Greenness and eosinophilic asthma: findings from the UK Biobank

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To the Editor:

Eosinophilic asthma is one of the most common subtypes of asthma diagnosed in adulthood, with around 50% of cases of mild to severe asthma of the eosinophilic subtype [1]. Although it is well acknowledged that residential environment plays a critical role in the progression of early-onset or late-onset asthma [2, 3], no prior study has had the primary objective of evaluating the association between residential greenness and eosinophilic asthma. The aim of our study was to explore whether there is an association between residential greenness and eosinophilic asthma in adults.

The present study is an analysis of data obtained by UK Biobank, a large sample sized population-based study that was undertaken of nearly 0.5 million adults aged 37 to 73 years between 2006 and 2010 across the UK [4]. Individual covariates were collected through touchscreen or nurse-led questionnaires, anthropometric measurements, and biological sampling. In the present study, eosinophilic asthma was defined as participant reporting asthma-related medication use and elevated eosinophil count of at least 150 cells per µL [5, 6]. Residential greenness exposure was measured by the mean Normalised Difference Vegetation Index (NDVI) [7], an index of greenery modelled from a series of very high resolution (0.50 m by 0.50 m) Bluesky Colour Infrared imagery derived from remotely sensed data. Summer-time mosaicking images of the study areas around UK Biobank assessment centres collected over similar temporal scales (2006–2010) were used to calculate the average NDVI values, thereby avoiding potential temporal mismatch and the resulting influence from seasonal variability in greenness [8]. The NDVI was a pre-defined index and was presented as means in 500 and 1000 m Euclidean buffers of participant's residence in the UK Biobank. The 500 m buffer measure was generated to take into account mobility and access to green space within a relatively short walk (*i.e.* less than 15 min). However, for the average NDVI in 1000 m buffer in UK Biobank, only one region's NDVI data (Wales) was publicly available (n=20 144). Therefore, we used the mean NDVI in 500 m buffer in the present study. The detailed measurement of NDVI has been described elsewhere [8, 9]. Briefly, because of the difference between the absorption of chlorophyll in the visible red region (630–690 nm) and the reflection of chlorophyll in the near-infrared region (760–900 nm) of electromagnetic spectrum, the NDVI can be illustrated by the following formula:

$$\mathrm{NDVI} = \frac{\mathrm{NIR} - \mathrm{RED}}{\mathrm{NIR} + \mathrm{RED}}$$

where NIR and RED represent the spectral reflectance measurements acquired in the near-infrared (NIR) and visible (RED band) regions of the electromagnetic spectrum, respectively. NDVI scores range from −1 to 1, with higher scores indicating higher green vegetation densities and *vice versa*.

We excluded participants with missing data on eosinophilic asthma (n=9534), greenness or air pollutants (n=130 979), and key covariates (n=10 250), leaving a total of 351 717 participants for current analysis. Informed consent was obtained from each participant.

Logistic regression models were performed to estimate the association between greenness and eosinophilic asthma. Covariates defined *a priori* were variables plausibly associated with outcome, including age, sex, body mass index (BMI), highest educational qualification, smoking, alcohol drinking, employment status,

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ethnicity, social activities and season. Additionally, single air pollutant ($PM_{2.5}$, PM_{10} (particles with a 50% cut-off aerodynamic diameter of 2.5 or 10 µm) and NO_2) was added into models to show the consistency of results. Moreover, we performed stratified analyses to explore potential interaction effect of age, sex and BMI on the greenness–asthma association. Lastly, to avoid the bias of under-diagnosis or under-treatment of asthma, we performed a sensitivity analysis by using self-reported wheeze symptoms as an alternative outcome.

