ORIGINAL RESEARCH

Urban Densification and 12-Year Changes in Cardiovascular Risk Markers

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***Background*—**Population densities of many cities are increasing rapidly, with the potential for impacts on cardiovascular health. This longitudinal study examined the potential impact of population-density increases in urban areas (urban densification) on cardiovascular risk markers among Australian adults.

***Methods and Results*—**Data were from the Australian Diabetes, Obesity and Lifestyle Study, in which adult participants' cardiovascular risk markers were collected in 3 waves (in 1999–2000, 2004–2005, and 2011–2012). We included 2354 participants with a mean age of 51 years at baseline who did not change their residence during the study period. Outcomes were 12-year changes in waist circumference, weight, systolic and diastolic blood pressure, fasting and 2-hour postload plasma glucose, high-density lipoprotein cholesterol, and triglycerides. The exposure was neighborhood population densification, defined as 12-year change in population density within a 1-km radius buffer around the participant's home. Multilevel linear growth models, adjusting for potential confounders, were used to examine the relationships. Each 1% annual increase in population density was related with smaller increases in waist circumference (b=−0.043 cm/y; 95% CI, −0.065 to −0.021 [$P<0.001$]), weight (b=−0.019 kg/y; 95% CI, −0.039 to 0.001 [$P=0.07$]), and high-density lipoprotein cholesterol (b=−0.035 mg/dL per year; 95% CI, −0.067 to −0.002 [$P=0.04$]), and greater increases in diastolic blood pressure (b=0.032 mm Hg/y; 95% CI, −0.004 to 0.069 [$P=0.08$]).

***Conclusions*—**Our findings suggest that, at least in the context of Australia, urban densification may be protective against obesity risk but may have adverse effects on blood lipids and blood pressure. Further research is needed to understand the mechanisms through which urban densification influences cardiovascular health. **(*J Am Heart Assoc*. 2019;8:e013199. DOI: 10.1161/JAHA.119.013199.)**

Key Words: environmental epidemiology • heart disease • population health • type 2 diabetes mellitus • urbanization

The global burden of cardiometabolic disease is increasing.[1,2] In 2015, an estimated 423 million people worldwide experienced cardiovascular disease[1] and 415 million had diabetes mellitus[3] A basic premise of preventive medicine is that a large number of people at low risk will contribute more to the burden of disease than a small number who are at high risk.[4] Thus, along with clinical approaches for those who are at high risk, community-wide strategies are also necessary to lower the risk for the total population. In this context, investigating the role of contextual factors has been identified as one of the key directions for the future of cardiovascular epidemiology.[5,6]

Population density—the number of people living per unit area can be a fundamental health-related attribute of neighborhood environments.[7] A number of studies, mostly conducted in Western countries, have reported associations of population density with health behaviors and outcomes. For example, an Australian study reported that higher-density

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Accompanying text S1, Tables S1 through S3, and Figure S1 and S2 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013199

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Clinical Perspective

What Is New?

- In the global context of urbanization, where cities are growing in size and urban population densities are increasing, this longitudinal study identified the potential impacts of urban densification on Australian adults' cardiovascular risk.

What Are the Clinical Implications?

- Characteristics of urban environments may have complex impacts on the susceptibility to cardiovascular disease: population-density increase may be protective against obesity but may elevate risk of hypertension.
- Clinicians can take into account such emerging risk exposures, which are broader and ubiquitous determinants of cardiovascular health.

urban neighborhoods with better access to local stores and services can facilitate active modes of travel, such as walking,[8] which are associated with lower cardiovascular risk.[9] Car use is predominant in sprawling lower-density outer suburbs in Australia.[10] Living in outer suburban neighborhoods has also been shown to increase obesity risk in Australia.[11] Cross-sectional studies have shown associations of higher population density with lower risk of obesity and type 2 diabetes mellitus in North America[12,13] and with lower risk of hypertension in France.[14] A longitudinal study has found that higher density at baseline was associated with reduced incidence of cardiovascular events in women in the United States.[15] A systematic review of longitudinal studies found evidence for potential long-term protective effects of higher walkability, typically consisting of measures related to population density, land use, and street layout, against cardiometabolic disease risk.[16]

Little is known, however, about how changes in population density in neighborhoods may influence residents' cardiovascular health. Examining the potential impacts of population-density increases (densification) is timely in the global context of widespread, rapid urbanization.[17] Urban dwellers increased from 30% of the world population in 1950 to 54% in 2015, and this is expected to reach 60% in 2030.[18] Although urban densification is a global trend, only a few studies have examined the cardiovascular health impacts of population density change over time.[16] For example, an increase in population density, measured at a large scale (metropolitan statistical area), was found to be inversely associated with an increase in body mass index over 30 years in the United States.[19] Also, increases in a composite environmental index (consisting of population density, land use, and density of destinations) have been found to be associated with smaller increases in body mass index and waist circumference over 9 years in the United States.[20] To better understand such impacts, research is needed on whether population-density increases at a local scale can influence indices of cardiovascular risk.

We examined longitudinal relationships of urban population densification with changes in Australian adults' cardiovascular risk markers over 12 years.

Methods

Data Source and Study Participants

We used data from the AusDiab (Australian Diabetes, Obesity and Lifestyle Study), an Australian national cohort study examining the risk factors, prevalence, and incidence of diabetes mellitus and cardiovascular disease. Survey and biomedical data were collected in 3 waves: 1999–2000 (AusDiab1), 2004–2005 (AusDiab2), and 2011–2012 (AusDiab3). Detailed descriptions of study design, recruitment procedures, and measurement methods have been published.[21] Briefly, AusDiab1 used a 2-stage stratified cluster sampling method in which study participants were randomly selected from 42 urban sites chosen from each of six Australian states and Northern territory. Each site consisted of contiguous Census Collection Districts (CCDs). A CCD was the smallest geographic area unit for the collection of Census data at the time of AusDiab1, averaging ≈225 dwellings.[22] In total, 11 247 adults aged 25 years and older with no physical or intellectual disabilities and who resided at their addresses for 6 months or longer before the survey were recruited. The overall response rate for biomedical examinations at baseline was 55.3%.[21]

From the baseline cohort, 6400 (59.3%) and 4614 (44.6%) participants completed surveys and biomedical examination for AusDiab2 and AusDiab3, respectively. There were 3968 participants who provided data in all 3 waves, and 646 who attended both AusDiab1 and AusDiab3. We excluded participants whose addresses were not accurately geocoded (n=81), those who were pregnant (n=39) during the data collection, and those who changed their residence during the study period (n=2140). "Movers" were excluded because their relocation date was not recorded, which prevented us from accurately examining neighborhood effects. The final sample retained for analyses was 2354 (2119 provided data at 3 waves, and 235 at the first and third waves only). The International Diabetes Institute and the Alfred Hospital ethics committee (no. 39/11) approved the study, and written informed consent was obtained from all participants.

