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Socioeconomic Position and Inflammatory and Immune Biomarkers of Cardiovascular Disease: Applications to the Panel Study of Income Dynamics

ALLISON E. AIELLO AND GEORGE A. KAPLAN

Department of Epidemiology, Center for Social Epidemiology and Population Health, University of Michigan, School of Public Health, Ann Arbor, Michigan

Biomarkers are an important aspect of research linking psychosocial stress and health. This article aims to characterize the biological pathways that may mediate the relationship between socioeconomic position (SEP) and cardiovascular disease (CVD) and address opportunities for further research within the Panel Study of Income Dynamics (PSID), with a focus on psychosocial stressors related to SEP. We review the literature on CVD biomarkers, including adhesion and proinflammatory molecules (interleukin-6, other cytokines, C-reactive proteins, fibrinogen, etc.) and microbial pathogens. The impact of socioeconomic determinants and related psychosocial stressors on CVD biomarkers mediated by behavioral and central nervous system pathways are described. We also address measurement and feasibility issues, including specimen collection methods, processing and storage procedures, laboratory error, and within-person variability. In conclusion, we suggest that PSID consider adding important assessments of specific CVD biomarkers and mediating behavioral measures, health, and medications that will ultimately address many of the gaps in the literature regarding the relationship between SEP and cardiovascular health.

Introduction

Many have argued that joint biological and social data are needed for proper specification of the linkages among social environment, psychosocial stressors, and physical health (Seeman and Crimmins 2001; Kristenson, Eriksen, Sluiter et al. 2004). Identification and measurement of biomarkers has become a key component of much research in this field, particularly important to research linking psychosocial stressors and health. Within this context, this article aims to characterize the biological pathways that may mediate the relationship between socioeconomic position (SEP) and cardiovascular health and address opportunities for further research within the Panel Study of Income Dynamics (PSID), with a particular focus on psychosocial stressors related to SEP. We focus on psychosocial stressors related to socioeconomic position because that is the greatest area of strength for the PSID. We concentrate our analysis on cardiovascular disease (CVD) in light of its significant impact on public health worldwide. In terms of biomarkers, we focus primarily

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Address correspondence to Allison E. Aiello, PhD, 3659 SPH Tower, 1415 Washington Heights, Ann Arbor, MI 48104-2548. E-mail: aielloa@umich.edu

on those that may link exposure to low SEP and psychological stressors to cardiovascular health (i.e., immunological and thrombolytic rather than conventional biomarkers such as hypertension, dyslipidaemia and diabetes). We discuss issues related to the definition and measurement of stress and what is known regarding the pathophysiological relationships among these biomarkers. This allows for a more informed discussion of the utility of these markers for testing hypotheses of the relationship between stress and physical health. Identification of stress-mediated biological pathways may be important in targeting interventions and designing policies for improving cardiovascular health, but we emphasize that reducing sources of stress is probably more important. The overall purpose of this article is to ensure that hypothesized pathways are specified and properly supported by our current understanding of psychosocial and biological mechanisms, that measurement error is minimal, and that the right samples at the right time are collected and rigorously processed. Although there are many crucial ethical concerns regarding collection of biomarkers, they are substantive enough to warrant a separate, thorough examination and will not be discussed here.

Defining Stress

The study of stress and physical health must by necessity begin with a discussion of the various definitions of *stress*. The varied uses of the terms are reminiscent of both a speech by Humpty Dumpty in *Through the Looking Glass* and the story of the blind men and the elephant. "When I use a word," Humpty Dumpty said, in a rather scornful tone, "it means just what I choose it to mean, neither more nor less." and the blind men who, as you recall, have very different views of exactly what this thing called an *elephant* is. Generally speaking, there are three main ways in which the term stress is used: as a marker of events that are presumed to be stressful (stressors) and that require action or adaptation; as a marker of processes of appraisal of such events, often with an affective component; and as a physiological response to all of the above. Figure 1 (adapted from Cohen, Kessler et al. 1995) illustrates the interconnections between these three views of stress.

There are a number of issues that follow from the conceptualization shown in Figure 1 and that are relevant to the study of stress and health in the PSID. Stressors, and the consequent processes that follow, can be characterized as either acute or chronic. At first glance this seems a straightforward characterization, yet there is no clear demarcation between what constitutes an acute or chronic stressor. In addition, acute stressors can be one-time or recurrent events, with the latter sometimes indistinguishable from chronic events.

Since the work of Selye (and before), it has been observed that the events that follow a stressor are dynamic and potentially involve cognitive, emotional, behavioral, and physiological processes that are interconnected and occur over time. Though appraisal processes are emphasized in the psychological literature, the measurement of such processes, as opposed to their emotional sequelae, is difficult and without any gold standard (Cohen et al. 1995).

Stressors may have direct physiological, and perhaps behavioral, effects without the appraisal process and its affective component. Environmental stressors, for example, can have direct physiological consequences. Appraisal processes can be shaped by many factors including the current emotional state of the individual and the meaning they attach to stressors. The former can be assessed with a variety of instruments; the latter is more difficult to assess (Cohen et al. 1995).

Understanding the links between stress and health outcomes requires a clear understanding of the nature of each endpoint. Some outcomes such as self-rated health or

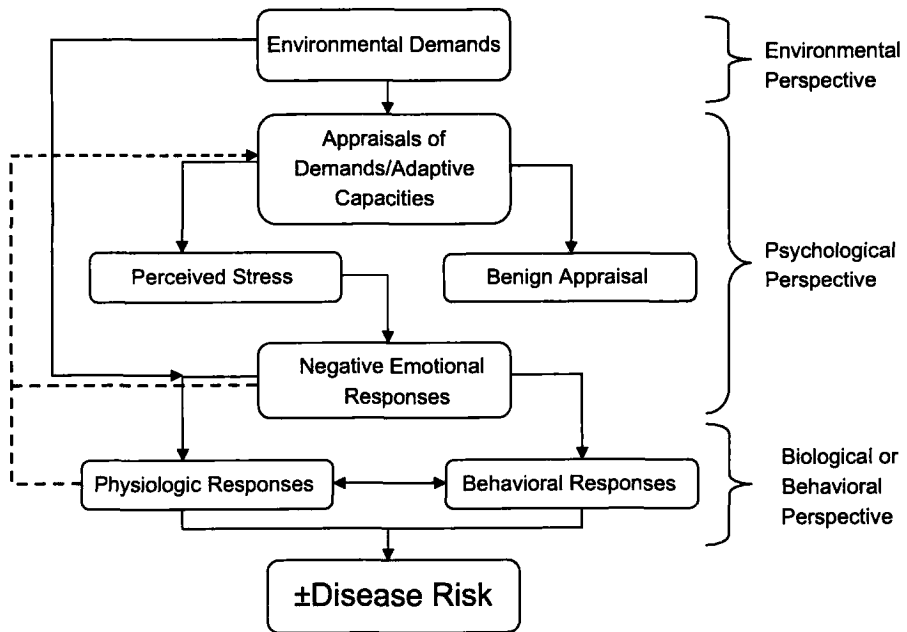


Figure 1. Three views of stress (Cohen et al. 1995).

depressive symptoms may be sensitive to short-term variations in stress (Cohen et al. 1995). However, for most chronic diseases the impact of stress must be understood within a framework that includes the factors associated with the initiation of the underlying physiologic processes, progression to clinically observable disease, self-treatment, access to and quality of care, transition to complications, etc., all of which generally occur over long periods of time.

