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Geographic uncertainties in external exposome studies: A multi-scale approach to reduce exposure misclassification

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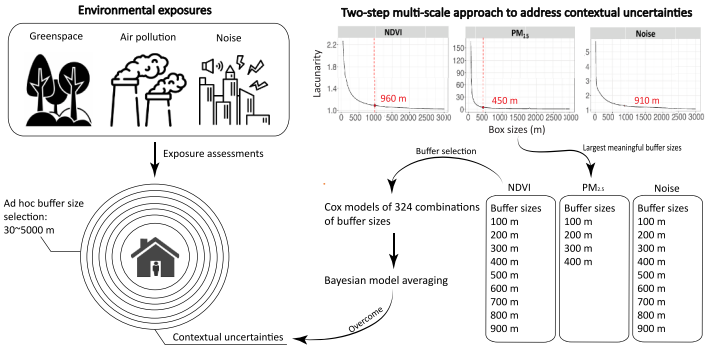
HIGHLIGHTS

- Delineating the geographic context of home addresses in exposome studies is challenging.
- We integrated lacunarity analyses with model averaging to address contextual uncertainties.
- Our multi-scale effect estimates differed from those using typical pre-selected buffer sizes.
- Green space was inversely, and noise was positively related to mortality with null associations for air pollution.
- Our analytic approach mitigated spur ious environment-health associations.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Many studies on environment-health associations have emphasized that the selected buffer size (i.e., the scale of the geographic context when exposures are assigned at people's address location) may affect estimated effect sizes. However, there is limited methodological progress in addressing these buffer size-related uncertainties.

Aim: We aimed to 1) develop a statistical multi-scale approach to address buffer-related scale effects in cohort studies, and 2) investigate how environment-health associations differ between our multi-scale approach and ad hoc selected buffer sizes.

Methods: We used lacunarity analyses to determine the largest meaningful buffer size for multiple high-resolution exposure surfaces (i.e., fine particulate matter [$PM_{2.5}$], noise, and the normalized difference vegetation index [NDVI]). Exposures were linked to 7.7 million Dutch adults at their home addresses. We assigned exposure estimates based on buffers with fine-grained distance increments until the lacunarity-based upper limit was reached. Bayesian Cox model averaging addressed geographic uncertainties in the estimated exposure effect sizes within the exposure-specific upper buffer limits on mortality. Z-tests assessed statistical differences between averaged effect sizes and those obtained through pre-selected 100, 300, 1200, and 1500 m buffers.

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Results: The estimated lacunarity curves suggested exposure-specific upper buffer size limits; the largest was for NDVI (960 m), followed by noise (910 m) and $PM_{2.5}$ (450 m). We recorded 845,229 deaths over eight years of follow-up. Our multi-scale approach indicated that higher values of NDVI were health-protectively associated with mortality risk (hazard ratio [HR]: 0.917, 95 % confidence interval [CI]: 0.886–0.948). Increased noise exposure was associated with an increased risk of mortality (HR: 1.003, 95 % CI: 1.002–1.003), while $PM_{2.5}$ showed null associations (HR:0.998, 95 % CI: 0.997–1.000). Effect sizes of NDVI and noise differed significantly across the averaged and prespecified buffers ($p < 0.05$).
Conclusions: Geographic uncertainties in residential-based exposure assessments may obscure environment-health associations or risk spurious ones. Our multi-scale approach produced more consistent effect estimates and mitigated contextual uncertainties.

1. Introduction

The accurate assessment of the geographic context to which people are exposed has moved to the forefront in external exposome studies (Hu et al., 2023; Turner et al., 2017). People are exposed to substantial environmental stressors contributing to mortality risk (Chen and Hoek, 2020; Fu et al., 2022; Zare Sakhvidi et al., 2022). For example, a growing number of studies have revealed associations between mortality risk and increasing levels of air pollution (Guo et al., 2022; Hu et al., 2022; Nabizadeh et al., 2019) and noise (Cai et al., 2021), while exposure to more green space appears health-protective (Yuan et al., 2021). However, these associations' effect sizes and statistical significance have not always been confirmed (Klompmaker et al., 2020, 2021; Li et al., 2017), and the causes for such heterogeneous findings are not yet fully understood.

A critical aspect of this debate is delineating the geographic context, possibly contributing to mixed findings (Helbich, 2018; Kwan, 2012; Labib et al., 2020a). Studies typically use administrative areas where people live (e.g., postal codes or census geographies) to determine people's health-influencing geographic context. However, this approach has been criticized (Flowerdew et al., 2008; Helbich, 2018). For example, each person within the same spatial unit gets similar exposure concentrations assigned, while those living close to the border may be more strongly affected by the exposure of the adjacent spatial unit than their own. Furthermore, administrative units vary in size and shape, possibly contributing to exposure uncertainties.

To reduce the error in exposure measurements, it is a common practice to superimpose discrete neighborhood zones, typically represented as buffers, onto people's geocoded residential address locations to assess environmental exposures (Bauwelinck et al., 2021; Vienneau et al., 2017; Villeneuve et al., 2012). This makes choosing an appropriate buffer size representing the geographic scale of the exposure window a critical analytical decision (Ho et al., 2022). However, neither theoretical guidance nor well-accepted empirical approaches exist that allow the selection of optimal buffer sizes, resulting in the reliably accurate delineation of the geographic contexts (Markevych et al., 2017; Su et al., 2019). Furthermore, previous comparative studies (Gonzales-Inca et al., 2022; Helbich et al., 2021b; James et al., 2014) have raised concerns that environment-health associations could be partially susceptible to contextual uncertainties arising from the chosen buffer size.

