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Lower prevalence of silent brain infarcts in the physically active

The Northern Manhattan Study

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ABSTRACT

Objective: To examine the independent association between physical activity and subclinical cerebrovascular disease as measured by silent brain infarcts (SBI) and white matter hyperintensity volume (WMHV).

Methods: The Northern Manhattan Study (NOMAS) is a population-based prospective cohort examining risk factors for incident vascular disease, and a subsample underwent brain MRI. Our primary outcomes were SBI and WMHV. Baseline measures of leisure-time physical activity were collected in person. Physical activity was categorized by quartiles of the metabolic equivalent (MET) score. We used logistic regression models to examine the associations between physical activity and SBI, and linear regression to examine the association with WMHV.

Results: There were 1,238 clinically stroke-free participants (mean age 70 ± 9 years) of whom 60% were women, 65% were Hispanic, and 43% reported no physical activity. A total of 197 (16%) participants had SBI. In fully adjusted models, compared to those who did not engage in physical activity, those in the upper quartile of MET scores were almost half as likely to have SBI (adjusted odds ratio 0.6, 95% confidence interval 0.4–0.9). Physical activity was not associated with WMHV.

Conclusions: Increased levels of physical activity were associated with a lower risk of SBI but not WMHV. Engaging in moderate to heavy physical activities may be an important component of prevention strategies aimed at reducing subclinical brain infarcts. *Neurology*® 2011;76:2112–2118

GLOSSARY

BMI = body mass index; **CI** = confidence interval; **HOMA** = homeostatic model assessment; **MET** = metabolic equivalent; **NOMAS** = Northern Manhattan Study; **OR** = odds ratio; **SBI** = silent brain infarcts; **SCVD** = subclinical cerebrovascular disease; **WMH** = white matter hyperintensity; **WMHV** = white matter hyperintensity volume.

Subclinical cerebrovascular disease (SCVD), as manifested by subclinical brain infarcts (SBI) or white matter hyperintensities (WMH) visualized on MRI, is common in the elderly. SCVD has significant public health impact as it has been associated with impaired mobility and falls,[1,2] cognitive dysfunction and dementia,[3,4] and incident ischemic stroke.[5]

Many of the risk factors for clinically apparent ischemic stroke are also associated with SCVD.[2,6] Physical activity is a component of the guidelines for ideal cardiovascular health, which advise at least 150 minutes per week of moderate intensity, or 75 minutes of vigorous intensity activity.[7] Physical activity has been associated with a lower risk of ischemic stroke in the Northern Manhattan Study (NOMAS) and others independently of other vascular disease risk factors.[8,9] There has been little literature on the association between physical activity and SCVD,[10,11] and few studies have included Hispanics. The purpose of this study is to examine the independent association between measures of physical activity and SCVD. We hypothe-

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sized that total physical activity would be associated with a lower odds of SBI and lower WMH volumes (WMHV).

METHODS

Recruitment of the cohort. NOMAS is a population-based prospective cohort study designed to evaluate the effects of medical, socioeconomic, and other risk factors on the incidence of stroke and other vascular outcomes in a stroke-free multiethnic community cohort. Methods of participant recruitment, evaluation, and follow-up have been previously reported.[12] A total of 3,298 participants were recruited between 1993 and 2001, and participants have been followed annually by telephone. Participants were invited to participate in an MRI substudy beginning in 2003. Participants were eligible for the MRI cohort if they 1) were older than 55; 2) had no contraindications to MRI; and 3) had not yet experienced a stroke. To maximize recruitment, an additional 199 participants who were household members but not first-degree relatives of existing NOMAS participants were recruited into the MRI cohort for a total of 1,290 participants.

Standard protocol approvals, registrations, and patient consents. The study was approved by the Institutional Review Boards at Columbia University Medical Center and the University of Miami. All participants gave informed consent to participate in the substudy.

Cohort evaluation. Data regarding baseline status and risk factors were collected through interviews of participants. Race-ethnicity was determined by self-identification. Standardized questions were asked regarding the following conditions: hypertension, diabetes, hypercholesterolemia, peripheral vascular disease, TIA, cigarette smoking, and cardiac conditions. Standard techniques were used to measure blood pressure, height, weight, and fasting serum glucose and lipid panels. Diabetes mellitus was defined as fasting blood glucose ≥126 mg/dL, the patient's self-report of diabetes mellitus, or insulin or hypoglycemic agent use.

