentrations were substantially attenuated after controlling for BMI, especially in African American, Chinese, and Japanese women. This suggests that differences in BMI may largely account for ethnic differences across groups, especially in African Americans who tend to have higher average BMI, as well as in Chinese and Japanese who tend to have lower average BMI, as compared to white Americans.

Recommendations: Given the associations between ethnicity and systemic inflammation, information on ethnicity should be routinely obtained. Furthermore, when study samples are large, the role of ethnicity as a potential moderator of associations between independent variables (i.e., BMI) and markers of inflammation should be examined. To control for the effects of ethnic variation in inflammation, sampling of groups who are comparable in terms of ethnic composition should be employed. At minimum, ethnicity should be statistically controlled when conducting analyses (Table 2).

3.4. Body mass index: influence of obesity

Tissue-resident macrophages, which may constitute up to 60% of all cells found in adipose, and adipocytes produce a wide range of inflammatory markers, including IL-6, TNF-α, and sTNF-Rs. It is estimated that in healthy subjects about 30% of total circulating concentrations of IL-6 originate from adipose tissue (Mohamed-Ali et al., 1998). Accordingly, data from several population-based cross-sectional studies indicate that obesity influences plasma levels of inflammatory markers irrespective of age and other potential confounders. Indeed, obesity indices (e.g., BMI) are consistently correlated with increases in circulating levels of IL-6, sTNF-Rs, and CRP (Himmerich et al., 2006; Panagiotakos et al., 2005; Rexrode et al., 2003; Thorand et al., 2006). Moreover, among obese participants, circulating markers of IL-6, TNF-α, sTNF-Rs, and CRP are elevated as compared to persons with normal weight (for reviews, see Berg and Scherer, 2005; Dandona et al., 2004; Nicklas et al., 2005).

In contrast to IL-6 and CRP, the correlation between measures of obesity and TNF-α plasma concentrations are weaker (Park et al., 2005), or completely absent (Hauner et al., 1998; Himmerich et al., 2006; Kern et al., 2001). The reason for this lack of association is not fully understood, although it is thought that TNF-α in adipose tissue has primarily localized functions, (Mohamed-Ali et al., 1997), leading to much higher TNF-α in adipose tissue in those with high vs. low BMI, yet no difference in the plasma levels (Kern et al., 2001). However, because of the sophisticated methodological procedures, the latter two studies were small ($N = 39$ and $N = 50$, respectively).

Most studies have focused on total adiposity as measured either indirectly by BMI or directly by body composition assessment. However, several (but not all) investigations have found that both waist circumference and waist to hip ratio, as indexes of abdominal (visceral) adiposity, are more closely associated with the variability of circulating IL-6, TNF-α, and CRP than BMI (Forouhi et al., 2001; Panagiotakos et al., 2005; Saijo et al., 2004).

Among studies of weight loss, a consistent reduction in circulating IL-6, TNF-α, sTNF-Rs, and CRP has been observed (for reviews, see You and Nicklas, 2006; Nicklas et al., 2005), regardless of

whether weight loss was achieved through hypocaloric dietary intake, exercise, or liposuction. The magnitude of decrease of BMI correlated with decreases in IL-6, TNF-α, sTNF-Rs, and CRP (Esposito et al., 2003; Heilbronn et al., 2001; Marfella et al., 2004; Nicklas et al., 2004; Xydakis et al., 2004; Ziccardi et al., 2002). Moreover, change in abdominal adiposity as measured by waist to hip ratio was more strongly associated with decreases of these markers than BMI (Ziccardi et al., 2002).

Recommendations: As with age, sex, and race, it is recommended that indices of obesity should be routinely obtained. Recognizing that is may not be possible to generate groups who are comparable in terms of BMI, differences in such measures should be statistically controlled. Furthermore, when resources are available to assess abdominal obesity with measurement of waist circumference and waist to hip ratio, these additional measures should be included to supplement the assessment of BMI (Table 2).

