The Impact of Neighborhoods on CV Risk

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ABSTRACT

Cardiovascular disease (CVD) continues to be the leading cause of death and a major source of health disparities in the Unites States and globally. Efforts to reduce CVD risk and eliminate cardiovascular health disparities have increasingly emphasized the importance of the social determinants of health. Neighborhood environments have emerged as a possible target for prevention and policy efforts. Hence there is a need to better understand the role of neighborhood environments in shaping cardiovascular risk. The MESA (Multi-Ethnic Study of Atherosclerosis) Neighborhood Study provided a unique opportunity to build a comprehensive place-based resource for investigations of associations between specific features of neighborhood physical and social environments and cardiovascular risk factors and outcomes. This review summarizes the approaches used to characterize residential neighborhood environments in the MESA cohort, provides an overview of key findings to date, and discusses challenges and opportunities in neighborhood health effects research. Results to date suggest that neighborhood physical and social environments are related to behavioral and biomedical risk factors for CVD and that cardiovascular prevention efforts may benefit from taking neighborhood context into account.

Despite overall declines in cardiovascular disease (CVD) mortality since the 1970s, it remains the leading cause of death in the United States and a major cause of health disparities [1–4]. A great deal of research over the past 50 years has investigated genetic, biological, and behavioral factors risk factors for CVD [5]. However, there has also been increasing recognition of the need to investigate the upstream causes of these more proximal risk factors. Efforts to reduce CVD risk and eliminate cardiovascular health disparities have increasingly emphasized the importance of the social determinants of health [6]. Signaling the growing awareness of this topic in the cardiovascular health community, a recent statement by the American Heart Association noted that "at present, the most significant opportunities for reducing death and disability from CVD in the Unites States lie within addressing the social determinants of cardiovascular outcomes" [4].

There is a long history in CVD epidemiology of efforts to understand how context broadly defined influences the distribution of CVD. A seminal paper in this area is "Sick Individuals and Sick Populations" by Geoffrey Rose [7], in which Rose makes a strong case for the need to examine not only the drivers of interindividual variability within populations (the "causes of cases") but also the causes of differences in the distribution of cardiovascular risk across populations ("the causes of incidence"). However, traditionally CVD epidemiology has been focused primarily on individual-level risk factors such as behaviors, biomedical risks factors, and more recently genetic factors, often divorced from their social and environmental contexts.

The MESA (Multi-Ethnic Study of Atherosclerosis) with its wealth of longitudinal behavioral, biomedical, and subclinical risk factor data collected across 6 diverse geographic sites and in a large multiethnic sample, presented a unique opportunity to link this rich individual-level information to broader social and environmental contexts. This review summarizes the approaches used to characterize neighborhood environments in the MESA cohort and highlights some of the key findings to date on the links between neighborhoods and cardiovascular risk that have emerged from the MESA Neighborhood Study. Challenges in identifying the health impact of neighborhood factors and ideas for future work are also discussed.

EARLY STUDIES OF NEIGHBORHOODS AND CARDIOVASCULAR DISEASE

Neighborhoods are not the only environmental contexts potentially relevant to the development and prognosis of CVD. Family contexts, work contexts, school contexts, and peer-group contexts among others are all likely to be relevant. Broader macrolevel factors (e.g., the reliance on processed foods, the dependence on the automobile for transportation, the marketing of sugar-sweetened beverages or cigarettes, and the presence of regulations or taxation of tobacco products) also likely play a key role. However, the "meso" level of neighborhoods is of interest for 3 important reasons. First, many of these broader social determinants are manifested, and directly affect individuals, through neighborhood social and physical environments. Thus the study of neighborhoods provides an opportunity to understand the processes linking these broader social and economic factors to CVD in very concrete ways. Second, the strong residential segregation by

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race and class that is present in the United States (and in many other countries) suggests that these neighborhood differences could be important contributors to disparities in CVD. Last but not least, differences across neighborhoods are not "natural" but are the result of the impact of policies (or the absence of policies) and are hence directly amenable to intervention.

In one of the earliest studies of neighborhood health effects, Haan et al. [8] used data from the Alameda County study to show that individuals living in federally designated poverty areas had higher all-cause mortality rates than did individuals residing in nonpoor areas. Subsequent studies used a similar approach to attempt to isolate the impact of "neighborhood socioeconomic context" on a range of outcomes including CVD. For example, Diez Roux et al. [9] used data from the Atherosclerosis Risk in Communities Study to show that living in disadvantaged neighborhoods, as measured by an index derived from census measures, was associated with a higher risk of coronary heart disease (CHD), independent of individual-level characteristics. Other studies have documented that living in socioeconomically disadvantaged neighborhoods is associated with a higher prevalence and incidence of CVD risk factors, [10,11] outcomes [9,12,13], and mortality [14−16].