Assessment of physical activity. At baseline, physical activity was measured using an in-person questionnaire adapted from the National Health Interview Survey of the National Center for Health Statistics.[13] This questionnaire records the duration and frequency of various leisure time/recreational activities for the 2 weeks prior to the interview. The participants were then asked if they engaged in any physical activity in the preceding 2 weeks, and those who answered "no" were coded as physically inactive. For each activity, the participant was asked the duration of activity, and the times they engaged in this same activity, and if this level of activity was typical of other weeks. If the duration of activity was less than 10 minutes, it was coded as "no activity." This questionnaire has been previously reported as reliable and valid in this population, demonstrating a crude concordance rate of 0.69 when proxies of the participants were asked.[9] This same measure also correlated with body mass index (BMI), activities of daily living scores, and activity scores on a quality of well-being scale.[9] Objective measures of physical fitness, moreover, as measured by exercise and treadmill testing or maximum oxygen uptake (VO_{2max}), correlate well with physical activity questionnaires.[14]

Questionnaires were correlated with compendia of physical activity to allow for categorization of total physical activity using metabolic equivalents (MET).[15] MET is a measure of intensity of physical activity and represents multiples of the resting metabolic activity (reference 1 MET). Total activity was summarized via the MET score, whereby the MET for each individual activity is multiplied by the frequency per week and duration.[16] The MET score was our primary exposure, categorized by the third and fourth quartile. Intensity was classified based on METs as light (between 1 and 5.5, representing activities including golfing or bowling), moderate (5.5–8, e.g., bicycling or swimming), or heavy activity (>8 METs, e.g., racquetball).[8]

MRI. Imaging was performed on a 1.5-T MRI system (Philips Medical Systems) at the Hatch Research Center. The processing of MRI scans in NOMAS has been described.[17] The presence or absence of brain infarction was determined from the size, location, and imaging characteristics of the lesion.[18] SBI was defined as a cavitation on the fluid-attenuated inversion recovery sequence of at least 3 mm in size, and distinct from a vessel due to the lack of signal void on T2 sequence, and of equal intensity to CSF. In a pilot reliability study, a total of 15 MRIs were read by 2 physicians to classify SBI (C.S.D., M.Y.). The proportion of observed agreement between the 2 raters was 93.3% (whereas the proportion of expected agreement by chance was 57.8%), leading to a simple kappa coefficient of 0.84 (95% confidence interval [CI] 0.55 to 1.00, p value = 0.003 for Fisher exact test), and suggesting an excellent interrater agreement. The interrater reliability of detection of SBI was in agreement with studies by others.[19] Analyses for WMHV were performed using semiautomated measurements of pixel distributions and mathematical modeling of pixel-intensity histograms for CSF and brain (white and gray matter) to identify the optimal pixel-intensity threshold to distinguish CSF from brain matter. Analyses were performed using a custom-designed image analysis package (QUANTA 6.2 using a Sun Microsystems Ultra 5 workstation). WMHV was calculated after correcting for total cranial volume to correct for differences in head size,[20] and log-transformed to achieve a normal distribution (log-WMHV) for analysis. All analyses were performed blind to participant identifying information.

Statistical analysis. We fitted 1) logistic regression models with SBI as a binary outcome to calculate odds ratio (OR) and 95% CIs and 2) linear regression models with log-WMHV as a continuous outcome to calculate parameter estimates (β) and 95% CI. Our primary exposure of interest was the MET score categorized in quartiles. Because 42.6% of our cohort engaged in no regular physical activity, the lower 2 quartiles were used as the reference. Given the small numbers of participants performing heavy activity, the categories of moderate and heavy were combined. In secondary analyses, physical activity was categorized as 1) any vs none, and 2) moderate to heavy intensity, light intensity, and none, accounting for intensity of all activities performed.[21]

Unadjusted and adjusted models with demographics (age, sex, race-ethnicity, and education) and vascular risk factors (systolic blood pressure, diastolic blood pressure, glomerular filtration rate, diabetes mellitus, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, moderate alcohol use, and smoking) were constructed. In order to adjust for potential bias, we adjusted our final models for time between physical activity assessments and MRI. We tested for interactions between physical activity and all baseline sociodemographic factors (age, sex, race-ethnicity, education, insurance status), and stratified models were carried out only when the p value for the interaction term was <0.05. All analyses were conducted using SAS version 9.2 (Cary, NC).

