Project Summary
The goal of this two-year Research Diversity Supplement for the "Analysis of Rural/Urban Disparities in Allostatic Load, Biological Risk Profiles, and Mortality" parent award (R24AG065159) is to provide Dr. Alexis R. Santos with the necessary skills to establish an independent research program in rural/urban health disparities with emphasis in stress, aging and mortality. Stress, measured as a combination of markers of physiological dysregulation, is associated with numerous causes of death among middle-age and older adults, and earlier onset of diseases and other health conditions. Although significant efforts have been made to elucidate rural/urban disparities in health, the role that stress and accelerated aging play in these disparities is vastly under-addressed in the extant scholarship. Thus, the overall objective of the current proposal is to identify the role that rural/urban residence plays in disparities in allostatic load, patterns of physiological dysregulation, and mortality. Dr. Santos' research will contribute to all four aims of the parent award: (Aim 1) developing an open and evolving network that draws participants from multiple regions, institutions, disciplines, career stages, and underrepresented groups; (Aim 2) designing activities to generate innovative research by enhancing the capacity of Network members and supporting formative research; (Aim 3) conducting novel research to understand the multilevel and multidimensional mechanisms driving rural-urban continuum and within-rural disparities in health and aging; and (Aim 4) disseminate data, analytic resources, and research findings to academic, policy, and public audiences through research briefs, webinars, data archiving, and other mechanisms. Most activities for this award will take place at The Pennsylvania State University (PSU) under the mentorship of Dr. Leif Jensen who is a Distinguished Professor of Rural Sociology and Demography, Associate Director of the Social Sciences Research Institute and Principal Investigator of the Parent Grant; (2) Dr. Martin Sliwinski who is Gregory H. Wolf Professor of Aging Studies, Professor of Human Development and Family Studies, Director of the Center for Healthy Aging at PSU, and INRPHA Co-I; and (3) Dr. Shannon Monnat who is an Associate Professor of Sociology, Lerner Chair for Public Health Promotion and INRPHA Co-PI and lead at Syracuse University. The training component of the award will include participation in mentoring meetings, coursework, seminars, conferences, and workshops sponsored by either INRPHA or the two collaborating institutions.

Narrative

Stress is associated with adverse health outcomes, earlier onset of chronic health conditions, and mortality. The proposed research will explore rural/urban disparities in these health outcomes by focusing on allostatic load, patterns of physiological dysregulation and mortality. This will lead to the creation of better strategies aimed at reducing rural/urban health disparities in the United States.

Specific Aims

In the United States, studies consistently find that older rural adults have worse self-rated health, higher chronic disease prevalence, and higher rates of Alzheimer's Disease and Related disorders than their urban peers[1–3]. Health insurance rates and access to health services are also more limited in rural areas[4]. Rural areas are also home to disproportionately larger shares of populations vulnerable to older age morbidity and premature mortality, including the poor, military veterans, and the disabled. After decades of lower or comparable mortality rates in rural areas in comparison to urban areas, an increase in rural mortality emerged in the 1980s and has grown each decade[5]. This trend reversal was due in part to smaller improvements in heart disease mortality in rural areas but increases in rural drug use[6] as well as alcohol deaths[7] and suicides, causes of death potentially linked to stress, also played an important role.

The study of stress with a focus on allostatic load (AL) could shed light on the increased morbidity and mortality found in rural areas. AL is a summary indicator of cumulative "*wear and tear*" experienced by the body due to repeated adjustments made in response to stressors[8]. It encompasses a multisystem approach to study of population health because it includes considerations of cardiovascular, metabolic and inflammation (immunological) responses. AL levels are determined by assessing whether specific markers of physiological activity operate within optimal ranges or not. The cumulative operation outside of these ranges constitutes physiological dysregulation and is measured by the AL score[9,10]. Given that AL is measured by directly assessing the levels of physiological function, it serves as an unbiased indicator of health that is not dependent on self-reports or a clinical diagnosis.

