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Considering the Inclusion of Metabolic and Cardiovascular Markers in the Panel Study of Income Dynamics

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Abstract

The inclusion of biomarkers in social surveys such as the PSID has the potential to answer many elusive questions in social science and public health, including the much-studied relationship between socioeconomic status and health. This paper reviews the potential inclusion of biomarkers of cardiovascular and metabolic risk in the PSID. We first discuss the considerable analytical benefits of adding these biomarkers to the PSID, including the exploration of life course hypotheses and the potential to test causal relationships between the social environment and biological systems. Next, we review evidence on the reliability of self-reports of cardiovascular and metabolic risk factors, concluding that the potential bias from relying on self-reports may be substantial. Based on evidence of biological importance as well as practical considerations of ease of in-home collection, our first tier of recommended biomarkers includes measured height, weight, waist and hip circumference, diastolic and systolic blood pressure, resting heart rate, total and HDL cholesterol, glycosylated hemoglobin (HbA1c), C-reactive protein (CRP), and cystatin C. Additional markers of secondary priority are also discussed.

Introduction

During the past decade, social scientists have expanded their focus on the social and economic determinants of health status to consider the underlying physiological pathways linking environmental factors to physical and mental health and survival. As a consequence, they have become involved in a type of data collection recently described as a “biosocial survey:” i.e., a population-based sample for which social, economic and demographic information is obtained through household interviews and biological markers based on physical assessments and laboratory analyses are collected in the home or in a clinical setting (Weinstein, Vaupel, & Wachter 2008). These surveys are providing researchers with markers of metabolic and cardiovascular disease, often combined with indicators of immune or neuroendocrine function, for relatively large community or national samples.

The development of biosocial surveys has the potential to answer many elusive questions in social science and public health. For example, scores of associations between health outcomes and socioeconomic status (SES) have been described, but debate about causal pathways still persists (Goldman 2001). In the public health literature, there has been little

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progress in moving beyond traditional indicators of education and income to understand which aspects of SES are most important for health. Similarly in social science research, the use of summary measures such as self-reported health status has limited understanding of the most salient biological pathways linking the social environment and health.

Adding biomarkers to a panel survey with the richness of the economic data in the Panel Study of Income Dynamics (PSID) would allow considerable analytical leverage to answer these important questions. Begun in 1968, the PSID is a longitudinal survey that is nationally representative of U.S. individuals and family units. The survey's traditional strengths have been measuring the dynamics of economic and demographic behavior over time, with a more recent move into additional health measurement. Much of the promise of adding biomarkers to the PSID derives from the longitudinal nature of the survey, suggesting that a decision to add biomarkers should be viewed in terms of a long-term rather than a one time commitment.

Cardiovascular disease is the leading cause of death in the U.S. Over 23 million U.S. adults have diabetes, with another 57 million estimated to suffer from impaired fasting glucose, or pre-diabetes (Centers for Disease Control and Prevention 2008.) Given the health importance and relative ease of measurement of many of the conventional risk factors for these conditions, any expansion of the PSID into biological data should seriously consider inclusion of these measures. Other multi-purpose longitudinal surveys in the U.S. have opted to include such risk factors in their first foray into biomarker collection. For example, the Health and Retirement Survey (HRS) collected the following biomarkers from a randomly selected half of the sample in the 2006 wave: height, weight, waist circumference, blood pressure, dried blood spots (analyzed initially for glycosylated hemoglobin and total and HDL cholesterol and subsequently for C-reactive protein and cystatin C), and saliva (for the extraction of DNA). L.A.FANS, a study of individuals and families in Los Angeles County that began in 2000, recently collected a similar set of biological measures from children and adults as part of its second wave of interviews.

The paper proceeds with a discussion of the unique opportunities for generating scientific knowledge to be gained by including biomarkers of cardiovascular and metabolic risk in the PSID. Next we review evidence on the reliability of self-reports of cardiovascular and metabolic risk factors, concluding that the potential bias from relying on self-reports may be substantial. Based on evidence of biological importance as well as practical considerations of ease of in-home collection, we provide a list of recommended biomarkers, classified into two levels of priority. The paper concludes with additional design considerations surrounding the inclusion of these markers in the PSID.

CVD/metabolic markers and opportunities for the generation of scientific knowledge

The scientific opportunities that would result from the inclusion of biomarkers of cardiovascular and metabolic risk in the PSID are substantial. Recently, life course perspectives in both epidemiology and the social sciences have turned attention to the potential long-term impacts of early life exposures for the development of chronic disease (Ben-Shlomo & Kuh 2002), as well as educational and economic outcomes (Case, Fertig, & Paxson 2005; Hayward & Gorman 2004; Heckman 2006). Nonetheless, the precise pathways (and thus potential interventions) linking early life conditions to later life outcomes are not well understood. The challenge of causal identification in the associations between health and social factors is also well known. Because levels of education, income, and health are not randomly assigned, it is difficult to ascertain the potential impact of interventions aimed at these factors. We consider the potential uses of biomarkers of

cardiovascular and metabolic function in the PSID for the generation of scientific knowledge in three broad categories, with a life-course framework and opportunities for causal identification over-arching each category.

