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Longitudinal neighbourhood determinants with cognitive health and dementia disparities: protocol of the Multi-Ethnic Study of Atherosclerosis Neighborhoods and Aging prospective cohort study

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ABSTRACT

Introduction The burden of Alzheimer's disease (AD) and AD-related dementias (ADRD) is increasing nationally and globally, with disproportionate impacts on lower-income, lower education and systematically marginalised older adults. Presence of inequalities in neighbourhood factors (eg, social context, physical and built environments) may affect risk of cognitive decline and be key for intervening on AD/ADRD disparities at the population level. However, existing studies are limited by a dearth of longitudinal, detailed neighbourhood measures linked to rich, prospective cohort data. Our main objective is to identify patterns of neighbourhood change related to prevalence of—and disparities in—cognitive decline and dementia.

Methods and analyses We describe the process of collecting, processing and linking extensive neighbourhood data to the Multi-Ethnic Study of Atherosclerosis (MESA), creating a 25+ years dataset. Within the MESA parent study, the MESA Neighborhoods and Aging cohort study will characterise dynamic, longitudinal neighbourhood social and built environment variables relevant to cognition for residential addresses of MESA participants. This includes administering new surveys, expanding residential address histories, calculating new measures derived from spatial data and implementing novel deep learning algorithms on street-level imagery. Applying novel statistical techniques, we will examine associations of neighbourhood environmental characteristics with cognition and clinically relevant AD/ADRD outcomes. We will investigate determinants of disparities in outcomes by socioeconomic position and race/ethnicity and assess the contribution of neighbourhood environments to these disparities. This project will provide new evidence about pathways between neighbourhood environments and cognitive outcomes, with implications for policies to support healthy ageing.

Ethics and dissemination This project was approved by the University of Washington and Drexel University Institutional Review Boards (protocols #00009029 and #00014523, and #180900605). Data will be distributed through the MESA Coordinating Center. Findings will be disseminated in peer-reviewed scientific journals, briefs, presentations and on the participant website.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Creates a robust, longitudinal, 25+ years dataset of neighbourhood measures relevant to ageing across six US cities.

⇒ Leverages comprehensive, longitudinal cognitive, clinical and adjudicated data for Alzheimer's disease and AD-related dementias (AD/ADRD) outcomes.

⇒ A multi-ethnic cohort (non-Hispanic white; non-Hispanic black; Hispanic; Chinese) facilitates examination of disparities in AD/ADRD or differential impacts of neighbourhoods for AD/ADRD across groups.

⇒ Data challenges remain in capturing ground reality using Geographic Information Systems or in holistically capturing all elements of neighbourhood context at all relevant spatial scales.

⇒ Power and generalisability may be limited for analyses of more intensive outcomes that are being collected on a subset of participants (eg, β-amyloid from positron emission tomography scan will be available in a subset of participants, at a subset of sites).

BACKGROUND

While substantial evidence has identified individual-level factors impacting cognitive health and dementia risk, a smaller and still growing body of literature supports the role that neighbourhoods and the environment play in cognition and dementia risk.[1 2] First, unsupportive environments may negatively impact risk factors for cognitive decline and Alzheimer's disease (AD) and AD-related
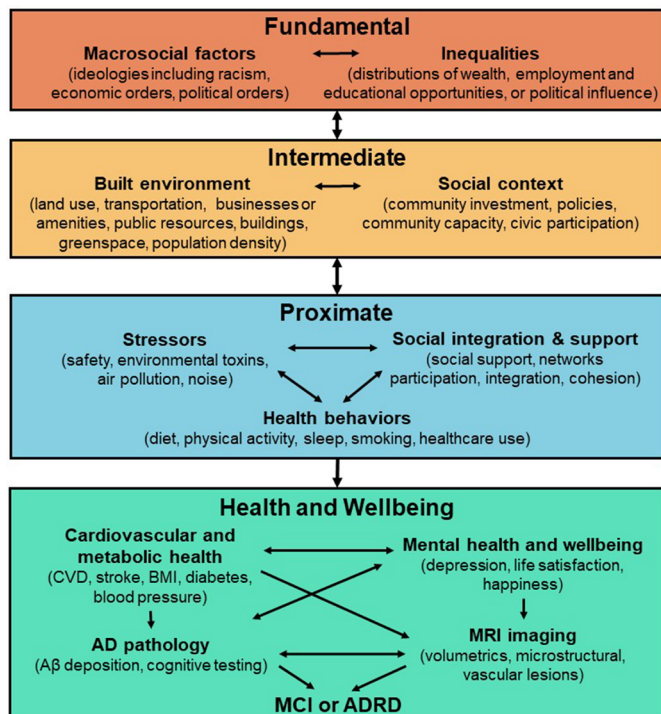
Figure 1 Conceptual framework through which social and environmental determinants impact ADRD. AD, Alzheimer's disease; ADRD, AD-related dementias; Aβ, β-amyloid; BMI, body mass index; CVD, cardiovascular diseases; MCI, mild cognitive impairment.