Table 1 Baseline demographics of the Northern Manhattan Study Magnetic Resonance Imaging Cohort (n = 1,238)

	Mean ± SD or n (%)
Sociodemographic characteristics	
Age at the time of MRI, y	70 ± 9
Women	738 (60)
Race-ethnicity	
Hispanic	807 (65)
Non-Hispanic black	215 (17)
Non-Hispanic white	188 (15)
Less than high school education	659 (53)
Medicaid or no insurance	581 (47)
Medical comorbidities	
Tobacco use	
Never used	587 (47)
Former smoker	453 (37)
Current user	198 (16)
Alcohol use, moderate[a]	510 (41)
Hypertension, systolic/diastolic blood pressures, mm Hg[b]	136 ± 17/78 ± 10
Diabetes mellitus[c]	231 (19)
Glomerular filtration rate	77.5 ± 20

[a] Moderate alcohol use = ≤2 servings of alcohol per day.
[b] Hypertension = systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg based on the average of 2 blood pressure measurements, a physician diagnosis of hypertension, or a patient's self-report of a history of hypertension or antihypertensive use.
[c] Diabetes mellitus was defined as fasting blood glucose ≥126 mg/dL, the patient's self-report of diabetes mellitus, or insulin or hypoglycemic agent use.

RESULTS

Description of the cohort and physical activity levels. There were 1,238 NOMAS MRI participants with data on physical activity and SCVD available. Baseline demographics of the cohort are presented in table 1. The MRI was obtained a mean of 6 ± 3 years after the physical activity assessment. The mean age at the time of MRI was 70 ± 9 years, and 60% were women; 65% of the cohort was Hispanic, 17% non-Hispanic black, and 15% non-Hispanic white. The physical activity characteristics of the cohort are outlined in table 2. Physical inactivity was common in the cohort (43% overall), but differed by race-ethnicity, with Hispanics (49%) being more likely to be inactive compared to non-Hispanic whites (28%, p for difference <0.001) and blacks (33%, p for difference <0.0001), consistent with our prior analyses.[8,22] Hispanics were also less likely to engage in moderate to heavy intensity activity (15%) compared to non-Hispanic whites (36%) and blacks (29%), and had a lower mean MET score (8.1 for Hispanics, 12.3 for blacks, and 14.3 for whites).

There were sex differences in physical activity as well. Women were more likely to be physically inactive (45%) vs men (39%), and to engage less in moderate to heavy intensity activities (table 2).

Association of physical activity and SBI. There were 197 participants (16%) with SBI in the cohort. In analyses adjusting for sociodemographic factors, participants who reported physical activity were less likely to develop SBI (adjusted OR for those with MET score in the fourth quartile vs no activity 0.6, 95% CI 0.4 to 1.0; table 3). There was no difference in the prevalence of SBI between those in the third quartile of MET score vs no activity (adjusted OR 0.9, 95% CI 0.6 to 1.4). After further adjusting for vascular disease risk factors, those in the fourth quartile of MET score were less likely to have SBI than the physically inactive (adjusted OR 0.6, 95% CI 0.4 to 0.9), while those in the third quartile were not (adjusted OR vs no activity 1.0, 95% CI 0.7 to 1.4).

