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Associations of long-term exposure to environmental noise and outdoor light at night with age at natural menopause in a US women cohort

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Background: Previous studies have suggested noise, especially at night time, and light at night (LAN) could cause neuroendocrine disturbance and circadian disruption, which may lead to ovarian follicle atresia and earlier onset of menopause. However, no study to date has directly investigated the associations of exposure to these factors and menopausal age.

Methods: Premenopausal women from the Nurses' Health Study II (NHS II) were followed from age 40 through 2015. Median daytime and nighttime anthropogenic noise and outdoor LAN exposure were measured from a geospatial prediction model and satellite images, respectively, at residential addresses throughout the follow-up. Time-varying Cox proportional hazard models were used to calculate the hazard ratios and 95% confidence intervals, adjusting for individual lifestyle, reproductive history, and neighborhood socioeconomic factors. Possible effect modification by region, smoking status, body mass index, race/ethnicity, history of rotating shift work, and census tract population density and median income was examined.

Results: A total of 63,380 of 105,326 women self-reported natural menopause during 1,043,298 person-years of follow-up. No associations were found for noise (both daytime and nighttime) and outdoor LAN exposure with age at natural menopause (hazard ratios = 0.99–1.00) in the fully adjusted models. Sensitivity analyses showed similar null associations. No meaningful effect modification was found for region, smoking status, body mass index, race/ethnicity, history of rotating shift work, and census tract socioeconomic measures in stratified analyses.

Conclusion: No associations were found between environmental noise and outdoor LAN exposure in mid-adulthood and menopausal age in this cohort of US women.

Key words: Noise; Outdoor light at night; Age at menopause; Reproductive aging

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Process to obtain data and code: Code can be obtained from the corresponding author, the process to access NHS II data are available at https://www.nurseshealthstudy.org/researchers

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Introduction

Environmental physical factors such as noise and artificial light at night have been associated with various health outcomes. A growing body of epidemiologic studies has suggested nonauditory effects of environmental noise exposure including sleep disturbance, mental disorders, and cardiovascular disease.[1–5] Studies have observed associations between outdoor light at night (LAN) exposure with breast and prostate cancer.[6–15] Possible mechanisms that explain the impacts of these exposure include systemic neuroendocrine disturbance from circadian disruption, emotional distress, and chronic stress.[16–19]

Menopause is a natural event of reproductive aging in women driven by the natural atresia of oocytes. Timing of menopause can be an important risk factor for a wide variety of diseases as younger age at menopause has been associated with a shorter life expectancy and a higher risk of cardiovascular disease, although older age at menopause has been associated with a higher risk of breast cancer.[20–25] Previous evidence has suggested both genetic and environmental determinants of age at menopause including

What This Study Adds

Environmental physical factors such as noise and outdoor light at night (LAN) may induce earlier onset of menopause with circadian disruption and neuroendocrine disturbance as potential pathways. In this prospective nationwide female cohort, we found no associations between noise and outdoor LAN exposure with age at natural menopause. To our knowledge, this is the first study on these factors and menopausal age. Although the data suggested null associations, our work contributed to understanding the relationship between environmental exposures and female reproductive aging.

smoking, excessive physical activity, low socioeconomic status, and negative life events, which were all associated with younger age at onset of menopause.[20,26–31] Many of these factors may potentially alter the neuroendocrine homeostasis in humans and thus resulting in accelerated ovarian aging and earlier menopause in women.[32–34] However, to the best of our knowledge, no studies have considered the associations of physical factors in the environment such as noise and LAN exposure with age at menopause.

In the present study, we sought to examine the associations between environmental noise and outdoor LAN with age at natural menopause in the Nurses' Health Study II (NHS II)—a large, prospective, female cohort in the United States. We also explored whether the associations varied by region, neighborhood socioeconomic status, and lifestyle factors.

Methods

Study population

The NHS II cohort is an ongoing, prospective cohort of 116,429 female registered nurses recruited in 1989. At baseline, all participants were between 25 and 42 years of age (mean age = 34 years) and resided in one of 14 states in the United States (California, Connecticut, Indiana, Iowa, Kentucky, Massachusetts, Michigan, Missouri, New York, North Carolina, Ohio, Pennsylvania, South Carolina, and Texas) but have moved to all 50 states and the District of Columbia. Questionnaires have been mailed to participants every 2 years collecting information on health conditions, major health risk factors, and residential address. For this analysis, we included NHS II participants who were still premenopausal when they reached age 40 during the follow-up period (1989–2015). Women who received a hysterectomy, oophorectomy, or cancer diagnosis (except for nonmelanoma skin cancer), who died, or who stopped responding to the questionnaires before age 40 were excluded. We further excluded women who had no geocoded residential addresses in the continental United States after age 40 for exposure assessment. This study was approved by the Institutional Review Board of Brigham and Women's Hospital, and the Human Subjects Committee of the Harvard T.H. Chan School of Public Health and informed consent was implied by return of the questionnaires.