dementias (AD/ADRD), as illustrated through studies on sleep,[3 4] physical activity,[5–8] nutrition,[9–12] diabetes[13 14] and cardiovascular risk.[15–19] Second, neighbourhood environments may play a direct role in maintenance of cognitive capacity. Access to transit, green spaces and walkable retail may encourage older adult social interaction and engagement which may help retain cognition.[20–22] Similarly, living in a neighbourhood with high social cohesion, safety and socioeconomic position may buffer against cognitive decline and provide the necessary resources to cope with changes in cognition through the ability to be more physically active, have connections to neighbours for support or navigate environments safely.[23–26] In these ways, residential environments (specifically built or physical environments and social context) represent a vital and tangible link as intermediate factors between fundamental societal structures (such as racial segregation or income inequality) and more proximate causes of cognitive health and well-being (figure 1).

However, existing studies are limited by measurement of the neighbourhood environment, a focus on single environmental features and a dearth of longitudinal neighbourhood data linked to prospective cohort data. Current work has generally focused on objective measures created from available spatial data, ignoring participant perceptions and features that cannot be captured using these data (eg, social cohesion). This is likely due to the difficulty in obtaining data which require participant contact and surveys, and the strong potential

for recall bias among those who are experiencing cognitive decline. Instead, work is needed that leverages pre-existing survey data (ie, data from neighbourhood studies started prior to cognitive decline) while collecting additional data specific to ageing outcomes. Another major challenge has been in understanding how best to examine multiple environmental features simultaneously (sometimes called the 'exposome'). Current approaches examine one domain of the environment at a time but ignore that features may operate in tandem or with heterogeneous effects. Existing[27–33] and ongoing (eg, R01 HL131610, PI Sanchez; 5K99AG066949-02, PI: Pescador Jimenez; R01AG072634, PI: Hirsch) work aims to address this, including this study. Further, most studies lack depth of objective cognitive phenotyping necessary to study AD/ADRD. Most existing research also lacks longitudinal data on both environments and cognition to address reverse causation, account for long-term, time-varying patterns of the environment and assess neighbourhood change processes/dynamics. New work is necessary to understand typologies of dynamic, interconnected shifts in social, natural and built environments and their subsequent impacts on cognition.

Critically, there are known disparities in AD/ADRD risk. African American and Hispanic individuals face the highest and most disproportionate risk for AD/ADRD.[34–36] Similarly, studies show a consistent pattern of disadvantage for individuals with low socioeconomic status.[37–39] Yet research examining cognition and AD/ADRD has traditionally excluded these populations[35 40] and failed to examine the same broad set of determinants within these populations. Given historic and current patterning of healthy neighbourhood factors by racial and socioeconomic characteristics,[41–44] the lack of healthy neighbourhood features may partially explain observed disparities in AD/ADRD risk. Research has identified inequalities in access to food stores,[43–45] recreation facilities,[41 46] green space[41 42 46–48] and transit,[49] that impact risk factors for AD/ADRD. These inequalities are not static, with evidence showing that environmental changes that support health behaviour are more prominent in white, wealthy neighbourhoods.[50 51] To date, there has been little research on the role of neighbourhood environments in disparities in AD/ADRD risk.

Given these gaps, we created an ancillary study that leverages the strengths of the existing Multi-Ethnic Study of Atherosclerosis (MESA) parent study and its detailed neurocognitive phenotyping. We plan to administer new, ageing-related neighbourhood questions, recalculate measures from new spatial data using Geographic Information Systems (GIS), explore new imagery measures and implement novel statistical techniques. We will use tradiational and deep learning techniques to elucidate patterns in social and built environments that represent dynamic neighbourhood change and enhance understanding of simultaneous impacts across a broad range of environmental features. Georeferenced images available from Google Street View (GSV) and deep learning algorithms

will be used to develop novel measures of the built environment representing an on the ground perspective. Leveraging the racial and geographic diversity of MESA, we will be able to examine the impact of neighbourhood factors across diverse populations and understand the role that inequalities in neighbourhood contexts might play in racial and socioeconomic AD/ADRD disparities. This manuscript outlines the protocol for the MESA Neighborhoods and Aging Study (R01AG072634, PI: Hirsch), including details for deep learning algorithms (5K99AG066949-02, PI: Pescador Jimenez).