It has been speculated that suboptimal geographic context choices may induce exposure measurement errors (Gotway and Young, 2002; Helbich et al., 2021b; Ho et al., 2022; Reid et al., 2018). Both the modifiable areal unit problem (i.e., suggesting that statistical analyses may be sensitive to the aggregation and zoning of geographic data) (Buzzelli, 2020; Helbich et al., 2021a; Lee et al., 2020) and the uncertain geographic context problem (i.e., suggesting that the geographic delineation of the context may affect exposure-outcome associations) (Kwan, 2012) exemplify contextual uncertainties that may pose issues for statistical assessments in environmental health studies. Although most studies have acknowledged that their geographic context choices result in delineating exposure assessments that might have altered statistical inferences (Parenteau and Sawada, 2011; Reid et al., 2018), very few have addressed this fundamental problem of appropriately delineating the 'true' causally relevant geographic context in their studies.

Reviews have repeatedly stressed inconsistencies in demarcating geographic contexts (Browning and Lee, 2017; Labib et al., 2020a; Markevych et al., 2017). Studies routinely select a single buffer size ranging from 30 m to 5 km as the primary exposure domain while performing robustness checks on several others (Labib et al., 2020a). Because such ad hoc buffer size selections rarely align with the causally relevant geographic context (Bauwelinck et al., 2021; Thacher et al., 2020; Wang et al., 2023), concerns about the validity of the reported effect sizes have been raised. To counter this, some scholars have relied on model fit criteria to identify the most appropriate buffer size. For example, Ribeiro et al. (2016) used the model with the lowest Akaike information criterion to base their choice of a proper buffer size. However, a simulation study questioned this type of practice earlier by showing that the best-fitting model probably risks spurious associations (Spielman and Yoo, 2009).

To respond to this critique, lacunarity analysis, a scale-dependent measure for assessing the textural properties of exposure surfaces, has been proposed (Labib et al., 2020b; Mandelbrot, 1994; Plotnick et al., 1996). However, the state-of-the-art lacunarity-based exposure assessment is conceptually problematic and has three methodological limitations. First, while lacunarity analysis guides the largest meaningful buffer size, the problem of which buffer size should be chosen within the upper range still needs to be addressed. Second, lacunarity-based analysis has only been applied cross-sectionally to green space metrics (Labib et al., 2020b). Nonetheless, there is recognition that other external exposome factors co-occur spatially (Rugel and Brauer, 2020). For example, $PM_{2.5}$ and traffic noise co-vary due to shared emission sources (Klompmaker et al., 2021), while green space absorbs pollutants (Lindén et al., 2023). Third, the gold standard in multi-exposure models is to use similar buffer sizes across exposures (Chakraborty et al., 2011), but the buffer size may depend on the exposure type. For instance, residences are possibly more affected by nearby sources of air pollution (e.g., roads) because pollution levels typically decrease significantly with increasing distance from the source. In this case, a smaller buffer size may be more appropriate for capturing the exposure levels. In contrast, the health benefits of green space may extend over a larger buffer size, as people are usually willing to walk larger distances to access green spaces (Cutts et al., 2009; Kaczynski et al., 2014; Kim et al., 2016; Labib et al., 2020a). Despite renewed awareness of this problem among scholars, delineating the geographic context in exposome studies remains an ongoing methodological issue with limited progress.

Given these gaps in the scholarly knowledge of residence-based exposure assessments, there is a critical need to develop a statistical approach for determining optimal buffer sizes for each specific environmental exposure under examination. Our goals in this paper are 1) to develop a multi-scale approach integrating lacunarity analysis with Bayesian model averaging to mitigate buffer-related scale effects when assessing environmental-health associations and 2) to empirically compare to what extent associations generated by our multi-scale approach differ from the associations generated from various ad hoc selected buffer sizes. We tested our approach using a large Dutch cohort

by examining the joint associations between green space, air pollution, and noise on all-cause mortality.

2. Materials and methods

2.1. Study population

We did a retrospective population-wide cohort study in the Netherlands employing administrative registers from Statistics Netherlands. As every person officially residing in the country has a unique personal identification code, this allowed us to link data from these registers to each individual in our cohort. The data linkage and analyses were performed in a secure environment at Statistics Netherlands. In line with Dutch privacy legislation, anonymized records were used. Due to no interaction with the subjects, informed consent was not required.

Our initial study population included approximately 20 million people between January 1, 2013, and December 31, 2021 (Fig. 1). We retrieved register-based information on individuals' residential address locations. To avoid exposure changes due to address changes (Brokamp et al., 2016), we restricted our cohort to those who did not change residence within the eight-year study period ($N = 9{,}705{,}811$). Based on people's address-based geolocations, we linked them to their environmental exposures at baseline. All residents aged at least 18 years on January 1, 2013, were eligible for study inclusion ($N = 7{,}808{,}237$). As summarized in Fig. 1, we excluded persons with missing demographics and exposures. In total, our cohort included 7,666,540 people.

2.2. All-cause mortality

We selected all-cause mortality as our outcome variable. Mortality data were ascertained from the cause of death register. Based on practice elsewhere (Klompmaker et al., 2021), we defined all-cause mortality following the 10th edition of the International Classification of Diseases as done elsewhere. The following causes of death were pooled: certain infections and parasitic diseases (A00-B99), neoplasms (C00-D48), blood diseases and immune system disorders (D50-D89), endocrine diseases, nutritional and metabolic disorders (E00-E90), mental and behavioral disorders (F00-F99), nervous system diseases (G00-G99), eye and adnexa diseases (H00-H59), ear and mastoid process diseases (H60-H95), heart and vascular system diseases (I00–199), respiratory system diseases (J00-J99), digestive system diseases (K00-K93), skin and subcutis diseases (L00-L99), bone, musculature, and connective tissue diseases (M00-M99), genitourinary system diseases (N00-N99), pregnancy (O00-O99), disorders originating in the perinatal period (P00-P96), congenital abnormalities (Q00-Q99), and unclassified disorders (R00-R99).

