Circulation Research

RESEARCH LETTER

Association of Neighborhood and Environmental Factors With Clinical Phenotypes and Outcomes in Heart Failure With Preserved Ejection Fraction

David A. Liem, Hitalo Silva, Erick Romero, Paulo Rocha, Pablo E. Acevedo, Miki R. Izu, Aditya Ballal, Mohammad Soroya, Javier E. López, Miriam A. Nuno, Arnib Quazi, Chitra Mukherjee, Wayne Linklater, Imo Ebong, Xiao-Dong Zhang, Leighton T. Izu, Padmini Sirish, Nipavan Chiamvimonvat, Martin Cadeiras

Heart failure with preserved ejection fraction (HFpEF) is heterogeneous with multiple comorbidities and limited therapeutic options.[1] Multiple pathologies contribute to the development of distinct clinical HFpEF phenogroups.[1] Evidence suggests that social determinants of health (SDoH) are pivotal in the pathogenesis of cardiovascular disease.[2] Defined by the Centers for Disease Control and Prevention and the World Health Organization, SDoH refers to the conditions in the environments where people are born, live, learn, work, play, worship, and age, influencing health outcomes and quality-of-life risks. SDoH encompasses 5 domains: (1) Education Access and Quality, (2) Economic Stability, (3) Social and Community Context, (4) Health Care Access and Quality, (5) Neighborhood and Built Environment.

Studies of how SDoH and environmental factors (Figure [A1]) impact HFpEF phenotypes are limited. Conceptualizing neighborhoods and built environments is essential to understanding how SDoH contributes to cardiovascular disease health inequities.[3] First, to decipher how SDoH impacts HFpEF, we determined population-level neighborhood environments (NEnv) of California from Census Data. Second, to determine Built Environments, we used the publicly available data sets of the California Office of Environmental Health Hazard Assessment, Crimegrade, and Howloud. Third, we conducted retrospective analyses of patients with HFpEF at UC Davis to correlate NEnvs with their phenotypes.

Our community clustering algorithm[4,5] used 24 sociodemographic and socioeconomic variables previously described,[5] across 5 main domains of SDoH, at ZIP code tabulation areas (ZCTA) level (from the American Community Survey, https://data.census.gov/cedsci/ [accessed 7 March, 2022]). Prominent variables were education level, access to health care, household income, and employment. We also included race/ethnicity as demographic features. An unsupervised machine learning algorithm stratified the variables into community clusters, unveiling 4 main NEnvs (1–4), each connected to ZCTAs (Figure [A2] and [A3]). NEnv-1 (602 ZCTAs) is predominantly rural, mostly resided by White and Hispanic individuals, with lower income, health insurance coverage, college education attainment, and employment. NEnv-2 (239 ZCTAs) is rural, predominantly older White individuals with low employment. The other two NEnvs are urban. NEnv-3 (481 ZCTAs) is mainly resided by White and Asian individuals, with fewer Hispanic individuals and a higher median age, higher rates of employment, income, education, and access to health insurance. NEnv-4 (418 ZCTAs) has the highest numbers of underserved multiethnic populations with lower income and moderate employment rates. NEnv-4 displays the highest rates for lead, air pollution, crime (neighborhood and property), ozone gas, drinking water pollution, and chemical waste, especially compared with NEnv-3. Pesticide exposure was highest in NEnv-1 (Figure [A4]).

Key Words: cardiovascular diseases ■ heart failure ■ social determinants of health