METHODS/DESIGN
Aims and hypotheses
We will conduct a longitudinal study to evaluate the role of dynamic, long-term, neighbourhood social and built environments on risk of cognitive decline and dementia among a national, multi-ethnic cohort of older adults in the USA. The goals of this study are to produce evidence on longitudinal predictors of objective cognitive impairment, incident cognitive decline and biomarkers indicative of AD/ADRD pathology among a diverse cohort, and evaluate the role that inequalities in neighbourhood contexts plays in disparities in these outcomes. Our central hypothesis is that older adults living in supportive neighbourhoods (eg, high walkability, high social cohesion) and which remain stable or improve over time will experience less cognitive decline and dementia. We aim to[1]: examine associations of neighbourhood environmental characteristics with cognition, cognitive impairment and evidence of AD biomarkers, and[2] characterise disparities in cognition and clinically relevant AD/ADRD outcomes by socioeconomic position and race/ethnicity and assess the contribution of neighbourhood environments to these disparities.

Design, setting and participants
We will recruit members of an existing study, MESA, and collect detailed social determinants of health information and updated addresses to add to address histories. The address histories will be used to characterise dynamic, longitudinal change in neighbourhood social and built environment variables (survey-based and GIS-derived) from 2000 to 2024. These study participants will be followed to characterise brain health, including administration of a neurocognitive battery and clinical interview, laboratory assessments, including brain MRI and β-amyloid from positron emission tomography (PET) scan (Aβ-PET) imaging (within a subsample), and adjudicated outcomes of mild cognitive impairment (MCI) and AD/ADRD.

In 2000–2002, the MESA parent study enrolled a sample of 6814 participants aged 45–84 years (39% non-Hispanic white, 22% Hispanic, 28% African American and 12% Chinese American) from six sites: Columbia (NY); Johns Hopkins (MD); Northwestern (IL); University of Minnesota (MN); UCLA (CA) and Wake Forest (NC).[52] MESA

was designed to evaluate subclinical cardiovascular disease and progression; participants with overt cardiovascular disease were excluded at baseline. Participants have since undergone six in-person assessments (see https://www.mesa-nhlbi.org/aboutMESAStudyTime.aspx). Participants are contacted every 9–12 months by telephone to assess clinical morbidity and mortality. Participation has remained consistent; 4655 participated in Exam 5 in 2010–2012 and 3303 completed Exam 6 (2016–2018). Any participant attending Exam 7 (planned 2022–2024) will be eligible to enrol in this MESA Neighborhood and Aging study. This MESA Neighborhood and Aging study will first create and collect neighbourhood data to cover through Exam 7 and then will link those data to detailed neurocognitive phenotyping from MESA-MIND (R01AG058969, MPI: Hughes, Hayden and Luchsinger) to create novel cognition-related neighbourhood data assessments for all examinations (2000–2024). The MESA Neighborhood and Aging study began in summer 2021 (with Exam 7 beginning in 2022) and will complete in winter 2026.

Neighbourhood measures-GIS
Geographic scale
We will calculate business establishment densities, built environment measures and socioeconomic status (SES) metrics for MESA participant residential neighbourhoods. These exposures will be created for multiple circular (eg, Euclidean 'straight line') and network (ie, following the street) distance buffers around participants' home addresses (ranging from 0.25 miles/0.4 km to 5 miles/8 km) and administrative boundaries to enable future users to examine associations at varying geographic scales. Measure created for administrative boundaries (census tracts, Zip Code Tabulation Areas), calculated for the contiguous USA, will also expand opportunities for linkage to additional cohorts. Although administrative boundaries shift over time, we anticipate using 2010 census boundaries for consistency across time since this is a midpoint between 2000 and present data. Most measures below will be available for all geographies. However, a few select data sources (eg, land use parcels, parks) may only be available within the six MESA field centre geographies.