PSID, SEP, and Pathways to Health

The PSID has extensive information on economic status and household composition. It currently collects very little data that are useful in characterizing stress appraisal processes or emotional states. Though the PSID might be able to implement collection of data on emotional well-being, it is questionable whether it could do so comprehensively enough to add to the existing literature on stress and health. The PSID is, however, extremely well-positioned to look at the impact of SEP and family composition, and changes/trajectories of both, on health outcomes. For these reasons, we believe that focusing on psychosocial stressors (stressful life events) related to specific measurements of SEP such as individual and household economic situation and changes in family composition provides the greatest potential for expansion in the PSID. Though there are many other stress-related areas of interest that would be useful to pursue, that is not where the comparative advantage of the PSID lies.

Importantly, the PSID has considerable strength in being able to distinguish between acute stressors such as economic shocks and chronic stressors associated with mid- and long-term economic position. The long time series of carefully collected socioeconomic data puts the PSID in a unique position to examine the relationship between acute and chronic

economic stressors, health outcomes, and the intervening biological pathways and their biomarkers. Many of the socioeconomic variables that have been examined in relation to biomarkers of CVD in other populations are available in the PSID (see Table 1). More recently, studies have begun to examine how socioeconomic trajectories within or across generations influence hemostatic and immune biomarkers of CVD, but the data are limited. For example, lower SEP over the life course was associated with increased fibrinogen in a large study of Finnish middle-aged men (T. W. Wilson, Kaplan et al. 1993). More recently, Tabassum, Kumari et al. (2008) showed that cumulative low social class from birth to midlife was associated with increased levels of fibrinogen and C-reactive protein (CRP) as an adult. The design of the PSID, with multiple survey follow-up and economic measures, represents an important resource for identifying how well-measured temporal changes in socioeconomic determinants influence these and other biomarkers of CVD.

Biomarkers of Cardiovascular Disease

CVD is a wide-ranging class of diseases, including coronary heart disease and atherosclerosis as well as less common manifestations such as endocarditis. Despite the large number of conditions that fall under this classification, all involve the cardiovascular system (i.e., heart and/or blood vessels) and have underlying similarities in causes and/or mechanisms. CVD is the leading cause of death in the United States (Anderson and Smith 2005). By the year 2020, CVD is expected to be the most prevalent, disabling disease across the globe (Lopez and Murray 1998). Given the extent of this disease and the breadth of information available on its biology, we have chosen CVD as our primary focus in demonstrating the link between socioeconomic position and physical health.

Cardiovascular disease is considered an immune-mediated condition with numerous hormonal, immunological, and metabolic alterations that influence the disease process. A main mechanistic feature of atherosclerosis is the deposition of lipids and other materials in the arterial wall, leading to plaque formation. Although the process is generally silent, it manifests clinically as plaque rupture and ensuing thrombosis, aneurysm, arterial stiffness, and reduced elasticity of blood vessels (Dotsenko, Chackathayil et al. 2008). Dysfunction of the endothelium leads to immunological alterations, including activation, adhesion, and aggregation of platelets to areas of damage (Dotsenko et al.). Platelets, in turn, release granulocytic contents, express cellular surface receptors, and produce procoagulant molecules. At the site of damage, cell adhesion molecules (e.g., intercellular adhesion molecule [ICAM], vascular cell adhesion molecule [VCAM], extracellular adhesion molecule [ECAM], etc.) and selectins (e.g., E, P, etc.) are produced (Tefamariam and DeFelice 2007; Dotsenko et al.). These adhesion molecules modulate circulating monocyte attraction where they become macrophages. A review by Dostenko et al. (2008) indicated that cholesterol is oxidized in the subendothelium. In its oxidized state, cholesterol becomes toxic and is therefore phagocytized by macrophages in the vessel wall. This process induces an inflammatory response through cytokines, including tumor necrosis factor (TNF)- α and interleukin (IL)-1. Chemokines and growth factors are also involved, including soluble CD40 ligand and platelet-derived growth factor, among others. The immune response results in continued activation and recruitment of macrophages and inflammatory proteins to the damage site. Importantly, some ruptured plaques never lead to thrombosis. Thus, other unspecified immune-mediated factors may ultimately be found to modulate the occurrence of clinical cardiovascular events (Dotsenko et al.).

Several proinflammatory molecules, including cytokines (e.g., IL-6, IL-1B, interferon [IFN]- γ , TNF- α , etc.), chemokines, and acute phase proteins have been implicated in CVD

Table 1
SEP and biomarkers related to CVD

Biomarker	Significantly associated SEP measure	References
CRP	Parental occupation status	(Tabassum et al. 2008)
	Occupation status	(Rosvall, Engstrom et al. 2007; Tabassum et al. 2008)
	Job loss/unemployment	(Arnetz, Brenner et al. 1991)
	Educational attainment	(Loucks et al. 2006; Muennig et al. 2007; Ranjit et al. 2007; Rosvall et al. 2007)
	Income	(Yarnell et al. 2005; Muennig et al. 2007; Ranjit et al. 2007)
Fibrinogen	Parental occupation status	(Pollitt et al. 2007)
	Occupation status	(Markowe et al. 1985; Steptoe et al. 2003a; Pollitt et al. 2007; Power, Atherton et al. 2007; Pollitt et al. 2008; Tabassum et al. 2008; Wilson et al. 1993)
	Job loss/unemployment	(Yarnell et al. 2005)
	Educational attainment	(Wilson et al. 1993; Yarnell et al. 2005; Pollitt et al. 2007, 2008)
	Area-level SES	(Pollitt et al. 2007, 2008)
	Income	(Wilson et al. 1993; Yarnell et al. 2005)
WBC	Occupation status	(Pollitt et al. 2008)
	Educational attainment	(Pollitt et al. 2008)
ICAM	Occupation attainment	(Hong, Nelesen et al. 2006)
	Educational attainment	(Hong et al. 2006; Loucks et al. 2006)
	Income	(Yarnell et al. 2005)
HbA1c	Parental occupation status	(Pollitt et al. 2007)
	Occupation status	(Power et al. 2007)
ET-1	Occupation status	(Hong et al. 2006)
	Educational attainment	(Hong et al. 2006)
IL-6	Occupation status	(Steptoe et al. 2002)
	Income	(Ranjit et al. 2007)
IL-1Ra	Occupation status	(Steptoe et al. 2002)
Factor VIII	Occupation status	(Steptoe et al. 2003b; Ramsay et al. 2008)
TNF- α	Occupation status	(Steptoe et al. 2002)
MCP-1	Educational attainment	(Loucks et al. 2006)
Cortisol	Job loss/unemployment	(Arnetz, Brenner et al. 1991)
PHA reactivity of lymphocytes	Job loss/unemployment	(Arnetz et al. 1991)
Prolactin	Job loss/unemployment	(Arnetz et al. 1991)

Notes: CRP = C-reactive protein; WBC = white blood cells; ICAM = soluble intercellular adhesion molecule; HbA1c = glycosylated hemoglobin; ET-1 = endothelin-1; IL-6 = interleukin-6; IL-1Ra = interleukin-1 receptor antagonist; TNF- α = tumor necrosis factor- α ; MCP-1 = monocyte chemoattractant protein-1; PHA = phytohemagglutinin. Results shown for any significant results; no distinctions were made for race, gender, or other stratification variables. Fully adjusted models were used when available; unadjusted shown otherwise.