1) CVD/metabolic markers as outcomes

CVD and metabolic markers have often been analyzed as outcomes of interest due to the heavy epidemiological interest in cardiovascular disease and its major risk factors over the last several decades, as well as the more recent obesity epidemic. Nevertheless, even within the rich social epidemiological literature on these markers, there is a paucity of longitudinal studies, and none with the high resolution of economic variables found in the PSID. The addition of CVD and metabolic biomarkers to the PSID would therefore have the potential to answer questions about the dynamic social and economic predictors of these important biological risks across a wide age range, rather than the snapshots offered by surveys such as NHIS and NHANES, or the emphasis on biomedical determinants in studies such as the Framingham Heart Study or CARDIA.

Early life

The “Barker hypothesis” made prominent the notion that early fetal environments could “program” development of an individual’s metabolic and cardiovascular systems (Barker 1995). Nutritional deprivation in the womb is thought to give cues to the fetus about its future environment, encouraging adaptive reductions in growth and slower metabolism. Maternal nutrition and low infant birth weight have been linked to higher rates of later life hypertension, high cholesterol, diabetes, and cardiovascular disease (Barker, Eriksson, Forsen, & Osmond 2002; Adair, Kuzawa, & Borja 2001; Fernandez-Twinn & Ozanne 2006). Much of this research utilizes birth weight records linked to health outcomes in adults, but few prospective studies have biological data starting at early ages to test these hypotheses. Since economic and other social stressors are hypothesized to contribute to early programming of physiological systems, this provides a unique opportunity to test hypotheses about the fetal and early childhood environment in relation to the early development of traditional biological risk factors. The timing and intensity of early life stressors (or buffers) are thought to be important from the developmental perspective, making studies like the PSID that capture moving pictures of individuals and families over time uniquely suited to answer these questions. Longitudinal collection of data on glucose and cholesterol levels in the PSID could, for example, allow analysis of the impact of stressors such as parental job loss or divorce during pregnancy or early childhood on lipid and glucose regulation.

There is increasing evidence that physiological adaptations to early environments can also be transmitted inter-generationally. Specifically, a fetus may tailor its adaptive response to not only its current environment, but the environment experienced by its mother and grandmother (Kuzawa 2005). This work suggests that the persistence of advantage or disadvantage could have a heritable component coming from the phenotype rather than the genotype of one’s parents. Utilizing the kinship and birth weight data in the PSID in conjunction with measures of glucose level for example, one could test persistence of these effects on glucose regulation in children who share disadvantaged grandparents but have more varied parental family backgrounds.

Middle and Later Life

Given the long etiology of many metabolic and cardiovascular diseases, longitudinal analysis of biological risk factors in middle age would allow researchers to test the micro as well as macro factors that predict changes in risk, perhaps long before the appearance of clinical disease or mortality. For those at older ages, the PSID distinguishes itself from the

HRS with its data on the lifetime economic status of older adults, with the potential to examine income and employment dynamics earlier in the life cycle and the relationship of downward and upward economic mobility to the development of health risk. At the macro level, the inclusion of biomarkers in the PSID would allow testing of the health impacts of economic and social policy changes as well as other macro level influences such as the recent mortgage and financial crisis.

Obesity

The rise in obesity has been dramatic in the U.S. over the last three decades (Ogden, Carroll, Curtin, McDowell, Tabak, & Flegal 2006). Evidence on the morbidity and mortality consequences of the obesity epidemic, however, is mixed. While a very low or very high BMI is associated with mortality, the shape of the relationship for the bulk of the distribution is not clear, with the overweight category recently found to be protective compared to normal weight (Flegal, Graubard, Williamson, & Gail 2007; Greenberg, Fontaine, & Allison 2007). While profiles of cardiovascular risk have improved across all BMI categories (Gregg, Cheng, Cadwell, et al. 2005), there is evidence that levels of functional impairment have become worse for obese adults (Alley & Chang 2007). One obstacle to clarifying the relationships between obesity and mortality has been the lack of information on individual lifetime exposure to obesity. Increases in obesity at all ages suggest that the average obese 40-year old may have spent a larger percentage of his life obese than an obese 40-year old twenty years ago. Moreover, beginning a lifetime of obesity during the formative childhood years of growth and development is a relatively new phenomenon that may confer additional health costs. The health, social, and economic consequences of increased lifetime exposure to obesity are unknown. The PSID has a significant opportunity to document trends in weight change over the life course, while at the same time investigating the social, economic, and health influences on and consequences of these changes.

Improved measurement of outcomes

The PSID has already excelled in capturing the dynamic nature of individual level employment, income, and changes in family structure during the prime working ages, and has linked these dynamics to self-reported measures of health and mortality (Amick III, McDonough, Chang, Rogers, Pieper, & Duncan 2002; McDonough, Duncan, Williams, & House 1997). Mortality is a crude health measure in the sense that it only captures the portion of the health distribution that has crossed a certain threshold, potentially missing a large portion of health change for the rest of the population. Especially at younger and middle ages, reliance on the relatively rare event of death also dramatically reduces the statistical power of an analysis to detect health effects. Self-reported health measures also have notable down sides. There is evidence that factors such as age, race, gender, and SES may impact the reporting thresholds for self-reports of global health status as well as reported levels of disability (Dowd & Zajacova 2007; Benyamini, Blumstein, Lusky, & Modan 2003; Ferraro & Kelley-Moore 2001; Melzer, Lan, Tom, Deeg, & Guralnik 2004). Self-reported health conditions may be biased by differences in access and use of care that impact the probability of diagnoses across groups, in addition to considerable reporting error among those with similar access to care (Baker, Stabile, & Deri 2004). The addition of biomarkers of CVD and metabolic risk to the PSID would mitigate many of the problems of bias and measurement error in self-reports, or the rarity of an event such as mortality.

