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J Endocrinol Metab. 2024;14(4):194-206

# Evaluation of Nine Forms of Metabolic Syndrome Diagnosis as Risk for Cardiovascular Disease: An Analysis of Isolated and Combined Metabolic Factors

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## Abstract

**Background:** Metabolic syndrome (MetS) is a pathological condition varying according to the guidelines used, leading to ongoing debate on whether all these forms of defining MetS offer the same level of risk for developing cardiovascular diseases (CVDs). The aim of the study was: 1) to determine the prevalence of each type of MetS; 2) to assess the association of each type with CVDs over a 5-year follow-up period; and 3) to analyze whether each possible combination of MetS carries the same level of risk for developing CVD in the time above frame.

**Methods:** This study is a secondary analysis of a Peruvian cohort database. The dependent variable was the development of CVD. In contrast, the independent variable was MetS, defined based on nine diagnostic methods: Adult Treatment Panel III (ATPIII), International Diabetes Federation (IDF), World Health Organization (WHO), Joint Interim Statement (JIS), European Group for the Study of Insulin Resistance (EGIR), American Heart Association and National Heart, Lung, and Blood Institute (AHA/NHLBI), American Association of Clinical Endocrinologists (AACE), Latin American Diabetes Association (ALAD), and International Lipid Information Bureau Latin America (ILIBLA). Results were presented as relative risk (RR).

**Results:** The overall prevalence of MetS was 40.59%, while the 5-year incidence of CVD was 1.69%. The lowest prevalence was found with ALAD criteria (5.6%), while the highest was ILIBLA (37%). Diagnostic forms of MetS according to ILIBLA (RR = 5.06; 95% confidence interval (CI): 1.64 - 15.62), AHA/NHLBI (RR = 5.06; 95% CI: 1.64 - 15.62), JIS (RR = 3.66; 95% CI: 1.22 - 10.97), and API (RR = 2.83; 95% CI: 1.11 - 7.20) showed a risk of CVD. Additionally, hyperglycemia, hypertriglyceridemia, and elevated blood pressure were found to be individually associated with the presence of CVD. In contrast, other factors, such as altered waist circumference (WC) and low high-density lipoprotein (HDL), are only associated with an increased risk in combination with other markers.

**Conclusions:** Significant variations in the prevalence of MetS according to the definition used were revealed, as well as significant differences in the risk of CVD associated with different types of MetS.

**Keywords:** Metabolic syndrome; Heart disease risk factors; Public health

Manuscript submitted March 7, 2024, accepted April 24, 2024
Published online July 5, 2024

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doi: https://doi.org/10.14740/jem945

## Introduction

Metabolic syndrome (MetS) is a pathological condition classically comprising abdominal obesity, elevated blood pressure, dyslipidemia, and hyperglycemia, and its prevalence continues to rise significantly worldwide [1]. In China, rates reach up to 24.5% [2], while in the United States, around 50% of adults have this condition [3]. In Latin America, prevalence ranges from 15% to 21% [4, 5]. The Peruvian population's prevalence varies between 25% and 45%, depending on the criteria [6].

The diagnosis of MetS is complex, as it varies according to the guidelines used for diagnosis [7-10]. Although MetS is generally recognized for its capacity to increase the likelihood of long-term cardiovascular disease (CVD), there is ongoing debate over whether all these forms of defining MetS present the same level of risk [11, 12].

Therefore, these discrepancies in risk assessment underscore the need for further research to ensure accurate and consistent cardiovascular risk evaluation in patients with MetS. Consequently, the objectives of the current study were as follows: 1) to determine the prevalence of each type of MetS; 2) to evaluate the association of each type with CVD over a 5-year follow-up period; and 3) to analyze whether each possible combination of MetS carries the same level of risk for developing CVD in the time above frame.

## Materials and Methods

### Design

This study is a secondary analysis of the PERU MIGRANT study database, which is a prospective cohort designed to assess the magnitude of differences between rural, rural-to-urban, and urban migrant groups about cardiovascular risk factors [13].