(Kuller, Tracy et al. 1996; Ridker, Cushman et al. 1997; Danesh, Collins et al. 1998; Hak, Stehouwer et al. 1999; Koenig, Sund et al. 1999; Ross 1999; Zhang, Cliff et al. 1999; Danesh, Whincup et al. 2000; Ford and Giles 2000; Rader 2000; Ridker, Hennekens et al. 2000; Ridker, Rifai et al. 2000; Torzewski, Rist et al. 2000; Libby 2001). Cytokines and acute phase proteins act as regulators of the immunological response to infection, injury, and repair (Kuby 1997). There are multiple functional characteristics of cytokines, including pleiotropy, redundancy, synergy, and/or antagonism, and the relationship among these markers is complex (Kuby). IL-6 is generally considered a proinflammatory cytokine and plays a direct role in the initiation of other inflammatory factors' synthesis, such as CRP and fibrinogen. Both IL-6 and CRP have been shown to predict cardiovascular disease among generally healthy individuals in population-based studies (P. W. Wilson 2004). CRP is synthesized in the liver as an immunological endpoint in the classical complement pathway for responding to infection and injury. CRP primarily appears to take part in the earlier stages of atherosclerosis in the inflammatory response of the vascular epithelium. (Vallance, Collier et al. 1997; Fichtlscherer, Rosenberger et al. 2000) It has also been shown to amplify inflammation by inducing monocyte activation (Cermak, Key et al. 1993; Torzewski et al.) and leukocyte recruitment to the endothelial layer via synthesis of adhesion molecules (Pasceri, Willerson et al. 2000). Furthermore, CRP is involved in the formation of fatty streaks and plaque in the arterial wall (Ross; Zhang et al.; Torzewski et al.). Nevertheless, there is still debate as to the specific role that CRP plays in CVD pathophysiology. It is possible that higher CRP may be a marker for instability and rupture of preexisting atherosclerotic plaques rather than an inducer of pathology (Casas, Shah et al. 2008). Another inflammatory mediator is serum amyloid A (SAA), an apolipoprotein molecule. Like CRP, SAA is an important component of the acute phase inflammatory response and is produced in the liver upon infection, injury, and immune insults. In regards to CVD pathways, SAA is secreted from high-density lipoproteins (HDL), replaces apolipoprotein A (apoA) on cholesterol particles, and modifies cholesterol delivery to cells (Johnson, Kip et al. 2004). SAA has been shown to be an independent predictor of future cardiovascular risk among diseased and nondiseased subjects, but results are mixed (Ridker, Hennekens et al.; Johnson et al.; P. W. Wilson).

Fibrinogen is considered an inflammatory marker of thrombogenesis. It acts as a signal for expression of cytokines and stimulates smooth muscle proliferation/migration and platelet aggregation (Folsom, Wu et al. 1997). Fibrinogen contributes to thickness and clotting of blood and has been recognized as an essential molecule in thrombolytic events triggering myocardial infarction and stroke (Wilhelmsen, Svardsudd et al. 1984). It has also been identified as a factor involved in plaque formation (Folsom et al.). Other important blood markers that are generally not considered under the immune and inflammatory category include oxidized low-density lipoprotein (OxLDL), apolipoproteins A and B, and reactive oxygen species. LDL is a major cholesterol carrier in human plasma and, like CRP, it is produced in the liver. ApoA, on the other hand, is present on HDL and has anti-atherogenic properties, including removal of arterial cholesterol (Chiesa and Sirtori 2003). Cellular exposure to oxidative stress causes oxidation of LDL into OxLDL (Itabe 2003, 2008). OxLDL is a well-studied risk factor for CVD and has been identified in atherosclerotic plaques (Holvoet, Lee et al. 2008). After stimulation by OxLDL, endothelial cells in the cardiovascular system begin to produce chemoattractants, which guide monocytes to the intima. Macrophages then bind to and uptake OxLDL. Upon uptake, macrophages develop into foam cells, catalyzing the process of intima thickening (Itabe 2003). Reactive oxygen species can be organic or inorganic molecules, including oxygen ions, peroxides, and free radicals, such as superoxides, and their production from endothelial cells is

induced by cytokines such as TNF- α , IL-1, and IL-6 (Tolando, Jovanovic et al. 2000). To our knowledge, the relationship between SEP and markers such as apoA, apoB, oxLDL, and reactive oxygen species has not been well explored.

In addition to the markers mentioned above, several microbial pathogens have been linked to cardiovascular disease in animal models and human epidemiological studies (Zhu, Quyyumi et al. 2000; Epstein 2002). The implicated infectious agents include cytomegalovirus (CMV), herpes simplex virus-1 (HSV-1), *Helicobacter pylori* (*H. pylori*) and *Chlamydia pneumoniae* (*C. pneumoniae*), but relationships have not always been consistent (Zhu et al. 2000; Epstein). Animal models have shown that persistent pathogens may cause direct or secondary pathological damage to cardiovascular tissue by acting as proinflammatory stimuli, resulting in endothelial tissue damage (Muhlestein, Anderson et al. 1998; Takaoka, Campbell et al. 2008). Although conclusions regarding the association between individual pathogens and cardiovascular disease in human populations have been conflicting, recent studies have more consistently identified associations between multiple persistent pathogens and cardiovascular disease processes (Zhu, Nieto et al. 2001; Georges, Rupprecht et al. 2003). The hypothesized mechanisms by which infection with multiple pathogens may contribute to cardiovascular disease include induction of a systemic proinflammatory cytokines and CRP or potential direct pathophysiological damage to cardiovascular tissue (Epstein).

Many of the biomarkers that are involved in or produced by atherosclerotic processes are listed in Table 2. We also present a description of the biological materials and methods that are required for their collection and laboratory analysis. In terms of intervention targets, the most useful biomarkers are those that occur at the earliest periods during the development of cardiovascular disease. Mechanistic research that maps out the temporal aspects and pathways involved in these physiological analytes is needed. For example, glucocorticoids stimulate production of IL-6, and IL-6 in turn induces CRP synthesis in the liver (Pradhan, Manson et al. 2001). Therefore, when interpreting the relationship between SEP and biomarkers it is also important to consider how the biomarkers relate to one another. Such endeavors would help better specify the kinds of pathways that are most pertinent to a particular socioeconomic measure and physiological response related to cardiovascular disease manifestation and clarify the reasons for observed association with increased CVD risk.