Although prior research has identified individual-level factors that increase AL levels, it has yet to be determined if (1) rural/urban residence is associated with levels AL, (2) differences exist in the incidence of biomarkers used to construct the AL score, and (3) whether AL interacts with rural/urban residential context to impact mortality risk. Understanding the levels of stress, and whether patterns vary by rural/urban residence could aid in the identification of the sources of disparities and in the deployment of interventions and policy initiatives to reduce them. The proposed project addresses this critical gap in knowledge by examining both the independent association between residential context and AL, and the interactive effects of these variables regarding mortality risk. This project will use the National Health and Nutrition Examination Survey III (NHANES III) and the 2015 Linked Mortality File. The NHANES III was collected between 1988 and 1994 for a nationally representative sample of the US population with oversampling for non-Hispanic Blacks and Mexican-Americans[11]. The NHANES III contains the necessary information to calculate the 10-item AL score and information about residential settings, which will be used to determine whether the respondents live in a rural or urban setting.

The primary objective of this Diversity Supplement is to test the central hypotheses that allostatic load levels differ by rural/urban setting; that patterns of allostatic load vary based on residential setting; and that this variation causes differences in the association between AL and mortality. It will add substantial knowledge about heterogeneity in stress and aging in the United States, by focusing on rural/urban differences. This will be accomplished through the following specific aims:

Aim 1: Assess the independent associations of rural/urban residence with AL and determine if demographic and socioeconomic characteristics are equally associated with AL based on residential stratification. Negative-binomial regression models will be used to study rural/urban differences and AL. A series of interactions and stratified regression models will be used to determine if the demographic and socioeconomic characteristics used as controls are equally associated with AL based on rural/urban residence.

Aim 2: Determine if patterns of the individual biomarkers underlying the allostatic load score vary based on residential setting. Latent Class Analysis will be used to determine the ways biomarkers are distributed among the study population (all sample), and whether these classes vary based on rural/urban residential settings.

Aim 3. Determine if allostatic load is differently associated with increased mortality risk based on rural/urban residence. Cox regression or proportional hazards regression models will be fit to study the association between AL, urban/rural residence and mortality. An interaction between AL and rural/urban residence, and stratified models, will be used to assess whether AL is equally associated with mortality across residential contexts and how this effect may differ.

This project will be the first to investigate the impact of rural/urban residence in allostatic load levels, differences in patterns of physiological dysregulation, and variations in the association between AL and mortality based on rural/urban residence. Knowledge generated from this project will contribute to public health efforts by emphasizing patterns of physiological dysregulation found in rural areas, and how these are contributing to rural/urban differences in mortality. The proposed Diversity Supplement will benefit the candidate by increasing his training in rural health, aging, and contextual determinants of health. While the candidate has a growing research portfolio, he lacks training in grant writing and, to date, none of his research proposals have been funded by external sources. The mentoring and training provided through this Diversity Supplement will equip the grantee to transition into an independent investigator role by preparing him to write, submit and carry out a project by submitting an R01 by the conclusion of the proposed supplement.

Project Narrative

Introduction and Background

The health of rural populations are a major public health issue in both the United States and the rest of world because these populations typically exhibit worse health outcomes and lower access to care than their urban peers[1,12]. The rapid aging of rural populations and the fact these populations are older and sicker calls for innovative approaches to understand the health and aging trends in the US[13]. Healthy aging is driven by multilevel and multidimensional factors, including those related to local demographics, economics, available social and health services, and natural environments[14–16]. Rural areas in the US are more demographically and economically diverse than ever before, and we cannot assess problems, develop policies, or deliver adequate services to rural areas without recognizing differences and without a clearer understanding of how multilevel and multidimensional exposures shape health and aging among different populations in different rural areas. The proposed study will build upon the existing literature on rural/urban health disparities by focusing on allostatic load (AL), patterns of physiological dysregulation and their association with mortality risk. The National Health and Nutrition Examination Survey III (NHANES III) contains biomarkers from the cardiovascular, metabolic and inflammation systems of the body[17]. These biomarkers are leveraged to produce the AL index - an indicator of physiological dysregulation - that is not dependent on self-reports or clinical diagnoses to assess the health status of the population of rural America. The analysis of AL provides an innovative way to explore rural/urban health disparities. These analyses will allow for the comparison of rural populations to their urban peers regarding their biological risk profiles. Furthermore, the proposed analyses will allow for the exploration of the role that AL has regarding rural/urban health disparities. This work will expand on the parent grant's scope by studying rural/urban differences in AL, an area of research that remains under-addressed in extant literature. This research will also contribute to better understanding and anticipation of rural health and aging needs by identifying patterns physiological dysregulation and assessing its role on mortality differences. The proposed Diversity Supplement will be the first to study population-level rural/urban differences in allostatic load, variation in patterns of physiological dysregulation, and whether residential setting mediates the association between AL and mortality. Moreover, the training component will allow Dr. Santos to obtain much needed theoretical foundations for his studies of rural/urban differences in allostatic load and mortality. These experiences will allow Dr. Santos to establish research collaborations in the area of rural population health and aging. Finally, the mentoring component, paired with the two other components will guide Dr. Santos towards the submission of an R01 to compare urban/rural disparities in health using a cross-national comparison approach.