Outcome assessment

Information on menopausal status, causes of menopause, and age at menopause were collected at baseline and in each follow-up questionnaire. The outcome of interest was natural menopause, which was identified when the participants reported menopause due to natural causes. All self-reported menopausal status and causes of menopause were verified by consistent reports in two adjacent questionnaires. Throughout follow-up, women who reported menopause due to surgery, chemotherapy, and radiation or did not indicate cause of menopause, who received a hysterectomy or oophorectomy, who were diagnosed with cancer (except nonmelanoma skin cancer), or who died were censored at the time of event confirmation or at return of the questionnaire. Death was confirmed by next-of-kin, postal authorities, or by searching the National Death Index. Cancer diagnosis was confirmed by searching the medical record review or linkage to cancer registries. Women who failed to report their menopausal status in two consecutive questionnaires were considered as lost to follow-up.

Exposure assessment

Noise exposure was obtained from a geospatial prediction model for environmental sound levels.[35] A random forest model was fit to approximately 1.5 million hours of long-term acoustical monitoring data collected during 2000–2014 from 492 unique urban and natural sites (representing anthropogenic and natural sources of environmental sound, respectively) across the contiguous United States and geospatial explanatory variables including climate, topography, land cover, hydrology, human activity, and seasonality. This model was used to predict time-integrated sound levels during 2000–2014 from anthropogenic sources by the time of the day (daytime and nighttime) at 270-m spatial resolution across contiguous United States. Cross-validation showed good model prediction performance.[35] For this analysis, we used the median A-weighting sound pressure (L50) from anthropogenic sources during the daytime (7 am to 7 pm, daytime L50) and the nighttime (7 pm to 7 am in the next day, nighttime L50) as our metrics of noise exposure. The L50 sound level was the sound level exceeded for 50% of the time during the measurement and thus represented typical sound levels. We assigned noise measurements to each geocoded residential address from age 40 until menopause, assuming noise levels were comparable throughout the follow-up in each location. For women who moved during the follow-up, we assumed they did so at the beginning of the questionnaire cycle.

Outdoor light at night (LAN) exposure was measured by the annual average nighttime visible and near-infrared radiance from the earth surface. This measurement was obtained from satellite images from the US Defense Meteorological Satellite Program's Operational Linescan System (DMSP-OLS) under the National Oceanic and Atmospheric Administration[36] and was available in 1996, 1999, 2000, 2002, 2004, 2005, and 2010 by 30-arc second grid cells (approximately 1 km^2). The raw satellite image data were processed to remove the outer quarter of satellite swath, sun and moon luminance, glare, clouds, atmospheric lightning, ephemeral events such as fires, and sensor saturation, calibrated across years and different satellites, and converted to unit of radiance ($nW/cm^2/sr$).[37] Exposure to outdoor LAN was then assigned to each geocoded residential address for each year from age 40 until menopause. For each location, exposure before 1996 was assigned with the 1996 LAN measurement and exposure after 1996 was assigned with the most recent LAN measure in previous years, assuming outdoor LAN levels were temporally comparable.

For each exposure, we considered two time windows: the cumulative average from age 40 to represent long-term exposures in the mid-adulthood and the cumulative average in age 40–45 to represent exposures in early mid-adulthood.

Covariates

We considered covariates that have been suggested to be predictors of age at natural menopause, risk factors of censoring events or associated with the exposure. Time-varying covariates were collected in questionnaires every 2 or 4 years, including body mass index (BMI, kg/m^2), smoking status (never, past, current) and intensity (<25 or ≥25 cigarettes/day), physical activity (metabolic equivalent task hours/week), alcohol consumption (0 g/day, 0.1–4.9 g/day, 5.0–14.9 g/day, and ≥15.0 g/day), diet quality (measured by the 2010 Alternate Healthy Eating Index),[38] US Census Bureau regions of residence (Northeast, Midwest, West, and South), marital status, oral contraceptive use (never, past, current), use of menopausal hormone therapy (never, past, current), parity (nulliparous, 1–2, 3 or more full-term pregnancies), history of breastfeeding (less than 1 month, 1–12 months, 13–24 months, and more than 24 months), diagnosis of uterine fibroids or endometriosis, age at first birth (under 20, 20–25, 26–30, and ≥31 years old), and neighborhood SES (Census tract level population density, median family income, and median home values). History of rotating shift work (including shift work status and duration) was collected retrospectively at baseline (total number of years worked in rotating shifts before 1989)

Table 1.

Characteristics (mean ± SD or %) of 105,326 eligible participants in the Nurses' Health Study II and by quartiles of noise and outdoor light at night exposures (1st vs. 4th quartiles).

