

Summary Working Group - Future Research Opportunities in the Hispanic Community Health Study – Study of Latinos (HCHS-SOL)

Meeting Summary August 11, 2010

Purpose: This meeting was convened by the NHLBI Division of Cardiovascular Sciences, Prevention and Population Sciences Program to obtain advice about future plans for a renewal of the Hispanic Community Health Study –Study of Latinos (HCHS-SOL). Experts in cardiovascular and pulmonary diseases, ophthalmology, social sciences and behavior, diabetes, metabolism, sleep disorders, infectious diseases, genetics/genomics and population studies were invited to discuss future research opportunities in the HCHS-SOL.

The Working Group was welcomed by the DCVS Director. The Associate Director, DCVS, presented an overview of the NHLBI Strategic Plan and the NIH Director's five research emphasis areas. The Project Officer provided a brief overview of the HCHS-SOL design, and charge for the Working Group. HCHS-SOL investigators provided an update on study progress and preliminary, unpublished data analyses. After addressing questions from the Working Group, the HCHS-SOL investigators departed.

Background: The HCHS-SOL is a multi-center observational study to designed to describe the prevalence of cardiovascular, pulmonary and other chronic diseases in a cohort of 16,000 persons of Hispanic background in the communities of San Diego, Chicago, Bronx and Miami. Other study aims are to identify factors that protect from or increase the risk of various chronic diseases, and understand the role of adaptation to a new culture on health and development of disease. The current contract period began in October, 2006 and will end in March, 2013. Six other Institutes, Centers and Offices have contributed funds and scientific components.

Discussion and Recommendations: Dr. Ileana Piña chaired the Working Group. Following is a summary of the research areas discussed and the Working Group recommendations.

(1) Biomarkers of cardiovascular disease and other conditions: The current contract of the HCHS-SOL study includes a baseline assessment of a detailed panel of biomarker assessments as well as the creation of a biorepository for plasma, serum, genomics, DNA, RNA, and urine. This biorepository will be available for future analysis of specific biomarkers in conjunction with the epidemiologic data. In future examinations, it was recommended to continue this detailed assessment and biobanking. Several specific cardiovascular markers of interest were discussed (e.g. natriuretic peptides, cardiac troponins) and it was recognized that these could be assayed in the future using banked specimens. Serial sampling of enrolled participants (e.g., repeat biomarker assessment performed at baseline at a future examination) was felt to be of very high scientific potential due to the ability to assess change in risk factor profile over time. In summary:

- Repeat detailed biomarker assessments collected at baseline

- Consider including natriuretic peptides, cardiac troponins.

(2) Vascular and heart imaging: The working group agreed that incorporating imaging procedures in the renewal of the HCHS-SOL would allow for correlations with future cardiovascular events, including stroke. Ultrasound-based techniques provide the best balance between sophistication and feasibility and the most favorable cost/benefit ratio. Among these, the performance of a Doppler echocardiogram was unanimously favored by the working group due to its non-invasive nature, relative low cost, reproducibility, and ability to provide multiple variables that reflect structural heart disease, left ventricular systolic and diastolic function and hypertrophy, right ventricular function, pulmonary artery pressures, and comprehensive assessment of valve function. In addition, the results could be compared to echocardiographic images obtained in Hispanic populations living in their own countries. The use of carotid intimal media thickness (CIMT) was considered less important due to its undetermined impact on coronary artery disease events, particularly in relation to other methods. Brachial artery flow-mediated dilation (FMD) as an index of endothelial function was not recommended due to its low reproducibility when performed by multiple sonographers at different sites. The incorporation of cardiac CT angiography was not recommended due to the use of radiation and contrast agent; however, electron beam computed tomography (EBCT) was viewed more favorably based on its lower cost and known impact on cardiovascular events, especially in the 45-74 year-old participants. Finally, the use of cardiac MRI (CMRI) was not encouraged due to its relatively high cost and relatively little additional information beyond that obtained with an echocardiogram.

In summary, the working group recommended:

- Doppler echocardiogram: highly recommended
- Carotid IMT: could be considered, particularly for prediction of stroke
- EBCT: recommended only for the 45-74 year-old participants
- Brachial artery FMD, cardiac CT angiography and CMRI: not recommended

(3) Body composition, adiposity and diabetes: Preliminary analysis of the participants demonstrates a high prevalence of diabetes and impaired fasting glucose, as well as a high prevalence of overweight and obesity. These findings are consistent with what is known about obesity and diabetes in the United States as a whole, and in other studies that have included Hispanic samples. Recent data from the Multi-Ethnic Study of Atherosclerosis (MESA) demonstrated that at a given waist circumference, Hispanics had a greater incidence of diabetes than either whites or African Americans. Therefore, a high incidence of diabetes in the HCHS-SOL is cohort is expected.