3.5. Exercise

Two dimensions of exercise behaviors are associated with circulating markers of inflammation: cardiorespiratory fitness level and acute exercise. Cardiorespiratory fitness is assessed during graded exercise tasks by measurement of peak oxygen consumption (peak VO_2 max) and heart rate, although self-report of frequency and duration of aerobic exercise practices are more commonly used as a surrogate index of fitness. Observational, as well as randomized controlled trial (RCT) studies, demonstrate a consistent association between greater cardiorespiratory fitness levels and lower circulating levels of CRP and IL-6 in healthy participants and in patient populations (for a review, see Plaisance and Grandjean, 2006). Although there is some debate (Hamer, 2007), cardiorespiratory fitness appears to be related to lower circulating levels of inflammation after controlling for BMI, especially in populations who generally have higher levels of inflammation (e.g., older adults). Although there are no established cutoffs for what level of cardiorespiratory fitness is needed to alter circulating levels of IL-6 and CRP, one recent review indicated that intense exercise can lower CRP levels in as little as 2 months (Plaisance and Grandjean, 2006).

An acute exercise bout can also impact circulating levels of inflammatory cytokines and such effects are driven in part by the existing cardiorespiratory fitness level, duration and intensity of the exercise bout, amount of muscle mass recruited, and how the muscle is used (Petersen and Pedersen, 2005). However, in general, IL-6 has been observed to increase exponentially during acute exercise bouts, with peak increases at the end of exercise and a recovery slope that depends on the factors listed above. For example, IL-6 levels have been found to return to baseline 30 min after completing a brief VO_2 max test in a sample of $N = 15$ (Steinberg et al., 2007). It is currently thought that exercise-induced IL-6 comes primarily from skeletal muscle and that this muscle-derived IL-6 mobilizes an anti-inflammatory cascade (Petersen and Pedersen, 2005). Consistent with this, acute exercise has been linked to increases in IL-1ra and IL-10 (Petersen and Pedersen, 2005). In contrast to exponential increases in IL-6, acute exercise appears to have little effect on CRP and TNF-α levels (small increases have been observed after completing ultra-marathons (Tomaszewski et al., 2004)).

Recommendations: Cardiorespiratory fitness levels should be evaluated with relevant surrogates (e.g., frequency of intense exercise). Where resources are available to provide quantitative measures of cardiorespiratory fitness, graded exercise tasks by measurement of peak VO_2 max and heart rate should be employed. In studies where IL-6 is a primary outcome of interest, study subjects should be instructed not to exercise during the day of assessment and to avoid significant physical exertion in traveling to the study site. Moreover, it is recommended that subjects sit quietly after arriving at the study site for as long as 30 min before any blood is drawn (Table 2).

3.6. Diet

A number of large, well-controlled cross-sectional studies have examined the relationship between dietary factors and markers of inflammation (Jiang et al., 2006; Lopez-Garcia et al., 2004, 2005; Nettleton et al., 2006) and found that a diet rich in whole foods (e.g., fruit, vegetables, fish, whole grains and nuts) was associated with lower levels of CRP and IL-6. In contrast, diets high in refined grains, red meat, high-fat dairy and processed food was associated with high levels of CRP and IL-6. Likewise, in experimental studies that involve manipulation of dietary fat intake, low-fat diets induce decreases of CRP. For example, in a sample of 29 overweight women (Rankin and Turpyn, 2007), CRP levels were found to increase 25% in those consuming a high fat, low carbohydrate diet vs. a 43% reduction in CRP for those whose intake was a low fat, high carbohydrate diet. However, both experimental groups showed increases of IL-6 levels. The inflammatory effect of long-term fasting and caloric restriction are beyond the scope of this review (but see Fontana et al., 2004).

Recommendations: These data suggest a relationship between dietary factors (e.g., fat consumption) and markers of inflammation and the possible need to assess participants' diet in relationship to inflammation. However, dietary assessment with instruments such as the food frequency questionnaire (FFQ) (Hu et al., 1999) generates considerable subject burden, which might compromise the validity of such assessments given the detailed nature of these questionnaires and reliance on subjective recall. Targeted reporting of the number of servings of fruits and vegetables, and processed or refined foods, is an option to characterize differences in dietary consumption where the FFQ is not possible (Table 2).