		Daytime L50		Nighttime L50		Outdoor LAN	
	Overall	Q1[a]	Q4[a]	Q1[a]	Q4[a]	Q1[a]	Q4[a]
Race/ethnicity							
Nonwhite	5	3	10	3	9	3	10
White	93	96	88	96	89	96	88
Missing	2	1	3	1	2	1	3
Age at menarche (years)							
Under 10	7	7	8	7	8	7	8
11–13	74	74	73	74	73	74	73
14–16	18	18	18	18	17	17	18
17 and above	1	1	1	1	1	1	1
US Census region of residence							
Northeast	35	43	27	50	23	37	33
Midwest	32	35	25	29	32	37	28
West	16	9	24	11	25	8	22
South	18	13	24	10	20	19	17
Never changed addresses after 40	70	72	68	72	69	75	69
Hormone therapy use							
Never user	74	74	75	75	74	74	75
Past user	14	13	13	13	13	14	13
Current user	12	12	11	11	12	12	11
Missing	1	1	1	1	1	1	1
Cigarette smoking							
Never smoker	66	67	64	65	66	68	64
Past smoker, <25 cigarettes/day	22	21	22	22	21	20	23
Past smoker, ≥25 cigarettes/day	3	3	3	4	3	3	4
Past smoker, unknown intensity	1	1	1	1	1	1	1
Current smoker, <25 cigarettes/day	7	7	8	7	7	7	8
Current smoker, ≥25 cigarettes/day	1	1	1	1	1	1	1
Current smoker, unknown intensity	0	0	0	0	0	0	0
Body mass index (kg/m^2)							
<21	12	11	12	11	12	11	13
21–25	31	30	30	31	30	29	30
25–29	24	25	23	25	24	26	23
≥30	21	22	22	22	22	24	21
Missing	11	11	12	11	12	11	12
Physical activity (MET-hours/week)							
<3	18	18	18	18	18	19	18
3–9	22	23	22	22	23	23	22
9–18	21	21	21	21	20	21	20
18–27	13	13	13	13	13	13	13
27–42	12	12	12	12	12	11	13
≥42	14	13	14	14	14	13	14
Age at first birth (years)							
Under 20	6	8	6	7	6	8	6
20–25	28	34	21	33	24	36	21
26–30	31	31	27	32	29	31	29
>30	16	13	18	14	17	12	19
Missing	18	13	28	14	24	12	26
Parity (full-term pregnancies)							
Nulliparous	17	12	26	13	23	12	24
1–2	53	54	50	53	52	54	51
3 or more	30	34	24	34	25	34	25
History of breastfeeding (months)							
<1	13	14	11	13	11	14	11
1–12	24	25	22	25	23	25	23
12–24	18	19	16	19	17	19	16
>24	17	20	14	19	15	19	15
Missing/nulliparous	27	22	37	23	33	22	35
Oral contraceptive use							
Never user	14	13	16	14	15	13	17
Past user	78	80	76	80	77	81	75
Current user	7	6	8	6	8	6	8
Married	80	87	70	86	74	87	72
History of rotating shift work							
Never	30	30	30	30	31	30	31
Ever, less than 5 years	58	58	57	58	56	58	57
Ever, more than 5 years	12	12	12	12	12	12	11

(*Continued*)

Table 1.

(*Continued*)

		Daytime L50		Nighttime L50		Outdoor LAN	
	Overall	**Q1[a]**	**Q4[a]**	**Q1[a]**	**Q4[a]**	**Q1[a]**	**Q4[a]**
Chronotype							
Morning	24	24	24	24	24	24	23
Evening	43	44	41	44	42	43	42
Neither	4	4	4	4	4	4	4
Missing	30	29	31	29	31	30	31
Uterine fibroids	16	15	17	16	17	15	17
Endometriosis	6	6	6	6	6	6	6
Alcohol consumption (g/day)							
0	35	40	34	37	36	42	33
0.1–4.9	32	30	31	31	32	30	32
5.0–14.9	17	16	18	17	17	15	18
≥15.0	7	6	8	7	7	6	7
Missing	8	8	9	8	9	8	9
Alternate heathy eating index (AHEI)	53.5 (12.1)	52.3 (12.1)	54.8 (12.1)	52.8 (12.1)	54.1 (12.1)	51.6 (11.9)	54.9 (12.1)
Missing AHEI	8	8	9	8	9	8	9
Census tract population density							
Q1	24	70	2	58	5	71	2
Q2	26	23	10	27	19	23	8
Q3	26	5	28	10	30	4	27
Q4	25	1	59	4	46	1	62
Census tract median family income							
Q1	23	36	23	34	22	39	18
Q2	24	31	23	28	24	32	20
Q3	26	19	26	20	26	18	27
Q4	28	15	28	18	27	11	35
Census tract median home values							
Q1	23	36	22	33	22	39	17
Q2	24	28	21	26	22	30	18
Q3	26	21	22	23	24	20	25
Q4	27	15	35	18	31	11	41

Values are standardized to the age distribution of the study population.

[a]Median exposure levels: daytime L50 Q1 = 41.2 dB, Q4 = 49.9 dB; nighttime L50 Q1 = 40 dB, Q4 = 46.5 dB; outdoor LAN Q1 = 3.6 nW/cm^2/sr, Q4 = 52.6 nW/cm^2/sr.

