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Residential surrounding greenspace and age at menopause: A 20-year European study (ECRHS)

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ABSTRACT

Background: Menopause is associated with a number of adverse health effects and its timing has been reported to be influenced by several lifestyle factors. Whether greenspace exposure is associated with age at menopause has not yet been investigated.
Objective: To investigate whether residential surrounding greenspace is associated with age at menopause and thus reproductive aging.
Methods: This longitudinal study was based on the 20-year follow-up of 1955 aging women from a large, population-based European cohort (ECRHS). Residential surrounding greenspace was abstracted as the average of satellite-based Normalized Difference Vegetation Index (NDVI) across a circular buffer of 300 m around the residential addresses of each participant during the course of the study. We applied mixed effects Cox models with centre as random effect, menopause as the survival object, age as time indicator and residential surrounding

Abbreviations: BMI, body mass index; CI, Confidence Interval; ECRHS, European Community Respiratory Health Survey; FSH, Follicle Stimulating Hormone; HR, Hazard Ratio; HRT, hormone replacement therapy; IQR, interquartile range; IU/L, International Units per Litre; NDVI, Normalized Difference Vegetation Index; NIR, near-infrared light; PCOS, polycystic ovary syndrome; pmol/L, Picomol per Litre; RED, visible red light

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greenspace as time-varying predictor. All models were adjusted for smoking habit, body mass index, parity, age at menarche, ever-use of contraception and age at completed full-time education as socio-economic proxy.

Results: An increase of one interquartile range of residential surrounding greenspace was associated with a 13% lower risk of being menopausal (Hazard Ratio: 0.87, 95% Confidence Interval: 0.79–0.95). Correspondingly the predicted median age at menopause was 1.4 years older in the highest compared to the lowest NDVI quartile. Results remained stable after additional adjustment for air pollution and traffic related noise amongst others.

Conclusions: Living in greener neighbourhoods is associated with older age at menopause and might slow reproductive aging. These are novel findings with broad implications. Further studies are needed to see whether our findings can be replicated in different populations and to explore the potential mechanisms underlying this association.

1. Introduction

Age at menopause is of fundamental interest at an individual as well as at a population level. It is a marker of health and disease (Lawlor et al., 2004; Parazzini et al., 1992; Gold, 2011) and may be associated with undesirable alterations in body physiology and mental health (Triebner et al., 2017; Triebner et al., 2016; Levine et al., 2016; Martinez Perez et al., 2011; Blumel et al., 2000). Later age at natural menopause has been positively associated with overall survival, life expectancy (Ossewaarde et al., 2005) and reduced all-cause and cardiovascular mortality (Jacobsen et al., 2003; van der Schouw et al., 1996). The timing of menopause has been reported to be influenced by lifestyle factors such as smoking, obesity, physical activity, parity and oral contraceptive use (Dratva et al., 2009; Parazzini, 2007; Gold et al., 2001; Nagel et al., 2005). Evidence on the potential influence of environmental factors on the timing of menopause is still scarce, but exposure to greenspace has been associated with improvement of physical and mental health and wellbeing (Twohig-Bennett and Jones, 2018; Gascon et al., 2015; Kondo et al., 2018; Gidlow et al., 2016; Roe et al., 2013; Lee et al., 2011). Reducing stress, increasing physical activity, enhancing social cohesion and interaction and mitigating exposure to urban-related environmental hazards such as air pollution, noise and heat have been suggested to underlie the health benefits of greenspace (Markevych et al., 2017). Through mechanisms such as physical activity (Dratva et al., 2009) and stress reduction (Bromberger et al., 1997), exposure to greenspace could be associated with age at menopause, but evidence on such an association is non-existent. The aim of the present study was to investigate whether long-term exposure to residential surrounding greenspace is associated with the age at menopause in a large, population-based cohort of European women.