2.3. External exposome data

2.3.1. Air pollution

We included ambient fine particulate matter ≤2.5 μm ($PM_{2.5}$) to assess people's exposure to long-term air pollutants (Shen et al., 2022). Daily $PM_{2.5}$ concentrations for 2010 were obtained from monitoring station data from the Airbase database V8 (European Environmental Agency, 2020). The daily concentrations were aggregated to annual averages, and predictions of $PM_{2.5}$ concentrations at unsampled locations were made using land-use regression models, which involved predictors including roads, satellite retrievals, land-use, and chemical transportation model estimates (Shen et al., 2022). The gridded air pollution map had a spatial resolution of 25 m.

2.3.2. Noise

Long-term noise estimates were obtained from the Dutch National Institute for Public Health and the Environment (RIVM). Traffic-related noise (i.e., road and rail), industrial, aviation, and wind turbine noise served as noise sources and were inputted into the Standard Model Instrumentation for noise assessments (Schreurs et al., 2010). The input noise data pertain approximately to the years 2016–20. The gridded noise data were downscaled to a 10 × 10 m spatial resolution representing average day/night/evening noise levels (Lden, in dB).

2.3.3. Green space

We used satellite-derived Normalized Difference Vegetation Indices (NDVI) as green space measures (Tucker, 1979). NDVI values range from −1 to 1. Higher positive values refer to greener environments (Drusch et al., 2012). To align the NDVI with the cohort baseline, we used atmospherically corrected Landsat scenes from May to September 2010, with a 30 m resolution. We excluded scenes with cloud coverage >40 % and pixels with a cloudiness score > 25. Pixels with negative values (i.e.,

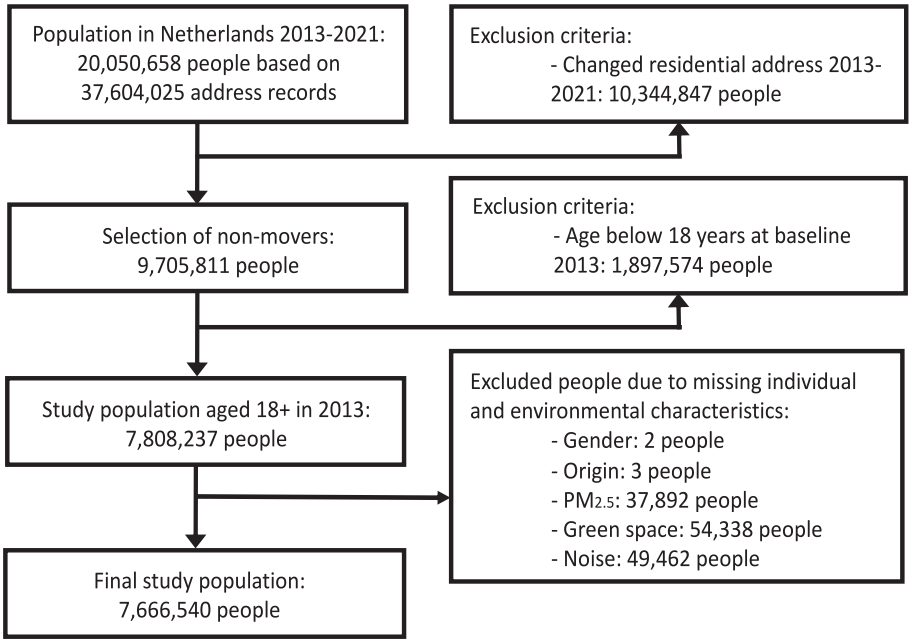

Fig. 1. Selection of the study population.

water bodies) were masked to reduce distortions before the green space assessment.

2.4. Analytical approach

2.4.1. Lacunarity analysis

Lacunarity analysis (Mandelbrot, 1994) allows measurement of the spatial heterogeneity of an exposure surface at different spatial resolutions (Dong, 2000a). Specifically, lacunarity enables the identification of the threshold value at which an exposure surface transfers from a heterogeneous to a homogeneous pattern. Using buffer sizes exceeding the threshold value would introduce contextual uncertainties in the statistical analysis because the individual variation in the exposure is masked when the surface becomes homogeneous (Labib et al., 2020b).

We applied the gliding box algorithm to our data for our lacunarity assessment (Allain and Cloitre, 1991). The algorithm starts from a square box of size $r \times r$ placed at one corner of the exposure surface. The box length r represents the scale of lacunarity. The box mass $S(r)$ is computed using the pixel values within the box. As our exposures were continuous raster surfaces, we employed the range of the pixel values to determine the box mass (Dong, 2000b; Labib et al., 2020b; Plotnick et al., 1996).

From its starting point, the box was incrementally moved to the right one pixel at a time, creating an overlapping series of box masses recomputed at each new raster location. This step was repeated until the box glided across the entire exposure surface. Given the study area's irregular shape, the total number of the square box $N[r]$ of length r was calculated as:

$$N[r] = (W - r + 1) \times (L - r + 1)$$

where W is the width and L is the length of the study area. Lacunarity $\Lambda(r)$ of scale r is computed as (Plotnick et al., 1993):

$$\Lambda(r) = 1 + \frac{Var\,[S(r)\,]}{E^2[S(r)\,]}$$

where $E[S(r)\,]$ is the mean box mass and $Var\,[S(r)\,]$ is the variance of the box mass for all boxes of length r. Following this initial step, the box length was increased in one-pixel increments. Taking the 30 m NDVI surface as an example, the start box length was 60 m (i.e., two pixels). Each increment of one pixel in box length increased the value of r by 30 m, with each newly incremented value, in turn, becoming the box length (e.g., 90 m, 120 m, 150 m) until either the width or the length of the study area was reached.

Exposures typically vary across urban and rural areas (e.g., cities have lower green space values), particularly in nationwide studies exemplified by the present study. Expanding on previous lacunarity analyses (Dong, 2000b; Labib et al., 2020b; Myint and Lam, 2005), we assigned each municipality to one of five urbanization levels ranging from rural to highly urbanized (Statistics Netherlands, 2013). Lacunarity was computed separately for each urbanization level before the results were averaged.