Updates of prior measures and additional measures of health-related amenities
We will process and calculate densities of all businesses related to health (eg, food, recreation facilities, social destinations, walking locations, etc) for all MESA residential addresses using updated data from the commercial National Establishment Time Series (NETS) database,[53] with classifications enhanced by data from Neilsen (TD/Linx).[54 55] NETS includes data on establishments compiled by Dun and Bradstreet since 1990 and updated annually. We will[1]: regeoreference all establishments to ensure consistency in geocoding over time[2]; create a system that classifies amenities according to the health

services and/or resources they provide, based on standard industrial codes, word and name searches, and other complementary data sources (eg, TD/Linx); and then[3] link establishments to buffers around participants' residential addresses and administrative boundaries as counts, densities, and calculated distances.

We will expand on neighbourhood measures by creating density measures individually and in aggregate for three ageing-related domains not previously used in MESA: cognitive enrichment destinations, gathering spaces for older adults and healthcare resources. Cognitive enrichment destinations facilitate cognitive improvement; enrichment may be passive (eg, performance-based entertainment such as ballet) or more interactive (eg, non-physical activity recreation clubs, such as bridge). This includes: performance-based entertainment; libraries; social clubs; museum/galleries; colleges/universities; political organisations; non-physical activity recreation clubs; multi-use physical activity facilities and religious organisations. Gathering spaces for older adults will include formal resources (eg, senior centres, recreation centres) as well as informal locations (ie, volunteer opportunities, cognitive enrichment locations above). Healthcare resources will include: physical therapy/massage; drug stores/pharmacies; mental and behavioural healthcare; hospital-based inpatient care (ie, hospitals and major medical centres); community-based care; ambulatory care; acute episodic care; offices/clinics of health practitioners; dental care; urgent care and all clinical treatment. We will also extend through 2023 longitudinal measures of the following health-related establishments previously calculated for MESA: recreational facilities (eg, indoor conditioning facilities, water activities); food stores/restaurants (eg, supermarkets, ice cream/candy shops, convenience stores, liquor stores, fast food); destinations for social engagement (eg, barber/beauty shops, entertainment, zoos, arboretums, religious organisations) and activities for daily living (eg, post service, banks).

Additional built environment measures
Novel data will incorporate policies for healthy ageing linked to neighbourhood, county or city, as appropriate. We will link the AARP nationwide neighbourhood Livability Index (https://livabilityindex.aarp.org/) to participants' addresses to obtain scores for each of AARP's seven livability domains and total livability. We will also create a binary variable indicating whether participants reside in a city or county in the AARP Network of Age-Friendly Communities. These communities are places that have made a commitment to becoming more livable over time.

We will also extend longitudinal built environment measures of land use mix, population density, street connectivity, transit proximity and park space to investigate urban form. We will collect land use data through direct contact with various government sources in the city in which each MESA site resides and also code parcels (eg, residential, retail) to calculate per cent of each land use type within residential buffers. Population density

will be created based on total population from 2020 Census block population data. Street connectivity will be measured by intersection density and network ratio using street files from 2000, 2010 and 2020, available for the entire USA. Distances to nearest train/subway stops and bus lines will be calculated based on public transit files obtained through government sources for the MESA field cities. Our team will collect data on parks from 36 counties in the six MESA metropolitan areas, including spatial datasets with park boundaries and calculate neighbourhood park space as per cent of buffer and distance to parks.[56 57]

Updated and new neighbourhood SES and demographic measures
We will process and create neighbourhood-level socio-economic and demographic measures for residential addresses 2000–2024 from US Census and American Community Survey data. We will calculate novel indicators of neighbourhood age composition and segregation. Age composition will be measured as proportion within specific age brackets (18–44, 45–64 and 65+ years). Age trajectory profiles will be calculated using finite mixture modelling identifying trajectory classes; our previous work found three classes stable, declining or increasing older adult populations.[58] Age segregation will be measured for 65+ using the local Gi* statistic.[59] The Gi* statistic returns a Z score for each neighbourhood (census tract), indicating the extent to which the age composition in the focal tract and neighbouring tracts deviates from the mean age composition of a larger areal unit (set of counties in each site). Positive Gi* scores indicate higher segregation/clustering (over-representation), scores near 0 indicate integration and negative scores suggest lower representation (under-representation).