The working group recommended the following be considered in a re-examination of the cohort:

- Repeat weight, waist and hip circumferences, and bioelectrical impedance measurements
- Include an additional measure of adiposity such as a CT abdomen slice to allow for calculation of visceral vs. other fat depots
- Repeat fasting plasma glucose, A1C, and insulin levels
- Repeat the OGTT and modify it to include fasting, 30 minutes and 120 minutes plasma glucose measurements

(4) Microvascular disease: Due to significant prevalence of diabetes mellitus across Hispanic groups, and high prevalence of hypertension in some groups, fundus photography (with a non-mydiatric camera) to assess diabetic retinopathy and other retinovascular changes was recommended. Retinopathy and retinovascular disease could be correlated with biomarkers, cardiac/vascular imaging and cardiac/vascular events. In addition to a retinal exam, an ocular exam for cataracts, glaucoma and visual acuity were recommended, if the resources are available.

With regard to renovascular disease and nephropathy, the group recommended repeating the measurement of serum creatinine and the spot urine collection (for microalbumin/creatinine ratio), and measuring serum cystatin C [in stored samples and at the follow-up visit(s)].

In summary, a future cohort examination should include:

- Fundus photography
- Repeat serum creatinine; add serum cystatin C
- Repeat urine microalbumin/creatinine ratio

(5) Psychosocial factors, migration and acculturation: Most social environmental factors affect health through the accumulation of psychosocial adversity and/or through the chronicity of exposure. Accordingly, it is important to have repeated measures of social exposures over time. A single cross-sectional measure does not capture the relevant social processes, including acculturation. In addition, an expanded set of measures of psychosocial factors, migration, and acculturation should be obtained. The working group recommended the following:

- Repeat measures of social exposures and acculturation
- Cultural norms and beliefs specific to behaviors that may be of interest to the NHLBI (e.g. tobacco use, alcohol intake, physical activity)
- Contextual and bi-directional effects of migration – effects of migration on the health of those who migrate to the U.S. and the sending communities
- Ethnic enclaves and built environment
- "Air-bridge" - back-and-forth migration or visits to the country of origin, especially to seek health-related services that are difficult to obtain in the U.S.
- Stress - self-reported and physiological (e.g. cortisol levels). The working group also recommended expanding the measures of stress to evaluate economic hardship (more in-depth understanding of financial stress, such as difficulty in making ends meet at the end of the month), acculturation stress (stressors linked to migration and problems speaking English), and working conditions (psychological and physical aspects of work).
- Repeat assessments on social networking, familismo, perceived discrimination, popular medicine beliefs, use of popular medicine remedies, etc
- Resilience and positive emotions – the assessments should not just focus on adversity and negative emotions
- Adherence to medical recommendations

(6) Pulmonary disease and sleep: Reassessing pulmonary function through pre- and post-bronchodilator spirometric assessment and correlating changes over time with CV events will be of

value in the understanding of the relationship between COPD and CVD in Hispanics and the general population. Measurement of exhaled nitric oxide in order to further differentiate between asthma and COPD (currently done in NHANES) could be considered. Extent of emphysema (assessed by CT imaging of the lung fields) has been negatively correlated with left ventricular end-diastolic volume, stroke volume and cardiac output, especially in smokers, in the MESA Lung Study. Thus, if resources are available, incorporation of chest CT imaging in the renewal may be considered. The downsides of incorporating this test are radiation exposure and incidental findings that may require medical follow-up in a population that is highly uninsured.

Incorporating questionnaires such as the modified Medical Research Council (MMRC) dyspnea scale and the St. George's Respiratory Questionnaire would allow assessment of pulmonary-related quality of life and correlations with future outcomes and endpoints.

The baseline polysomnography study can be correlated with future cardiovascular events. It is unclear whether a repeat polysomnography study will add more knowledge about the risk factors for sleep apnea or the interaction between sleep apnea and CVD. The working group recommended:

- Repeat pre- and post-bronchodilator spirometry
- Add one or more questionnaires to assess pulmonary function-related quality of life
- Consider adding exhaled nitric oxide measurement and lung CT imaging

(7) Genetics and genomics: In recent years, genome-wide association studies (GWAS) have been carried out for a variety of phenotypes relevant to the NHLBI mission. However, GWAS have thus far not identified causal variants nor proven very useful in clinical prediction. Even so, recent developments in technology, analytic approaches, and scientific collaborations seek to bring GWAS past some of these limitations and could be harnessed by the HCHS-SOL to push the frontier of knowledge.

Several opportunities are evident with regard to HCHS-SOL. Not only could HCHS-SOL replicate findings conducted in populations of European origin in Latinos, but it could also catalyze the discovery of new associations that are either specific to Latinos or more frequent in Latinos; it could be among the first to extend findings into lower frequency variants; it could contribute to ongoing meta-analyses; it could leverage admixture methods as a complementary gene discovery tool; it has particular strength around quantitative traits, which have been measured in the entire cohort of 16,000 participants; it could help unravel the relative contribution of environmental variables, and it could facilitate the exploration of gene-sex, and gene-diet (nutrigenetic) interactions. Finally, it could provide crucial information about the health effects of migration and acculturation by comparing the findings of the HCHS-SOL cohort with present and future studies of Hispanic cohorts in their countries of origin.

