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Urban densification over 9 years and change in the metabolic syndrome: A nationwide investigation from the ORISCAV-LUX cohort study

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ABSTRACT

A growing body of evidence suggests that urban densification may be protective against obesity, type 2 diabetes, and cardiometabolic diseases, yet studies on how built environmental features relate to metabolic syndrome (MetS) and its components are scarce. This longitudinal study examines the associations of baseline urban density and densification over 9 years with MetS and MetS components, among 510 participants enrolled in both waves of the ORISCAV-LUX study (2007–2017) in Luxembourg. A continuous MetS score (siMS) was calculated for each participant. Six features of residential built environments were computed around participants' home address: street connectivity, population density, density of amenities, street network distance to the nearest bus station, density of public transport stations, and land use mix. A composite index of urban densification (UDI) was calculated by averaging the six standardized built environment variables. Using adjusted generalized estimating equation (GEE) models, one-SD increase in UDI was associated with a worsening of the siMS score ($\beta = 0.07$, 95% CI: 0.02, 0.13), higher triglyceride levels ($\beta = 0.05$, 95% CI: 0.02, 0.09), and lower HDL-c levels ($\beta = -1.29$, 95% CI: −2.20, −0.38). The detrimental effect of UDI on lipid levels was significant only for participants living in dense areas at baseline. Higher baseline UDI, as well as increased UDI over time among movers, were also associated with greater waist circumference. There were no associations between UDI, fasting plasma glucose and systolic blood pressure. Sex and neighborhood socio-economic status did not moderate the associations between UDI and the cardiometabolic outcomes. Overall, we found limited evidence for an effect of urban densification on MetS and its components. Understanding urban dynamics remains a challenge, and more research investigating the independent and joint health effect of built environment features is needed to support urban planning and design that promote cardiometabolic health.

1. Introduction

The global burden of cardiometabolic diseases (such as heart attack, stroke, diabetes, insulin resistance, and non-alcoholic fatty liver disease) is increasing (Roth et al., 2017). In 2019, cardiometabolic diseases were responsible for about 1.7 million deaths (37 percent of all deaths) and constitute the leading cause of death in Europe (OECD/European Union, 2022). The burden of cardiometabolic diseases is attributable to combinations of various individual and environmental risk factors (Abbafati et al., 2020). Thus, implementing effective public health policies to tackle these diseases requires the use of ecological frameworks accounting for the complex interactions between individual and environmental factors in health (Lang and Rayner, 2012).

At the local level, planning of the urban built environment is now recognized as an important factor that could affect cardiometabolic health by influencing a complex network of exposure to environmental, social, and behavioral risks (Giles-Corti et al., 2016). The rapid pace of urbanization over the last century has been the main driver of changes in the urban built environment in Europe. Between 1960 and 2020, the urban population in Europe increased from 59 to 75 percent and is expected to expand further over the coming years (World Bank Data, 2018). Urban design and public transportation have evolved to cope with this rapid growth, leading to two distinct phenomena: *urban densification* and *urban sprawl* (European Environment Agency, 2016). Despite the lack of a unanimously accepted definition, *urban densification* refers to process of the concentration of urban infrastructures within

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city centers, resulting in a high population density, mixed land use, and easy access to public transport (Burton, 2002). Conversely, *urban sprawl* refers to a dynamic of the city spreading into suburban areas, leading to low-density residential housing, poor access to infrastructure, and increased dependency on automobile transport (Galster et al., 2001).

Growing evidence suggests that living in dense and low-sprawled areas is more likely to be protective against obesity, type 2 diabetes, and cardiovascular diseases (Chandrabose et al., 2019c; DenBraver et al., 2018; Feng et al., 2010; Leal and Chaix, 2011; Mackenbach et al., 2014; Malambo et al., 2016; Sallis et al., 2012). Reduced car dependency — and consequently less traffic exposure, pollution, and noise — as well as improved access to public transport, footpaths, and local stores are all features of more compact and dense cities that could positively influence health outcomes (Giles-Corti et al., 2016; Nieuwenhuijsen, 2016). However, previous studies have relied extensively on cross-sectional designs, which are particularly susceptible to reverse causation and self-selection and do not permit causal inference (Lamb et al., 2020). In addition, longitudinal studies have mainly focused on obesity, whereas the effect of urban densification on other cardiometabolic outcomes — and in particular on metabolic syndrome (MetS) — has been little investigated (Chandrabose et al., 2019c).

MetS is nevertheless a burgeoning public health concern that affects about 25 percent of the European adult population (Scuteri et al., 2015). It refers to the co-occurrence of several metabolic abnormalities: abdominal obesity, raised triglyceride levels, low high-density lipoprotein, high blood pressure, and elevated fasting plasma glucose (Alberti et al., 2009). People with MetS have a higher risk of developing cardiometabolic diseases, making it a good predictor for the early detection of people at high risk of cardiometabolic complications (Galassi et al., 2006; Mottillo et al., 2010). A few studies on urban densification and MetS have been conducted in non-European settings, and mixed results have been found (Barnett et al., 2022; Coffee et al., 2013; Daniel et al., 2019; Fong et al., 2019; Müller-Riemenschneider et al., 2013). This further emphasizes the importance of investigating the influence of urban densification on MetS in a European context. In addition, there is a need for future longitudinal studies to disentangle the effect of the built environment features to better inform future urban planning and design (Chandrabose et al., 2019c).