Based on earlier measures,[60] we will create two SES indices at the census tract level using principal factor analysis of measures of educational attainment, occupation, income, wealth, poverty, employment status, housing characteristics and race/ethnicity. We will extend existing data through 2024 to assess racial/ethnic residential segregation for blacks, whites, Asians and Hispanics using the local Gi* statistic, which better reflects spatial segregation than simple proportion measures.[59 61 62] We will calculate additional age and race/ethnicity segregation measures using other metrics from the field (eg, Index of Concentration at the Extremes), as appropriate.[63]

Neighbourhood measures-survey
We will administer a questionnaire to assess neighbourhood aesthetic quality (three items), walking environment (four items), availability of healthy foods (two items), safety (two items) and social cohesion (four items). Responses for each item will range from 1 (strongly agree) to 5 (strongly disagree). We have added novel ageing-related questions around lighting, restroom access, physical function supports (eg, curb cuts, benches), cognitive function supports (eg, wayfindings, public art), educational opportunities and more. Based

on theoretical impacts of neighbourhood change and perceived racism on cognition, we will include the novel PACER (Perceptions About Change in Environments and Residents) survey. Our team designed PACER to measure overall change, changes in amenities, changes in the physical environment, changes in the social environment, changes in population composition and feelings about changes. PACER has been piloted on a sample of the BeHeardPhilly panel study and found to be both consistent with objective measures based on spatial data and a distinct measure of neighbourhood change.[64] Survey is included in online supplemental appendix 1.

Neighbourhood measures-imagery and machine learning

We will use deep learning segmentation algorithms applied to nationwide GSV images. GSV images offer the opportunity to generate refined estimates of exposure to built environment (eg, green space, benches) as individuals experience it. The pyramid scene parsing network (PSPNet)[65] is the deep learning algorithm we will use to segment out up to 150 specific features of the built environment down to the pixel level, including natural features such as trees, shrubs, grass, plants and flowers, and physical features such as building types, sidewalks and benches. Driven by powerful deep neural networks,[66–69] PSPNet applies pixel-level prediction tasks using a convolutional neural network.[70–72] PSPNet also incorporates local and global contextual cues together yielding a >93% overall accuracy in predicting built environment features.[73] We will download georeferenced GSV images from the Google Maps Application Programming Interface for a 100 m grid along the street network of all cities where MESA participants live by date. We will process each GSV image using the PSPNet deep learning algorithm. The output for each image will be percentages of pixels of built environment features within each image. The percentages will be averaged across four images (0°, 90°, 180° and 270° horizontal field-view angles) to create percentages of built environment features within view at GSV image locations near grid cells in the cities. We will spatially join each residential address over follow-up to all images within 1500 m, as well as the average of all images in a 100 m buffer. As a result, each residential address will be linked to GSV-derived built environment metrics from 2007 (the first date GSV images are available) to 2020 (updated intermittently).

Outcome measures

Assessments of MESA participants' cognition have been ongoing since 2010 and expanded as part of MESA-MIND and will be continued through 2024. The following outcomes will be linked to the neighbourhood trajectories to achieve our study aims.

Cognitive assessments

Beginning in 2010, MESA participants completed a brief cognitive examination, including: the Cognitive Abilities Screening Instrument (CASI),[74 75] Digit Symbol Coding (DSC) and Digit Span (DS)[76 77] tests to assess changes over follow-up. Beginning in 2016 with select sites and 2019 with all MESA sites, the Uniform Data Set V.3 (UDS v3) was combined with MESA tests.[78] The UDS v3 is currently the core assessment tool administered at NIH-funded AD Research Centers across the USA and includes the neurocognitive battery and a clinical interview. The battery comprises the Montreal Cognitive Assessment,[79] Craft Story,[80 81] Benson Complex Figure Test,[82] Number Span, Category Fluency (animals, vegetables), Phonemic Fluency and the Trail Making Test Parts A and B.[83 84] The Wide Range Achievement Test[85] is added to ascertain reading proficiency and vocabulary. Informants, designated by MESA participants, are interviewed using a modified UDS protocol including: the Quick Dementia Rating Scale,[86] Neuropsychiatric Inventory Questionnaire and the Functional Abilities Questionnaire. We will use both a composite of the core tests and domain composites from the UDS and MESA tests. These tests and questionnaires are translated and administered in English, Spanish, Mandarin and Cantonese languages spoken by MESA participants and their informants. These batteries have also been adapted to telephone and video based administration. Standardised normative data for these tests are available non-Hispanic white and African-Americans.[87]