Meet the First Author, see p 5

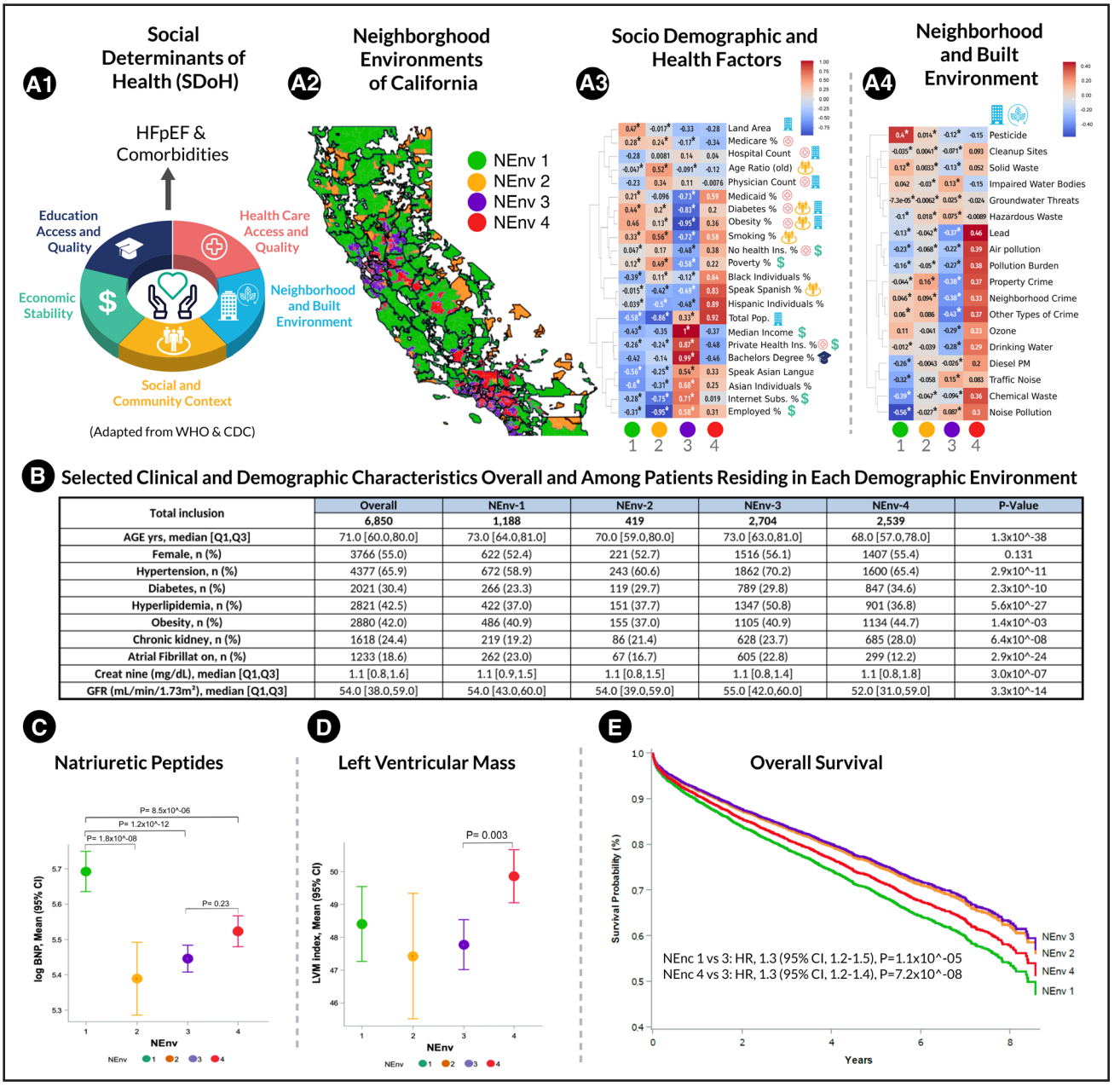
THIS MANUSCRIPT WAS ORIGINALLY SUBMITTED IN RESPONSE TO THE CALL FOR ORIGINAL RESEARCH LETTERS TO ACCOMPANY THE COMPENDIUM ON ENVIRONMENTAL IMPACTS ON CARDIOVASCULAR HEALTH AND BIOLOGY.

Correspondence to: Martin Cadeiras, MD, Department of Medicine, Division of Cardiovascular Disease, UC Davis Medical Center, 4860 Y Street, Suite 2820, Sacramento, CA. Email mcadeiras@ucdavis.edu; or David A. Liem, MD, PhD, Department of Medicine, Division of Cardiovascular Disease, UC Davis Medical Center, 4860 Y Street, Suite 2820, Sacramento, CA. Email daliem@ucdavis.edu

For Sources of Funding and Disclosures, see page 157.