The aim of the current study was to assess the longitudinal associations of baseline urban density and urban densification over 9 years with MetS and its components in the Grand Duchy of Luxembourg. We hypothesized that urban densification is protective against developing MetS, and that associations will vary by both MetS components and the characteristics of the built environment.

2. Material and methods

2.1. Study population

Data was obtained from two waves of the nationwide population-based survey monitoring cardiometabolic health in the adult population of the Grand Duchy of Luxembourg: ORISCAV-LUX (2007–2008) and ORISCAV-LUX 2 (2016–2017). Details of the two surveys have been published elsewhere (Alkerwi et al., 2010, 2019). Briefly, in the first survey, a random sample of Luxembourg residents aged 18 to 69, stratified by gender, age categories, and districts was drawn from the national insurance registry (n = 1432). The second survey combined a follow-up of the participants from the first survey with an additional random sample (n = 1558). In both waves, participants were invited to complete self-administered questionnaires, as well as undergoing clinical and anthropometric examinations. The present study includes participants who took part in both surveys (n = 660, 46.1% of the baseline sample). We excluded participants who did not want their data to be reused (n = 27), those with self-reported chronic conditions (myocardial infarction, stroke, angina, or cancer) (n = 59), or with any missing data (n = 64), resulting in a final sample of 510 study participants (Fig. 1). As

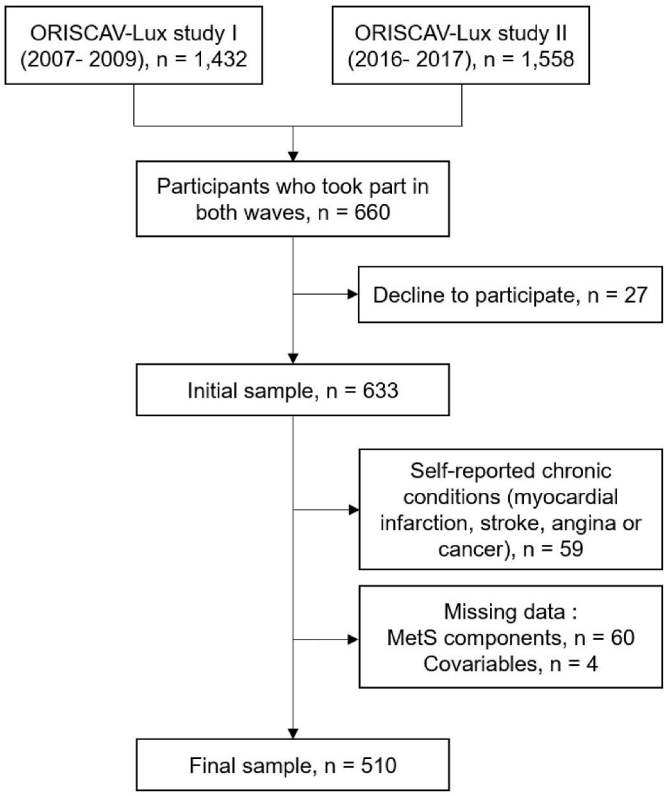

Fig. 1. Flow chart of study participants.

the number of complete cases in the data was above 95 percent, a Complete Case Analysis (CCA) was performed. Using the rule of thumb that in scenarios when the proportion of missing data is less than 5 percent, the benefits of alternative approaches of dealing with missing data, such as Multiple Imputation (MI), tend to be negligible in terms of reducing any bias (Schafer, 1999). Participants in the final sample had similar sociodemographic characteristics to the ORISCAV-LUX I study population, with the exception of a lower percentage of less-educated people (Supplemental Table 1).

The study was approved by the National Ethics Committee for Research (Ref: 202104/03 V2.0).

2.2. MetS components and MetS score (siMS)

Metabolic syndrome (MetS) is defined as the accumulation of the following cardiometabolic risk abnormalities: abdominal obesity, insulin resistance, raised triglycerides, lowered high-density lipoprotein cholesterol, impaired glucose metabolism, and hypertension (Eckel et al., 2010; Samson and Garber, 2014). Anthropometric measurements, blood pressure, and a venous blood sample were collected by a nurse during the clinical examinations. The resting systolic blood pressure (after 30 min of sitting) was measured three times with a minimum a 5-min intervals and the mean of the three measurements was used in the analysis. The blood samples were analyzed by an accredited laboratory (Ketterthill, Esch-sur-Alzette, Luxembourg) for the biological measurements.

To better quantify the spectrum of metabolic abnormalities, we computed a continuous score of MetS (Aguilar-Salinas et al., 2005) using the siMS score developed by Soldatovic et al. (2016):

siMS score = 2(Waist/Height) + (FPG/ref.) + (TG/ref.) + (SBP/ref.) - (HDL-c/ref. male/female).

The reference values represent the cut-off values used for the diagnosis of the MetS. We used cut-offs from the latest harmonized definition

of MetS given by the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) and the International Diabetes Federation (IDF), namely fasting plasma glucose (FPG) ≥ 100 mg/dL, fasting triglycerides (TG) ≥ 150 mg/dL, high-density lipoprotein cholesterol (HDL-c) < 40 mg/dL in men or < 50 mg/dL in women, systolic blood pressure (SBP) ≥ 130 mmHg (Alberti et al., 2009).

