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Associations between air pollution, residential greenness, and glycated hemoglobin (HbA1c) in three prospective cohorts of U.S. adults

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abstract

Background: While studies suggest impacts of individual environmental exposures on type 2 diabetes (T2D) risk, mechanisms remain poorly characterized. Glycated hemoglobin (HbA1c) is a biomarker of glycemia and diagnostic criterion for prediabetes and T2D. We explored associations between multiple environmental exposures and HbA1c in non-diabetic adults.

Methods: HbA1c was assessed once in 12,315 women and men in three U.S.-based prospective cohorts: the Nurses' Health Study (NHS), Nurses' Health Study II (NHSII), and Health Professionals Follow-up Study (HPFS). Residential greenness within 270m and 1,230m (normalized difference vegetation index, NDVI) was obtained from Landsat. Fine particulate matter ($PM_{2.5}$) and nitrogen dioxide (NO_2) were estimated from nationwide spatiotemporal models. Three-month and one-year averages prior to blood draw were assigned to participants' addresses. We assessed associations between single exposure, multi-exposure, and component scores from Principal Components Analysis (PCA) and HbA1c. Fully-adjusted models built on basic models of age and year at blood draw, BMI, alcohol use, and neighborhood socioeconomic status (nSES) to include diet quality, race, family history, smoking status, postmenopausal hormone use, population density, and season. We assessed interactions between environmental exposures, and effect modification by population density, nSES, and sex.

Results: Based on HbA1c, 19% of participants had prediabetes. In single exposure fully-adjusted models, an IQR (0.14) higher 1-year 1,230m NDVI was associated with a 0.27% (95% CI: 0.05%, 0.49%) lower HbA1c. In basic component score models, a SD increase in Component 1 (high loadings for 1-year NDVI) was associated with a 0.19% (95% CI: 0.04%, 0.34%) lower HbA1c. CI's crossed the null in multi-exposure and fully-adjusted component score models. There was little evidence of associations between air pollution and HbA1c, and no evidence of effect modification.

Conclusions: Among non-diabetic adults, environmental exposures were not consistently associated with HbA1c. More work is needed to elucidate biological pathways between the environment and prediabetes.

Keywords

environmental exposures; air pollution; greenness; glycated hemoglobin; prediabetes; diabetes

I. Introduction

The CDC estimates that 38% of U.S. adults have prediabetes, an intermediate glucose category which places them at higher risk for developing type 2 diabetes (T2D) and cardiovascular disease. (CDC, 2022) From 1990 to 2010 alone, there was a 21% increase in

U.S. prediabetes prevalence. (Bullard et al., 2013) Research suggests that among individuals with prediabetes, interventions aimed at decreasing body weight and increasing physical activity can reduce or delay progression to T2D diagnosis. (American Diabetes Association, 2010) Given the magnitude of the public health burden of T2D, and the growing evidence of associations between environmental exposures and T2D, it is important to investigate the role of non-lifestyle factors in glucose homeostasis. (Ccami-Bernal et al., 2023; F. Liu et al., 2019; Yang et al., 2020)

The American Diabetes Association adopted glycated hemoglobin (HbA1c) as a diagnostic criterion for prediabetes and diabetes in 2010 (prediabetes: 5.7–6.4%, diabetes: ≥ 6.5%) as an alternative to impaired fasting glucose. (Leong et al., 2018) Since red blood cells have a lifespan of about 120 days, HbA1c reflects a glycemic history of average blood glucose levels over the preceding two to three months. Elevated HbA1c indicates greater risk of progression from prediabetes to diabetes, as well as greater risk of cardiovascular complications. (Davis et al., 2018; Heianza et al., 2011; Morris et al., 2013) Although environmental exposures represent potentially modifiable risk factors, studies of their effects on HbA1c have been limited. Epidemiologic research has identified associations between environmental exposures and T2D risk, supported by toxicological studies suggesting pathways between pollutants and impaired glucose tolerance and insulin resistance. (Puett et al., 2019) Increased exposure to fine particulate matter ($PM_{2.5}$) and nitrogen dioxide (NO_2) has been consistently associated with higher T2D incidence. (F. Liu et al., 2019; Yang et al., 2020) Findings from studies on air pollution exposure and HbA1c have been mixed, with some suggesting positive associations (Chuang et al., 2010; Honda et al., 2017; C. Liu et al., 2016; Riant et al., 2018; Yitshak Sade et al., 2016) and others not identifying any association. (Bloemsma et al., 2019; Wolf et al., 2016) Meanwhile, evidence that neighborhood greenness may be associated with lower T2D risk is growing. (Astell-Burt & Feng, 2020; Ccami-Bernal et al., 2023; Jimenez et al., 2021) To date, there have been very few studies of the association between greenness and HbA1c. (Bloemsma et al., 2019; Gallo et al., 2022)

Environmental exposures are often correlated as they co-occur in space. Studies have begun to examine the effects of these multiple environmental exposures on T2D risk through mutually adjusted models, which may address some residual confounding and allow effects of the individual exposures to be disentangled in the absence of strong collinearity. However, none have applied mixture methods to account for collinearity or possible synergism between exposures. While several analyses of air pollution and HbA1c have used two-pollutant models (Chuang et al., 2010; Honda et al., 2017; F. Liu et al., 2022; Mei et al., 2023; Riant et al., 2018), only one has incorporated greenness as a co-exposure. (Bloemsma et al., 2019)