In total, 351 717 (women, 54.3%) subjects contributed to the analyses. The median (interquartile range) age of the study population was 58 (50–63) years at recruitment. The prevalence of eosinophilic asthma was 2.7%. In the fully adjusted model, compared with the lowest quartile of greenness, odds ratios (95% confidence intervals) for eosinophilic asthma were 0.943 (0.891, 0.998), 0.941 (0.889, 0.996) and 0.938 (0.886, 0.993) for participants in the second, third and highest quartile of greenness, respectively (figure 1a, model 1). Results of bivariate models by adding air pollutants ($PM_{2.5}$, PM_{10} and NO_2) showed similar findings (figure 1a, models 2–4). In stratified analyses, the association between greenness (highest *versus* lowest quartile) and eosinophilic asthma were prominent in subjects with age⩾60 years (OR 0.914, 95% CI 0.838, 0.997), male subjects (0.902, 95% CI 0.828, 0.983), and subjects with BMI ⩾25 $kg \cdot m^{-2}$ (0.922, 95% CI 0.862, 0.986) (figure 1b). However, no effect modification by age, sex or BMI was found (all p-values for interaction >0.05) (figure 1b). In sensitivity analysis, a significant association between greenness and self-reported wheeze symptoms was also observed, with or without adjustment for air pollutants (figure 1c).

We found that higher levels of residential greenness exposure were associated with decreased odds of eosinophilic asthma, and the favourable association appears to be independent from air pollutants, implying that greenness may be a beneficial factor for eosinophilic asthma in adults. It has been speculated that increased residential greenness may protect against respiratory/immune conditions through its positive impact on environmental biodiversity and subsequently the human microbiome [10, 11]. Previous studies have reported that the outdoor microbiome varies with the surrounding vegetation, and a growing body of literature has linked the microbiome with allergic diseases [12]. Therefore, the findings of our study may be congruent with postulations of the biodiversity hypothesis, that contact with natural environments enriches the human microbiome, promotes immune balance and protects from allergy and inflammatory disorders [11, 13]. In addition, increased access to residential greenness has also been linked with improved weight outcomes, increased physical activity, promoted psychological restoration, and reduced psychological stress [8, 14]. These may further improve human health. Given the considerable prevalence of eosinophilic asthma in UK adults, more studies are warranted to demonstrate the biological mechanisms related to greenness exposure, which may substantially benefit public health.

Many studies provide evidence for the value of different types of vegetation (*e.g.* streetscape greenery) on human health [14, 15]. The potential causal mechanisms are presumed to be environmental comfort (*e.g.* shade and shelter) and perceptions of green space, environmental quality, safety and aesthetics [14]. However, the type of vegetation may not be obtained based on the NDVI in the present study; we thus performed a sensitivity analysis using domestic garden percentage (refers to the field ID 24504) as an alternative exposure assessment of private greenness. The results were similar to our main findings (data not shown). With this in mind, revealing the effects of different types of vegetation on human health in future studies may have a profound impact on urban policy-making.

The results of the present study have important implications for urban policies. In order to manage and minimise the burden of eosinophilic asthma in adults, optimising the green space surrounded in built environment may be a targeting strategy. From an individual perspective, subjects who have more opportunities to access a green environment may gain more benefits in improving respiratory health.

Several potential limitations should be acknowledged. First, the temporal or causal relationships cannot be inferred because of the cross-sectional design. Participants with asthma might have migrated to greener areas and therefore could result in the underestimation of the effect of greenness on eosinophilic asthma. Second, common to most previous studies, greenness exposures estimated based on a single address cannot rule out potential exposure misclassification caused by outside activities. Third, eosinophilic asthma defined using blood eosinophil count rather than sputum eosinophil count may result in potential misclassification. Fourth, this study did not examine the potential exposure sensitive windows across lifetime span (*e.g.* prenatal, childhood or adulthood exposure). Lastly, although the NDVI has its strength on the standardised and objective measure of greenness, it could not adjust for individual perceptions of greenness, including proxies of aesthetics and safety, which might influence usage of public green space.