3.7. Caffeine

Coffee is a widely consumed beverage and one of the main sources of caffeine in the Western diet. Whereas coffee contains over 2000 components, amounts of these factors vary depending on the method of preparation (e.g., filtered, boiled, espresso, decaffeinated) (Ranheim and Halvorsen, 2005), with possible effects on cardiovascular, neuroendocrine and inflammatory responses especially in the context of acute psychological stress (Hamer et al., 2006). For example, consumption of boiled coffee—a common method of preparation outside of the US—at moderate levels (greater than 2 cups of coffee per day) is associated with increased IL-6 and CRP levels ($N = 3032$) (Zampelas et al., 2004). However, this level of coffee consumption was not associated with changes in inflammatory markers among healthy American women ($N = 730$) and healthy European men ($N = 1031$) (De Bacquer et al., 2006; Lopez-Garcia et al., 2006), possibly due to different methods of preparation in Europe and North America (Ranheim and Halvorsen, 2005). The complex interactions between coffee consumption and variations in diet and exercise, both of which modulate inflammatory markers, has received limited attention (Bonita et al., 2007).

Recommendations: Given the difficulties in assessing differences in caffeine consumption due to the subjective reporting of intake, varying sources of caffeine, and differences in methods of preparation of coffee that impact caffeine amounts, reliable evaluation of amount of caffeine consumed per day is unlikely. However, evidence suggests that laboratory studies that examine the acute effects of psychological stress should discourage participants from the use of caffeine before an immune assessment. Additionally, the daily number of caffeinated beverages can be quantified in order to exclude subjects above a threshold based on the population

distribution (e.g., greater than 8–10 cups of coffee per day exceeds 2 standard deviations) (Table 2).

3.8. Smoking

The mechanisms between cigarette smoke in the lungs and circulating proinflammatory cytokines is complex, but across several large-scale and well-controlled studies (Haddy et al., 2005; Nanri et al., 2007; Yanbaeva et al., 2007) current histories of tobacco smoking lead to increases in IL-6 and CRP, as observed in the STANISLAS cohort (Haddy et al., 2005), the British Regional Heart Study (Wannamethee et al., 2007), the Women's Health Study (Bermudez et al., 2002), and the ULSAM cohort (Helmersson et al., 2005). The effects of smoking on CRP have not been found in all populations (Frohlich et al., 2003; Helmersson et al., 2005), but this may be due to sex differences; higher CRP values were observed in male smokers from Italy (Bo et al., 2005) and Brazil (Nazmi et al., 2008), but not in women.

In addition to the effect of current smoking status on IL-6 and CRP, there also appears to be a graded relationship between the amount smoked over a lifetime and increases in these inflammatory markers (Bazzano et al., 2003; Bermudez et al., 2002; Mendall et al., 2000). For example, among male subjects aged 60–79, IL-6 levels were found to be elevated in former smokers compared to non-smokers, and diminished with the passing of abstinent years (Wannamethee et al., 2007). Interestingly, levels of IL-6 also were positively associated with the number of cigarettes smoked/day (Wannamethee et al., 2007).

In contrast to the effects of tobacco smoking on IL-6 and CRP, an inverse relationship between smoking and TNF-α was observed in the STANISLAS cohort (Haddy et al., 2005), whereas a smaller population-based study found no difference in TNF-α levels between smokers and non-smokers (Mendall et al., 1997). However, the concentration of sTNFr-II, but not sTNFRI, has been reported to be elevated among smokers as compared to non-smokers in some (Fernandez-Real et al., 2003), but not all studies (Levitzky et al., 2008). Likewise, increases of circulating levels of IL-1ra have been found in smokers as compared to non-smokers in a study of 42 participants (Cullup et al., 2004), with additional data suggesting that tobacco smoking leads to increases of IL-8 (Berrahmoune et al., 2006).

Recommendations: Tobacco smoking is typically via self-report measures, and given the associations between current smoking status and increases of IL-6, CRP, and possibly certain cytokine receptors antagonists, lifetime tobacco-smoking histories should be assessed with possible inclusion of information regarding quantity of tobacco smoking (e.g., pack-years) and date of abstinence if currently a non-smoker. Investigators may consider excluding smokers with recognition that some populations have a higher base rate (e.g., substance abuse, depression, etc.). When necessary, recent smoking exposure can be assessed via measurement of serum cotinine levels (Welsh et al., 2008) (Table 2).