Outcome Measures

The outcomes of this study were the changes in cardiovascular risk markers over 12 years. These included waist circumference (WC), body weight (weight), systolic blood

pressure (BP), diastolic BP (DBP), fasting plasma glucose (fpg), 2-hour postload plasma glucose (2-hour PG), high-density lipoprotein cholesterol (HDL-C), and triglycerides. They were measured at local data collection centers at each time point. Details of the instruments used to measure these markers have been described elsewhere.[21] Methods to calculate the annual change for each outcome are described below in the Statistical Analysis section.

Exposure Measure

The exposure variable was population densification, which was defined as the change in population density during the study period. Population density is defined as the number of individuals living in a geographical unit divided by its area.[23] In this study, we calculated population density for each participant for the area within a 1-km radius buffer around his/her residence using Census data corresponding to each data collection time point. We used a straight-line buffer rather than a street-network buffer to have the same geographical area across all the waves. The population count data in the smallest geographical units covering all Australia (CCDs in 2001 for AusDiab1; mesh blocks in 2006 and 2011 for AusDiab2 and AusDiab3) were obtained from the relevant Census unit. Population counts for an individual buffer were calculated by summing the population counts of the Census areas included in the buffer. If the buffer intersected a Census unit (CCD or mesh block), that unit's population count corresponding to the percentage of the area within the buffer was added. Population density was expressed as persons per hectare (pph). Methods to calculate population densification are explained below in Statistical Analysis. We expressed the population densification as a relative measure in percentage [(density change/baseline density)×100] so that a unit increase had the same magnitude relative to the baseline density. We also used an absolute measure of densification, pph per year, as a secondary unit. ArcGIS (version 10.6) was used for calculating population density.

Covariates

Potential covariates included time, which corresponded to repeated measures of outcome variables; time-constant covariates: sex, education, height (only for weight), family history of diabetes mellitus, baseline population density; and time-varying covariates assessed at each wave: age, marital status, employment status, household income, household children status (having a child or children in the household), medication use for hypertension, medication use for high cholesterol, energy intake, tobacco smoking, alcohol intake, and area-level socioeconomic status. For area-level socioeconomic status, we used the Index of Relative Socio-Economic Disadvantage (IRSD),[24] which is a composite variable defined for geographic areas, derived using measures such as income, education, employment, household structure, and car ownership, with higher scores indicating lower levels of disadvantage. The IRSD was defined at the Statistical Local Area of participants' residence and obtained for each AusDiab wave from the corresponding Censuses. Because of potential overadjustment, we did not adjust for physical activity variables (eg, walking) that may mediate the relationships examined.[25]

Statistical Analysis

To calculate participants' annual change in cardiovascular risk markers, we fitted an unconditional linear growth model, in which we used fixed continuous time metrics: t=0 for AusDiab1 (baseline); t=5 for AusDiab2 (5-year follow-up); and t=12 for AusDiab3 (12-year follow-up). The participant-specific random slopes of this growth model were used as the annual changes in the risk marker.[26] We also fitted an unconditional linear growth model of population density with corresponding Census years as time metrics (t=1 for 2001, t=6 for 2006, and t=11 for 2011). The participant-specific random intercepts (at t=0) and the random slopes of this growth model were used as the baseline population density at year 2000 and annual population densification, respectively. This method enabled us to obtain robust estimates of annual changes in outcomes and exposure by utilizing the information available at all 3 waves and corresponding Census years.[27]

Multilevel linear growth models[28] were used to examine associations of population densification with changes in cardiovascular risk markers. In the multilevel models, the model intercept was allowed to vary between participants and between study sites, to account for intraindividual correlations attributable to repeated measures and area-level clustering attributable to stratified cluster sampling. Three sets of models were fitted for each outcome. Model 1 adjusted for baseline population density. Model 2 further adjusted for individual-level sociodemographic variables and IRSD. Model 3 further adjusted for health- and behavior-related factors including family history of diabetes mellitus (only for fpg and 2-hour PG), medication use for hypertension (only for systolic BP and DBP), medication use for high cholesterol (only for HDL-C and triglycerides), energy intake, tobacco smoking, and alcohol intake. Further details of multilevel growth models are explained in accompanying text S1 and Figure S1.

We conducted sensitivity analyses focusing on residents of metropolitan areas. The AusDiab study included sites from both metropolitan and regional cities of Australia. Since population densification can be considered more prominent in

metropolitan areas, we ran model 3 after excluding participants who resided in regional cities (n=1080), as defined by Australian Statistical Geography Standard Remoteness Area Classification.[29]

Multilevel modeling of repeated measures over time assumes a missing at random mechanism implying that models will result in unbiased estimates if all variables related to attrition are included in the model.[28] Statistical analyses were performed in STATA (version 15.0; StataCorp). Statistical significance was set at $P<0.05$.

Results

Table 1 shows the baseline characteristics of study participants. The mean follow-up duration was 11.9 years (range: 11.0 to 12.4 years). The comparison of baseline characteristics of those included in the current study (stayers), excluded from the study (movers), and who dropped out of the AusDiab study is shown in Table S1. Compared with the stayers, the movers consisted of slightly more women and more workers, and the dropouts were more likely to be older, had lower educational qualifications, had lower income levels, did not work, did not live with a partner or children, and had poorer health profiles at baseline.