### Study population

The characteristics of the PERU MIGRANT study settings and the enrolled participants have been detailed elsewhere [13]. Briefly, a single-stage random sampling method was used across all study groups, stratified by age group and sex. Rural participants were selected from the adult population permanently residing in San Jose de Secker in Ayacucho. Urban participants were born and lived in Pampas de San Juan de Miraflores, a neighborhood in Lima, Peru. Rural-to-urban migrants were held in Ayacucho and lived in Pampas de San Juan de Miraflores. For re-evaluation, participants were re-contacted in the same environment where they were initially enrolled.

Initially, the primary study recruited a total of 989 participants. For this manuscript, specific exclusion criteria were applied: participants without necessary data for MetS diagnosis were removed. Additionally, only those participants who completed the 5-year study follow-up were included.

### Variables and measurement

The response variable in this study was the diagnosis of CVD, defined as the presence of at least one of the following events: myocardial infarction, heart failure, or cerebrovascular disease. This variable was assessed during the second visit through participant self-report. If the respondent reported the presence of at least one of these events, they were considered to have developed CVD. Thus, the response variable was dichotomous, categorized as "yes" if CVD developed and "no" otherwise.

The independent variable was MetS, defined based on nine diagnostic forms: 1) According to the Adult Treatment Panel (ATP) III, MetS is defined by the presence of at least three of the following factors: abdominal obesity, measured through waist circumference (WC) > 102 cm in men and > 88 cm in women, triglycerides ≥ 150 mg/dL, low high-density lipoprotein (HDL) levels < 40 mg/dL in men and < 50 mg/dL in women, blood pressure ≥ 130/85 mm Hg or treatment for hypertension, and fasting glucose ≥ 100 mg/dL or treatment for hyperglycemia [8]. 2) The International Diabetes Federation (IDF) defines MetS as the presence of abdominal obesity if WC > 94 cm in men and > 80 cm in women plus at least two of the other four factors used by the ATPIII [10]. 3) The World Health Organization (WHO) defines MetS as the presence of fasting glucose ≥ 110 mg/dL and at least two of the following factors: obesity (by body mass index ≥ 30 kg/m$^2$ or waist-to-hip ratio ≥ 0.9 in men or ≥ 0.8 in women), dyslipidemia (triglycerides ≥ 150 mg/dL or HDL < 35 mg/dL in men and < 39 mg/dL in women), and blood pressure ≥ 140/90 mm Hg. While microalbuminuria is also considered, it was not included in this study [9]. 4) The Joint Interim Statement (JIS) defines MetS as the presence of any three of the five factors used by the ATPIII, but with an abdominal obesity definition of WC > 90 cm in men and > 80 cm in women [7]. 5) The European Group for the Study of Insulin Resistance (EGIR) defines MetS as presenting insulin resistance (IR) or altered fasting insulin in non-diabetic patients and two or more of the following criteria: triglycerides ≥ 178 mg/dL, HDL ≤ 39 mg/dL, and blood pressure ≥ 140/90 mm Hg [14]. 6) The American Association of Clinical Endocrinologists (AACE) primarily targets the clinical criterion of the five factors; it was decided in this case that the definition of MetS be if presenting three or more of the following criteria: obesity (by body mass index ≥ 30 kg/m$^2$, triglycerides ≥ 150 mg/dL, low HDL levels < 40 mg/dL in men and < 50 mg/dL in women, blood pressure ≥ 130/85 mm Hg, and fasting glucose ≥ 100 mg/dL [15]. 7) The Latin American Diabetes Association (ALAD) considers MetS if presenting type 2 diabetes mellitus (T2DM) or altered fasting glucose ≥ 100 mg/dL plus abdominal obesity if WC > 94 cm in men and > 80 cm in women, plus at least two of the following criteria: triglycerides ≥ 150 mg/dL, low HDL levels < 40 mg/dL in men and < 50 mg/dL in women, blood pressure ≥ 130/85 mm Hg [16]. 8) The International Lipid Information Bureau Latin America (ILIBLA) incorporates the definition of MetS as part of its dyslipidemia management guide, where they define MetS as meeting three or more of the following criteria: obesity, measured through waist-to-hip ratio ≥ 0.9 in men or ≥ 0.8 in women, triglycerides ≥ 150 mg/dL, low HDL levels < 40 mg/dL in men and < 50 mg/dL in women, blood pressure ≥ 130/85 mm Hg, and fasting glucose ≥ 100 mg/dL [17]. 9) The American Heart Association and National Heart, Lung, and Blood Institute (AHA/NHLBI) define MetS in the same way as the ATPIII, with the difference that the cohort points used to describe abdominal obesity would be considered according to the population and specific definitions taken by each country [18]. 10) A global MetS was also considered if meeting at least one of the nine MetS above criteria.