2.3. Built environment variables and urban densification

Previous frameworks have identified urban design, density of population and amenities, access to public transport infrastructure, and diversity of urban spaces as features of the local built environment that could influence health and well-being (Giles-Corti et al., 2016). We investigated these four features through six built environment variables described in Table 1. Street connectivity, population density, density of amenities, density of public transport stops, and land use mix were calculated for a 1000 m road-network buffer around each participant's residence (equivalent to a 10- to 15-min walk) — a commonly-used distance to define residential neighborhoods (Lovasi et al., 2012). The road network measurement was chosen over circular buffers, as the former provided a more accurate representation of the neighborhood accessible to participants as they travel along the road (Li et al., 2022). The distance (in meters) from each respondent's home to the nearest bus station was computed using the shortest path.

To account for the joint effects of built environment variables that occur simultaneously in urban areas, we created a composite index of urban densification (UDI) by averaging the six standardized built environment variables (i.e., z-scores with a mean of 0 and standard deviation of 1), at each wave. For the shortest path to the nearest bus station, the opposite z-score was used, so that higher values indicated greater access to bus stations.

2.4. Covariates

A directed acyclic graph (DAG) was created to facilitate the identification of potential confounders (Supplemental Fig. 1). DAGs are diagrams that display *a priori* causal assumptions about the relationships between variables (Greenland et al., 1999). Based on our DAG, a set of individual-level and environmental-level covariates were considered. The individual-level covariates included sex, age, country of birth (Luxembourg, European country, or non-European country), educational level (no diploma, secondary education, or higher diploma), working status (employed, not employed, stay-at-home parent, disabled or retired), marital status (married/living with partner, single/never married, or divorced/widowed). Data was obtained for both waves from the self-administered questionnaires.

Environmental-level variables included the neighborhood socio-economic status and the healthiness of the retail food environment. The average housing price (in euros per square meter) was used as a proxy of neighborhood socio-economic status (Coffee et al., 2020; Ware, 2019). The average sales prices (in euros per m^2) for the years 2008 and 2017 at the level of participants' municipality of residence were obtained from the Housing Observatory of the Ministry of Housing. Tertiles of housing prices in our sample were used to create three groups, with the values reclassified according to an ordinal level of measurement: low, intermediate, and high housing prices. The Modified Retail Food Environment Index (mRFEI) was used to estimate the healthiness of the retail food environment. The mRFEI measures the percentage of food retailers that provide healthy food items such as fruit and vegetables, using the following formula: mRFEI = 100 *x* (# of Healthy Food Retailers)/(# of Healthy Food Retailers + # of Less Healthy Food Retailers) (CDC, 2011). Healthy food retailers included supermarkets and large grocery stores, greengrocers and open markets, and less healthy food retailers included convenience stores/gas stations and fast food restaurants (CDC, 2011). The mRFEI ranges from 0 to 100% and was classified into four categories: no food retailers, no healthy food retailers (mRFEI = 0), rather unhealthy food retail environment (mRFEI≤50), rather healthy food retail environment (mRFEI>50).

2.5. Statistical analysis

Multi-level generalized estimating equation (GEE) was used to examine the relationship between changes in residential densification variables and cardiometabolic outcomes. GEE is a marginal model commonly used in longitudinal data analysis (Fitzmaurice et al., 2012). To test for the effect of baseline and change in UDI on changes in cardiometabolic outcomes over time we included the following variables in the models: time, baseline UDI (potential impact of baseline UDI on mean level in cardiometabolic outcomes over time), change in UDI (computed as the difference of UDI between the two waves, and representing the potential impact of change in UDI on mean level in cardiometabolic outcomes over time), interaction term between time and baseline UDI (potential impact of baseline UDI on changes in cardiometabolic outcomes over time), and interaction term between time and change in UDI (potential impact of change in UDI on changes in cardiometabolic outcomes over time). Both baseline and change in UDI were standardized (mean = 0; SD = 1) to model one-SD increase. GEE models were fitted with an identity link function and considering an

Table 1
Description of the residential built environment variables used in the study.

Residential design features	Built environment components	Description	Data source
Design	Street connectivity	Number of three-or-more-way intersections divided by the neighborhood area (in nb/km^2)	BD-L-TC (ACT) (2008, 2015)
Density	Population density	Sum of number of inhabitants per address divided by the neighborhood area (nb inhab./km^2)	General Inspectorate of Social Security (IGSS) (2009, 2019)
	Density of amenities[a]	Number of amenities divided by the neighborhood area (in nb/km^2)	BDD Equipment (2009), Spatial Development Observatory – LISER (2017). Crosscheck on Open Street Map, Editus.lu, Google street view, Google maps
Public transport infrastructure	Street network distance to the nearest bus station	Shortest distance to the nearest bus station (in m)	BD-L-TC (ACT) (2008, 2015); Public transport timetables and stops, Public Transport Administration, LISER (2009–2018)
	Density of public transport stations	Number of bus, public bike and train stations divided by the neighborhood area (in nb/km^2)	Public transport timetables and stops, Public Transport Administration, LISER (2009–2018) Mvel'OH! (List of stations), City of Luxembourg (2016) Vël'OK, CIGL Esch-sur-Alzette (2019)
Diversity	Land use mix	Level of diversity of land use types within the neighborhood	Land Information System Luxembourg (LIS-L) Land use change layer 2007–2015