Inclusion of these markers would allow analysis of the impact of changes in micro and macro level social and economic conditions on sensitive indicators of physiological function that are among the major risk factors for disease. These types of analyses could detect changes within a wider health range and would be complementary to similar designs that

investigate acute outcomes such as major health events or hospitalizations, which are relatively rare and lie at the end of a long spectrum of disease development. Additionally, unlike the black box of a measure like global self-reported health status, the addition of biomarkers for different physiological systems can give insight into the specific pathways through which these changes impact the body.

2.) CVD/metabolic markers as predictors

For many of the reasons mentioned above, the PSID is also in a unique position to answer questions about the consequences of physiological function/dysfunction for human capital accumulation and labor market outcomes across the life course. Low birth weight has been previously linked to important adult health and economic outcomes in the PSID (Conley & Bennett 2000; Johnson & Schoeni 2007), and the addition of biomarkers of risk starting at young ages would allow researchers to test the pathways through which low birth weight damages future prospects. The PSID is unique in its detailed information on families before, during, and after the pregnancy of a child. Feedbacks from early life health to achievement and the accumulation of human capital may be driven by more subtle differences in health at the subclinical level, especially in children where chronic disease is less likely to be manifest. The effects of childhood health on later educational and economic outcomes may be underestimated by looking only at the effects of overt disease or low birth weight. For example, proper glucose regulation is thought to be important for memory and learning at both young and old ages (Jurdak, Lichtenstein, & Kanarek 2008; Korol & Gold 1998). Obesity in German boys aged 2–4 was found to be associated with delays in verbal and other skills controlling for family characteristics, and this was true even for children not attending day care, suggesting a biological rather than social pathway (Cawley & Spiess 2008). Human adipose tissue also releases inflammatory cytokines, and levels of inflammation are higher in overweight children (Visser, Bouter, McQuillan, Wener, & Harris 2001). Elevated levels of cytokines during immune response to infection are known to affect various aspects of behavior including exploration of novel environments, learning, and cognitive function (Larson & Dunn 2001; Reichenberg, Yirmiya, Schuld, et al. 2001). Despite this work, there is little known about the potential effects of childhood obesity or low-grade inflammation on learning and achievement. Measurement of relevant biomarkers in the Child Development Supplement, in conjunction with the cognitive and behavioral assessments, school and family information, would go a long way towards answering some of those questions.

In adults, existing work on links from poor health to lower income has focused on overt illness or disability limiting one's ability to work, but, as in children, it is plausible that subclinical or preclinical metabolic or cardiovascular disease could affect individuals in subtle ways for years before disease is evident or diagnosed. In addition to the effects of glucose and insulin on cognition mentioned above, it is likely that poor glucose regulation could lead to increased fatigue, which in turn could affect decision-making about labor market participation. Even small changes in behavior could accumulate over many years to result in different economic trajectories. Markers of inflammation are associated with declines in executive functioning at older ages (Schram, Euser, de Craen, et al. 2007). It is conceivable that long-term low grade inflammation could have more subtle influences on the brain, affecting parameters of economic interest such as risk preference and decisions about savings and expenditures, a hypothesis that the PSID would be well suited to test. In later life, the addition of metabolic and CVD biomarkers as predictors could help identify trajectories of decline in older adults before clinical symptoms are manifest, and the subsequent impact of these trajectories on economic and social variables of interest.

3.) CVD/metabolic markers as controls for risk

While not as analytically exciting as examining biomarkers as outcomes or predictors, an additional category of research potential is worth mentioning. As previously discussed, CVD is the most common cause of death in the U.S. Although individual-level prediction is less reliable, the presence of markers of CVD risk including hypertension, cholesterol, and smoking can account for most cases of CVD at the population level (Greenland, Knoll, Stamler, et al. 2003; Stamler 2007; Lynch, Davey Smith, Harper, & Bainbridge 2006). Longitudinal measurements of these important major risk factors will be a major improvement for a variety of empirical models that wish to control for existing risk. Any analysis of the impact of social, economic, or environmental factors on health outcomes (or vice versa) in the U.S. can use these measures as controls for baseline health risk. Self-reported health status in the previous period is often used in longitudinal analysis to control for baseline health, but the use of markers of major physiological risk would be a vast improvement over these self-reports for reasons previously discussed. This improved measurement of existing risk factors can also help answer questions about the social or economic factors that contribute to resiliency or vulnerability in health—which individuals fare better or worse in actual outcomes than their cardiovascular risk factors might predict.