L50 indicates median A-weighting sound pressure; LAN, light at night; MET, metabolic equivalent task; Q1, 1st quartile; Q4, 4th quartile.

and prospectively during the follow-up. We used this information to create a time-varying variable combining shift work status (never or ever) and the cumulative duration (less or more than 5 years) for our models. Age at menarche and race/ethnicity were included as time-invariant covariates. Chronotype was collected in the 2009 questionnaire. We also measured air pollution levels and road proximity to ensure that the observed associations were not confounded by these factors. Exposure to air pollution, including particulate matter with aerodynamic diameters ≤10 (PM_{10}), 2.5–10 ($PM_{2.5-10}$), and ≤2.5 μm ($PM_{2.5}$) were predicted from validated spatial-temporal models at each residential address.[39] Residential road proximity was measured as the distance to A1–A3 roads by the US Census Feature Class Codes (including highways to secondary roads with more than 2 lanes). The missing indicator method was used for missing values in covariates.

Statistical analysis

Person-years of follow-up were calculated from age 40 until self-reported natural menopause, the report of any censoring events, or the return of 2015 questionnaire, whichever came first. We then used a time-varying Cox proportional hazard model with age as the time scale to compute the hazard ratio (HR) and 95% confidence interval (95% CI) of natural menopause for an interquartile range increase of exposure to noise or outdoor LAN in separate models. An HR greater than 1 indicates an earlier onset of menopause with the exposure, and an HR less than 1 indicates a later menopause. All models were stratified by calendar year to control for time trends. To avoid overadjusting, we fitted a basic model adjusting for age and calendar year only, a parsimonious model additionally adjusting for region, race/ethnicity, BMI, smoking, and neighborhood SES, and a full model adjusting for all individual characteristics and neighborhood SES. Nonlinear exposure-outcome responses were examined using cubic splines. We also fitted two-exposure models for noise and LAN to adjust for coexposure.

Effect modification by race/ethnicity (white, nonwhite), region, smoking status, BMI (<25, 25–29.9, and ≥30 kg/m^2), history of rotating shift work (never and ever), chronotype (morning, evening, and neither), Census tract-level population density (<1,000 and ≥1,000 people per km^2), and Census tract median family income (by quartiles) was tested by first adding multiplicative interaction terms in the models and then computing HRs and 95% CIs by strata of the modifier in separate models.

To examine the robustness of our results, we considered several sensitivity analyses by (1) restricting to women who entered the follow-up after 1996 for outdoor LAN and 2000 for noise, respectively, to reduce the potential for exposure measurement error due to the temporal mismatch in availability in exposures; (2) restricting to women who never changed their residential addresses since age 40; and (3) restricting to women who never used menopausal hormone therapy and who did not use oral contraceptives after age 40. To further examine whether the exposure was associated with early menopause (clinically defined as having natural menopause before age 45), we ended the follow-up at age 45 for all participants. We further examined potential confounding of air pollution and traffic exposure by adjusting for ambient PM_{10}, $PM_{2.5-10}$, $PM_{2.5}$, and road proximity in the models. Considering a number of our participants were night workers, we examined the association of noise exposure in sleep time calculated by assigning daytime noise to women

who reported worked in rotating night shifts in the corresponding questionnaire and nighttime noise to the others. Long-term exposure from 1989 was also included to examine exposures in earlier life stages. All statistical tests were 2-sided with an α level of 0.05. All analyses were conducted in SAS 9.4 (SAS Institute, Cary, NC) or R (version 3.6.3) (R Foundation for Statistical Computing, Vienna, Austria).

Results

During the 1,043,298 person-years of follow-up among 105,326 women, 63,380 women reported natural menopause after age 40. Overall, these participants were predominantly White, married, and never smokers (Table 1). Throughout the study period, participants whose noise or LAN exposure was in the lowest quartile were more likely to be white and married and to live in the Northeast or Midwest and in areas with lower population density and home values. The mean cumulative average daytime L50 noise, nighttime L50 noise, and outdoor LAN exposure were 46.1 [standard deviation (SD) = 4.1] dB, 43.2 (SD = 3.3) dB, and 26.5 (SD = 19.8) nW/cm^2/sr, respectively (eTable 1; http://links.lww.com/EE/A136). Within each exposure time window, there were moderate to high correlations among daytime L50, nighttime L50, and outdoor LAN (Spearman r = 0.62–0.80), and very high correlations were found between exposure time windows for all exposures (Spearman r = 0.99). Noise and outdoor LAN had moderate correlations with PM (Spearman r = 0.25–0.49) and were weakly and negatively correlated with distance to A1-A3 roads (Spearman r = −0.33 to −0.17) (Figure 1). The median age at natural menopause was 51 years old, which was comparable to the median menopausal age in western countries reported in the literature.[20]

We found no evidence of nonlinear associations between noise and outdoor LAN and the log HR of natural menopause (p for derivation of linearity = 0.38–1.00). As shown in Table 2, we did not observe associations of daytime L50, nighttime L50, and outdoor LAN with natural menopause in any window of exposure. Similar null associations were found when restricting the analysis to women who reached age 40 after 1996 or 2000, to women who never changed residential address after age 40, who

