TITLE

Urbanization, mainly rurality, but not altitude is associated with dyslipidemia profiles

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Short title: Dyslipidemia patterns, high altitude and urbanization level

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ABSTRACT

Background: Geographical and environmental features such as urbanization and altitude may influence individual's lipid profiles because of the diversity of human-environment interactions including lifestyles.

Objective: To characterize the association between altitude and urbanization, and lipid profile among Peruvian adults aged ≥35 years.

Methods: Cross-sectional analysis of the CRONICAS Cohort Study. The outcomes of interest were six dyslipidemia traits: hypertriglyceridemia, high LDL-c, low HDL-c, non-isolated low HDL-c, isolated low HDL-c, and high non-HDL-c. The exposures of interest were urbanization level (highly urban, urban, semi-urban and rural) and altitude (high altitude vs. sea level). Prevalence ratios (PR) and 95% confidence intervals (95% CI) were calculated using Poisson regression models with robust variance adjusting for potential confounders.

Results: Data from 3,037 individuals, 48.5% males, mean age 55.6 (SD±12.7) years, was analyzed. The most common dyslipidemia pattern was high non-HDL-c with a prevalence of 88.0% (95% CI 84.9% - 90.7%) in the rural area and 96.0% (95% CI 94.5% - 97.1%) in the semi-urban area. Relative to the highly urban area, living in rural areas was associated with a lower prevalence of hypertriglyceridemia (PR=0.75; 95% CI 0.56–0.99) and high non-HDL-c (PR=0.96; 95% CI 0.93–0.99), whereas living in semi-urban areas was associated with higher prevalence high LDL-c (PR=1.37; 95% CI 1.11–1.67). Compared to sea-level areas, high altitude areas had lower prevalence of high non-HDL-c (PR=0.97; 95% CI 0.95–0.99).

Conclusion: Urbanization but not altitude was associated to several dyslipidemia traits, with the exception of high non-HDL-c in high altitude settings.

Keywords: urbanization, rurality, altitude, dyslipidemia, enviroment.

Highlights

- Levels of urbanization but not altitude were associated with dyslipidemia traits.
- People in rural areas had lower prevalence of dyslipidemia traits in comparison to urban areas.
- Population from semi-urban areas showed high prevalence of some dyslipidemia traits.

INTRODUCTION

While cardiovascular diseases (CVD) continue being the leading cause of death worldwide, the prevalence of dyslipidemia –the key underlying process contributing to most CVD– continues increasing worldwide (1). Indeed, high prevalence of dyslipidemia has been reported in low- and middle-income countries, especially in Latin America, such as 57% of individuals with low levels of high-density lipoprotein cholesterol (HDL-c) in Lima, 32% of hypertriglyceridemia (high TG) in Mexico city, and 24% of high low-density lipoprotein-cholesterol (LDL-c) levels in Buenos Aires (2).

Levels of serum lipids are influenced by several environmental factors. For instance, fatty acid and carbohydrate content and composition in diet, adiposity, physical activity, and alcohol intake have been shown to be important determinants of lipoprotein secretion and metabolism (3). However, the role of environmental factors directly related to place of residence, such as urbanization or altitude, has not been fully understood.

The potential association between high altitude and dyslipidemia remains controversial. Some studies in Peru have found a positive association between high altitude with hypertriglyceridemia and low HDL-c (4, 5). Also a study conducted in Lhasa, Tibet, located at 3,660 meters above sea level (m.a.s.l.), found a high prevalence of hypertriglyceridemia and low concentrations of HDL-c (6). On the other hand, one study in Peru reported a low prevalence of hypercholesterolemia, hypertriglyceridemia, and low HDL-c in high altitude (>3,000 m.a.s.l.) compared to sea level population (7). Another study in Arab populations found higher levels of HDL-c in people who live at 2,000 m.a.s.l. relative to those who live at sea level (8). These studies denote the controversial results in the association between high altitude and dyslipidemia patterns, and do not account for the rural/urban effect that is also be present event at different altitudes.