Neuroimaging

MESA includes multimodal neuroimaging used to characterise cerebral structure and function and inform aetiology of cognitive syndromes. Brain MRI is obtained two times 3–5 years apart (between 2017 and 2024). Brain MRI will be acquired at all six field centres for all participants on 3T MRI scanners with a high resolution 20-channel head/neck coil. MRI sequences include: T1 (for volumetrics and morphology), T2 FLAIR (to quantify white matter hyperintensities, WMH), BOLD/fMRI (for resting state brain connectivity also repeated with breath-hold), 3D arterial spin labelling (for quantification of regional cerebral blood flow),[88] diffusion tensor imaging, and susceptibility weighted imaging and quantitative susceptibility mapping (QSM). QSM enables the quantification of cerebral microbleeds and cortical microinfarcts. Aβ-PET imaging is obtained on a subsample of MESA participants (at three sites between 2016 and 2024) who completed brain MRI using the [11C] Pittsburgh Compound B (PiB) PET. The extent of Aβ deposition in the brain is quantified by [11C]PiB uptake visualised by PET using standardised uptake volume ratio of six primary cortical areas (ie, anterior cingulate, prefrontal cortex, lateral temporal cortex, posterior parietal cortex, precuneus cortex and anteroventral striatum) relative to the uptake in the cerebellum.

MCI and AD/ADRD

All cognitive and clinical data will be assessed by a convened consensus conference of clinicians (eg, neurologists, neuropsychologists, and geriatric psychiatrists, geriatricians) experienced in adjudication of MCI and AD/ADRD in English, Spanish and Chinese languages.

All available case materials including cognitive testing results, and clinician impression, and other clinical data are included in the adjudication. NIA-Alzheimer's Association criteria is used to identify MCI, AD and other dementias.[89–91]

Approaches

We will select from a variety of statistical approaches as best suited to research questions particulary, including linear or logistic longitudinal models to investigate associations of neighbourhood characteristics with cognitive (eg, CASI, DSC and DS) and imaging outcomes (eg, Aβ-PET, WMH), while accounting for the correlation among outcomes within individual and between individuals within the same neighbourhood. We will use multi-level models to tease apart three potential impacts on cognitive decline/imaging measures[1]: how between-person differences in exposure impact between-person differences in outcome[2]; how between-person differences in exposure impact disease progression and[3] impacts of within-person change in environmental features on change in outcomes. These will be adjusted for other time-invariant and time-varying individual-level and neighbourhood-level characteristics, determined a priori (eg, comorbidities, medication use, social determinants). We will also model outcomes using an econometrics difference-in-difference approach.[92 93] This strategy controls for unobserved and unmeasured time-invariant confounders, such as residential preferences.

We will use interval-censored survival analysis to investigate neighbourhood effects on incident (adjudicated) MCI and AD/ADRD. Interval-censored methods are advantageous because, instead of having to specify a date onset—which is difficult if not impossible to obtain—for classical Cox models, only a time window when onset occurred is needed. In our case, the window will be defined based on study visit. Moreover, the models will use participant's age as the timescale, enabling us to detect neighbourhood effects on onset of dementia at younger ages (vs onset alone).

We will use novel statistical techniques from our team[27–33] to allow associations to vary by space and time. Because results could be sensitive to geographic unit (ie, using 1-mile vs 5-mile radius exposure) we will use our group's statistical methodology to examine sensitivity to geographic scale[27 28]; these novel methods estimate the associations of interest as depending smoothly on the distance between participants' residential locations and community amenities, thereby enabling visualisation of the distance at which the associations reach the null value. We will also investigate associations of the outcomes with cumulative exposures and examine long-term impacts of environments on cognition using lags; this modelling strategy is relevant as exposure effects may accrue slowly over time. We will leverage innovative statistical methodology from our team[27–33] to determine the best approach to accumulate exposure over time. For instance, instead of a simple sum or average of exposure history, our methods enable data-adaptive weights to optimally up/down weigh exposures that occurred more recently/farther in the past. These models can include contemporaneous exposure at the outcome visit to separate long-term from current exposure.

Because neighbourhoods and their effects are complex, the study will apply leading-edge statistical methods for comprehensive, geographically referenced neighbourhood data to examine the interplay of multiple environmental features (novel to AD/ADRD research). For example, we will examine contributions of multiple environmental features simultaneously, such as the joint effect of park space and destinations for cognitive engagement on the study outcomes. To accomplish this, we will leverage novel strategies under development by the study team (R01 HL131610; 5K99AG066949-02).