With the availability of GWAS data in the HCHS-SOL, the study's unique strengths and characteristics could be leveraged to great effect in the next stage of genome exploration and its interaction with the environment, with fundamental implications for global health and health disparities. Based on the above, the working group recommended:

- A dense, third generation GWAS using the Illumina 2.5 chip + Hispanic supplemental array in the full HCHS-SOL cohort.

(8) Women's health: The capacity to study pregnancy and cardiovascular health in the HCHS-SOL study would greatly enhance the study's contribution to Latino cardiovascular health. It would also contribute to the burgeoning field of study of pregnancy and cardiovascular disease, which has the potential to sway if not shift prevailing paradigms about the role of pregnancy in women's health throughout the life course. If history has been accrued about previous pregnancy and complications, then the incidence of new onset diabetes and hypertension can be measured in later years. In addition, the prevalence of these complications during pregnancy has not been reported in the Hispanic population. To address these knowledge gaps, the working group recommended the following:

- Examine the effects of pregnancy on CVD both prospectively in younger women and retrospectively in older participants.

(9) Chagas' disease: Chagas' disease is the most common cause of cardiomyopathy and cardiac conductive disorders in Central and South America. It is primarily transmitted via a vector, and also via the placenta. It is estimated that 1.5% of South American migrants and 0.6-5.9% of Central American and Mexican migrants in the U.S. have Chagas' disease.

Most prevalence estimates of Chagas' disease are based on blood donor seroprevalence, thus not including those at the highest risk (e.g. rural areas, low SES, etc). Testing for Chagas' disease can be done by identifying *T. cruzi* through ELISA or direct hemagglutination. Serology can be performed on banked specimens. These tests are available at the CDC Division of Parasitic Diseases.

Evaluation of Chagas' seropositive participants consists of a 30-sec lead II ECG, in addition to echocardiography (if available). Treatment of seropositive participants would need to be coordinated through CDC. Evaluation of children of seropositive women would need to be considered, given risk of congenital transmission and benefit of treatment in children. Chagas' disease uniquely impacts Latinos compared to other ethnic/racial groups. However, because Chagas is not endemic in most of the Caribbean, not all the HCHS-SOL cohort would need to be screened. Given relatively low estimated prevalence (< 10%), the working group recommended the following:

- Perform serological testing for Chagas' disease in participants with risk factors
 - o 1st generation migrant (since congenital infection is rare)
 - o Non-Caribbean country of origin
 - o Rural background in country of origin
 - o Low SES

In addition, consider case-control (samples can be tested retrospectively) versus targeted seroprevalence study.

(10) Cardiovascular and pulmonary morbidity and mortality: In addition to repeating some of the baseline examination components and adding new components (as described above), the working

group recommended the continuation of the cohort follow-up. The group recommended continuing the collection of changes in health status, cardiovascular and pulmonary disease health events and medication use, as well as adjudicating diagnoses from emergency room visits, hospitalizations and fatalities as in the current design. This part of the research plan will enrich the understanding of the risk and protective factors observed at baseline and their interaction with psychosocial factors, genetics and other variables in predicting clinical events in this publication.

- Continue observational component of the study (changes in health status, collect CV and pulmonary disease events, medication use, adjudicate diagnoses from ER visits, hospitalizations and fatalities).

The meeting was adjourned at 4:30pm.

Working Group Members:

Ileana Piña, MD, MPH (Chair), Ana L. Abraído-Lanza, PhD, Alain Bertoni, MD, PhD, Gerard Criner, MD, Michael Felker, MD, José Florez, MD, PhD, Willa Hsueh, MD, Visheh K. Kapur, MD, MPH, Amit Khera, MD, MSc, Barbara Klein, MD, MPH, Marian McDonald, DrPH, MPH, MA, Kathleen Page, MD, MPH, Julio A. Panza, MD, José Ordovas, PhD, David Williams, PhD

HCHS-SOL Investigators:

Greg Talavera, MD, MPH, Lisa LaVange, PhD, Gerardo Heiss, MD, PhD, Diane Catellier, PhD

NIH and NHLBI attendees:

Michael Lauer (NHLBI) Diane Bild (NHLBI) Larissa Avilés-Santa (NHLBI) Lorraine Silsbee (NHLBI) Paul Sorlie (NHLBI) Catherine Stoney (NHLBI) Gina Wei (NHLBI) Hanyu Ni (NHLBI) Cheryl Nelson (NHLBI) Richard Fabsitz (NHLBI) George Papanicolaou (NHLBI) Ann Alston (NHLBI) Elizabeth Zoller (NHLBI) Ligia Artiles (NIMHD) Paul Eggers (NIDDK) Peter Savage (NIDDK) Frances Kim (NIDCR)

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