The majority of the biomarkers of atherosclerosis shown in Table 2 can be assayed in serum and therefore require a venipuncture. Some, such as CRP and antibodies to infection (HSV and CMV), now have standardized methodologies for assessment in minimally invasive blood spots (McDade, Williams et al. 2007). Other markers, however, require whole blood (e.g., IL-6, TNF- α). For many of the markers laboratory assays are standardized, relatively simple, low cost, and commercially available. It is important to note that most of the assay techniques include enzyme-linked immunosorbent assay (ELISA), which is a simple and standard method for analyzing blood specimens and spots. Further discussion regarding sample collection and analysis are found in section 4.

Pathways between SEP and Biomarkers of CVD

Kaplan and Keil (1993) summarized the available data on the association between various measures of socioeconomic position and a variety of CVD endpoints. In addition to strong relationships, they found that most risk factors for CVD were inversely related to income, education, and other markers of SEP. Since then the list of SEP measures that are associated with increased CVD risk has grown. For example, investigators have observed that childhood socioeconomic circumstances are related to adult CVD (Galobardes, Smith et al.

Table 2
Biomarkers of atherosclerotic plaque formation and progression

Process	Biomarker	Material tested	How sample analyzed	Reference
Inflammation	OxLDL	Serum	ELISA	(Miller et al. 2005; Huang, Mai et al. 2008)
	apoA, apoB	Serum	ELISA, immunoturbidimetry, nephelometry	(Cerne, Ledinski et al. 2000; Ashavaid, Kondkar et al. 2005)
	CRP*	Serum	ELISA, immunoturbidimetry, nephelometry	(Sisman, Kume et al. 2007; Gori, Cesari et al. 2008; Wettero, Nilsson et al. 2008)
	Cytokines (IL-6*, IL-1B, -10, TNF- α)	Serum, PBMCs	ELISA, flow cytometry	(Napoleao, Santos et al. 2007; Profumo, Buttari et al. 2008; Souza, Oliveira et al. 2008)
	sCD40L	Serum	ELISA	(Napoleao et al. 2007)
	Chemokines (MCP-1, IL-8) and their receptors	Serum	ELISA, lateral flow immunoassay	(Kim, Park et al. 2006)
	Serum amyloid A	Serum	Nephelometry, ELISA	(Rifai, Joubran et al. 1999; Johnson et al. 2004)
	PECAM-1	Serum	Flow cytometry	(Bernal-Mizrachi, Jy et al. 2003; Pirro, Schillaci et al. 2006)
Thrombogenesis/lysis	Adiponectin	Serum	ELISA, radioimmunoassay	(Cheng, Hashmi et al. 2008)
	Cell adhesion molecules (E-selectin, ICAM-1, VCAM-1, P-selectin, L-selectins)	Leukocytes, serum	FACS analysis, ELISA	(Glowinska, Urban et al. 2005; Napoleao et al. 2007; O'Brien, Ling et al. 2008)
	Fibrinogen	Serum (plasma)	Fibrinogen analysis (coagulation analysis)	(Green, Foiles et al. 2008)
	sCD40L	Serum	ELISA	(Napoleao et al. 2007)
	Lp(a)	Serum (plasma)	ELISA	(Ranga, Kalra et al. 2007)

(Continued)

Table 2
(Continued)

Process	Biomarker	Material tested	How sample analyzed	Reference
Endothelial dysfunction/ damage	LDL, OxLDL	Serum	Homogeneous LDL assay, ELISA	(Nauck, Graziani et al. 2000; Miller et al. 2005a; Koba, Hirano et al. 2006)
	Cell adhesion molecules	Leukocytes, serum	FACS analysis, ELISA	(Glowinska et al. 2005; Napoleao et al. 2007; O'Brien et al. 2008)
	ROS	Monocytes and Granulocytes	Flow cytometry, chemiluminescence	(Eid, Lyberg et al. 2002)
	Microbe antigens: HSV,* CMV*	Serum	Microimmunofluorescence, ELISA	(Schumacher, Seljeflot et al. 2005)
Oxidative stress	Inflammatory cytokines (IL-6*, IL-18, CRP*)	Serum	ELISA, flow cytometry	(Souza et al. 2008)
	OxLDL	Serum	ELISA	(Miller et al. 2005a)
	ROS	Monocytes and granulocytes	Flow cytometry, chemiluminescence	(Eid et al. 2002)

Notes: OxLDL = oxidized low-density lipoprotein; ELISA = Enzyme-linked immunosorbent assay; apoA = apolipoprotein A; apoB = apolipoprotein B; CRP = C-reactive protein; IL-1B, -6, -8, -10, -18 = interleukin-1B, -6, -8, -10, -18; TNF- α = tumor necrosis factor- α ; PBMCs = peripheral blood mononuclear cells; sCD40L = soluble CD40 ligand; MCP-1 = monocyte chemoattractant protein-1; PECAM-1 = platelet-endothelial cell adhesion molecule 1; ICAM-1 = intercellular adhesion molecule 1; VCAM-1 = vascular cell adhesion molecule 1; FACS = fluorescence-activated cell sorting; Lp(a) = lipoprotein (a); LDL = low-density lipoprotein; ROS = reactive oxygen species; HSV = herpes simplex virus; CMV = cytomegalovirus. *Can be assessed by blood spot techniques.

2006), as is socioeconomic disadvantage over the life course (Wamala, Lynch et al. 2001). In addition, we now know that job loss, a major economic shock, is associated with increased CVD risk (Gallo, Teng et al. 2006), as is living in a poor neighborhood (Diez Roux, Merkin et al. 2001).

Socioeconomic position may influence cardiovascular health through several pathways, including behaviors and psychosocial stress levels, both of which may influence biological markers of inflammation, coagulation, and adhesion. Alterations in these biomarkers may be a consequence of hormonal and metabolic dysregulation resulting from changes in stress-related behaviors or direct effects of stress exposures on the central nervous system (CNS), hypothalamic-pituitary-adrenal axis (HPA) and sympathetic nervous system (SNS) activity (see Figure 2). There are also other important biological pathways between SEP and CVD not shown in Figure 2, including increases in cholesterol and hypertension. Comprehensive reviews on the relationship between SEP and hypertension have been published previously (Pickering 1999; Grotto, Huerta et al. 2008).

Socioeconomic Position and Biomarkers Related to CVD

There is accumulating evidence supporting a relationship between socioeconomic position and inflammatory, coagulation, adhesion, and other immune biomarkers of CVD (see Table 2). Chronic and systemic inflammatory upregulation has been shown to play a central role in atherosclerosis. There is strong evidence that individuals living in poverty have higher CRP levels, even after controlling for numerous potential confounding factors, such as age and gender and current health status (Alley, Seeman et al. 2005; Nazmi and Victora 2007). A comprehensive review of 32 studies examining the relationship between SEP and CRP reported that the majority identified an inverse association between CRP levels and SEP (Nazmi and Victora). Several of the studies reviewed were population-based studies and were mainly conducted in high-income countries. Of note, there was great variability in covariate adjustment across the studies (Nazmi and Victora). Indeed, some of the studies did not adjust for other factors at all and several adjusted for potential mediators such as BMI and smoking (Nazmi and Victora). Even after adjustment for mediators (potentially overadjusting), the relationship between SEP and CRP remained in