Table 2 shows the mean overall change (from AusDiab1 to AusDiab3) and the mean annual change (estimated from the unconditional growth models) of each cardiovascular risk marker. On average, participants increased their WC, weight, BP, and glucose levels but improved their lipid profiles (increased HDL-C and decreased triglycerides) over the 12-year period.

The mean baseline population density was 13.0 pph (SD=7.4, median=12.1, range: 0.5 to 52 pph). The mean annual relative population densification estimated from the unconditional growth model was 0.8% per year (SD=1.3, median=0.7, range: −4.1 to 7.8% per year). The mean annual absolute population densification was 0.09 pph/y (SD=0.13, median=0.08, range: −0.20 to 1.23 pph/y). Approximately one fifth of participants (19%) lived in areas where population density decreased during the study period. It should be noted that the relative and absolute densification are distinct measures of population-density changes. Although they were correlated ($r=0.65$, $P<0.01$), higher relative densification tended to occur in areas with lower baseline density, while higher absolute densification was more likely to take place in areas with higher baseline density (Figure S1 and S2).

Table 3 shows the results of multilevel linear growth models, examining linear associations of annual relative densification with annual changes in cardiovascular risk markers. After adjusting for baseline population density (model 1), a 1% annual increase in population density was associated with smaller increases in WC (b=−0.047 cm/y; 95% CI, −0.067 to −0.026 [$P<0.001$]), weight (b=−0.025 kg/y; 95% CI, −0.044 to −0.006 [$P=0.01$]), and HDL-C (b=−0.038 mg/dL per year; 95% CI, −0.067 to

Table 1. Selected Characteristics of Study Participants (N=2354) at Baseline in AusDiab (1999–2012)

Baseline Characteristics	Mean±SD or Percentage
Age, y	51.1±10.8
Women	53.6
Education	
High school or less	34.5
Technical or less	43.3
Bachelor's degree or higher	22.2
Employment status	
Working	70.7
Not working	28.8
Other	0.4
Weekly household income	
<$600	31.0
$600 to 1500	46.2
>$1500	22.8
Marital status, couple	85.2
Children in household	45.2
Cardiovascular risk markers	
WC, cm	89.7±13.4
Weight, kg	76.2±15.6
SBP, mm Hg	128.3±17.5
DBP, mm Hg	70.8±11.5
FPG, mg/dL	99.5±18.9
2-h PG, mg/dL	109.2±37.4
HDL-C, mg/dL	55.4±14.4
Triglycerides, mg/dL	131.5±87.9
Health-related behaviors	
Energy intake, kJ/d	8131±3277
Tobacco smoking, current or past smoker	38
Alcohol intake, g/d	14.3±17.9
Family history of diabetes mellitus	19.6
Medication use	
For hypertension	12.1
For high cholesterol	7.7
Index of relative socioeconomic disadvantage	1023±62

2-h PG indicates 2-hour postload plasma glucose; AusDiab, Australian Diabetes Obesity and Lifestyle Study; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; WC, waist circumference.

Table 2. Overall Changes and Annual Change Rates in Cardiovascular Risk Markers in AusDiab (1999–2012)

Cardiovascular Risk Marker	Mean±SD Overall Changes*	Mean±SD Annual Change Rates†
WC, cm	5.20±7.53	0.433±0.237
Weight, kg	2.02±7.08	0.163±0.322
SBP, mm Hg	2.77±18.18	0.283±0.167
DBP, mm Hg	1.81±12.69	0.169±0.462
FPG, mg/dL	0.37±20.32	0.042±0.855
2-h PG, mg/dL	2.73±36.01	0.307±0.988
HDL-C, mg/dL	3.39±10.63	0.292±0.278
Triglycerides, mg/dL	−12.66±75.53	−1.076±2.377

2-h PG indicates 2-hour postload plasma glucose; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; WC, waist circumference.
*Measure at AusDiab3 (Australian Diabetes Obesity and Lifestyle Study)—measure at AusDiab1.
†Estimated from the unconditional growth model.

−0.009 [*P*=0.009]). Statistical adjustment for sociodemographic (model 2) and behavior- and health-related factors (model 3) did not markedly alter the regression coefficients and statistical significance for WC but slightly attenuated the associations for weight (*P*=0.07 in model 3) and HDL-C (*P*=0.04 in model 3). Additionally, in model 3, a 1% annual increase in population density was marginally associated with a greater increase in DBP (b=0.032 mm Hg/y; 95% CI, −0.004 to 0.069 [*P*=0.08]).

The regression results obtained using the absolute measure of densification (pph/y) are shown in Table S2. We observed consistent but more statistically significant inverse associations for WC, weight, and HDL-C, and an additional significant association for 2-hour PG. In model 3, each 1-pph annual increase in population density was associated with smaller increases in WC (b=−0.38 cm/y; 95% CI, −0.60 to −0.15 [*P*<0.001]), weight (b=−0.19 kg/y; 95% CI, −0.40 to 0.02 [*P*=0.08]), 2-hour PG (b=−1.96 mg/dL per year; 95% CI, −3.16 to −0.77 [*P*=0.001]), and HDL-C (b=−0.59 mg/dL per year; 95% CI, −0.93 to −0.25 [*P*=0.001]).

The results of the sensitivity analyses, focusing only on participants who resided in metropolitan areas (n=1274), are shown in Table S3. Similar to those reported in Table 3 (model 3), relative densification was associated with changes in WC and HDL-C (borderline significant). However, relative densification in metropolitan areas was also associated with greater increases in DBP and systolic BP (borderline significant). The absolute population densification in metropolitan areas was associated with changes in HDL-C (same as model 3 in Table S2) but was not associated with WC and 2-hour PG changes.