Studying the isolated effect of high altitude and urbanization on lipid levels is challenging, as both are strongly associated with different lifestyle behaviors compared with sea level and rural counterparts, respectively. For example, lifestyle in rural areas includes a dietary intake characterized by high levels of carbohydrates (9, 10), as well as greater levels of physical activity compared to urban areas (11). Understanding the diversity of human-environment interactions with regard to dyslipidemias is important, especially if in 2014, 88% of Latin America and Caribbean population lived in urban areas (12), and it is calculated that 35 million people live above 2,500 m.a.s.l in South America between the cities of Bolivia, Colombia, Ecuador and Peru (13). Also, between 10 and 17 million people live at over 2500 m.a.s.l. in the Andes.(14)

Previous studies in dyslipidemias were predominantly conducted in rural areas in high altitude or urban sea level cities. The CRONICAS Cohort Study was designed to evaluate Peruvian adults from four settings differing on the levels of altitude and urbanization, allowing for combinations of rural-urban and sea level-high altitude settings. As such, it offers a unique opportunity to test our hypothesis and characterize the association between altitude and urbanization and lipid profiles.

METHODS

Study design, settings and participants

Baseline information from the CRONICAS Cohort Study, collected in 2010-2011, was analyzed in the present study. The CRONICAS Cohort Study was conducted in four different settings: Pampas de San Juan de Miraflores, a highly urbanized community of approximately 15,000 inhabitants/km^2 and located within Lima, the capital city of Peru, at sea level. Tumbes, a semi-urban site with 250 inhabitants/km^2 is located in the northern coast of Peru, also at sea level. Puno, the high-altitude site, is located on the shore of Lake Titicaca at 3,825 m.a.s.l., and contributed with an urban site and a rural site with population densities of 9,940 inhabitants/km^2 and 31 inhabitants/km^2, respectively (15). (Figure 1)

All participants were ≥35 years, full-time residents in the study area, and provided informed consent. Participants were excluded if they were pregnant, had any physical disability that would difficult take measurements, and had active pulmonary tuberculosis. A sex- and age-stratified (35-44, 45-54, 55-64,

≥65 years) random sampling technique was conducted using the most updated census available in each site. In Puno, recruitment was stratified to include 500 participants in each of the urban and rural sites (15).

Variables definition

Six dyslipidemia traits were chosen as the main outcomes of interests. Three of them were selected because are the most common dyslipidemia indicators that have been described to be associated with cardiovascular disease and mortality, including hypertriglyceridemia (TG ≥200 mg/dL), high low-density lipoprotein-cholesterol (LDL-c ≥160mg/dL), and low high-density lipoprotein-cholesterol (HDL-c<40 mg/dL in men, and <50 mg/dL in women). A fourth indicator, high non-HDL-c (non-HDL-c ≥160 mg/dL), emerging as a new cardiovascular risk factor (16), was also evaluated in the whole sample. The two other dyslipidemia traits, non-isolated low HDL-c (low HDL-c accompanied by high TG and/or high LDL-c) and isolated low HDL-c (low HDL-c and TG<200 mg/dL and LDL-c<160mg/dL), correspond to a subgroup of low-HDL-c, a highly prevalent pattern of dyslipidemia as reported in previous studies in Peru and Latin America (16, 17).

The exposures of interest were: urbanization level (highly urban, urban, semi-urban and rural) and altitude (high altitude vs. sea level). It is important clarify that highly urban and semi-urban areas were at sea level and urban and rural areas were at high altitude level. The urbanization level was define for the population density 15,000; 9,940; 250 and 31 inhabitants/km^2

Other variables included in the analysis were sociodemographic, lifestyle factors, body mass index and comorbidities. Sociodemographic variables were: Sex, age, educational level (<7, 7–11 and ≥12 years), and socio-economic status assessed through a wealth index derived from assets possession and household facilities, in tertiles. Lifestyle variables were: Current daily smoking was self reported and defined as smoking at least one cigarette per day. Hazardous drinking was considered if the participant had an score ≥8 using the Alcohol Use Disorder Identification Test (18). Physical activity levels was measured combining leisure time and transportation-related physical activity domains of the International Physical Activity Questionnaire (IPAQ) and classified as high/moderate vs. low physical activity (19). Patterns of consumption of certain foods, each variable representing the daily consumption of several types of food and divided in tertiles. Body mass index (BMI) was included and categorized as normal (≥18.5 to <25 kg/m^2), overweight (≥25 to <30 kg/m^2), and obese (≥30 kg/m^2). Clinical variables were: Hypertension, blood pressure was measured three times, and SBP and DBP were calculated from the average of the second and third measurements and hypertension was defined as having a systolic blood pressure (SBP) ≥140 mmHg, or diastolic blood pressure (DBP) ≥90 mmHg, or self-report of physician diagnosis or use of antihypertensive medication. Diabetes was defined as having a fasting blood glucose ≥126 mg/dL [≥7 mmol/L] or self-report of physician diagnosis or use of antidiabetic medication and impaired fasting glucose was defined as having a fasting blood glucose between 110 and <126 mg/dL (20).