To examine disparities in outcomes by individual and neighbourhood race/ethnicity and SES, we will extend the modelling approach described above. We can examine heterogeneity in neighbourhood effects by race/ethnicity (controlling for individual SES), and by individual SES (controlling for race/ethnicity) by including interactions between race/ethnicity (or SES) and neighbourhood factors in models. Since we recognise that stratification is also useful for interpretation and to more fully account for potential differences in confounders, we will conduct stratified analysis to ensure robustness of study results. Mediation analyses will investigate contributions of neighbourhood environments towards explaining differences in outcomes by race/ethnicity using novel methods for mediation analysis of neighbourhood effects.[94 95]

Subanalyses will explore effect modification by age and sex, because, in addition to NIH guidance,[96] prior research shows variability in neighbourhood associations for some outcomes.[28 97–101]

Sample size calculations

Table 1 shows detectable differences for relevant outcomes, computed using a simulation-based approach that accounts for the nested structure of the data (two or three measures within participants and participants within neighbourhoods; also see table notes). For instance, for aim 2, the smallest detectable risk ratio is 1.33 per an SD change in neighbourhood environments, and the effect size for Aβ-PET is 0.072.

ETHICS AND DISSEMINATION
Ethics

Governance of the parent MESA study, the MESA Coordinating Center (CC) and site PIs, ensure a high standard of adherence to policies and procedures. The administration of the survey component of this project within the MESA field sites as part of Exam 7 was approved by the sIRB at the University of Washington (MESA CC sIRB) (#00009029 and #00014523). Creation of GIS measures from address data and all secondary data analyses related to ageing outcomes have been approved by the Drexel

Table 1 Detectable effect sizes for each aim

	CASI, DSC, DS N*=4392	Incident MCI or ADRD N*=2700; risk=3%	Aβ-PET N*=1500	WMH N*=3000; risk=50%	MRI-based outcomes N*=3000
	Effect size†	OR	Effect size†	OR	Effect size†
Overall	0.032	1.33	0.072	1.10	0.040
African American	0.061	1.70	0.135	1.18	0.075
Chinese	0.110	2.32	n/a	1.37	0.135
Hispanic	0.073	1.80	0.244	1.23	0.090
White	0.050	1.54	0.161	1.15	0.061

Row labelled 'overall' shows the effect sizes for overall associations. Subsequent rows show effect sizes within race/ethnic groups, applicable for effect measure modification.

Standardised effect size; for longitudinal analysis, it represents the SD of change in outcome per one SD change in neighbourhood exposure; for cross-sectional analysis, it is the difference in the outcome, in SD units, associated with a 1 SD difference in neighbourhood exposure.

*Sample sizes are approximate. Up to three measures per person, starting with N=4392 for Exam 5, then 3000, in and 2400.

†Incident dementia by among those free of dementia in Exam 7; WMH and MRI-based outcomes have two repeat measures, assumes N=3000 drops off to 2400. Analyses assume within-person correlation of 0.5 and neighbourhood intraclass correlation coefficient of 0.001. Sample sizes for subgroups assume per cent of African American, Chinese, Hispanic, white are: 28.7, 8.9, 20.1, 42.3. Multi-Ethnic Study of Atherosclerosis sites where β-amyloid from positron emission tomography scan examinations occur do not have Chinese participants.

CASI, Cognitive Abilities Screening Instrument; DS, Digit Span; DSC, Digit Symbol Coding; MCI, mild cognitive impairment; WMH, white matter hyperintensities.

IRB (protocol #180900605). All participants provide informed consent.

Data access and dissemination

New aggregate geographic datasets derived during this study from administrative, business or municipal data (eg, census-tract level estimates) will be shared on request, subject to terms of any license restrictions or data use agreements. New data produced by this study that is specific to MESA participants addresses (ie, all measures calculated for buffers around MESA participants' homes and all participant survey data) will be transferred to the MESA Coordinating Center where it will be incorporated into the MESA database and for which datasets (and documentation) are subsequently created that follow predefined study formats and standards. MESA Coordinating Center serves as the central repository and clearing house for transfer and dissemination of data between the various MESA entities which includes this MESA study and other MESA investigators. Information related to data sharing for MESA and MESA ancillary studies can be found on the MESA website (www.mesa-nhlbi.org/). Requests to collaborate on data generated by the MESA Neighborhoods and Aging study should be directed to the corresponding author.

Dissemination of findings to scientists, physicians, patients and public

Findings will be disseminated to scientists and physicians in peer-reviewed scientific journals, at national and international conferences, on social media platforms and in-person communications. MESA participants will be kept informed of results from this Ancillary Study through the MESA participant website (www.mesa-nhlbi.org/ParticipantWebsite/default.aspx). This site includes a 'News' section that can highlight new study components,

'The MESA Messenger' a newsletter sent approximately once a year in three languages (English, Spanish and Chinese) and archived on the participant website, and a 'Discoveries' section with lay summaries of research findings. Summaries of results from this work will be posted on this website, as well as on the MESA Neighborhood website (https://mesa-neighborhoods.org/) written for a general audience. Aside from dissemination to scientists, physicians and participants, findings will be disseminated to the public, national networks, policy-makers and other relevant stakeholders through fact sheets, infographics, data briefs, blog posts, social media and presentations or webinars.