Discussion

In this cohort of Australian adults, participants' cardiovascular risk increased on average during the 12-year study period, with the exception of a slight improvement in lipid profiles. In Australia, the mean annual increase in WC is about 0.45 cm among adults,[30] which is consistent with the estimated annual increase in our sample. We found that changes in some cardiovascular risk markers varied by population densification. Increases in urban population density were

Table 3. Associations of Annual Relative Population Densification With Changes in Cardiovascular Risk Markers in AusDiab (1999–2012)

Cardiovascular Risk Markers	Unstandardized Regression Coefficients (95% CI)		
	Model 1	Model 2	Model 3
WC, cm	−0.047 (−0.067 to −0.026)*	−0.048 (−0.069 to −0.026)*	−0.043 (−0.065 to −0.021)*
Weight, kg	−0.025 (−0.044 to −0.006)†	−0.018 (−0.038 to 0.002)‡	−0.019 (−0.039 to 0.001)‡
SBP, mm Hg	0.020 (−0.029 to 0.070)	0.021 (−0.031 to 0.073)	0.018 (−0.037 to 0.072)
DBP, mm Hg	0.025 (−0.01 to 0.059)	0.028 (−0.007 to 0.063)	0.032 (−0.004 to 0.069)‡
FPG, mg/dL	−0.018 (−0.073 to 0.038)	−0.019 (−0.071 to 0.033)	−0.008 (−0.062 to 0.045)
2-h PG, mg/dL	−0.077 (−0.182 to 0.027)	−0.084 (−0.193 to 0.026)	−0.076 (−0.191 to 0.039)
HDL-C, mg/dL	−0.038 (−0.067 to −0.009)§	−0.036 (−0.067 to −0.006)†	−0.035 (−0.067 to −0.002)†
Triglycerides, mg/dL	0.007 (−0.197 to 0.211)	0.058 (−0.155 to 0.271)	0.034 (−0.190 to 0.258)

Regression coefficients correspond to 1% annual increase in population density relative to the baseline population density. Model 1: adjusted for baseline population density and corrected for clustering. Model 2: further adjusted for age, sex, education, employment status, household income, marital status, household children status, height (only for weight), and Index of Relative Socio-Economic Disadvantage. Model 3: further adjusted for energy intake, tobacco smoking, alcohol intake, family history of diabetes mellitus (for fasting plasma glucose [FPG] and 2-hour plasma glucose [2-hour PG] only), hypertensive medication use (for systolic blood pressure [SBP] and diastolic blood pressure [DBP] only), and cholesterol medication use (for high-density lipoprotein cholesterol [HDL-C] and triglycerides only). AusDiab indicates Australian Diabetes Obesity and Lifestyle Study; WC, waist circumference.
*$P<0.001$; †$P<0.05$; ‡$P<0.10$; §$P<0.01$.

beneficially associated with changes in obesity-related measures, after adjusting for multiple potential confounders including energy intake. The estimated effect size was greater for WC change than for body weight change, suggesting that increasing urban densification may have a protective effect against abdominal obesity, which is a strong marker of cardiometabolic disease risk.[31]

We found that the study areas varied by 12% in their annual population densification (range: −4% to 8%). Since the regression coefficient for WC change was −0.043 cm for 1% annual density increase, those living in areas with −4% densification would have an additional 0.52 cm (=0.043×12) greater increase in WC per year, relative to those living in areas with 8% densification. At the population level, such differences in WC increases accumulated over years would be substantial. The potential protective effects of increasing population density against obesity may be greater in Australian capital cities such as Sydney and Melbourne, where large populations reside in neighborhoods with increasing density, which was around 4% annually in the past 5 years.[32]

Our findings on the associations between population densification and obesity measures are consistent with 2 previous longitudinal studies conducted in the United States.[19,20] Although these studies did not use a direct measure of population-density change measured at a local scale, our findings along with these studies suggest that increasing population density may reduce the risk of obesity in localities with lower population density. Increasing population density can increase access to more walkable destinations in the neighborhood.[17] Residents in such neighborhoods may, for example, engage in more active travel and rely less on cars for transport, which can have a protective effect against chronic diseases over time.[33,34] Further research is needed to examine the potential role of active travel and car use in the impact of densification on obesity.

We did not find associations of relative or absolute densification with BP changes, except for a borderline adverse association between relative densification and DBP. However, in the sensitivity analysis undertaken on metropolitan participants, we found higher relative densification to be associated with greater increases in the BP measures. This finding was unexpected. There is strong longitudinal evidence for the relationships between higher walkability (a composite measure including population density) and lower risk of hypertension.[16,35] Thus, it was anticipated that increasing population density would have beneficial effects on BP. It is not possible to explain our present findings (no associations for the whole sample, but adverse associations for the metropolitan sample). Potential explanations may include nonlinear relationships between densification and BP changes, or detrimental impacts by unmeasured factors related to urban densification (eg, increased air and noise pollution from traffic, reduced exposure to green space, and enhanced access to unhealthy food and alcohol). If the beneficial impact of densification on obesity-related measures is attributable to physical activity, there may be other pathways for BP that overshadow the benefits from being active. Given that cities across the globe are increasing their density, further studies are needed to examine multiple pathways and quantify each of their potential mediating effects to fully understand both the beneficial and detrimental impacts of urban densification. Future research can explore further how to avoid or mitigate harmful cardiovascular health effects of densification.

No associations were found between relative densification and blood glucose measures. However, absolute densification was beneficially associated with 2-hour PG in all models, but not with fasting plasma glucose (Table S2). Overall, it can be argued that increasing population density has some modest benefits for blood glucose, potentially attributable to physical activity increases. On the contrary, we found that both relative and absolute densification measures had adverse effects on HDL-C, but they were not associated with triglycerides (Table 3 and Table S2). It is unclear as to why densification had differential impacts on blood glucose and lipid measures. It is also unclear why the 2 densification measures produced distinct results for postload blood glucose (significant results found for absolute densification). It is not possible to disentangle the effects of densification on blood glucose and lipids, but these findings suggest that densification may be both beneficial and detrimental to cardiometabolic health. Studies on potential mediating factors may provide insights into the way population densification influences residents' blood glucose and lipid measures.