2. Methods

2.1. Study population

The European Community Respiratory Health Survey (ECRHS) is a population-based, international and prospective cohort study started in 1990 (Janson et al., 2001; Burney et al., 1994). The participants were followed-up, in 1999–2001 and in 2010–2013. The present analysis is based on women participating in all three surveys (over 20 years) from 18 study centres in nine countries (Huelva, Albacete, Barcelona, Galdakao and Oviedo in Spain, Grenoble and Paris in France, Erfurt in Germany, Antwerp South and Antwerp City in Belgium, Ipswich and Norwich in the United Kingdom, Gothenburg, Uppsala and Umea in Sweden, Tartu in Estonia, Reykjavik in Iceland as well as Bergen in Norway). For the current study, we excluded women with premature menopause before the age of 40 years (N = 157), thus we included a total of 1955 women. The examinations consisted of an interviewer-led questionnaire on anthropometrics, lifestyle factors and reproductive health as well as blood sampling for a subgroup of the population. Further details about the cohort have been published elsewhere (Burney et al., 1994; Committee, n.d.). Ethical approval was obtained from the appropriate ethics committees of each study centre and all participants provided informed written consent.

2.2. Outcome characterization

To define the outcome, age at menopause, we used the reported age at the last menstrual period. Women for whom hormone measurements were available (N = 1308) were classified as menopausal if 17β-estradiol was below 74 pmol/L and at the same time Follicle Stimulating Hormone (FSH) was above 80 IU/L. For study centres with available blood samples, we measured FSH using enzyme-linked immunosorbent assays (Demeditec Diagnostics, Germany) and 17β-estradiol was measured using liquid chromatography-tandem mass spectrometry at the Core Facility for Metabolomics (University of Bergen, 2017) (Triebner et al., 2014). The between day coefficient of variation, expressed as the standard deviation of the daily means of the quality control samples multiplied by 100, divided by their total mean, for the FSH analysis was 7.0% and accuracy was 106%. The between day coefficients of variation for the 17β-estradiol analysis ranged from 4.4% to 7.8% (high to low concentrations) and accuracy was 96%. Women lacking hormone measurements were classified as menopausal if they reported the removal of both ovaries (bilateral oophorectomy) or no menstrual periods (amenorrhea) for at least 12 months.

2.3. Greenspace exposure

We applied Normalized Difference Vegetation Index (NDVI) to characterize greenspace surrounding residential addresses of each participant during the course of the study (Tucker, 1979). NDVI is a satellite-derived index, calculated based on the knowledge that plants strongly absorb visible red light (RED) for use in photosynthesis while strongly reflecting near-infrared light (NIR) to prevent overheating. The equation for NDVI is based on spectral reflectance measurements acquired in corresponding light wavelengths: $NDVI = (NIR - RED) / (NIR + RED)$. Thus, NDVI values are unitless and range from -1 to $+1$, with higher numbers indicating more photosynthetically active land-cover (National Aeronautics and Space Administration, 2018). The NDVI was calculated from Landsat 4–5 Thematic Mapper satellite images for all included study centres from satellite images taken during most vegetation-rich months close in time to all three ECRHS surveys at a resolution of 30 m by 30 m. The specific images are listed in the online data supplement (Supplementary Table 1). Residential surrounding greenspace was defined as the mean value of NDVI in a circular 300 m buffer around each participant's residential address at each survey. Thus, all NDVI variables are time-specific even if the home address of a participant remained the same across study waves. For the statistical analysis, time-specific NDVI estimates were averaged over available surveys in line with Dadvand et al. (2017).

2.4. Statistical analyses

2.4.1. Main analyses

Given the multi-level nature of our data (individuals within study centres), we conducted survival analysis, applying a mixed effects Cox regression model with menopause as the survival object (event), age as the time indicator, residential surrounding greenspace as the time-varying fixed effect predictor, and centre as random effect. For non-menopausal women, the age at the third survey was included as censored observation. The model was adjusted for an a priori selected set of covariates: smoking habit at the third survey (lifelong non-smoker (reference); ex-smoker; current smoker), body mass index (BMI) at baseline, parity (continuous), age at menarche (continuous), ever-use of oral contraception (yes/no), and age at completed full-time education (< 17 years (reference); 17–20 years; > 20 years) as a proxy for socio-economic status. The exponential of the resulting regression coefficient, the Hazard Ratio (HR), represents an instantaneous risk of the event. Hazard ratios are reported for increments of one interquartile range and the predicted median age at menopause is reported for the overall population as well as for each quartile of NDVI. We evaluated linearity by plotting a locally weighted estimate smooth of the NDVI against the Martingale residuals of the null Cox proportional hazards model (Supplementary Fig. 2).