Relationship with Parent Grant

The proposed training and research plan are highly relevant to and expand upon the collaborations created through the parent project and will ultimately (1) strengthen the collaboration between scholars at The Pennsylvania State University and Syracuse University, and (2) contribute to knowledge on the role of rural/urban settings and allostatic load and the impact of their interaction regarding mortality risk. The activities outlined in this supplement are consistent with the core principles of the parent project. Specifically, it facilitates innovative research on the multidimensional exposures shaping and being shaped by health and aging with emphasis in rural populations in the United States. Furthermore, it addresses two of the five key priority areas of the Interdisciplinary Network on Rural Population Health and Aging (INRPHA): (1) Identify trends and disparities in middle-age and older adult health and well-being across different types of rural areas among different vulnerable populations within rural areas and identify the mechanisms driving these trends and disparities; and (2) Identify the implications of population health and aging trends in rural areas. This proposal addresses a knowledge gap on the rural differences in allostatic load, differences in patterns of physiological dysregulation by analyzing clusters of biomarkers, and the effect of allostatic load in mortality differentiating by residential setting. Further, this study promises new knowledge about heterogeneity in stress and aging in the United States, by focusing on rural/urban differences. Conclusions from this supplement will highlight differences in allostatic load and biological markers of physiological dysregulation based on rural/urban residential settings. As an outcome, it will provide new insights into the similarities and contrasts of rural/urban populations and the role that allostatic load has in mediating mortality differences.

Theoretical Framework

Bronfenbrenner's Socio-Ecological Model

The theoretical framework that guides this research is Bronfenbrenner's Socio-Ecological Model[18,19], which reflects the complex interplay between multiple individual, relational, community, and societal factors on health and allows us to understand the individual and contextual factors that put people at risk of or protect against adverse health and aging outcomes. Differences in health are driven by complex interactions between macro-, state-, and local-level economic and political structures, local health and social infrastructure and amenities, environmental conditions, family and social network relationships, individual human capital and relative vulnerability of residents, and location along the rural-urban continuum[14,15,20–24]. A key innovation of the proposed research is to concentrate on rural/urban disparities in AL (Aim 1), variation in patterns of physiological dysregulation based on prevalence of individual biomarkers based on rural/urban residential setting (Aim 2), the association between AL and rural/urban residential setting, and implications for mortality

differences (Aim 3). The proposed analysis will serve as a foundation for future research on how place - the characteristics of the contexts in which people live[4] - influence health and aging trends. Of particular interest are future analyses of rural/urban health disparities that will consider these stressors and shocks.

Analytic Sequence

Over the course of the supplement, Dr. Santos will read and discuss advanced readings on rural heath, with emphasis in aging, stress, allostatic load and mortality. His work to complete Aim 1 will be guided by the Bronfenbrenner's Socio-Ecological Model. He will study the association between rural/urban residential setting and AL, and whether the association between demographic and socioeconomic characteristics and AL differs by residential setting. To complete Aim 2, Dr. Santos will leverage the analytic sample used in Aim 1 to study whether patterns of physiological dysregulation, individual or groups of biomarkers, vary by rural/urban setting. In the first section of the analysis, he will determine the biological risk profiles found when the analysis is performed on the full sample. The second part of the analysis consists of determining whether these patterns vary when the rural and urban subsamples are analyzed independently. For Aim 3, Dr. Santos will study the interaction between rural/urban setting and AL pertaining mortality risk. Models will be fit stratifying by rural/urban residential setting to assess the association between AL and mortality when these populations are analyzed independently.