Study Strengths and Limitations

Our study has several strengths. We used robust objective measures for both the outcomes and exposure at 3 time points with a 12-year follow-up duration. The study sites ranged from metropolitan to regional cities, which provided a wide range of variation in population density changes. We used multilevel growth models to analyze the relationships between densification and within-participant changes in cardiovascular risk markers, sequentially adjusting for potential time-constant and time-varying confounders. A limitation is that while our findings may be generalizable to localities with lower population density, they may not be applicable to very high-density cities. Future research needs to investigate the impacts of density increase in higher-density localities as further densification may produce adverse cardiovascular health effects. The attrition rate was relatively high because of the longer follow-up period (55%). Our modeling approach assumes a "missing at random" mechanism, where it has

been shown that up to 60% attrition was less likely to produce biased estimates under this missingness mechanism.[36] However, if attrition was caused by a "missing not at random" mechanism, the effect sizes may have been underestimated.[36] Further selection of participants as a result of their relocation status could also lead to selection bias, if the relocation status is patterned by participants' cardiovascular risk status.[36] Since the aim of our study was to examine the total effects (through direct and potential pathways) of population densification on cardiovascular risk changes over time, we did not examine the mediating mechanisms or effect modifications. Understanding mechanisms (contextual variables such as access to public transport or individual behaviors such as physical activity) through which urban densification influences cardiovascular health is an important future research topic. Research is also needed to examine whether the potential cardiovascular impacts of densification varies by population subgroups (eg, sex, socioeconomic status, and ethnicity) and among different levels of area-level socioeconomic status, for whom disparities in cardiovascular health has been observed.[37]

Conclusions

Urban densification is a global phenomenon, which also applies to Australian cities. The expansion of growth boundaries to allow low-density residential development in urban peripheries is a commonly used strategy to accommodate urban population increases. Our findings suggest that increasing population in existing neighborhoods (while not expanding the growth boundary) may be protective against obesity. However, we also found potential detrimental effects of densification on BP and on blood lipids. Further studies in different localities with higher baseline density such as Asian and European cities and investigating behavioral and other factors that may mediate the effects are warranted to better understand the potential cardiovascular impacts of urban densification. Research is also needed to test whether there are population-density thresholds above which further population increases may elevate cardiovascular disease risk.

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Disclosures

None.

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Supplemental Material

Data S1.

Multilevel Growth Models

Multilevel modeling (MLM) is a commonly used statistical method in studies on neighborhood and health, where participants are clustered within study sites. Failing to account for this clustering (violation of independent observations) in the regression modeling can increase the probability of committing Type I error (so resulting in false "significant" findings). MLM is one way of appropriately analyzing such data structures. A longitudinal study design in the context of neighborhood and health research has an additional level of clustering due to repeated measures for each participant. For data with three-level structure (i.e., repeated observations are nested within study participants who are in turn nested within study sites, see Figure S1), multilevel growth models (MGM) can account for both the dependence between repeated measures within participants, and the spatial clustering within study sites.

Further, MGM can be used to answer the question about if and to what extent between-participant differences in changes of the outcome variables (within-participant) can be explained by between-participant differences in the explanatory variables that may or may not vary over time. In the current study, MGM was used to examine associations of changes in cardiovascular risk markers with neighborhood population densification, by adjusting for potential time-constant and time-varying confounders. In this supplementary material, we describe the development of MGM with explanations of the model parameters and the analytical strategy used in the current study.

Development of the MGM

For simplicity, we first explain the development of a two-level MGM, in which repeated observations (Level 1) are nested within study participants (Level 2). Then, we outline the three-level MGM used in the current study.

- **The null model (no-growth model)**

The null model (no-growth model) is used as a starting point because this model hypothesizes that the outcome variable does not change with time. A null model can be written as a sequence of two model equations for each level as follows:

- Level 1 (time-level) model ⇒ $y_{ti} = b_{0i} + e_{ti}$
- Level 2 (participant-level) model ⇒ $b_{0i} = \beta_0 + u_{0i}$,

where at Level 1 (time-level), y_{ti} is the value of the outcome variable measured at time point t for study particpant i; b_{0i} is the randon intercept indicating the mean of y_{ti} across the multiple time points for particpant i; e_{ti} is the time-specifc residual [$e_{ti} \sim N(0, \sigma_e^2)$]. At Level 2 (particpant-level), β_0 is the overall mean of y_{ti} across all participants; u_{0i} is the random part of the intercept indicating the deviation of b_{0i} from β_0 [$u_{0i} \sim N(0, \sigma_{u0}^2)$] for participant i.

- **<u>The unconditional linear growth model</u>**

The above-specified model can be extended as a "growth model" by entering the *time metric* (e.g., measurement time in the study) into the Level 1 equation and allowing its coefficient (time slope) to vary between participants. The sequence of the models are written as

- Level 1 (time-level) model ⇒

$$y_{ti} = b_{0i} + b_{1i}t + e_{ti}$$

- Level 2 (participant-level) models ⇒

$$b_{0i} = \beta_0 + u_{0i}$$
$$b_{1i} = \beta_1 + u_{1i},$$

where, b_{0i} is the random intercept at t=0 of the outcome variable for particpant i (i.e., starting point); b_{1i} is the random slope of the time metric – indicating the linear change in the outcome variable for one-unit incease in time for particpant i (i.e., the rate of change). Together, b_{0i} and b_{1i} capture the growth trajectory of the outcome variable for particpant i. As the statrting point and rate of change can have a specific value for each participant, they are allowed to vary between particpants at Level 2 by specifying the mean intercept (β_0) and mean slope of the time metric (β_1) of the population. The random components (u_{0i} and u_{1i}) indicate the between-person variability in the individual intercepts and slopes. Jointly, u_{0i} and u_{1i} are assumed to follow a Multivariate Normal distribution with a null mean vector and a covariance matrix $\left(\text{i.e. } u_{0i}, u_{1i} \sim MVN\left(\begin{bmatrix}0\\0\end{bmatrix}, \begin{bmatrix}\sigma_{u0}^2 & \\ \sigma_{u01} & \sigma_{u1}^2\end{bmatrix}\right)\right)$. In the unconditional linear growth model, there are six parameters to be estimated: β_0, β_1, σ_{u0}^2, σ_{u1}^2, σ_{u01}, σ_e^2. Note that the no-growth model <u>should be rejected</u> in favor of the unconditional linear growth model in order to have a significant *change* in the outcome.