Circulation Research is available at www.ahajournals.org/journal/res

RESEARCH LETTER



B Selected Clinical and Demographic Characteristics Overall and Among Patients Residing in Each Demographic Environment

Total inclusion	Overall 6,850	NEnv-1 1,188	NEnv-2 419	NEnv-3 2,704	NEnv-4 2,539	P-Value
AGE yrs, median [Q1,Q3]	71.0 [60.0,80.0]	73.0 [64.0,81.0]	70.0 [59.0,80.0]	73.0 [63.0,81.0]	68.0 [57.0,78.0]	1.3x10^-38
Female, n (%)	3766 (55.0)	622 (52.4)	221 (52.7)	1516 (56.1)	1407 (55.4)	0.131
Hypertension, n (%)	4377 (65.9)	672 (58.9)	243 (60.6)	1862 (70.2)	1600 (65.4)	2.9x10^-11
Diabetes, n (%)	2021 (30.4)	266 (23.3)	119 (29.7)	789 (29.8)	847 (34.6)	2.3x10^-10
Hyperlipidemia, n (%)	2821 (42.5)	422 (37.0)	151 (37.7)	1347 (50.8)	901 (36.8)	5.6x10^-27
Obesity, n (%)	2880 (42.0)	486 (40.9)	155 (37.0)	1105 (40.9)	1134 (44.7)	1.4x10^-03
Chronic kidney, n (%)	1618 (24.4)	219 (19.2)	86 (21.4)	628 (23.7)	685 (28.0)	6.4x10^-08
Atrial Fibrillat on, n (%)	1233 (18.6)	262 (23.0)	67 (16.7)	605 (22.8)	299 (12.2)	2.9x10^-24
Creat nine (mg/dL), median [Q1,Q3]	1.1 [0.8,1.6]	1.1 [0.9,1.5]	1.1 [0.8,1.5]	1.1 [0.8,1.4]	1.1 [0.8,1.8]	3.0x10^-07
GFR (mL/min/1.73m^2), median [Q1,Q3]	54.0 [38.0,59.0]	54.0 [43.0,60.0]	54.0 [39.0,59.0]	55.0 [42.0,60.0]	52.0 [31.0,59.0]	3.3x10^-14

Figure. Neighborhood and environmental stressors are correlated to distinct Heart failure with preserved ejection fraction (HFpEF) phenotypes.

A1, Patients with HFpEF phenotype and outcome may be determined by 5 domains of Social Determinants of Health (SDoH), adapted from the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC). **A2**, We clustered communities into four NEnvs using socioeconomic and demographic variables. Clusters were computed using Python (with the following libraries: Pandas, Numpy, Scipy, Sklearn, StatModels, Seaborn, and GeoPandas). **A3**, Each sociodemographic and economic variable on the heatmap can be assigned to the 5 domains of SDoH. We also considered race/ethnicity as demographic features next to SDoH. NEnv-1 is predominantly rural, mostly resided by White and Hispanic individuals, with lower income, health insurance (ins) coverage, college education attainment, and employment. NEnv-2 is also rural, predominantly White individuals, lower income, and advanced age. NEnv-3 is urban, predominantly White and Asian individuals, with higher income (private) health insurance and education. NEnv-4 is urban, lowest portion of White individuals, the highest portion of the Hispanic and Black community, the lowest income, low health insurance, and lower education level. Numbers in this table (and for A4) are the difference between cluster-mean-score and overall-mean-score (original units from census data were converted to *z* scores), where red shading indicates positive *z* scores and blue, negative *z* scores (color-scale-bar normalized between −1 and 1). Differences between scores were evaluated using the nonparametric Kruskal-Wallis test. **A4**, Air pollution, lead levels, noise pollution, drinking water pollution, and crime rates exhibited the highest levels in NEnv-4 and the lowest in NEnv-3, while pesticide pollution showed the highest rate in NEnv-1 (color-scale bar normalized between minimum −0.6 to maximum 0.5). **B**, We mapped 6850 patients with HFpEF onto the 4 NEnv's to analyze their phenotype and neighborhood correlation. Median age was higher in NEnv-1 and NEnv-3, and younger in NEnv-4. Sex was equally distributed across NEnv-1 to NEnv 1-4. Hypertension had the highest prevalence in NEnv-3 (70%) and was >50% in all groups. NEnv-4 displayed the highest prevalence for diabetes, obesity, and chronic kidney disease. NEnv-1 and NEnv-3 displayed the highest prevalence for atrial fibrillation. (*Continued*)