2.4.2. Sensitivity analyses

For our main analyses, we chose a circular 300 m buffer to abstract residential surrounding greenspace. To investigate the robustness of our findings to this choice, we abstracted alternative sets of residential surrounding greenspace, using buffers of 100 m and 500 m. We repeated the analyses using these exposure estimates. To explore consistency across geographic and cultural borders, we conducted a random effects meta-analysis of the centre-specific associations. To investigate potential differences due to urbanicity we repeated the analyses separately for areas that were classified as densely or thinly populated throughout the study period, according to the standard European classification of degree of urbanisation (European Commission, 2011). In order to ensure results were not driven by surgical menopause or gynaecological conditions we repeated the analyses, separately by excluding women who reported oophorectomy, removal of the womb (hysterectomy), persistent irregular menstruation, which is suggestive of polycystic ovary syndrome (PCOS) or had ever used hormone replacement therapy (HRT). Furthermore, to increase the understanding of the relationship between residential surrounding greenspace and age at menopause we ran models with additional adjustment for a proxy of air pollution (averaged nitrogen dioxide exposure estimated at the participants' residential address(es) in 2005, 2006, 2007 and 2010 (Sunyer et al., 2006; Castro-Giner et al., 2009), averaged particulate matter with a diameter of 2.5 µm or less, measured at each survey ($PM_{2.5}$), averaged particulate matter with a diameter between 2.5 and 10 µm, measured at each survey (PM_{10}), traffic noise (approximated by the self-reported frequency of cars and trucks passing in close proximity to the residential address), occupation (managers and professionals, non-manual labourer; manual labourer; unclassifiable) and physical activity (self-reported frequency and duration at the second survey, as baseline data was not available), respectively. Lastly, since residential surrounding greenspace is included as a time varying variable in the model it is possible that part of the exposure happens only after the event (e.g. participants moving to a greener area after menopause). To ensure this was not distorting associations, we repeated the analysis limited to participants who lived in areas with similar greenspace across the study period (NDVI ± 0.05, N = 763).

2.4.3. Further analyses

We carried out stratified analyses and tested for interactions as the effect of greenspace on age at menopause, e.g. through specific use, may depend in some way on smoking habits, as current smoking is a strong predictor of earlier menopause (Dratva et al., 2009), BMI categories (18–25 kg/m^2; < 18 kg/m^2; 25–30 kg/m^2; > 30 kg/m^2), as adipose tissue has endocrine activity (Kershaw and Flier, 2004), age at completed full-time education, since health benefits of exposure to greenspace might vary across the strata of education (Maas et al., 2006; McEachan et al., 2016) and an older age at completed full-time education is associated with an older age at menopause (Li et al., 2012; Gold et al., 2013); We further stratified the study population into Southern Europe (Albacete, Huelva, Galdakao, Oviedo and Barcelona), Central Europe (Grenoble, Paris, Erfurt, Antwerp South, Antwerp City, Ipswich and Norwich) and Northern Europe (Gothenburg, Tartu, Uppsala, Bergen, Umea and Reykjavik) to evaluate potential differences of the effect of greenspace between different parts of Europe. We tested as well for an exposure – response relationship using the Mann Kendall trend test. All analyses were performed using R (version 3.5.1) (R Development Core Team, 2018; Therneau, 2015; Therneau, 2018; Gordon and Lumley, 2017).

3. Results

The current study included 1955 women of whom 1224 became menopausal during the study period. Characteristics of all participants and participants stratified by menopausal status at the third survey are presented in Table 1. The median NDVI for the 300 m buffer was 0.263 (IQR: 0.116–0.366). The NDVI distribution across centres is presented as boxplot in the supplementary material (Supplementary Fig. 1).

Table 1
Characteristics of the study population by menopausal status, median [IQR] unless specified otherwise.

