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Residential green space and age at menarche in German and Australian adolescent girls: a longitudinal study

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Corresponding Author:	Iana Markevych, Ph.D. Jagiellonian University Krakow, Please Select POLAND
First Author:	Iana Markevych, Ph.D.
Order of Authors:	Iana Markevych, Ph.D.
	Thomas Astell-Burt
	Hicran Altug
	Kai Triebner
	Marie Standl
	Claudia Flexeder
	Joachim Heinrich
	Tamara Schikowski
	Sibylle Koletzko
	Gunda Herberth
	Carl-Peter Bauer
	Andrea von Berg
	Dietrich Berdel
	Xiaoqi Feng
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	limitations of our study, researchers should not be discouraged to further explore environmental risk factors of early menarche.
Suggested Reviewers:	Mat White mathew.white@univie.ac.at
	Payam Dadvand payam.dadvand@isglobal.org
	Matilda van den Bosch matilda.vandenbosch@isglobal.org

Prof. Antonia Calafat, Prof. Holger Koch
Editors-in-Chief
Environmental Research

September 13, 2021

Dear Editors,

For your consideration, please find enclosed the manuscript entitled „**Residential green space and age at menarche in German and Australian adolescent girls: a longitudinal study**", submitted as an original manuscript to *The International Journal of Hygiene and Environmental Health.*

In the current study, we explored whether exposure to residential green space was related to the age at menarche in 1,706 German and 1,474 Australian adolescent girls. Although the results of our analysis do not support the hypothesis that residing in places with more green space can influence timing of menarche, we observed that residents of urban areas were more likely to have earlier menarche, and this association was consistent across two countries and continents. To the best of our knowledge, we are the first study on green space and age at menarche, and the second study on green space and reproductive events, after Triebner et al. 2019 (https://www.sciencedirect.com/science/article/pii/S0160412019311298).

The manuscript has been prepared according to the Instructions for Authors of *The International Journal of Hygiene and Environmental Health*. The work in this manuscript has not been submitted elsewhere. All co-authors have approved the final text for publication.

Sincerely,

Dr. Iana Markevych on behalf of all co-authors

Residential green space and age at menarche in German and Australian adolescent girls: a longitudinal study

Iana Markevych [1,2,3], Thomas Astell-Burt [4,5,6,7], Hicran Altug [8], Kai Triebner [9,10], Marie Standl [3], Claudia Flexeder [3], Joachim Heinrich [1,11], Tamara Schikowski [8], Sibylle Koletzko [12,13], Gunda Herberth [14], Carl-Peter Bauer [15], Andrea von Berg [16], Dietrich Berdel [16], Xiaoqi Feng [17,4,5,6]

[1] Institute and Clinic for Occupational, Social and Environmental Medicine, University Hospital, LMU Munich, Munich, Germany

[2] Institute of Psychology, Jagiellonian University, Krakow, Poland

[3] Institute of Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany

[4] Population Wellbeing and Environment Research Lab (PowerLab), School of Public Health, Faculty of Arts, Social Sciences and Humanities, University of Wollongong, Wollongong, Australia

[5] National Institute of Environmental Health, Chinese Center for Disease Control and Prevention, Beijing, China

[6] Menzies Centre for Health Policy, University of Sydney, Sydney, Australia

[7] School of Public Health, Peking Union Medical College and The Chinese Academy of Medical Sciences, Beijing, China

[8] IUF, Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany

[9] Department of Clinical Science, University of Bergen, Bergen, Norway

[10] Core Facility for Metabolomics, University of Bergen, Bergen, Norway

[11] Allergy and Lung Health Unit, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Australia

[12] Department of Pediatrics, Dr. von Hauner Children's Hospital, University Hospital, LMU Munich, Munich, Germany

[13] Department of Pediatrics, Gastroenterology and Nutrition, School of Medicine Collegium Medicum University of Warmia and Mazury, Olsztyn, Poland

[14] Department of Environmental Immunology/Core Facility Studies, Helmholtz Centre for Environmental Research - UFZ, Leipzig, Germany

[15] Department of Pediatrics, Technical University of Munich, Munich, Germany

[16] Research Institute, Department of Pediatrics, Marien-Hospital Wesel, Wesel, Germany

[17] School of Population Health, Faculty of Medicine, UNSW, Sydney, Australia

Corresponding author:
Dr. Iana Markevych
Institute of Psychology, Jagiellonian University
Ingardena 6, 30-060 Krakow, Poland
iana.markevych@uj.edu.pl

Abstract

Background. A large multicentre European study reported later onset of menopause among women residing in greener areas. This influence on the timing of a reproductive event like menopause, raises the question whether similar associations can be observed with timing of menarche. We investigated whether exposure to residential green space was related to the age at menarche in German and Australian adolescent girls.

Methods. The analytic samples comprised of 1,706 German and 1,474 Australian adolescent girls. Percentage of green space was calculated in 1,000 m buffers around a residential address or its surrogate at the previous follow-up. Mixed effects Cox proportional hazard models were used to explore the associations. The survival object was the occurrence of menarche at the time of follow-up (15-year follow-up of the German cohorts and the study wave at 14-15 years in the Australian cohort) and number of years since baseline (10-year follow-up in the German cohort and the study wave at 10-11 years in the Australian cohort). Participants who did not reach menarche were included as censored observations.

Results. A greener residence was not associated with the age at menarche. Null findings were consistent in the general population and in analyses stratified by socioeconomic status or urbanicity in both countries. Urban residents were more likely to have earlier menarche, and this association was consistent across Germany and Australia.

Conclusion. The results of our analysis do not support the hypothesis that residing in places with more green space can influence timing of menarche. However, given the limitations of our study, researchers should not be discouraged to further explore environmental risk factors of early menarche.