In the present study among women and men who provided blood samples in NHS, NHSII, and the Health Professionals Follow-up Study (HPFS), we hypothesized that higher air pollution and lower neighborhood greenness are individually associated with elevated HbA1c levels. Given that relationships between air pollution, greenness, and HbA1c are likely complex, we further hypothesized that these exposures may interact. While there have been few studies considering the potential interactive effects of air pollution and greenness

on health overall, and fewer still focused on cardiometabolic outcomes, advancing this area of understanding is important, as it may help inform policy or urban planning decisions on where to target interventions to protect health. A recent review across health outcomes suggests that greener areas generally experience smaller associations between air pollution and health. (Son et al., 2021) Meanwhile, one study on cardiometabolic disease found inconsistent evidence for any interaction between air pollution and greenness, including some evidence of the opposite result, i.e., larger air pollution-health associations in greener areas. (Klompmaker et al., 2019) This opposite direction of interaction was also found in a recent mortality study. (Ji et al., 2020) A small number of studies have looked at air pollution as a modifier of the greenness-health association; at least one study on risk of gestational diabetes found that the protective effects of greenness are stronger in less polluted areas. (Yu et al., 2023) Drawing on the prior literature, we also examined the impact of different exposure windows (three months and one year prior to blood draw). As this was a study of pathways to diabetes risk, we focused our analysis on individuals without diabetes at the time of blood draw.

II. Methods

Study population

NHS, NHSII, and HPFS are ongoing prospective cohort studies of health professionals in the U.S. NHS and NHSII both consist of women who were recruited as registered nurses. In 1976, NHS enrolled 121,700 women, and in 1989, NHSII enrolled 116,686 women. In 1986, 51,529 male health professionals (dentists, pharmacists, optometrists, osteopath physicians, podiatrists, and veterinarians) were recruited to form the HPFS cohort. NHS and NHSII participants were initially recruited from 11 and 14 states, respectively, but are now distributed throughout the conterminous U.S. HPFS participants were recruited nationwide. Participants in all three cohorts completed biennial questionnaires by mail regarding lifestyle and health-related factors. Mailing addresses were updated throughout follow-up and geocoded. NHS and NHSII used residential addresses. HPFS participants had the option of receiving their questionnaire at either their home or work address. In 1988, they indicated whether the address utilized was home, work, or both. For participants who indicated that the address was used for both home and work (e.g., teleworkers or individuals who reside above their office), we counted the address as home. Lastly, we classified the small percentage of participants who did not specify whether the address was home or work as having a missing address type.

Participants in each of the studies were invited to provide blood samples between 1989–1993 in NHS (n=32,826), between 1996–2000 in NHSII (n=29,611), and between 1993–1998 in HPFS (n=18,000). Participants in these biospecimen collections were sent a blood collection kit and completed a short questionnaire at the time of blood draw. They returned whole blood samples to the laboratory via overnight courier where the samples were immediately processed, separated into plasma, red blood cell, and white blood cell components, and stored in vapor phase liquid nitrogen freezers. These biospecimen collections, as well as the current study, were approved by the Internal Review Board of

Brigham and Women's Hospital. Informed consent was implied through completion and return of the questionnaires and via consent forms for the blood samples.

For the current study, we took advantage of existing HbA1c measurements from a series of case-control studies. HbA1c assays were available from 23 substudies in NHS (n=7,207), 7 substudies in NHSII (n=2,537), and 9 substudies in HPFS (n=3,964). The year of HbA1c blood draw was, on average, 1990 for participants in NHS, 1998 for participants in NHSII, and 1994 for participants in HPFS. This analysis was conducted among participants who were free of cancer other than non-melanoma skin cancer at the time of blood draw. As this is a study of pathways to T2D risk, we also excluded participants with diagnoses of type 1 diabetes, type 2 diabetes, or secondary diabetes (defined as temporally associated with conditions or medications) at blood draw. Diabetes diagnoses were obtained through self-reported questionnaire, with cases confirmed by a validated supplementary questionnaire on diabetes symptoms, diagnostic tests, and treatment. (Manson et al., 1991) Participants with erroneous records, infeasible HbA1c values (<1%), or missing exposure data were also dropped. The extreme Studentized deviate (ESD) many-outlier approach was applied to identify and remove 10 outlier HbA1c observations. (Rosner, 1983) After these exclusions, our study population consisted of 6,457 NHS participants, 2,485 NHSII participants, and 3,373 HPFS participants for a total of 12,315.

Outcome measurement

HbA1c levels were determined on the Roche P Modular system using turbidimetric immunoinhibition (Roche Diagnostics, Indianapolis, IN) We used batch correction to address technical variation across and within substudies, which may occur due to lab drift or differences in participants in each batch. Substudies were treated as one batch when coefficients of variation within the substudy were low (<15%). We used the average batch method and included potential confounders as described below. (Rosner et al., 2008)

Exposure assessment

We estimated average exposures to particulate matter (PM), nitrogen dioxide (NO_2), and greenness at participants' addresses in the three months as well as in the one year prior to blood collection.