Plotting the lacunarity curve (i.e., lacunarity values against the box length) permitted us to assess how the exposure's spatial heterogeneity varied across the applied scales. The tipping point at which heterogeneity became homogeneity can be seen as a reasonable upper limit for residence-based buffers (Plotnick et al., 1996). To determine the exact location of this tipping point analytically (i.e., where the curve flattens out), we fitted a power function to the lacunarity curve and computed its maximum curvature. Lacunarity analyses were performed separately for each exposure surface.

2.4.2. Bayesian model averaging of cox regressions

Lacunarity assessment only yields the upper-scale limit of the buffer. Nonetheless, fluctuations in the estimated effect sizes for health-environment associations are likely even when using buffer sizes within this range. To address this issue, we propose Bayesian model averaging (BMA) (Hoeting et al., 1999). BMA tackles model-related uncertainties in terms of the variations in effect sizes arising from different model settings, such as buffer sizes. Our approach averaged multiple confounder-adjusted Cox Proportional Hazard models, each using different buffer sizes for each exposure. Such model averaging yields more robust and reliable effect estimates, as demonstrated elsewhere (Fragoso et al., 2018; Rizopoulos et al., 2014; Volinsky et al., 1997; Wasserman, 2000).

We estimated the person-specific survival time from baseline to the year of death, censoring, or the end of follow-up, whichever occurred first. The models were adjusted at baseline for age (in years), gender (male, female), origin (Dutch, non-Dutch), yearly household income (in Euros), and the urbanicity level of the residential place ("rural areas," "little urbanization," "moderate urbanization," "high urbanization," and "very high urbanization"). Given that each exposure may operate on its specific geographical scale, Cox model averaging involves three steps outlined in Fig. 2.

First, we generated circular buffers centered upon a person's home address with a fixed increment (100 m) up to the upper buffer limit for each exposure. Using 100 m increments in the buffer sizes was driven primarily by computational considerations. Buffers with smaller increment sizes (e.g., 25 m or 50 m) would greatly increase the computational demand, given that our study was a large national cohort. We assigned the average exposure concentrations within each buffer to each person. Second, we averaged Cox regressions across all possible combinations of exposure-specific buffer sizes $(M_1, \ldots, M_k)$. Third, to receive averaged effect estimates for each exposure, model-specific estimates (i.e., hazard ratios [HRs]) weighted by the posterior probability $Pr(M_k|D)$ were computed as follows:

$$\sum_{k=1}^{k} exp(\beta_k) Pr(M_k|D)$$

β_k refers to the coefficient of the model $M_k, Pr(M_k|D)$ of M_k is given as:

$$Pr(M_k|D) = \frac{Pr(D|M_k)Pr(M_k)}{\sum_{l=1}^{k} Pr(D|M_l)Pr(M_l)}$$

where M_k is one of the potential underlying models for our data D with a prior probability $Pr(M_k)$, In our study, the prior probability was assumed by the uniform distribution prior, that is, $Pr(M_k) = 1/k$, and

$$Pr(D|M_k) = \int Pr(D|\beta_k, M_k) Pr(\beta_k|M_k) \mathrm{d}\beta_k$$

refers to the integrated likelihood of model M_k, $Pr(D|\beta_k, M_k)$ is the likelihood, and $Pr(\beta_k|M_k)$ is the prior probability distribution of β_k in the model M_k. The analyses were conducted in R, version 4.21 (R Core Team, 2022). The workflow, including the lacunarity analyses and the averaged Cox model, is available as an R package (https://github.com/TTgeoheath/BMA.geocontext).

2.4.3. Comparisons with traditionally selected buffer sizes

Informed by previous studies (James et al., 2016; Klompmaker et al., 2020; Plans et al., 2019; Roscoe et al., 2022), we compared the averaged effect estimates with those of a traditional Cox model using ad hoc buffer sizes of 100 m, 300 m, 1200 m, and 1500 m. The same buffer sizes were used for each exposure. We applied z-tests to assess whether the estimated coefficients for each exposure from the averaged and traditional Cox mode differed statistically (Paternoster et al., 1998).

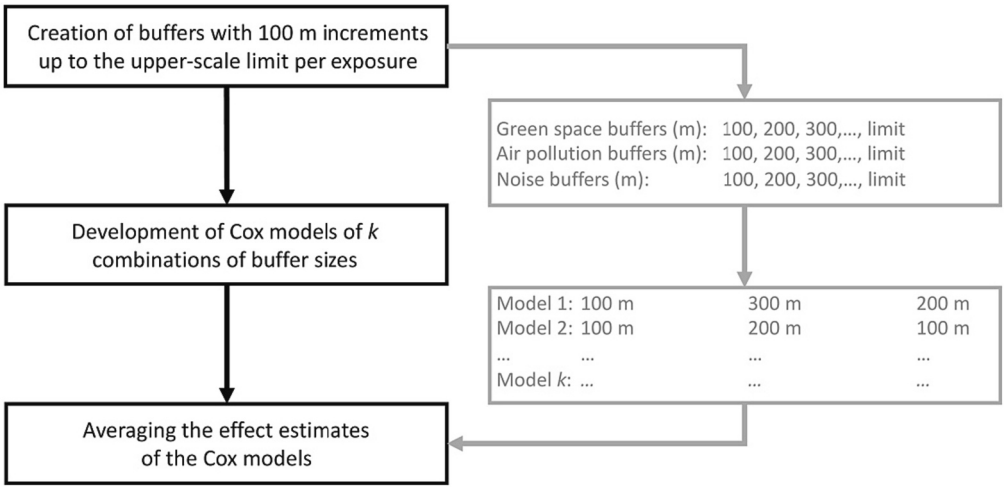

Fig. 2. Overview of the workflow to average across the Cox regression models.

3. Results

3.1. Descriptive statistics of the study population

Our study population included 7,666,540 people. Of the 845,229 people who died from all causes, 52 % were male, 97 % were Dutch, and 35 % earned <40,000 Euros annually. Most deaths (77 %) occurred in older adults. Further information is provided in Supplementary Table S1.