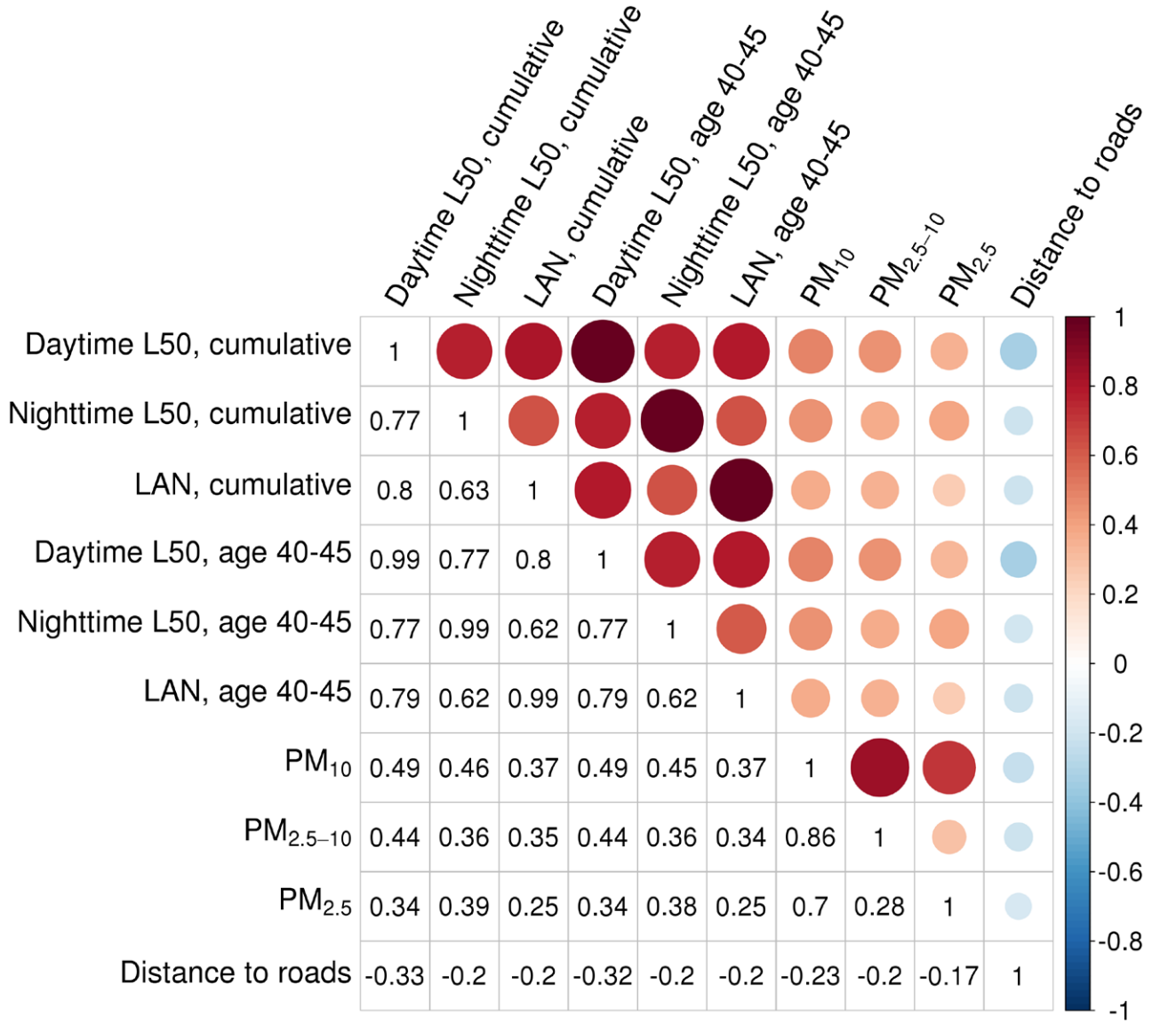

Figure 1. Spearman correlation coefficients of environmental exposures in 105,326 NHS II participants (1989–2015). Distance to roads was measured as distance to A1–A3 class of roads according to the US Census Feature Class Codes. L50 indicates median anthropogenic noise; LAN, light at night; $PM_{2.5–10}$, particulate matter with an aerodynamic diameters between 2.5 to 10 μm; $PM_{2.5}$, particulate matter with an aerodynamic diameters less than or equal to 2.5 μm; PM_{10}, particulate matter with an aerodynamic diameters less than or equal to 10 μm.

Table 2.

Hazard ratios and 95% confidence intervals of noise and outdoor light at night exposure with age at natural menopause in the Nurses' Health Study II cohort (1989–2015).