Patient and public involvement

None.

DISCUSSION

This project is poised to provide robust new evidence about pathways between neighbourhood environments and cognitive outcomes, with important implications for built environment science, AD/ADRD research and interventions to support healthy ageing. By creating and combining data on residential context and ageing outcomes, it will produce the most comprehensive longitudinal neighbourhood dataset on a diverse sample with detailed cognitive and AD/ADRD outcomes for widespread dissemination to a network of hundreds of MESA researchers and collaborators. However, several practical and operational issues remain. Namely, selection bias, data limitations and contingencies for COVID-19 or similar disaster. Nonetheless, methods employed for this study ensure reproducibility with similar cohorts to advance the field.

Studies of cognition are susceptible to selection bias as cognitively impaired individuals may be less likely to participate or more likely to drop out, including drop out due to competing mortality. We will address this using methods[102] that simultaneously account for missing data (using multiple imputation) and drop out (using inverse probability of selection weights, IPSW). Our team has previously used these methods to upweight participants who are less likely to remain in the sample due to cognitive impairment or death,[103 104] and examine disparities and trends in cognitive outcomes.[105]

Despite our best efforts, data limitations may remain. Built environment measures calculated from administrative spatial datasets may not match ground realities due to delays in updates by cities and errors in records or geolocation within original datasets. This may be especially true for NETS which may not accurately identify cognitive or social engagement destinations that are not based in a set location or that are difficult to identify using industrial codes. Hence, we use both the survey responses from MESA participants and GSV Imagery to represent both perceptions of participants and timelier assessments of resources within neighbourhoods from a ground-based viewshed. Nonetheless, it remains challenging to holistically capture all elements of neighbourhood context. Similarly, in our data products, we will produce exposure measures for multiple neighbourhood definitions (ie, buffers and administrative units) to facilitate examination of associations at varying geographic scales. However, this may not represent the relevant spatial scale for participants nor for the association between neighbourhoods and outcomes. Note that our analyses will use novel methods and the full set of distances to amenities to examine how associations vary across geographic scales. Due to logistical challenges implementing Aβ-PET imaging, Aβ-PET is being collected in ~1000 participants at three sites (NC, NY and MD). Given differences in neighbourhood environments by geographies (eg, varying histories of urban development) results examining Aβ-PET may be less generalisable. In subanalyses we will repeat all analyses on this subset to examine potential bias introduced through reduction of sample. Nevertheless, the amount of and type of data used in this study are unprecedented for studies involving brain scans and neighbourhoods.

Participants may be concerned about attending future MESA visits in-person. In response to COVID-19, MESA-MIND developed a telephone-based version of the UDS v3 for the network of NIH funded Alzheimer's Disease Research Centers; this was been implemented in MESA in July 2020, regardless of willingness to attend clinic visits. While we plan in-person survey administration to match historic neighbourhood data, field centres are prepared to use alternate methods (eg, phone, online, in-home visits). All GIS processing and analyses can be accomplished using residential address records obtained through telephone interviews and are accessible remotely, should individual ability, COVID-19 or any similar disaster require.

This study will open new avenues for AD/ADRD research into the environmental and SES determinants of AD/ADRD in a multi-ethnic cohort. The parent MESA study has been ongoing for 20 years with 150+ ancillary studies and 1700+ published papers. Measurement tools applied for cognition, AD/ADRD and MRI follow existing studies and are reproducible. Members of our team have created similar neighbourhood measures in other cohorts, ensuring comparability: REGARDS (Reasons for Geographic and Racial Differences in Stroke), CHS (Cardiovascular Health Study) and CARDIA (Coronary Artery Risk Development in Young Adults). MESA is similar to these studies in important ways: aims to investigate racial/ethnic differences; measures risk factors and subclinical markers of cardiovascular disease; measures cognition and provides geographic diversity spanning at least four cities. Thus, MESA, REGARDS, CARDIA and CHS may be used in key reproducibility studies of each other. Team members of our project are actively involved with proposed consortia of neurocognitive outcomes from these and other NIH studies. This project will provide key evidence about pathways and links between neighbourhood environments and cognitive outcomes, with important implications to identify actionable, community interventions to address racial and socioeconomic inequalities.

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