Although intriguing, these types of studies cannot be used to draw firm conclusions regarding causation. They present methodologic challenges regarding the ability to isolate contextual factors from compositional factors (because the neighborhood measure used is itself an aggregate of the socioeconomic characteristics of residents). Most importantly, they do not allow identification of what neighborhood factors are the true causal factors. Strengthening causal inference requires identifying the specific factors that might be relevant. This is also critical for the development (and subsequent testing) of policies and interventions.

THE CHARACTERIZATION OF NEIGHBORHOOD ENVIRONMENTS IN MESA

The MESA Neighborhood Study was designed to investigate the impact of a set of specific features of neighborhood physical and social environments on CVD risk and the contributions of these specific features to disparities in CVD risk. Critical elements of the study design included the measurement of time-varying neighborhood environments and the ability to link these measures to rich longitudinal risk factor and outcome data collected as part of the MESA parent study.

The hypotheses investigated in the MESA Neighborhood Study and the neighborhood assessments performed were guided by a conceptual framework (Figure 1) that provides an overview of the aspects of neighborhood environments that may be relevant and the potential pathways linking these features to CVD. A major emphasis of the MESA Neighborhood Study was the development and operationalization of a diverse set of strategies to characterize the neighborhood environments of MESA participants over time. This required a careful tracking of the residential locations of MESA participants as well as the

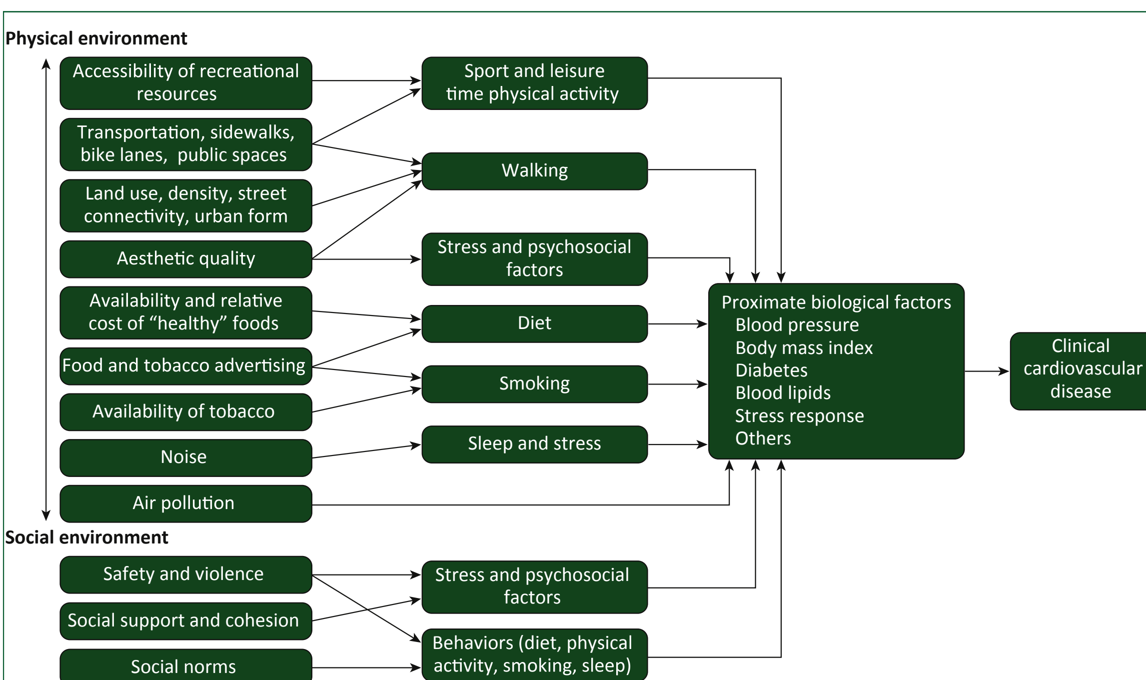

FIGURE 1. Schematic conceptual model of the hypothesized links between neighborhood environments and cardiovascular disease.

periodic measurement of features of neighborhood social and physical environments. This allowed the study to characterize exposure to neighborhood environments not only at the study baseline, but also as cumulative exposure over time, as well as changes in exposures (resulting from residential mobility or from changes in specific neighborhoods over time). The ability to track neighborhood exposures longitudinally was critical to many study hypotheses and specifically to the ability to strengthen causal inferences by linking changes in exposures to changes in outcomes.

