Effects of Greenness and Noise Exposure on Health

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Abstract

Environmental epidemiology has begun to investigate attributes of the physical environment in which people live, work and play daily that are associated with health. Features of the environment bear on risk factors for chronic diseases prevalent in the U.S. and elsewhere. For example, physical inactivity, overweight and obesity all profoundly influence downstream health, and the physical environment may provide opportunities to intervene for desirable outcomes. Interventions in the physical environment can complement education and behavior change activities already being pursued, such as incentives to exercise and education on healthy diets.

Among these attributes of the physical environment important for health, researchers have begun to study the effects of exposure to nature. Growing evidence seems to suggest that nature (often operationalized as exposure to vegetation, or vegetative density) may positively influence many health endpoints. Another recent exposure of interest is neighborhood noise level, which has been investigated not solely as a cause of annoyance or auditory effects but as a potential contributor to cardiovascular disease.

Both of these relatively new research areas provide opportunities for environmental health interventions. The evidence base, however, would benefit from prospective studies in large cohorts. The objective of my doctoral research was to examine the association between these exposures and prevalent risk factors and health outcomes prospectively. Using data from the long-running cohort of professional women, the Nurses' Health Study, I examined the relationship between surrounding greenness and depression, finding that those who lived in the greenest areas were statistically significantly less likely to develop depression over the course

of follow-up. I also considered the relationship between surrounding greenness and incident overweight and obesity in the Nurses' Health Study II, finding little evidence for an association. Finally, I examined the association between nighttime residential noise level and incident hypertension in the Nurses' Health Study II. I found that greater noise levels were statistically significantly associated with increased risk for incident hypertension.

These studies contribute to our understanding of how attributes of the physical environment may influence health, incorporating information from large prospective cohort studies in the U.S.

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Introduction

In recent years, environmental epidemiology has expanded its purview from investigating specific agents in air, water, agriculture and industry. The field has begun investigating how the physical environments in which people live, work and play daily may affect health, and especially how they may bear on risk factors for chronic diseases so prevalent in the U.S. and developed countries. As physical inactivity, overweight and obesity affect an increasingly large proportion of society, changes to the physical environment can complement other avenues for education and behavior change. Environments that encourage exercise, healthy food choices, social cohesion and more can reap health benefits. Accordingly, some recent exposures of interest in environmental health include constructs like safety and perceptions of safety, walkability, and access to destinations that may influence physical activity. Increasingly, researchers are studying the potential effects of exposure to nature, based on growing evidence that nature (often operationalized as vegetative density, or greenness) may have therapeutic effects on mental health, and could encourage exercise and weight maintenance—thereby affecting other downstream health outcomes.[1] Other incipient research has examined neighborhood noise level, because of findings that point to a positive association between noise and cardiovascular disease.[2] Both of these relatively new research areas show promise for environmental public health interventions, but the evidence base would benefit from prospective studies in large cohorts.

The objective of my doctoral research was to explore the association between some of these prevalent and lesser studied environmental exposures, and health outcomes common in the developed world. I focused on access to nature, operationalized as greenness, and its relationship with both mental health and weight. I also considered the relationship between neighborhood noise level and hypertension, a common risk factor for cardiovascular disease. In

all three papers, I took advantage of longitudinal data to analyze any association between exposure and outcome prospectively; I was able to assess mediation by certain characteristics or behaviors; and I often explored effect modification by factors that seemed likely to affect the exposure-response relationship.

My first paper built on existing research showing a beneficial relationship between surrounding greenness and reduced mental distress.[3,4] In it, I examined the relationship between greenness around the residential address and incident depression in a cohort of older women during ten years of follow-up. The results appeared to show that increased residential greenness was independently associated with reduced likelihood of subsequently developing depression, a relationship not mediated by social interaction or physical activity. However, adjusting the models for region of the country attenuated the effect substantially—potentially because region and the climatic conditions that produce greenness were closely bound with greenness itself.

In my second paper, I explored another potential consequence of exposure to greenness: its relationship to the development of overweight and obesity. Research on this topic has been inconclusive, with some evidence indicating a beneficial relationship,[5-7] some finding no association,[8] and one study finding a harmful association.[9] In my study of middle-aged American women, there was no association between greenness and incident overweight or obesity, nor did those who lived in greener areas exercise more than their counterparts in less green areas. This study's findings were consistent with those that showed no relationship between greenness and weight status.

Finally, in my third paper, I considered another environmental exposure: noise level. Linking data from a National Park Service noise model to our participants' residential addresses, I was able to estimate both nighttime and daytime ambient sound levels for participants across the

U.S. Based on research showing a positive association between nighttime noise levels and cardiovascular disease,[2] I examined the association between nighttime noise levels and hypertension, a common cardiovascular risk factor. I found a positive association between nighttime noise levels and incident hypertension that was even stronger among those who moved to noisier areas over follow-up.

All of these analyses were conducted using data from two cohorts established by Harvard and Brigham and Women's Hospital: the Nurses' Health Study and Nurses' Health Study II. The Nurses' Health Study (NHS) is a prospective cohort study of U.S. women established in 1976. A total of 121,701 married registered nurses aged 30-55 and living in 11 states initially enrolled by responding to a questionnaire on their medical history and lifestyle factors. The Nurses' Health Study II (NHS II) is a similar prospective cohort study of 116,430 female registered nurses who were initially enrolled in 1989 from 14 states. Every two years, participants in both cohorts complete surveys on their lifestyle, health-related behaviors, and medical history. Questionnaire mailing addresses since the start of follow-up have been geocoded and updated with changes of address to create a residential address history for each cohort. The duration of follow-up information allowed me to study associations prospectively, adjust for many different socioeconomic and behavioral potential confounders, consider regional geography, and address potential reverse causation.

The physical environment provides opportunities to intervene to improve health behaviors, mental health, risk factors and chronic diseases outcomes. Together, these papers explore the effects of certain features of the physical environment on health. They contribute to the literature by examining these associations prospectively, a limitation in the current, mostly cross-sectional evidence base for these research questions.

Greenness and Depression Incidence Among Older Women

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Abstract

Background: Recent evidence suggests that lower levels of residential greenness may contribute to worse mental health. Despite this, few studies have considered impact on depression, and most are cross-sectional.

Objective: The objective of this study was to examine surrounding residential greenness and depression risk prospectively in the Nurses' Health Study.

Methods: A total of 38,947 women (mean age 70y [range 54-91y]) without depression in 2000 were followed to 2010. Residential greenness was measured initially in 2000 and updated each year using the satellite-based Normalized Difference Vegetation Index (NDVI) and defined as the mean greenness value within 250 meter and 1,250 meter radii of the women's residences in July of each year. Incidence of depression was defined according to either self-reported physician-diagnosed depression or regular antidepressant use. We used Cox proportional hazards models to examine the relationship between greenness and depression incidence, and assessed physical activity as a potential effect modifier and mediator.

Results: Over 315,548 person-years, 3,612 incident depression cases occurred. In multivariable-adjusted models, living in the highest quintile of residential greenness within 250 meters was associated with a 13% reduction in depression risk (HR=0.87 [95% confidence interval (CI) 0.78, 0.98]) compared to the lowest quintile. The association between greenness and depression did not appear to be mediated by physical activity, nor was there evidence of effect modification by physical activity. Additionally adjusting for U.S. climatic region attenuated the inverse associations between greenness and depression risk.

Conclusions: In this population of women, we observed an inverse relationship between surrounding summer greenness and the risk of self-reported depression only in models that did not include climatic region of the U.S.

Introduction

In recent years, greenness, a feature of the natural environment reflective of the quantity of trees, plants, forests, parks, and gardens, has received increasing attention due to its potential health benefits. Studies have linked higher greenness to reduced obesity prevalence, reduced risk of cardiovascular disease and mortality, and improved birth outcomes.[3] Green spaces may promote health by providing opportunities for physical activity,[10] fostering social cohesion which has been linked with better health,[11] enhancing psychological wellbeing,[12] and by reducing exposure to noise, air pollution, and heat, environmental stressors that have been linked with adverse health outcomes.[3] Accessible green spaces provide these benefits to all populations, thereby enhancing social equity.[13]

Several studies have found beneficial associations between greenness and various mental health outcomes.[4] While these studies hypothesize a causal relationship, almost all are cross-sectional, including ones examining depression using self-report, psychological symptom scales, and data from electronic medical records.[14-20] Additionally, some of these studies relied on subjective greenness assessments rather than objective measures.[16] Because depression is the fourth leading cause of disability globally, can precipitate or exacerbate comorbidities, and adversely affects a range of outcomes including educational attainment, employment, and marital stability,[21] identifying modifiable contributors to depression is a priority.

Potential mental health benefits of green exposure may be related to its effects modulating stress and related distress. Studies have shown that greater neighborhood green space is

negatively associated with perceived stress and salivary cortisol levels, a biomarker of stress.[22] Chronic stress has been shown to contribute to depression onset,[23] so its amelioration by natural environments could reduce depression risk.

The objective of this study was to estimate the association between residential greenness and the subsequent risk of developing depression in a cohort of U.S. women, adjusting for an array of potential confounders not considered in previous studies, including those shown to be related to depression in this population, such as social network strength and caregiving responsibilities. We also considered the role of physical activity, which prior work has shown to be related to greenness [10] and to promote mental health. We hypothesized that greenness could promote physical activity, thereby reducing depression risk. Thus, we assessed potential mediation and also effect modification by physical activity.[24,25]

Methods

Study Population

The Nurses' Health Study (NHS) is a prospective cohort study of U.S. women established in 1976. A total of 121,701 married registered nurses aged 30-55 and living in 11 states (California, Connecticut, Florida, Maryland, Massachusetts, Michigan, New Jersey, New York, Ohio, Pennsylvania and Texas) enrolled by responding to an initial questionnaire on their medical history and lifestyle factors. Participants receive biennial questionnaires on risk factors and disease diagnoses, with a response rate ~ 90%.[26] Questionnaire mailing addresses have been geocoded and updated with changes of address to create a residential address history. Currently, at least ten participants reside in each of the 48 contiguous states. The study was

approved by the Institutional Review Board of Brigham and Women's Hospital, Boston, MA, and informed consent was implied through return of the questionnaires.

The information on the greenness exposure variable we used was available starting in 2000. Thus, the current analysis included all women who, as of 2000 were alive, returning questionnaires, and had objective residential greenness information (n=64,727). We excluded participants who reported being diagnosed with depression before 2000 or who had severe depressive symptoms in 1992 or 1996 as measured by the Mental Health Inventory-5 (n=10,142), or those for whom we did not have depression information (n=15,638). We excluded those with cancer, diabetes, and heart disease (myocardial infarction or stroke) (n=6,215), because having a major chronic disease can lead to depression[21] and may confound the primary association of interest. After these exclusions, compared to the original population, the population included for analysis (n=38,947) consumed slightly more alcohol and accumulated more pack-years of smoking, had slightly higher prevalence of marriage and higher prevalence of secondary education among husbands, exercised more, had slightly higher prevalence of good physical function, had lower prevalence of bodily pain, and had less trouble sleeping.

Exposure

Residential greenness was characterized objectively using the Normalized Difference Vegetation Index (NDVI), derived from imagery collected by the MODerate-resolution Spectroradiometer (MODIS) onboard NASA's Terra satellite.[27] The sensors measure the visible light absorbed and near-infrared light reflected by vegetative growth during photosynthesis, calculating the ratio of the difference between these two measures to their sum. Values of the

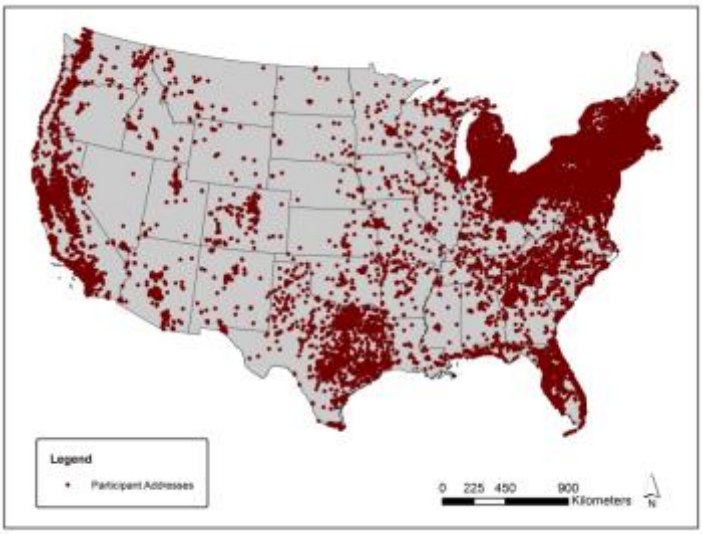
index range between -1 and 1, with higher values representing greater vegetative cover. MODIS provides an image every 16 days at a 250 m pixel size (Figure 1.1).