Table 2 Baseline physical activity characteristics in the Northern Manhattan Study Magnetic Resonance Imaging Cohort

	Mean MET score ± SD	Physically inactive, n (%)	Light intensity activity, n (%)[a]	Moderate to heavy intensity activity,[b] n (%)
Overall (n = 1,226[c])	10.0 ± 16.2	543 (43)	445 (36)	271 (21)
Men (n = 497)	12.5 ± 18.7	192 (39)	178 (36)	127 (26)
Women (n = 729)	8.4 ± 14.1	327 (45)	267 (37)	135 (19)
Non-Hispanic whites (n = 188)	14.3 ± 19.0	53 (28)	68 (36)	67 (36)
Non-Hispanic blacks (n = 215)	12.3 ± 17.1	71 (33)	81 (38)	63 (29)
Hispanics (n = 795)	8.1 ± 14.2	389 (49)	284 (36)	122 (15)

Abbreviation: MET = metabolic equivalent.
[a] Light intensity physical activity includes, for example, golf, walking for exercise, or dancing.
[b] Moderate to heavy intensity physical activity includes, for example, hiking, tennis, swimming, bicycling, jogging, or racquetball.
[c] Physical activity questionnaires were not available in 8 participants.

Table 3 Association between measures of physical activity and subclinical brain infarctions

	Univariate analysis, OR (95% CI)	Model 1,[a] OR (95% CI)	Model 2,[b] OR (95% CI)
MET score >14 (upper quartile)[c]	0.8 (0.5–1.2)	0.6 (0.4–1.0)	0.6 (0.4–0.9)
MET score 3–14 (third quartile)[c]	1.0 (0.7–1.5)	0.9 (0.6–1.4)	1.0 (0.7–1.4)
Total intensity of physical activity (moderate to heavy vs none)	0.8 (0.5–1.2)	0.6 (0.4–1.0)	0.6 (0.4–0.9)
Total intensity of physical activity (light vs none)	1.0 (0.7–1.4)	0.8 (0.6–1.2)	0.8 (0.6–1.2)
Any physical activity vs none	0.9 (0.7–1.3)	0.7 (0.5–1.0)	0.8 (0.5–1.1)

Abbreviations: CI = confidence interval; MET = metabolic equivalent; OR = odds ratio.
[a] Model 1: adjusted for age, race-ethnicity, sex, insurance (Medicaid/none vs others), and completing high school education.
[b] Model 2: further adjusted for low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, current tobacco use, moderate alcohol use, systolic blood pressure, diastolic blood pressure, glomerular filtration rate, and diabetes.
[c] Reference: lowest 2 quartiles of the MET score.

Physical activity was also analyzed by total intensity and exhibited a threshold effect for association with SBI. In adjusted models, those who engaged in moderate to heavy intensity physical activity were significantly less likely to have SBI compared to those who were inactive (adjusted OR 0.6, 95% CI 0.4 to 1.0). Those in light intensity activities were not significantly different from the physically inactive (adjusted OR 0.8, 95% CI 0.6 to 1.2). In a fully adjusted model, those who engaged in moderate to heavy intensity activity compared to no activity were significantly less likely to have SBI (adjusted OR 0.6, 95% CI 0.4 to 0.9), while those in light intensity were not significantly different (adjusted OR 0.8 compared to no activity, 95% CI 0.6 to 1.2). In order to account for possible bias, we adjusted our final models for time between the physical activity assessment and MRI and noted that our parameter estimates did not change. Performance of any physical activity (vs none) was not associated with SBI in any of the analyses.

In previous analyses in our cohort, we found that insulin resistance was associated with ischemic stroke,[23] and therefore we fitted models among nondiabetic participants who had laboratory measures allowing calculation of the homeostatic model assessment (HOMA) index (n = 632). Compared to those who were physically inactive, those in the upper quartile of the MET score had lower odds of SBI (adjusted OR 0.4, 95% CI 0.2 to 0.8). We found similarly stronger associations when examining moderate to heavy intensity activity (adjusted OR 0.4 compared to no activity, 95% CI 0.2 to 0.9), and any activity vs none (adjusted OR 0.5, 95% CI 0.3 to 0.9).

We found evidence of a significant interaction ($p = 0.03$) between health insurance status and physical activity for SBI, with an improvement in model fit after the inclusion of the interaction term (likelihood ratio test, χ^2 2 degrees of freedom, $p < 0.05$). Compared to those who were physically inactive, those in the fourth quartile of MET score were less likely to have SBI if they had Medicare or private insurance (adjusted OR 0.4, 95% CI 0.2 to 0.7), but not if they were uninsured or had Medicaid (adjusted OR 1.0, 95% CI 0.5 to 1.8).