Overall Synergies with the PSID

The PSID offers opportunities for the generation of scientific knowledge using biomarkers of physiological functioning that are far beyond the opportunities found in other surveys that include such markers. As mentioned above, the longitudinal nature of the PSID allows unique exploration of life-course hypotheses and causal pathways resulting from unexpected changes in micro and macro level environments. Given the large interest in socioeconomic status and health outcomes, the PSID more than many other surveys allows an unpacking of which aspects of SES are most important for health. Debate persists about the relative role of psychosocial stress due to low status or actual material deprivation in contributing to SES gradients in health. The detailed information on expenditures and housing characteristics in the PSID could help shed light on this neo-material versus psychosocial debate. Details on job changes over the life course can help identify whether the permanent or transitory components of SES are most important for health. The family design of the PSID allows unique research designs that model the role of shared environment and shared genetics. The work that has been done in this regard with low birth weight could be greatly extended by looking at biomarkers of glucose and lipid regulation and inflammation from an early age. The addition of biomarkers would also enrich work on the intergenerational persistence of socioeconomic status by helping to disentangle the biological and environmental contributors to this persistence.

Accuracy of self-reported measures

Despite the popularity of including biomarkers in social science surveys, the fact that most respondents in the US are likely to know their height and weight and have some information pertaining to clinically measured risk factors for diabetes and heart disease compels us to consider whether accurate estimates of these markers could be obtained by self-reports at much lower cost and complexity than a biomarker collection.

Findings from numerous studies suggest large variation in the accuracy of self-reports across and within samples, with potentially seriously biased estimates resulting from the use of self-reported data compared to physical and clinical measurements. For example, several studies suggest that height is especially likely to be overestimated for men and for older persons of both sexes and weight is most likely to be underreported by women (Kuczmarski, Kuczmarski, & Najjar 2001; Nyholm, Gulberg, Merlo, Lundqvist-Persson, Rastam, &

Lindblad 2007). Sensitivity estimates for the correct classification of overweight status (BMI ≥ 25) based on data in NHANES III range from 73% to 96% across age and sex-specific groups (Kuczmarski, Kuczmarski, & Najjar, et al. 2001). Reports of health conditions are generally more problematic than those of height and weight, perhaps because they depend on respondents' use of health services. In general, self-reports are likely to underestimate the true prevalence of chronic conditions, but the magnitude of the discrepancy varies substantially by characteristics of the respondent and the sample as well as by the particular health condition. For example, estimates of the sensitivity of self-reports of hypertension are as low as 35% and 49% in studies in the Netherlands (Molenaar, Ameijden, Grobbee, & Numans 2007) and Taiwan (Goldman, Lin, Weinstein, & Lin 2003) respectively. Other studies of self-reported hypertension suggest a range of estimated sensitivities from 43% to 82% (Molenaar, Ameijden, Grobbee, et al. 2007). The corresponding estimates for diabetes are substantially better, with a range from 67% to 85% (Molenaar, Ameijden, Grobbee, et al. 2007). Estimates of specificity are generally high for both of these conditions. Sex, age, and recent use of health care have frequently been found to be associated with the accuracy of these self-reports (Molenaar, Ameijden, Grobbee, et al. 2007; Goldman, Lin, Weinstein, et al. 2003).

Although it is possible that large-scale studies in the US have more complete reporting than many of the studies cited in the literature, we suspect that self-reports are still likely to be problematic. Comparisons between the PSID and NHIS suggest fairly consistent estimates, but both surveys are based on self-reports and comparisons with NHANES suggest underreporting of hypertension and diabetes in the NHIS, differentially by race and SES (Raghunathan 2006). Recent unpublished analyses from SHARE suggest substantial underreporting of chronic health conditions across many European surveys. Other data from Europe (Thomas, Walker, Emberson, et al. 2005; Hauner, Hanisch, Bramlage, et al. 2008) indicate a non-trivial prevalence of undiagnosed diabetes and impaired fasting glucose levels, underscoring the difficulties of collecting complete information from self-reports.

Biomarkers pertaining to metabolic and cardiovascular function

In Table 1, we provide a list of markers related to metabolic and cardiovascular function that should be considered for inclusion in the PSID or similar household surveys to achieve the research objectives described above. Selection of these particular markers is based on the following criteria: demonstrated association with downstream health outcomes, experience with inclusion of the biomarker in other population-based surveys, ease of collection by interviewers and minimal invasiveness for the respondent. This list does not comprise all metabolic and cardiovascular markers that have been collected in population-based surveys. For example, epidemiological surveys focused on heart disease, such as Framingham, CARDIA and the Cardiovascular Health Study, collect various markers not mentioned in Table 1; many of these biomarkers require venous blood or clinical assessments [see, for example, biomarkers included in Wang, Gona, Larson, et al. (2006) or Zethelius, Berglund, Sundstrom, et al. (2008)]. We prioritize the markers in Table 1 into two groups based largely on the ease with which these markers can be obtained from respondents in their homes with current technology.