[a] Local amenities included are: community-serving retail outlets (banks, ATMs, post offices, pharmacies, and town halls), medical services (general practitioners, hospitals, and clinics), education services (primary, secondary, and high schools), cultural places (cinemas, theaters, and concert halls), and sport facilities (public swimming pools, sports fields, and gymnasiums).

exchangeable working correlation structure. We considered two levels of adjustment. Model 1 was adjusted for individual socio-economic variables (sex, age, country of birth, educational level, working status). Model 2 was further adjusted for the environmental-level variables (housing price in the municipality of residence and mRFEI). The data is presented as estimates (β) and 95 percent confidence intervals (CIs). We performed restricted cubic spline regressions to examine the dose-response relationship between UDI and the investigated cardiometabolic outcomes, using the SAS macro written by Desquilbet and Mariotti (2010), considering the median of the exposure distribution as the reference value and three knots located at the 5th, 50th, and 95th percentiles.

2.6. Sensitivity analysis

We performed several sensitivity analyses to test the robustness of our results. First, we added a triple interaction between time, baseline UDI and change in UDI to investigate whether levels of urban density at

Table 2
Individual and environmental-level characteristics of the study population by tertile of continuous metabolic syndrome score (siMS) at follow-up, n = 510 adults from ORISCAV-LUX study (2007–2017) [a].

	Total sample	siMS score at wave 2			
	(n = 510)	Low (n = 171)	Intermediate (n = 169)	High (n = 170)	P value[b]
Baseline individual-level characteristics					
Sociodemographic					
Age (years)	43.8 (11.7)	40.3 (11.8)	44.6 (11.4)	46.48 (11.2)	<.0001
Women	258 (50.6)	111 (64.9)	85 (50.3)	62 (36.5)	<.0001
Working status					
Employed	365 (71.6)	129 (75.4)	117 (69.2)	119 (70)	<.0001
Not employed	44 (8.6)	18 (10.5)	14 (8.3)	12 (7.1)	
Stay-at-home parent	52 (10.2)	15 (8.8)	22 (13)	15 (8.8)	
Disabled or retired	49 (9.6)	9 (5.3)	16 (9.5)	24 (14.1)	
Education level, n (%)					
No diploma	78 (15.3)	18 (10.5)	27 (16.0)	33 (19.4)	0.025
High school or vocational diploma	256 (50.2)	84 (49.1)	79 (46.7)	93 (54.7)	
Higher diploma	176 (34.5)	69 (40.4)	63 (37.3)	44 (25.9)	
Marital status					
Married/living with partner	386 (75.7)	124 (72.5)	130 (76.9)	132 (77.6)	0.445
Single/never married	77 (15.1)	33 (19.3)	23 (13.6)	21 (12.4)	
Divorced/widowed	47 (9.2)	14 (8.2)	16 (9.5)	17 (10)	
Country of birth, n (%)					
Not European country	27 (5.3)	10 (5.8)	8 (4.7)	9 (5.3)	0.922
European country	168 (32.9)	52 (30.4)	59 (34.9)	57 (33.5)	
Luxembourg	315 (61.8)	109 (63.7)	102 (60.4)	104 (61.2)	
Cardiometabolic					
Waist circumference (cm)	88.0 (12.7)	79.6 (9.3)	87.8 (10.3)	96.5 (12.1)	<.0001
Fasting plasma glucose (mg/dL)	93.2 (14.1)	88.9 (8.3)	91.4 (8.8)	99.4 (19.8)	
HDL-cholesterol (mg/dL)	63.2 (17)	73.9 (17)	62.8 (13.6)	52.7 (12.8)	
Triglycerides (mg/dL)	107.2 (88.1)	71.4 (27.8)	96.5 (48.4)	153.7 (129.1)	
Systolic blood pressure (mmHg)	128.3 (15.7)	121.5 (13.9)	129 (14.1)	134.4 (16.4)	
Environmental-level characteristics					
Relocation, n (%)	165 (32.4)	61 (35.7)	50 (30.0)	54 (31.8)	0.478
Built environment components					
Baseline UDI	0 (0.8)	0 (0.8)	0 (0.8)	0 (0.7)	0.556
Change in UDI	0 (0.6)	−0.1 (0.6)	−0.1 (0.6)	0.1 (0.5)	0.006
Baseline street connectivity	90 (49.3)	91 (49.1)	91 (49.1)	84.2 (45.6)	0.133
Change in street connectivity	2.2 (35.2)	−2.2 (38.1)	−2.2 (38.1)	9.3 (27.5)	0.005
Baseline population density	1857.8 (1685.2)	1952.5 (1807.6)	1952.5 (1807.6)	1678.5 (1506.7)	0.236
Change in population density	146.2 (1252.2)	−2.9 (1365.3)	−2.9 (1365.3)	322.6 (1001.2)	0.053
Baseline density of amenities	11.2 (12.6)	11 (11.4)	11 (11.4)	10.3 (11.6)	0.312
Change in density of amenities	0.2 (10.8)	−1.7 (10.6)	−1.7 (10.6)	2.9 (10.8)	<0.001
Baseline distance to the nearest bus station	288.8 (213.2)	291.9 (197.4)	291.9 (197.4)	279.2 (237.5)	0.764
Change in distance to the nearest bus station	−4.1 (188.9)	−5.1 (157.6)	−5.1 (157.6)	−5.9 (222.1)	0.972
Baseline density of public transport stations	5.7 (4.4)	5.7 (4.4)	5.7 (4.4)	5.4 (4.1)	0.368
Change in density of public transport stations	0.6 (3.8)	0.4 (4)	0.4 (4)	1.2 (3.8)	0.028
Baseline land use mix	0.7 (0.1)	0.7 (0.1)	0.7 (0.1)	0.7 (0.2)	0.793
Change in land use mix	0 (0.1)	0 (0.1)	0 (0.1)	0 (0.1)	0.327
Baseline housing price in the municipality of residence[c]					
Low	170 (33.3)	57 (33.3)	51 (30.2)	62 (36.5)	0.479
Intermediate	179 (35.1)	63 (36.8)	56 (33.1)	60 (35.3)	
High	161 (31.6)	51 (29.8)	62 (36.7)	48 (28.2)	
Baseline healthiness of the retail food environment[d]					
No RFE	212 (41.6)	66 (38.6)	73 (43.2)	73 (42.94)	0.878
mRFEI = 0	82 (16.1)	29 (16.96)	27 (15.98)	26 (15.29)	
mRFEI ≤50	88 (17.3)	29 (16.96)	26 (15.38)	33 (19.41)	
mRFEI >50	128 (25.1)	47 (27.49)	43 (25.44)	38 (22.35)	