The diagnosis of diabetes mellitus was taken by self-report. It was the same by self-report in relation to high blood pressure. IR was measured with the homeostasis model assessment of insulin resistance (HOMA-IR) index, which was calculated using the formula = (glucose (mmol/L) × insulin (μU/mL))/22.5 [19]. The results were categorized as "IR" if HOMA-IR ≥ 2.8 [20] and "no IR" if HOMA-IR < 2.8.

Additionally, a sub-analysis was performed by subdividing each patient group according to the different combinations of factors that meet the nine definitions above of MetS. This analysis aimed to assess whether all combinations of factors within each definition of MetS present the same level of risk for CVD. In this way, a specific number of unique combinations were generated for each definition of MetS, allowing for a more accurate evaluation of the cardiovascular risk associated with each combination.

At the initial assessment, variables examined included age brackets of 30 to 45 years, 46 to 59 years, and 60 years or

more; biological sex; migration background of urban, rural, or migrant; socioeconomic standing of low, medium, or high; and current smoking habits of yes or no; and alcohol consumption of low vs. high. The level of education attained, ranging from none/incomplete primary schooling to the completion of secondary school, in addition to the amount of physical activity undertaken weekly as evaluated by the International Physical Activity Questionnaire, which categorizes both the number of days with physical exercise and the estimated metabolic equivalents expended per minute into high, medium, or low levels, were considered.

### Procedures

The initial data collection for the descriptive cross-sectional study, which was conducted from 2007 to 2008, gathered information while the longitudinal study, performed several years later from 2012 through 2013, obtained its data 5 years after the prior described research.

During the examination, total height and sitting height were measured with 0.1 cm accuracy using a stadiometer and standard stools, and weight was recorded wearing light clothing with 0.05 kg accuracy using a SECA 940 electronic scale. WC and hip circumference were taken in triplicate at the point of maximum circumference over the buttocks. Waist and hip measurements were made in the horizontal plane, with participants standing, and a tape measure was used to record the measurements with up to 1 cm accuracy. It was measured three times at the midpoint between the last rib and the iliac crest. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured with cuffs suitable for arm circumference in a seated position, on the right arm, and at chest level. Three measurements were taken with an interval of at least 5 min between each, using an oscillometric device (Omron M5-i, Omron, Japan) previously validated for the adult population. The average of the last two measurements of SBP and DBP was used for the analysis. Field staff performed weight and WC measurements three times, applying standardized techniques.

Venous blood samples were collected in the morning after fasting for at least 8 h. The first fasting blood samples were taken and analyzed in a single laboratory, ensuring the quality of the analyses through regular external standards and internal control duplicates supervised by Bio-Rad. Triglycerides and HDL were measured in serum. Glucose and insulin were determined in plasma using an enzymatic colorimetric method (GOD-PAP; Modular P-E/Roche-Cobas, Grenzach-Whylen, Germany).

### Statistical analysis

For the statistical analysis, R software version 4.0.5 was used. An initial descriptive analysis, including all participants from the first assessment, presented categorical variables in frequencies and percentages. Bivariate analysis was performed with data from participants who completed the second assessment. Given the absolute nature of the response variable, the Chi-square test of independence was employed when the exposure variable was also categorical. Additionally, a bar graph was developed to compare the prevalence of each type of MetS, accompanied by their respective 95% confidence intervals (95% CIs).

Subsequently, a generalized linear model of the Poisson family with robust variance was implemented, adjusted for the covariates above. This model was applied to each unique combination of MetS factors and for each possible combination. The measure of association used was the relative risk (RR) and its respective 95% CI.