Anthropometry

The anthropometric measures shown in the first column of Table 1 permit the calculation of various measures of obesity and stunting (or reduced height more generally), that in turn are risk factors for numerous chronic conditions including diabetes and heart disease. The most frequently used measures of overweight and obesity in the medical and epidemiological literatures are based on the body mass index (BMI, defined as weight in kilograms divided by height in meters squared), with a BMI ≥ 25 designating overweight and BMI ≥ 30

designating obesity among adults. Despite its widespread use, most researchers consider BMI to be an inadequate measure of obesity because it fails to take into account body composition, most notably the distinction between fat and muscle. Moreover, studies suggest that abdominal obesity may be a more important risk factor than overall obesity for cardiovascular disease. Thus, the ratio of waist circumference to hip circumference (waist-hip ratio or WHR) or simply waist circumference on its own may be related to cardiovascular events in circumstances where the BMI is not (Price, Uauy, Breeze, Bulpitt, & Fletcher 2006; de Koning, Merchant, Pogue, & Anand 2007), underscoring the importance of collecting these additional measurements.

Measures of height are also needed for determination of stunting. Leg length and knee height, which we designate as lower priority, are more sensitive measures of diet and infection in early childhood than overall height, especially among older adults. Their inclusion could be warranted if substantially reduced height is a sufficiently common occurrence among PSID respondents (e.g., among some immigrant groups). Although skinfold thickness, typically measured with a caliper at multiple sites (e.g., biceps, triceps) may provide useful information regarding body fat mass beyond BMI or circumference measurements (Garcia, Wagner, Hothorn, Koebnick, Zunft, & Trippo 2005), and is frequently used to assess body density in children and adolescents (Sarria, Garcia-Llop, Moreno, Fleta, Morellon, & Bueno 1998), it is somewhat cumbersome to obtain from respondents and is not considered in the highest priority category for inclusion in the PSID. More sophisticated and costly measures of body composition, such as bioelectrical impedance, or assessment of proteins produced by fat cells (e.g., leptin) are not considered in this paper.

Blood pressure and heart rate

We recommend incorporating three of the four measures related to blood pressure/heart rate: diastolic blood pressure, systolic blood pressure and average heart rate. Diastolic and systolic blood pressure measurements provide the inputs for determination of hypertension. Although there is a lack of consensus on the importance of an elevated heart rate for cardiovascular disease, numerous studies demonstrate an association between a resting heart rate and hypertension, coronary heart disease, and mortality (Fox, Borer, Camm, et al. 2007; Palatini & Julius 1997). All three of these measures can be obtained readily from an inexpensive electronic home blood pressure device, which the respondent can use on his or her own or the reading can be taken by an interviewer.¹ A serious drawback of blood pressure measurements too often ignored by researchers is variability – blood pressure varies by time of day, type of activity, and setting, and its measurement depends on the nature of the instrument (automatic monitor vs. mercury sphygmomanometer) and the person taking the reading. For example, “white coat hypertension,” typically thought of as a transient increase in blood pressure brought about by the anxiety associated with medical personnel, could also affect readings taken by interviewers. Perhaps most troubling is that numerous studies comparing measurements taken at home with those taken at a clinic suggest substantial discrepancies between the two: many studies reveal higher measurements at the clinic (e.g., Divison, Sanchis, Artigao, et al. 2004; Narkiewicz 2007), but this is not always the case – e.g., the SEBAS study in Taiwan found that the home readings were higher than those taken at a hospital several weeks later, with correlations equal to about 0.6 between the two sets of readings. In addition, there is evidence from a study that used blood pressure devices with memory storage that, if respondents are asked to take their own measurements, they may alter the true readings or report fictitious ones (Bachmann, Steurer, Holm, & Vetter 2002). In most household surveys, determination of

¹Because there is substantial variation in accuracy among such devices, only validated models should be used.

blood pressure is based on at least three measurements, taken by the respondent or more often a trained interviewer using an automatic device, with a brief interval between readings. Improved protocols record measurements on multiple days, although this is likely to pose logistical difficulties for fieldwork.

The final measure shown in the second column of Table 1 – heart rate variability (HRV), an indicator of autonomic nervous system control of the heart – is not recommended for inclusion in the PSID at this stage. Despite reduced heart rate variability being a significant predictor of mortality for persons with cardiovascular disease and of coronary disease in the general population (Dekker, Schouten, Klootwijk, Pool, Swenne, & Kromhout 1997; Dekker, Crow, Folsom, et al. 2000; Tsuji, Larson, Venditti, et al. 1996) and its inclusion in several recent surveys (e.g., a 24-hour Holter monitor in the Moscow biomarker study and a 3-lead ECG reading in the MIDUS II study), measurement of HRV places a substantial burden on the respondent and adds considerably to the cost and complexity of the biomarker collection. Moreover, recent research has questioned the reliability of HRV measurements (Sandercock, Bromley, & Brodie 2005).

Biomarkers derived from blood specimens

All of the remaining biomarkers listed in Table 1 are derived from blood specimens. Venous blood had been the most common mechanism for blood drawing in earlier surveys, but has the serious disadvantage for population-based samples of requiring trained phlebotomists (as well as complicated blood treatment and processing protocols in some cases). In recent years, many population-based surveys have collected dried blood spots (DBS) – a minimally invasive procedure in which drops of whole blood obtained from a finger prick are collected on filter paper. As described in detail in McDade, Williams, & Snodgrass (2007), there are many advantages of DBS over venipuncture: not only is the collection less intrusive for the respondent, but the blood samples do not need to be centrifuged, separated or frozen right after collection; they are relatively stable at room temperature for at least a week and they can remain in laboratory freezers for long periods to be analyzed at a later time. The most serious disadvantage of DBS is that standard laboratory and assay protocols are designed for serum or plasma; thus, new protocols must be developed and validated for DBS and the resulting measures may not be comparable with those from serum or plasma. Nevertheless, in conjunction with the proliferation of biosocial surveys, new DBS methods are constantly being developed and evaluated so that the range of biomarkers that can be analyzed with DBS continues to expand.