3.9. Alcohol

The association between alcohol consumption and proinflammatory cytokines typically follows a U- or J-shaped pattern (Albert et al., 2003; Imhof et al., 2004; Pai et al., 2006; Volpato et al., 2004). For example, circulating levels of CRP are typically lower in moderate drinkers as compared to non-drinkers and heavy drinkers as observed in the Health Professionals Follow-up Study and Nurse's Health Study II (NHSII) cohorts, (Pai et al., 2006) and MONICA study (Imhof et al., 2004), with a replication of these data across European (Raum et al., 2007) and Asian populations (Wang et al., 2008). Similar findings are found for circulating levels of IL-6 (Pai et al., 2006; Volpato et al., 2004), although the relationship may be linear, rather than U-shaped, (Mendall et al., 1997) and that the effects are more robust in men (Welsh et al., 2008).

The threshold at which alcohol consumption leads to increases in CRP and IL-6 is not well defined partly due to differences in the way alcohol intake is reported. In general, moderate drinking as defined by 1–7 alcohol drinks per week (Albert et al., 2003; Volpato et al., 2004), or 15–30 g of alcohol/day is associated with lower levels of markers of systemic inflammation (Imhof et al., 2004; Pai et al., 2006; Raum et al., 2007), with some data suggesting these effects are maintained up to alcohol use at 20–70 g/day (Wang et al., 2008). An alcohol-intake-controlled trial has, found that drinking 30 g of alcohol per day (i.e., two drinks) for 12 weeks resulted in lower levels of CRP as compared to abstinence (Estruch et al., 2004), with similar results for those that drank 30–40 g of alcohol per day for 3 weeks (Sierksma et al., 2002). These last two studies were $N < 50$.

Negative correlations between alcohol intake and circulating levels of sTNFr-I and sTNFr-II (Pai et al., 2006), and TNF-α levels (Mendall et al., 1997) have been shown, but no relationship has also been demonstrated (Volpato et al., 2004). A randomized intake-controlled trial showed no differences for TNF-α between drinkers and non-drinkers (Estruch et al., 2004).

Recommendations: The association of IL-6 and CRP with alcohol consumption is widely reproducible across studies. Importantly, the correlation between IL-6 and CRP with alcohol intake is mediated by amount and not the type of alcoholic beverage consumed. Therefore, current alcohol consumption histories should be used as a control variable in studies of CRP and IL-6, with consideration of standardization of drinking categories (e.g., abstainer, moderate drinker, heavy drinker) and possible exclusion of those with current alcohol dependence (Table 2).

3.10. Sleep disruption

Sleep and circadian rhythms (i.e., daily biological cycles) are an important consideration in the measurement of many biological processes. Although studies have shown circadian variations in some cytokine levels, this variability is manifested primarily by differences between the nocturnal and diurnal periods; there is little variability within the diurnal period (Dimitrov et al., 2007).

Several studies have explored the relationship between sleep disruption and cytokine levels. Most of these studies focused on the impact of laboratory sleep deprivation with predominantly young to middle aged male subjects. Following one night total sleep deprivation, Vgontzas et al. (1999) showed that IL-6 daytime levels were higher and nighttime levels were lower than during the period of normal sleep. Frey et al. (2007) similarly found significant increases after sleep deprivation in IL-1β, and IL-1RA, and decreases in CRP and IL-6 after controlling for circadian phase. Moreover, when sleep is restricted from 8 to 6 h for 1 week, increases of IL-6 and TNF-α were found (Vgontzas et al., 2004). Likewise, in the comparison of individuals sleeping 8 h per night vs. those sleeping 4 h per night for 12 nights, IL-6, CRP, and sTNF-R were increased in the restricted sleeping group (Haack et al., 2007). All of these sleep studies are $N < 50$, primarily because laboratory protocols and careful controls make these studies complex and costly.