At the time of the inception of the MESA Neighborhood Study, the measurement of neighborhood exposures was in its infancy. The majority of studies of neighborhoods and health relied on information from the U.S. Census Bureau and indicators of neighborhood disadvantage. A major contribution of the MESA Neighborhood Study has been the use a diverse set of strategies to characterize environmental contexts. Given the heterogeneous nature of the constructs that needed to be assessed, a combination of measurement strategies was necessary, including survey-based measures, measures based on linking various resources to study participants using geographic information systems (GIS), and audit-type measures [17].

Flexibility in the spatial definition of "neighborhoods" was important given that the appropriate definition of "neighborhood" could vary based on the process being investigated (e.g., for some causal processes, the immediate neighborhood may be important but for others a broader area, perhaps not even identified as a neighborhood by residents, might be more causally relevant). In addition, for some data sources, such as census data, only certain definitions (e.g., census tracts) would be possible based on availability. Hence some measures were created for census tracts (used as proxies for neighborhoods in much previous work) and others were created for buffers of varying size around a person's home in order to allow flexibility in the size of the area investigated, as well as sensitivity analyses.

Survey-based measures

Surveys can be used to assess each individual's perception of his or her neighborhood or aggregated across multiple respondents (who serve as neighborhood "informants") in order to derive more valid and reliable measures of the objective features of neighborhoods by averaging across individual subjectivities. The use of measures based on aggregating multiple respondents also avoids "same source bias" that may arise in using individual neighborhood perceptions when an underlying factor affects both the individual's perceptions of the neighborhood (e.g., whether it is safe or not) as well as self-reported health outcomes (e.g., depression), creating spurious associations. Both approaches were used in MESA. MESA participants themselves were queried about their neighborhoods at several visits and a separate random sample of residents of MESA neighborhoods was surveyed via phone or mail at varying time points at various sites over the course of the study.

A series of scales were used to capture a range of neighborhood constructs including aesthetic quality, walking/physical activity environment, availability of healthy foods, safety, violent crime, social cohesion, activities with neighbors, neighborhood problems, and social and physical disorder [18–21]. Survey items were based on previous work when possible [22–24]. Survey respondents were asked to refer to an area about 1 mile (or a 20-minute walk) surrounding their home [18]. An important contribution of the MESA Neighborhood Study was the investigation of not only the psychometric but also the "ecometric" properties of these scales, that is, the extent to which they reliably capture group-level constructs and the extent to which respondents within a neighborhood agree in their assessments [18]. Another important methodologic innovation was the use of empirical Bayes estimation to derive estimates of neighborhood-level constructs for individual census tracts [25]. This approach improves the reliability of the estimates as a whole by shrinking estimates for neighborhoods with small numbers of respondents to an overall or conditional mean [26].

GIS-based measures

Built environment and access to food, recreational resources and social destinations. An important strength of the MESA Neighborhood Study is the breadth and depth of measures of the built environment. We gathered GIS layers and processed them using ArcGIS (ESRI, Redlands, California) to produce a multitude of measures on density, placement of land uses, street network, and access to destinations around MESA participants' homes. Specific measures were tailored to investigate environmental domains that city and regional planners might be able to influence (e.g., street connectivity, land-use mix, public transportation). Land-use parcel files were obtained from local planning departments, city governments, and regional entities. Areas with higher percentages of land zoned for retail use and lower percentages zoned for residential use were considered to have a higher land-use mix. Land-use mix was also measured as entropy [27] to quantify the similarity in the proportion of the area in parcels devoted to different land uses.

Files containing data on bus routes were obtained from local planning departments, city governments, and regional entities and were used to calculate distance to nearest bus route. Street calculations were performed using StreetMap and StreetMap Premium for ArcGIS (ESRI) [28]. Street connectivity was characterized by the network ratio, which is the proportion of a buffer created using Euclidean distance that is covered by a buffer created using network distance. Composite measures include Walk Score and Transit Score, two commercial measures of neighborhood walkability and transportation access (Front Seat Management, Seattle, Washington).