Starting in 2000, we linked each address with an NDVI value using geographic information systems (GIS) software (ArcMap, ESRI, Redlands, CA) to estimate the mean value inside the 250 m radius and 1,250 m radius around each residence. The 250 m buffer was intended to reflect the more immediate visual environment around the nurse's residence, while the 1,250 m buffer was intended to reflect the higher end of the distance range people may be willing to walk from their homes to an environmental feature.[28] We considered these two buffer sizes to address uncertainty around the appropriate context for measuring residential greenness. In this study population, the highest levels of NDVI occurred in July. Therefore, we analyzed NDVI levels from July of each year of follow-up, reflecting participants' maximal residential greenness exposure contemporaneous to each questionnaire period.

Outcome

Incident depression was defined as the first self-report of physician/clinician diagnosis of depression or new regular use of antidepressants on biennial NHS questionnaires. Nurses reported whether they had clinician-diagnosed depression or had taken an antidepressant regularly over the past two years; cases were indexed to the midpoint of the questionnaire cycle or to the previous cycle as specified.

1.1



1.2

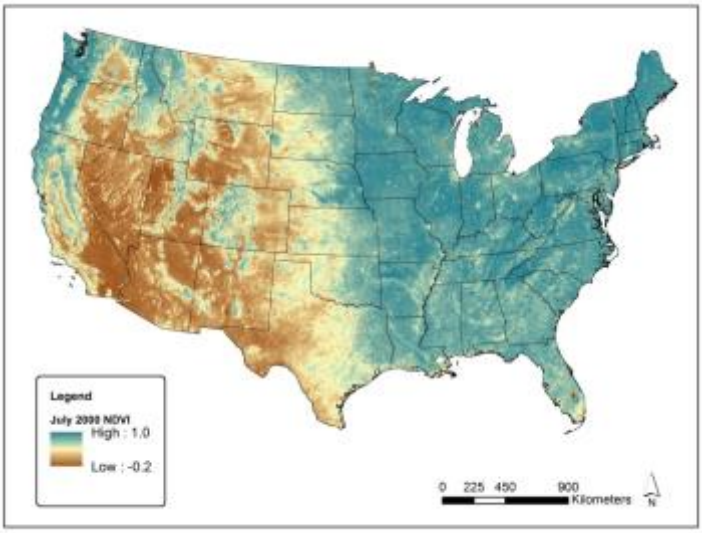


Figure 1.1) Nurses' Health Study addresses at baseline (2000); Figure 1.2 Normalized Difference Vegetation Index (NDVI) Values in July 2000

Covariates

Time-varying information for known and suspected risk factors for depression was available from the biennial questionnaires. These included current age (in months), race, body mass index (BMI) (kg/m^2), physical activity (self-reported Metabolic Equivalent of Task (MET) hours per week), bodily pain (none, mild, moderate, severe, very severe, reported only in 2000), physical function (good versus poor, based on activities of daily living able to perform, updated every four years), cigarette smoking (smoking status and pack-years smoked), alcohol consumption (grams per day, updated every four years), depressive symptoms at baseline (score on Mental Health Inventory-5), social network strength based on the Berkman-Syme Index (including marital status, social contact, and group membership, updated every four years), self-reported difficulty sleeping (reported in 2000), and regular care to ill family members (hours per week of caregiving, reported in 2000). To account for individual socioeconomic status, we adjusted for nurses' educational attainment (registered nurse, bachelors, or masters/doctoral degree) and husband's highest level of educational attainment (less than high school, high school graduate, or more than high school). Most of these covariates were conceptualized as risk factors for depression, while some were also conceptualized as pathway variables (e.g. physical activity level and social network strength), potentially affected by greenness while influencing depression risk. We also considered area-level characteristics, including socioeconomic status (Census tract median home value and median income), population density (Census tract median population density), climate region (from the nine National Oceanic and Atmospheric Administration climate region designations based on temperature and precipitation), and air pollution (12-month average particulate matter less than 2.5 microns in aerodynamic diameter ($PM_{2.5}$) predicted at the residential address from spatio-temporal generalized additive mixed models).[29] These covariates were updated as available each questionnaire cycle, and changes of address were incorporated when they occurred.

Statistical Analysis

We used a Cox proportional hazards model to compute hazard ratios (HR) and 95% confidence intervals (CI) for the association between quintiles of NDVI and risk of developing depression. The data were structured in Andersen-Gill counting process format, with a single record for each nurse in each questionnaire cycle. Nurses contributed person-time from the date of receipt of their 2000 questionnaire to the date of their last questionnaire return, occurrence of depression, death, or through 2010, whichever occurred first. We conducted ordinal tests for trend across NDVI quintiles, and used restricted cubic regression splines to determine the linearity of exposure-response relationships.[30] We fit models with *a priori* confounders (minimally-adjusted model) as well as models with additional possible confounders and pathway variables (full model).

We evaluated physical activity as a potential mechanism by which greenness might affect depression incidence. Comparing models adjusted and unadjusted for physical activity level using the publicly available %Mediate macro (http://www.hsph.harvard.edu/faculty/spiegelman/mediate.html), we calculated the proportion of the risk (and 95% CI) for depression explained by higher exposure to greenness attributable to physical activity. Briefly, the macro compares the exposure effect estimate from the full model that includes the exposure, one or more potential intermediate variables, and any covariates to the exposure effect estimate obtained from a partial model that leaves out the potential intermediate variable or variables. The mediation proportion is the proportion of depression risk explained by higher exposure to greenness that can be attributed to elevated levels of physical activity. Confidence intervals for the mediation proportion were calculated using the data duplication method.[31] We also investigated effect modification by physical activity. We assessed

the statistical significance of the interaction through partial likelihood ratio tests and obtained stratum-specific estimates.

Results

The 38,947 participants eligible for analysis contributed 315,548 person-years of follow-up, and 3,612 incident depression cases occurred between 2000-2010. The study population was on average 70.1 years old, mostly white (95%), and mostly currently married (73%) over follow-up (Table 1.1). The greatest proportion of study participants lived in the Northeast (52%), and 82% lived in metropolitan areas.

Table 1.1 Nurses' Health Study Participant Characteristics over Follow-Up by Quintiles of Contemporaneous Summer Normalized Difference Vegetation Index (NDVI) within 250m from 2000-2010 (N=38,947) (Values are age-adjusted)

	Total (315,548 person-years)	NDVI Quintile 1[b] (63,039 person-years)	NDVI Quintile 2 (62,956 person-years)	NDVI Quintile 3 (63,111 person-years)	NDVI Quintile 4 (63,174 person-years)	NDVI Quintile 5 (63,268 person-years)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Average NDVI (250 m buffer)	0.7 (0.2)	0.4 (0.1)	0.6 (0.1)	0.7 (0.1)	0.8 (0.1)	0.9 (0.1)
Age (years)[a]	70 (7)	71 (7)	71 (7)	70 (7)	69 (7)	69 (7)
BMI (kg/m^2)	25.9 (4.9)	25.6 (4.8)	25.9 (5.0)	26.0 (4.9)	25.9 (4.8)	25.9 (4.8)
Pack-Years of Smoking	10.9 (17.8)	11.1 (18.1)	11.3 (18.1)	11.0 (17.9)	10.8 (17.5)	10.3 (17.0)
Baseline score on MHI-5[c]	83.7 (9.5)	83.9 (9.5)	83.7 (9.5)	83.6 (9.4)	83.5 (9.4)	83.5 (9.6)
Census tract median income ($)	64,318 (24,586)	63,945 (25,180)	61,722 (24,853)	62,917 (22,017)	66,290 (23,759)	66,821 (26,508)
Census tract median home value ($)	173,892 (128,212)	223,888 (167,138)	167,124 (142,487)	152,438 (98,838)	161,352 (97,593)	164,799 (107,687)
12-month average $PM_{2.5}$ (μg/m^2)	11.5 (2.7)	11.7 (3.8)	11.7 (2.5)	11.9 (2.3)	11.5 (2.3)	1063 (2.3)
	%	%	%	%	%	%
White	95	93	95	96	96	96
Physical Activity, MET hrs./wk.						
<3	17	17	18	18	17	17

3 to <9	20	20	20	21	20	20
9 to <18	21	21	22	21	21	21
18 to <27	15	15	14	14	15	15
>=27	27	28	26	26	27	28
Poor physical function	53	53	54	54	53	52
Moderate, severe or very severe bodily pain	17	17	17	18	17	17
Alcohol Consumption, g/day						
0-4.9	63	60	65	66	63	63
>=5	33	36	32	31	34	33
Educational attainment						
RN	68	61	69	70	70	69
Bachelors	21	26	21	20	20	20
Masters or Doctorate	11	13	10	10	10	11
Married	73	71	71	73	75	77
Husband's Highest Education						
Less than high school	4	4	4	5	5	5
High school grad	33	30	33	34	32	33
More than high school	49	51	47	48	49	49
Berkman-Syme Social Network Score[d]						
Low/Medium-Low	32	30	33	34	33	32
Medium-High	67	69	67	66	66	68
Care to ill family members, >=6hrs./week	22	21	22	23	23	22
Trouble sleeping some or all of the time	28	28	28	28	28	28
Census Tract Urbanicity[e]						
Metropolitan	82	89	85	82	80	75
Micropolitan	10	7	10	11	12	13
Small town or rural	7	5	5	7	8	13
Climatic Region						
Northeast	52	19	40	56	68	78
Central	11	4	13	16	13	9
East North Central	7	2	9	10	9	6
Southeast	11	13	16	11	8	5
South	5	9	10	4	1	0
West North Central	0	0	0	0	0	0
Southwest	2	7	1	0	0	0
Northwest	1	1	1	1	1	0
West	12	45	10	2	1	0

[a] Value is not age-adjusted

[b] Least green quintile

[c] Mental Health Inventory 5-Item scale scores range from 0-100, with lower values indicating distress

[d] Social network strength based on the Berkman-Syme Index including marital status, sociability (number and frequency of social contacts), and group membership

[e] Urbanicity classified as metropolitan (urban area ≥50,000 people), micropolitan (urban cluster of 10,000-49,999), or small town/ rural (urban cluster of <10,000) Census tract

In age-adjusted models for both buffer sizes, the greatest NDVI level was associated with decreased incidence of depression, though the trend was not statistically significant (Table 1.2). There was no evidence of deviations from linearity in any of the models. In models including hypothesized confounders (minimally-adjusted model) as well as possible pathway variables (full model), the inverse association between greenness and depression risk became stronger. For the 250 m buffer, the risk of incident depression was 13% lower (95% CI 0.78, 0.98) in the most compared to least green quintiles for both minimally-adjusted and full models (trend p-value 0.02 for both). For the 1,250 m buffer, the risk of incident depression was reduced by 10% (95% CI 0.80, 1.02) in the most compared to least green quintiles in the minimally-adjusted and full models, though neither trend was statistically significant (trend p-value 0.20 and 0.22 respectively). After including climatic region in the models, the association between 250m NDVI and depression risk was no longer statistically significant, and the association between 1,250m NDVI and depression indicated that higher levels of greenness were associated with higher depression risk.