A third not well-publicized option for collecting biomarkers in population-based surveys is the Demecal Set. This procedure was developed in the Netherlands, is also available in Japan, and is slated for use in other countries including the US in the near future (www.demecal.nl). Through detailed instructions and an inexpensive do-it-yourself kit (about \$50 in Japan), individuals generate a tube of plasma from one or more drops of blood obtained via a finger puncture. The tube can be sent by regular mail to a laboratory and feedback is provided within several days. As of spring 2008, about 16 tests are available through Demecal, including cholesterol measurements, glucose, glycosylated hemoglobin, albumin, creatinine and C-reactive protein. Although designed for convenient widespread diagnostic testing, the Demecal Set has been used in household surveys (e.g., the 2008 Malawi Longitudinal Study of Families and Health). This procedure could provide an alternative to DBS in the near future, although the absence of stored specimens for later use may be a serious drawback.

Because of the logistical complexity associated with the collection of venous blood in a household survey and the current unavailability of the Demecal Set in the US, in the ensuing discussion we designate higher priority for those blood-based biomarkers for which DBS

assays have been developed and evaluated. However, we recognize that, given the rapid pace of development of assays for DBS, this situation is likely change in the near future, even before the start of the PSID fieldwork. We emphasize the possibility of using frozen DBS samples in later years to perform assays that were not available or well-tested at the time of the initial laboratory work for the PSID. We also recognize that, although it is possible for respondents to self-administer a DBS procedure and subsequently mail back the specimens, this is likely to yield low response rates. For example, in a diabetes study that was carried out as a supplement to the 2002 wave of HRS, the rate of return of blood kits was 52% among eligible survivors (Weir 2008). Thus, achievement of a respectable response rate in the PSID will likely necessitate in-home interviews with trained personnel.

The four measures of cholesterol level shown in the third column of Table 1, which typically comprise a routine lipid profile, are associated with the risk of heart disease: high levels of LDL cholesterol and triglycerides are risk factors for atherosclerosis – a build-up of plaque in the arteries which is a principal cause of coronary and other types of cardiovascular disease – whereas high levels of HDL cholesterol are protective of heart disease. We recommend collection of total and HDL cholesterol (via dried blood spots). The ratio of total to HDL cholesterol is considered a more useful predictor of heart disease than total cholesterol on its own. Although information on LDL cholesterol and triglycerides improves the prediction, the measurement of these components requires a 9- to 12-hour fast, which may substantially reduce respondent compliance.²

Two measures of glucose concentration in the blood, which are indicative of poor glycemic control (e.g., diabetes), are shown in the fourth column of Table 1: glycosylated hemoglobin (typically abbreviated as HbA1c) and fasting glucose. Measurement of glycosylated hemoglobin – i.e., the percent of hemoglobin in the blood that is chemically bound to glucose – has two notable advantages over measurement of fasting glucose, even though fasting glucose is the indicator generally used for diagnostic purposes. The first is that, because red blood cells survive in the bloodstream for about four months, HbA1c provides an average measure of glucose metabolism over a period of several months prior to the test; in contrast, fasting glucose indicates the concentration at the time of sample collection. The second is that HbA1c does not require fasting prior to the blood test. Glucose and HbA1c can be measured from dried blood spots.

Because a substantial literature documents the importance of inflammatory markers as risk factors for heart disease, we list several pro-inflammatory cytokines (IL-6 and TNF- α) and acute phase reactants (CRP and fibrinogen) in the next column of Table 1. C-reactive protein (CRP) is involved in the acute phase response to an infection or to some other source of inflammation or tissue damage. As is the case with many inflammatory markers, CRP is a sensitive but non-specific marker of acute inflammation; levels rise in response to inflammation but do not indicate the site of the inflammation. Although there is some concern regarding the utility of CRP as a screening tool (Lloyd-Jones, Liu, Tian, & Greenland 2006), many studies have demonstrated that healthy persons with elevated basal levels of CRP have increased risk of hypertension, cardiovascular disease, diabetes, and dementia (Wilson, Ryan, & Boyle 2006; Rifai 2005). CRP has several characteristics that make it ideal for inclusion in a household survey. A “high sensitivity” CRP (hs-CRP) test, used clinically to assess cardiovascular risk, can be performed with dried blood spots (as has been done in several recent surveys including HRS, L.A.FANS, WISE and MxFLS).

²Fasting is required to obtain a reliable measure of triglyceride levels. The level of LDL-cholesterol is generally derived from the Friedewald calculation, based on measured values of triglycerides, total cholesterol and HDL-cholesterol (Nauck, Warnick, & Rifai 2002).