	All	Nonmenopausal	Menopausal	p-Value[a]
N	1955	731	1224	
Age (3rd survey), [years]	54.2 [48.1–59.8]	46.7 [44.0–49.8]	58.0 [54.4–62.1]	< 0.001
Age at menarche, [years]	13.0 [12.0–14.0]	13.0 [12.0–14.0]	13.0 [12.0–14.0]	0.317
Age at completed education, n (%)				< 0.001
< 17 years	400 (20.5)	101 (13.8)	299 (24.4)	
17–20 years	656 (33.6)	258 (35.3)	398 (32.5)	
> 20 years	899 (46.0)	372 (50.9)	527 (43.1)	
BMI (baseline), [kg/m^2]	22.5 [20.6–25.0]	22.0 [20.2–24.5]	22.8 [20.9–25.3]	< 0.001
Smoking habit (3rd survey), n (%)				0.002
Lifelong nonsmoker	944 (48.3)	354 (48.4)	590 (48.2)	
Ex-smoker	676 (34.6)	226 (30.9)	450 (36.8)	
Current smoker	335 (17.1)	151 (20.7)	184 (15.0)	
17β-Estradiol (3rd survey), [pmol/L]	23.0 [8.8–185.6]	218.4 [115.6–381.5]	11.9 [6.6–23.3]	< 0.001
FSH[b] (3rd survey), [IU/L]	87.5 [17.9–147.2]	14.3 [8.9–26.2]	131.0 [92.2–174.2]	< 0.001
Parity	2.0 [1.0–2.0]	2.0 [1.0–2.0]	2.0 [1.0–2.0]	0.947
Ever use of oral contraception, n (%)	1513 (77.4)	602 (82.4)	911 (74.4)	< 0.001

[a] Difference between menopausal and nonmenopausal women (Chi squared test for categorical variables and Mann-Whitney *U* test for continuous variables).
[b] Follicle Stimulating Hormone.

3.1. Main analyses

A one IQR increase in residential surrounding greenspace was associated with a 19% lower risk of being menopausal (Hazard Ratio (HR): 0.81, 95% CI: 0.73–0.88) in the crude model and a 13% lower risk of being menopausal (HR: 0.87, 95% CI: 0.79–0.95) in the adjusted model. The estimated median age at menopause was 50.6 years (95% Confidence Interval (CI): 50.3–50.9 years), adjusted for smoking habit at the third survey, BMI at baseline, parity, age at menarche, ever-use of oral contraception and age at completed full-time education. Stratified by quartiles of NDVI, the estimated ages at menopause were 50.3 years (95% CI: 49.9–50.7 years), 50.0 years (95% CI: 49.7–50.9 years), 51.0 years (95% CI: 50.5–51.4 years) and 51.7 years (95% CI: 51.0–52.0 years), for the first, second, third, and fourth quartile, respectively (see Fig. 1).

Women living in areas with little greenspace (1st NDVI quartile) became menopausal 1.4 years earlier compared with women living in highly green areas (4th NDVI quartile). The Mann-Kendall trend test did not show a statistically significant exposure – response relationship ($p_{trend} = 0.17$) for the median age at menopause. However, women exposed to NDVI below the median (quartiles 1 and 2) had a significantly lower age at menopause (50.0 years, 95% CI: 49.8–50.5 years) compared to women in quartiles 3 and 4, who were exposed to NDVI above the median (51.3 years, 95% CI: 50.7–51.7, $p_{T\text{-}Test} = 0.008$).

3.2. Sensitivity analyses

The combined estimate resulting from the random effects meta-analysis was consistent with that of the main analysis in terms of direction, strength, and statistical significance (HR: 0.88, 95%CI: 0.78–0.98; $I^2 = 48.6\%$, 95% CI: 6.6%–71.7%), despite the inverse association of the study centre Albacete and formally not significant trends for several other centres (Fig. 2). The sensitivity analysis, investigating consistently urban and rural areas separately, showed a lower HR for rural areas, although confidence intervals completely overlapped (Supplementary Fig. 3). Sensitivity analyses using the exposure estimates of 100 m and 500 m buffers, excluding gynaecological conditions and further adjustment of the analyses for air pollution, traffic related noise, occupation and physical activity, showed similar results compared with the main analysis (Supplementary Fig. 3).