Key words: greenspace; greenness; sexual maturation; puberty; children; epidemiology

Abbreviations

DAG	Directed Acyclic Graph
DEGURBA	Degree of Urbanisation
GINIplus	German Infant Study on the influence of Nutrition Intervention PLUS environmental and genetic influences on allergy development
LISA	Influence of life-style factors on the development of the immune system and allergies in East and West Germany
LSAC	The Longitudinal Study of Australian Children
MMU	Minimum mapping unit
PA	Physical activity
SA2	Statistical area 2
SES	Socioeconomic status

Introduction

Menarche – the first occurrence of menstruation – is the most memorable puberty event in a woman's life, and it marks sexual maturation and fertility onset (Jones & Lopez 2014). Most females reach menarche between 11 and 15 years (Jones & Lopez 2014), but slight differences are observed across geographic regions (InterLACE Study Team, 2019). Age at menarche predetermines female health and aging during the lifespan (Forman et al. 2013). For example, early menarche has been linked to an increased risk of breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer 2012), cardiovascular events (Lee et al. 2019), diabetes (Elks et al. 2013), and obesity (Prentice & Viner 2017).

Therefore, it is important to build evidence for public policy options that reduce the risk of early menarche at a population-level. However, most research so far has tended to focus on genetic and nutritional factors, as well as the general health status as predictors of sexual maturation (Yermachenko & Dvornyk 2014; Calthorpe et al. 2019; Juul et al. 2017; Webster et al. 2014).

Nevertheless, the currently increasing trend of urban greening (Haahland & van den Bosch 2015; Hartig & Kahn 2016), might be a favourable option that is easily implemented and comes along with numerous other beneficial health effects, such as relieving stress (Shuda et al. 2020), lowering adiposity risk (Luo et al. 2020), and supporting physical activity (PA) (Wilkie et al. 2019). All of the above factors are known to be related to the timing of reproductive events (Yermachenko & Dvornyk 2014; Calthorpe et al. 2019; Juul et al. 2017; Webster et al. 2014). It can thus be speculated that green space can affect age at menarche or menopause via reducing psychological stress, facilitating physical activity, and decreased obesity (Markevych et al. 2017).

Indeed, one study conducted in 18 study centres across nine European countries reported later onset of menopause among women residing in greener areas (Triebner et al. 2019). However, no study tested whether green space may also support risk reduction of early menarche. In this study, we investigated whether exposure to residential green space was related to the timing of menarche in adolescent girls residing in Germany and Australia.

Methods

Study populations

The current analysis is based on the data collected within the two multicentre German birth cohorts – German Infant Study on the influence of Nutrition Intervention PLUS environmental and genetic influences on allergy development (GINIplus) and Influence of life-style factors on the development of the immune system and allergies in East and West Germany (LISA) - and the nationwide Australian the Longitudinal Study of Australian Children (LSAC) cohort.

GINIplus and LISA are ongoing population-based multicentre birth cohorts that recruited healthy full term and normal birth weight neonates in selected maternal wards (Heinrich et al. 2017). GINIplus participants were enrolled in the cities of Munich and Wesel between 1995 and 1998 (n=5,991, including 3,270 girls). LISA participants were enrolled in the cities of Munich, Wesel, Leipzig, and Bad Honnef between 1997 and 1999 (n=3,094, including 1,510 girls). While LISA was a regular population-based cohort, GINIplus consisted of an arm that participated in an intervention trial with hypoallergenic feeding formulae and the observational arm. Mainly, data from the 10-year (2005 to 2009) and 15-year (2011 to 2014) follow-ups were extracted and used for the current analysis. Data from the cohorts were combined as their designs were harmonised. Eligible participants had to have available data on age at menarche, geocoded home addresses at age 10 (to assign green spaces variables), and selected confounders. The analytic German sample thus comprised 1,706 girls recruited in

Munich (n = 1,008), Wesel (n = 629), and Leipzig (n = 159). A detailed flowchart of the German participants is provided in Figure S1.

The LSAC kindergarten cohort is a population-based nationwide study recruited in 2004, aged 4 to 5 years, from postcodes distributed across Australia (Australian Institute of Family Studies, 2013). The Medicare database was used for recruitment, and a spatially clustered sampling was applied to ensure representative coverage across all states and territories (LSAC Technical Paper No. 1, 2005). A single child per family was selected. The response rate was 79.4%. Data were mainly extracted from the 2010 (10-11 year-olds) and 2014 (14-15 year-olds) waves of the cohort. To be eligible for our study, participants had to be born at full-term and with normal birth weight with available data on age at menarche, and confounders. The analytic Australian sample comprised 1,474 girls. A detailed flowchart of the Australian participants is provided in Figure S2.

GINIplus and LISA studies were approved by the ethical committees at the Bavarian Board of Physicians, the University of Leipzig, and the Board of Physicians of North Rhine-Westphalia. The Australian Government Department of Social Services and the ethical committee from the University of Wollongong (HREC 2019/015) approved the data analysis from the LSAC study. All families of the three cohorts provided written informed consent.

Age at menarche

In both German and Australian samples, occurrence of menarche and age at menarche was collected using questionnaires. In Germany, the data were self-reported at the 15-year follow-up. In Australia, these data were collected from parental reports when the girls were 10-15 years old.

Green space

Percentage of structured green space was calculated in 1000 m buffers around the residential address of each child at the previous follow-up, or the surrogate of a residential address.

In Germany, residential addresses were collected and geocoded at the 10-year follow-up. A combination of CORINE land cover and Urban Atlas land use data from 2012 was used to derive green space across Germany. The rationale for combining these two datasets was their coverage and resolution. Urban Atlas uses a minimum mapping unit (MMU) of 0.25 ha but it covers only metropolitan areas of Europe (i.e. with population >=100,000 residents). CORINE data cover Europe entirely but the MMU is 25 ha, which reduces its utility for assessing green space availability within urban areas where pocket parks and gardens are prevalent but not captured (Mitchell et al. 2011; Annerstedt van den Bosch et al. 2016). Thus, in the combined dataset, Urban Atlas covers urban areas/suburban areas while CORINE covers rural areas. Urban green spaces, sport and leisure facilities, forests, and shrubs were included in the definition of green space.