Particulate Matter—Spatiotemporal generalized additive mixed models covering the conterminous U.S. were used to predict monthly levels of exposure to PM < 2.5 μm in aerodynamic diameter (PM2.5). The models incorporate nearby point source, urban land use, elevation, and meteorological data in addition to nationwide monitoring data from multiple academic and governmental sources. Due to the lack of EPA monitoring data for $PM_{2.5}$ before 1999, the models instead used pre-1999 PM_{10} levels, post-1999 $PM_{2.5}/PM_{10}$ ratios, and airport visibility data to predict pre-1999 $PM_{2.5}$ levels. Ten-fold cross-validation demonstrated low bias and high precision for $PM_{2.5}$ predictions. (Yanosky et al., 2014)

Nitrogen Dioxide—Likelihood-based spatiotemporal models with a universal kriging framework were used to estimate monthly NO_2 levels. (Kirwa et al., 2021) Data sources included tropospheric NO_2 data from the Aurora satellite, as well as monitoring data from

regulatory and non-regulatory monitors, some of which was collected via a researcher-led exposure monitoring campaign designed to capture near-source (road) gradients. Further, the models are optimized to handle irregular monitoring data. They also reflect proximity and buffer-based geospatial predictors such as roads and commercial zones. High predictive accuracy was observed with a cross-validated R^2 of 0.87 and a spatially clustered R^2 of 0.77. (Kirwa et al., 2021)

Greenness—We defined greenness using the normalized difference vegetation index (NDVI), an indicator of quantity of photosynthetically active vegetation. NDVI ranges from −1 to 1, with negative values indicating water and higher values indicating more greenness. (Kriegler et al., 1969) In keeping with the recent literature, we set negative values to zero. (Klompmaker et al., 2018) Landsat satellite data at 30m resolution was used to calculate NDVI within a 270m and 1,230m radial buffer of each participant's address. We used the NDVI value for the season of blood draw to represent the three-month exposure window and the average of NDVI for the year of blood draw as a measure of annual exposures.

Covariates

We selected covariates that were potential confounders or predictors of HbA1c *a priori* using directed acyclic graphs (DAGs). We used the values from the follow-up questionnaire prior to the time of blood draw in each cohort (i.e., 1988 for NHS, 1995 for NHS2, and 1992 for HPFS) or the closest available questionnaire prior to blood draw. The covariates included age and year at blood draw, season of blood draw, race/ethnicity (White, Black, or other/unknown), family history of diabetes (yes/no), Census tract population density from the 1990 U.S. Census, postmenopausal hormone (PMH) use (female, premenopausal/never used; female, past or current user; or male), body mass index (BMI, < 25.0, 25.0 – 29.9, or ≥ 30.0 kg/m^3), smoking status (never, former, or current), alcohol consumption (0, 0.1–14.9, 15.0–29.9, or ≥30 g/day) and Alternative Healthy Eating Index (AHEI) 2010 scores (0–99, where higher scores indicate a healthier diet). (Chiuve et al., 2012) We evaluated neighborhood socioeconomic status (nSES) at the Census tract level with a composite score created by z-standardizing and summing 17 variables from the 1990 U.S. Census, where higher nSES scores indicate higher SES. (DeVille et al., 2023)

Statistical analysis

We evaluated pairwise Spearman correlations between the exposures within each time window, and across the time windows (three-month and one-year averages prior to blood draw). We log transformed HbA1c to improve normality of residuals. In linear regression models applied to data pooled across the three cohorts, we estimated the percentage difference and 95% confidence interval (CI) in HbA1c associated with an interquartile range (IQR) difference in exposure. Beta coefficients were transformed to represent a percentage change in HbA1c associated with a change in exposure. We first applied basic models adjusted for age and year at blood draw, BMI, alcohol use, and nSES. In fully adjusted models, we also included AHEI diet score, race, family history of diabetes, smoking status, PMH use, population density, and season. For each exposure in each time window, we constructed single exposure multivariate linear regression models. Linearity was assessed with restricted cubic splines, using a likelihood ratio test to compare the

model with and without the cubic spline term. (Durrleman & Simon, 1989) We assessed interactions between each pair of environmental exposures (type of exposure and time window) using likelihood ratio tests comparing a model with both exposures and their pairwise interaction, to a model which includes both exposures but not their interaction. Lastly, we added multiplicative interaction terms to the single exposure linear models to assess effect modification by population density (<1,000 people per square mile or ≥1,000 people per square mile) and nSES (quartiles).

To address potential correlation in the exposures, for each time window we ran multi-exposure multivariate linear regression models. We also applied principal components analysis (PCA) to the full set of exposure variables, including all exposures/time window combinations, to create component variables summarizing the information contained in sets of highly correlated exposures. We decided how many components to retain based on the following criteria: the inflection point in the scree plot, eigenvalues greater than one, and the percent of variance explained (>80%). Since PCA components are uncorrelated and can be included jointly in models without multicollinearity concerns, we ran basic and fully adjusted linear models with the PCA components as simultaneous exposures.

In secondary analyses, we explored potential differences in associations by sex. We compared the model results among women (NHS/NHSII) to those among men (HPFS). As a sensitivity analysis, we also restricted the dataset to participants with home addresses only. For HPFS participants, this was limited to those who indicated home as the address type. In an additional sensitivity analysis, we dropped any individuals with prediabetes, thereby restricting the dataset to individuals without prediabetes only.

All statistical tests were two-sided and p values <0.05 were considered statistically significant. All analyses were conducted in SAS 9.4 (SAS Institute, Cary, NC).

III. Results

Table 1 illustrates participant characteristics overall and by cohort at the time of blood collection, which took place on average in 1990 in NHS, 1998 in NHSII, and 1994 in HPFS. Air pollution levels have declined over time. Accordingly, predicted air pollution exposures were the highest in NHS. The overall 1-year average $PM_{2.5}$ and NO_2 exposures were 14.7 $\mu g/m^3$ and 14.3 ppb, respectively. NDVI estimates were comparable across the cohorts, with an average 270m 1-year NDVI of 0.33.