Table 1.2 Hazard ratios (HR) and 95% confidence intervals (CI) for the effect of residential contemporaneous summer greenness on incident depression in the Nurses' Health Study (N=38,947 with 3,612 depression cases over 315,548 person-years of follow-up, 2000-2010)

	Cases/Person-Years	Age-Adjusted HR (95% CI)	Minimally Adjusted HR[b] (95% CI)	Full HR[c] (95% CI)	Minimally Adjusted with Region HR[†] (95% CI)	Full with Region HR[c] (95% CI)
250 m Buffer						
Quintile 1[a]	725/63,039	Ref	Ref	Ref	Ref	Ref
Quintile 2	738/62,956	1.02 (0.92, 1.13)	0.98 (0.88, 1.09)	0.98 (0.88, 1.09)	1.02 (0.91, 1.14)	1.02 (0.91, 1.15)
Quintile 3	723/63,111	0.99 (0.90, 1.10)	0.93 (0.84, 1.04)	0.92 (0.83, 1.03)	1.01 (0.89, 1.14)	1.01 (0.89, 1.15)
Quintile 4	739/63,174	1.02 (0.92, 1.13)	0.95 (0.85, 1.06)	0.95 (0.84, 1.06)	1.05 (0.92, 1.20)	1.06 (0.93, 1.21)
Quintile 5	687/63,268	0.94 (0.85, 1.05)	0.87 (0.78, 0.98)	0.87 (0.78, 0.98)	0.99 (0.86, 1.14)	1.01 (0.87, 1.15)
P for Trend	--	0.34	0.02	0.02	0.98	0.79
1250 m Buffer						
Quintile 1[a]	696/63,071	Ref	Ref	Ref	Ref	Ref
Quintile 2	688/62,975	0.99 (0.89, 1.10)	0.94 (0.84, 1.05)	0.92 (0.82, 1.03)	1.05 (0.92, 1.19)	1.04 (0.91, 1.18)
Quintile 3	805/63,052	1.15 (1.04, 1.27)	1.07 (0.96, 1.19)	1.06 (0.95, 1.18)	1.29 (1.12, 1.48)	1.30 (1.12, 1.49)
Quintile 4	735/63,171	1.04 (0.93, 1.15)	0.96 (0.86, 1.08)	0.95 (0.84, 1.06)	1.21 (1.04, 1.40)	1.21 (1.04, 1.40)
Quintile 5	688/63,279	0.98 (0.88, 1.10)	0.90 (0.80, 1.02)	0.90 (0.80, 1.02)	1.18 (1.00, 1.39)	1.20 (1.02, 1.42)
P for Trend	--	0.87	0.20	0.22	0.04	0.02

[a] Least green quintile

[b] Hazard ratios are adjusted for age, race, baseline mental health, marital status, educational attainment, husband's educational attainment, Census tract population density, Census tract median income, Census tract median home value, $PM_{2.5}$ level

[c] Hazard ratios are adjusted for covariates in parsimonious model + BMI, smoking status and pack-years of smoking, alcohol consumption, physical activity, physical function, bodily pain (baseline), social network strength, care to ill family members (baseline), difficulty sleeping (baseline)

There was no evidence that the association between NDVI and depression in analyses without region was mediated by physical activity. There was no statistically significant effect modification by physical activity, either, though stratified results suggested that individuals who exercised less experienced a decreased risk of depression with increasing NDVI exposure (Table 1.3) relative to those who exercised more. This relationship was more pronounced, though still not statistically significant, within the 250m buffer compared to the 1,250 m buffer (results for 1,250 m models not shown). The interaction between region and NDVI was not statistically significant (Table 1.4).

Table 1.3 Stratum-specific hazard ratios (HR) and 95% confidence intervals (CI) for the effect of residential contemporaneous summer greenness (250 m buffer) on incident depression within physical activity levels in the Nurses' Health Study (N=38,947 with 3,612 cases over 315,548 person-years of follow-up, 2000-2010)

	<3 MET hrs./wk.	3-<9 MET hrs./wk.	9-<18 MET hrs./wk.	18-<27 MET hrs./wk.	>=27 MET hrs./wk.
Quintile 1[a]	Ref	Ref	Ref	Ref	Ref
Quintile 2	0.99 (0.79, 1.25)	0.85 (0.67, 1.08)	0.99 (0.78, 1.26)	1.05 (0.76, 1.44)	1.11 (0.88, 1.40)
Quintile 3	0.91 (0.72, 1.16)	0.89 (0.70, 1.13)	1.04 (0.81, 1.33)	0.97 (0.70, 1.35)	0.87 (0.68, 1.12)
Quintile 4	0.85 (0.66, 1.10)	0.92 (0.72, 1.17)	0.94 (0.73, 1.21)	1.19 (0.87, 1.63)	0.92 (0.72, 1.18)
Quintile 5	0.88 (0.67, 1.14)	0.78 (0.61, 1.01)	0.92 (0.70, 1.20)	0.92 (0.65, 1.30)	0.90 (0.71, 1.17)
			P for Interaction=0.23		

MET=Metabolic Equivalent of Task

[a] Least green quintile

Hazard ratios are adjusted for age, race, BMI, smoking status and pack-years of smoking, alcohol consumption, physical function, bodily pain (baseline), marital status, social network strength, care to ill family members (baseline), difficulty sleeping (baseline), baseline mental health, educational attainment, husband's educational attainment, Census tract population density, Census tract median income, Census tract median home value, $PM_{2.5}$ level

Table 1.4 Stratum-specific hazard ratios (HR) and 95% confidence intervals (CI) for the effect of residential contemporaneous summer greenness (250 m buffer) on incident depression within NOAA climate regions[†] in the Nurses' Health Study (N=38,947 with 3,612 cases over 315,548 person-years of follow-up, 2000-2010)

	Northeast	Central	E. N. Central	Southeast	South	W. N. Central, Southwest, Northwest	West
Cases/Person-Years	1,771/164,727	435/34,191	247/22,941	425/33,119	212/14,898	94/8,064	428/37,609
Depression (incidence rate per 1,000 person-years)	10.75	12.72	10.77	12.83	14.23	11.66	11.38
Average NDVI (250 m buffer) (range)	0.73 (-0.20 - 1.00)	0.70 (-0.16 - 0.99)	0.70 (-0.19 - 0.98)	0.60 (-0.18 - 0.98)	0.55 (-0.09 - 0.99)	0.43 (0 - 0.93)	0.42 (-0.07 - 0.93)
Quintile 1[b]	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Quintile 2	1.08 (0.86, 1.35)	1.03 (0.66, 1.60)	0.86 (0.49, 1.52)	0.95 (0.71, 1.26)	1.13 (0.75, 1.71)	1.45 (0.63, 3.34)	1.14 (0.85, 1.53)
Quintile 3	1.16 (0.93, 1.44)	0.82 (0.52, 1.28)	0.58 (0.32, 1.04)	0.89 (0.64, 1.24)	1.26 (0.72, 2.23)	1.45 (0.36, 5.89)	1.27 (0.76, 2.11)
Quintile 4	1.07 (0.86, 1.34)	1.17 (0.74, 1.84)	0.88 (0.50, 1.56)	1.21 (0.84, 1.75)	1.61 (0.70, 3.70)	0.68 (0.13, 3.43)	1.36 (0.63, 2.91)
Quintile 5	1.07 (0.85, 1.34)	1.00 (0.62, 1.62)	0.57 (0.30, 1.09)	0.82 (0.52, 1.28)	1.30 (0.26, 6.54)	1.23 (0.19, 7.87)	1.51 (0.47, 4.90)
				P for Interaction=0.74			

[a] National Oceanic and Atmospheric Administration (NOAA) designates nine U.S. regions that are climatically consistent. In this analysis, the West North Central, Southwest and Northwest regions were collapsed due to sparse cases in those regions.
[b] Least green quintile
Hazard ratios are adjusted for age, race, BMI, smoking status and pack-years of smoking, alcohol consumption, physical activity, physical function, bodily pain (baseline), marital status, social network strength, care to ill family members (baseline), difficulty sleeping (baseline), baseline mental health, educational attainment, husband's educational attainment, Census tract population density, Census tract median income, Census tract median home value, $PM_{2.5}$ level

Discussion

In this population of older, professional women in the U.S. between 2000 and 2010, residential greenness was associated with lower risk of depression in some models; however, adjusting for climatic region attenuated the estimates. A greater reduction in depression incidence in the 250m models unadjusted for climate suggested that greenness in the visual environment may be more important for depression, and was consistent with our finding that physical activity did not mediate the association. After adjusting for climatic region, however, the association between greenness and depression incidence became null in the 250 m buffer, and increasing greenness was associated with greater depression risk in the 1,250 m buffer.

Our initial findings of a beneficial effect of greenness on depression risk are consistent with a number of other studies considering an array of mental health outcomes.[4] They also generally agree with prior studies that found beneficial associations between residential greenness and depression, though our study suggested further nuances related to climatic region. These prior results were generally stronger among studies that used NDVI to characterize greenness as opposed to those that used land use databases, potentially because NDVI assesses existing vegetation whereas land use databases may incorrectly classify "green" land types.[14-20]

After additionally adjusting for region, there was no apparent association between greenness and depression risk in the 250 m buffer and a significantly increased risk of depression in the 1,250 m buffer. We speculate several reasons for this. Including region may induce a high degree of co-linearity, making estimates of both region and greenness subject to finite sample bias. Upon stratifying, less greenness variability and fewer cases may have limited our ability to observe statistically significant differences in the effect of greenness within regions (Table 1.4). It is also likely that the greenness construct may be less applicable for certain regions; other

metrics of exposure to natural environments (that are not primarily "green") may be more relevant to specific geographic areas. In our population, rates of self-reported clinician diagnosis and antidepressant use—which inherently depend on clinician behavior—also varied by region; though differences were small, they were highest in the West followed by the Midwest and South, and lowest in the Northeast. This fact may suggest regional differences in healthcare utilization and clinician behaviors regarding screening for or treating depression. In general in the U.S., prescribing practices for older adults have also been shown to vary by region: while the overall number of prescription fills per beneficiary is highest in the eastern U.S., antidepressant prescription fills are highest in the southern U.S.[32]

Several studies have explored both effect modification and mediation of the greenness effect by physical activity. Contrary to our findings, physical activity modified the greenness-mental health relationship in two studies: Annerstedt et al. found a reduced risk of poor mental health only among women who were physically active and had access to green space associated with the qualities of 'serenity' and 'space.'[24] Similarly, another study showed that greater green space was protective against psychological distress among more physically active subjects, but not among the least active.[25] Two studies found that physical activity did not mediate the relationship between perceived or objective greenness and mental health,[18,33] while one found it was a partial mediator.[34] In this study, the observed association between NDVI and depression was not mediated by physical activity level.

Our study had several limitations. While NDVI provides an objective measure of green space, it does not convey information about green space quality or usability. The NHS did not collect information on participants' perceptions of their environment, so we could not assess how perceived greenness was related either to NDVI or depression incidence. Additionally, we calculated NDVI around the women's homes, but did not have information about their

workplaces or other natural environment exposures. In general, uncertainty in this area of study persists over the appropriate location and scale for accurately measuring greenness exposures.

Depression misclassification may be a concern, as some cases of incident depression are likely to go undiagnosed or untreated; conversely, antidepressants may be used for indications other than depression.[35] In a population of health professionals, however, missed diagnoses may be less likely, and unlikely to vary systematically by NDVI. Since the population was older and we considered incident depression, which has lower incidence rates than those observed in young and mid-adulthood,[21] we may have selected healthy survivors and therefore obtained a conservative estimate. Generalizability of this study may be limited by the fact that this population consisted of mostly white, older, professional women.

Our study also had several strengths. This is the first prospective study of greenness and depression risk in a U.S. cohort of which we are aware, and the prospective design addresses concerns about potential reverse causality. The availability of detailed follow-up information in the NHS allowed us to model risk of depression over time among those not previously depressed, and to account for time-varying potential confounders such as socioeconomic status. We were also able to explore whether the effect of greenness on depression risk differed either because of or depending on physical activity level; in fact our findings suggest physical activity does not play a significant role in the relation between green space and incident depression in this population.

Conclusions

This paper contributes to our understanding of whether greenness, a modifiable feature of the environment, may influence depression, a leading cause of global disease burden. Additional studies, along with exploration of the role of region in the association, will help clarify if greenness could be a potential environmental intervention for mental health. Over half the world's population currently lives in urban areas, with 66% projected to live in cities by 2050 [36]. Urban green spaces have been shown to provide co-benefits to health, social equity, and climate change mitigation and adaptation efforts. While municipalities can enhance greenness through planning measures, the particular context in which these interventions take place may affect their efficacy for improving mental health.