In Australia, the Statistical Area 2 (SA2) was the smallest geographical unit available to characterize residential address. SA2 broadly corresponds to Australian suburbs of approximately 10,000 residents on average (Australian Statistical Geography Standard 2011). The population-weighted centroid of each SA2 was used as a surrogate of a residential address at 10-11 years. Mesh Blocks v2011 classified by the Australian Bureau of Statistics as “parkland” were considered green space. Australian “parkland” definition is very similar to the German green space definition.

Since the green space variables were highly right skewed in both analytical samples, we classified them into country-specific tertiles. Green space as continuous variables were used as a sensitivity analysis.

Confounders and effect modifiers

Determinants of the age at menarche, beyond genetic factors (Day et al. 2017), have been scarcely investigated. However, socioeconomic status (SES), growing up without a father, maternal smoking during pregnancy, birth weight, childhood nutrition, prepubertal adiposity, prepubertal PA, and rural or urban residence have been found to be related to age at menarche (Yermachenko & Dvornyk 2014; Calthorpe et al. 2019; Juul et al. 2017; Webster et al. 2014). We constructed a directed acyclic graph (DAG), as implemented in dagitty.net (Textor et al. 2016), to select a minimum sufficient set of confounders (Greenland et al. 1999) (Figure 1). SES, growing up without a father, and urbanicity were selected as confounders. For better comparability we used as similar as possible definitions of the above confounders for the two samples.

Maternal education was used as a proxy for SES and defined as the highest number of school years a child's mother spent in education (<10 years vs =10 years vs >10 years). In Germany, residential urbanicity at 10 years follow-up was defined according to the standard EU Degree of Urbanisation (DEGURBA) (European Commission 2011) classification for the year 2014. Briefly, Degree of Urbanisation (DEGURBA) classifies all EU municipalities (LAU2) into three categories: (i) cities (densely populated areas), (ii) towns and suburbs (intermediate density areas), and (iii) rural areas (thinly populated areas). In Australia, the Australian Bureau of Statistics (ABS) classifies SA2s into 'Section of State' categories as follows: (i) "major urban" (all urban centres with a population of 100,000 or more); (ii) "other urban" (all urban centres with a population between 1,000 and 99,999); (iii) "bounded locality" (represents a combination of all localities); (iv) "rural balance" (represents the remainder of all states and territories). "Bounded localities" and "rural balance" categories were aggregated due to small numbers and in line with published guidance (Australian Statistical Geography Standard, 2016). In Germany, a proxy for growing up without a father was an affirmative parental response to the question "*Are you a single parent?*" at 10-year-follow-up questionnaire. In Australia, an affirmative parental response to the question *"Were study child's biological parents ever married?"* was used when the study child was aged 10-11 years old.

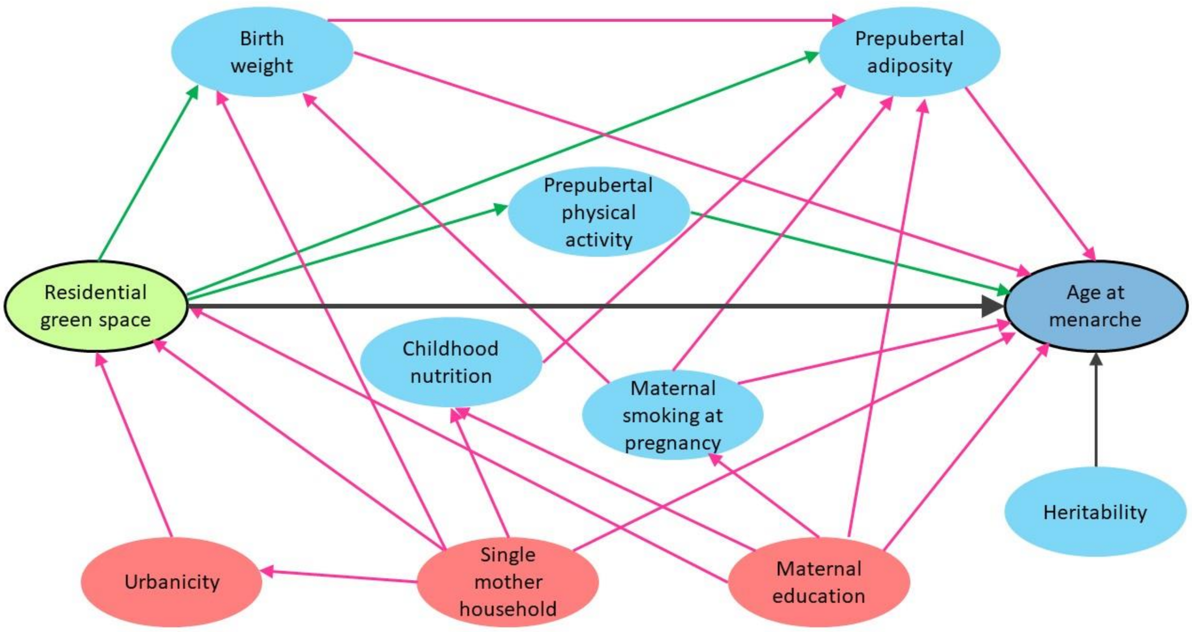

Figure 1. Directed Acyclic Graph (DAG) for the association between residential green space and age at menarche.

Identified minimal sufficient adjustment set included maternal education, single mother household, and urbanicity (red ovals). Maternal smoking during pregnancy is controlled for by adjustment for maternal education. Heritability is only related to the outcome and therefore is not a confounder. Birth weight, prepubertal physical activity, and prepubertal adiposity are identified as factors on the pathway between residential green space and age at menarche and therefore should not be adjusted for (green arrows mark mediation pathways).

Statistical analysis

The German and the Australian samples were analysed in parallel to compare findings across these countries. First, we applied univariate log-rank test to check the survival distribution over different groups, including green space tertiles and categories of each confounder. Both German and Australian data were hierarchically sampled. Therefore, we fitted mixed effects Cox proportional hazard models on both samples. For analysing the German data, a cluster variable was created as a combination of area (Munich, Wesel, Leipzig) and study (GINIplus intervention, GINIplus observation, LISA). In Australia, SA2 served as a cluster variable. Survival object was the occurrence of menarche (yes, no) at the time of follow-up (15-year follow-up in German data and 14-15 years study wave in Australian data) and number of years since baseline (i.e., 10-year follow-up in German data and 10-11 years study wave in Australian data). Participants who did not reach menarche within the study time were included as censored observations. The proportional hazards assumption was checked based on the scaled Schoenfeld residuals. The models were adjusted for the aforementioned DAG-defined confounders. In addition, models on Australian data were also adjusted for age at baseline.