GIS-based measures of access to food stores, alcohol outlets, physical activity resources, walking destinations, and social engagement destinations were created using data obtained from the NETS (National Establishment Time Series) database from Walls and Associates for the years 2000 to 2010 [29]. We used Standard Industrial Classification (SIC) codes to identify supermarkets and grocery stores, and fruit and vegetable markets, which we classified as healthy food stores [30]. Additional supermarket data was obtained from Nielsen/TDLinx to enhance the supermarket list [31,32]. Alcohol outlets were derived from SIC codes for food stores, and subcodes representing liquor stores and drinking places (consumption on-site) were selected.

For physical activity resources, 114 SIC codes were selected to represent establishments with indoor conditioning, dance, bowling, golf, team and racquet sports, and water activities derived from lists used in previous studies [33,34]. Walking destinations were defined as locations that are common places to walk to [35]. Social engagement destinations were defined as locations that facilitate social interaction and promote social engagement [35]. Simple (unweighted) and kernel (weighted) [36] densities per square mile were created for a range of buffer sizes (one-half, 1, 3, 5 miles) around each residential address.

Data on parks, including the total number of parks, unique types of amenities within parks, and total number of amenities within parks, was also collected using data from municipal or county planning, parks, and recreation departments, the ESRI and TeleAtlas ('s-Hertogenbosch, the Netherlands) [37]. Access to parks was characterized by the percentage of Euclidean buffer devoted to parkland and by densities of types of amenities available within the parks for the range of buffer sizes.

Other GIS-based measures. Additional GIS-based measures included data on crime and foreclosures. Police-recorded crime data for years 1999 to 2012 were available for the Chicago MESA site from the Chicago Police department. Measures for the total number of incidents within crime categories for buffer sizes of one-quarter, one-half, and 1 mile around participants' addresses were created using ArcGIS (version 9.1) [38,39]. Geocoded foreclosure data was obtained from RealtyTrac (Irvine, California) for the years 2005 to 2012 [40,41]. A count of the number of foreclosures within a one-quarter—mile Euclidean buffer around each MESA participant's residence was calculated for each year between exams 4 and 5 using ESRI ArcGIS (version 10.1).

Census-based measures

Neighborhood-level racial/ethnic residential segregation was measured separately for blacks, whites, and Hispanics by using the local *Gi** statistic [42], based on U.S. Census Bureau data. The *Gi** statistic indicates the extent to which the racial/ethnic composition in the focal tract and neighboring tracts deviate from the mean racial composition of some larger areal unit surrounding the tract (in our case, the set of counties represented in each MESA site).

Summary census-based measures of the socioeconomic environment were derived to use for adjustment purposes or for questions related to neighborhood socioeconomic context generally. Census-tract measures were obtained from the U.S. Census 2000 [43], and American Community Surveys [44,45]. We conducted principal factor analysis with orthogonal rotation of 21 census variables reflecting race/ethnicity, crowding, foreign-born, education, occupation, income and wealth, poverty, employment, and housing. Five factors capturing 74% of the variance explained were retained [46].

In addition, we obtained 20-year residential history information prior to MESA baseline. We derived estimates of tract-level poverty by linking residential history to U.S. Census Bureau data from 1980, 1990, and 2000 from the NCDB (Neighborhood Change Data Base) [47]. Using this approach, we derived a measure of average exposure to neighborhood poverty for the 20-year period for each person.

Neighborhood audits

Neighborhood audits and systematic social observation [48] have been proposed as a strategy to characterize important aspects of neighborhoods that cannot be captured using surveys or GIS measures. Extensive systematic social observation was not possible across the 6 diverse sites of MESA. However a substudy at the Baltimore site did an assessment of healthy food availability using a validated store assessment tool. These data were used to demonstrate variability in healthy food availability across stores located in different types of neighborhoods [49] and to examine associations of objectively assessed healthy food availability with diet [50].

SELECT FINDINGS TO DATE

Cross-sectional analyses

Initial analyses focused on investigating the cross-sectional associations between specific neighborhood measures and behaviors or biomedical risk factors.

Neighborhood environments and diet. MESA food environment studies were among the first to use complementary measures of the local food environment across an extended geographic area to examine the robustness of associations of the environment with dietary quality. Analyses of 3 different measures of the local food environment (individual perceptions, neighborhood aggregate survey measures, and supermarket densities) indicated that individuals who lived in less supportive environments were less likely to have a healthy diet than those living in more supportive local food environments [51,52]. Other aspects of neighborhood environments, including social cohesion, were also associated with having a healthy diet [53]. Environment measures were positively but not highly correlated, suggesting that they may tap into complementary constructs [54]. Directly measuring the availability of various healthier foods within stores located in the residential areas of the MESA participants also confirmed that less availability of healthy foods was associated with lower dietary quality [49,50]. MESA has also provided insight into eating out behavior by demonstrating that greater neighborhood exposure to fast food is associated with a poorer diet and greater fast food consumption [55].