3.2. Exposure distribution and correlations

The environmental exposures (Supplementary Fig. S1) based on 100 m buffers were stratified for each covariate (Supplementary Table S1). The mean environmental exposures showed slight variance across gender and age. Dutch people living in areas with significantly lower $PM_{2.5}$ and noise concentrations also lived in areas with higher NDVI scores. With decreased urbanization levels and increased income, we observed an NDVI increase. Contrarily, $PM_{2.5}$ and noise increased with urbanization and reduced income.

Supplementary Table S2 shows Pearson correlations across the exposures. NDVI was moderately negatively associated with $PM_{2.5}$ (-0.34, $p < 0.05$) and noise (-0.33, $p < 0.05$). Noise and $PM_{2.5}$ were positively correlated (0.29, $p < 0.05$).

3.3. Determining the upper buffer size using lacunarity analyses

Fig. 3a illustrates the results of the lacunarity analyses for each exposure. The lacunarity curves indicated that, as box sizes increased, the spatial patterns of the exposures changed from heterogeneity to homogeneity. The maximum curvatures of the lacunarity curves (i.e., the upper-scale limits for exposure-specific buffer sizes) were 960 m for NDVI, 450 m for $PM_{2.5}$, and 910 m for noise. That pattern is also reflected in Fig. 3b, illustrating the corresponding changes in selected box sizes per exposure. There is pronounced variation with smaller box sizes, whereas variation sharply declines with larger ones (e.g., 60 m vs. 3000 m).

3.4. Environment-mortality associations

Based on the results of the lacunarity analyses, we fitted 324 Cox models using different buffer settings. Supplementary Fig. S2 summarizes the distribution of the HRs. For $PM_{2.5}$ and noise, the range of HRs was narrower and exhibited less fluctuation than for NDVI. These results suggest that buffer sizes within our upper scale limits produce more consistent estimates for $PM_{2.5}$ and noise than for NDVI.

Fig. 4 depicts the averaged HR and the HR for each ad hoc buffer size model. Averaged effect sizes tended to fall between the effect sizes obtained from the small and large buffers and were more circumscribed in their magnitudes than effect sizes for individual models. Notably, the effect estimates of models based on ad hoc buffers differed and were partially contradictory in the directions of the associations (e.g., the NDVI-mortality association was significant at larger buffer sizes but insignificant at smaller buffer sizes). See Supplementary Table S3 for the numeric results.

The averaged effect estimates showed that NDVI values were significantly negatively associated with all-cause mortality (HR: 0.917, 95 % CI: 0.886–0.948). However, the NDVI-mortality association was insignificant using 100 m and 300 m buffers. In contrast, when using 1200 m (HR: 0.858, 95 % CI: 0.829–0.889) and 1500 m buffers (HR: 0.844, 95 % CI: 0.815–0.873), we observed a negative NDVI-mortality association. As shown in Fig. 5, the averaged effect estimates differed statistically from the others ($p < 0.05$). The estimates from the 100 m and 300 m buffers differed significantly from the 1200 m and 1500 m buffers ($p < 0.05$).

The pooled effect estimates $PM_{2.5}$ were insignificantly associated with mortality (HR: 0.998, 95 % CI: 0.997–1.000). However, when fitting the model with the individual 100–1500 m buffers, we observed broadly comparable effect sizes, but the directions of the associations were counterintuitive. With increasing buffer sizes, the effect estimates attenuated slightly and more closely approached null. The $PM_{2.5}$ effect sizes across the models did not show significant differences at the 5 % level (Fig. 5).

Noise was significantly positively associated with mortality (HR: 1.003, 95 % CI: 1.002–1.003) in the averaged model, and the effect size was comparable with the models using 100 m and 300 m buffers. The corresponding z-tests were insignificant ($p > 0.05$). However, we observed considerable differences with larger buffers ($p < 0.05$). While the association with the 1200 m buffer was insignificant, the direction of association of the noise-mortality reversed the trend found with the 100 m and 300 m buffers.

4. Discussion

We assessed how geographic uncertainties in the exposure assessment at individuals' residential addresses translated into differing model estimates of the environment-mortality associations. Although numerous studies concluded that environment-health associations were not consistently found and scale effects were repeatedly recognized (Labib et al., 2020b; Zhang and Tan, 2019), little methodological