The measures of association were presented through a forest plot for both the general model and the sub-analysis. All illustrated graphics were created in the Python program.

### Ethical aspects

The database is publicly accessible, including the first assessment and the follow-up [21]. The survey information is freely accessible, without personal identifiers, and there was no contact with human subjects. Therefore, it was not considered necessary to conduct a review by an ethics committee. The study was conducted in accordance with the ethical standards of the responsible institution on human subjects, as well as with the Declaration of Helsinki.

## Results

The total number of participants was 946. The overall prevalence of MetS was 40.59%, while the 5-year incidence of CVD was 1.69%. At the start of the study, women made up 53.49%, 13.32% were elderly. Sixty percent were migrants. Regarding lifestyles, 44.78% had high physical activity, 10.99% smoked during that period, and 8.88% consumed high amounts of alcohol. The rest of the characteristics can be seen in Table 1. The bivariate analysis can be seen here (Supplementary Material 1, www.jofem.org).

Figure 1 visualizes the prevalence of MetS according to the criterion used. The lowest prevalence was found with the ALAD criteria (5.6%), while the highest was ILIBLA (37%). The rest of the requirements fluctuated around 10% to 20% (AHA, WHO, and EGIR) and 2030% (AACE, ATPIII, IDF, and JIS).

Figure 2 shows that the forms of MetS diagnosis global (RR = 4.21; 95% CI: 1.34 - 13.11), according to ILIBLA (RR = 5.06; 95% CI: 1.64 - 15.62), AHA/NHLBI (RR = 5.06; 95% CI: 1.64 - 15.62), JIS (RR = 3.66; 95% CI: 1.22 - 10.97) and ATPIII (RR = 2.83; 95% CI: 1.11 - 7.20) present a certain level of risk of CVD.

Figure 3 shows the possible combinations of each definition of MetS. It was found that both hyperglycemia and hypertriglyceridemia are statistically significantly associated with presenting CVD individually. In contrast, other factors, such as altered WC and low HDL, are only associated with an increased risk in combination with other factors. Furthermore,

**Table 1.** Demographic Characteristics of Participants

| Characteristic | Results (n = 946) |
|---|---|
| Sex, n (%) | |
| Female | 506 (53.49%) |
| Male | 440 (46.51%) |
| Age group, n (%) | |
| 29 - 44 years | 423 (44.71%) |
| 45 - 59 years | 397 (41.97%) |
| 60 years to more | 126 (13.32%) |
| Group, n (%) | |
| Rural | 183 (19.34%) |
| Migrant | 573 (60.57%) |
| Urban | 190 (20.08%) |
| Wealth index, n (%) | |
| Lowest | 320 (33.83%) |
| Middle | 318 (33.62%) |
| Highest | 308 (32.56%) |
| Educational level, n (%) | |
| None/some primary | 305 (32.31%) |
| Primary complete | 142 (15.04%) |
| Secondary to more | 497 (52.65%) |
| Physical activity, n (%) | |
| Low | 244 (26.01%) |
| Moderate | 274 (29.21%) |
| High | 420 (44.78%) |
| Current smoker, n (%) | |
| No | 842 (89.01%) |
| Yes | 104 (10.99%) |
| Alcohol volume, n (%) | |
| Low | 862 (91.12%) |
| High | 84 (8.88%) |
| Body mass index, n (%) | |
| Normal weight | 384 (40.59%) |
| Overweight | 370 (39.11%) |
| Obesity | 192 (20.30%) |
| Mets global, n (%) | |
| No | 562 (59.41%) |
| Yes | 384 (40.59%) |
| Cardiovascular disease, n (%) | |
| No | 930 (98.31%) |
| Yes | 16 (1.69%) |

MetS: metabolic syndrome.

the ATPIII and EGIR definitions showed the highest number of combinations as a risk of CVD. In contrast, IDF only showed risk in its forms, and no combination of WHO showed any risk.