3.3. Further analyses

Stratifying the main model by age at completed full-time education, BMI, geographic location and smoking habits showed an interaction between NDVI and age at completed full-time education ($p_{interaction} = 0.002$), as well as with geographic location ($p_{interaction} = 0.01$), but not with BMI or smoking habit (Supplementary Fig. 4). While there was no clear pattern for age at completed full-time education, we found that the effect of greenspace is strongest in Northern Europe, it becomes weaker in Central Europe and attenuates in Southern Europe.

4. Discussion

To our knowledge, this is the first study investigating associations between exposure to greenspace and age at menopause. It was based on prospectively collected data of a well-established representative cohort including 1955 women living across Europe who were followed over 20 years, together with time-varying measures of greenspace over the course of the study. We observed that higher residential surrounding greenspace was associated with an older age at menopause and these findings were robust to a number of sensitivity analyses.

Due to the lack of other studies it is not possible to compare our findings with those of others; however, our observed associations are plausible because of several potential underlying mechanisms: Stress in humans is reflected by a high level of cortisol (Kudielka and Kirschbaum, 2005), which is reduced by exposure to greenspace (Tyrväinen et al., 2014; Beil and Hanes, 2013; Van Den Berg and Custers, 2011; Ewert and Chang, 2018). Lower cortisol levels have in turn been associated with higher 17β-estradiol levels (Roney and Simmons, 2015), which makes it plausible that women with less stress, thus lower cortisol, might maintain higher 17β-estradiol levels and therefore transition later into menopause. It seems nevertheless likely that this process is multi-factorial, since both 17β-estradiol and cortisol play crucial roles in many physiological processes. Other possible influence may originate from 17β-estradiol increasing the cortisol-