Approach and Methods

The research proposed in this supplement will leverage data from the National Health and Nutrition Examination Survey III (NHANES III) to explore the three aims (described below), which are directly related to the type of research facilitated and encouraged by the parent grant (R24AG065159). NHANES III consists of a nationally representative sample of the population of the US collected between 1988 and 1994 for which a public-use version of the 2015 Linked Mortality File is available, making it an appropriate dataset for the proposed research.

Data

National Health and Nutrition Examination Survey III (NHANES III): Data for the proposed analysis come from the public-use NHANES III (1988-1994)[25]. The NHANES, conducted by the National Center for Health Statistics (NCHS) uses stratified, multistage probabilistic sampling to provide national estimates of health and nutritional status for the civilian, non-institutionalized population of the United States[26]. For this Diversity Supplement, Dr. Santos will use data collected from surveys administered to the target individual as well as clinically assessed markers of physiological activity within the body (Aims 1 and 2). The sample selected for the first two aims will include Non-Hispanic Whites, Non-Hispanic Blacks, and Hispanics aged 25 and older with valid information for the variables included in this analysis (n=14,020, rural n=6,601 and urban n=7,419). Special considerations will be taken for cases with missing values in in each biomarker (see *Exposure and Determinants*). For Aim 3, the NHANES III will be matched with the *Linked Mortality File 2015*, which includes information for: eligibility for mortality follow-up, mortality status, exposure time (time to death). The analyses will be limited to respondents eligible for mortality follow-up based on CDC eligibility criteria[27,28] and adjusted for complex survey design following the methodological guidelines. The number of persons who are dead in 2015 by residential setting is: rural residents (n dead=2,901) and urban residents (n dead=2,511).

Measures:

*Allostatic Load***:** Allostatic load (AL) is the dependent variable for Aims 1 and 2. It will be measured as an index indicating the number of biomarkers that exceed clinically determined thresholds. The AL index takes in consideration three types of biomarkers: cardiovascular, metabolic and inflammation. Cardiovascular markers considered in this study are: diastolic blood pressure (mmHg), systolic blood pressure (mmHg) and pulse rate at 60 seconds. Metabolic markers considered are: total cholesterol (mg/dL), HDL cholesterol (mg/dL), triglycerides (mg/dL) and glycohemoglobin (%), and body mass index (BMI, measured as kg/m^2). Inflammation markers (immunological response) considered in this study are: albumin (g/dL) and C-reactive protein (mg/dL). This index ranges between 0 (low AL) and 10 (high AL), has been previously validated, and takes into consideration ten biomarkers collected during the medical examination component of the NHANES[17,29–32]. The interpretation for this score is that the higher the score, the more "*wear and tear*" an individual has accumulated and vice versa. AL is the outcome for the analysis proposed in Aim 1, and the components of the score are the main variables of interest for Aim 2. ***Missing values in biomarker information:*** Regression-based imputation will be performed for cases in which a biomarker is missing using demographic and socioeconomic characteristics to predict these values and then calculate the AL index[33]. The models used to produce the imputed values will consist of a generalized linear regression model using the GLM procedure[34], and each imputation model will account for sex, age, race/ethnicity, education, marital status and poverty status. Robustness of the results will be assessed by replicating the findings with multiple imputation methods. Descriptive analysis of the ten biomarkers with and without imputed values, the clinically determined thresholds, and incidence of cases above clinical thresholds within the analytic sample will be reported following established practices[17,29,35].

Mortality: Mortality is the dependent variable for the analysis proposed in Aim 3, and comes from the LMF. Dr. Santos will create a dichotomous variable indicating whether the respondent was dead or alive (censored). **Exposure Time:** Differences in exposure for persons who were interviewed in different times are accounted for by controlling for person-months of follow-up within the empirical models. This variable indicates how many months passed from the moment of interview to death (person-months). The public version of the NHANES III-LMF provides a variable that indicates the number of person-months of follow-up from the date of interview or examination, which is used to conduct survival analysis[31,36]. Respondents who are assumed alive (right censored) are assigned the person-months corresponding to December 31, 2015. If the proportional odds assumption is not met when conducting the analysis, the dataset will be transformed in a person-year arrangement. This transformation will produce a file that contains as many observations as years lived by the respondents included in the analytic sample. Individuals who were still alive by the end of follow-up will contribute up to 27 person-years. The consideration of exposure time is only relevant for the analyses proposed in Aim 3.