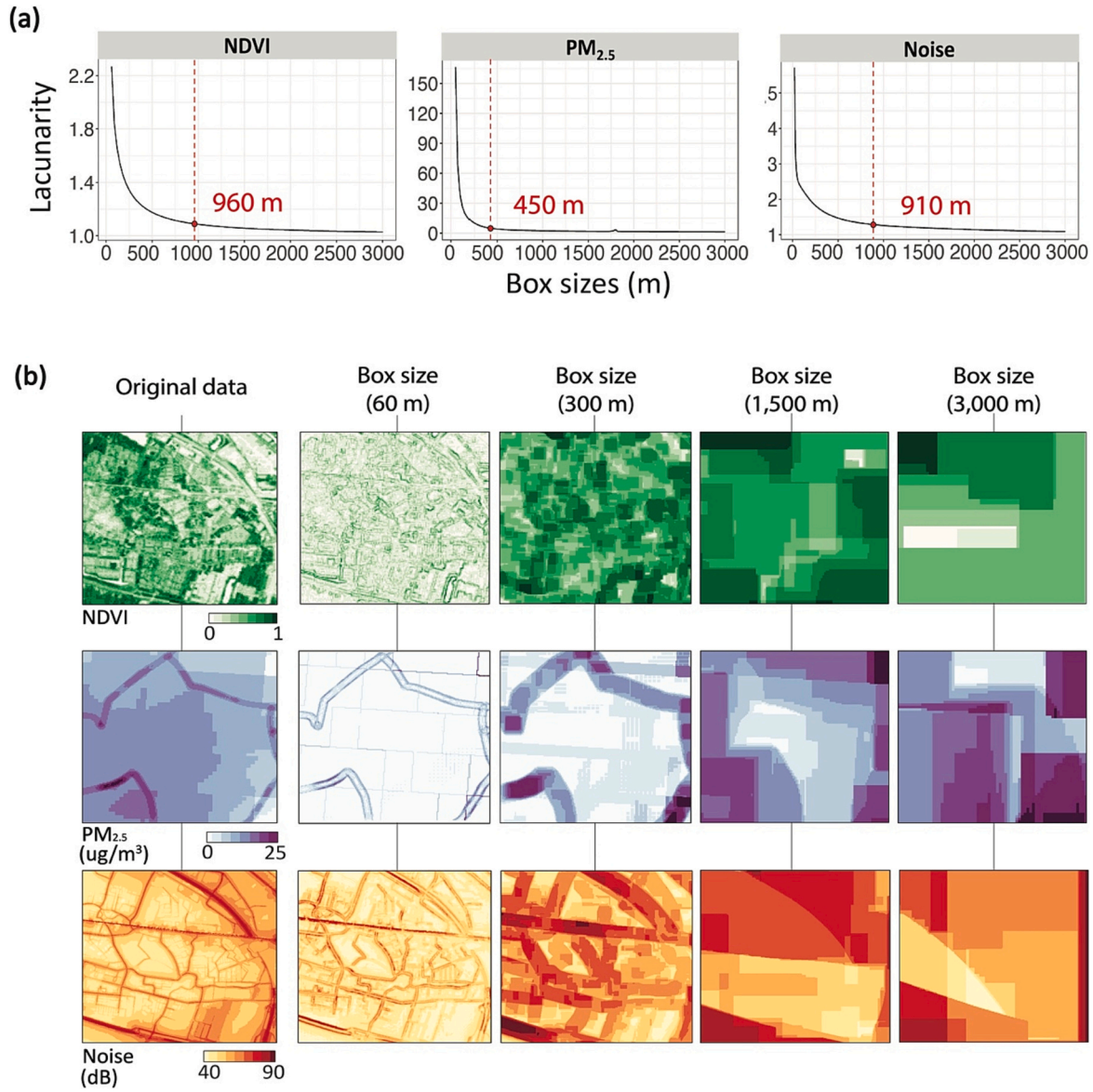

Fig. 3. Lacunarity-based assessments of the upper widths of the buffer analyses. (a) Exposure-specific lacunarity curves. The numbers in red refer to the upper limit of the buffer size. The x-axes were truncated for visualization purposes. (b) Comparisons of the box mass (i.e., range) values for NDVI, $PM_{2.5}$, and noise across different box sizes for a subset of the study area.

progress has been made in assessing individualized exposures at their home addresses (Lee et al., 2020; Parenteau and Sawada, 2011; Tuson et al., 2020). Our study responded to this need by proposing a statistical approach to handle contextual uncertainties in multi-exposure models.

4.1. Major findings

A central finding was that estimations of environment-mortality associations were sensitive to the selected buffer sizes. We found substantial variation in the magnitude of the estimated effect sizes and, for some exposures (i.e., green space, noise), even the direction varied between small (i.e., 100 m and 300 m buffers) and large buffers (i.e., 1200 m and 1500 m buffers). To mitigate such geographic uncertainties in exposure assessments, we integrated lacunarity analyses and Bayesian model averaging. Our results advanced on previous studies showing that each exposure had an upper scale limit. Green space exhibited the highest upper-scale value, followed by noise and $PM_{2.5}$.

The averaged multi-scale exposure effect sizes were more reliable, as the estimates fluctuated less across exposures. While greater exposure to green space was protectively associated with mortality, noise exposure increased mortality risk in the averaged model. These estimated effect sizes differed statistically significantly from models using typical ad hoc buffer specifications (i.e., 100–1500 m). The latter suggested a counterintuitive air pollution-mortality association, while the averaged model suggested no association. These findings raise awareness for future studies that reported associations could be scale sensitive. Our multi-scale approach could address such model-specific uncertainties.

4.2. Interpretation of the exposure-mortality associations

The observed averaged effect sizes were broadly consistent with prior studies. Similar to our findings, a meta-analysis reported an inverse association between green space and all-cause mortality (Rojas-Rueda et al., 2019). Compared to our effect size, the pooled HR was slightly lower with 0.96 (95 % CI: 0.94–0.97) for each increment of 0.1 NDVI in 500 m (or smaller) home-based buffers. Mechanisms underlying the health-supportive effects of green space may include support of increased physical activity and social interaction (Hartig et al., 2014), as