Association of physical activity and WMHV. There were no significant associations between measures of physical activity and WMHV. In fully adjusted models, those in the fourth quartile of the MET score had no difference in WMHV compared to those who engaged in no activity (change in log-WMHV = 0.02, 95% CI −0.11 to 0.16). Moderate to heavy intensity activity vs none (change in log-WMHV = −0.04, 95% CI −0.18 to 0.10), and any activity vs none (change in log-WMHV = 0.02, 95% CI −0.08 to 0.13; table 4), also showed no association. Our parameter estimates were not different after adjusting for time to MRI.

DISCUSSION In our study, we found that higher levels of leisure time physical activity were independently associated with a lower prevalence of SBI, but not total WMHV, in a multiethnic urban population-based cohort. Subclinical infarcts, also called silent infarcts, are more clinically significant than the name would imply, as they can have effects on functional and clinical outcomes.[3,4,6,24] In exploratory analyses in the subsample for whom we could calculate the HOMA index, we found that leisure time physical activity is associated with fewer silent infarcts even after adjusting for insulin resistance. Engaging in physical activity may be an important strategy to reduce the prevalence of SBI and thus, potentially, improve functional outcomes.

In our analyses, moreover, only those in the highest categories of physical activity had a reduced prevalence of SBI. We did not find an association with SBI for the third quartile of MET score or light-intensity activity. These observations are consistent

Table 4 Association between measures of physical activity and log-total white matter hyperintensity volume

	Univariate analysis, parameter estimate (95% CI)	Model 1,[a] parameter estimate (95% CI)	Model 2,[b] parameter estimate (95% CI)
Any physical activity vs none	0.05 (−0.06 to 0.16)	−0.005 (−0.11 to 0.09)	0.02 (−0.08 to 0.13)
Total intensity of physical activity (moderate to heavy vs none)	−0.04 (−0.19 to 0.10)	−0.07 (−0.21 to 0.06)	−0.04 (−0.18 to 0.10)
MET score (upper quartile vs none)	0.09 (−0.05 to 0.23)	0.004 (−0.13 to 0.13)	0.02 (−0.11 to 0.16)

Abbreviation: CI = confidence interval.
[a] Model 1: adjusted for age, race-ethnicity, sex, insurance (Medicaid/none vs others), and completing high school education.
[b] Model 2: further adjusted for low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, current tobacco use, moderate alcohol use, systolic blood pressure, diastolic blood pressure, glomerular filtration rate, and diabetes.

with our prior finding in the NOMAS prospective cohort that only the highest levels of physical activity were inversely associated with incident ischemic stroke.[8] Other groups have also found a similar threshold association with total physical activity, such that light intensity activity was not associated with risk of stroke.[16,25,26] A meta-analysis summarizing the association between physical activity and ischemic stroke similarly found that higher intensity activity was consistently protective, while less intense activities were not.[27]

Physical activity was associated with a lower prevalence of SBI independently of conventional stroke risk factors. We cannot exclude the possibility of residual confounding, though physical activity has independent health benefits through modulation of inflammation, endothelial function, and vascular reactivity.[28] Our findings are in keeping with the current recommendations for vascular disease primary and secondary prevention that call for a target of reasonably high intensity and energy levels of activity rather than just performing low-level activity.[7,29–31]

An additional novel finding in our study was that moderate to heavy physical activity was not associated with a lower odds of SBI among NOMAS participants who were uninsured or had Medicaid. We did not collect information on household income, but believe that being uninsured or having Medicaid is a proxy for socioeconomic status, though it may also indicate poor access to medical care. It may be that the overall adverse life experience for those who are uninsured or have Medicaid mitigates the protective effect of leisure time physical activity. It is likely that being uninsured or having Medicaid is a reflection of lower socioeconomic status, and is consistent with the extensive literature on social status being associated with a higher risk of cardiovascular disease independently of access to care.[32]