RFE: retail food environment; mRFEI: Modified Retail Food Environment index.

[a] Data is presented as means and standard deviations or numbers and percentages where appropriate.

[b] P-value for ANOVA test of equality of means (continuous variables) or $\chi 2$ test for dependency (categorical variables).

[c] Categorization based on tertile (low: housing price ≤3317 €/m2; intermediate: 3317 €/m2 < housing price ≤3889 €/m2; high: housing price >3889 €/m2).

[d] Estimated by the Modified Retail Food Environment index (mRFEI). mRFE = 100 *x* (# of Healthy Food Retailers)/(# of Healthy Food Retailers + # of Less Healthy Food Retailers).

baseline influence level of urbanization over time and trajectory in the cardiometabolic outcomes. In case of significant triple interactions, baseline UDI was dropped off the model and stratification by tertile of baseline UDI was performed. Second, we explored potential effect modifications by sex, housing price by adding a multiplicative interaction term between baseline and change in UDI and these variables in the fully adjusted model. Third, we rerun the main models on specific subpopulations, by stratifying the models on: 1) relocation status (movers vs non-movers), and 2) level of urbanity, categorized as dense cities (Luxembourg and Esch-sur-Alzette), peri-urban areas (first and second-ring suburbs), and lower-density areas, based on previous classifications (Carpentier, 2006). Fourth, we examined sensitivity to buffer size by testing different road-network buffer sizes of 500 m, 800 m and 2000 m.

ArcGIS (Version 9.3.1; ESRI, Redlands, CA, USA, 2010) was used to geocode participant's home address, delineate neighborhood boundaries and handle the residential built environment variables. Z score transformation, creation of the UDI and data analysis were conducted in SAS 9.4 software (SAS Institute, Inc., Cary NC). An α of 0.05 or less was used to determine statistical significance.

3. Results

3.1. Descriptive statistics

The characteristics of the study participants at baseline are shown in Table 2. Mean baseline age of participants was 43.8 years and 50.6% were female. Mean siMS score was 2.3 (SD: 0.9; range: 0.3–11.8) at baseline and increased by 0.2 units over the 9-year period ($p < 0.0001$). MetS components worsened over the 9-year ($p < 0.0001$), with the exception of triglyceride levels and blood pressure, which remained stable over time (data not shown). A third of the participants ($n = 165$) had relocated between the two waves. Compared with the rest of the sample, participants in the upper tertile of the siMS score at wave 2 were older, less educated, and more likely to be male. Median UDI was -0.17 (range: -3.0 – 3.3; IQR: 1.45) at baseline and increased by 0.03 units over the 9-year period ($p = 0.019$). Participants in the upper tertile of the siMS score at wave 2 had a higher increase in UDI, street connectivity, density of amenities and density of public transport stations than the rest of the sample.

3.2. Urban densification, siMS score and MetS components

There were no significant interactions between baseline UDI or change in UDI with time, so the interaction terms were removed from the models. Table 3 shows the associations of baseline measures and change in UDI with the siMS score and MetS components. In the fully adjusted model, one-SD increase in UDI over time was associated with a slightly higher siMS score (β = 0.07, 95% CI: 0.02, 0.13), greater triglyceride levels (β = 0.05, 95% CI: 0.02, 0.09) and with lower HDL-c levels (β = −1.29, 95% CI: −2.20, −0.38). A higher value of UDI at baseline was also associated with higher waist circumference (β = 1.28, 95% CI: 0.14, 2.42). There was no statistically significant relationship between UDI, fasting plasma glucose and systolic blood pressure. Restricted cubic spline regressions showed no evidence of non-linear association between UDI and cardiometabolic outcomes (data not shown). The associations of each of the six built environment variables with the siMS score and MetS components are provided in Supplementary Table 2. One-SD increase in the density of amenities over 9-year was associated with greater siMS score (β = 0.09, 95% CI: 0.03, 0.14), greater triglyceride levels (β = 0.05, 95% CI: 0.01, 0.08), and lower HDL-c levels (β = −1.47, 95% CI: −2.32, −0.62). One-SD increase in the density of public transport stations was associated with greater siMS score (β = 0.07, 95% CI: 0.01, 0.13) and lower HDL-c levels (β = −1.45, 95% CI: −2.32, −0.59). One-SD increase in street connectivity, population density and land use mix were associated with greater triglyceride levels (β = 0.05, 95% CI: 0.01, 0.08), lower HDL-c levels (β = −1.09, 95% CI: −2.11, −0.06) and greater waist circumference (β = 0.94,