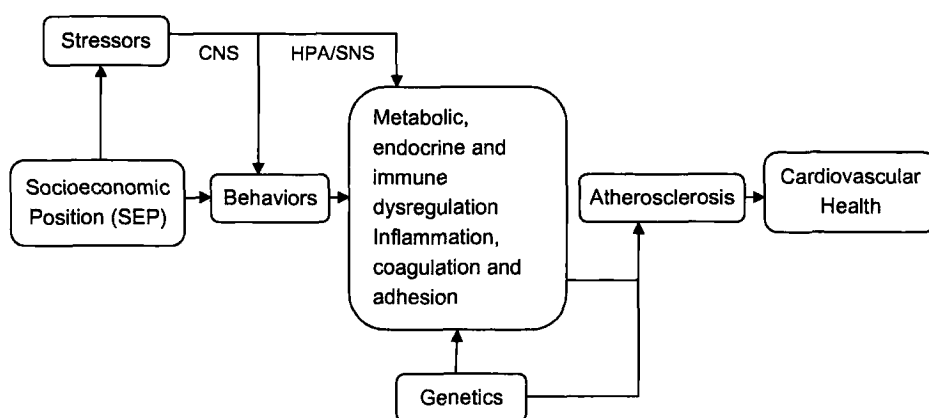


Figure 2. Pathways between SEP, biomarkers, atherosclerosis and cardiovascular health. CNS = central nervous system, HPA = hypothalamic-pituitary-adrenal axis, SNS = sympathetic nervous system.

a number of studies, suggesting that other pathways, possibly through psychosocial stress effects on immune function, may influence CRP levels.

Elevated levels of inflammatory markers have been associated with low SEP at multiple life stages, suggesting that life course SEP exposures may lead to chronic long-term changes in inflammatory biomarker levels. For example, lifetime exposure to low education and social class has been shown to be significantly associated with elevated levels of CRP and higher white blood cell counts (Pollitt, Kaufman et al. 2008). More recently, a study by Janicki-Deverts, Cohen et al. (2008) showed that having a history of unemployment at year 10 of their study was associated with higher CRP levels at year 15, adjusting for age, race, body mass index (BMI), year-7 CRP levels, year-15 unemployment, and average income across years 10–15. A few studies suggested that low adult SEP is more strongly correlated to high CRP than childhood SEP (Pollitt, Kaufman et al. 2007; Pollitt et al. 2008). Elevated CRP has been linked to several SEP markers, including lower adult occupational status, lower educational attainment, receipt of welfare (Nazmi and Victora 2007), and lower income levels (Table 1; Loucks, Sullivan et al. 2006; Muennig, Sohler et al. 2007; Nazmi and Victora 2007; Pollitt et al. 2007; Tabassum, Kumari et al. 2008). Occupation and education levels have also been associated with a number of other inflammatory biomarkers, including cytokines such as TNF- α , IL-1R α , and IL-6 (Steptoe, Owen et al. 2002; Ranjit, Diez-Roux et al. 2007). However, the behavioral, stress-related, and biological mechanisms by which SEP may lead to increases in CRP and cytokines has been less well studied. Therefore, the likely contribution of behaviors, diet, obesity, or stress as mediating factors is still unclear. Moreover, the behaviors and health factors accounted for in many of the available studies shown in Table 1 vary widely. In addition, few have controlled for factors that could alter immunity and may be differential by SEP, such as medication use and autoimmune conditions.

Several studies also supported a relationship between SEP, fibrinogen, and adhesion molecules. One of the first studies to examine the relationship between life course SEP and fibrinogen was conducted in Finland among middle-aged men (T. W. Wilson et al. 1993) After adjusting for alcohol consumption, BMI, physical fitness, smoking, coffee consumption, HDL cholesterol, LDL cholesterol, blood leukocyte count, and prevalent disease (at least one sign of ischemic heart disease, hypertension, diabetes, or previous stroke), there was a persistent association between low education, low current income, or lifetime occupation and increased fibrinogen (T. W. Wilson et al.). Given that many of these factors are mediators, these data suggest that life course SEP may influence fibrinogen through other pathways. Analysis of the joint effect of childhood and adult socioeconomic status indicated that those who were economically disadvantaged at both times had the highest fibrinogen levels, but the fibrinogen levels of those who were not poor as adults had no variation by childhood socioeconomic status (Wilson et al.). In a more recent study of more than 10,000 men aged 50–59 years who were initially free of coronary heart disease (CHD), low SEP was associated with significantly higher fibrinogen levels (Yarnell, Yu et al. 2005); this relationship held whether SEP was measured in terms of years of education or employment level. Similarly, a study of 639 men ages 50 and older showed that, among nonsmokers, there was a significant, inverse relationship between occupational class and fibrinogen level, with those in the highest class showing the lowest levels (Rosengren, Wilhelmsen et al. 1990). In addition to SEP-based studies, some studies have documented a relationship between stress and fibrinogen levels, with increasing job stress levels associated with increasing fibrinogen concentrations in men (Markowe, Marmot et al. 1985; Steptoe, Kunz-Ebrecht et al. 2003a).

In contrast to the results available for adults, data collected from children and adolescents show no association between SEP and fibrinogen levels. In one study of children ages 10–11 years in the UK, fibrinogen was shown to be unrelated to the participants' towns or to the occupational social classes of the participants' parents (Cook, Whincup et al. 1999). Similarly, lower parental education was not associated with higher fibrinogen levels when measured among 887 adolescents in the United States (Goodman, McEwen et al. 2005). These data suggest that differences in fibrinogen by SEP may be difficult to detect in younger cohorts or that these disparities do not manifest themselves until older ages.

In addition to inflammatory and thrombolytic markers discussed above, recent data suggest that there are strong socioeconomic differentials in pathogens that have been implicated in cardiovascular disease (Dowd, Haan et al. 2008; Dowd, Aiello et al. 2009; Simanek, Dowd, and Aiello 2009; Zajacova, Dowd et al. In press; Aiello, Diez-Roux, Noone, Ranjit, Cushman, Tsai, and Szklo Under review). The primary hypothesized mechanism is that the implicated pathogens may also influence inflammatory biomarkers of CVD. Some studies have investigated socioeconomic differences in infections with individual pathogens that have been implicated in cardiovascular disease (Xu, Schillinger et al. 2002; Schillinger, Xu et al. 2004; Staras, Dollard et al. 2006; Dowd et al. 2009), but fewer studies have examined differences in cumulative pathogen burden by SEP. Recent work has shown that increased pathogen burden, including HSV-1, CMV, hepatitis B virus, and *H. pylori*, was significantly associated with lower income and education in a U.S. nationally representative study (Zajacova et al.). An earlier study from the UK reported that employment grade was related to pathogen burden (sum of seropositive status to CMV, HSV-1, and *C. pneumoniae*) (Steptoe, Shamaei-Tousi et al. 2007). Examining the role of psychosocial stressors as a mediator of the impact of SEP on infection is also important, given the observed associations of chronic stressors with susceptibility to novel infections and reactivation of persistent pathogens such as CMV and HSV (Glaser, Kiecolt-Glaser et al. 1985; Cohen, Frank et al. 1998; Stowe, Mehta et al. 2001). More recently, Simanek et al. (2009) reported that CMV infection partially mediates the relationship between SEP and cardiovascular disease history in a large U.S. representative population. Together, these studies suggested that persistent pathogens may reside on the pathway between SEP and cardiovascular health.