Moreover, CRP is more stable than some other inflammatory markers, does not have diurnal variation and is relatively inexpensive and reliable to analyze.

We have designated the remaining proteins associated with acute inflammatory response – fibrinogen, IL-6, and TNF- α – as lower priority because these measures are not currently obtainable from dried blood spots. Fibrinogen plays an important role in the blood clotting process. Studies have shown associations between fibrinogen levels and cardiovascular disease, cancer, and diabetes, even in the presence of other risk factors, suggesting that fibrinogen may be involved in the pathogenesis of these conditions (Ernst & Resch 1993; Mirshahi, Vasse, Vincent, et al. 2001; Kannel, Wolf, Castelli, & D'Agostino 1987). Although fibrinogen levels can be measured from blood serum or plasma, to the best of our knowledge it can not be ascertained from dried blood spots at this time. In addition, fibrinogen obtained from venous blood requires special preparation within a short period after blood drawing.

TNF- α (tumor necrosis factor-alpha) and IL-6 (interleukin-6) are cytokines involved in systemic inflammation. Chronically high levels of both of both factors are associated with pathology, but the two markers appear to act independently and have distinct biological functions (Bruunsgaard, Ladelund, Pedersen, Schroll, & Jorgensen 2003). TNF- α has been implicated in a wide range of diseases, including arthritis, multiple sclerosis, diabetes and cancer (Chen & Goeddel 2002). High levels of IL-6 are also associated with a large number of chronic conditions and diseases, including diabetes, Alzheimer's disease, arthritis, and cardiovascular disease (partly through the involvement of IL-6 in the production of CRP) as well as with functional decline (Papanicolaou, Wilder, Manolagas, & Chrousos 1998; Kiecolt-Glaser, McGuire, Robles, & Glaser 2002; Reuben, Cheh, Harris, et al. 2002). IL-6 is considered to be one of the most important mediators of the acute phase immune response and dysregulation of IL-6 is believed to be an important component of the aging process. IL-6 has been incorporated into several biosocial surveys (e.g., MacArthur and SEBAS) and has emerged as a significant predictor of survival. Despite the potential importance of both of these markers, neither IL-6 nor TNF- α can be assayed from dried blood spots at this time. The significance of linkages between IL-6 and health in recent studies, however, underscores the importance of collecting IL-6 should validated DBS assays be available in the near future.

In the final column of Table 1 we include four additional markers. As with the inflammatory markers, all of these biomeasures appear to have strong associations with morbidity, including cardiovascular disease, and mortality. Cystatin C and creatinine are indicators of kidney function, which is an important prognostic factor for cardiovascular disease. Creatinine is a chemical waste molecule that is generated from muscle metabolism and is transported through the bloodstream to the kidney where it is filtered into the urine. High levels of serum creatinine are often a consequence of impaired kidney function and are associated with cardiovascular disease and survival (Wannamethee, Shaper, & Perry 1997). Information on serum creatinine together with data on age, sex, and weight, can be used to estimate creatinine clearance (which reflects the glomerular filtration rate – GFR) to identify kidney dysfunction. Cystatin C, a protein produced by most human cells, is a relatively new marker that is thought to be a better indicator of the GFR and can detect kidney disease at earlier stages than serum creatinine. In a recent study of an older population-based sample (the Cardiovascular Health Study), cystatin C showed a stronger association with mortality than serum creatinine (Shlipak, Sarnak, Katz, et al. 2005). Cystatin C, but not serum creatinine, can be assayed from dried blood spots; serum creatinine levels can be measured with the Demecal Set.

Homocysteine is an amino acid in the blood. Levels of homocysteine are strongly affected by diet, particularly folic acid and vitamins B6 and B12. High levels of homocysteine are associated with cardiovascular disease, possibly through damage to the linings of the arteries and promotion of blood clots, and may be related to inflammation and immune system activation. Evidence from genetic and prospective studies suggests that the associations are causal, but scientists are not in complete agreement on this issue (Wald, Law, & Morris 2002; Moat 2008). Interpretation is complicated because high homocysteine levels can arise from many factors, including diet and medications, and are associated with increasing age. Thus, although homocysteine levels can be ascertained from dried blood spots, we have designated it as lower priority. Albumin, the protein of highest concentration in blood serum, is thought to reflect an individual's general health and nutritional status (Corti, Guralnik, Salive, & Sorkin 1994). Albumin is involved in the transport of small molecules in the blood and in the maintenance of osmotic pressure. *Low* albumin levels are associated with inflammation and various diseases, including cardiovascular disease, liver disease, and cancer as well as all-cause mortality (Corti, Guralnik, Salive, et al. 1994; Schalk, Visser, Bremmer, Penninx, Bouter, & Deeg 2006; Djousse, Rothman, Cupples, Levy, & Ellison 2002). As with many of these markers, researchers remain uncertain about the extent to which low levels of albumin reflect poor health (e.g., liver or kidney disease or malnutrition) or are part of underlying causal mechanisms (Schalk, Visser, Bremmer, Penninx, Bouter, & Deeg 2006). Albumin levels can not be ascertained from dried blood spots, but are available from the Demecal Set.