Nearly all participants were White (95%). The season of blood collection was evenly distributed except for HPFS, which had a higher proportion of summer blood draws (37%). The average age was 57 years old. NHSII participants were the youngest (45) while HPFS were the oldest (64). Age differences were reflected in the distribution of PMH use for female participants, with 52% past or current users in NHS, compared to only 10% in NHSII. HbA1c averaged 5.53% overall. HPFS participants had the highest HbA1c readings – close to 5.7% -- and were more likely to have pre-diabetes at blood draw (28%, vs 19% overall). Meanwhile, they had the lowest family history of T2D (23%, vs 30% overall). As for risk factors, HPFS had higher consumers of alcohol and the highest percentage of

past smokers (50%), but the lowest percentage of current smokers (9%). NHSII had the highest percentage of never smokers (64%), but the lowest average diet score (44, vs 52 overall). Just under half (43%) of HPFS addresses were known to be work rather than home addresses, and 8% were of an unknown address type.

We did not identify any high correlations between the different environmental exposures (Figure 1). However, there were high correlations across time windows for each of the air pollutants (r=0.81 for 3-month and 1-year $PM_{2.5}$, and r=0.96 for 3-month and 1-year NO_2). We found moderate-high correlations between the two NDVI buffer sizes in the same time window. There were moderate negative correlations between NO_2 and 1-year NDVI.

Since we did not find consistent evidence of deviation from linearity in the relationship between any of the exposures and HbA1c (p-value of test for nonlinear relation >0.05), we present linear exposure effect estimates throughout. In both the three-month and one-year exposure windows, there was little evidence of associations between any of the environmental exposures (air pollutant concentrations and NVDI) and HbA1c. (Table 2) In the one-year exposure window, the single-exposure fully-adjusted model for 1,230m NDVI indicated a modest negative association with HbA1c (−0.27%; 95% CI: −0.05%, −0.49%), with an effect size robust to co-adjustment when moving from the basic to fully-adjusted model. However, in the multi-exposure model, the CI for this association crossed the null. We did not find evidence of effect modification by population density or nSES, nor did we observe interactions between the environmental exposures (p-for interaction >0.05).

Three components were retained from the PCA analysis, which explained 83% of the variance (Figure 2). Component 1 had high loadings for 1-year average NDVI in both buffer sizes. Component 2 had high loadings for both air pollutants at both time points. Component 3 had high loadings for 3-month NDVI in both buffer sizes. NO_2 also loaded in a negative direction on Component 1. In the basic linear model with the PCA components included as simultaneous exposures, a 1 SD increase in Component 1 (1-year NDVI) was associated with a 0.19% (95% CI: 0.04%, 0.34%) lower HbA1c (Table 3). Additionally, a 1 SD increase in Component 2 (air pollution) was associated with a 0.20% (95% CI: 0.03%, 0.36%) lower HbA1c. However, in fully adjusted models, no associations persisted.

In supplemental analyses, we failed to find any evidence of effect modification by sex (p-for interaction >0.05). (Table S1). In a sensitivity analysis where we included only participants who had provided home addresses (n=10,594), the effect estimates were largely similar to the main model results (Table S2). Differences between the effect estimates for 270m versus 1,230m NDVI were a bit more pronounced than in the main model results, with the 270m coefficients being more consistently negative in the main results. However, the positive coefficients for 270m NDVI were small in size, with confidence intervals crossing the null in both main and sensitivity analyses. Meanwhile, in a separate sensitivity analysis restricted to individuals without prediabetes (n=10,107), our findings remained unchanged from the main model results (Table S3).

IV. Discussion

This U.S.-based study of men and women who provided blood samples as part of nationwide cohorts is one of the first to examine associations between individual and joint air pollution and greenness exposures and HbA1c, an important indicator of diabetes risk. While greenness was modestly associated with HbA1c in single exposure models, we did not find consistent evidence of any associations in fully adjusted models with individual exposures or component scores.

Earlier studies of greenness and HbA1c similarly found no evidence of an association. (Bloemsma et al., 2019; Gallo et al., 2022) The study in the Netherlands investigated $PM_{2.5}$ and NO_2 along with greenness, in single and multi-exposure models, like our study. No associations were found for the air pollutants and HbA1c, either. (Bloemsma et al., 2019) A study in Germany also did not detect associations between $PM_{2.5}$, NO_2, and HbA1c. (Wolf et al., 2016) While the Dutch study was among adolescents, the German study had a mean participant age very close to ours (56 years old).

Meanwhile, several studies have identified positive associations between air pollution and HbA1c, across vastly different exposure ranges. A study among women of child-bearing age in the Programming Research in Obesity, Growth, Environment, and Social Stressors (PROGRESS) cohort in Mexico City detected a small, positive association between 6-month average $PM_{2.5}$ exposure and HbA1c. (He et al., 2022) In a study sampled from the Health and Retirement Study cohort, among non-diabetic older Americans (57 years old and above) with similar exposure levels to ours, an IQR increase in 1-year average NO_2 exposure was associated with a 0.8% increase in HbA1c. (Honda et al., 2017) This association remained statistically significant in models jointly adjusted for $PM_{2.5}$. The opposite was true in a Taiwanese study, two Chinese studies, and a French study, where only particulate matter remained a significant predictor in two-pollutant models. (Chuang et al., 2010; F. Liu et al., 2022; Mei et al., 2023; Riant et al., 2018) In contrast, several studies of $PM_{2.5}$, NO_2, and T2D incidence have found the NO_2 relationship to be more robust. (Coogan et al., 2012; Sade et al., 2021; Thiering et al., 2016)