Table 3
Estimates (β) and 95% Confidence Intervals (CI) for associations of 1-SD increase in baseline levels and change in UDI, with MetS (continuous score: siMS score) and its components.

	siMS		Waist circumference		Triglycerides[a]		HDL-cholesterol		Fasting plasma glucose[a]		Systolic blood pressure	
	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value
					Model 1[b]							
Baseline UDI	0.02 (−0.05, 0.08)	0.585	0.39 (−0.57, 1.36)	0.425	−0.01 (−0.05, 0.03)	0.704	−0.79 (−1.91, 0.32)	0.165	0.01 (0.00, 0.02)	0.211	−0.92 (−2.08, 0.24)	0.120
Change in UDI	**0.06 (0.01, 0.11)**	**0.017**	0.58 (−0.25, 1.41)	0.168	**0.04 (0.01, 0.08)**	**0.018**	**−1.34 (-2.21, -0.48)**	**0.002**	0.00 (−0.01, 0.00)	0.403	−0.65 (−1.62, 0.32)	0.187
					Model 2[c]							
Baseline UDI	0.02 (−0.07, 0.11)	0.641	**1.28 (0.14, 2.42)**	**0.028**	0.00 (−0.05, 0.06)	0.940	−0.74 (−2.14, 0.67)	0.305	0.01 (−0.01, 0.02)	0.269	−1.19 (−2.67, 0.29)	0.115
Change in UDI	**0.07 (0.02, 0.13)**	**0.007**	0.81 (−0.03, 1.64)	0.058	**0.05 (0.02, 0.09)**	**0.005**	**−1.29 (-2.20, -0.38)**	**0.005**	0.00 (−0.01, 0.00)	0.342	−0.57 (−1.59, 0.44)	0.266

Significant results are highlighted in bold.

[a] Variables were log-transformed to improve normality.

[b] Adjusted for individual-level socio-economic variables: age, country of birth (Luxembourg, European country, or non-European country), educational level (no diploma, secondary education, or higher diploma), working status (employed, not employed, stay-at-home parent, disabled, or retired), marital status (married/living with partner, single/never married, or divorced/widowed).

[c] Model 1 + average housing price in the municipality of residence (low: housing price ≤3317 €/m^2; intermediate: 3317 €/m^2 < housing price ≤3889 €/m^2; high: housing price >3889 €/m^2) and modified Retail Food Environment Index (mRFEI) (no food retailers, no healthy food retailers: mRFEI = 0, rather unhealthy food retail environment: mRFEI≤50, rather healthy food retail environment: mRFEI>50).

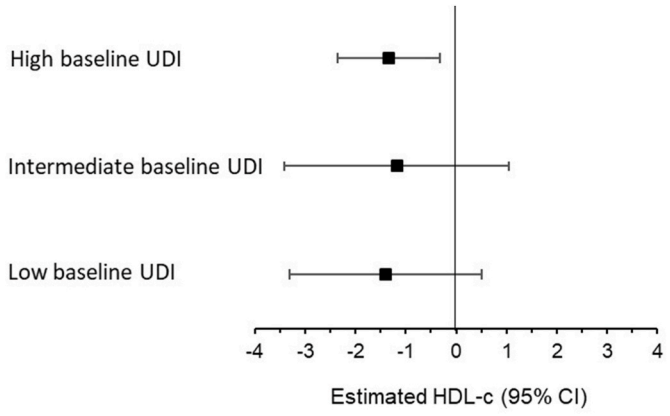

Fig. 2. Estimates (β) and 95% Confidence Intervals (CI) for associations between change in UDI and HDL-cholesterol (HDL-c), stratified by baseline standardized UDI, n = 510 adults from ORISCAV-LUX study (2007–2017).

95% CI: 0.19, 1.68), respectively.

3.3. Sensitivity analysis

A triple interaction between baseline UDI, change in UDI and time was observed for HDL-c ($p = 0.041$). Stratification on tertile of baseline UDI, revealed that the negative association between change in UDI and HDL-c was significant only for participants in the upper tertile of baseline UDI at baseline ($\beta = -1.34$, 95% CI: −2.36, −0.32) (Fig. 2). Moderation analyses showed no significant interactions between change in UDI, sex and housing price (data not shown). In stratified analyses by relocation status, the negative associations between increase in UDI and HDL-c, and the positive associations between UDI (both baseline and increase) and waist circumference were significant only in those who relocated between the two waves (Supplemental Table 3). Stratification by degree of urbanity showed the positive association between increase in UDI and triglyceride levels to be significant only in those living in dense cities (Supplemental Table 4). Main results tended to be consistent across buffer sizes with higher effect size observed for the 1000 m buffer, except for the association between baseline UDI and waist circumference, which was stronger when considering a 2000 m buffer size (Supplemental Table 5).