Procedures

Fieldwork activities and procedures of the CRONICAS Cohort Study have been described in detail elsewhere (15). Trained community health workers applied face-to-face questionnaires. After completing the questionnaire, an appointment for a clinical assessment was arranged to ensure an adequate fasting period, between 8 and 12 hours, where a total of 13.5 mL of blood was drawn. Standing height was measured using standardized techniques. After a 5-minute resting period, blood pressure was measured using an automatic monitor OMRON HEM-780 (OMRON, Tokyo, Japan) validated for adult population.

For laboratory procedures, Cobas® Modular Platform automated analyzer and reagents from Roche Diagnostics were used to measure triglycerides, total cholesterol and HDL-c. Also, LDL-c was measure with this method, in participants with triglycerides ≥400 mg/dL. However, if participants had triglycerides below 400 mg/dL, the Friedewald equation was used to calculate LDL-c in mg/dL. Non-HDL-c was also estimated by subtracting HDL-c from total cholesterol. Serum glucose was measured using an enzymatic colorimetric method (GOD-PAP; Modular P-E/Roche-Cobas, Grenzach-Whylen, Germany).

Statistical analysis

All statistical analyses were performed using Stata 12.0 (Stata Corp, College Station, TX, USA). Prevalence and 95% confidence intervals (95% CI) of lipid profile patterns by altitude and level of urbanization were estimated. Chi-squared was used to show the association between altitude, level of urbanization, sociodemographic, lifestyle factors, BMI and comorbidities with dyslipidemia patterns.

Different models were generated to evaluate the crude and adjusted association of dyslipidemia patterns with our main exposures (urbanization level and altitude). We used Poisson regression with robust variance, and prevalence ratios (PR) and 95% CI were reported (21). Our first models compared specifically: (i) hypertriglyceridemia vs. normal triglycerides; (ii) high LDL-c vs. normal LDL-c; (iii) low HDL-c vs. normal HDL-c; (iv) high non-HDL-c vs. normal non-HDL-c. Also the subgroups of low HDL-c: (v) isolated low HDL vs. normal HDL-c; and (vi) non-isolated low HDL-c vs. normal HDL-c. Models were adjusted by different variables: Model 1 was adjusted by sociodemographic variables: age, sex, education and wealth index; Model 2 provided estimates adjusting for lifestyle factors and clinical variables, namely daily smoking, hazardous drinking, physical activity, hypertension, and diabetes. Model 3, in addition to the aforementioned variables, included adjustment for BMI as well as checking for collinearity. The analytical approach, including the selection of variables used for adjustment in the models, was decided using the criteria of prior information (22).

Ethics

The Institutional Review Boards of Universidad Peruana Cayetano Heredia and Asociación Benéfica PRISMA in Lima, Peru, and Johns Hopkins University in Baltimore, US, approved the study. Participants received information about the objectives and procedures of the study and gave oral consent due to high rates of illiteracy, mainly in rural and semi-urban areas.

RESULTS

Response rate at baseline was 62.9% (4,325/6,872), and of these 83.3% (3,601/4,325) had completed questionnaires. Among those with completed questionnaires, 84.3% (3,037/3,601) had complete lipid profile parameters for the analysis. The characteristics of the participants included vs. those not included in the analysis are available in Supplementary Table 1. Differences in education level, socioeconomic status, hazardous drinking, physical activity, hypertension and diabetes were found between the participants included compared to those not included in this analysis.

Data from 3,037 participants, 48.5% males, mean age 55.6 years (SD±12.7) was used in the analyses. The characteristics of the study population according to study site are presented in the Supplementary Table 2. In these bivariate analyses, there was evidence of an association between study site and education level, socioeconomic status, daily smoking, hazardous drinking, physical activity, hypertension, and diabetes.

Mean levels of triglycerides was 149.0mg/dL (SD±70.0), LDL-c levels was 127.2 mg/dL (SD±34.5), HDL-c levels was 41.9 mg/dL (SD±11.4) whereas non-HDL-c was 156.9 mg/dL (39.5) with differences between study sites (Table 1).