Rural/Urban Residential Setting: The key independent variable of this study will be residential setting, which will be measured dichotomously indicating whether the respondent lives in an urban or rural county. The NHANES III, includes information about respondent's residential setting, and whether they lived in counties with over 500,000 persons. First, individuals are categorized as: (1) living in central counties of metropolitan areas of 1 million population or more/living in adjacent counties to metropolitan areas, and (2) all other areas. Second, among those who live in other areas, those living in counties with over 500,000 persons are also categorized as living in metropolitan areas. The combination of metropolitan codes and population size, which is employed in previous literature[3], results in 6,601 respondents classified as living in rural settings and 7,419 respondents classified as living in an urban setting. While we recognize that the reality of rural/urban settings is **not reducible to a dichotomy**, the proposed analysis will guide future lines of inquiry for the analysis of health experiences that will incorporate additional contextual characteristics. The NHANES III affords some limited ability to employ alternative specifications. Our findings will be assessed by exploring whether the expected patterns are found when respondents are classified as living in: (1) Metropolitan (n=6,605), (2) Micropolitan (n=814) and (3) Non-Core (n=6,601).

Covariates

Health Behaviors: Models will control for two health behaviors that vary by rural/urban setting and are associated with allostatic load[37] and premature mortality. *Smoking* will be measured as a categorical variable: non-smoker (reference), current smoker, and former smoker. *Alcohol consumption* will be measured in three categories: non-drinker (reference), 1-3 drinks per day, and over 3 drinks per day.

Demographic and Socioeconomic Characteristics: Analyses will control for several key demographic and socioeconomic variables that are associated with rural/urban residence, allostatic load, and mortality risk. Age will be measured as a categorical variable: 25-44 years (reference), 45-64 years, and 65 years and older. Race/ethnicity will be measured in four categories: non-Hispanic whites (reference), non-Hispanic Blacks, Hispanics and non-Hispanic others. Sex will be measured dichotomously indicating whether the respondent was a male or a female (reference). Education will be measured by self-report and recoded in three categories: less than high school (reference), high school diploma, and more than a high school diploma. Marital status will be measured by self-report and recoded in four categories: never married (reference), married, divorced/separated/widowed, and cohabitating. Poverty status will be derived from the income-to-poverty ratio and operationalized as poor for those who had a ratio of 1.30 and higher and non-poor (reference) for those with a lower value.

Spatial Differences: Models will also account for *Census Region* which is measured as a categorical variable: Northeast (reference), Midwest, South, and West. Robustness of the results will be assessed by adding state-level fixed effects.

Analytic Approach

Aim 1: Assess the independent associations of rural/urban residence with AL and determine if demographic and socioeconomic characteristics are equally associated with AL based on residential stratification. Santos will estimate rural/urban differences in allostatic load. We will first document differences in the distribution of the allostatic load index based on rural/urban residential setting. Then, we will study: (1) the independent association between rural/urban residential setting and allostatic load levels, and (2) whether this association varies when accounting for demographic and socioeconomic characteristics and health behaviors. Furthermore, we will study whether the determinants of allostatic load vary by residential setting. We hypothesize that differences in AL exist based on rural/urban setting, even when accounting for potential covariates with those in rural areas having higher AL levels, and that individual characteristics contribute differently to AL score differences based on residential setting. **Negative Binomial Models:** Following previous modeling approaches, we use negative binomial regression models to examine the relationship between rural/urban residence and allostatic load levels[29,38]. Regression models will be fit in a nested structure to assess the association between rural/urban residence and allostatic load levels. The second model incorporates demographic and socioeconomic characteristics and the third model will incorporate health behaviors. The two final models will show the difference in associations between demographic and socioeconomic characteristics, and health behaviors by using the rural/urban-stratified analyses.