4. Discussion

To our knowledge, this is the first study to investigate the longitudinal associations between neighborhood environmental features and MetS in an EU setting. The effect of change in urban density on the trajectory of the outcomes was not significant (interaction terms between UDI and time were not significant), therefore we cannot interpret the results as the effect of UDI on the change in the cardiometabolic outcomes, but rather as overall long-term association between change in UDI and the outcomes. Overall, the results did not confirm our initial hypothesis that urban densification has a protective effect against MetS. By contrast, we found that urban densification assessed by a composite index of six built environment variables (UDI) was associated with a worsened continuous MetS score, lipid levels (for triglycerides and HDL-c) and waist circumference. There were no associations between UDI, fasting plasma glucose and systolic blood pressure.

The literature on the long-term relationships between the built environment and cardiometabolic outcomes remains limited, and to date is dominated by US and Australian longitudinal observational studies, relying mainly on walkability index (consisting typically of objectively measured residential density, street connectivity, and access to resources) to describe the residential built environment (Chandrabose et al., 2019c). To the best of our knowledge, only three previous studies have investigated the longitudinal association between urban densification and MetS (treated as a binary or an ordinal variable) in adult populations, and they found no direct association (Braun et al., 2016a; Daniel et al., 2019; Fong et al., 2019). Although these studies used the common categorization of MetS as the presence/absence of its components, this classification has been criticized for not fully capturing the continuous spectrum of metabolic abnormalities (Aguilar-Salinas et al., 2005). This might have concealed associations with the built neighborhood environments. Contrary to our results, longitudinal observational studies treating MetS components as a continuous variable found higher neighborhood walkability to be associated with lower blood pressure at one-year follow-up in an older US population (Li et al., 2009), and smaller increases in weight, systolic blood pressure, and HDL-cholesterol over 12 years in the Australian population (Chandrabose et al., 2019a). However, bias from neighborhood self-selection cannot be excluded, as exposure measurements were made at a single time point (Lamb et al., 2020), and the few studies that have assessed the dynamics of urbanization over time have found inconsistent associations with MetS components (Braun et al., 2016a, 2016b; Lang et al., 2022).

Our results suggest an adverse effect of urban densification on MetS, lipid levels and waist circumference. There is nevertheless substantial evidence that neighborhoods with enhanced walkability, compact design, and good transportation infrastructure are supportive of active transportation and physical activity (Prince et al., 2022), which in return could reduce the risk of cardiometabolic diseases (Lear et al., 2017; Wahid et al., 2016). Cardiometabolic health being a more distal outcome than physical activity, it is more likely to be influenced by a variety of individual and environmental factors that could explain some of the inconsistencies in the association with built environments (Braun et al., 2016a). In our study, the adverse effect of densification on triglyceride levels was found to be significant only for participants living in dense cities at baseline. These participants had the lowest triglyceride levels at baseline and the highest increase over time (data not shown), and therefore the risk of regression to the mean in this population cannot be ruled out (Barnett et al., 2005). Similarly, the negative association between UDI and HDL-c levels was significant only for participants with high UDI at baseline, these participants having the greatest decrease in HDL-c over time (data not shown). For participants living in a dense neighborhood at baseline, change of urban features is less likely to influence health behaviors, and worsening of cardiometabolic outcomes over time could be due to factors other than the built environment. For example, growing evidence suggests that ambient air pollution could contribute to lipid profile dysregulation, inflammation, metabolic imbalance and obesity (Gaio et al., 2019; Shi et al., 2022). Other contextual factors such as education or social environment may also play an important role in shaping cardiometabolic health (Letellier et al., 2022). For participants who did not live in a dense neighborhood at baseline, the limited change in UDI over time may have contributed to the lack of effect on measured outcomes. Modelling the densification of cities, by increasing land use density and diversity and reducing average distance to public transport by 30%, was found to reduce the burden of diabetes, cardiovascular disease, and respiratory disease with overall health gains of 420–826 disability-adjusted life-years (DALYs) per 100 000 population (Stevenson et al., 2016). Yet, in Luxembourg, densification over 9 years was very moderate and far from a 30% increase, questioning the ecological validity of this compact city scenario in the country.

Stratification by relocation status showed the adverse effect of UDI on waist circumference and HDL-c levels to be only significant among movers. While movers tended to stay in communes with similar degree of urbanity and socio-residential contexts, about 7% of them moved from urban areas to suburbans and low density-areas (data not shown), leading to a global decrease of UDI among movers. Residential self-selection is a well-known confounding factor in neighborhood and health studies, as the selection of a neighborhood may be related to both the neighborhood exposure and the health outcome of interest (Boone-Heinonen et al., 2011;

McCormack and Shiell, 2011). Self-selection into neighborhoods for various reasons (e.g. house price, neighborhood design, closeness to specific amenities, school/work, parks, family/friends) is likely to support both health-related behaviors (Boone-Heinonen et al., 2011; McCormack and Shiell, 2011), and consequently better cardiometabolic health, which may bias the results and explain the unexpected association between UDI, waist circumference and HDL-c.