Psychosocial Stress and Biomarkers of CVD

Various measures of psychosocial stress, often associated with lower SEP, have been shown to be significantly correlated with increases in systemic inflammatory markers associated with cardiovascular disease, including CRP, IL-6, and TNF- α (Appels, Bar et al. 2000; Glaser, Robles et al. 2003; Kiecolt-Glaser, Preacher et al. 2003; Graham, Robles et al. 2005; Kiecolt-Glaser, Loving et al. 2005; Miller, Freedland et al. 2005a, 2005b). In a population of elderly individuals, chronic stress related to caregiving for a spouse with dementia was significantly predictive of a four times faster rate of IL-6 increase over a 6-year period compared to noncaregivers (Kiecolt-Glaser et al. 2003). Other studies have demonstrated a relationship between chronic stress, glucocorticoid production, cytokines, and various measures of cellular immune function (Herbert and Cohen 1993b; Pariante, Carpiniello et al. 1997; Vedhara, Cox et al. 1999). The reported associations between various psychosocial stressors and inflammatory biomarkers of CVD have not always been consistent. It is likely that the relationship varies with types of stressors (e.g., acute vs. chronic) and across demographic characteristics. Moreover,

measurement and adjustment for potential confounders and mediators often vary across studies making it difficult to synthesize findings (Di Napoli, Schwaninger et al. 2005).

Central Nervous System

Socioeconomic conditions contribute to levels of chronic and acute stressors. Factors that are likely to increase psychosocial stress levels include exposure to adverse social environments; discrimination and structural disadvantage, such as crowding, neighborhood crime, pollution; and exposure to institutionalized racism (Baum, Garofalo et al. 1999). The notion that exposure to psychosocial stressors is linked with morbidity and mortality has been recognized throughout history (Sternberg 1997). There is considerable evidence showing a link between stressors and psychopathology, hormonal alterations, and immunological functioning (Herbert and Cohen 1993a, 1993b). Pathways that may link psychosocial stressors and alterations in hormonal biomarkers include activation of HPA and SNS via CNS responses to stress exposures (Herbert and Cohen 1993a, 1993b). Activation of HPA and SNS modulates the release of hormonal biomarkers such as cortisol, epinephrine, and norepinephrine, which are important mediators of an immune response (Herbert and Cohen 1993a, 1993b). Sustained cortisol response can lead to increases in risk factors for CVD such as insulin resistance, obesity, increased lipid accumulation, coagulation, and hypertension (Girod and Brotman 2004). Changes in levels of cortisol may also directly influence immune function leading to alterations in cellular processes and the regulation of cytokine production, including IL-6, TNF- α , and IFN- γ , which have important mediating effects on cardiovascular health (Vedhara, Fox et al. 1999; Glaser and Kiecolt-Glaser 2005; Soderberg-Naucler 2006). The biological relationship between CNS and the immune system most likely consists of a bidirectional feedback mechanism producing interactions between endocrine hormones, cytokines, and other immunotransmitters (Glaser and Kiecolt-Glaser). Although chronically elevated cortisol is one commonly suggested mechanism through which low SEP may affect health, the findings regarding this relationship have been inconsistent (Brandtstadter, Baltes-Gotz et al. 1991; Owen, Poulton et al. 2003; Strike and Steptoe 2004; Ranjit, Young et al. 2005; Dowd and Goldman 2006; Doyle, Gentile et al. 2006). A major hurdle associated with cortisol assessment in population-based samples is measurement error. Human cortisol follows a circadian rhythm resulting in substantial within-individual variations, requiring multiple sample compliance throughout the day for valid assessments (Young, Abelson et al. 2004; Adam, Hawkley et al. 2006; Levine, Zagoory-Sharon et al. 2007). In addition to cortisol, researchers have begun to explore assessment of immune and inflammatory biomarkers that may lie within the pathway between SEP and cardiovascular disease (see Table 1).

Behavioral Pathways

SEP has been shown to be associated with lower levels of physical activity, poorer diets, alcohol use, and obesity (Baltrus, Lynch et al. 2005). In turn, these behavioral factors may lead to increased risk for metabolic conditions, poorer immune functioning, and higher levels of peripheral inflammatory markers related to cardiovascular disease, including CRP, IL-6, and others. Studies have also shown that the relationship between SEP and behaviors may be mediated by exposure to psychosocial stressors. Indeed, individuals exposed to psychosocial stressors are also more likely to demonstrate behavioral risk factors for cardiovascular disease, including smoking, lack of exercise, poor diets, obesity, and alcohol abuse (Kiecolt-Glaser, McGuire et al. 2002; Cohen 2005). For example,

adverse social environment, low educational level, and unemployment are significantly associated with adult alcohol abuse and smoking (Kestila, Koskinen et al. 2006; Kestila, Martelin et al. 2008). Smoking has been widely cited as a risk factor involved in cardiovascular diseases (Hae Guen, Eung Ju et al. 2008; Rudolph, Rudolph et al. 2008). The pathway through which smoking may affect cardiovascular health likely involves the cholinergic system, initiation of oxidative stress, and inflammation (Park, Lee et al. 2007; Huang, Okuka et al. 2008; Rudolph et al. 2008). Smoking also increases CVD-related coagulation factors such as fibrinogen (Folsom, Wu et al. 2000) and inflammatory markers including CRP (Mendall, Patel et al. 1996).

Obesity is a major predictor of elevated levels of CRP (Hak et al. 1999; Visser, Bouter et al. 1999; Yudkin, Stehouwer et al. 1999; Tracy 2001) and many inflammatory cytokines (Cacciari 1988; Ferguson, Gutin et al. 1998; Shea, Isasi et al. 1999). Adipose tissue contributes to the synthesis of IL-6 and adipokines (Mohamed-Ali, Goodrick et al. 1997; Bastard, Jardel et al. 1999). Epidemiological evidence supports the assertion that physical activity is inversely and strongly associated with CVD, possibly through its effects on reduction in adiposity among other mechanisms (Blair, Kampert et al. 1996; Manson, Hu et al. 1999; Myers, Prakash et al. 2002; Kokkinos 2008; Kokkinos, Myers et al. 2008). Although the cellular and molecular mechanisms by which exercise can improve CVD-related outcomes are not currently well understood, physical activity may promote CVD-protective events such as increased antioxidant defenses and nitric oxide (NO) bioactivity, reduced oxidative stress, and reduction of free radicals (Leaf, Kleinman et al. 1999; Leeuwenburgh and Heinecke 2001; Steinberg and Witztum 2002; de Nigris, Lerman et al. 2003; Napoli, Williams-Ignarro et al. 2004; Ignarro, Balestrieri et al. 2007). With respect to diet, individuals who eat high-fat diets are at increased risk of CVD (Yu-Poth, Zhao et al. 1999); conversely, individuals with diets high in fruits and vegetables often have a lower prevalence of CVD risk factors such as hypertension, obesity, and type 2 diabetes (Ignarro et al.). As with physical activity, the biologic mechanisms by which diets high in fruits and vegetables exert their protective effects are not currently well understood; nutrients and phytochemicals in these items, such as fiber, potassium, and folate, may contribute both independently and jointly to a reduced risk of CVD (Bazzano, Serdula et al. 2003; Houston 2005).