			HR (95% CI)		
	Events	Person-years	Basic[a]	Parsimonious[b]	Full[c]
Single exposure models					
Cumulative average					
Daytime L50 (IQR = 4.6 dB)	63,380	1,043,298	1.01 (1.00, 1.02)	1.00 (0.99, 1.02)	0.99 (0.98, 1.01)
Nighttime L50 (IQR = 3.4 dB)	63,380	1,043,298	1.00 (1.00, 1.01)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)
Outdoor LAN (IQR = 29.1 nW/cm^2/sr)	63,380	1,043,298	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)	1.00 (0.98, 1.01)
Age 40–45					
Daytime L50 (IQR = 4.6 dB)	63,380	1,043,298	1.01 (1.00, 1.02)	1.01 (0.99, 1.02)	1.00 (0.98, 1.01)
Nighttime L50 (IQR = 3.4 dB)	63,380	1,043,298	1.01 (1.00, 1.01)	1.01 (1.00, 1.02)	1.00 (0.99, 1.01)
Outdoor LAN (IQR = 29.6 nW/cm^2/sr)	63,380	1,043,298	1.01 (1.00, 1.02)	1.01 (0.99, 1.02)	1.00 (0.98, 1.01)
Two exposure models					
Daytime L50 + LAN, cumulative average					
Daytime L50 (IQR = 4.6 dB)	63,380	1,043,298	1.00 (0.99, 1.01)	1.00 (0.98, 1.01)	0.99 (0.98, 1.01)
Outdoor LAN (IQR = 29.1 nW/cm^2/sr)	63,380	1,043,298	1.01 (1.00, 1.03)	1.01 (0.99, 1.02)	1.00 (0.99, 1.02)
Nighttime L50 + LAN, cumulative average					
Nighttime L50 (IQR = 3.4 dB)	63,380	1,043,298	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)
Outdoor LAN (IQR = 29.1 nW/cm^2/sr)	63,380	1,043,298	1.01 (1.00, 1.03)	1.01 (0.99, 1.02)	1.00 (0.98, 1.01)
Daytime L50 + LAN, age 40–45					
Daytime L50 (IQR = 4.6 dB)	63,380	1,043,298	1.00 (0.99, 1.02)	1.00 (0.99, 1.02)	1.00 (0.98, 1.01)
Outdoor LAN (IQR = 29.6 nW/cm^2/sr)	63,380	1,043,298	1.01 (1.00, 1.02)	1.00 (0.99, 1.02)	1.00 (0.98, 1.01)
Nighttime L50 + LAN, age 40–45					
Nighttime L50 (IQR = 3.4 dB)	63,380	1,043,298	1.00 (0.99, 1.01)	1.01 (0.99, 1.02)	1.00 (0.99, 1.01)
Outdoor LAN (IQR = 29.6 nW/cm^2/sr)	63,380	1,043,298	1.01 (1.00, 1.02)	1.00 (0.99, 1.02)	0.99 (0.98, 1.01)

[a]Adjusted for age and calendar years.

[b]Additionally adjusted for body mass index, smoking status, race/ethnicity, region, and Census tract median income, median home values, and population density.

[c]Additionally adjusted for physical activity, parity, age at first birth, histories of breastfeeding, female hormone use, oral contraceptives use, histories of rotating shift work, alternate healthy eating index, marital status, diagnosis of endometriosis and uterine fibroids, and age at menarche.

CI indicates confidence intervals; HR, hazard ratios; IQR, interquartile range; L50, median anthropogenic noise; LAN, light at night.

never used menopausal hormones, who never used or stopped using oral contraceptives after age 40, and who reported menopause between age 40–45 (eTable 2; http://links.lww.com/EE/A136). No associations were found for long-term exposure to noise and LAN from 1989 or for noise exposure during sleep periods (eTable 2; http://links.lww.com/EE/A136). Results from models with additional adjustments for PM and road proximity were similar to our main analysis (eTable 3; http://links.lww.com/EE/A136).

We did not observe effect modification for any exposure by race/ethnicity, BMI, history of rotating shift work, chronotype, census tract population density, or census tract median family income (p-for-interaction = 0.07–0.97) (data not shown). However, there were suggestive effect modifications by region and by smoking status for noise but not for outdoor LAN (Figure 2). For example, we found an interquartile range increase of nighttime L50 was associated with slightly earlier menopause (cumulative average, HR = 1.01, 95% CI = 0.99, 1.04; age 40–45, HR = 1.02, 95% CI = 1.00, 1.04) among women lived in the West but with later menopause among women who lived in the South (cumulative average, HR = 0.97, 95% CI = 0.94, 1.00; age 40–45, HR = 0.97, 95% CI = 0.94, 1.00) (p-for-interaction = 0.06 for cumulative average and 0.03 for exposure in age 40–45). In addition, higher daytime and nighttime L50 exposure were suggestively associated with later menopause for current smokers (p-for-interaction: 0.05 for both cumulative average daytime and nighttime L50, 0.03 and 0.04 for daytime and nighttime L50 at age 40–45, respectively).

Discussion

In this large, prospective female cohort, we did not observe associations between exposure to daytime and nighttime anthropogenic noise and outdoor LAN with the timing of natural menopause. Little evidence of effect modification was found for race/ethnicity, BMI, history of rotating shift work, census tract population density, and census tract median family income. There were suggestions of effect modification by region and by smoking status; however, the magnitude of the stratum-specific associations was quite small. To the best of our knowledge, this is the first study examining the associations of environmental noise and outdoor LAN with menopausal age.