Neighborhood environments and physical activity. MESA has provided evidence that participants who live in supportive neighborhood environments report higher levels of physical activity. Overall physical activity level was found to be positively associated with density of recreational resources [56]. Additionally, MESA work suggests that walking may be an important mechanism through which neighborhoods affect physical activity. MESA participants whose residence had higher Walk Scores and Transit Scores had higher levels of walking for transportation [57]. Analyses of specific neighborhood built environment features found greater walking for transportation to be associated with higher population density [58], greater land area devoted to retail uses [58], and greater pedestrian-oriented uses for social interaction such as community centers and other gathering places [59]. Higher perceptions of neighborhood safety and lower levels of neighborhood criminal incivilities were also found to be associated with more walking for transportation and for leisure [39]. Higher neighborhood social cohesion was also associated with more regular physical activity [53].

Neighborhood environments and other health-related behaviors. Neighborhood social environments characterized by less disorder, and higher safety and social cohesion were associated with longer self-reported [60] and objectively measured sleep duration [61]. Adverse neighborhood social and physical environments, and lower neighborhood SES were associated with greater sleepiness, but associations with physical environments were no longer statistically significant after adjustment for sociodemographic characteristics. Residents of neighborhoods with worse walking environments also had higher odds of severe sleep apnea, with this relationship being stronger in male participants and obese individuals [62]. Neighborhood characteristics were not associated with insomnia [60], sleep efficiency, or sleep fragmentation [61]. Neighborhoods that are more socially cohesive [63] and have greater safety and aesthetic quality were associated with lower smoking prevalence (Mayne SL et al., personal communication, August, 2016). Findings for alcohol use were more mixed: a greater density of alcohol outlets was found to be associated with greater alcohol use but only among men [64].

Neighborhood environments and hypertension, body mass index, and insulin resistance. One of the first studies investigating associations between neighborhood physical and social environment indicators and hypertension prevalence was conducted in MESA using data from 3 study sites [65]. Individuals living in neighborhoods with better healthy food availability, opportunities for physical activity, safety, and social cohesion had a lower prevalence of hypertension than did individuals living in worse environments [65]. However, it was difficult to disentangle the effects of race and place in this sample. Subsequent analyses showed that racial/ethnic differences in hypertension prevalence and in an ideal cardiovascular health score were reduced after adjusting for neighborhood-level chronic stressors and other measures of neighborhood physical, social, and socioeconomic environments (Mujahid MS et al., personal communication, August, 2016) [66].

Cross-sectional studies conducted in MESA suggest that living in neighborhoods with better physical environments, based on a summary measure of healthy food availability and opportunities for physical activity, was associated with a lower body mass index (BMI) [25]. The magnitude of the associations were stronger in women than in men. There were no significant associations between neighborhood social environments (a summary measure of safety, social cohesion, and aesthetic quality) and average BMI among women, however, among men, findings were in the unexpected direction. Living in neighborhoods with better social environments was associated with a higher BMI compared with that of men living in lower social environments. Another cross-sectional study in MESA extended these analyses to consider not only the environment of the residential neighborhood, but also the neighborhood environment of the workplaces of employed MESA participants [67]. Associations between neighborhood walkability and BMI were stronger when both residential and work exposures were considered using a weighted average approach (compared with residential exposures alone), suggesting that both contexts may affect behaviors [67].

MESA analyses showed that living in neighborhoods with better physical activity and healthy food resources was associated with a lower insulin resistance and impaired fasting glucose [68]. Other analyses examined the role of resources outside the neighborhood and showed that living further from wealthy areas was associated with higher insulin resistance, independent of the local poverty rate [69]. In an illustration of the potential cumulative impact of neighborhood environments on multiple cardiovascular risk factors, healthy food stores, physical activity resources, walking/physical activity environment, and neighborhood socioeconomic status were associated with higher odds of having an ideal cardiovascular health score [70].

Neighborhood environments and psychosocial or stress-related measures. Neighborhoods may also affect cardiovascular risk through their impact on stress-related processes. Neighborhoods characterized as more stressful (higher poverty, more violence) were found to be associated with lower wakeup cortisol values [19], slower early decline [19,71], and flatter wake-to-bed slope [71].

Higher social cohesion and safety were associated with higher wake-up cortisol, steeper early decline, and steeper wake-to-bed slope [71]. This flattening of the cortisol curve has been hypothesized to be related to adverse health outcomes.