- **<u>MGM with time-invariant and time-varying covariates</u>**

Now the above specified unconditional linear growth model can be extended by entering the covariates (the term covariates include both exposure and confounding variables) into the models. Here, two type of covariates can be entered: time-constant and time-varying covariates. Time-constant covariates (TCC) are participant-specific characteristics which do not change with time (e.g., gender). Time-varying covariates (TVC) do change with time (e.g., age). Note that TVCs are entered into the Level 1 equation and TCCs are entered into the Level 2 equation. Let x be a TCC and z be a TVC. Then, the sequence of the models are written as

- Level 1(time-level) model ⇒

$$y_{ti} = b_{0i} + b_{1i}t + b_2 z_{ti} + e_{ti}$$

- Level 2 (participant-level) models ⇒

$$b_{0i} = \beta_0 + \beta_{01}x_i + u_{0i}$$
$$b_{1i} = \beta_1 + \beta_{11}x_i + u_{1i},$$

where, z_{ti} is the value of a TVC measured at time point t for particpant i, and x_i is the value of a TCC for particpant i. For TCC x, β_{01} and β_{11} are the regression coefficients indicating the relationship between x and individual intercepts and time slopes of the outcome variable, respectively. For instance, β_{11} is interpreted as expected difference in the time slope of the outcome variable (i.e., the rate of change in the outcome) for one unit difference in x. For time-varying covariate z, b_2 is the regression coefficient indicating the expected difference in y for one unit difference in z. Thus, any given repeated measure of the outcome variable is jointly determined by the underlying growth trajectory (i.e., the starting point and the rate of change – both depend on TCCs) and the impact of the TVCs at that time period.

The single equation model by combining the Level 1 and Level 2 models:

$$y_{ti} = \beta_0 + \beta_1 t + \beta_{01}x_i + \beta_{11}x_i t + b_2 z_{ti} + u_{0i} + u_{1i}t + e_{ti}$$

Analytical Strategy of the Current Study

The current study has a three-level data structure; time (three repeated measures), participants, and study sites. The exposure variable of the study is neighborhood population densification (i.e., the annual change in neighborhood population density). To calculate this exposure variable, we first fitted a two-level unconditional linear growth model of neighborhood population density with Census years as time metrics (t=1 for 2001, t=6 for

2006, t=11 for 2011). The estimated random intercepts (at t=0) and the random slopes were used as the baseline neighborhood population density at the year 2000 and the annual neighborhood population densification, respectively, and entered into the Level 2 models. Participants' gender and education were treated as TCCs (as participants were 25 years and over at baseline), and entered into the Level 2 models. Participants' characteristics which may change with time (age, marital status, employment status, household income, household children status, energy intake, tobacco smoking, and alcohol intake) were treated as TVCs, and were entered into the Level 1 model. Area-level socioeconomic status (Index of Relative Socioeconomic Disadvantage- IRSD), which is a study site characteristic but available for three corresponding waves from Australian Census, was treated as a TVC, and entered into the Level 1 model. In the current analyses, we sequentially adjusted for baseline density, socio-demographic covariates, and health- and behavior-related covariates. In the multilevel growth model analysis, when modelling each risk marker, we excluded participants who had only one time point value for the relevant risk marker (as it is not possible to calculate a change measure). Multilevel models utilized the available information on covariates, assuming those missing data are missing at random.

The null-model fitted in the current study:

- Level 1 (time-level) model ⇒ $y_{tij} = b_{0ij} + e_{tij}$
- Level 2 (participant-level) model ⇒ $b_{0ij} = \beta_{00j} + u_{0ij}$
- Level 3 (site-level) model ⇒ $\beta_{00j} = \gamma_{000} + v_{00j}$,

where, y_{tij} is the value of the outcome variable (i.e., cardiovascular risk marker) measured at time point t for study particpant i who is in study site j; the random intercept b_{0ij} is the mean of y_{tij} across the time points for a particpant i who is in a site j; b_{0ij} is allowed to vary between-particpants at Level 2 around β_{00j} (mean of y_{tij} across the time points for all particpants in a study site j); β_{00j} is allowed to vary between-sites at Level 3 around the overall mean γ_{000}.

The multivariate MGM (model 3) fitted in the current study:

- Level 1 (time-level) model ⇒

$$y_{tij} = b_{0ij} + b_{1i}t + b_2 age_{ti} + b_3 marital_{ti} + b_4\, employment_{ti} + b_5\, income_{ti} + b_6\, children_{ti} + b_7\, energy_{ti} + b_8\, smoking_{ti} + b_9\, alcohol_{ti} + b_{10}\, IRSD_{ti} + e_{tij}$$

- Level 2 (participant-level) models ⇒

$$b_{0ij} = \beta_{00j} + \beta_{01}\, densification_i + \beta_{02}\, baseline.density_i + \beta_{03}\, gender_i + \beta_{04}\, education_i + u_{0ij}$$

$$b_{1i} = \beta_1 + \beta_{11}\, densification_i + \beta_{11}\, baseline.density_i + \beta_{11}\, gender_i + \beta_{11}\, education_i + u_{1i}$$

- Level 3 (site-level) model ⇒

$$\beta_{00j} = \gamma_{000} + v_{00j}$$

Further, family history of diabetes as a TCC (only for blood glucose outcomes in Level 2), hypertension medication use as a TVC (only for blood pressure outcomes in Level 1), and cholesterol medication use as a TVC (only for lipid outcomes in Level 1), were also entered.

By incorporating the Level 3 and Level 2 equations in the Level 1 equation, we obtain the single equation model. The estimated values of β_{11} and their confidence intervals were used to report the associations between neighboourgood population densification and changes in cardiovascular risk markers.