Even though composite indices have commonly been used to account for the synergic effect of the joint presence of urban features (Chandrabose et al., 2019c), they do not allow the identification of which urban characteristics are most likely to influence health outcomes. We found the associations to vary by both the characteristics of the built environment and the MetS components, supporting previous recommendations to further disentangle the effect of built environment features to better inform future urban planning and design (Chandrabose et al., 2019c). Nevertheless, relatively few studies have attempted to isolate the effect of specific built characteristics of neighborhoods on cardiometabolic risk factors (Carroll et al., 2020; Chandrabose et al., 2019b; Hirsch et al., 2014; Lee et al., 2017). In accordance with our results, an Australian cohort found that population densification over 12 years had an adverse effect on HDL-c, and no effect on fasting plasma glucose and triglyceride levels (Chandrabose et al., 2019b). An increase in dwelling density over 10 years was also found to be predictive of greater waist circumference in the Australian NWAH study (Carroll et al., 2020). Conversely, in US cohorts, the intensity of development over time (including higher density of walking destinations, greater population density and lower proportion of residential areas) was associated with decreases in waist circumference (Hirsch et al., 2014), and higher intersection density was associated with smaller increases in abdominal visceral adipose tissue and fasting plasma glucose (Lee et al., 2017). The heterogeneity of study designs, environmental measurements, and findings makes it difficult to draw definitive conclusions, and additional longitudinal evidence is needed to clarify inconsistencies and to draw firmer conclusions on the pathway by which the built environment may affect cardiometabolic health.

Our study has several strengths, including its longitudinal design; the 9-year evaluation period; its national scale; the use of objective anthropometric, biological, and environmental measurements; the definition of neighborhoods using fine-scale road network buffers rather than larger pre-defined administrative units as in most studies on the built environment and cardiometabolic health (Chandrabose et al., 2019c; Leal and Chaix, 2011); and the ability to adjust for various individual and neighborhood-level confounders. We also nevertheless acknowledge some limitations of the study. First, the ORISCAV-LUX study has only one follow-up. Two-wave studies lack temporal granularity to assess curvilinear change, which may distort effect sizes and reliability (Ployhart and MacKenzie Jr, 2015). Second, participants who completed the two waves of the ORISCAV-LUX were slightly more educated than the baseline population, and therefore may have had better cardiometabolic health (Raghupathi and Raghupathi, 2020). Nevertheless, prevalence of MetS was similar in our sample and ORISCAV-LUX I study (20 and 23% respectively) (Alkerwi et al., 2011). Third, the study was limited to the built environment in the neighborhood of residence, and thus does not fully capture exposure to non-residential environmental characteristics experienced over the course of a day. For example, specific features of the workplace environment might also shape cardiometabolic health (Sarkar et al., 2022). Fourth, housing price might not fully capture all the socio-economic, physical, and social aspects of neighborhood deprivation, although it has been found to be a reliable variable to assess spatial socio-economic disparities (Coffee et al., 2020; Drewnowski et al., 2016; Ware, 2019). Lastly, although we adjusted for key socio-demographic and environmental covariates, the possibility of residual confounding cannot be excluded. For example, a previous observational study showed that the unfavorable total effects of several built environment features on specific cardiometabolic risk factors vanished after adjustment for air pollution (Cerin et al., 2022), which is recognized as a major risk factor for cardiovascular diseases (Al-Kindi et al., 2020).

5. Conclusion

Overall, we observed a small increase in urban density in Luxembourg over the past decade, associated with worsening of MetS and lipid levels (for triglycerides and HDL-c). A higher level of urban density at baseline was associated with greater waist circumference and urban densification over time with greater waist circumference only for participants who relocated during the two waves. Associations between UDI, triglyceride and HDL-c levels were significant only for participants living in dense areas at baseline, and therefore with limited increase in densification over time, suggesting that environmental factors other the built environment may have contributed to the worsening of MetS and its components. There was no association with fasting plasma glucose and systolic blood pressure. While the model of compact cities is put forward as a way to sustainably enhance urban population health, more longitudinal studies accounting for potential biases and conducted in different contexts are needed to support evidence-based urban planning and policies that foster cardiometabolic health.

Credit author statement

Marion Tharrey: Methodology, data analysis, Roles/Writing - original draft, *Laurent Malisoux:* Conceptualization, Funding acquisition, Supervision, Writing - review and editing, *Olivier Klein:* Conceptualization, Funding acquisition, Supervision, Writing - review and editing, *Torsten Bohn*: Conceptualization, Funding acquisition, Supervision, Writing - review and editing, *Camille Perchoux:* Conceptualization, Funding acquisition, Supervision, Writing - review and editing.

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Baseline standardized UDI was categorized based on tertiles (low: baseline zUDI ≤ -0.57; intermediate: $-0.57 <$ baseline zUDI≤ 0.35; high: baseline zUDI >0.35).

Fully-adjusted model on age, country of birth (Luxembourg, European country, or non-European country), educational level (no diploma, secondary education, or higher diploma), working status (employed, not employed, stay-at-home parent, disabled, or retired), marital status (married/living with partner, single/never married, or divorced/widowed), average housing price in the municipality of residence (low: housing price $\leq$3317 €/m^2; intermediate: 3317 €/m^2 $<$ housing price $\leq$3889 €/m^2; high: housing price $>$3889 €/m^2) and modified Retail Food Environment Index (mRFEI) (no food retailers, no healthy food retailers: mRFEI $= 0$, rather unhealthy food retail environment: mRFEI$\leq$50, rather healthy food retail environment: mRFEI$>$50).

Declaration of competing interest

None.

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.socscimed.2023.116002.

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