As a sensitivity analysis on the German sample, percentage of structured green space within 500 m buffers around a residential address (in tertiles and as a continuous variable) was used as exposure variable. As we only had a surrogate for a residential address for the Australian sample, this analysis was not performed on Australian data.

To check potential effect modification, analyses across both samples were stratified by maternal education (> 10 years, = 10 years, < 10 years) and urbanicity (in Germany: urban, suburban, rural; in Australia: major urban, other urban, rural). In addition, analyses conducted on the German sample were stratified by study centre (Munich, Wesel, Leipzig).

The German data were analysed using packages *survival* and *survminer* as implemented in R v.4.0.2 (Vienna, Austria). The Australian data were analysed using the *stcox* command with robust standard errors to allow for spatial clustering (Williams 2000) in Stata v14 (College Station, TX, USA).

Results

All but 4.3% German adolescent girls reported menarche by the age of 15 years (Table 1). In the Australian sample, this value was 5.1% by the age of 14-15 years.

The log-rank test univariate descriptive analyses provided little evidence of a likely association between time to menarche and green space in either of the samples (Table 1). No differences in age at menarche were observed by maternal education level. However, German and Australian adolescent girls residing outside of urban areas were less likely to have experienced menarche than their urban peers. Single parent households were also related to earlier age at menarche in German girls, while in Australian girls, this association was in the other direction and borderline significant only.

Results from the Cox proportional hazards models were entirely in line with the univariate findings (Table 2). Residing in places with larger amounts of green spaces was not related to the timing of menarche in German or Australian girls. This null finding was consistent irrespective of how green space data were treated: as tertiles (Model 1 in table 2), or as continuous variable (Model 2). Rural residence was associated with later menarche in both samples across two models. Single parent households were linked to earlier menarche in German girls and not related to age at menarche in Australian girls. Results did not materially change when a 500 m buffer was considered as exposure (Table S1).

Urbanicity or maternal education did not modify the association between green space and age at menarche (Figure 2). Association between green space and age at menarche remained null in all study areas in Germany (Figure S3).

Table 1. Descriptive characteristics of the German and Australian samples of adolescent girls

German adolescent girls							**Australian adolescent girls**
Menarche		N	%	N	%		Menarche
No		73	4.3	75	5.1		No
Yes		1,633	95.7	1,399	94.9		Yes
Age at menarche, years		N	%	N	%		Age at menarche, years
10		42	2.6	30	2.0		10
11		184	11.3	27	1.8		11
12		503	30.8	384	26.1		12
13		604	37.0	376	25.5		13
14		283	17.3	375	25.4		14
15		17	1.0	207	14.0		15
Log-rank test for equality of survivor function							
Green space	N (%)	Events observed	Events expected	N (%)	Events observed	Events expect ed	Green space
Tertile 1 [0 - 7.19 %]	569 (33.4)	538	563	492 (33.4)	451	472	Tertile 1 [0 - 5.7 %]
Tertile 2 (7.19 - 16.9 %]	568 (33.3)	549	526	492 (33.4)	464	455	Tertile 2 (5.8 - 12.6 %]
Tertile 3 (16.9 - 70.3 %]	569 (33.4)	546	544	490 (33.2)	454	442	Tertile 3 (12.7 - 100.0 %]
p-value			0.1389			0.2753	p-value
Maternal education	N (%)	Events observed	Events expected	N (%)	Events observed	Events expect ed	Maternal education
< 10 years	156 (9.1)	148	147	61 (4.1)	54	47	< 10 years
= 10 years	676 (39.6)	646	653	281 (19.1)	261	264	= 10 years
> 10 years	874 (51.2)	842	833	1,118 (75.9)	1040	1041	> 10 years
p-value			0.7738			0.5117	p-value

Single parent household	N (%)	Events observed	Events expected	N (%)	Events observed	Events expected	Single parent household
No	1525 (89.4)	1,456	1,476	1,107 (75.1)	1029	1043	No
Yes	181 (10.6)	177	157	79 (5.4)	69	77	Yes
p-value			**0.0190**			0.0767	p-value

Urbanicity of the residence	N (%)	Events observed	Events expected	N (%)	Events observed	Events expected	Urbanicity of the residence
Urban	625 (36.6)	606	580	941 (63.8)	882	841	Major urban
Suburban	808 (47.4)	773	773	310 (21.0)	280	304	Other urban
Rural	273 (16.0)	254	280	223 (15.1)	207	224	Rural
p-value			**0.0324**			**0.0091**	p-value

				N (%)	Events observed	Events expected	Age at baseline
				1,002 (68.0)	911	911	10
				472 (32.0)	458	458	11
						0.9836	p-value

Table 2. Associations between residential green space and age at menarche in German and Australian adolescent girls, as measured by multi-level[1] Cox proportional hazards models