Measurement/Feasibility Issues

Measurement and feasibility are major concerns in studies of biomarkers in population-based samples. There are a number of factors that can influence validation and this area has been reviewed by others (Tworoger and Hankinson 2006). There are four common sources of measurement error that should be considered when examining biomarkers in population-based studies: biological specimen collection methods; processing and storage procedures; laboratory error (i.e., intra-assay and inter-assay variability); and within-person variability over time (Tworoger and Hankinson).

Biological specimen collection, or sample collection, involves a number of considerations that can impact measurement error. Although many types of specimens are theoretically available for collection from willing participants, including white or red blood cells, tissue biopsies, and saliva, it is critically important to choose the type of sample based first upon hypotheses of interest and second upon the feasibility and ease of collection (Tworoger and Hankinson 2006). Regarding the latter, sample collection for a particular biomarker can in some instances be completed by study participants without assistance, including saliva or urine. In these cases, the cost of the sample collection may be low but

may be counterbalanced by a higher level of error because the collection protocol would be implemented by many, perhaps even thousands of, individuals rather than one or a few trained clinical research assistants. Regarding the former, the biomarker under consideration should be selected in consultation with the laboratory staff to determine which type of sample is best suited to the biomarker assay of interest, as well as the appropriate method to process and store the sample. For example, if an investigator is interested in collecting blood specimens in order to test cytokine levels via ELISA, it is important to determine the time period within which samples need to be processed in order to retain their integrity, as well as the type of anticoagulant to use, because both of these factors have been shown to impact assay results (Flower, Ahuja et al. 2000). Sample collection and storage issues become increasingly complex in research involving multiple biomarkers, which may require that different types of samples be collected under different conditions. In these cases, extensive pilot studies that assess collection feasibility can help to reduce measurement error (Tworoger and Hankinson). Inflammatory and infectious markers such as CRP, IL-6, and herpesvirus immunoglobulin G (IgG) antibody levels have been shown to be relatively stable over repeat measures and in frozen serum (Zweerink and Stanton 1981; Rao, Pieper et al. 1994; Macy, Hayes et al. 1997; Breen, McDonald et al. 2000; McDade, Stallings et al. 2000; McEwen 2000; Ockene, Matthews et al. 2001; Aziz, Fahey et al. 2003; Kvarnstrom, Karlsten et al. 2004; Rosa-Fraile, Sampedro et al. 2004).

For some biomarkers, there may be multiple types of biological samples that can be used to assess circulating marker levels. For example, cortisol can be assayed from saliva, plasma, and urine. Although there have been strong associations between levels of plasma-free cortisol and salivary samples (Kirschbaum and Hellhammer 1994; Levine et al. 2007), the correlations between salivary and urinary levels are inconsistent (Yehuda, Halligan et al. 2003). This may also be an issue for other biomarkers such as cytokines that can be measured in plasma and serum (Kropf, Schurek et al. 1997; Jankowiak, Zamzow et al. 1998). Thus, correspondence between biological samples is an important consideration when comparing results across or within studies.

Laboratory error represents an additional important source of variation that can contribute to measurement error. Intra-assay variability is an inherent component of most biomarker assays, such that replicates of the same specimen will always yield a distribution of results, rather than a single, repeated value (Tworoger and Hankinson 2006). In contrast, inter-assay variability occurs when conducting a separate run or batch of an assay contributes an additional amount of variation to the value being measured. Both inter- and intra-assay variability can lead to a bias in effect estimates toward the null and reductions in statistical power (Vineis 1997). Technological improvements can mitigate some of these problems, producing greater accuracy and precision in both intra- and inter-assay testing; for example, in a multicenter study of cytokine levels in serum and other fluids, a recently developed electrochemiluminescence-based assay showed low inter-laboratory and intra-assay variation and was among the most discriminative of all the seven platforms that were tested in the study (Fichorova, Richardson-Harman et al. 2008). In addition, running the assay in duplicate or more, using the same technician, conditions, and techniques, as well as increasing the sample size, can also minimize bias. The inclusion of quality control samples provides a further opportunity to assess assay variability, both within and between runs (Tworoger and Hankinson).

Biological variation in biomarkers within an individual over time represents a third important source of variation that can contribute to measurement error in biomarker-based studies. In this case, a single measurement of the biomarker within an individual may fail to accurately depict that individual's long-term exposure to a particular disease or

condition. An important example is cortisol. There is large diurnal variability in cortisol secretion and significant within-person variation in the diurnal pattern. Thus, rather than collecting data on cortisol at a single time point, some have employed collection of repeated saliva measurements over one or more days (Hruschka, Kohrt et al. 2005; Adam et al. 2006; Hellhammer, Fries et al. 2007; Levine et al. 2007). Importantly, CRP and inflammatory cytokines such as IL-6, are more stable throughout the day. Nevertheless, acute infections, autoimmune condition, and other serious conditions can lead to fluctuation of these markers (de Maat, de Bart et al. 1996; Breen et al. 2000; McDade, Burhop et al. 2004; Wong, Freiberg et al. 2008).

Multiple measurements over time can also assist in detecting significant effects that may otherwise be missed even with accurate, single time point measurements. For example, initial responses to experimentally induced psychological stress was shown to be similar among low-, medium-, and high-SEP participants, as measured by Factor VIII, plasma viscosity, and blood viscosity levels; however, 45 minutes after the stressor was applied, these markers remained more elevated in lower SEP participants (Stephoe, Kunz-Ebrecht et al. 2003a). This finding is significant in that, over many years of differential stress exposure, these small but detectable differences in the duration of activation of procoagulant pathways could translate into increased cardiovascular disease risk among low-SES individuals (Stephoe and Marmot 2002). Without multiple measurements of these biomarkers over even a relatively short period of time, these significant differences may have been missed.

Acute bacterial or viral infections, recent injury, autoimmune disease, chronic health conditions, and medication use may influence results from biological sample testing. To assess the effects of these factors on biological markers of interest, it is important to obtain a medical history and record concurrent medication data from the time of biological sample collection. Trained interviewers should inspect all prescription and over-the-counter medications and identify and code them according to standard drug data base systems. A list showing some examples of medications that may be associated with variability in cellular and inflammatory markers of interest is presented in Table 3. This table displays some of the major classes of drugs that (a) may be associated with treatment of acute infection or (b) have been associated with minimal to profound effects on immune functioning and inflammatory parameters (Basterzi, Aydemir et al. 2005; Busti, Hooper et al. 2005; Barnes 2006; Greenwood, Steinman et al. 2006; Rogatsky and Ivashkiv 2006; Steffens and Mach 2006). There are different types of medication coding programs, such as the Medispan™ system, that may be used to organize medication information obtained from participants. Each drug in these programs is associated with a code that is added to a directory of general drug categories and subcategories (e.g., analgesic, statin, anti-infective). For analytical purposes, one would want to create groups of drugs as outlined in Table 3 (i.e., infectious disease, autoimmune disease, etc.) for adjustment in statistical models.