Consistent with these experimental data, several observational studies have shown that shift workers (Zheng et al., 2006) and insomniacs (Burgos et al., 2006) show increases in circulating levels of inflammatory markers, as do older adults, who have poorer sleep than younger adults (Vgontzas et al., 2003) (although these three studies were $N < 50$ as well). Moreover, there are epidemiologic data that suggest that poor self-reported sleep quality is associated with elevations in CRP after controlling for potential confounding variables among men (Liukkonen et al., 2007). Difficulty falling asleep is also independently associated with higher CRP levels in mid-life adults (McDade et al., 2006). Finally, sleep

apnea is associated with elevations in cytokine levels, particularly CRP (Punjabi and Beamer, 2007), although the interrelationships among obesity, sleep apnea and CRP remain somewhat unclear (Sharma et al., 2008).

Recommendations: Self-reported sleep quantity and quality should be measured in studies of inflammatory markers. Given the association between sleep duration and insomnia and alterations of CRP, IL-6 and other inflammatory markers, it would be optimal to obtain assessment of sleep–wake activity by daily sleep diaries for one or more weeks. Finally, the robust effects of acute sleep loss on inflammatory markers would suggest that subjects who have experienced significant acute sleep loss (e.g., 3–4 h of sleep loss on the prior night) and those with primary sleep disorders be excluded from testing (Table 2).

3.11. Medication

Given the possible association between certain medication types (i.e., selective serotonin uptake inhibitors (SSRIs), aspirin and statins) with inflammation, and the prevalence of such medication use among populations commonly being studied by biobehavioral scientists (Stagnitti, 2005), consideration of the effects of these medication on markers of inflammation is provided in this review.

3.11.1. SSRIs

Depressive disorders are associated with an up-regulation in expression of proinflammatory markers (Irwin, 2002). However, the degree to which antidepressant medications, specifically SSRIs, modulate inflammatory responses is less clear, and no studies have examined the effects of SSRI use on proinflammatory cytokines independent of depression. SSRI treatment of patients with major depression for 6 weeks has shown a significant decrease in TNF-α and CRP (Tuglu et al., 2003) ($N = 43$), to levels found in healthy controls, and these changes paralleled self-reported decreases of depressive symptoms. Likewise, Basterzi and colleagues (2005) found that IL-6 levels were significantly lower after treatment in patients with major depression ($N = 23$) with replicated decreases in a larger sample ($N = 92$) for IL-6, and also IL-1β and TNF-α (Leo et al., 2006). The effect of SSRI treatment on inflammatory markers may be independent of changes in depressive symptom, as 8 weeks of fluoxetine treatment induced declines of IL-1β regardless of treatment response in a small sample ($N = 28$) (Lee et al., 2004). In a larger sample ($N = 115$), Maes et al. (1995) failed to observe changes in IL-6 or sIL-6R following a course of fluoxetine, despite a significant decrease in depressive symptoms. Similar negative results in small studies ($N < 50$) are found for IL-6 (Sluzewska et al., 1995; Tsao et al., 2006), TNF-α, IL-1β, and CRP (Hinze-Selch et al., 2000; Lee et al., 2004; Tsao et al., 2006) following SSRI treatment in depressed samples, although findings from these studies are constrained by the relatively short period of time in which SSRI therapy was administered (Hernández et al., 2008).

3.11.2. Aspirin

Aspirin has been studied with respect to inflammatory markers in healthy and chronic disease populations (primarily cardiovascular disease). A randomized crossover study in a healthy sample ($N = 37$) showed that treatment with aspirin (325 mg/day) did not affect CRP or IL-6 levels (Azar et al., 2003), consistent with placebo-controlled trials that showed no dose-dependent effects of aspirin on CRP levels (Feldman et al., 2001). In contrast to healthy samples, aspirin impacts levels of inflammatory markers among clinical populations. In cardiovascular disease, aspirin administration was found to induce reductions in CRP and IL-6 (Ikonomidis et al., 1999; Solheim et al., 2003), with sample sizes of 40 and 310, respectively.