German adolescent girls	HR (95% CI)	HR (95% CI)	Australian adolescent girls
Model 1			**Model 1**
Green space in tertiles (ref.: Tertile 1 [0 - 7.19 %])	1	1	Green space in tertiles (ref.: Tertile 1 [0 - 5.7 %])
Tertile 2 (7.19 - 16.9 %]	1.087 (0.963; 1.228)	1.014 (0.918; 1.121)	Tertile 2 (5.8 - 12.6 %]
Tertile 3 (16.9 - 70.3 %]	1.034 (0.915; 1.168)	1.040 (0.943; 1.146)	Tertile 3 (12.7 - 100.0 %]
Maternal education (ref.: < 10 years)	1	1	Maternal education (ref.: < 10 years)
= 10 years	1.006 (0.841; 1.204)	0.890 (0.689; 1.150)	= 10 years
> 10 years	1.040 (0.873; 1.240)	0.884 (0.697; 1.120)	> 10 years
Single parent household (ref.: No)	1	1	Single parent household (ref.: No)
Yes	**1.178 (1.006; 1.380)**	0.912 (0.744; 1.118)	Yes
Urbanicity (ref.: Urban)	1	1	Urbanicity (ref.: Major urban)
Suburban	0.941 (0.844; 1.048)	**0.874 (0.786; 0.972)**	Other urban
Rural	**0.854 (0.734; 0.994)**	**0.889 (0.796; 0.993)**	Rural
		0.998 (0.919; 1.083)	Age at baseline, years
Model 2			**Model 2**
Green space continuous (per 10 % increase)	1.019 (0.981; 1.059)	1.009 (0.979; 1.039)	Green space continuous (per 10 % increase)
Maternal education (ref.: < 10 years)	1	1	Maternal education (ref.: < 10 years)
= 10 years	1.000 (0.836; 1.197)	0.895 (0.693; 1.016)	= 10 years
> 10 years	1.032 (0.865; 1.231)	0.887 (0.700; 1.124)	> 10 years
Single parent household (ref.: No)	1	1	Single parent household (ref.: No)
Yes	**1.186 (1.013; 1.389)**	0.912 (0.744; 1.118)	Yes
Urbanicity (ref.: Urban)	1	1	Urbanicity (ref.: Major urban)
Suburban	0.937 (0.842; 1.043)	**0.872 (0.786; 0.967)**	Other urban
Rural	**0.848 (0.730; 0.984)**	**0.882 (0.796; 0.978)**	Rural
		0.998 (0.920; 1.083)	Age at baseline, years

Abbreviations: CI – confidence interval; HR - Hazards Ratio.

[1] In German data, a cluster variable was created as a combination of an area (Munich, Wesel, Leipzig) and a study (GINIplus intervention, GINIplus observation, LISA). In Australia, SA2 served as a cluster variable.

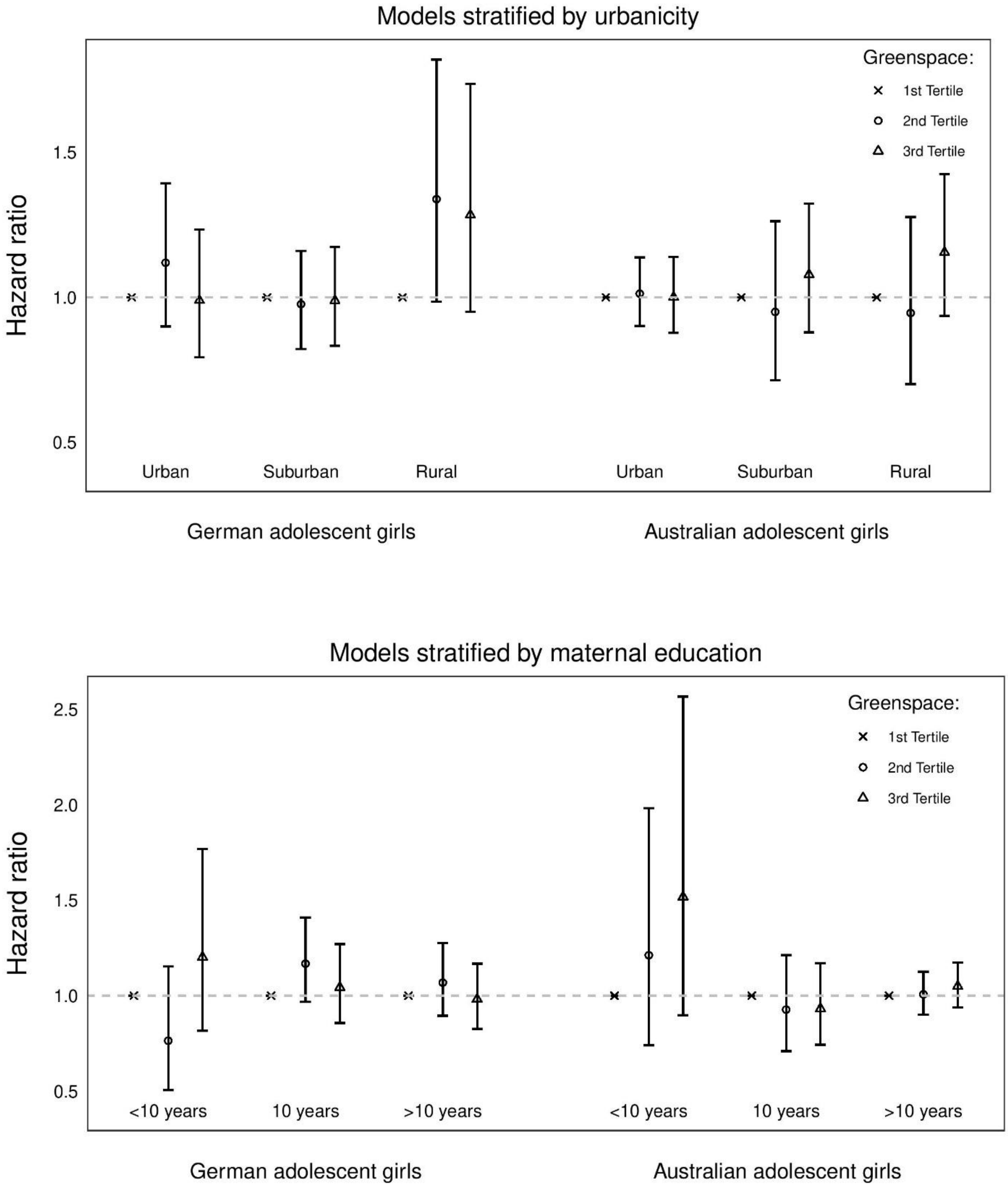

Figure 2. Models stratified by urbanicity (upper panel) and education (lower panel). Results are from multilevel Cox proportional hazards models adjusted for single parent household, age at baseline (Australian data), maternal education (in stratified by urbanicity models only), and urbanicity (in stratified by maternal education models). In German data, a cluster variable was created as a combination of an area (Munich, Wesel, Leipzig) and a study (GINIplus intervention, GINIplus observation, LISA). In Australia, SA2 served as a cluster variable.