Table 2 and table 3 show the bivariate association between socio demographic, lifestyle, BMI, and other clinical variables with dyslipidemia traits. Age and BMI were associated with all dyslipidemia patterns. Female sex was associated to high LDL-c, low HDL-c, and its subgroups. Also hypertriglyceridemia, low HDL-c and high LDL-c were associated to high socioeconomic status.

Lipid profiles by level of urbanization and altitude

High non-HDL-c was the most common lipid trait in all study sites followed by low HDL-c. In general, in terms of urbanization, a common pattern was observed where the rural site had the lowest prevalence of all lipid profiles studied compared to all other study sites, with the exception of isolated low HDL where no differences were observed. When both rural and urban Puno sites were combined into a high-altitude variable, the same pattern described before was observed, with the high altitude setting having a lower prevalence of lipid traits than the sea-level sites. The prevalence of dyslipidemia traits by urbanization and altitude are shown in Figures 2, 3 and 4, and the point prevalence estimates and 95% CIs are presented in Supplementary Table 3.

Association between level of urbanization and lipid traits

In the crude analyses, we found evidence of an association between level of urbanization, especially in the rural site, and the six primary outcomes of interest. Further adjustment by sociodemographic, lifestyle factors and clinical variables maintained the association in five out of the six dyslipidemia traits in the rural site.

Relative to the highly urban site, participants living in rural areas had 40% lower prevalence of hypertriglyceridemia and 6% lower prevalence of high non-HDL-c (Table 4, adjusted model 2). In addition, there was evidence of a 37% higher prevalence of high LDL-c among individuals living in the semi urban area relative to those in the highly urban area.

Association between altitude and lipid traits

We found evidence of an association between altitude and five out of the six primary outcomes focused on single dyslipidemia traits, with the exception of isolated low HDL. These associations remained present in the crude and non-BMI adjusted models, even when sociodemographic, lifestyle factors and clinical variables were included (Table 4).

The role of BMI: BMI-adjusted models

In terms of urbanization, when BMI was included in the models, associations remained in the rural site for hypertriglyceridemia and high non-HDL-c outcomes, and for high LDL-c in the semi-urban area. In the case of altitude, additional adjustment for BMI attenuated all of the estimates and the association disappeared in all cases with the exception of high non-HDL-c (Table 3, adjusted model 3). The addition of BMI to these models did not show evidence of collinearity with the other variables used for adjustment.

DISCUSSION

Main findings

Our findings show that it was largely urbanization, particularly rurality rather than altitude, the main driver in the association with dyslipidemia traits. The analysis pooling data into high-altitude versus sea-level sites do carry the predominant associations observed in the rural high-altitude site. This observation favors the interpretation that it is urbanization the exposure that is strongest associated with the outcomes of interest.

Comparison with other studies

The study of dyslipidemia according to urbanization and altitude as joint exposures and within the same population is limited. Most studies have compared rural vs. urban areas without considering the effect of altitude. For example, studies in India and Peru reporting higher rates of isolated low HDL-c in rural in comparison to urban populations (17, 23), not confirmed in our study, and associations between hypercholesterolemia, hypertriglyceridemia and high LDL-c with urban residence (23). Among the later, we were able to replicate the association with hypercholesterolemia and hypertriglyceridemia but not high LDL-c. One potential explanation lies on the fact that not all rural areas are necessarily identical, and whilst they share some commonalities in terms of population size, it is possible that lifestyle across rural and urban areas carry other differences, particularly in relation to diet (24), physical activity (11) or other factors (25), that could alter the relationship with the lipid-related outcomes of interest. In relation to dietary patterns, a Peruvian national nutritional survey has reported that individuals from Lima, our highly urban site, had a slightly lower consumption of fried foods in comparison to the rest of the coast but higher consumption than people from rural highlands (26); whereas, respect to protein intake Lima had higher consumption in comparison to the rest of the country (27). It is also known that blood lipids are highly susceptible to the intake of protein and carbohydrates, with higher levels of triglycerides and LDL-c among those with lower protein intake, despite the similar amount of carbohydrates consumed (28, 29).

With regards to altitude and lipid profiles, previous studies have compared high altitude vs. sea level population. Previous studies from Peru have included rural populations living at 4,100 m.a.s.l. vs. urban sea-level groups (5), as well as groups at ≥3000 m.a.s.l. vs <1000 m.a.s.l. (7). These studies showed crude estimates and did not adjust by potential confounders nor by BMI, limiting the comparability with our findings. A separate study from Oman, in the Arabian peninsula, compared HDL-c levels in families living at different altitudes, i.e. 2,000 vs. 700 m.a.s.l., and found that this marker was lower in the population living at higher altitude in the order of -0.39 mmol/L [15 mg/dL] (8), a difference that may not have much clinical relevance. In our study, we did not observe an association between low HDL-c and altitude.