Table S1. **Baseline characteristics of stayers, movers, and drop-outs, AusDiab study (1999-2012).**

Baseline characteristics	Mean (SD) or Percentage		
	Stayers (N=2,354)	Movers (N=2,140)	Drop-outs (N=6,588)
Age, years	51.1 (10.8)	50.0 (11.3)	53.5 (16.0)
Sex, % Women	53.6%	56.2%	54.7%
Education			
% High school or less	34.5%	32.4%	46.4%
% Technical or less	43.3%	44.3%	41.0%
% Bachelor's degree or more	22.2%	23.2%	12.7%
Employment status			
% Working (incl. students)	70.7%	76.2%	50.6%
% Not working	28.8%	23.5%	49.0%
% Others	0.4%	0.3%	0.4%
Weekly household income			
% Less than $600	31.0%	29.2%	51.3%
% $600-1500	46.2%	48.6%	36.5%
% >$1500	22.8%	22.2%	12.2%
Marital status, % couple	85.2%	78.5%	72.1%
Children in household, % yes	45.2%	46.7%	34.5%

Cardiovascular risk markers			
WC (cm)	89.7 (13.4)	89.2 (13.7)	92.0 (14.2)
Weight (kg)	76.2 (15.6)	76.4 (16.1)	76.7 (16.6)
SBP (mmHg)	128.3 (17.5)	124.7 (16.0)	131.6 (19.9)
DBP (mmHg)	70.8 (11.5)	69.0 (11.3)	70.3 (12.0)
FPG (mg/dL)	99.5 (18.9)	98.3 (19.4)	102.4 (23.8)
2-hr PG (mg/dL)	109.2 (37.4)	107.2 (35.3)	118.7 (47.3)
HDL-C (mg/dL)	55.4 (14.4)	55.8 (14.7)	54.7 (14.9)
TG (mg/dL)	131.5 (87.9)	126.9 (83.6)	143.6 (100.9)
Health-related behaviors			
Energy intake (kJ/day)	8131 (3277)	8155 (3147)	7909 (3764)
Tobacco smoking, % current /past	38%	41%	49%
smoker	14.3 (17.9)	13.6 (16.8)	12.4 (18.0)
Alcohol intake (g/day)			
Family history of diabetes, % yes	19.6%	18.7%	18.1%
Medication use			
For hypertension, % yes	12.1%	9.1%	19.5%
For high cholesterol, % yes	7.7%	5.8%	10.1%
Population density (persons/ hectare)	13.0 (7.4)	12.6 (7.4)	13.7 (8.0)

AusDiab, Australian Diabetes Obesity and Lifestyle Study; WC, Waist Circumference; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; FPG, Fasting Plasma Glucose; 2-hr PG, 2-hour Postload Plasma Glucose; HDL-C, High-Density Lipoprotein Cholesterol; TG, Triglycerides; pph, persons per hectare . In total, 11,247 participants were recruited at the baseline. Of those, 4,614 participants completed surveys and biomedical examination at the 12-years follow-up. After excluding participants whose addresses were not geocoded (N=81), there were 2,369 stayers and 2,164 movers. Participants who were pregnant during the data collection time were further excluded from each category [stayers (N=15), movers (N=24), drop-outs (N=45)].

Table S2. **Associations of annual absolute population densification with changes in cardiovascular risk markers, AusDiab study (1999-2012).**

Cardiovascular risk markers	Unstandardized regression coefficients (95% CI)		
	Model 1	Model 2	Model 3
WC (cm)	-0.393 (-0.598, -0.188) ***	-0.431 (-0.652, -0.210) ***	-0.377 (-0.604, -0.150) **
Weight (kg)	-0.225 (-0.419, -0.031) *	-0.216 (-0.420, -0.012) *	-0.190 (-0.400, 0.019) †
SBP (mmHg)	0.370 (-0.129, 0.868)	0.372 (-0.163, 0.906)	0.295 (-0.270, 0.859)
DBP (mmHg)	0.192 (-0.154, 0.538)	0.247 (-0.112, 0.607)	0.241 (-0.136, 0.619)
FPG (mg/dL)	-0.347 (-0.905, 0.212)	-0.446 (-0.979, 0.087)	-0.409 (-0.962, 0.143)
2-hr PG (mg/dL)	-1.480 (-2.536 -0.423) **	-1.866 (-2.994 -0.738) **	-1.964 (-3.160 -0.768) **
HDL-C (mg/dL)	-0.656 (-0.946, -0.367) ***	-0.608 (-0.922, -0.293) ***	-0.590 (-0.925, -0.254) **
TG (mg/dL)	0.362 (-1.689, 2.412)	0.557 (-1.623, 2.736)	0.308 (-2.006, 2.622)

AusDiab, Australian Diabetes Obesity and Lifestyle Study; WC, Waist Circumference; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; FPG, Fasting Plasma Glucose; 2-hr PG, 2-hour Postload Plasma Glucose; HDL-C, High-Density Lipoprotein Cholesterol; TG, Triglycerides.
Regression coefficients correspond to 1 pph/year increase in population density.

*** $P<0.001$, **$P<0.01$, * $P<0.05$; † $P<0.10$.
Model 1: adjusted for baseline population density and corrected for clustering
Model 2: further adjusted for age, sex, education, work status, household income, marital status, household children status, height (only for weight), and Index of Relative Socio-economic Disadvantage
Model 3: further adjusted for energy intake, tobacco smoking, alcohol intake, family history of diabetes (for FPG and 2-hr PG only), hypertension medication use (for SBP and DBP only), and cholesterol medication use (for HDL-C and TG only)

Table S3. Associations of annual population densification with changes in cardiovascular risk markers among metropolitan residents (N = 1,274 [54% of analytical sample] after excluding 1,080 participants resided in the regional cities), AusDiab study, 1999-2012.