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Greenness and Weight in a Population of U.S. Women

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Abstract

Background: Epidemiologic evidence suggests that exposure to greenness, or natural vegetation, may protect against several adverse health outcomes, potentially by promoting physical activity. Findings for an association with weight, however, have been mixed.

Objective: The objective of this study was to examine the prospective association between residential greenness exposure and the incidence of overweight and obesity in the U.S.-based nationwide Nurses' Health Study II. We hypothesized that greater residential greenness would be associated with reduced incidence of overweight or obesity.

Methods: A total of 43,869 aged 37-67 women with healthy body mass index (BMI, 18.5-24.9) and 75,680 women with healthy or overweight BMI (18.5-29.9) (including the subset of 43,869 women with healthy BMI) in 2001 were followed through 2011. Residential greenness exposure was estimated using the satellite-based Normalized Difference Vegetation Index (NDVI) and defined as the mean greenness value within 250 meter and 1,250 meter radii of the participants' residences for each season. BMI was assessed based on self-reported weight and height. Incident overweight (BMI 25-<30) was identified among those with a healthy BMI at baseline, and incident obesity (BMI 30 or greater) was identified among those with a healthy or overweight BMI at baseline. We used Cox proportional hazards models to examine the association between greenness and overweight/obesity incidence.

Results: Among 43,869 participants with a healthy BMI at study baseline, 10,126 women became overweight, and among 75,680 participants with a healthy or overweight BMI at study baseline, 8,969 became obese over 10 years of follow-up. Overall, in multivariable-adjusted models, there was no statistically significant association between greenness and risk of incident

overweight or obesity. There was, however, a suggestive association between increasing summer greenness within 250m around the residence and reduced risk of becoming overweight (HR for overweight in greenest quintile 0.91; 95% confidence interval (CI) 0.84, 0.99 compared to the least green quintile, p for trend=0.06).

Conclusions: In this population of women, we found limited evidence for a protective association between residential greenness and risk of incident overweight or obesity.

Introduction

In recent years, environmental epidemiologists have investigated greenness, or natural vegetation, as a potentially beneficial exposure for health. Studies across a diverse range of populations and geographies have shown greenness to be associated with benefits to mental health, pregnancy outcomes, child development, and other outcomes.[1] Greenness may enhance health by offering opportunities for physical activity;[10] promoting social cohesion, which has been linked with better health;[11] improving psychological wellbeing;[12] and by reducing exposure to noise, air pollution, and heat, environmental stressors that have been linked with adverse health outcomes.[3]

Overweight and obesity affect 69% of American adults, and increase subsequent risk of type 2 diabetes, cardiovascular disease, depression, reproductive issues, and certain cancers.[37,38] As more populations adopt a Westernized diet and lifestyle, overweight and obesity continue to increase globally.[39] Environmental conditions and cues can facilitate behaviors associated with weight maintenance; this principle underlies the Active Design movement that seeks to provide

opportunities for routine physical activity in daily life.[40] Some researchers have proposed increasing greenness as a strategy for promoting health through exercise.[41]

In the growing literature on possible health benefits of greenness, several studies have considered the relation between greenness and weight status, testing the hypothesis that greater greenness is associated with less overweight and obesity. To date, findings have been mixed. Some cross-sectional research has shown associations between greater greenness exposure and lower prevalence of overweight and obesity.[5-7] Investigators speculated this relation occurred because individuals near areas of greater greenness would likelier have a location for both routine and recreational physical activity.[42-45] However, one cross-sectional study found no association between greenness and weight status.[8] Another study actually found that increasing greenness was associated with higher prevalence of overweight or obesity.[9] Most of these studies have been cross-sectional, and could not address temporality of the relationship. Moreover, few studies considered relationships between greenness, physical activity and weight within a single analysis,[6,7] leaving open the question of whether greenness may affect weight through physical activity level.

In this study, we aimed to assess prospectively the relationship of greenness with overweight and obesity, to test the hypothesis that living in areas of higher greenness would be associated with reduced risk of becoming overweight or obese over a 10 year follow-up period. We considered a range of potential confounders (e.g., race, income, education level) selected based on prior literature.[46-48] We also investigated the degree to which physical activity might mediate any relationship between greenness and overweight or obesity, since a key reason

green spaces might be protective for weight status is because they can promote physical activity.[42-45]

Methods

Population

The Nurses' Health Study II (NHS II) is a prospective cohort study of 116,430 female registered nurses initially enrolled from 14 states in 1989. From the time they were enrolled, participants have completed biennial surveys on lifestyle, health-related behaviors and medical history. Questionnaire mailing addresses since the start of follow-up have been geocoded and updated with changes of address to create a residential address history. The institutional review board at Brigham and Women's Hospital, Boston, MA reviewed and approved the study. Participants implied consent through the return of completed questionnaires.

For the current study, we examined the risk of becoming overweight among those with a healthy body mass index (BMI, kg/m^2) of 18.5-<25 at study baseline, and the risk of obesity among those with a healthy or overweight BMI (18.5-29.9). Therefore, as applicable for the analysis, we excluded those who were overweight (n=34,708) or obese (BMI of 30 or greater, n=33,296) at study baseline, those who had died (n=825), those who were currently pregnant (n=1,478 among the healthy BMI population; n=2,627 among the healthy/overweight BMI population), and those for whom we were missing address or exposure information (n=550 among the healthy BMI population; n=832 among the healthy/overweight BMI population). We also excluded (and censored during follow-up) those with cancer, diabetes, and cardiovascular disease (myocardial infarction or stroke) (n=1,478 among the healthy BMI population; n=2,822 among the

healthy/overweight BMI population), because having a major chronic disease can lead to weight changes[49] and may obscure the primary association of interest.

Exposure

Residential greenness was characterized objectively using the Normalized Difference Vegetation Index (NDVI), derived from imagery collected by the MODerate-resolution Spectroradiometer (MODIS) sensors onboard NASA's Terra satellite.[27] The sensors measure the visible light absorbed and near-infrared light reflected by vegetation growth during photosynthesis, calculating the ratio of the difference between these two measures to their sum. Values of the index range between -1 and 1, with higher values representing greater vegetation cover. MODIS provides an image every 16 days at a 250m pixel size, and we used measures every three months.

From 2001 forward, when the data became available, we linked each address with an NDVI value (updated each questionnaire year) using geographic information systems (GIS) software (ArcMap, ESRI, Redlands, CA). Since there is still uncertainty with regard to the most appropriate exposure metric in greenness and health research, we explored several different exposure definitions. We estimated the mean NDVI value inside radii of 250m and 1,250m around each residence, and considered NDVI levels in representative months (January, April, July, October) of each season.

Outcome

Nurses self-reported their height at the study inception, and reported their weight on each subsequent questionnaire. From these data, participant BMI was calculated for each questionnaire cycle, with BMI in 2001 providing information on baseline weight status. Incident

overweight was defined as a newly reported BMI of 25-29.9, and incident obesity was defined as a newly reported BMI of 30 or greater. For those missing weight information in a given questionnaire cycle, weight from the previous questionnaire was carried forward. Previous work in the cohort confirmed that self-reported weight correlated closely (0.96) with actual body weight.[50,51]

Covariates

Time-varying information for known and suspected risk factors for weight gain was available from the biennial questionnaires. These included current age (in months), race (white or non-white), physical activity (self-reported total Metabolic Equivalent of Task (MET) hours per week, updated every four years), cigarette smoking (current, past, or never smoking status and pack-years smoked), diet (using the Alternative Healthy Eating Index,[52] updated every four years), oral contraceptive use (never, past, or current), parity (zero, one, two, three or more children), menopausal status (pre-menopausal, post-menopausal, uncertain menopausal status), and hormone replacement therapy (never, past, current). To account for individual socioeconomic status, we adjusted for nurses' personal income ($30,000 or less, $30-74,000, $75-99,000, $100-149,000, or $150,000 and above, reported in 2001), educational attainment (registered nurse degree), marital status (married or non-married), and husband's highest level of educational attainment (less than high school, high school graduate, or more than high school). We also considered area-level characteristics, including socioeconomic status (2000 Census tract median home value and median income), neighborhood walkability (index of residential density, land use mix, street connectivity within a 1,200m network buffer),[28] urbanicity (residence in a metropolitan (urban area ≥50,000 people), micropolitan (urban cluster of 10,000-49,999), or small town/rural (urban cluster of <10,000) Census tract),[53] air pollution (12-month average particulate matter less than 2.5 microns in aerodynamic diameter ($PM_{2.5}$) predicted at

the residential address from spatio-temporal generalized additive mixed models),[29] and region of the country (Northeast, Midwest, West, and South). $PM_{2.5}$ was updated biennially, and all other residence-based measures were updated only when a participant changed addresses. We accounted for missing covariate information using the missing indicator method.

Statistical Analysis

We used a Cox proportional hazards model to compute hazard ratios (HR) and 95% confidence intervals (CI) for the association between NDVI and risk of developing overweight or obesity.[54] The data were structured in an Andersen-Gill counting process format, with a single record for each nurse in each questionnaire cycle.[55] Participants contributed person-time from the date of receipt of their 2001 questionnaire to the date of their last questionnaire return, occurrence of incident overweight or obesity, or death through 2011, whichever occurred first. We conducted a test for trend based on the median value for each quintile to summarize evidence for a dose-response relationship, and used restricted cubic regression splines to assess deviations from linearity for exposure-response relationships.[30] We tested for violations of the proportional hazards assumption by including interaction terms of NDVI and participants' age and performed partial likelihood ratio tests comparing models with and without interaction terms. In a sensitivity analysis, we examined how changes in residential NDVI during follow-up affected subsequent changes in weight using generalized estimating equations to account for repeated measures. We hypothesized that in greener locations, participants would maintain weight or gain it more slowly than in less green places.

We evaluated physical activity as a potential mechanism by which greenness might affect weight incident overweight or obesity. Comparing models adjusted and unadjusted for physical activity level using the publicly available %mediate macro

(http://www.hsph.harvard.edu/faculty/spiegelman/mediate.html), we calculated the proportion of the weight change (and 95% CI) explained by higher exposure to greenness attributable to physical activity. Briefly, the macro compares the exposure effect estimate from the full model that includes the exposure, potential intermediate variables, and any covariates to the exposure effect estimate obtained from a partial model that leaves out the potential intermediate variables. Confidence intervals for the mediation proportion were calculated by using the data duplication method.[31] All analyses were conducted in SAS 9.4 (SAS Institute, Inc., Cary, North Carolina).

Results

Among the 43,869 participants who had a healthy BMI at baseline, 10,126 (23%) became overweight during follow-up. Among the 75,680 participants who had a healthy or overweight BMI at baseline 8,969 (12%) became obese during follow-up. On average, over the person-time of follow-up, the population of healthy/overweight participants was 51 years old, predominantly white, tended to live in metropolitan areas and was concentrated in the Northeast and Midwest (Table 2.1). Those who lived in greener areas had lower Census tract incomes and home values, were more likely to be white and married, and were less likely to live in metropolitan areas.