We built different models to explore our association of interest, including a final model that adjusted by BMI. In so doing, such adjustment markedly reduced the strength of the associations, attenuating towards the null the majority of them.

BMI is independently associated with patterns of dyslipidemia and also with level of urbanization and altitude, for these reason BMI was treated as a confounder. It is well known that obesity causes high LDL-c, hypertriglyceridemia and low HDL-c (30). In terms of the relationship between BMI and our exposures of interest, previous studies have found that obesity increases with some aspects of urbanization like lower diet quality scores and less physical activity (31), and longitudinal studies have found that urban populations have a 9-time increased risk of developing obesity relative to rural population (32). With regards to altitude, a study from Spain reported that living at higher altitude was inversely associated with the risk of developing overweight or obesity (33). Whilst some may consider that obesity lies in the causal pathway of the association between our exposures of interest and lipid profiles, we decided to maintain the adjustment for BMI as separate results, so that it can guide the assessment of our estimates and ensure comparability with other studies.

Potential explanation to our findings

The basis to explore altitude as a predictor of alterations in lipid profiles has a physiological basis. Periodic hypoxemia produce an alteration in the oxidation of lipids in the hepatic cells (34), acute exposure to high altitude found increased levels of HDL and decrease levels of triglycerides (35). One of challenges observed is that unravelling the effects of altitude on lipid profiles is difficult given the predominance of studies focused on rural high-altitude areas only, without the assessment of urban high-altitude settings. Our study capitalizes on the opportunity of studying both, urban and rural sites at the same level of altitude, thus removing the effect of urbanization on our association of interest. Hence, we contend that it is rurality, but not altitude, the main driver of the associations observed. It is possible that lifestyle factors associated with urbanization may largely explain our findings rather than physiological parameters observed at high altitude. For instance, most of the dyslipidemia traits studied had a lower prevalence in the rural population than in the urban one.

Strengths and Limitations

The CRONICAS Cohort Study affords us the study of a combination of different sites by their specific features of altitude and urbanization, thus providing a unique opportunity to test our hypothesis. However, we only compare two different levels of altitude where high altitude includes urban and rural populations, and sea level included semi-urban and highly urbanized populations. Nevertheless, our study is one of the few studies that evaluates the association of patterns of lipid profile among people living different levels of urbanization and altitude. Other limitations:. first, it may be argued that the genetic background may have a role in determining the differences observed. However, our results are not likely to be fully explained by different genetic backgrounds. The genetic admixture in Peruvians is very high (36) with many groups sharing common Native American ancestry, and the European ancestry component is relatively small (<10%).(37) This decreases, but does not eliminate, the role that genetics may play in the associations observed. Even if genetics had a role, this is likely to be superseded by the effect of lifestyle factors on lipid profiles. (38) Second, it has been described that the environment is related to lifestyle and dietary patterns (39, 40) and we did not explore dietary patterns in our study populations. A more detailed diet assessment would have informed our study, yet conducting such measurements in large population-based studies is not always feasible nor free from limitations (41). Third, some selection bias may be present in our analysis as participants with data available for the analysis differed in certain socioeconomic characteristics from those who did not contributed data to the analysis. Four, population density is a criteria to define different urbanization levels. However, in many countries some additional criteria is necessary to define different degrees of urbanization.(42)

Conclusions

Levels of urbanization but not altitude were associated with dyslipidemia traits. People living in rural areas had a lower prevalence of dyslipidemia traits than their urban counterparts. In the case of the population from semi-urban areas, they showed a higher prevalence of high LDL-c and non-HDL-c compared to the highly urban area. Taken together, these finding supports discarding a relationship between high-altitude and lipid traits, but rather placing emphasis on urbanization as a key factor linked to lipid patterns.

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CONFLICTS OF INTEREST

None

CONTRIBUTIONS:

MLP, ABO, and JJM conceived and designed the overall study. MLP, ABO and RQ drafted the first version of the manuscript. MLP and ABO conducted the statistical analysis. LS, WC, GM, and RG gave their input to latest version of the manuscript. All of the authors contributed to the revising of the manuscript for important content and gave their final approval of the version submitted for publication.

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