Additional Considerations

Once preliminary decisions regarding budget constraints and prioritization of markers are made, additional issues will need to be considered before proceeding to data collection. While a full discussion of these issues is beyond the scope and space constraints of the current paper, we outline some of these practical considerations below. Given the thorough collection protocols developed by other surveys such as NHANES, L.A.FANS, and HRS for most of the biomarkers described in this paper, we recommend that the PSID look to these surveys for developing their own protocols.

Age

The markers we have recommended could in theory be measured at most ages. Given the unique opportunities for insight into life course determinants of health and economic well-being, our recommendation would be for biomarker collection to be as inclusive as possible at early ages. Even markers such as CRP that may not be highly correlated with current child health status could be invaluable as individuals are followed for the rest of their lives. Nonetheless, because some markers such as cystatin C, creatinine, and albumin are likely to be useful indicators of functioning only at middle or older ages, it may make sense to exclude younger respondents from some components of the biomarker collection.

Collection concerns

Overall, the biomarkers recommended in Table 1 are considered non-invasive. Collection of anthropometric measures is fairly straightforward and has already been carried out in the PSID Child Development Supplement. Respondents are typically excluded from these measurements if they are unable to stand. For very high blood pressure readings (e.g., systolic of 180mm Hg or higher or diastolic of 110mm Hg or higher for adults), interviewers are typically advised to terminate the interview and collection of health measures, record the relevant information, and explain to the respondents the urgent need to have their pressure checked by a health care provider. In rare cases, respondents may faint or feel faint during collection of dried blood spots. Collection of dried blood spots has been carried out

successfully with young respondents in L.A.FANS, but the complexities of obtaining compliance from children need to be carefully considered.

Additional survey questions

Proper interpretation of these markers, especially at middle and older ages, will necessitate the collection of information concerning medications currently taken, including the name, dosage, and frequency. Since CRP levels rise significantly with recent infection, a question asking about illnesses in the last 30 days is recommended. Questions about adherence to fasting would need to be included for any biomarkers requiring fasting.

Frequency of collection

While we acknowledge the substantial burden and cost issues associated with frequent collection, the majority of the opportunities for generating knowledge that we highlighted require longitudinal data, and we recommend collecting biomarkers at regular intervals. The ability to detect causal impacts of exogenous changes in social factors on biomarkers, for example, will be diminished with long lag times between biomarker collections.

Reliability/validity

We strongly recommend checking reliability and validity during the piloting of the project or early stages of the fieldwork by sending blind samples to more than one laboratory and multiple samples to the laboratory selected for the project. One additional challenge arising from longitudinal collection of biomarkers is potential changes in assay techniques. Stored samples may be needed to validate consistent measurement through changing technology over time.

Ethical Issues

There is an ethical obligation to inform respondents of the results of tests for which there are established clinical cut-off points associated with high risk, despite the potential effects on future behavior. Informed consent will need to include permission for the use of stored DBS for later use. Parental consent and informed consent for older children will need to be carefully considered for the child sample. The protocol will require procedures to ensure confidentiality, which is particularly complex for longitudinal data.

Respondent burden and response rate

The markers chosen should impose minimal burden to respondents; nevertheless, some individuals may object to providing dried blood spots. Other surveys that introduced biomarker collections at later waves (e.g., SEBAS) found no evidence of increased non-participation (Chang, Gleib, Goldman, & Weinstein 2008). The potential effects on response rates in the PSID can be assessed with a pilot sample.

Cost

Our recommendation to collect markers that can be obtained from dried blood spots rather than venipuncture comes from concern for affordability and the logistical ease of in-home collection without the need for a trained phlebotomist. McDade estimates a range of 10 to 20 assays that can realistically be obtained from a single finger prick. Collection materials for DBS are estimated to cost \$1.50-\$2.00 per respondent, with laboratory labor and assay costs ranging from \$5 to \$20 depending on the marker (McDade, Williams, & Snodgrass 2007).

Conclusion

Biomarkers of cardiovascular and metabolic disease measure important risks that account for a large portion of the burden of disease in the United States. The PSID offers unique opportunities for generating scientific knowledge regarding these markers, especially for the exploration of life-course hypotheses and identification of causal pathways between health and the social and economic environment. Given the interdependence of physiological systems (in particular the importance of the hypothalamic pituitary axis for metabolic functioning), the addition of biomarkers from other domains would only multiply the opportunities for scientific insights to be gained from these markers in the PSID. While the risks of increased burden and attrition to a venerable survey such as the PSID need to be taken seriously, the potential contributions to scientific knowledge are considerable.

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Table 1

Metabolic and cardiovascular markers considered for inclusion in the PSID

Anthropometry	Heart rate/blood pressure	Cholesterol	Glucose	Inflammatory	Other
<i>Highest priority</i>					
Height	Diastolic blood pressure	Total cholesterol	HbA1C	CRP	Cystatin C
Weight	Systolic blood pressure	HDL cholesterol			
Waist circumference	Heart rate				
Hip circumference					
<i>Additional markers</i>					
Leg length/knee height	Heart rate variability	LDL cholesterol	Fasting glucose	Fibrinoge	Creatinine
Skinfold thickness		Triglyceride		IL-6	Homocysteine
				TNF-α	Albumin