Another factor that may influence the results of biological sample testing is fasting status. Depending on the type of test, fasting may be recommended for 8–12 hours or more. In most cases, subjects are asked to continue medications during the fasting period as prescribed unless otherwise determined by their medical doctor. In a study of more than 30 of the most common blood tests conducted at Helsinki City Hospitals, the majority of blood tests demonstrated statistically significant variability among fasting versus nonfasting samples (Leppanen and Dugue 1998). In a study by Dugue and Leppanen (1998), significant decreases in the concentration of IL-6 were observed following the consumption of breakfast. Therefore, it is essential to develop protocols regarding fasting versus nonfasting requirements. Additionally, for the purposes of analysis, it is important to record

Table 3

Examples of medications associated with variability in cellular and inflammatory markers

Conditions	Example agents	Example medications
Infectious diseases	Anti-infectives, antifungals, antiviral agents, over-the-counter medications (decongestant, expectorant, analgesic, antihistamine)	Antiretrovirals (efavirenz, atazanavir+ritonavir), antivirals (acyclovir, ganciclovir, etc.); antibiotics (penicillins, cephalosporins, tetracycline, etc.); cough/cold/allergy medications (pseudoephedrine, phenylpropanolamine, phenylephrine, guaifenesin)
Autoimmune disease	Disease-modifying antirheumatic and anti-inflammatory agents	Methotrexate, azathioprine, leflunomide, D-penicillamine, hydroxychloroquine, TNF- α receptor antagonists, anakinara, tacrolimus, cyclosporine, etc.
Inflammatory, cardiovascular, or psychological conditions	Nonsteroidal anti-inflammatory agents, cyclooxygenase (COX)-2 inhibitors, statins, antidepressants	Diclofenac, naproxen, indomethacin, etc.; celecoxib, rofecoxib, valdecoxib, etc.; simvastatin, pravastatin, etc.; mao-inhibitor, selective serotonin reuptake inhibitors (prozac, celexa, paxil, etc.)
Inflammatory states	Corticosteroids	Cortisone, prednisone, dexamethasone, etc.

the time and date an individual consumed anything other than water prior to biological sample collection and to control for such deviations from protocol in statistical models.

The collection of biological samples also raises important ethical issues related to respondent burden (Finch, Vaupel et al. 2001). In any given population, respondent burden will vary depending on many factors, including, but not limited to an individual's perception of the risk versus benefit of providing a sample, the method of sample collection, fasting requirements, the amount of time/travel required, an individual's prior experience with research or sample provision, individual fear or anxiety levels related to clinical procedures, religious/cultural values, and health status. There are many protocol measures one can employ to help reduce respondent burden. For example, studies can provide ethical incentives for participants, travel to an individual's home/business for sample collection, utilize highly accessible collection sites, and reimburse travel expenses. In addition, it is important to explain the "bigger picture" of the research, involve respected community leaders in the research process, provide counseling to participants, and highlight the maintenance of anonymity provided by numerically coded labeling of collected specimens. In addition, offering an alternate method of collection to individuals who initially decline consent may reduce burden and increase participation levels. For example, when collecting blood, an individual refusing venipuncture, which involves the insertion of a needle into the vein, may consent to a blood spot, in which the tip of the finger is pricked, when presented with this alternative.

Conclusions and Applications of Biomarkers in PSID

The relationship between SEP, psychosocial stress and health outcomes, and their intermediate biological pathways, is complex. It is worth thinking about where the PSID can be most useful in understanding this relationship. In particular, we draw a distinction between large studies such as the PSID that view this relationship from “20,000 feet” and smaller studies that have the ability to measure behavioral and biological pathways with precision and detail. We have argued earlier that with its exquisite measurement of socioeconomic position and family composition over long periods, and changes in both, the PSID is exceptionally well suited to assess the associations between the SEP-related psychosocial stressors associated with these and other health outcomes such as risk of death. The longitudinal nature of the PSID could also be useful in analyzing not only the impact of SEP and related psychosocial pathways on health but the extent to which socioeconomic resources mitigate or amplify the impact of exogenous shocks (job loss due to recession, disasters, etc.) on biomarkers and health outcomes. With adequate waves of biomarker data collection, subsequent effects of biomarkers and health conditions could also be assessed. In our review of life course SEP studies, the majority utilized retrospective recall of early life SEP. Indeed, Galobardes, Lynch et al. (2008) and Kauhanen, Lakka et al. (2006) have found that adult recall of SEP measures from childhood tend to systematically underestimate the true association between objective measures of childhood SEP and adult CVD outcomes. Thus, the PSID can help fill this gap by providing a large range of SEP measures that are not based solely on retrospective reports. Going beyond such analyses, to a finer characterization of stress, the critical behavioral and biological pathways and more specific health outcomes carries with it challenges that must be addressed in the PSID and other studies like it.

Though the size of the PSID sample and the quality of its data are compelling, one cannot help but focus on some of its limitations. For example, generally there is no consistent pattern of data collection on the important psychological and behavioral pathways that are critical in interpreting any observed association between life course SEP, psychosocial stressors and health outcomes, or their biological pathways. In addition, though self-reported measures of medically diagnosed health conditions can be valuable, they are also biased by access to medical care, health literacy of respondents, and nonspecificity of responses. Parenthetically, though self-rated health status is widely used as an outcome in social science, its general nature means that observed associations between it and biological pathways linking stress and health outcomes is not likely to be informative. In addition, the lack of clinical detail in self-reported health data, compared to examination-based or record linkage-based information, makes it difficult to interpret observed associations with psychosocial stressors. Indeed, where there are carefully measured biomarker data, the quality of such data may be so superior to the behavioral, psychological, and health data as to make for very confusing results. In addition, where the biomarker data are not collected with the level of control and precision available in smaller studies, the connection of these biomarkers to health outcomes may be severely compromised. Finally, though there is often great biological plausibility and enthusiasm associated with the importance of many biomarkers, the evidence for their associations with psychosocial stressors is often far from conclusive, as is the evidence relating them to clinically significant health outcomes.

In our view, links between stress and health can, with the above provisos, be studied in the PSID, but the inclusion of biomarker data should be very carefully considered. We do not view the PSID as an appropriate venue for exploring stress-health links and the

underlying biological pathways for novel markers. However, assuming that criteria for measurement, transport, assay, and storage can be met; that the psychological and behavioral pathways linking stress to specific health outcomes are well understood from smaller focused studies; and that the links between biomarkers and well-characterized health conditions are known, the PSID can add considerably to our knowledge of the ways in which psychosocial stressors associated with socioeconomic position and family composition are linked to poorer health and some of the biological pathways.

In conclusion, the PSID should consider assessments of biomarkers of CVD discussed here. We suggest specifically those measures reported to be relatively stable over time, such as IL-6, TNF- α , CRP, fibrinogen, ICAM-1, VCAM-1, P- and L-selectins, CMV, and HSV, and not those that are subject to acute context effects or that require multiple measurements throughout the day. We also suggest that PSID consider adding important assessments of mediating behavioral measures, health, and medication assessments that will ultimately address many of the gaps in the literature regarding the relationship between SEP and biomarkers of cardiovascular health.

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