Several MESA publications focused on the links between neighborhood environments and depression or depressive symptoms [62,72–74]. Living in neighborhoods with lower levels of social cohesion [62,73], lower densities of social engagement destinations [74], poorer aesthetic quality [75], and higher levels of neighborhood problems and violence [63,73] was found to be associated with higher levels of depressive symptoms. Findings also documented that living in a neighborhood with a higher percentage of residents of the same race/ethnicity was associated with higher Center for Epidemiologic Studies Depression (CES-D) scores in African American men, but with lower CES-D scores in Hispanic men and women, possibly reflecting the different environmental correlates of these compositional characteristics in different race/ethnic groups [72].

An intriguing body of work has suggested that chronic stress could affect health (including cardiovascular health) through its impact on telomere shortening [75–77]. We found that respondents who lived in neighborhoods characterized by lower aesthetic quality, safety, and social cohesion had shorter telomeres than those who lived in neighborhoods with a more salutary social environment [78].

Longitudinal analyses

A major goal of the MESA Neighborhood Study was to capitalize on longitudinal data to investigate not only whether neighborhood factors are related to changes over time in risk factors or incident disease, but also to investigate the impact of cumulative exposures and to examine whether changes in exposures are related to changes in outcomes. Longitudinal analyses are ongoing and will continue as MESA follow-up continues. A few recent examples are described here.

Behaviors. Physical activity (including walking) has been the behavior most investigated in relation to neighborhoods in MESA. This is because multiple repeated measures of physical activity are available (in contrast to diet where only baseline and 1 follow-up measure are available) and because it can be hypothesized that changes in neighborhood environments may show relatively quick effects on physical activity behaviors. While overall physical activity decreased over time in MESA, increases in the neighborhood density of recreational resources were associated with a less pronounced decline over time [79]. In econometric fixed-effects models [80], MESA participants who moved to a location with higher Walk Score experienced a simultaneous increase in walking for transportation [81]. Moving to an area with higher walkability, however, was not associated with walking for leisure [81], perhaps because the Walk Score measure heavily focuses on access to destinations. Density and street connectivity were the most consistently associated with positive transportation walking trajectories [82].

Neighborhoods with higher baseline population density, land zoned for retail, density of destinations for social engagement, density of walking destinations, and street connectivity were associated with greater increases in walking for transportation over time [82]. In contrast, higher baseline levels of land zoned for residential uses or being farther from buses at baseline were associated with less pronounced increases (or decreases) in walking for transportation [82]. Increases over time in the number of destinations (for both walking and social engagement) and street connectivity were associated with greater increases in walking for transportation [82]. No associations were observed between change over time in specific environmental features and leisure walking trajectories [82]. No associations were found between changes in perceived safety and changes in either walking for transportation or for leisure [38]. However, residing in a neighborhood that experienced an increase in homicides was associated with decreases in transport walking [38].

Increases in liquor store densities [46] and neighborhood foreclosures were associated with increases in weekly alcohol consumption (Crawford N et al., personal communication, August, 2016). No association was observed between changes in the social environment and changes in smoking risk over time (Mayne et al., personal communication, August, 2016). However, longitudinal analyses of smoking and alcohol use are limited by the relative stability of these measures over time in MESA.

Diabetes, obesity, and hypertension. Two of the first studies to examine associations of neighborhood physical and social environments with incidence of type 2 diabetes were conducted in MESA [21,83]. The first study found that among those free from type 2 diabetes at baseline, better neighborhood physical activity and healthy food resources at baseline was associated with a lower incidence of type 2 diabetes [83]. These analyses were restricted to individuals at 3 of 6 MESA sites who were followed for an average of 5 years. In a subsequent study, extended to include all MESA sites and both survey-based and GIS-based measures of cumulative exposures, a 1 SD better healthy food availability and a 1 SD better access to physical activity resources were associated with a 12% and 21% lower risk of developing type 2 diabetes, respectively, over an average of 8.9 years of follow-up [21]. The survey-based measures had the most consistent associations with type 2 diabetes. Increases in neighborhood foreclosures were associated with small increases in fasting glucose but hypothesized associations with other risk factors were not observed [84].