Aim 2: Determine if patterns of the individual biomarkers underlying the allostatic load score vary based on residential setting. Data produced in the analysis from Aim 1 will provide the analytic sample to study rural/urban differences in biological risk profiles. In this analysis we will use latent class analysis to examine whether the distribution of individual biomarkers used in the AL score vary by residential setting, and whether patterns of physiological dysregulation exist within the overall population, and by rural/urban residence. A descriptive analysis of demographic and socioeconomic characteristics and health behaviors of these classes will be performed to better understand these populations. We hypothesize that rural/urban settings will have different profiles pertaining to the distribution of the biomarkers that contribute to the AL score. **Latent Class Analysis (LCA):** Latent class analysis (LCA) will be employed to study differences in the prevalence of the ten biomarkers. The LCA is a method that identifies a number of classes (n) among study populations using observed variables[39]. The LCA models will be estimated using the LCA procedure in SAS 9.4[40], incorporating survey design specifications to make the results representative of the US population. Fit statistics will be obtained to select the model that better explains patterns of these biomarkers in the analytic sample. The quality of the models will be evaluated using G-Square, log-likelihood, AIC, and BIC. The final determination will also be aided by examination of the Entropy index, which indicates the highest certainty in classifications. The analysis will also incorporate an assessment of classes by restricting the analytic samples based on residential setting (rural/urban). This approach follows conventional approaches when there is interest in studying subpopulations contained within diverse analytic samples[41].

Aim 3. Determine if allostatic load is differently associated with increased mortality risk based on rural/urban residence. NHANES III data will be matched with the 2015 Linked Mortality File using a common identifier to produce the analytical dataset. We will limit the analysis to respondents who were eligible for mortality follow-up based on CDC eligibility criteria who were part of the analytic sample used in Aims 1 and 2. Using Cox models, we will examine whether allostatic load is differentially associated with mortality risk based on rural/urban residence. We hypothesize that AL score will be differently associated with mortality risk based on rural/urban residence. **Cox Models:** Cox-Models will be used to study the association between AL and mortality, emphasizing the interaction between AL and rural/urban residential setting, individually and net of controls for demographic and socioeconomic characteristics, and health behaviors. Finally, models will be estimated stratified by rural/urban setting to assess the association between AL and mortality by residential setting. This approach is well-established within the literature that aims to establish differences in effects of AL and specific outcomes[17,42]. Analysis will include appropriate adjustments for survey design as directed by NHANES guidelines. Analyses will be conducted by using SAS, version 9.4[43]. The SURVEYFREQ and SURVEYPHREG procedures will be employed to account for complex sampling design. Given these adjustments, our results are generalizable to the U.S. population. If the proportional odds assumption is not met, the data will be transformed in a person-year arrangement and analyzed using the SURVEYLOGISTIC procedure[44] (Aim 3).

Mentoring Plan

While Dr. Santos has worked on the topic of AL, he has no formal training on physiology and aging, nor on the theoretical frameworks employed in the study of rural/urban health disparities. This supplement will provide two years of support to Dr. Santos, during which the mentoring team will provide training and guidance on seminal and foundational readings required to understand rural/urban health disparities. The proposed diversity supplement will help Dr. Santos build an independent research project, especially as relates to stress, cognitive aging, and contextual factors. We focus on four key areas: **(1) Orientation and evaluation**: The PI and co-Investigators will serve as mentors to Dr. Santos, and each will take responsibility as outlined in this proposal. Dr. Santos will meet with Dr. Jensen and Dr. Monnat on a **bi-weekly basis**, to receive guidance on the planned activities, discuss readings and any other issue associated with the proposed project. Dr. Santos will join the SU Lerner Center where he will be exposed to research being conducted by Faculty Fellows and Affiliates. Through the Lerner Lab, he will also have the opportunity to present and get feedback on his research. Dr. Santos will be incorporated in the weekly meetings of the Sliwinski Lab where issues related to aging are discussed through a series of paper discussions and workshops. The integration of Dr. Santos to the Sliwinski Lab will allow him to build a network with pre- and post-doctoral trainees of the Pathways Training Program (NIA Grant: T32AG049676) and be exposed to Lectures and Seminars organized around the topic of population aging. Dr. Santos will also receive guidance and feedback from the faculty affiliates of PSU's Center for Healthy Aging who attend these meetings. Every six months, Dr. Santos will submit a progress report including a self-assessment and goal, and expectations for the coming six months. The mentoring team will monitor and assess progress toward professional goals. **(2) Publications and Presentations:** Dr. Santos will attend and present at the annual meetings of the Rural Sociological Society, Interdisciplinary Association for Population Health Sciences, and the Population Association of America. Santos will also collaborate with his mentorship team on articles for submission to peer-reviewed journals. Potential outlets include: (1) Demography, (2) The Journal of Rural Health, (3) American Journal of Public Health, (4) Social Sciences and Medicine - Population Health, and (5) Biodemography and Social Biology. Santos will also prepare research briefs as part of a joint initiative between the Lerner Center and the Population Research Institute at PSU. These briefs are among several outputs proposed by the INRPHA R24 parent grant. Within INRPHA, Dr. Santos will participate in the **Annual Meetings** and **working groups** that are being