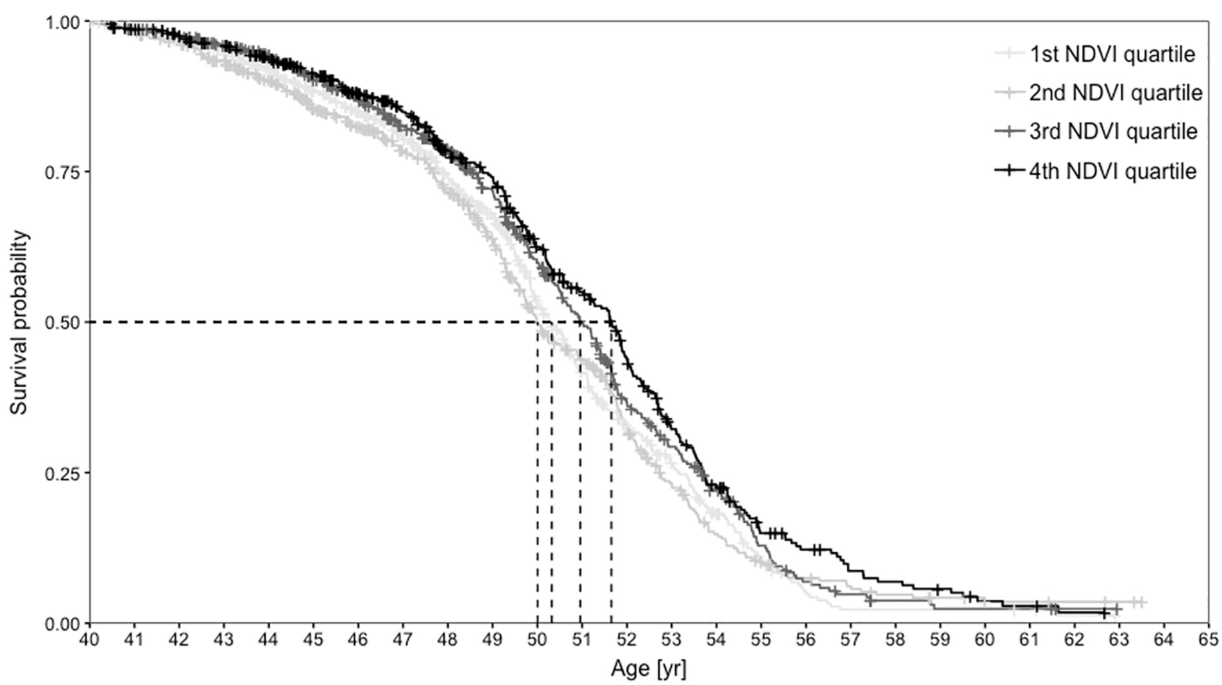

Fig. 1. Survival curves for each quartile of NDVI (dashed lines: median age at menopause for each group).

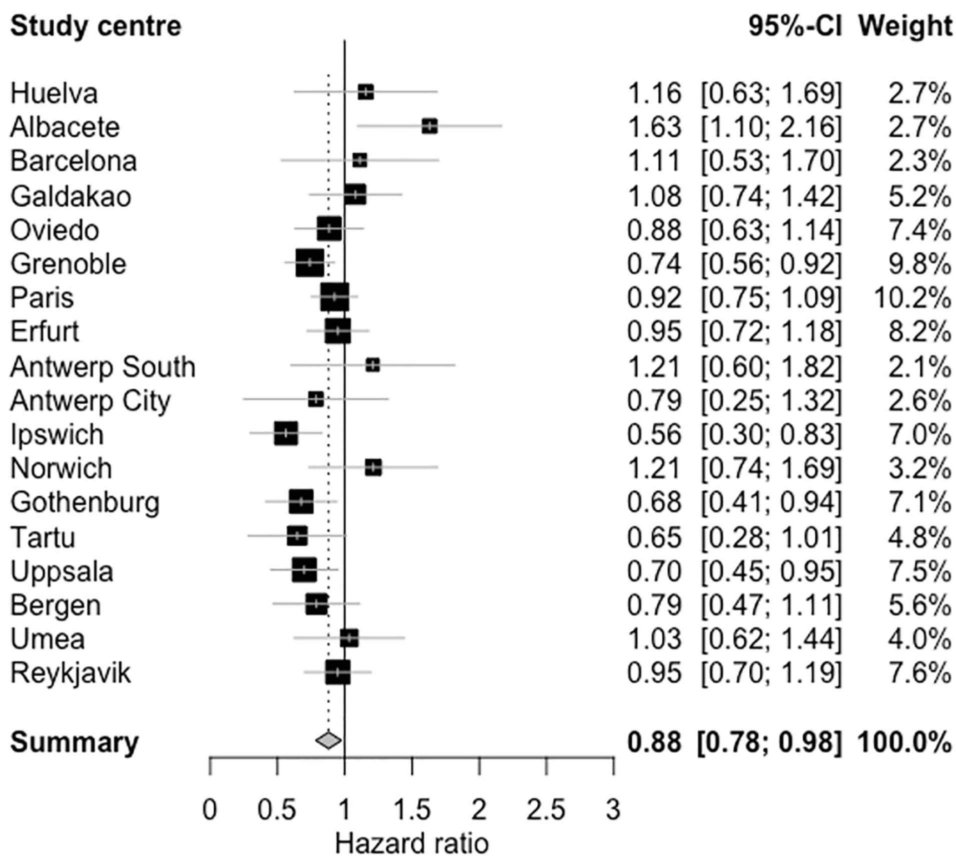

Fig. 2. Meta-analysis of study centres specific associations, ordered by ascending geographical latitude.

mediated negative feedback on adrenocorticotropic hormone secretion (Sharma et al., 2014). Additionally, exposure to greenspace is associated with reduced mental health conditions, such as depression (Sugiyama et al., 2008), which in turn is associated with younger age at menopause (Harlow et al., 1995). Unfortunately, we did not have appropriate data on stress to validate this assumption.