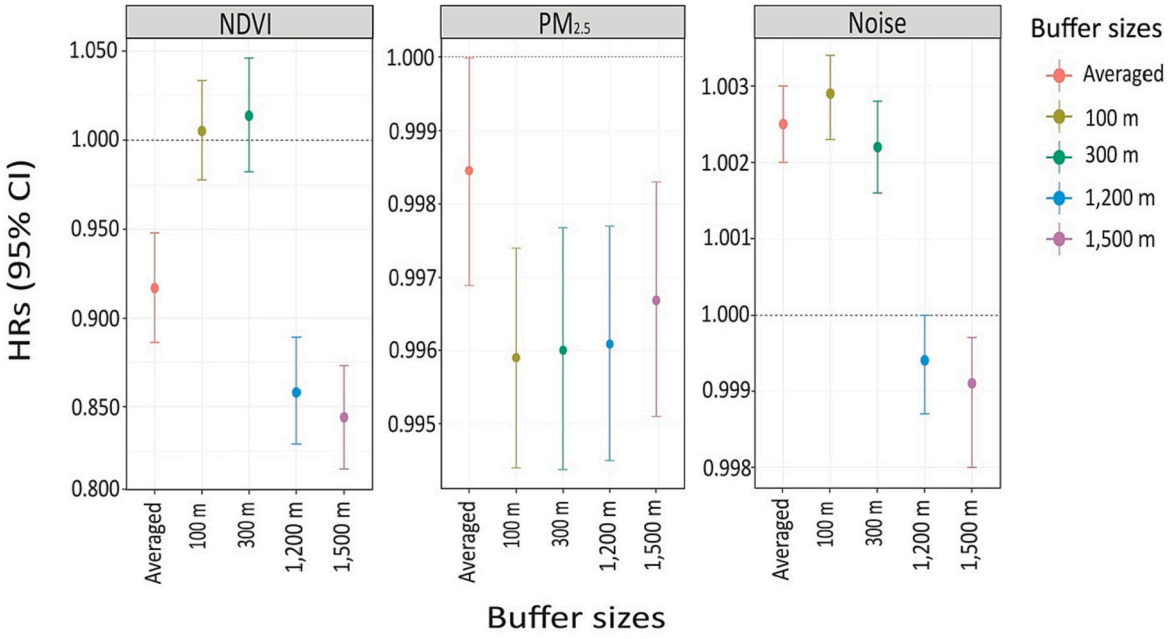

Fig. 4. Hazard ratios (HRs) and 95 % confidence intervals (CIs) for residential exposures on all-cause mortality using Cox model averaging and four ad hoc selected buffer sizes of 100 m, 300 m, 1200 m, and 1500 m. The models were covariate-adjusted for age, gender, origin, yearly household income, and urbanicity.

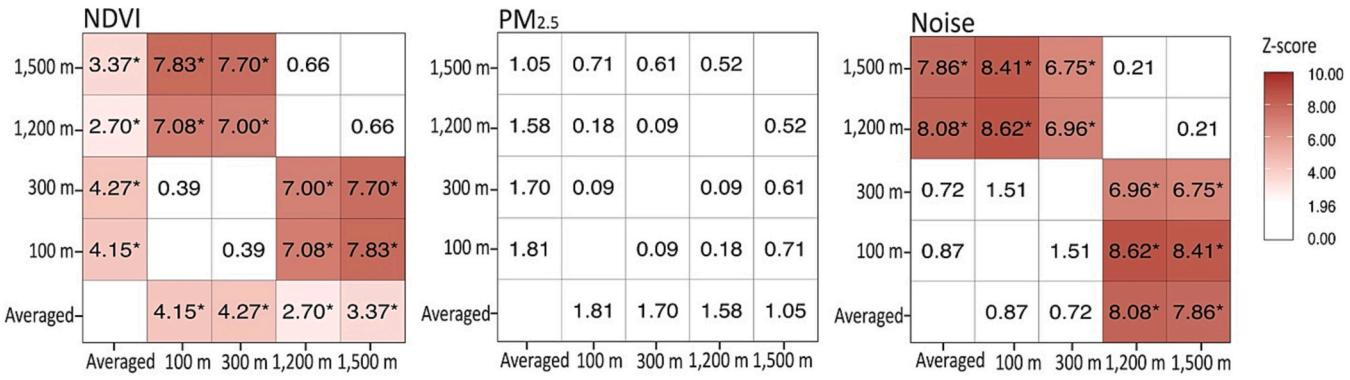

Fig. 5. Statistical assessment of the effect size differences based on *z*-tests. Insignificant *z*-values ($z < 1.96$, $p > 0.05$) are not colored. '*' indicates $p < 0.05$.

well as reduced noise and air pollution levels (Lindén et al., 2023).

Contrary to our results, a meta-analysis of 53 studies found that $PM_{2.5}$ was associated with all-cause mortality due to systemic oxidative stress and inflammatory vascular dysfunction (Vodonos et al., 2018). Our null association, however, aligned with another Dutch cohort study (Klompmaker et al., 2020). A possible explanation for the lack of an association could be methodological issues, such as our study population characteristics, the adjustment of confounders (Klompmaker et al., 2020; Vodonos et al., 2018), or the $PM_{2.5}$ maps predicted with different data sources and land-used regression models in other studies.

A meta-analysis of long-term exposure to traffic noise and how it affects all-cause mortality found an insignificant relationship; however, the supporting evidence was weak and of very low to low quality (Cai et al., 2021). Studies in the Netherlands also found no associations (Klompmaker et al., 2020, 2021); by contrast, we found a significant positive relationship. This finding could be because we analyzed noise data from multiple sources with heterogenous noise sources causing more substantial health effects than single-source noise data (e.g., traffic only). While the exact biological mechanisms are still being debated, proposed pathways include sleep disruption, bodily stress response, and effects on the cardiovascular system (Cai et al., 2021).

4.3. Methodological implications

Identifying upper-scale limits is critical to circumventing misclassification by over-aggregation of exposures (Jimenez et al., 2022). We measured lacunarity for each exposure surface separately to get a bias-variance trade-off (i.e., smaller buffers tend to have a smaller bias but face a larger variance). Although not a result that was reported consistently in previous research (Browning and Lee, 2017), smaller buffer sizes might result in weaker associations as they capture people's exposure more precisely (Annerstedt et al., 2012). Conversely, larger buffers may overestimate associations, as they increase the likelihood of including environmental settings where people are only marginally exposed (Reid et al., 2018). Buffer sizes obtained were larger for green space (960 m) and noise (910 m) than for air pollution (450 m). The only other lacunarity-based study we are aware of only assessed green space and reported an upper limit of just half of the value we obtained (Labib et al., 2020b). However, these differences may partly be attributed to differences in the study areas. While our area comprised the full urban-rural spectrum, the earlier lacunarity-based study was restricted to Greater Manchester (UK).