## Discussion

### Prevalences of MetS according to the criterion used

The present study highlights a global prevalence of MetS of 40.59%, a finding that underscores the increasing burden of this condition on public health. This prevalence is notably higher than reported globally, where estimates vary widely depending on the region and diagnostic criteria. For example, recent studies in China and the United States have reported prevalences of approximately 20% and 37.6%, respectively, reflecting significant geographical and methodological variations [22, 23]. Furthermore, compared to data from Latin America, prevalences fluctuate between 15% and 21% [4, 5]. Thus, our results suggest that the Peruvian population may face a particularly elevated risk of MetS, possibly due to specific regional or methodological factors. Among these factors, we consider specific genetic variations of the Peruvian population, regional differences in diet and lifestyle, variability in access to health services, and significant socioeconomic differences that affect various regions of the country.

A crucial observation from this study is the notable variation in the prevalence of MetS according to the diagnostic criterion used, reflecting this condition's inherent complexity and heterogeneity. Our study observed the lowest prevalence with the ALAD criteria (5.6%), while the highest was with ILIBLA (37%). These differences are consistent with the existing literature, which indicates substantial variability in the prevalence rates of MetS depending on the diagnostic criteria applied [12, 24, 25]. For example, previous studies have shown that JIS and IDF criteria tend to report higher prevalences compared to other criteria such as ATPIII or WHO, underscoring the influence of measurement parameters on the epidemiological assessment of MetS [12 25, 27]; moreover, several studies have reported prevalence variations according to the criterion used [28-31].

The discrepancies between different diagnostic criteria for MetS complicate comparing epidemiological studies and pose severe clinical and public health challenges. The variability in criteria can lead to situations where an individual is diagnosed with MetS according to one criterion but not according to another. This inconsistency has direct implications for the identification and management of patients at risk of CVDs and diabetes. Individuals could be erroneously excluded from crucial preventive or therapeutic interventions based on a diagnostic criterion that does not reflect their metabolic risk status. Therefore, these criteria differences affect epidemiological accuracy and can have real consequences in health management and public policies.

### MetS and subtypes as a risk of CVD

Our study revealed notable heterogeneity in the risk of CVD associated with different types of MetS. In particular, it was observed that specific definitions of MetS, such as those proposed by ILIBLA and AHA/NHLB, presented a significantly higher risk of CVD. In contrast, others, like those of WHO,

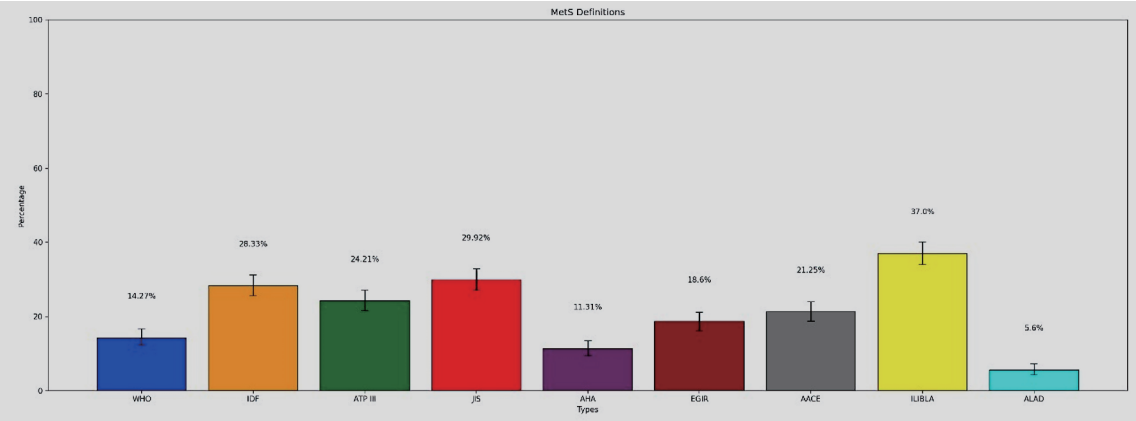


**Figure 1.** Prevalence of each definition of MetS. MetS: metabolic syndrome; ATPIII: Adult Treatment Panel III; IDF: International Diabetes Federation; WHO: World Health Organization; JIS: Joint Interim Statement; EGIR: European Group for the Study of Insulin Resistance; AHA: American Heart Association; AACE: American Association of Clinical Endocrinologists; ALAD: Latin American Diabetes Association; ILIBLA: International Lipid Information Bureau Latin America.