Biological mechanisms linking air pollution exposure and diabetes risk have been studied in animal models and epidemiologic studies, and may include inflammation, impaired glucose metabolism, oxidative stress, and insulin resistance. (Puett et al., 2019) More specifically, air pollution has been associated with overproduction of pro-inflammatory cytokines, resulting in inhibited insulin signaling and oxidative stress. (Mei et al., 2023) Earlier research in the NHS and HPFS cohorts identified the strongest associations between NO_2 exposure and C-Reactive Protein (CRP) in women in 1-,3-, and 12-month averaging windows, and between $PM_{2.5–10}$ and CRP in men in the shorter 1- and 3-month windows. (Iyer, Hart, Fiffer, et al., 2022) HbA1c may be an important biomarker on this pathway, as it reflects average blood glucose over a two-to-three-month time frame. Risk of diabetes rises disproportionately with increasing HbA1c. (American Diabetes Association, 2010)

Meanwhile, the specific mechanisms linking greenness and T2D risk are still unknown. (Frumkin et al., 2017) Broad pathways between greenness and health include lower adverse

environmental exposures, better stress recovery, and enhanced opportunities for physical activity and social connection. (Kuo, 2015; Markevych et al., 2017) Since intervention studies indicate that physical activity can help halt the progression from prediabetes to T2D diagnosis, it is also plausible that increased greenness might contribute to this mechanism, even though we did not observe a consistent association with NDVI in this study. (Bullard et al., 2013) On a biological level, reductions in psychosocial stress through contact with nature may in turn decrease physiologic stress through lower levels of inflammation. (Iyer, Hart, James, et al., 2022) Among the NHS and HPFS participants who provided blood samples, one prior study constructed an inflammation z-score based on the inflammatory biomarkers CRP, adiponectin, interleukin-6, and soluble tumor necrosis factor receptor-2. Protective associations were found between 270m NDVI and the inflammation score, in women only. (Iyer, Hart, James, et al., 2022)

Since we pooled data from two female cohorts (NHS and NHSII) and one male cohort (HPFS), we had the opportunity to assess potential differences in associations by sex. Other studies that have assessed effect modification by sex have similarly found no statistically significant interaction. (C. Liu et al., 2016; Riant et al., 2018; Wolf et al., 2016) This finding runs counter to previous studies on air pollution and T2D, which have indicated that women may experience stronger associations than men. (Eze et al., 2015; F. Liu et al., 2019; Rao et al., 2015) As the age range and dates of blood collection were different for the men and women in our study, potentially impacting exposure patterns and variability, our ability to draw conclusions about effect modification by sex may be somewhat limited. The one other study that examined potential effect modification by urbanicity, like ours, did not find evidence of any differences in association. (Riant et al., 2018)

The main limitation of this study was its reliance on secondary data from nested case-control studies. As a considerable proportion of these participants went on to develop major diseases later, they may not be representative of the broader NHS, NHSII, and HPFS populations. While we excluded participants with a diagnosis of diabetes at blood draw, our study population was at higher risk for prediabetes than the general population in the 1990s. For comparison, in a study using U.S. NHANES data, the mean HbA1c was 5.17% in 1999/2000, which is lower than our study population mean HbA1c of 5.54%. (Bullard et al., 2013) Our outcome, HbA1c, was only available at one time point, and we used measures of air pollution and greenness relatively close to the time of blood draw. However, research applying variable time windows ranging from one-year to five-year averages suggests that associations between air pollutants and HbA1c are strongest in the one-year average time window. (Honda et al., 2017) Further, our study was conducted among a predominantly white population of well-educated adults, who were recruited as health professionals, and lived in areas with low air pollutant exposures relative to other parts of the world. As such, our results may not be generalizable to populations with different age, racial/ethnic, socioeconomic, or exposure distributions. We primarily used exposure measures at residential addresses, which could lead to measurement error as they do not capture exposure in other locations where participants spend time. Since some HPFS addresses were work rather than home addresses, there was a possibility of differences in associations by address type. However, in a sensitivity analysis restricted to home addresses, the conclusions were unchanged. Finally, while certain types of greenspace may influence HbA1c more than

others, our measure of greenness, NDVI, is a quantitative metric which does not capture type, quality, or access to greenspace.

This study has several strengths. It leverages highly resolved spatiotemporal exposure data and several large nationwide prospective cohort studies among women and men. It is one of the first studies to investigate simultaneous air pollution and greenness exposures in relation to HbA1c. We considered potential interactions among exposures (though we did not find any), and applied PCA analysis to enable assessment of simultaneous environmental exposures without introducing multi-collinearity concerns. We were able to adjust for many individual and area-level confounders. Of the small number of studies that have been conducted, the largest and most consistent associations have been found among individuals with diabetes, as we might expect based on research on the role of diabetes as an effect modifier in association with cardiovascular disease. (Hart et al., 2015; Sacks et al., 2011) In contrast, we focused on individuals free of diabetes at the time of blood draw, seeking to shed light on the biological pathways between the environment and diabetes development. Disentangling the importance of environmental exposures on HbA1c may offer potential avenues for intervention prior to diabetes onset.