Our results suggested that estimated effect sizes are sensitive to the scale delineating the geographic context. Thus, we averaged the models

within the upper limits using Bayesian model averaging, which weights models according to their posterior probabilities (Volinsky et al., 1997). The modeling results suggested that our averaged effect estimates were more robust and stable than individual models using a single buffer size (Fang et al., 2016). Furthermore, model averaging assigns higher weights to better-fitting models, which is desirable when numerous plausible models exist (Hoeting et al., 1999). Our longitudinal results regarding the impact of geographic uncertainties on statistical estimates were partially consistent with cross-sectional evidence. For example, Su et al. (2019) found that measuring green space using larger buffers showed stronger associations with health outcomes. Some other studies also reported that aggregating exposures within various geographical contexts yielded differing results. Some differences were slight, while others might change the statistical inferences (Gonzales-Inca et al., 2022; Ho et al., 2022; Jimenez et al., 2022; Reid et al., 2018).

4.4. Limitations

Although rigorous in its design, our study was restricted to circular buffers (Zhang and Tan, 2019). We acknowledge that typically used street network buffers could also be employed for accessibility-related exposures (e.g., food outlets) (Athens et al., 2016). Some comparative studies reported moderately high exposure correlations across buffer shapes (Helbich et al., 2021b), while others did not (Frank et al., 2017; James et al., 2014). Therefore, expanding our multi-scale approach to multi-shape buffers is an area fruitful of future study that remains to be explored.

Our approach was computationally intensive. The use of very high-resolution exposure surfaces (e.g., orthophotos (Helbich et al., 2021b), WorldView2 imagery (Su et al., 2019)) is increasing. However, analysis of such imagery using raster algebra for lacunarity analysis quickly becomes computationally demanding, particularly for nationwide studies (Kazemiparkouhi et al., 2020). Consequently, when applied to large cohorts, vector-based buffer analyses may become computationally infeasible. However, this issue might be mitigated going forward due to continued increases in computing capacity, ongoing improvements in model parallelization, and increased access to cloud computing, allowing computational loads to be distributed across many nodes (Zhu et al., 2021). Moreover, the computational burden is also dependent on the number of exposures. Our R package is based on multi-core processing to reduce computational time.

Another limitation is that our data-driven method was developed for residence-based exposome studies. However, we believe a similar approach could be adopted for mobility-based exposure assessments where people's activity locations and travel paths are tracked (e.g., via the smartphone). Elsewhere, it has been shown that exposures outside the residential location shape human health (Lan et al., 2022). Thus, neglecting out-of-home exposures possibly leads to exposure misspecification (Helbich, 2018; Park and Kwan, 2017; Wei et al., 2023).

Our cohort was limited regarding the exposures it could access (Turner et al., 2017) and data for some confounders were unavailable in the administrative registers (Klompmaker et al., 2021). Thus, we cannot rule out residual confounding. For example, people's lifestyles (e.g., smoking, physical activity) remained unrecognized (Strak et al., 2017). We measured people's survival time in years rather than days which may have misclassified mortality events and underestimated the HRs (Paez and Diggle, 2009). Furthermore, our analyses assessed only time-invariant exposures which were not consistently available for a single year. This assumption may have affected our effect estimates, but a significant bias was unlikely since, for example, annual average air pollutant values are spatiotemporally relatively stable (de Hoogh et al., 2018). To safeguard against exposure changes due to changes of residence (Kazemiparkouhi et al., 2020), cohort participants were limited only to those who did not change residence. Finally, due to the study's observational nature, we caution against inferring causalities from our results.

4.5. Strengths

We extended earlier lacunarity-based studies by acknowledging that each exposure may operate on its respective spatial scale and that urban-rural exposure variations occur. The approach is based on evidence that exposures spatially co-vary and should be jointly incorporated to circumvent mutually confounding (Rugel and Brauer, 2020). Although our lacunarity analysis dealt with continuous exposure surfaces, it can also handle binary exposure surfaces by adjusting the box mass calculation (e.g., replacing the range with the sum for the box mass calculation for binary data) (Malhi and Román-Cuesta, 2008). Our results suggest that using box mass calculations in the context of binary data warrants further development.

This study was among the first to demonstrate that the selected buffer size could affect estimated associations (Browning and Lee, 2017) and proposed a data-driven method to mitigate scale effects when estimating environment-health associations. With a follow-up period of eight years and a 7.7-million-person cohort, another strength of the present study was its national longitudinal design. This large scale ensured our analytical results were robust and guaranteed we could detect weak environmental associations with mortality. Finally, to facilitate future studies, we made our multi-scale approach available to all researchers as an R package (the link is given above).

5. Conclusions

Due to a lack of consensus about suitable buffer sizes in external exposome studies, geographic uncertainty likely results in residence-based exposure assessments biasing environment-health associations. Our study found no universal optimal buffer size and that the geographic context definition may affect the estimated associations. While it appears challenging to remedy scale effects fully, we proposed a two-step statistical approach combining lacunarity analysis to identify the upper-scale buffer limits separately for different exposures and Bayesian model averaging to pool estimated effect sizes within the upper buffer range. Our results suggested that green space was inversely associated with mortality in a Dutch cohort, while noise exposure was a mortality risk factor. We found null associations for airborne fine particulate matter. Finally, our results demonstrated substantial fluctuations in environment-mortality associations based on typically used buffer sizes.

Despite our promising results, we do not know precisely how closely our approach mimics the 'true' causally relevant geographic context. Nevertheless, by incorporating model-based averages, our multi-scale approach appears to be more robust, and effect sizes fluctuated less than with buffer sizes that are selected on an ad-hoc basis. We caution against an uncritical application of geographic context definitions and advise carefully evaluating uncertainties because spurious environment-health associations are possible.

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CRediT authorship contribution statement

Tian Tian: Conceptualization, Methodology, Formal analysis, Visualization, Writing – original manuscript. Mei-Po Kwan: Funding acquisition, Writing – revision. Roel Vermeulen: Funding acquisition, Project administration. Marco Helbich: Conceptualization, Methodology, Writing – original manuscript, Supervision.

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Declaration of competing interest

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.

Data availability

The authors do not have permission to share data.

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