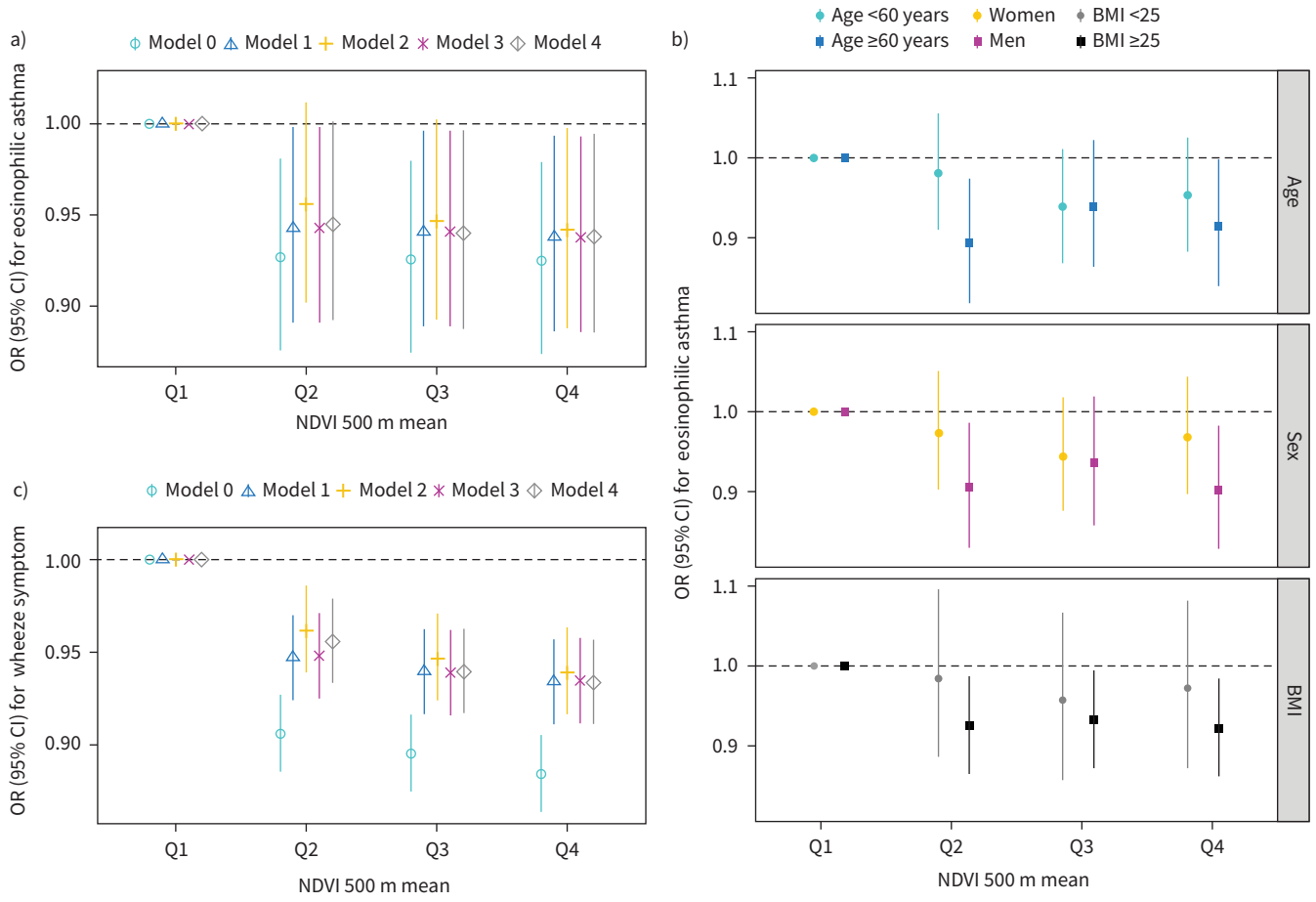

FIGURE 1 a) Effects of residential greenness in a 500-m buffer around residence addresses on eosinophilic asthma prevalence. b) Association between residential greenness and odds of eosinophilic asthma stratified by age, sex and body mass index (BMI). c) Effects of residential greenness in a 500-m buffer around residence addresses on the prevalence of self-reported wheeze symptom. Q1: <0.028; Q2: 0.028–0.157; Q3: 0.157–0.277; Q4: >0.277. Model 0: crude model; model 1: adjusted for age, sex, BMI, highest educational qualification, smoking, alcohol drinking, employment status, ethnicity, social activities and season; model 2: adjusted for model 1, and $PM_{2.5}$; model 3: adjusted for model 1, and PM_{10}; model 4: adjusted for model 1, and NO_2.

In conclusion, our findings from a large-scale study suggest negative association between individual-level exposures of greenness and eosinophilic asthma in adults, providing new evidence to the existing investigations on health effect of green space.

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