Among MESA participants without obesity at baseline and followed for an average of 5 years, living in neighborhoods with a better healthy food and physical activity environment was associated with a lower incidence of obesity [85]. In subsequent analyses that extended the follow-up and included time-varying neighborhood data over the

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10-year follow-up, improvements in the healthy food and physical activity environment were associated with a decrease in BMI among those obese at baseline but associations were in the unexpected direction among persons with normal weight at baseline (Barrientos-Gutierrez T et al., personal communication, August, 2016). Changes in the built environment including increases in intensity of developments (e.g., higher density of walking destinations) were associated with less pronounced increases in BMI and waist circumference during a median of 9.1 years of follow-up, but there was no association between changes in connected retail centers (e.g., higher percentage of retail and street connectivity) or public transportation (e.g., distance to a bus) and changes in BMI or waist circumference [86]. There were also significant associations between moving to a location with a better walking environment and reductions in BMI over time within the subset of 700 MESA participants who moved between 2004 and 2012 [82]. Studies investigating associations between the social environment and obesity found that perceptions of improved neighborhood safety were associated with lower adiposity (BMI and waist circumference) over a 10-year follow-up for men but the opposite effect was observed in women [87]. There were no associations between police-reported crime and adiposity measures [87]. However, these analyses had limited power because they were restricted to participants within the Chicago site.

Among MESA participants free from hypertension at baseline and followed for a median of 10 years, a 1 SD higher healthy food availability score was associated with a 12% lower incidence rate of hypertension [88]. There were no associations between other neighborhood physical and social environment indicators and incident hypertension.

Psychosocial and stress factors. An early MESA report based on 4 to 5 years of follow-up found that adverse neighborhood social environments were associated with incident depression, defined by CES-D $\geq$16 or taking an antidepressant medication in women, but confidence intervals were wide and no association was seen for men [73]. In subsequent analyses, we found that long-term cumulative exposure to social cohesion, safety, and social engagement destinations were not associated with changes in depressive symptoms over time [74], but within-person increases in safety [74] and social cohesion [20,74] were associated with decreases in CES-D. No association was found between changes in social engagement destinations [74] or neighborhood foreclosures and changes in CES-D (Crawford ND et al., personal communication, August, 2016). In other analyses, neighborhood poverty and social environments were not consistently related to changes in cortisol over time [71], although these analyses were likely limited by the complexity of measuring changes in cortisol profiles.

Subclinical atherosclerosis and cardiovascular events. Few studies have investigated the impact of neighborhoods on subclinical atherosclerosis or incidence of cardiovascular events. If neighborhoods affect the development of atherosclerosis or the incidence of events, they must do so over very long periods, limiting the utility of even 10-year cohort studies such as MESA to detect such effects. However, the MESA Neighborhood Study has begun to explore some of these associations within the constraints of the data available. Neighborhood poverty, both a contemporaneous measure and a cumulative 20-year long-term exposure, was inversely associated with common carotid intima-media thickness in women [89,90]. Recent analyses suggest that increases in density of neighborhood healthy food stores may be associated with decreases in coronary artery calcification [91]. Changes in recreational resources and survey-based availability of healthy food, walking environment, and social environment were not associated with within-person change in coronary artery calcification. These findings warrant replication.

Residential segregation by race may result in differences in neighborhood physical and social environments with important consequences for health [92]. The availability of measures of racial segregation made it possible to investigate this question in MESA. Among blacks, each standard deviation increase in black segregation was associated with a 12% higher hazard of developing CVD after adjusting for potential confounders (95% confidence interval [CI]: 1.02 to 1.22). For whites, higher white segregation was associated with lower CVD risk after adjusting for demographics (hazard ratio, 0.88; 95% CI: 0.81 to 0.96), but not after further adjustment for other neighborhood characteristics. Segregation was not associated with CVD risk among Hispanics [93].

In other preliminary analyses, there was a nonlinear relationship between neighborhood-level stressors and incident CHD. Participants in the medium category had 49% higher CHD risk (95% CI: 1.06 to 2.10) compared with those in the low category; those in the high category had 27% higher CHD risk (95% CI: 0.83 to 1.95) [94]. Analyses linking neighborhood physical and social environments to CVD incidence are awaiting the compilation of additional events in the MESA cohort.

Strengths and limitations

The diversity of the MESA cohort in terms of geography, race/ethnicity, and socioeconomic characteristics is critical for improving understanding of the role of neighborhoods in shaping cardiovascular health and health disparities. A second major strength is the rich neighborhood-level data that has been linked to the cohort. Creating measures across multiple neighborhood domains using a multiplicity of measurement approaches allows for a rich set of analyses. A third major strength is the time-varying nature of both neighborhood and individual-level data allowing investigation of how changes in neighborhood environments are associated with changes in health outcomes over time. More specifically, the design allows the use of econometric fixed-effects models to examine how within-person change in neighborhood exposures is related to within-person change in outcomes while tightly controlling for time invariant characteristics [95].