3.11.3. Statins

Cholesterol-lowering medications, known as statins, consistently reduce CRP levels (Prasad, 2006). Most studies have been conducted in patients with cardiovascular disease. Randomized clinical trials (RCTs) in these populations show that statin use decreased CRP levels in a dose-dependent manner (Koh et al., 2004; Yu et al., 2007), with sample sizes of 32 and 112, respectively. However, some trials show no effect of statin treatment compared to placebo (Krum et al., 2007). Statins can also reduce CRP levels in healthy individuals, as demonstrated in a primary prevention RCT of lovastatin in over 5000 healthy individuals, which reduced CRP by 14.8% at one-year follow up (Ridker et al., 2001). No studies have explicitly studied the impact of long-term statin treatment on IL-6 and TNF-α levels in healthy adults.

3.11.4. Antihypertensive medications

Hypertension is common, affecting over 50% of individuals over the age of 55 (Fields et al., 2004). Approximately 63% of all hypertensive adults reported taking antihypertensive medication (Gu et al., 2006). The major classes of antihypertensive medications reviewed here are diuretics, angiotensin-converting enzyme (ACE) inhibitors and β-blockers (Gu et al., 2006). Most studies on antihypertensives and inflammatory markers enroll patients that have mild to moderate hypertension, and/or patients with existing chronic conditions (e.g., cardiovascular disease).

In a large cross-sectional study, individuals taking diuretics had similar multivariate adjusted CRP levels as individuals not taking diuretics (Palmas et al., 2007).

In both small and large observational studies, ACE inhibitor use is related to lower inflammatory marker levels (Di Napoli and Papa, 2003; Gage et al., 2004; Palmas et al., 2007). In cross-sectional studies, individuals taking β-blockers had lower CRP ($N = 2340$) (Palmas et al., 2007) and potentially lower IL-6 ($N = 118$) (Gage et al., 2004) compared to individuals not taking β-blockers.

Recommendations: Medication use (dosage, dosing frequency) should be thoroughly documented, possibly through chart review or by asking participants to bring in their medications; both are preferable to patient self-report that is less accurate. Medication logs that evaluate adherence may also be necessary for evaluating aspirin used primarily for symptomatic management of pain.

Given prevalence of use of aspirin and statin medication (particularly in older adults and chronic disease population), we do not recommend excluding participants who regularly use these medications unless there is specific, *a priori* reasons for doing so. This is in part because aspirin use has minimal effects on inflammatory markers in healthy samples. Nevertheless, among populations with chronic disease (i.e., cardiovascular disease), aspirin use should be statistically controlled. Because of the effect on CRP, studies using this outcome variable should control for statin and antihypertensive use. In contrast, use of SSRI medications should be recognized as a possible exclusion criterion, especially in comparison of healthy volunteers vs. psychiatric populations in which the study question is focused on inflammation in relation to psychiatric morbidity. However, given the relative paucity of data on the effects of SSRIs on inflammatory markers, an alternative strategy would be to control for such medication in the statistical analysis, recognizing that this would require a larger sample (Table 2).

4. Summary

Investigation of inflammatory biology is a rapidly growing area due to links with clinical disease endpoints (e.g., diabetes, CVD, cancer, etc.). Inflammatory processes are influenced by a number of biobehavioral factors, which if not considered in either screening or assessment, may confound associations with psychosocial

variables. One limitation of the currently available literature to review is that cytokines can also affect behavior and because the majority of studies reviewed were not experimental we cannot conclusively determine the directionality of the effects. However, in most cases, the most straightforward hypothesis is that the behavior influences the cytokines, rather than vice versa.

This manscript provides empirically based recommendations about key factors that should be assessed, controlled for, and in some cases, serve as exclusion criteria for research protocols that include inflammatory markers. These recommendations provide a framework for observational and intervention studies investigating linkages between psychosocial and behavioral factors and inflammation. Although this manuscript is intended primarily for investigators interested in these psychosocial-inflammation linkages, we end with a note for investigators studying the effects of demographic and other factors on the inflammatory system that may use this review to control for confounding factors. For those investigators outside the biobehavioral field, we highlight that it is also critical to control for exposure to stressful life events and depression since both are associated with increases in inflammatory markers (Segerstrom and Miller, 2004; Zorrilla et al., 2001).

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