Figure Continued. Creatinine was higher in NEnv-4 vs NEnv-1 to NEnv-3, while glomerular filtration rate (GFR) was lower in Env-4. Kruskal-Wallis and χ^2 tests were used for continuous and categorical variables, respectively. **C**, B-type natriuretic peptide (BNP) levels were highest in NEnv-1 and NEnv-4 (mean, 5.7 [95% CI, 5.6–5.7] pg/dL and 5.5 [95% CI, 5.5–5.6] pg/dL, respectively). **D**, Left ventricular mass index to height was significantly higher in patients residing in NEnv-4 when compared with the rest of the groups. **E**, Cox regression survival analysis adjusted for age and sex showed that patients residing in NEnv-1 and NEnv-4 with lower income and more environmental stressors had higher mortality than patients residing in NEnv-3 with higher income and milder environmental stressors. Asterisk (*) indicates statistical difference compared with NEnv-4 ($P<0.05$). HR indicates hazards ratio; PM, particulate matter; and pop., population.

Nonstandard Abbreviations and Acronyms

HFpEF	heart failure with preserved ejection fraction
NEnv	neighborhood environments
SDoH	social determinants of health
ZCTA	ZIP code tabulation areas

We mapped 6850 patients with HFpEF at UC Davis to their ZCTAs to analyze their phenotype-neighborhood correlation (Figure [B]). We found that 1188 patients resided in NEnv-1, 418 in NEnv-2, 2704 in NEnv-3, and 2539 in NEnv-4. Statistical analysis was conducted with SAS 9.4. As expected from our clustering of NEnv that includes race/ethnicity as variables, while 53% of 6850 were White patients, NEnv-1 exhibited the highest percentage of White patients (71.3%) followed by NEnv-3 (60.7%). First, NEnv-4 had the lowest percentage of White (36.2%) patients and the highest percentages of Black (21%) and Hispanic (16.7%) patients compared with NEnvs1 to 3 (≈10% or lower, $P=3.0\times10^{-160}$). Notably, we observed remarkable phenotype differences across NEnv's. Patients from NEnv 2 and 3 were older (median [interquartile range] age, 70.0 [59.0–80.0] and 73.0 [63.0–81.0] years, respectively) versus NEnv-2 and NEnv-4 (69.1 and 66.6 years, respectively). Second, NEnv-4 exhibited the highest percentage of diabetes (34.6%) and obesity (44.7%). NEnv-3 displayed the highest hyperlipidemia prevalence (50.8%). Prevalence of atrial fibrillation was higher in NEnv-1 and NEnv-3 (23% and 22.8%, respectively) versus NEnv-2 and NEnv-4 (16.7% and 12.2%, respectively) likely due to the more advanced age. Third, while most laboratory values showed no statistically significant difference (NS) across the NEnvs, median (interquartile range) creatinine 1.1 (0.8–1.8) mg/dL was higher and glomerular filtration rate of 52.0 (31.0–59.0) mL/min was lower in NEnv 4 versus NEnv-1 to NEnv-3, indicating a higher risk for kidney dysfunction. Median (interquartile range) B-type natriuretic peptide levels were significantly higher in NEnv-1 and NEnv-4 which could indicate different HF severity and phenotypes (Figure [C]). Fourth, echocardiographic parameters including tricuspid annular pulmonary systolic excursion and left ventricular ejection fraction were NS across the 4 NEnvs (mean left ventricular ejection fraction of 60%); however, left ventricular mass index was significantly higher in patients with HFpEF in NEnv-4 ($P=0.004$; Figure [D]). Finally, Survival analysis (adjusted for age) showed that patients with HFpEF from NEnv-3 (urban, higher income) had the highest survival compared with NEnv-1 (rural, lower income, high pesticide) and NEnv-4 (urban, lower income, excessive environmental stressors) over 8 years ($P<0.001$; Figure [E]). It is critical that our study is interpreted with caution. Although NEnvs were partly determined by race/ethnicity, they are not SDoH because race/ethnicity are not modifiable factors. SDoH are upstream modifiable factors known to explain differences in cardiovascular disease among race/ethnic groups. Patients with HFpEF exhibit phenotypic differences in survival associated with NEnvs. Hence, Neighborhoods and Built Environments in SDoH, can stratify health-risk for patients with HFpEF, which may be reduced by targeted community-driven interventions.