The MESA Neighborhood experience has highlighted important challenges. Despite the intense effort invested in characterizing neighborhoods, many of the measures remain crude. For example, the density of supermarkets is necessarily a very imperfect proxy of access to healthy foods given that the quality and quantity of healthy foods present in supermarkets may vary substantially across places [49]. The time-resolution of some of the data remains limited; for example, the survey measures capture only limited time-variability over follow-up and diet was only assessed at 2 time points. Some important measures such as objectively measured crime could not be obtained with adequate spatial resolution across all sites. Despite many years of research on neighborhood health effects, there is still very little theory or evidence on which to base the definition of the appropriate spatial scale for different causal processes. The MESA Neighborhood Study grappled with this question by creating flexible measures (e.g., buffers of different sizes), but this can also introduce multiple testing issues and other methodologic challenges.

Although the ability to employ econometric fixed-effects models is an important advance, these models are very inefficient when there is low within-person change in exposures or outcomes. This has been a challenge in MESA data because of limited variability in many variables over time linked in part to the age and stability of the cohort. More fundamentally, an older cohort such as MESA may not be the best sample in which to investigate how changes in neighborhoods may relate to changes in behaviors or biomedical risk factors over time. In addition, cardiovascular risk factors in older adults are likely to be influenced by life-course exposures and may be much less responsive to changes in environments than they would be in younger samples.

A major challenge in MESA has been the confounding of neighborhood exposures by race/ethnicity and study site. Strong residential segregation by race has sometimes made it difficult to isolate race differences from neighborhood differences. Although the presence of 6 sites has added important geographic and neighborhood diversity, there is always the lingering question as to whether site is exerting an “independent” effect on the outcomes through mechanisms that do not involve neighborhoods and should therefore be adjusted for. This however may result in the site absorbing much of the neighborhood variance and power for within-site analyses is often low. Some of the individual-level outcome data have also posed challenges. Repeat measures of physical activity measures have been very useful but objectively measured physical activity would likely have been more informative. The power for event analyses, a key goal of the study, is still low due to relatively low event rates in the sample.

The MESA Neighborhood Study shares some of the limitations of other neighborhood studies. Information on other contexts (work or family) is limited. Even with the use of longitudinal methods, causal inference is limited by the observational nature of the study if underlying predispositions linked to the outcomes affect residential location (a matter that should itself be the subject of empirical inquiry). It is often challenging if not impossible to isolate the effects of multiple correlated neighborhood measures, and yet this is critical to identifying promising interventions. Although having 6 diverse geographic sites is a major advance over single-site studies, these sites are by no means representative of geographic variability across the United States. This may limit the ability to detect important effects and to generalize findings to other contexts.

SUMMARY AND FUTURE DIRECTIONS

Results from the MESA Neighborhood Study point to the relevance of environmental contexts to cardiovascular risk. The study documented that better food and physical activity environments are generally related to better dietary and physical activity behaviors. Moreover, favorable changes in physical activity environments were found to be associated with favorable changes in physical activity behaviors (especially walking). Healthier neighborhood food and physical activity environments were also related to lower incidence of diabetes and hypertension and to favorable changes in BMI over follow-up (in some subgroups). Adverse neighborhood social environments (characterized by less safety, more violence, higher disorder, or lower social cohesion) were associated with shorter sleep duration, altered daily cortisol patterns, and higher levels of depressive symptoms. Living in segregated areas was associated with higher incidence of CVD in African Americans.

Additional follow-up of the cohort will allow for additional longitudinal analyses that are necessary to strengthen causal inferences. The eventual linkage of the cohort to geographically and time-varying policy data may allow more specific evaluation of the impact of various policies by capitalizing of natural experiments. Future studies will need to consider the interactive effects of policies as well as potential unintended effects (e.g., increasing walkability resulting in greater exposure to traffic-related air pollution) [96].

Analyses examining interactions between neighborhood factors and individual-level variables (e.g., degree of dependence on neighborhoods for various resources, utilization of neighborhood amenities, or genetic factors) may yield additional insights on the circumstances under which neighborhood factors are likely to be most relevant. Ultimately, a series of complementary approaches including observational studies such as the MESA Neighborhood Study, policy evaluations, and simulation modeling will be necessary to identify effective neighborhood interventions to improve cardiovascular health [97].

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