Table 2.1. Basic characteristics of the healthy and overweight BMI study population[a] over follow-up by summer Normalized Difference Vegetation Index from 2001-2011 (N=75,680) (values are age-adjusted)

	Total	Quintile 1[b]	Quintile 2	Quintile 3	Quintile 4	Quintile 5
			Mean (SD)			
Summer NDVI	0.7 (0.2)	0.4 (0.1)	0.6 (0.0)	0.7 (0.0)	0.8 (0.0)	0.8 (0.0)
Age[c]	51.3 (5.7)	52.0 (5.7)	51.4 (5.7)	51.2 (5.8)	51.0 (5.8)	50.7 (5.7)
BMI (kg/m^2)	24.0 (2.9)	23.8 (2.9)	24.0 (2.9)	24.1 (2.9)	24.1 (2.9)	24.1 (2.9)
Pack-years of smoking	4.4 (9.2)	3.7 (8.4)	4.6 (9.6)	4.4 (9.4)	4.5 (9.4)	4.7 (9.4)
Census tract median income ($1,000)	67 (25)	70 (27)	67 (25)	66 (22)	66 (23)	65 (26)
Census tract median home value ($1,000)	35 (24)	48 (34)	34 (25)	30 (16)	30 (17)	30 (21)
12-month average $PM_{2.5}$ (µg/m^2)	12.0 (2.6)	11.8 (3.7)	12.1 (2.5)	12.6 (2.2)	12.2 (2.1)	11.1 (2.2)
			%			
White	93	84	92	95	95	96
Married	59	53	56	60	61	63
Husband's highest education						
HS grad	12	8	11	12	14	16
More than HS	66	65	65	67	66	65
Physical activity MET hrs./wk.						
<3	10	9	9	9	10	10
3 to <9	13	12	13	13	13	13
9 to <18	14	14	14	15	15	15
18 to <27	10	10	10	11	11	10
27 to <42	11	10	10	11	11	11

>=42	13	14	13	13	13	13
Census tract urbanicity[d]						
Metropolitan area	84	93	89	85	81	73
Micropolitan area	9	4	7	10	11	13
Small town or rural area	7	3	4	6	8	14
Region of the country						
Northeast	33	10	21	29	43	61
Midwest	31	7	41	47	36	25
West	16	63	11	3	2	1
South	20	21	27	21	19	13

[a] Members of the study population who had a healthy or overweight BMI at baseline

[a] Quintile with lowest greenness exposure

[c] Value is not age adjusted

[d] Urbanicity classified as metropolitan (urban area ≥50,000 people), micropolitan (urban cluster of 10,000-49,999), or small town/ rural (urban cluster of <10,000) Census tract

Associations between residential greenness and overweight risk are presented in Table 2.2, and associations between greenness and obesity risk are presented in Table 2.3. In age-adjusted models, few associations were evident in any season with the exception that increasing greenness during summer within a 1,250m radius of residence was statistically significantly associated with 11% (95% CI 4%, 19%) greater risk for becoming overweight, with p for trend 0.003 (Table 2.2). In models adjusted for the full set of covariates, living in the greenest quintile in any season was not statistically significantly associated with risk for overweight with either buffer size (Table 2.2). However, living in the greenest quintile of summer NDVI (within a 250m radius of residence) was suggestively associated with a reduced risk of incident overweight (HR

0.91, 95% CI 0.84, 0.99; p for trend 0.058). Restricted cubic regression spline analyses did not provide evidence of a deviation from linearity.

In age-adjusted models, increasing winter NDVI (using 250m and 1,250m buffers) was statistically significantly associated with reduced risk for becoming obese (Table 2.3). In fully adjusted models, increasing greenness did not appear to be statistically significantly associated with obesity risk, despite point estimates in the expected direction for the greenest quintiles across most seasons and buffer sizes (Table 2.3).

In our study population, the association between greenness and weight status appeared to be primarily driven by race and socioeconomic status. Including physical activity level in models did not affect effect estimates for overweight or obesity risk, suggesting that physical activity does not provide a pathway between greenness and weight in this population. The results of the mediation analysis indicated that there was no mediation by physical activity.

In a sensitivity analysis, there was no association between prevalent greenness or change in greenness and change in weight among participants. This was true for all seasons at both buffer sizes (results not shown).

Table 2.2. Hazard ratios (HR) and 95% confidence intervals (CI) for the association between residential greenness and incident overweight[a] in the Nurses' Health Study II (N=43,869 with 10,126 cases over 424,159 person-years of follow-up, 2001-2011)

Age-Adjusted Models								
	Buffer size 250m				**Buffer size 1,250m**			
	Summer	**Fall**	**Winter**	**Spring**	**Summer**	**Fall**	**Winter**	**Spring**
Q1[b]	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Q2	1.04 (0.97, 1.11)	1.04 (0.97, 1.11)	0.98 (0.91, 1.04)	0.99 (0.93, 1.06)	1.14 (1.07, 1.21)	1.07 (1.01, 1.15)	0.98 (0.91, 1.04)	0.99 (0.93, 1.05)
Q3	1.05 (0.98, 1.12)	1.09 (1.02, 1.16)	1.01 (0.95, 1.08)	1.02 (0.95, 1.08)	1.12 (1.05, 1.20)	1.10 (1.03, 1.18)	0.99 (0.93, 1.06)	1.04 (0.97, 1.11)
Q4	1.08 (1.01, 1.15)	1.08 (1.01, 1.15)	1.00 (0.94, 1.07)	1.04 (0.98, 1.11)	1.09 (1.02, 1.17)	1.11 (1.04, 1.18)	1.04 (0.97, 1.11)	1.01 (0.95, 1.08)
Q5	1.00 (0.94, 1.06)	1.01 (0.95, 1.08)	0.95 (0.89, 1.02)	1.01 (0.94, 1.07)	1.11 (1.04, 1.19)	1.03 (0.97, 1.10)	0.96 (0.90, 1.03)	1.04 (0.98, 1.11)
p value, test for trend	0.44	0.25	0.41	0.46	0.003	0.07	0.86	0.16
Fully-Adjusted Models[c]								
	Buffer size 250m				**Buffer size 1,250m**			
	Summer	**Fall**	**Winter**	**Spring**	**Summer**	**Fall**	**Winter**	**Spring**
Q1[b]	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Q2	0.96 (0.89, 1.03)	0.99 (0.92, 1.06)	1.03 (0.97, 1.11)	0.96 (0.90, 1.03)	1.07 (0.99, 1.15)	1.01 (0.94, 1.09)	1.02 (0.96, 1.09)	0.96 (0.89, 1.02)
Q3	0.95 (0.88, 1.02)	1.01 (0.93, 1.08)	1.05 (0.97, 1.13)	0.98 (0.92, 1.05)	1.01 (0.93, 1.10)	1.02 (0.94, 1.10)	1.02 (0.95, 1.10)	1.01 (0.94, 1.08)
Q4	0.97 (0.90, 1.05)	1.01 (0.93, 1.09)	1.04 (0.96, 1.12)	0.99 (0.93, 1.06)	0.99 (0.91, 1.08)	1.02 (0.94, 1.10)	1.09 (1.01, 1.17)	0.98 (0.91, 1.05)
Q5	0.91 (0.84, 0.99)	0.96 (0.89, 1.04)	1.03 (0.96, 1.12)	0.97 (0.90, 1.04)	1.02 (0.94, 1.12)	0.98 (0.90, 1.06)	1.04 (0.96, 1.12)	1.01 (0.94, 1.08)
p value, test for trend	0.058	0.51	0.42	0.56	0.81	0.68	0.15	0.72

[a] Incident overweight defined as newly reported BMI of 25-<30

[b] Quintile with lowest greenness exposure

[c] Hazard ratios are adjusted for age, calendar year, race, diet, smoking, physical activity, educational attainment, marital status, husband's education, income, oral contraceptive use, parity, menopausal status, hormone replacement therapy, Census tract median income, median home value, urbanicity, $PM_{2.5}$, neighborhood walkability, region of the country

Table 2.3. Hazard ratios (HR) and 95% confidence intervals (CI) for the association between residential greenness and incident obesity[a] in the Nurses' Health Study II (N=75,680 with 8,969 cases over 783,349 person-years of follow-up, 2001-2011)

Age-Adjusted Models								
	Buffer size 250m				**Buffer size 1,250m**			
	Summer	**Fall**	**Winter**	**Spring**	**Summer**	**Fall**	**Winter**	**Spring**
Q1[b]	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Q2	1.15 (1.07, 1.23)	1.16 (1.09, 1.25)	0.93 (0.87, 0.99)	0.96 (0.89, 1.02)	1.15 (1.08, 1.24)	1.23 (1.15, 1.32)	0.97 (0.90, 1.04)	0.98 (0.92, 1.05)
Q3	1.09 (1.01, 1.16)	1.15 (1.07, 1.23)	0.96 (0.89, 1.03)	1.00 (0.94, 1.07)	1.13 (1.05, 1.21)	1.20 (1.11, 1.28)	0.99 (0.92, 1.06)	0.99 (0.93, 1.06)
Q4	1.06 (0.99, 1.14)	1.10 (1.03, 1.18)	0.94 (0.88, 1.01)	0.98 (0.92, 1.05)	1.14 (1.06, 1.22)	1.17 (1.09, 1.25)	0.98 (0.91, 1.05)	0.99 (0.92, 1.06)
Q5	1.08 (1.01, 1.15)	1.02 (0.95, 1.09)	0.87 (0.81, 0.93)	0.96 (0.90, 1.02)	1.13 (1.06, 1.21)	1.08 (1.01, 1.16)	0.89 (0.83, 0.95)	0.96 (0.90, 1.03)
p value, test for trend	0.13	0.58	0.003	0.39	<0.001	0.035	0.014	0.32
Fully-Adjusted Models[c]								
	Buffer size 250m				**Buffer size 1,250m**			
	Summer	**Fall**	**Winter**	**Spring**	**Summer**	**Fall**	**Winter**	**Spring**
Q1[b]	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Q2	1.04 (0.96, 1.12)	1.08 (1.00, 1.16)	0.97 (0.91, 1.05)	0.95 (0.89, 1.02)	1.02 (0.94, 1.11)	1.14 (1.05, 1.23)	1.01 (0.94, 1.08)	0.97 (0.91, 1.04)
Q3	0.95 (0.88, 1.03)	1.02 (0.94, 1.10)	0.98 (0.91, 1.06)	1.00 (0.93, 1.07)	0.95 (0.87, 1.04)	1.08 (0.99, 1.17)	1.01 (0.94, 1.09)	0.99 (0.92, 1.06)
Q4	0.94 (0.87, 1.02)	1.00 (0.92, 1.08)	0.97 (0.90, 1.05)	0.96 (0.89, 1.03)	0.97 (0.88, 1.06)	1.05 (0.96, 1.14)	1.00 (0.92, 1.08)	0.97 (0.90, 1.04)
Q5	0.98 (0.90, 1.06)	0.96 (0.88, 1.04)	0.95 (0.88, 1.03)	0.93 (0.87, 1.00)	0.99 (0.90, 1.08)	1.01 (0.92, 1.11)	0.96 (0.89, 1.05)	0.93 (0.86, 1.00)
p value, test for trend	0.12	0.099	0.31	0.088	0.42	0.49	0.50	0.073

[a] Incident obesity defined as newly reported BMI of 30 or greater
[b] Quintile with lowest greenness exposure
[c] Hazard ratios are adjusted for age, calendar year, race, diet, smoking, physical activity, educational attainment, marital status, husband's education, income, oral contraceptive use, parity, menopausal status, hormone replacement therapy, Census tract median income, median home value, urbanicity, $PM_{2.5}$, neighborhood walkability, region of the country

Discussion

In this study, over ten years of follow-up, we found little evidence for an association between greenness and the development of overweight and obesity. We examined greenness in the immediate residential environment and in the participants' neighborhood environment, and considered peak greenness for each of the four seasons within these radii. The relationship between greenness and overweight or obesity appeared moderately positive or negative depending on buffer size and season before adjustment. After full multivariable adjustment, we observed no consistent associations between greenness and incident overweight or obesity, although point estimates in fully adjusted models for the 250m buffer size generally suggested a protective association.

Our prospective finding is consistent with another study that found no association between green space and BMI in a cross-sectional study in a population of Egyptian adults.[8] Our results are not consistent with several other studies, mostly cross-sectional, throughout Europe, Australia and Canada that did find protective associations between greater greenness or green space exposure and lower prevalence of overweight and obesity.[5-7] Two of these studies found these relationships only in women but not men.[5,6] One observed that women with over 80% green space within a 1km catchment area had relative risk ratios of 0.90 (95% CI 0.83, 0.97) for overweight and 0.83 (95% CI 0.74, 0.94) for obesity.[5,6] However, because these studies were cross-sectional, they could not evaluate directionality in these effects, and further could not adjust for level of urbanicity or walkability, nor could they finely account for socioeconomic status. Moreover, one cross-sectional study in England found effects in the opposite direction to

that expected, with residence in the greenest areas associated with a 12% greater prevalence of overweight and a 23% increased prevalence of obesity.[9]

Our ability to finely account for individual and neighborhood socioeconomic status, as well as other potential confounders, may have contributed to our finding of no association between greenness and incident overweight and obesity. The relationships between race, socioeconomic status and neighborhood greenness may manifest differently in American cohorts than in the other geographies where greenness has been studied, which may also account for our findings relative to others.