Discussion

The results of our analysis in two samples of adolescent girls from Germany and Australia do not support the hypothesis that residing in places with more green space can influence timing of menarche. This null finding was consistent when tested in the general population and when subjected to stratified analyses by SES and urbanicity.

To the best of our knowledge, our study is the first to explore potential association between green space and menarche timing. Only one study was published on timing of reproductive events (menopause) and green space, and it has revealed the protective effect (i.e. later menarche) of green space (Triebner et al. 2019). There are several foundations to believe menarche can be affected by greener residence: green space has stress-reduction properties, as has been shown by many experimental (Ohly et al. 2016) and epidemiological studies (Shuda et al. 2020). In turn, early-life and preadolescence stress triggers menarche (Yermachenko & Dvornyk 2014). In addition, greener living environment can motivate people be more physically active (Markevych et al. 2017).

We were able to confirm the already known association of earlier puberty onset in urban areas (Hesketh et al. 2002; Ajong etal. 2020; Devi et al. 2018; Said-Mohamed et al. 2018). In low-income countries, the association is postulated to be explained by a better nutritional status of girls living in urban areas that facilitates the process of maturation (Hesketh et al. 2002; Ajong etal. 2020; Devi et al. 2018; Said-Mohamed et al. 2018). The same mechanism is assumed to generally have shifted age at menarche over the last century (InterLACE Study Team 2019). We speculate that in our two high-income countries, a different mechanism is more likely to serve as an explanation, for instance, higher levels of air pollution in cities compared to less urbanized areas. There is some research suggesting air pollution can decrease age at menarche (e.g. Jung et al. 2018), although this association is scarcely researched.

Our findings should be interpreted considering the limitations of our data. The increments of one year for age at menarche possibly blurred the observed picture and availability of these data with monthly increments instead could have helped us to detected potentially small underlying effects. Nevertheless, bearing in mind that at least the Australian data were parent-reported, asking for age at menarche in years instead of months could have prevented a substantial amount of recall bias. To a lesser extent, the same holds true for the self-reported German data. The data in both samples were collected prospectively. However, residential history was not exhaustive to use lifelong exposure to green space instead of exposure from preadolescence. While we had home addresses for German girls, for Australian girls, population-weighted centroids of SA2 areas had to be employed as address proxies. All of the above could have introduced measurement error and distorted the precision of the effect estimates.

The publicly available green space data included structured green spaces but excluded vegetation outside of them, like street trees, small private gardens, or flower beds, which are also relevant at least considering the stress alleviation properties of green space. Even more importantly, we did not have information on the amount of time girls were spending in green spaces. Less crucial but still not to be neglected was, that neither our SES proxy, nor proxies for growing up without a father were ideal. The former did not include household income and professional status of parents and had to rely only on maternal education. The latter could not be captured in any of the datasets: a father can still play a meaningful role without being married (Australian data) or living in the same household (German data). In 5% of cases in the German sample, fathers were respondents. This means that small fraction of the households were single fathers, not mothers.

Apart from those limitations, our study has also several strengths. This is the first study, which tested whether living in green areas impacts the onset of menarche. An improved understanding of modifiable factors for the onset of early menarche has far reaching implications from a public health perspective. Furthermore, we conducted the analyses in two different countries and continents with substantial differences in green space quality, presumably the usage of green space, and health characteristics of underlying populations, but we found consistent results. We consider the prospectively collected data of relatively large study populations as a further strength. We cautiously selected confounders and made our two parallel analyses as much in line with each other as it was possible.

To conclude, although our analyses did not confirm the association between green space and age at menarche, researchers are not discouraged to further explore potentially modifiable environmental risk factors of early menarche, because of the uncertain understanding of modifiable factors for menarche onset and the limitations of our study.

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Author contributions

This study was conceptualised and planned by IM, TAB, MS, XF, JH and CF during meetings held at the University of Wollongong and Ludwig Maximillian University Munich in 2019. IM pre-processed German geographical data, assigned GIS variables to GINIplus/LISA Munich and Leipzig participants, and visualised the results. HA assigned GIS variables to GINIplus/LISA Wesel participants. TAB and XF pre-processed Australian geographical data and assigned GIS variables to all LSAC participants. IM conducted the statistical analyses of GINIplus and LISA cohorts. TAB conducted the statistical analyses of the LSAC. KT assisted with statistical analysis and visualised the results. Drafting of the manuscript was led by IM and TAB, with substantial intellectual contributions and critical revisions from MS, JH, CF, KT and XF. JH, MS, TS, SK, GH, CPB, AvB and DB contributed to the funds acquisition and data collection of the GINIplus and LISA studies. All authors were involved in the result interpretation and text revision. All authors approved the final version of the manuscript for publication.

Conflict of interests

The authors declare that they have no conflict of interest.

References

1270.0.55.004 - Australian Statistical Geography Standard (ASGS): Volume 4 - Significant Urban Areas, Urban Centres and Localities, Section of State, July 2016 [Article online]. Available from https://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/1270.0.55.004~July%202016~Main%20Features~Design%20of%20SOS%20and%20SOSR~12.

Ajong AB, Tankala NN, Yakum MN, Azenoi IS, Kenfack B. Knowledge of peri-menarcheal changes and a comparative analysis of the age at menarche among young adolescent school girls in urban and rural Cameroon. BMC Public Health. 2020;20(1):1661.

Annerstedt van den Bosch M, Mudu P, Uscila V, Barrdahl M, Kulinkina A, Staatsen B, Swart W, Kruize H, Zurlyte I, Egorov AI. Development of an urban green space indicator and the public health rationale. Scand J Public Health 2016;44(2):159-67.

Australian Institute of Family Studies: The Longitudinal Study of Australian Children: An Australian Government initiative. Data User Guide. Canberra, Australian Government, 2013.