We did not, however, find an association between physical activity and WMHV. Others have also failed to find an association between physical activity and WMHV. In the NHLBI Twin Study, physical activity was not associated with WMHV, while it was associated with other measures of brain morphology.[10] In the Cardiovascular Health Study, physical activity was not associated with WMHV at baseline, or with worsening over time.[2] The explanations for the lack of association between physical activity and WMHV could be due to the heterogeneity of pathology underlying WMHs. While evidence links a heavy burden of WMHs to numerous vascular risk factors, retinal vascular changes,[33] subcortical cerebral infarction, and intracerebral hemorrhage,[34] the pathologic basis remains poorly characterized, with only small series providing definite pathologic correlation with MRI. In many of the pathologic series, cellular changes in myelin, astrocytes, and endothelial cells are seen in areas of affected white matter, with concomitant blood–brain barrier breakdown. While these changes can occur with chronic cerebral ischemia,[35] nonarteriolar and nonischemic mechanisms for WMHs have also been proposed, including endothelial dysfunction and venous sclerosis with subsequent venous hypertension.[36,37] While nonischemic lesions can be mislabeled as infarcts, SBI may be less prone to misclassification and, unlike WMHs, they share many of the pathologic features of clinical lacunes[38] and have similar risk factors, including physical inactivity.

Our study has important strengths, with a large proportion of participants who are Hispanic, older, with Medicaid or no insurance, and urban dwelling, all of which have been underrepresented in previous studies of risk factors and measures of SCVD. Previous studies on the association between physical activity and cardiovascular disease are often difficult to interpret given the variable methods used to categorize physical activity. In our study we characterized physical activity by several methods.

Our study also has some important weaknesses, however. Risk factors for SBI and WMH were measured several years before MRI, and it may be that changes in risk factor status may be more informative

than measurement at one time.[39] We adjusted for time between the physical activity questionnaire and MRI and noted that our results did not change. Furthermore, our methodology makes it less likely that participants engaged in less physical activity because of the findings on MRI and allows us to gain additional information from a temporality. We did not have available direct measures of physical fitness, though in previous studies questionnaires correlate well with measures of oxygen consumption.[14] It is possible that light intensity activity is also protective against SBI, but we may be underpowered to find more subtle benefits. It is important to note that light-intensity physical activity is likely to have protective effects against multiple other conditions associated with aging and our findings should not discourage individuals from performing even light intensity activities. Finally, as with any epidemiologic study, it is not possible to establish causation. A decline in physical activity is a hallmark of frailty, which in and of itself may be partly influenced by SCVD.[40] Further studies will be required to clarify these causal pathways.

In our study, we found that physical activity was associated with a reduced prevalence of SBI, but not WMHV. This may have potential therapeutic implications given the multiple adverse health outcomes associated with SBI in older individuals. These interventions will however have to consider socioeconomic status and access to care limitations so as to gain the maximum benefit from exercise.

DISCLOSURE

Dr. Willey has received research support from the NIH/NINDS (Trainee). Y.P. Moon reports no disclosures. Dr. Paik serves as Statistics Editor for the *Journal of General Internal Medicine*. Dr. Yoshita reports no disclosures. Dr. DeCarli serves as Editor-in-Chief for *Alzheimer Disease and Associated Disorders*; serves as a consultant for Takeda Pharmaceutical Company Limited and Avanir Pharmaceuticals; and receives research support from Merck Serono and the NIH (NIA, NHLBI). Dr. Sacco serves on a data safety monitoring board indirectly sponsored by Pfizer Inc; serves on the editorial boards of *Stroke* and *Neuroepidemiology*; and receives research support from the NIH and the Evelyn McKnight Brain Institute. Dr. Elkind serves as Resident and Fellow Section Editor for *Neurology*®; serves as a consultant to Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership, GlaxoSmithKline, Jarvik Heart, and Tethys Bioscience, Inc.; serves on speakers' bureaus for Boehringer-Ingelheim, Genentech, Inc., and Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership; receives research support from diaDexus, Inc., Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership, and the NIH/NINDS; and has given expert testimony on behalf of Merck Serono (Vioxx® litigation), Pfizer Inc. (Shiley valve and Celebrex®/Bextra® litigation), and Novartis (Zelnorm® and stroke litigation). Dr. Wright has received authorship honoraria from UpToDate, Inc.; and receives research support from the NIH/NINDS, the American Heart Association, and the Evelyn F. McKnight Center.

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