In our study, race and socioeconomic status appeared to be strong predictors of incident overweight and obesity. Our ability to account for individual and neighborhood socioeconomic status and other potential confounders in a more nuanced manner, as well as our ability to examine the association prospectively, may have contributed to our finding of no association between greenness and weight status. The relationships between race, socioeconomic status and neighborhood greenness may manifest differently in American cohorts than in the other geographies where greenness has been studied, which may also account for our findings relative to others.

Our observation that including physical activity level in models did not affect effect estimates is aligned with previous studies that found no relationship between greenness and physical activity.[56,57] Furthermore, our study agrees with two studies that found a negative association between greenness and weight was not mediated by physical activity levels.[5,6] A consistent

relationship between physical activity and weight status has not always been shown in this cohort,[47] nor did there appear to be a relationship between greenness and physical activity in our sample.

Our study had several limitations. NDVI provides an objective measure of greenness, but does not convey information about green space quality. For example, measuring vegetative density does not tell us if it is pleasant or useable. Nor did we have information on study participants' perceptions of or use of their environment, so we could not assess how perceived greenness or use was related either to NDVI or the development of overweight and obesity. It is possible that individuals who live in green spaces but perceive those spaces as not being walkable or safe, for instance, do not benefit from greenness in the same way. In our study, weight was self-reported and could therefore be prone to error. However, previous work in the cohort confirmed that self-reported weight correlated closely (0.96) with actual body weight.[50,51] Finally, generalizability of this study may be limited by the fact that this population consisted of mostly white, professional women.

Our study had several important strengths. This is the first prospective study of greenness and risk of becoming overweight or obese over ten years of follow-up among adults in a nationwide U.S. cohort of which we are aware. The prospective design may address concerns about reverse causality regarding associations observed in previous cross-sectional studies. The availability of detailed follow-up information in NHS II allowed us to account for a broad range of potential confounders, such as socioeconomic status, and to do so in a time-varying way. We were also able to explore whether any association between greenness and weight might be mediated by physical activity level.

In this study, over ten years of follow-up in a large prospective cohort of middle-aged women in the U.S., higher residential greenness was not consistently associated with incident overweight or obesity. This was somewhat surprising given prior findings that found a beneficial association between greenness and weight. Our ability to incorporate temporality and address socioeconomic status may account for the findings in the opposite direction from expectation. Future research on this topic should continue to analyze the association prospectively, incorporate metrics of greenness quality and usability, and attempt to adjust for an array of potential confounders.

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Exposure to Noise and Incident Hypertension in a Nationwide Prospective Cohort Study

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Abstract

Background: Epidemiologic evidence suggests that noise may be linked with cardiovascular disease (CVD) risk, but few studies have examined the relationship between noise and a common CVD risk factor, hypertension. Determining if noise may increase risk for hypertension may help clarify how it affects CVD risk.

Objective: The objective of this study was to examine the prospective association between residential nighttime noise exposure and incident hypertension in women from the U.S. based nationwide Nurses' Health Study II. We hypothesized that higher levels of nighttime noise exposure would be associated with greater risk for incident hypertension.

Methods: A total of 82,398 women without hypertension in 2001 were followed through 2013. Residential nighttime noise was estimated using a geospatial sound model based on measured acoustical metrics and non-acoustic environmental factors such as topography, climate, hydrology, and anthropogenic activity. Incidence of hypertension was defined by self-reported clinician-diagnosed hypertension or new regular antihypertensive medication use. We used Cox proportional hazards models to examine the association between nighttime noise and hypertension incidence. Because the association between noise and hypertension could vary according to the duration and degree of exposure, we considered effect modification by whether participants had moved over the course of the study and the duration of night shift work. We assessed mediation by difficulty sleeping.

Results: Over 846,711 person-years of follow-up, 23,738 incident hypertension cases occurred. In multivariable-adjusted models, exposure to the highest versus lowest quintile of nighttime noise exposure was associated with a 6% increase in hypertension risk (95% confidence

interval (CI) 1.00, 1.11), p-value for linear trend 0.003. There was no evidence of effect modification by whether participants moved to areas with more or less noise or stayed at the same noise level, or by the extent to which participants worked night shifts. Only a small proportion of the overall association between nighttime noise and hypertension appeared to be mediated by difficulty sleeping.

Conclusions: In this population of women, we observed a positive relationship between nighttime noise exposure and hypertension risk. Effects were only partially attenuated when considering sleep difficulty.

Introduction

In recent years, environmental epidemiologists have expanded our understanding of the health effects of noise, or unwanted sound. Not only does noise cause annoyance and interrupt sleep,[58,59] but it can also influence health. In particular, emerging experimental and observational studies suggest a deleterious relationship between noise exposure and cardiovascular disease (CVD).[2] Less research has considered the relationship between noise and hypertension, a common risk factor for cardiovascular disease. Determining if noise may increase risk for hypertension may help clarify how it affects CVD risk, as well as identify a lesser known risk factor for hypertension.

Epidemiologic studies have indicated that nighttime noise in particular may be more strongly associated with cardiovascular health than daytime noise exposure.[2,60] Most mechanisms proposed to explain the relationship between noise and cardiovascular health identify noise as a

stressor[61] that can provoke adverse physiological and psychological responses, with detrimental consequences for health. Nighttime noise could engender a sequence of physiological and psychological stress responses whether or not sleep is disturbed. In experimental settings, noise exposure has been shown to have acute effects including increasing blood pressure, heart rate and cardiac output along with stress hormones.[62,63] Research suggests that a sustained decrease in blood pressure during the night may be important for long-term cardiovascular health; for individuals chronically exposed to nighttime noise, the resultant recurring stress response may impair their ability to experience this sustained blood pressure decrease.[2]

Nighttime noise exposure may contribute to the onset of hypertension, and this may be part of the mechanism by which noise can lead to other cardiovascular health outcomes. An alternate complementary hypothesis suggests that noise exposure during the night raises risk for hypertension by disturbing sleep,[58] since shorter sleep duration has been shown to be associated with increased risk of hypertension.[64] Either stress or sleep disruption occurring in response to noise exposure could precipitate downstream behavioral responses that are themselves associated with hypertension risk, such as smoking, poor diet, and reduced physical activity.[65,66]

Some research has begun to directly examine the association of noise exposure with intermediate conditions on the pathway to CVD such as hypertension. European studies of participants close to airports found significant positive associations between higher airport and road traffic noise exposure and hypertension prevalence in cross-sectional analyses.[67,68] Other cross-sectional studies, and one prospective one,[69] have also found positive relationships between more road traffic and railway noise exposure and odds of hypertension.[70-73] Conversely, one cross-sectional study found no association between noise and self-reported

hypertension.[74] Most of these studies used modeled rather than measured noise exposure, involving more uncertainty in actual exposure levels, and one incorporated information on noise-exposed building façades in the model for a finer estimate.[75] Though these studies involved a range of populations, almost all were cross-sectional, and almost all have been conducted in Europe, making extrapolation to the U.S., with different noise sources and housing stock, uncertain.[61] In addition, most studies were unable to account for other potential confounders, including health behaviors and socioeconomic status. In particular, individuals more likely to develop hypertension may also be more likely to be exposed to high levels of noise due to socioeconomic status or other prior common causes.

To assess more comprehensively whether noise might be a contributing determinant of incident hypertension, we performed a prospective examination of the relationship between noise and hypertension. We also conducted a secondary analysis of sleep duration as a potential mediator, since noise is associated with difficulty falling asleep and experiencing poor sleep.[58] Finally, because the association between noise and hypertension could vary according to the duration and degree of exposure, we aimed to assess effect modification by whether participants had moved over follow-up, and by the extent to which they had worked night shifts. Moves over follow-up would affect the chronic nature of noise exposure; we hypothesized that the association between nighttime noise and incident hypertension would be stronger among those who had not moved. We hypothesized that the association between nighttime noise and incident hypertension would be weaker among those who worked night shifts, since they were likely not be experiencing the exposure level ascribed to their home.

Methods

Population

The Nurses' Health Study II (NHSII) is a prospective cohort study of 116,430 female registered nurses who were initially enrolled in 1989 from 14 states. Every two years, participants complete surveys on their lifestyle, health-related behaviors, and medical history. Questionnaire mailing addresses since the start of follow-up have been geocoded and updated with changes of address to create a residential address history.

For this analysis, we excluded those who were prevalent cases at the start of follow-up for this study (i.e. who reported a clinician's diagnosis of hypertension or regular use of antihypertensive medications before 2001, when exposure information became available) (n=28,098), who had died or stopped responding to questionnaires (n=1,779), and those for whom we were missing address or noise exposure information (n=1,358). We excluded (and censored, during follow-up) those with cancer, diabetes, and cardiovascular disease (myocardial infarction or stroke) (n=2,765), because having a major chronic disease at the study outset could obscure the primary association of interest.[76-78] The institutional review board at Brigham and Women's Hospital, Boston, MA reviewed and approved the study. Participants implied consent through the return of completed questionnaires.

Outcome

Biennial questionnaires included questions about medical diagnoses, including hypertension. Questionnaires also included questions about regular medication use within the last two years, including antihypertensive medications (by drug class, including thiazide diuretics, beta-blockers, calcium channel blockers, angiotensin-converting-enzyme inhibitors, and other

antihypertensive drugs). We considered respondents who reported a new clinician diagnosis of hypertension or new use of antihypertensive medication since the prior questionnaire, as cases. In a previous validation study of 147 participants who self-reported clinician-diagnosed hypertension, 94% were confirmed by medical records, suggesting accurate self-report in this population.[79]

Exposure

Noise data were obtained from a nationwide map of predicted environmental sound levels generated by researchers at the National Park Service. Regression models were developed by relating acoustical measurements to non-acoustic environmental features such as topography, climate, hydrology, and anthropogenic activity.[26] The acoustical measurements included 1.5 million hours of long-term measurements from 492 urban and rural sites located across the contiguous U.S. collected between 2000-2014.[80,81] The method used random forest, a tree-based machine learning algorithm, was used to create a predictive model. The resulting geospatial sound model produced non-time varying estimates of sound levels at ~270m resolution across the entire U.S. All noise levels were projected for the summer season.

There are several ways of summarizing environmental sound using various time scales and frequency ranges. Because we hypothesized that nighttime noise increases risk of hypertension by inducing physiological stress or disrupting sleep, we examined the anthropogenic nighttime (7PM to 7AM) A-weighted L_{50} sound pressure level metric as our primary measure of noise exposure. The L_{50} is an exceedance metric, indicating the value at which the sound pressure level was exceeded 50% of the time. A-weighting is an adjustment reflecting the human perception of sound across the frequency spectrum. In addition to predicting total ambient sound pressure levels, the geospatial sound model also predicted natural sound levels

(including contributions from biotic and physiographic sources only) by minimizing the influence of all anthropogenic factors. The anthropogenic sound pressure level is then calculated by logarithmic subtraction of the natural from the total sound pressure levels. Because the geospatial sound model provided a time-averaged estimate of exposure over the years 2001-2013, we assigned a single, non-time varying nighttime noise value to each geocoded address for questionnaire years from 2001-2013 using ArcGIS (ESRI, Redlands, CA). Therefore, exposures only varied over time for those women who changed addresses during follow-up. We conducted secondary analyses using alternative measures of anthropogenic daytime sound (7AM to 7PM): A-weighted L_{90} (background level, exceeded 90% of the time) and A-weighted L_{50} (median of the data, representing typical sound) to explore whether daytime sound might also affect hypertension risk. Across the noise metrics we considered, cross-validated residuals indicated that root mean squared error ranged from 4.5-4.9 dB, median absolute deviation ranged from 2.3-2.4 dB, and the percent of variance explained ranged from 80-84% relative to the null model.