ARTICLE INFORMATION

Affiliations

Department of Medicine, Division of Cardiovascular Disease (D.A.L., H.S., E.R., P.R., P.E.A., M.S., J.E.L., A.Q., C.M., I.E., X.-D.Z., P.S., N.C., M.C.), Department of Pharmacology, School of Medicine (A.B., L.T.I., N.C.), and Department of Public Health (M.A.N.), University of California, Davis. Department of Environmental Studies, Sacramento State University (W.L.). NIH HeartShare Center: Next Generation Phenomics to Define HFpEF, Davis (D.A.L., E.R., P.E.A., J.E.L., I.E., L.T.I., P.S., N.C., M.C.). AHA Strategically Focused Research Network to Study Chronic Psychosocial Stressors, Davis (D.A.L., H.S., A.B., J.E.L., M.A.N., W.L., I.E., X.-D.Z., L.T.I., P.S., N.C., M.C.). VA Northern California Health Care System, Mather (N.C.). Department of Economics, University of San Francisco (M.R.I.).

Sources of Funding

This study was supported by the National Institutes of Health (NIH) HeartShare: Next Generation Phenomics to Define HFpEF (NIH U01HL160274); NIH R01 HL085727, HL085844, HL137228, and VA Merit Review grant I01 BX000576 and I01 CX001490 (N. Chiamvimonvat), HL149431 and R35 HL166575 (L.T. Izu), American Heart Association (AHA) 23SFRNCCS1052478, 23SFRNPCS1060482, and Research Award from the Rosenfeld Foundation (N. Chiamvimonvat, M. Cadeiras, J.E. López); American College of Cardiology Foundation (M. Cadeiras, J.E. López), NIH R01 HL158961 and AHA 23SFRNPCS1061606 (X.-D. Zhang); NIH R56 HL167932, 23SFRNPCS1060482, and T32KT4729 from University of California Office of President (P. Sirish1). N. Chiamvimonvat is the holder of the Roger Tatarian Endowed Professorship in Cardiovascular Medicine and a part-time staff physician at VA Northern California Health Care System, Mather, CA. The other authors report no conflicts.

Disclosures

None.

REFERENCES

1. Redfield MM, Borlaug BA. Heart failure with preserved ejection fraction: a review. *JAMA*. 2023;329:827–838. doi: 10.1001/jama.2023.2020

2. Powell-Wiley TM, Baumer Y, Baah FO, Baez AS, Farmer N, Mahlobo CT, Pita MA, Potharaju KA, Tamura K, Wallen GR. Social determinants of cardiovascular disease. *Circ Res*. 2022;130:782–799. doi: 10.1161/CIRCRESAHA.121.319811
3. Kershaw KN, Magnani JW, Diez Roux AV, Camacho-Rivera M, Jackson EA, Johnson AE, Magwood GS, Morgenstern LB, Salinas JJ, Sims M, et al; Council on Quality of Care and Outcomes Research; Council on Epidemiology and Prevention; Council on Clinical Cardiology; Council on Hypertension; Council on Cardiovascular and Stroke Nursing; Council on Peripheral Vascular Disease; and Council on the Kidney in Cardiovascular Disease. Neighborhoods and cardiovascular health: a scientific statement from the American Heart Association. *Circ Cardiovasc Qual Outcomes*. 2024;17:e000124. doi: 10.1161/HCQ.0000000000000124
4. Rocha P PD, Cadeiras M, Bastos-Filho C. Towards automatic clustering analysis using traces of information gain: the InfoGuide method. The 33rd International FLAIRS Conference. 2020;https://arxiv.org/abs/2001.08677
5. Rocha P, Pinheiro D, de Paula Monteiro R, Tubert E, Romero E, Bastos-Filho C, Nuno M, Cadeiras M. Adaptive content tuning of social network digital health interventions using control systems engineering for precision public health: cluster randomized controlled trial. *J Med Internet Res*. 2023;25:e43132. doi: 10.2196/43132