In conclusion, in single and multi-exposure models using individual exposures and component scores, we did not uncover any consistent associations between air pollution, greenness, and HbA1c.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- This study drew on U.S. cohorts of adults without diabetes (some with prediabetes).
- This study investigated simultaneous air pollution and greenness exposures.
- Environmental exposures were not consistently associated with HbA1c.
- Residential greenness was modestly associated with HbA1c in single exposure models.
- More work is needed to elucidate pathways between the environment and prediabetes.

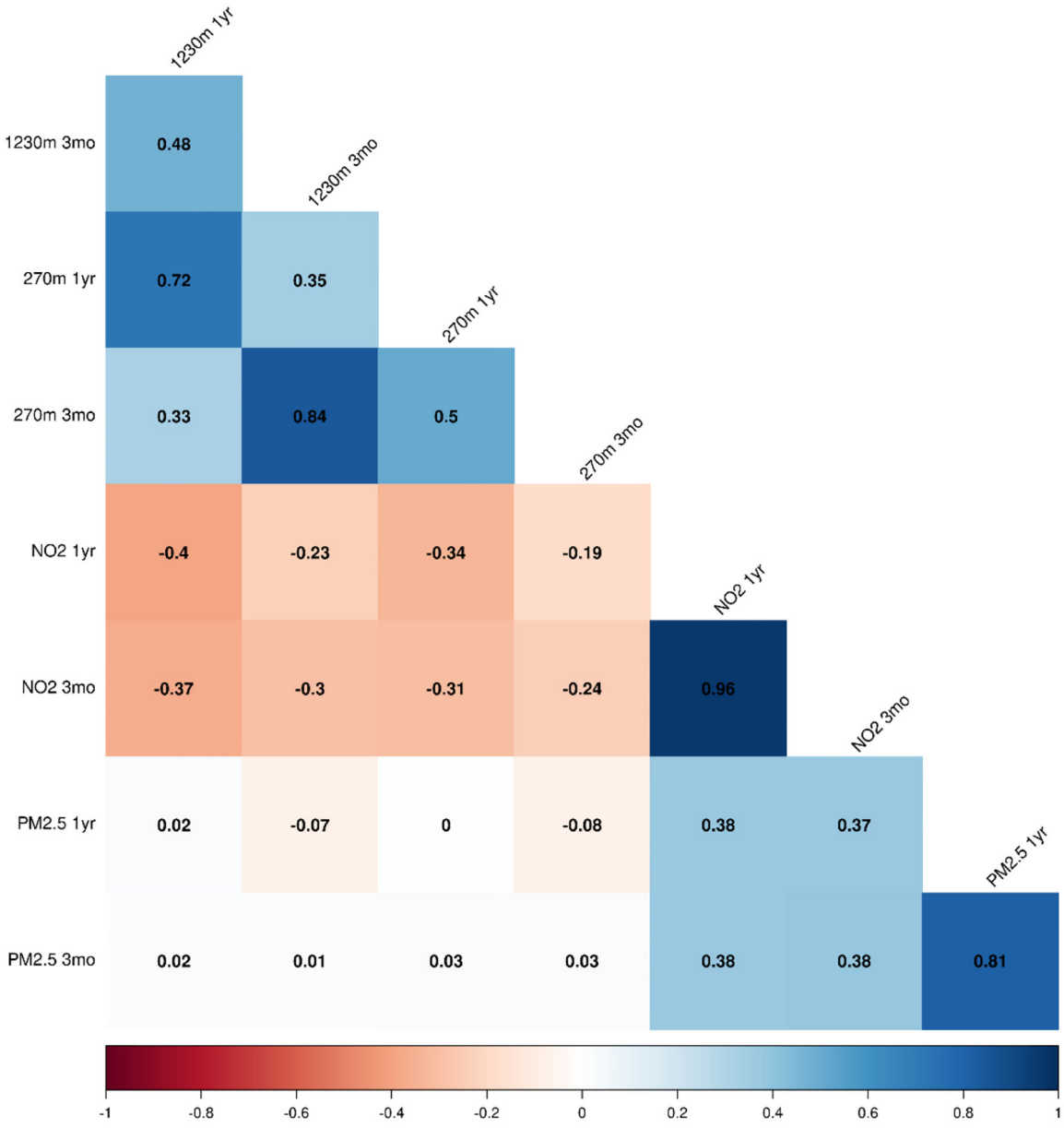

Figure 1.

Spearman correlation coefficients among measures of 270m and 1,230m NDVI, $PM_{2.5}$ and NO_2 air pollution across two time windows (3 month and 1 year avg) among women and men in the Nurses' Health Study, Nurses' Health Study II, and Health Professionals Follow-up Study.