Covariates

Using the detailed information obtained from biennial surveys, we were able to adjust for a range of known or suspected risk factors for hypertension. Our models included the following variables, modeled in a time-varying fashion: age, race/ethnicity, body mass index (BMI) (kg/m^2), diet (using the Alternative Healthy Eating Index,[52] updated every four years), smoking status (never, past, or current) and pack-years smoked, physical activity (self-reported Metabolic Equivalent of Task (MET) hours per week, updated every four years), menopausal status (pre-menopausal, post-menopausal, or uncertain), oral contraceptive use (never, past, or current), non-narcotic analgesic intake (ibuprofen, aspirin, or acetaminophen twice or more per week), statin use, family history of hypertension, sleep duration (hours of sleep per night, self-

reported in 2001), and night shift work (none, 0-12 months, or over 12 months of night shift work since 2001). To adjust for individual socioeconomic status, we also included the participants' educational attainment (receipt of registered nurse degree), marital status, husband's highest educational attainment (if married), and personal income ($30,000 or less, $30-74,000, $75-99,000, $100-149,000, or $150,000 and above, self-reported in 2001). At the area level, we adjusted for 2000 Census tract median home value and median income,[82] neighborhood walkability (index of residential density, land use mix, and street connectivity),[83] air pollution level at the address (average $PM_{2.5}$ estimated from GIS-based spatio-temporal models),[29,84] urbanicity (residence in a metropolitan (urban area ≥50,000 people), micropolitan (urban cluster of 10,000-49,999), or small town/rural (urban cluster of <10,000) Census tract),[85] and region of the country. $PM_{2.5}$ was updated biennially, and all other residence-based measures were updated only when a participant changed addresses. The missing indicator method was used to account for any missing covariates.

Statistical Analysis

To examine the association between environmental sound and incident hypertension, we used Cox proportional hazards models[86] to obtain hazard ratios (HR) and 95% confidence intervals (95% CI) for quintiles of each noise metric and incident hypertension using the lowest quintile as the reference group. We modeled the exposure using quintiles to compare relative noise levels as opposed to absolute differences, and because quintiles would be appropriate even if tests indicated a deviation from linearity. A test for trend based on the median value for each quintile was used to summarize evidence for a dose-response relationship. Participants contributed person-time until diagnosis, death, loss to follow-up, or the end of follow-up. We checked for deviations from linearity of the exposure-response relationship using restricted cubic regression

splines.[30,87] We obtained estimates for age-adjusted models as well as models adjusted for known and suspected hypertension risk factors. We tested for violations of the proportional hazards assumption by including interaction terms for noise exposure with age and performed likelihood ratio tests. Finally, we conducted a sensitivity analysis using only cases based only on hypertension diagnosis, since certain antihypertensive medications may be prescribed for other uses.

Because the relationship between environmental sound and hypertension could be mediated by sleep duration, we assessed mediation by difficulty sleeping. The 2001 questionnaire included a question on whether participants had difficulty falling or staying asleep. Using the publicly available %mediate macro (http://www.hsph.harvard.edu/faculty/spiegelman/mediate.html), we calculated the proportion of hypertension incidence (and 95% CI) explained by higher exposure to noise attributable to poor sleep duration in the fully-adjusted model. Briefly, the macro compares the exposure effect estimate from the full model that includes the exposure, one or more potential intermediate variables, and any covariates to the exposure effect estimate obtained from a partial model that leaves out the potential intermediate variable or variables. Confidence intervals for the mediation proportion were calculated using the data duplication method.[31]

The relationship between noise and incident hypertension could differ according to duration and degree of exposure. Accordingly, we assessed effect modification by characteristics that would influence these aspects of exposure. These characteristics included whether participants had moved to areas with more or less noise or remained at the same noise level during follow-up, and the number of months since 2001 they had worked night shifts, since participants who worked night shifts would be less likely to experience the nighttime noise level at their place of residence during that time. We added interaction terms for each potential categorical effect

modifier with noise quintiles and conducted likelihood ratio tests to determine their statistical significance; we also obtained strata-specific hazard ratios. All analyses were conducted in SAS 9.4 (SAS Institute, Inc., Cary, North Carolina).

Results

The population for analysis consisted of 82,398 participants who contributed 846,711 person-years, during which time, 23,738 incident hypertension cases occurred. On average, over the course of follow-up, the population was 51 years old, predominantly white, slightly overweight, tended to live in metropolitan areas and was concentrated in the Northeast and Midwest (Table 3.1). Those who lived in areas with higher noise exposure were less likely to be married or white, had higher Census tract median incomes and home values, and were more likely to live in metropolitan areas and in the Midwest.

Table 3.1. Basic characteristics of the study population over follow-up by nighttime L_{50} anthropogenic noise exposure from 2001-2013 (N=82,398) (values are age-adjusted)

	Total (N=82,398)	Quintile 1[b] 9-41 dbA	Quintile 2 41-43 dbA	Quintile 3 43-44 dbA	Quintile 4 44-46 dbA	Quintile 5 46-54 dbA
	Mean (SD)					
L_{50} nighttime anth. noise dBA	43.0 (3.6)	37.6 (3.5)	42.0 (0.5)	43.4 (0.4)	44.7 (0.4)	47.1 (1.3)
Age (years)[a]	51.2 (6.0)	51.3 (6.1)	51.0 (6.0)	51.0 (6.0)	51.2 (5.6)	51.3(6.0)
BMI (kg/m^2)	25.8 (5.3)	25.9 (5.3)	25.9 (5.2)	25.7 (5.3)	25.6 (5.2)	26.0 (5.5)
Pack-years of smoking	4.2 (8.9)	4.4 (9.2)	4.1 (8.8)	4.1 (8.9)	4.1 (8.8)	4.1 (8.9)
Census tract median income ($1,000)	67 (25)	59 (22)	65 (23)	71 (25)	73 (26)	66 (24)
Census tract median home value ($1,000)	174 (13)	144 (95)	154 (100)	185 (126)	205 (148)	182 (143)
12-month average $PM_{2.5}$ (μg/m^2)	12.0 (2.6)	9.8 (2.3)	11.7 (2.2)	12.6 (2.2)	12.5 (2.4)	13.3 (2.7)
			%			

White	93	96	96	94	92	89
Married	61	66	64	62	59	55
Husband's highest education						
HS grad	13	18	14	12	10	10
More than HS	65	64	66	67	66	63
No night shifts	69	69	69	70	70	68
<=12 months night shifts	6	7	6	6	5	6
>12 months night shifts	6	7	6	6	5	5
Physical activity MET hrs./wk.						
<3	11	11	11	11	11	11
3 to <9	14	14	14	13	13	14
9 to <18	15	15	15	15	14	14
18 to <27	10	10	11	11	10	10
27 to <42	10	11	11	10	11	10
>=42	13	14	12	13	13	12
Analgesic use >=2 days/wk.	22	23	22	22	22	21
Statin use	7	7	8	8	7	7
Census tract urbanicity[c]						
Metropolitan area	84	63	81	89	94	96
Micropolitan area	9	17	12	7	4	4
Small town/rural area	7	20	7	4	2	1
Moved to greater noise exposure during follow-up	5	4	4	5	5	7
Moved to less noise exposure during follow-up	6	8	7	6	5	4
Region of the country						
Northeast	33	47	38	31	28	20
Midwest	32	27	37	35	27	33
West	16	14	8	13	21	25
South	19	11	18	21	24	21

[a] Value is not age adjusted

[b] Quintile with lowest noise exposure

[c] Urbanicity classified as metropolitan (urban area ≥50,000 people), micropolitan (urban cluster of 10,000-49,999), or small town/ rural (urban cluster of <10,000) Census tract

Associations between nighttime noise exposure (as well as other noise metrics) and hypertension risk are presented in Table 3.2. In age-adjusted models, there was no association between anthropogenic nighttime noise and incident hypertension. In fully-adjusted models adjusted for age, race, BMI, diet, smoking status and pack-years smoked, physical activity, marital status, oral contraceptive use, menopausal status, family history of hypertension, non-

narcotic analgesic intake, statin use, education, husband's education, income, night shift work, Census tract median income and home value, neighborhood walkability, $PM_{2.5}$, urbanicity, and region of the country, living in the highest quintile of anthropogenic nighttime noise was associated with increased risk of incident hypertension compared to the lowest quintile (HR 1.06, 95% CI 1.00, 1.11, p-value for linear trend 0.003). Restricted cubic regression spline analyses indicated a statistically significant deviation from linearity in the nighttime noise models, validating the use of quintiles; similar deviations from linearity however were not evident in the daytime noise models. While noise appeared to be associated with lower risk of incident hypertension in age-adjusted models, there was no association evident between exposure to daytime L_{50} or L_{90} anthropogenic noise and risk of incident hypertension in fully-adjusted models. A sensitivity analysis in which the case definition was based only on hypertension diagnosis, rather than medication use, yielded similar results (not shown).

In formal mediation analyses considering sleep as a potential mediator, we observed evidence that difficulty falling or staying asleep partially mediated, to a very small degree, the association between increasing nighttime anthropogenic noise and increased incidence of hypertension. In the fully adjusted model, difficulty falling or staying asleep was responsible for 2.9% (95% CI 0.9%, 9.1%) of the association between higher nighttime noise exposure and increased risk of incident hypertension.

Table 3.2. Hazard ratios (HR) and 95% confidence intervals (CI) for the association between residential noise exposure and incident hypertension[a] in the Nurses' Health Study II (N=82,398 with 23,738 hypertension cases over 846,711 person-years of follow-up, 2001-2013)

	Cases/Person-years	Age-Adjusted HR (95% CI)	Fully Adjusted HR(95% CI)[c]
		L_{50} nighttime anthropogenic noise	
Quintile 1[b]	4,767/169,256	Ref	Ref
Quintile 2	4,679/169,208	0.99 (0.95, 1.03)	0.99 (0.95, 1.04)
Quintile 3	4,689/169,521	0.99 (0.95, 1.03)	1.01 (0.96, 1.05)
Quintile 4	4,670/169,348	0.97 (0.94, 1.01)	1.03 (0.98, 1.08)
Quintile 5	4,933/169,378	1.03 (0.99, 1.07)	1.06 (1.01, 1.11)
p-value, test for trend		0.415	**0.003**
		L_{90} daytime anthropogenic noise	
Quintile 1[b]	4,937/169,069	Ref	Ref
Quintile 2	4,703/169,336	0.96 (0.92, 0.99)	0.97 (0.93, 1.02)
Quintile 3	4,815/169,262	0.97 (0.93, 1.01)	1.02 (0.97, 1.07)
Quintile 4	4,763/169,442	0.96 (0.92, 1.00)	1.03 (0.98, 1.08)
Quintile 5	4,520/169,601	0.90 (0.87, 0.94)	1.01 (0.95, 1.06)
p-value, test for trend		**<.001**	0.297
		L_{50} daytime anthropogenic noise	
Quintile 1[b]	4,866/169,056	Ref	Ref
Quintile 2	4,757/169,271	0.97 (0.93, 1.01)	0.98 (0.94, 1.03)
Quintile 3	4,733/169,457	0.97 (0.93, 1.01)	1.01 (0.96, 1.06)
Quintile 4	4,732/169,412	0.96 (0.92, 1.00)	1.01 (0.97, 1.06)
Quintile 5	4,650/169,516	0.94 (0.90, 0.98)	1.01 (0.96, 1.07)
p-value, test for trend		**0.002**	0.365

[a] Incident hypertension defined according to self-reported clinician diagnosis or regular use of antihypertensive medication

[b] Quintile with lowest noise exposure

[c] Hazard ratios are adjusted for age, race, BMI, diet, smoking status and pack-years smoked, physical activity, marital status, oral contraceptive use, menopausal status, family history of hypertension, non-narcotic analgesic intake, statin use, education, husband's education, income, night shift work, sleep duration, Census tract median income and home value, urbanicity, neighborhood walkability, $PM_{2.5}$, region of the country

The association between nighttime noise exposure and incident hypertension appeared to vary by degree but not by duration of exposure (Tables 3.3-3.4). There was no statistically significant interaction between noise level and moving status (p-value 0.99), although stratified analyses suggested nighttime noise was more strongly associated with hypertension risk among those who moved to areas with more noise exposure (HR for quintile 5 vs. 1: 1.18, 95% CI 0.91, 1.53) compared to those who moved to areas with less noise exposure (HR for quintile 5 vs. 1: 1.00, 95% CI 0.79, 1.28) or those whose exposure remained the same (HR for quintile 5 vs. 1: 1.06, 95% CI 1.01, 1.12) (Table 3.3). There was no statistically significant interaction between noise level and night shift work (p-value 0.28) (Table 3.4). Point estimates were somewhat higher among those who worked up to 12 months of night shifts (HR for quintile 5 vs. 1: 1.16, 95% CI 0.95, 1.42) compared to those who worked no night shifts (HR for quintile 5 vs. 1: 1.07, 95% CI 1.01, 1.13) or those who worked over 12 months of night shifts (HR for quintile 5 vs. 1: 1.10, 95% CI 0.89, 1.35).