Australian Statistical Geography Standard (ASGS): Volume 1 - Main Structure and Greater Capital City Statistical Areas [article online], 2011. Available from http://www.abs.gov.au/ausstats/abs@.nsf/mf/1270.0.55.001. Accessed Date Accessed: 01/02/2017.\

Calthorpe L, Brage S, Ong KK. Systematic review and meta-analysis of the association between childhood physical activity and age at menarche. Acta Paediatr. 2019;108(6):1008-1015.

Collaborative Group on Hormonal Factors in Breast Cancer. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. Lancet Oncol;13(11):1141-51.

Day FR, Thompson DJ, Helgason H, Chasman DI, Finucane H, Sulem P, Ruth KS, Whalen S, Sarkar AK, Albrecht E, Altmaier E, Amini M, Barbieri CM, Boutin T, Campbell A, Demerath E, Giri A, He C, Hottenga JJ, Karlsson R, Kolcic I, Loh PR, Lunetta KL, Mangino M, Marco B, McMahon G, Medland SE, Nolte IM, Noordam R, Nutile T, Paternoster L, Perjakova N, Porcu E, Rose LM, Schraut KE, Segrè AV, Smith AV, Stolk L, Teumer A, Andrulis IL, Bandinelli S, Beckmann MW, Benitez J, Bergmann S, Bochud M, Boerwinkle E, Bojesen SE, Bolla MK, Brand JS, Brauch H, Brenner H, Broer L, Brüning T, Buring JE, Campbell H, Catamo E, Chanock S, Chenevix-Trench G, Corre T, Couch FJ, Cousminer DL, Cox A, Crisponi L, Czene K, Davey Smith G, de Geus EJCN, de Mutsert R, De Vivo I, Dennis J, Devilee P, Dos-Santos-Silva I, Dunning AM, Eriksson JG, Fasching PA, Fernández-Rhodes L, Ferrucci L, Flesch-Janys D, Franke L, Gabrielson M, Gandin I, Giles GG, Grallert H, Gudbjartsson DF, Guénel P, Hall P, Hallberg E, Hamann U, Harris TB, Hartman CA, Heiss G, Hooning MJ, Hopper JL, Hu F, Hunter DJ, Ikram MA, Im HK, Järvelin MR, Joshi PK, Karasik D, Kellis M, Kutalik Z, LaChance G, Lambrechts D, Langenberg C, Launer LJ, Laven JSE, Lenarduzzi S, Li J, Lind PA, Lindstrom S, Liu Y, Luan J, Mägi R, Mannermaa A, Mbarek H, McCarthy MI, Meisinger C, Meitinger T, Menni C, Metspalu A, Michailidou K, Milani L, Milne RL, Montgomery GW, Mulligan AM, Nalls MA, Navarro P, Nevanlinna H, Nyholt DR, Oldehinkel AJ, O'Mara TA, Padmanabhan S, Palotie A, Pedersen N, Peters A, Peto J, Pharoah PDP, Pouta A, Radice P, Rahman I, Ring SM, Robino A, Rosendaal FR, Rudan I, Rueedi R, Ruggiero D, Sala CF, Schmidt MK, Scott RA, Shah M, Sorice R, Southey MC, Sovio U, Stampfer M, Steri M, Strauch K, Tanaka T, Tikkanen E, Timpson NJ, Traglia M, Truong T, Tyrer JP, Uitterlinden AG, Edwards DRV, Vitart V, Völker U, Vollenweider P, Wang Q, Widen E, van Dijk KW, Willemsen

G, Winqvist R, Wolffenbuttel BHR, Zhao JH, Zoledziewska M, Zygmunt M, Alizadeh BZ, Boomsma DI, Ciullo M, Cucca F, Esko T, Franceschini N, Gieger C, Gudnason V, Hayward C, Kraft P, Lawlor DA, Magnusson PKE, Martin NG, Mook-Kanamori DO, Nohr EA, Polasek O, Porteous D, Price AL, Ridker PM, Snieder H, Spector TD, Stöckl D, Toniolo D, Ulivi S, Visser JA, Völzke H, Wareham NJ, Wilson JF; LifeLines Cohort Study; InterAct Consortium; kConFab/AOCS Investigators; Endometrial Cancer Association Consortium; Ovarian Cancer Association Consortium; PRACTICAL consortium, Spurdle AB, Thorsteindottir U, Pollard KS, Easton DF, Tung JY, Chang-Claude J, Hinds D, Murray A, Murabito JM, Stefansson K, Ong KK, Perry JRB. Genomic analyses identify hundreds of variants associated with age at menarche and support a role for puberty timing in cancer risk. Nat Genet. 2017;49(6):834-841.

de Hoogh K, Chen J, Gulliver J, Hoffmann B, Hertel O, Ketzel M, Bauwelinck M, van Donkelaar A, Hvidtfeldt UA, Katsouyanni K, Klompmaker J, Martin RV, Samoli E, Schwartz PE, Stafoggia M, Bellander T, Strak M, Wolf K, Vienneau D, Brunekreef B, Hoek G. Spatial PM2.5, NO2, O3 and BC models for Western Europe - Evaluation of spatiotemporal stability. Environ Int. 2018;120:81-92.

Devi KS, Dhall M, Kapoor S. Adiposity markers and its association with age at menarche: A comparative study among rural and urban Meitei females of Manipur, North-East India. Diabetes Metab Syndr. 2019 Jan-Feb;13(1):500-503.

Elks CE, Ong KK, Scott RA, van der Schouw YT, Brand JS, Wark PA, Amiano P, Balkau B, Barricarte A, Boeing H, Fonseca-Nunes A, Franks PW, Grioni S, Halkjaer J, Kaaks R, Key TJ, Khaw KT, Mattiello A, Nilsson PM, Overvad K, Palli D, Quirós JR, Rinaldi S, Rolandsson O, Romieu I, Sacerdote C, Sánchez MJ, Spijkerman AM, Tjonneland A, Tormo MJ, Tumino R, van der A DL, Forouhi NG, Sharp SJ, Langenberg C, Riboli E, Wareham NJ; InterAct Consortium. Age at menarche and type 2 diabetes risk: the EPIC-InterAct study. Diabetes Care. 2013;36(11):3526-34.