The number of oocytes in the ovary decreases continuously after birth and menopause occurs when this number reduces to approximately 1,000. Throughout a woman's lifetime, only a small proportion of oocytes are ovulated, although the rest undergo atresia, and the timing of menopause is affected by the rate of atresia.[40,41] Among factors affecting atresia, inflammation, and oxidative stress can induce atresia, although estrogen is suggested to inhibit atresia.[42–46] Noise exposure has been found to induce inflammation and oxidative stress and has been associated with elevated levels of stress hormones such as adrenaline.[17,47–49] One study in South Korea showed exposure to high levels of environmental noise (>55 dB) was associated with male infertility.[50] It has been suggested that stress response may inhibit ovarian endocrine function and suppress estrogen release through hypothalamic regulation, leading to follicle atresia.[51,52] Animal and human studies have shown that exposure to light at night has systemic neuroendocrine effects as consequences of circadian disruption, and previous studies have also suggested associations of rotating shift work with menstrual disorder and earlier menopause.[18,19,53,54] In addition to disrupting the hormonal rhythm in the reproduction system, circadian disruption could suppress melatonin, a strong endogenous antioxidant that may prevent oocyte atresia.[55–59] However, the underlying mechanisms are still not fully established and warrant further investigation.

Despite the biologic plausibility of our hypotheses, we did not observe associations of daytime and nighttime anthropogenic noise with age at natural menopause. Although the exposure measures were not directly comparable, residential noise exposure levels in our participants were unlikely to exceed the US