created around the focal areas relevant to the proposed Diversity Supplement. **(3) Grant proposal preparation:** Dr. Santos will participate in grant proposal preparation in collaboration with mentoring team in relation to opportunities to advance his own research agenda. Within the Lerner Center, the Sliwinski Lab and INRPHA he will receive mentoring and feedback on proposal writing. **(4) Professional Development and collaborations:** The mentoring team is committed to helping Dr. Santos launch a successful independent research career after the Diversity Supplement by providing orientation, assisting with publications and grant writing, helping craft a competitive R01 application. The proposed diversity supplement will allow Dr. Santos to obtain formal training on the frameworks employed in the study of rural disparities, the demographic composition and transformations of rural populations and the how residential characteristics affect health outcome. To accomplish this, he will complete the following graduate course sequence: (1) Use of Theory in Rural Sociology and (2) Change in Rural Society at PSU, and (3) Health and Place (with Monnat). Aside from the networking opportunities afforded by the incorporation of Dr. Santos to the activities conducted at the Lerner Center, the Sliwinski Lab and INRPHA, he will also participate in the monthly seminars offered by the NIA-funded (P30AG066583) Syracuse University Center for Aging and Policy Studies (CAPS) wherein Monnat is an affiliate. Further, he will participate as a *Visiting Researcher* in the SU Lerner Center for Public Health Promotion (directed by Monnat) during summer of 2022. During his research stay, he will (1) produce policy briefs based on the work completed through this Diversity Supplement, (2) meet graduate students, post-doctoral fellow, affiliate faculty and other visiting scholars to expand his professional network and discuss his research agenda, (3) participate in Lerner Center and CAPS research activities and (4) engage in collaborations with affiliates. The mentoring team will aid him in building professional networks (across disciplines and institutions, and through INRPHA), coach him on effective publication and dissemination strategies, and provide leadership opportunities.

Timeline

Aims	Period: September 1, 2021, to May 31, 2023			
	Fall 2021	**Winter/Summer 2022**	**Fall 2022**	**Winter/Spring 2023**
Aim 1: Assess the independent associations of rural/urban residence with AL	Exposure to science readings with emphasis on rural/urban disparities in stress and aging	Estimate rural/urban differences in AL, and stratified analysis by residential setting		
Aim 2: Determine if patterns of the individual biomarkers underlying the AL score vary based on residential setting	Readings on Latent Class Analyses	Start the analysis on clustering of biomarkers based on residential setting	Determine patterns of biomarkers and differences by residential setting	
Aim 3: Determine if allostatic load is differently associated with increased mortality based on residential setting.		Participate as a *Visiting Scholar* at the Lerner Center for Public Health Promotion (SU)	Readings on rural/urban disparities in mortality	Estimate the association between AL and mortality, and the interaction between AL and residential setting
Coursework	Use of Theory in Rural Sociology (PSU)	Change in Rural Society (PSU)	Health and Place (SU)	
Expected outcomes	1 review manuscript	Aim 1 completed, 1 manuscript of Aim 1	Aim 2 completed, 1 manuscripts corresponding to Aim 2	Aim 3 completed, 1 manuscript corresponding to Aim 3, and 1 grant (R01) submitted

Future Research

The proposed research will close the gaps in the study of rural/urban differences in stress and aging by focusing on allostatic load. It will also answer important questions about whether patterns of physiological dysregulation vary by rural/urban settings. This project will serve as the foundation for future studies on rural/urban differences in stress and aging, by focusing on allostatic load and its association with mortality. Furthermore, this project builds upon the network created through the parent grant by incorporating the expertise of scholars in rural sociology and demography (Dr. Leif Jensen), aging (Dr. Martin Sliwinski) and rural population health and health disparities (Dr. Shannon Monnat). The proposed Diversity Supplement will build upon the INRPHA to establish a research collaboration between scholars at PSU and SU.

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