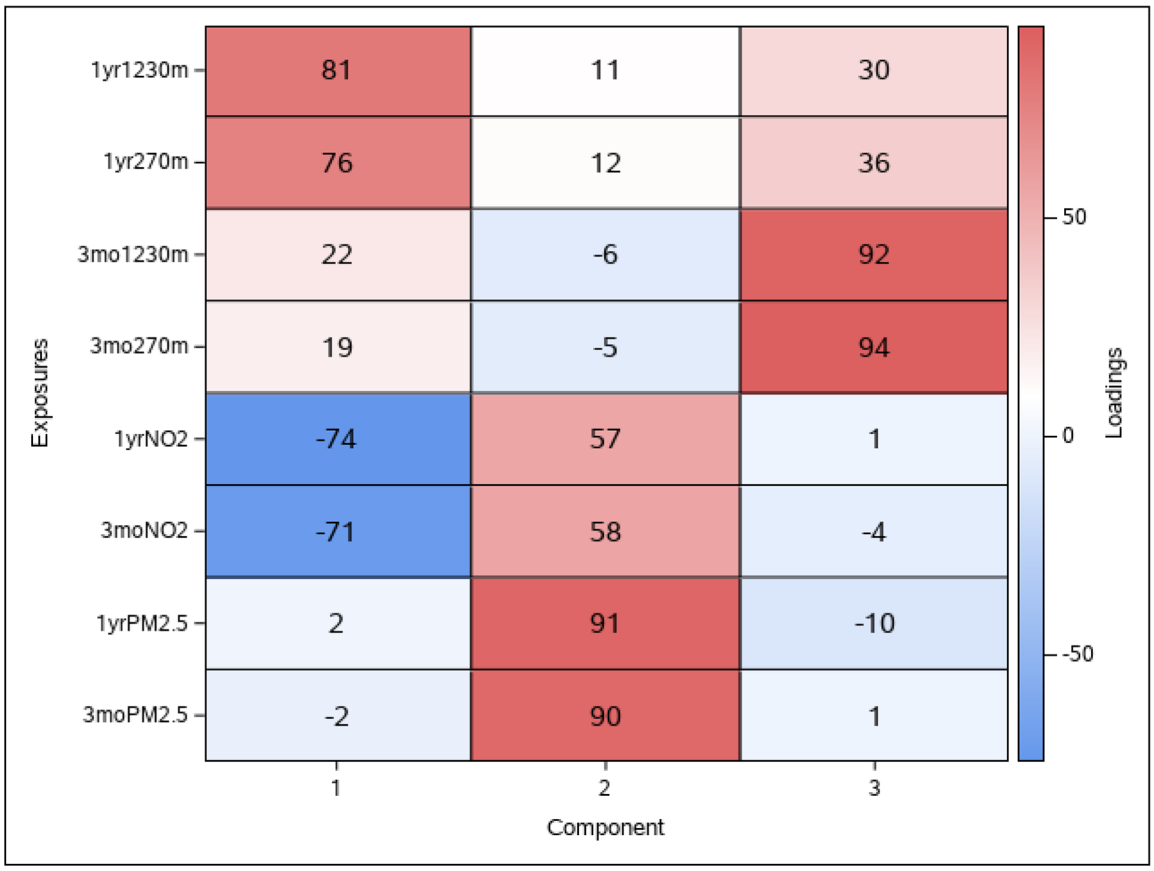

Figure 2.

Heatmap of PCA component loadings for measures of surrounding greenness (1yr1230m, 1yr270m, 3mo1230m, and 3mo270m), NO_2 (1yrNO2 and 3moNO2) and $PM_{2.5}$ (1yrPM2.5 and 3moPM2.5) exposure.

Table 1.

Age-standardized characteristics (mean ± SD or %) at time of blood collection among 12,315 participants in the Nurses' Health Study (women), Nurses' Health Study II (women), and Health Professionals Follow-up Study (men).

	Overall n=12,315	NHS n=6,457	NHSII n=2,485	HPFS n=3,373
Year of blood collection *	1992 ± 3	1990 ± 1	1998 ± 1	1994 ± 1
Age at blood collection *	57.19 ± 9.60	58.49 ± 6.77	44.78 ± 4.35	63.85 ± 8.59
HbA1c, % *	5.53 ± 0.55	5.48 ± 0.45	5.48 ± 0.52	5.68 ± 0.70
Log(HbA1c) *	1.71 ± 0.09	1.70 ± 0.07	1.70 ± 0.08	1.73 ± 0.11
Pre-diabetes, % [1]	19	15	17	28
AHEI Diet Score	51.67 ± 11.70	53.29 ± 10.94	44.04 ± 10.06	54.22 ± 11.90
Family history of diabetes, %	30	33	31	23
nSES	0.0074 ± 3.76	0.0003 ± 3.73	0.03 ± 3.74	0.0043 ± 3.82
Population density, per sq mi	3,249 ± 6,589	3,242 ± 6,187	3,137 ± 7,264	3,346 ± 6,808
Smoking status				
Never, %	45	41	64	38
Past, %	39	40	25	50
Current, %	15	19	12	9
Alcohol consumption, g/day				
0, %	33	37	37	21
0.1–14.9, %	48	48	48	46
15.0–29.9, %	8	5	6	14
≥ 30.0, %	6	4	2	13
Missing, %	6	5	7	6
Physical activity, MET-hours/week				
<3, %	19	22	20	13
3 to <9, %	22	26	26	13
9 to <18, %	21	22	23	18
18 to <27, %	13	12	11	15
27 to <42, %	12	10	11	17
≥ 42, %	12	8	9	25