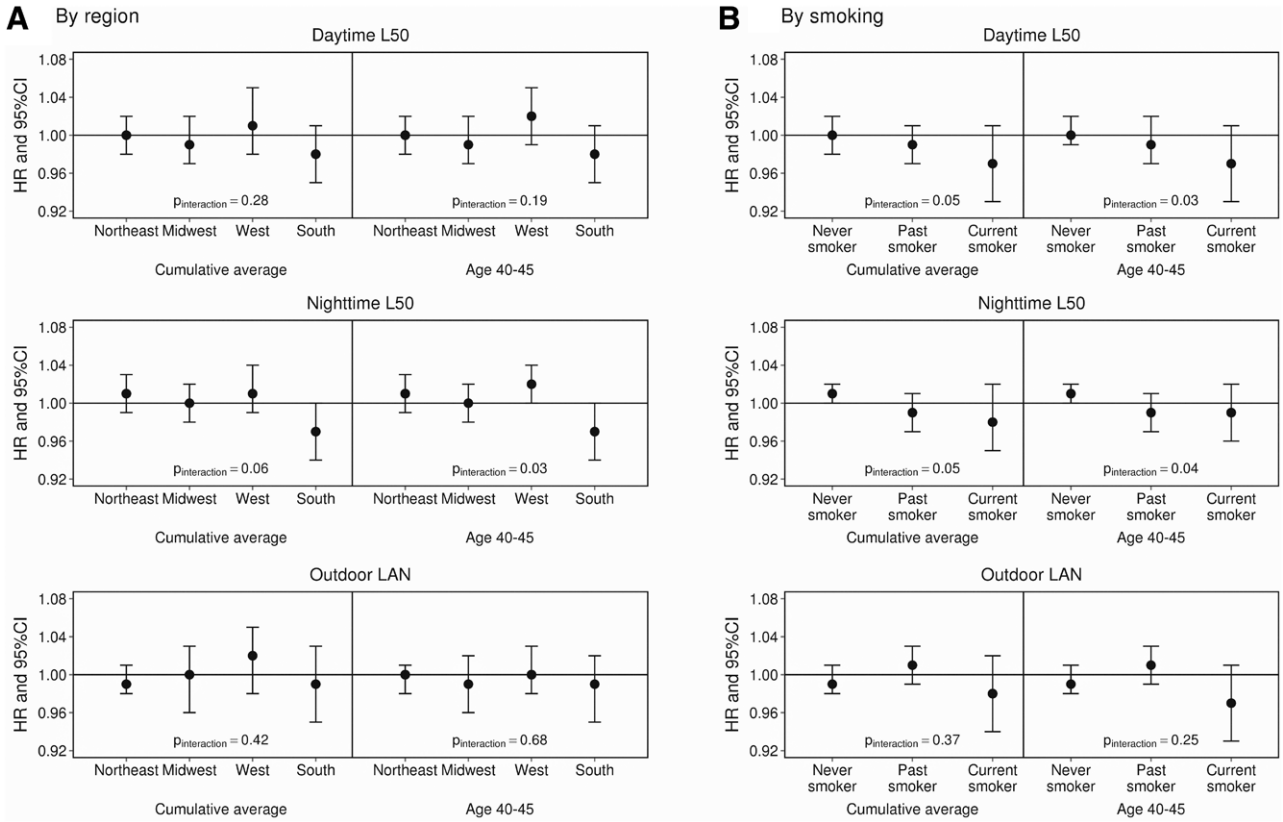

Figure 2. HRs and 95% confidence intervals of noise and outdoor light at night exposure with age at natural menopause by regions (A) and by smoking status (B). All HRs were calculated as an interquartile range increase of the exposure and adjusted for age, calendar years, body mass index, smoking status, race/ethnicity, region, physical activity, parity, age at first birth, histories of breastfeeding, female hormone use, oral contraceptives use, histories of rotating shift work, alternate healthy eating index, marital status, diagnosis of endometriosis and uterine fibroids, age at menarche, and Census tract median income, median home values, and population density. IQRs were 4.6 dB for daytime L50 (both cumulative average and age 40–45); 3.4 dB for nighttime L50 (both cumulative average and age 40–45), 29.1 nW/cm^2/sr for cumulative average outdoor LAN, and 29.6 nW/cm^2/sr for outdoor LAN in age 40–45, respectively. HR indicates hazard ratios; IQR, interquartile range; L50, median anthropogenic noise; LAN, light at night.

EPA's 55 dB limit for outdoor day-night average sound levels for public health and welfare.[60] There was little evidence of susceptible subpopulations, with the exception of women living in the West. Interestingly, we found suggestive associations between nighttime noise with earlier menopause among women from the West but with later menopause among those in the South, although the magnitudes were small. This effect heterogeneity could be due to exposure measurement error, unmeasured regional characteristics, or findings by chance.

Exposure measurement error was notable in this study. Although the geospatial sound models showed high correlations between the predicted values and actual measurements in cross-validation, it is possible that the predicted values may not accurately reflect the actual noise levels our participants experienced.[35] The geospatial sound models had more monitoring sites in the West than the other regions, which indicates a possibility that the suggestive associations found in the West may be due to reduced exposure measurement error.[35] Besides, the residential noise exposure metric had limited temporal variation as the noise predictions were time-integrated for each location, and thus our participants only had time-varying noise exposure if they changed their residential address during the follow-up. For person-years before 2000 and 1996, we had to use the most recent measures of noise and LAN as surrogates, respectively, assuming the exposure levels were temporally comparable. However, sensitivity analysis showed similar null associations with reduced temporal mismatch. The satellite-based ambient light measurement did not measure light intensity by wavelength and was less sensitive to blue light, which may explain our null results as blue light has been suggested to have stronger association with human health.[61–63] However, another study in NHS II found similar impacts on melatonin rhythms by photopic illuminance and exposure to blue light.[64] In addition, these estimates of ambient LAN have been shown to be poor proxies of actual personal exposure to nighttime artificial light as satellites cannot capture light exposure indoors (e.g., use of screens, lights, and light-blocking materials).[65] Therefore, improved exposure assessment are needed for future studies.

Another notable characteristic of our study population is that approximately 70% of the study participants have ever been night workers. It has been suggested that light exposure in nighttime may predominantly affect individuals who were awake and had their eyes open.[66,67] Indeed, a previous study in NHS II has linked women who had ever worked in rotating shift with earlier onset of menopause especially before age 45, and we observed suggestive associations of shift work but not exposures to noise and LAN with earlier menopause in this analysis (data not shown).[54] However, our sensitivity analysis using noise exposure during the sleep period also showed null associations. The ambient residential noise and LAN measures can hardly capture the actual personal exposure (e.g., at workplace) for these night workers. Therefore, we may have limited ability to further confirm that the younger age at menopause among night workers as found previously can be explained by these nighttime exposures.

There were several other limitations to our study. Although we adjusted for PM and road proximity in the sensitivity analysis, coexposure to other environmental factors was not addressed.

The self-reported menopausal status and age at menopause in the follow-up of NHS II were queried as whether the participant's period has ceased permanently and the age of last period. This definition was less precise than the criteria commonly used in epidemiologic studies and may be subject to the impact of irregular uterine bleeding at perimenopausal stage, both resulting in the potential for outcome measurement error.[68] However, the influence of irregular cycles can be minimal. A previous validation study showed high consistency in the self-reported age at menopause over a two-year period (mean difference = 0.06 years), and we only used reports of menopausal status that were consistent in two adjacent questionnaire in our analysis.[69] We only considered exposure in adulthood in the analysis, although exposures in other susceptible time windows such as in childhood and adolescence were not available. Additionally, the noise prediction model used in this analysis was not specifically developed for the NHS II participants, and noise exposure was not validated at the NHS II addresses. Finally, the NHS II participants were mostly white and professionals. Therefore, our results may have very limited generalizability to the general US female population if their exposure levels are not representative, or if there are mechanisms that may be particular to this population.

Conclusion

We did not observe associations between noise and outdoor LAN exposure with the timing of natural menopause in this large, nationwide, prospective female cohort. To our knowledge, this is the first study examining the association between environmental physical factors and reproductive aging. Although no associations were found in our analysis, future studies with improved exposure assessment are needed for confirmation.

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