We found only minor changes in effect estimates after additional adjustment for several factors, which are generally being hypothesized to facilitate beneficial mechanisms of greenspace (urbanicity, air pollution, traffic noise). While these factors are associated with greenspace, there appears to be no association with age at menopause. The results were also not driven by changing address, surgical menopause, gynaecological conditions, or smoking, as there appears to be an association with age at menopause, but not with greenspace exposure. The existing evidence for an association of physical activity with age at menopause is rather weak (Dratva et al., 2009) and inconsistent, concerning the association with greenspace (Markevych et al., 2017; Lachowycz and Jones, 2011). It seems likely that different components of greenspace exposure promote different health benefits.

We observed a suggestion for potentially different associations for categories of age at completed full-time education and geographic location. Concerning education, associations are strongest for the low and high education levels at the same time, which hints towards differing mechanisms. Population groups with low socioeconomic status are hypothesized to have the worst health status and may therefore benefit more from their surrounding greenspace than groups with an intermediate socioeconomic status, hence better health despite a similar living environment. In comparison, the group with the highest socioeconomic status is able to afford living in areas with the highest exposure to greenspace and possesses over the highest mobility, which may explain the observed association. The stratified analyses showed further that the effect of greenspace becomes stronger from Southern to Northern Europe, which might be due to different land use and socioeconomic situations. We have however no evidence-supported explanation for the variation between proximate centres and the inverse association in the study centre Albacete. We suppose there are two main factors influencing the observed variation; one is the available amount of greenspace and the other is the type and/or quality of greenspace, which predefines use.

It is noteworthy that the median residential surrounding greenspace in the three southernmost centres (Huelva, Albacete and Barcelona) is extremely low ($NDVI_{Huelva} = 0.03$, ~~median~~ $NDVI_{Albacete} = 0.02$ $NDVI_{Barcelona} = 0.06$ vs. $NDVI_{All\ centres} = 0.26$), which might explain the observed associations. For the other two centres with an effect estimate above 1.10 (Antwerp South and Norwich) it is less clear, why effect estimates are as high, especially compared to neighbouring centres (Antwerp City and Ipswich). We hypothesize that subtle differences in location (use of greenspace) and microclimate as well as seasonal fluctuations (availability of greenspace) might be responsible for the differences. For instance, both Antwerp City and Ipswich are located in close proximity to a natural river delta, which might be used recreationally.

Our study faced some limitations. We did not have information on the use of greenspace or the time spent in the neighbourhood. Applying satellite-derived NDVI enabled us to characterize greenspace surrounding residential addresses of participants in different parts of Europe and different time points in a standardized and objective way; however, NDVI, is not able to separate different types of vegetation nor provide information on quality aspects of greenspace which may affect the use of greenspace and in consequence could have influenced our findings. Also investigations of health effects of greenspace should ideally be additionally adjusted for socio-economic status at a neighbourhood level to minimize the likelihood of residual confounding. Despite not having access to indicators of neighbourhood socioeconomic status, our findings were robust to adjustment for the age at completed full-time education, as well as to additional adjustment for occupation.

Moreover, we did not have appropriate stress data and to determine the menopausal status for women without available hormone measurements we relied on self-reported data on menstruation and oophorectomy, which could have introduced recall bias. However, existing literature shows that women report reproductive data with high reliability (Garamszegi et al., 1998; Taylor et al., 2004; Real et al., 2008; Real et al., 2007; Harlow et al., 2000; Brambilla et al., 1994). Since menopause can only be determined retrospectively, the well-established criteria (12 months without menstrual period) (Harlow et al., 2012) could have led to minor misclassifications e.g. excluding women who became recently menopausal or including women with amenorrhea due to other reasons.

5. Conclusions

We observed that living in greener neighbourhoods is associated with 1.4 years older median age at menopause (1st NDVI quartile vs. 4th NDVI quartile), even after adjusting for smoking and factors related to socioeconomic status. Residing in green spaces might reduce stress- and thereby promote an older age at menopause. These findings, if confirmed by future studies, could add to the evidence base for policymakers to implement interventions aimed at decelerating reproductive aging in our rapidly urbanizing world. In order to shed more light on this topic, further studies should focus on mechanisms of greenspace and their effect on likely underlying processes for menopause such as the ovarian follicle count.

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Declaration of competing interest

None.

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Appendix A. Supplementary data

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