Table 3.3. Stratum-specific hazard ratios[a] (HR) and 95% confidence intervals (CI) for the association between nighttime L_{50} anthropogenic noise exposure and incident hypertension[b] by moving status[c] in the Nurses' Health Study II (N=82,398 with 23,738 hypertension cases over 846,711 person-years of follow-up, 2001-2013)

	Cases/Person-years	Moved to less noise	No change	Moved to more noise
Quintile 1[d]	4,767/169,256	Ref	Ref	
Quintile 2	4,679/169,208	0.96 (0.80, 1.15)	0.99 (0.95, 1.04)	1.07 (0.84, 1.36)
Quintile 3	4,689/169,521	1.03 (0.85, 1.26)	1.01 (0.96, 1.06)	0.92 (0.71, 1.19)
Quintile 4	4,670/169,348	1.01 (0.81, 1.25)	1.03 (0.98, 1.09)	1.05 (0.82, 1.36)
Quintile 5	4,933/169,378	1.00 (0.79, 1.28)	1.06 (1.01, 1.12)	1.18 (0.91, 1.53)
		p-value for interaction=0.99		

[a] Hazard ratios are adjusted for age, race, diet, smoking status and pack-years smoked, physical activity, marital status, oral contraceptive use, menopausal status, family history of hypertension, non-narcotic analgesic intake, statin use, education, husband's education, income, night shift work, sleep duration, Census tract median income and home value, urbanicity, neighborhood walkability, PM2.5 level, region of the country

[b] Incident hypertension defined according to self-reported clinician diagnosis or regular use of antihypertensive medication

[c] Based on changing addresses to another Census tract during follow-up

[d] Quintile with lowest noise exposure

Table 3.4. Stratum-specific hazard ratios[a] (HR) and 95% confidence intervals (CI) for the association between nighttime L_{50} anthropogenic noise exposure and incident hypertension[b] within classes of night shift work[c] in the Nurses' Health Study II (N=82,398 with 23,738 hypertension cases over 846,711 person-years of follow-up, 2001-2013)

	Cases/Person-years	No night shift work	1-12 months night shift work	>12 months night shift work
Quintile 1[d]	4,767/169,256	Ref	Ref	Ref
Quintile 2	4,679/169,208	1.01 (0.96, 1.06)	1.05 (0.88, 1.25)	1.01 (0.85, 1.20)
Quintile 3	4,689/169,521	1.00 (0.95, 1.06)	1.10 (0.91, 1.32)	1.02 (0.84, 1.23)
Quintile 4	4,670/169,348	1.00 (0.95, 1.06)	1.12 (0.92, 1.35)	1.21 (0.99, 1.47)
Quintile 5	4,933/169,378	1.07 (1.01, 1.13)	1.16 (0.95, 1.42)	1.10 (0.89, 1.35)
			p-value for interaction=0.28	

[a] Hazard ratios are adjusted for age, race, diet, smoking status and pack-years smoked, physical activity, marital status, oral contraceptive use, menopausal status, family history of hypertension, non-narcotic analgesic intake, statin use, education, husband's education, income, sleep duration, Census tract median income and home value, urbanicity, neighborhood walkability, PM2.5 level, region of the country

[b] Incident hypertension defined according to self-reported clinician diagnosis or regular use of antihypertensive medication

[c] Night shift work categories based on number of months working night shifts since 2001. Least night shift work: 0 months; moderate night shift work: 0-12 months; most night shift work: over 12 months.

[d] Quintile with lowest noise exposure

Discussion

In this nationwide prospective study of female nurses, we found a modest positive and independent association between higher residential nighttime noise exposure and greater risk for incident hypertension in models fully adjusted for a broad range of covariates. Difficulty sleeping may be a modest partial mediator of the association between nighttime noise and hypertension. Neither moving nor night shift work statistically significantly modified the effect of nighttime noise on hypertension risk.

Our results are consistent with current mechanistic findings related to noise's effects on cardiovascular health. Noise may affect cardiovascular health by acting as a stressor, with direct physiological and indirect behavioral effects, and may also precipitate hypertension by disrupting sleep.[61] Nighttime noise can engage the autonomic nervous system whether or not a person's sleep is disturbed. Experimentally, noise exposure has been shown to increase blood pressure, heart rate, cardiac output and stress hormones, and impair endothelial function.[62,63] A sustained decrease in blood pressure during the night, precluded by noise-related arousals, may be important for long-term cardiovascular health.[2] Repeated activation of the stress response, with attendant stress hormone elevation and subsequent circulatory changes, can manifest in hypertension and endothelial dysfunction, which are involved in the development of atherosclerosis and atherosclerotic cardiovascular disease.[88,89] The subjective experience of noise may also influence physiological and psychological responses—including coping behaviors that can affect health--at other times of day. Finally, noise may also increase risk for hypertension by disturbing sleep.[58] Both the objective and subjective experience of noise appear to affect sleep: one study found that noise annoyance (but not modeled noise) was statistically significantly associated with self-reported sleep quality, while modeled noise (but not annoyance) was statistically significantly associated with sleep efficiency.[90]

Our findings of an association between noise and hypertension risk are congruent with those from other studies. A meta-analysis of 24 studies in Europe and Japan found a statistically significant association between higher exposure to road traffic noise and higher odds of hypertension; OR 1.03 (95% CI 1.01, 1.06) for each 5 dBA increase in noise (LAeq16Hr).[61] A host of European studies, mostly cross-sectional, have also found statistically significant associations between greater exposure to airport and railway noise and higher odds of hypertension.[67,68,70-73] One prospective study in Denmark found a similar adverse relationship between railway noise and incident hypertension.[69] Conversely, one cross-sectional study in Swedish adults found no association between noise and self-reported hypertension.[74]

To date, less work has investigated potential mediators of the association between noise and hypertension. One study, to our knowledge, considered this question in an experimental study of nighttime aircraft noise and endothelial function (flow-mediated dilation), and did not find that sleep was a mediator.[62] It is possible that any mediating role of sleep may be more clearly analyzed in prospective studies, as shorter experimental studies may not adequately characterize sleep quality.

Other research has identified effect modifiers of the relationship between noise and hypertension. Although we did not observe statistically significant evidence of effect modification by participants' moving status, point estimates suggested that the association was stronger among those who moved to areas with more noise exposure during follow-up. These stratified results are in line with one study that found that the association was stronger among those who had lived at an address for more than ten years,[91] and another that found that an association only occurred among those who lived at an address for more than ten years, indicating that a longer duration of exposure may be important for disease development.[70] Small numbers of

movers may have reduced our power to detect a statistically significant effect in this sample. Although there was no statistically significant effect modification by extent of night shift work, somewhat surprisingly, point estimates were stronger among those who worked some or many months of night shifts, rather than weaker, as hypothesized. This may be because increased noise exposure or disruptions to sleep cycles and circadian rhythm entailed in working night shifts could raise hypertension risk independently, or jointly, in those working night shifts. Finally, three other studies identified statistically significant associations between noise and hypertension risk only in men, finding no association in women.[71,69,92] Having longer duration of follow-up and ability to adjust for many hypertension risk factors may have enhanced our ability to detect a positive association among women.

This study had several limitations. Modeling noise entails error, and the spatial resolution of the noise exposure information was somewhat coarse, at 270m. We were only able to account for outdoor noise, not participants' indoor noise exposure. We also did not have information from study participants on their dwelling type and insulation, or room location and orientation with respect to outdoor noise. However, we adjusted for individual and area-level income, which may serve as a proxy for housing quality. Another limitation was that we did not have time-varying noise exposure information. However, because the relationships between noise and non-acoustic geospatial factors used in the model remains somewhat stable over time, we would similarly expect the rank order of the participants' exposure to remain fairly stable. We only had information on participants' objective noise exposure, rather than perceived exposure, which could be instrumental for stress and behavioral response. Our case definition could have included those using antihypertensive medications for other prescribed uses, however, results from a sensitivity analysis in which the case definition was based only on hypertension diagnosis were similar (results not shown). Since people who are healthier may intentionally move to neighborhoods that promote health, we cannot rule out residential self-selection as a

contributing factor to the results. This study was largely composed of white, middle-aged professional women, and generalizations to other demographic groups may be limited.

This study also had a number of strengths. It was one of the first to consider noise exposure and health nationwide in the U.S. It took advantage of residence-level information on multiple noise exposure metrics from a validated noise model. It also capitalized on a large, ongoing prospective cohort study over a long period of follow-up with detailed and time-varying health and lifestyle information. Additionally, we were able to examine mediation by difficulty sleeping, determining that it accounted for only a small proportion of the association. Finally, we assessed effect modification by night shift work, which had not been examined before, to our knowledge.

In this study, over twelve years of follow-up in a large prospective cohort of women in the U.S., higher levels of nighttime noise were associated with a statistically significant, though modest, increased risk for incident hypertension. This association was independent of personal characteristics and socioeconomic status, and it appeared to be partially mediated by sleep difficulties. It appeared to be stronger among those who worked night shifts than those who did not. While individual behaviors and family history determine much of hypertension risk, environmental characteristics such as noise may be important additional avenues to pursue. Future observational research on this topic should also analyze associations prospectively, and should investigate the association in broader population groups with more racial/ethnic and socioeconomic diversity, where exposure ranges and disease prevalence could vary. Experimental studies on physiological and sleep changes in response to reductions in noise exposure would enhance our understanding of the mechanisms at play in this association. In concert with behavioral interventions, identifying additional environmental contributors to hypertension, such as noise, could suggest other avenues for disease mitigation.

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Conclusions

While individual predispositions and behaviors contribute to shaping health, the environment in which we live can interact with genetic and biologic tendencies and influence behavioral responses and mood, and ultimately health. In certain cases, aspects of the physical environment present opportunities to intervene on population health by promoting physical activity, healthy diet, and social engagement. Some potential modifiable environmental exposures include natural areas and noise levels.

The aim of my doctoral research was to help quantify the effect of nature exposure and noise level exposure on specific mental and physical health outcomes. Research on these questions has been growing, but much of it is cross-sectional or geographically limited, conducted in a single metropolitan area or in a European cohort where generalizability to the U.S. is uncertain.

My doctoral research contributes prospective analyses on this topic in a nationwide cohort, on topics in which the bulk of existing limited in duration of follow-up and geographic scope. Furthermore, I was able to adjust for a range of potential confounders not always available in other cohorts. Similarly, I was able to evaluate a number of potential mediators and effect modifiers not previously considered in other studies.

My first paper agrees with other studies finding a beneficial relationship between surrounding greenness and reduced mental distress.[1] It augments our understanding of the association by showing that neither social interaction nor physical activity mediates that association. The question of regional variation in depression—or depression diagnosis—deserves more exploration; including region in the models may over-adjust for the same conditions that produce greenness.

My second paper, which found little evidence for an association between residential greenness and weight status, agrees with another that observed no association between greenness and weight.[8] The studies do not concur with other cross-sectional studies that observed a beneficial relationship between greenness and weight.[5-7] Our ability to examine the association prospectively and adjust for a broad array of potential confounders may have resulted in this finding. In our study, we were also able to explore the relation with physical activity, and found that, adjusting for walkability and urbanicity, those in greener settings were no more likely to exercise than those in less green settings.

My third paper found a positive association between nighttime noise levels and incident hypertension, a common cardiovascular risk factor. That this association was somewhat stronger in those who moved to areas with more noise underscores that nighttime noise may be deleterious for cardiovascular disease risk.

This work adds to work evaluating whether features of the physical environment bear on our health in important ways. The environment provides cues and opportunities for behavior besides having direct effects on mental and physical health. Importantly, many features of the environment are amenable to change. Green spaces and ambient noise levels, for example, can be modified through improvement initiatives and local, state and federal policies and funding.

This work expands on previous research exploring these questions, most of it cross-sectional and much of it conducted in European cohorts. In order to better understand these associations, more prospective studies should be carried out, in U.S. cohorts and in other geographies. More accurate effect estimates will also result from more nuanced adjustment for potential

confounders, most notably socioeconomic status. Finally, it is difficult to characterize the effects of environmental features without information on how they are perceived by participants. Work on perceived environmental quality related to greenness, and annoyance related to noise level, will help describe the contribution of perception of environmental features to health.