Cardiovascular risk markers	Unstandardized regression coefficients (95% CI)	
	Relative densification	Absolute densification
WC (cm)	-0.032 (-0.062, -0.001)*	-0.153 (-0.461, 0.155)
Weight (kg)	-0.010 (-0.038, 0.018)	-0.035 (-0.316, 0.246)
SBP (mmHg)	0.063 (-0.011, 0.136) †	0.129 (-0.622, 0.881)
DBP (mmHg)	0.062 (0.013, 0.112) *	0.109 (-0.397, 0.614)
FPG (mg/dL)	0.039 (-0.035, 0.114)	0.066 (-0.692, 0.824)
2-hr PG (mg/dL)	-0.045 (-0.205, 0.115)	-1.324 (-2.964, 0.316)
HDL-C (mg/dL)	-0.041 (-0.086, 0.005) †	-0.661 (-1.122, -0.200) **
TG (mg/dL)	-0.040 (-0.336, 0.256)	-0.025 (-3.035, 2.984)

AusDiab, Australian Diabetes Obesity and Lifestyle Study; WC, Waist Circumference; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; FPG, Fasting Plasma Glucose; 2-hr PG, 2-hour Postload Plasma Glucose; HDL-C, High-Density Lipoprotein Cholesterol; TG, Triglycerides.
For relative densification: regression coefficients correspond to 1% annual increase in population density relative to the baseline population density.
For absolute densification: regression coefficients correspond to 1 pph/year increase in population density
**P<0.01, * P <0.05; † P <0.10.
Model was adjusted for baseline population density, age, sex, education, work status, household income, marital status, household children status, height (only for weight), Index of Relative Socio-economic Disadvantage, energy intake, tobacco smoking, alcohol intake, family history of diabetes (for FPG and 2-hr PG only), hypertensive medication use (for SBP and DBP only), and cholesterol medication use (for HDL-C and TG only).

Figure S1. Three-level data structure of the current study.

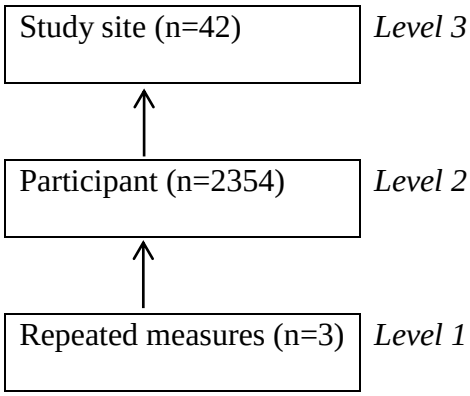
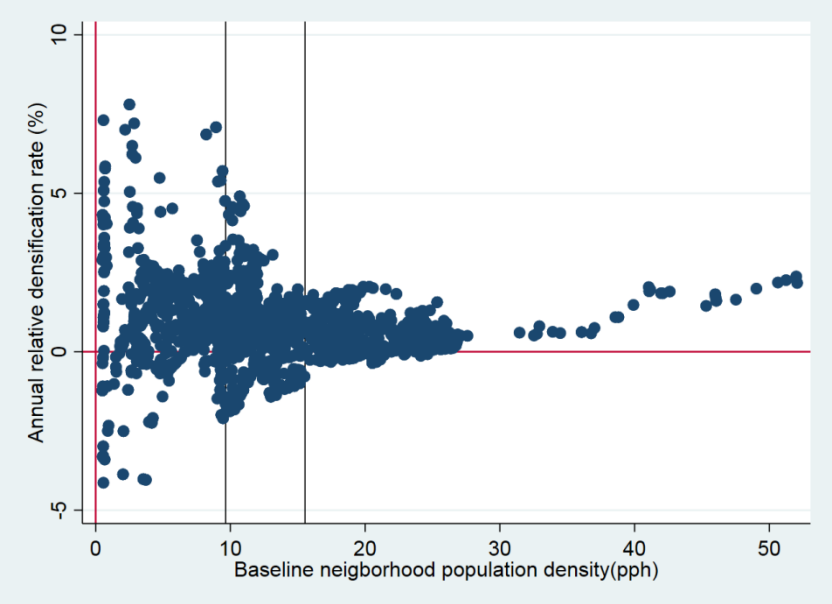
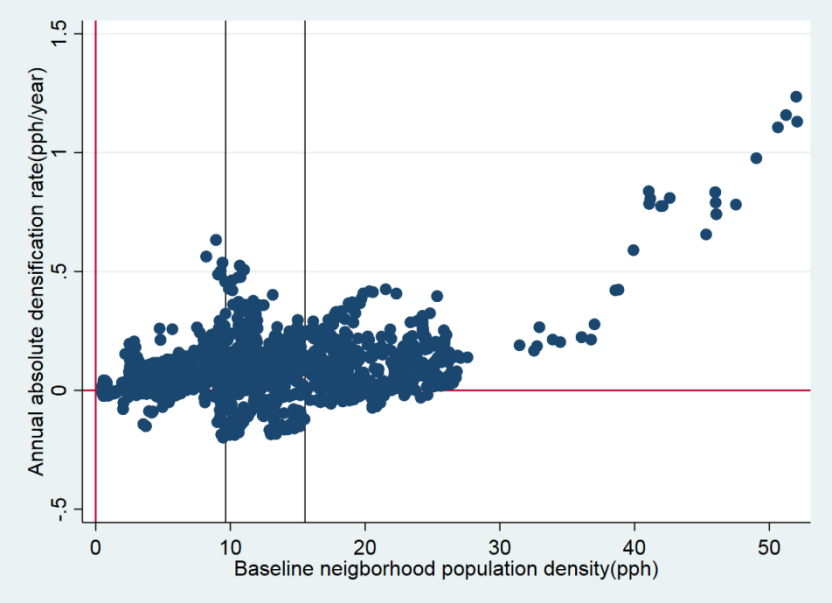


Figure S2. Scatterplots showing the relationships of annual relative population densification (top) and annual absolute population densification (bottom) with baseline population density.





Vertical lines indicate the baseline population density tertiles. Higher values of relative densification are found where baseline density is low (top), while higher values of absolute densification are found where baseline density is high (bottom).

SUPPLEMENTAL REFERENCES:

1. Curran PJ, Bauer DJ. The disaggregation of within-person and between-person effects in longitudinal models of change. *Annual review of psychology*. 2011; 62: p. 583-619.
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5. Hox JJ, *Multilevel analysis: Techniques and applications*. 2010: Routledge.