European Commission. Degree of Urbanisation Classification - 2011 Revision. DG AGRI and DG REGIO of the European Commission with the support of the Joint Research Center (JRC) and Eurostat. https://ec.europa.eu/eurostat/web/gisco/geodata/reference-data/population-distribution-demography/degurba.

Forman MR, Mangini LD, Thelus-Jean R, Hayward MD. Life-course origins of the ages at menarche and menopause. Adolesc Health Med Ther. 2013;4:1-21.

Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology 1999;10:37e48.

Haaland, C, van Den Bosch CK. Challenges and strategies for urban green-space planning in cities undergoing densification: A review. Urban forestry & urban greening 2015;14(4):760-771.

Hartig, T, Kah, PH. Living in cities, naturally. Science 2016;352(6288):938-940.

Heinrich J, Brüske I, Cramer C, Hoffmann U, Schnappinger M, Schaaf B, von Berg A, Berdel D, Krämer U, Lehmann I, Herbarth O, Borte M, Grübl A, Bauer CP, Beckmann C, Behrendt H, Ring J, Koletzko S. GINIplus and LISAplus - Design and selected results of two German birth cohorts about natural course of atopic diseases and their determinants. Allergol Select. 2017;1(1):85-95.

Hesketh T, Ding QJ, Tomkins A. Growth status and menarche in urban and rural China. Ann Hum Biol. 2002 May-Jun;29(3):348-52.

InterLACE Study Team. Variations in reproductive events across life: a pooled analysis of data from 505 147 women across 10 countries. Hum Reprod. 2019;34(5):881-893.

Jung EM, Kim HS, Park H, Ye S, Lee D, Ha EH. Does exposure to PM10 decrease age at menarche? Environ Int. 2018;117:16-21.

Juul F, Chang VW, Brar P, Parekh N. Birth weight, early life weight gain and age at menarche: a systematic review of longitudinal studies. Obes Rev. 2017;18(11):1272-1288.

Lee JJ, Cook-Wiens G, Johnson BD, Braunstein GD, Berga SL, Stanczyk FZ, Pepine CJ, Bairey Merz CN, Shufelt CL. Age at Menarche and Risk of Cardiovascular Disease Outcomes: Findings From the National Heart Lung and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation. J Am Heart Assoc. 2019;8(12):e012406.

LSAC Technical Paper No. 1: Sample Design [article online], 2005. Available from http://www.growingupinaustralia.gov.au/pubs/technical/tp1.pdf. Accessed Date accessed: 01/02/2017.

Luo YN, Huang WZ, Liu XX, Markevych I, Bloom MS, Zhao T, Heinrich J, Yang BY, Dong GH. Greenspace with overweight and obesity: A systematic review and meta-analysis of epidemiological studies up to 2020. Obes Rev. 2020;21(11):e13078.

Markevych I, Schoierer J, Hartig T, Chudnovsky A, Hystad P, Dzhambov AM, de Vries S, Triguero-Mas M, Brauer M, Nieuwenhuijsen MJ, Lupp G, Richardson EA, Astell-Burt T, Dimitrova D, Feng X, Sadeh M, Standl M, Heinrich J, Fuertes E. Exploring pathways linking greenspace to health: Theoretical and methodological guidance. Environ Res. 2017;158:301-317.

Mitchell R, Astell-Burt T, Richardson EA. A comparison of green space indicators for epidemiological research. J Epidemiol Community Health. 2011;65:853-858.

Ohly H, White MP, Wheeler BW, Bethel A, Ukoumunne OC, Nikolaou V, Garside R. Attention Restoration Theory: A systematic review of the attention restoration potential of exposure to natural environments. J Toxicol Environ Health B Crit Rev. 2016;19(7):305-343.

Prentice P, Viner RM. Pubertal timing and adult obesity and cardiometabolic risk in women and men: a systematic review and meta-analysis. Int J Obes (Lond). 2013;37(8):1036-43.

R Core Team: R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2012. [http://www.R-project.org/].

Richard E. Jones, Kristin H. Lopez. Chapter 6 – Puberty. In: Human Reproductive Biology (Fourth Edition). Academic Press, 2014, p. 103-118.

Said-Mohamed R, Prioreschi A, Nyati LH, van Heerden A, Munthali RJ, Kahn K, Tollman SM, Gómez-Olivé FX, Houle B, Dunger DB, Norris SA. Rural-urban variations in age at menarche, adult height, leg-length and abdominal adiposity in black South African women in transitioning South Africa. Ann Hum Biol. 2018 Mar;45(2):123-132.

Shuda Q, Bougoulias ME, Kass R. Effect of nature exposure on perceived and physiologic stress: A systematic review. Complement Ther Med. 2020;53:102514.

Textor J, van der Zander B, Gilthorpe MK, Liskiewicz M, Ellison GTH. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. International Journal of Epidemiology 2016;45(6):1887-1894.

Triebner K, Markevych I, Hustad S, Benediktsdóttir B, Forsberg B, Franklin KA, Gullón Blanco JA, Holm M, Jaquemin B, Jarvis D, Jõgi R, Leynaert B, Lindberg E, Martínez-Moratalla J, Muniozguren Agirre N, Pin I, Sánchez-Ramos JL, Heinrich J, Gómez Real F, Dadvand P. Residential surrounding greenspace and age at menopause: A 20-year European study (ECRHS). Environ Int. 2019;132:105088.

Webster GD, Graber JA, Gesselman AN, Crosier BS, Schember TO. A life history theory of father absence and menarche: a meta-analysis. Evol Psychol. 2014;12(2):273-94.

Wilkie S, Townshend T, Thompson E, Ling J. Restructuring the built environment to change adult health behaviors: a scoping review integrated with behavior change frameworks. Cities Health. 2019;2(2):198-211.

Williams R. A note on robust variance estimation for cluster-correlated data. Biometrics 2000;56(2):645-46.

Yermachenko A, Dvornyk V. Nongenetic determinants of age at menarche: a systematic review. Biomed Res Int. 2014;2014:371583.