	Overall n=12,315	NHS n=6,457	NHSII n=2,485	HPFS n=3,373
BMI				
Under/normal, %	45	50	44	38
Overweight, %	32	31	26	39
Obese, %	18	18	30	9
Missing, %	4	0	0	15
Postmenopausal hormone use/sex				
Female, Premenopausal/never used, %	42	45	90	0
Female, Past or current user, %	29	52	10	0
Male, %	27	0	0	100
Missing, %	2	3	0	0
Race				
White, %	95	95	95	95
Black, %	1	1	2	0
Other/unknown, %	4	4	3	5
Season				
Spring, %	25	25	26	25
Summer, %	29	29	21	37
Autumn, %	24	22	32	24
Winter, %	21	24	21	14
Address type				
Home, %	86	100	100	49
Work, %	12	0	0	43
Missing, %	3	0	0	8
3-mo avg Predicted $PM_{2.5}$, $\mu g/m^3$	14.72 ± 4.85	16.30 ± 4.87	13.61 ± 3.76	12.52 ± 4.42
3-mo avg Predicted NO_2, ppb	13.54 ± 8.41	14.91 ± 9.06	11.86 ± 6.86	12.17 ± 7.67
3-mo avg NDVI, 270m	0.35 ± 0.16	0.35 ± 0.17	0.36 ± 0.16	0.34 ± 0.16
3-mo avg NDVI, 1230m	0.33 ± 0.16	0.32 ± 0.16	0.34 ± 0.16	0.35 ± 0.15
1-yr avg Predicted $PM_{2.5}$, $\mu g/m^3$	14.71 ± 3.94	16.41 ± 3.83	13.52 ± 2.89	12.35 ± 3.23
1-yr avg Predicted NO_2, ppb	14.28 ± 8.49	15.96 ± 9.24	11.95 ± 6.67	12.77 ± 7.41
1-yr avg NDVI, 270m	0.33 ± 0.10	0.33 ± 0.09	0.36 ± 0.10	0.31 ± 0.11

	Overall	NHS	NHSII	HPFS
	n=12,315	n=6,457	n=2,485	n=3,373
1-yr avg NDVI, 1230m	0.31 ± 0.10	0.30 ± 0.09	0.34 ± 0.10	0.32 ± 0.10

Values are means ± SD or percentages and are standardized to the age distribution of the study population.

Values of polytomous variables may not sum to 100% due to rounding.

*Value is not age adjusted

1Based on HbA1c at blood draw using range of 5.7–6.5%.

Abbreviations: HbA1c, hemoglobin A1c; BMI, Body Mass Index; AHEI, Alternate Healthy Eating Index; g/day, grams per day; mo, month; μg/m^3, micrograms per cubic meter; PM, particulate matter; NO_2, nitrogen dioxide.

Table 2.

Percentage change (95% CIs) in HbA1c with an interquartile range increase of each exposure in single and multi-exposure[a] models among the 12,315 women and men in the Nurses' Health Study, Nurses' Health Study II, and Health Professionals Follow-up Study.

	IQR	Single exposure – Basic[b]	Multi-exposure – Basic[b]	Single exposure – fully adjusted[b,c]	Multi-exposure – fully adjusted[b,c]
3-month exposure window					
$PM_{2.5}$ (μg/m^3)	6.44	−0.15 (−0.36, 0.06)	−0.17 (−0.40, 0.06)	−0.06 (−0.27, 0.16)	−0.04 (−0.28, 0.20)
NO_2 (ppb)	9.82	−0.04 (−0.23, 0.15)	0.06 (−0.16, 0.28)	0.04 (−0.17, 0.24)	0.02 (−0.21, 0.25)
NDVI 270m	0.24	0.15 (−0.07, 0.37)	0.22 (−0.20, 0.64)	−0.11 (−0.37, 0.14)	0.22 (−0.21, 0.65)
NDVI 1230m	0.23	0.10 (−0.11, 0.32)	−0.06 (−0.47, 0.36)	−0.23 (−0.47, 0.01)	−0.39 (−0.81, 0.03)
1-year exposure window					
$PM_{2.5}$ (μg/m^3)	5.52	−0.29 (−0.52, −0.07)	−0.28 (−0.54, −0.02)	−0.11 (−0.34, 0.13)	−0.07 (−0.33, 0.19)
NO_2 (ppb)	10.03	0.01 (−0.19, 0.20)	−0.01 (−0.25, 0.23)	0.05 (−0.16, 0.26)	0.00 (−0.25, 0.24)
NDVI 270m	0.14	−0.22 (−0.43, −0.02)	−0.13 (−0.44, 0.18)	−0.18 (−0.40, 0.04)	0.02 (−0.30, 0.34)
NDVI 1230m	0.14	−0.26 (−0.47, −0.04)	−0.15 (−0.47, 0.17)	−0.27 (−0.49, −0.05)	−0.28 (−0.59, 0.04)

[a] Multi-exposure models include $PM_{2.5}$, NO_2, NDVI 270m, and NDVI 1230m exposures for the time window indicated (either 3-month or 1-year).

[b] Adjusting for batch, age at blood draw, year, body mass index, alcohol use, and neighborhood SES.

[c] Adjusting for AHEI diet score, race, family history of diabetes, smoking status, postmenopausal hormone use/sex, population density, and season.

Table 3.

Percentage change (95% CIs) in HbA1c with a standard deviation increase of each component in models among the 12,315 women and men in the Nurses' Health Study, Nurses' Health Study II, and Health Professionals Follow-up Study.

	Basic[a]	Fully adjusted[a,b]
Component 1[c]	−0.19 (−0.34, −0.04)	−0.14 (−0.31, 0.03)
Component 2[d]	−0.20 (−0.36, −0.03)	−0.07 (−0.24, 0.10)
Component 3[e]	0.11 (−0.03, 0.26)	−0.09 (−0.27, 0.08)

[a]Adjusting for batch, age at blood draw, year, body mass index, alcohol use, and neighborhood SES.

[b]Adjusting for AHEI diet score, race, family history of diabetes, smoking status, postmenopausal hormone use/sex, population density, and season.

[c]Characterized by high loadings for NDVI 1yr.

[d]Characterized by high loadings for $PM_{2.5}$ and NO_2.

[e]Characterized by high loadings for NDVI 3mo.