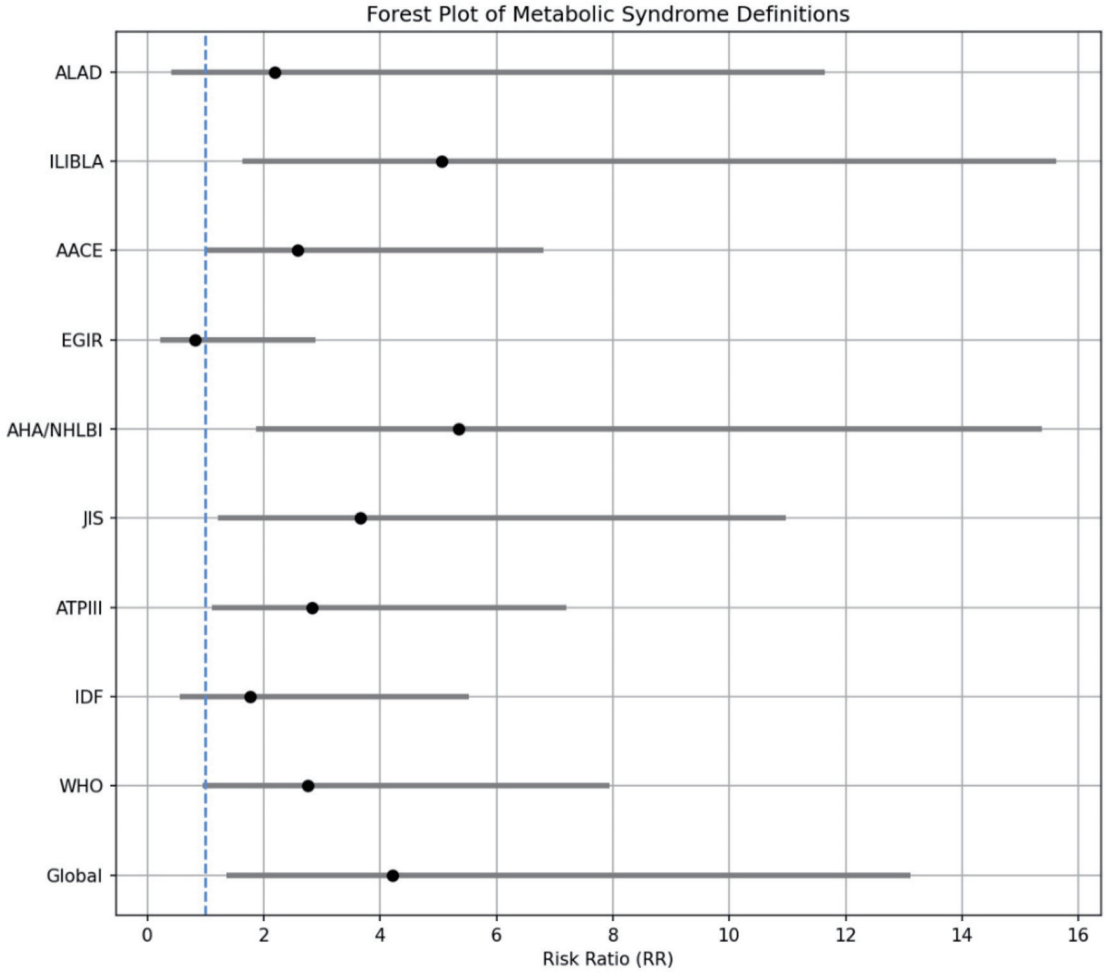


**Figure 2.** Forest plot regression analysis of each definition of MetS as risk of cardiovascular disease. MetS: metabolic syndrome; ATPIII: Adult Treatment Panel III; IDF: International Diabetes Federation; WHO: World Health Organization; JIS: Joint Interim Statement; EGIR: European Group for the Study of Insulin Resistance; AHA/NHLBI: American Heart Association and National Heart, Lung, and Blood Institute; AACE: American Association of Clinical Endocrinologists; ALAD: Latin American Diabetes Association; ILIBLA: International Lipid Information Bureau Latin America.

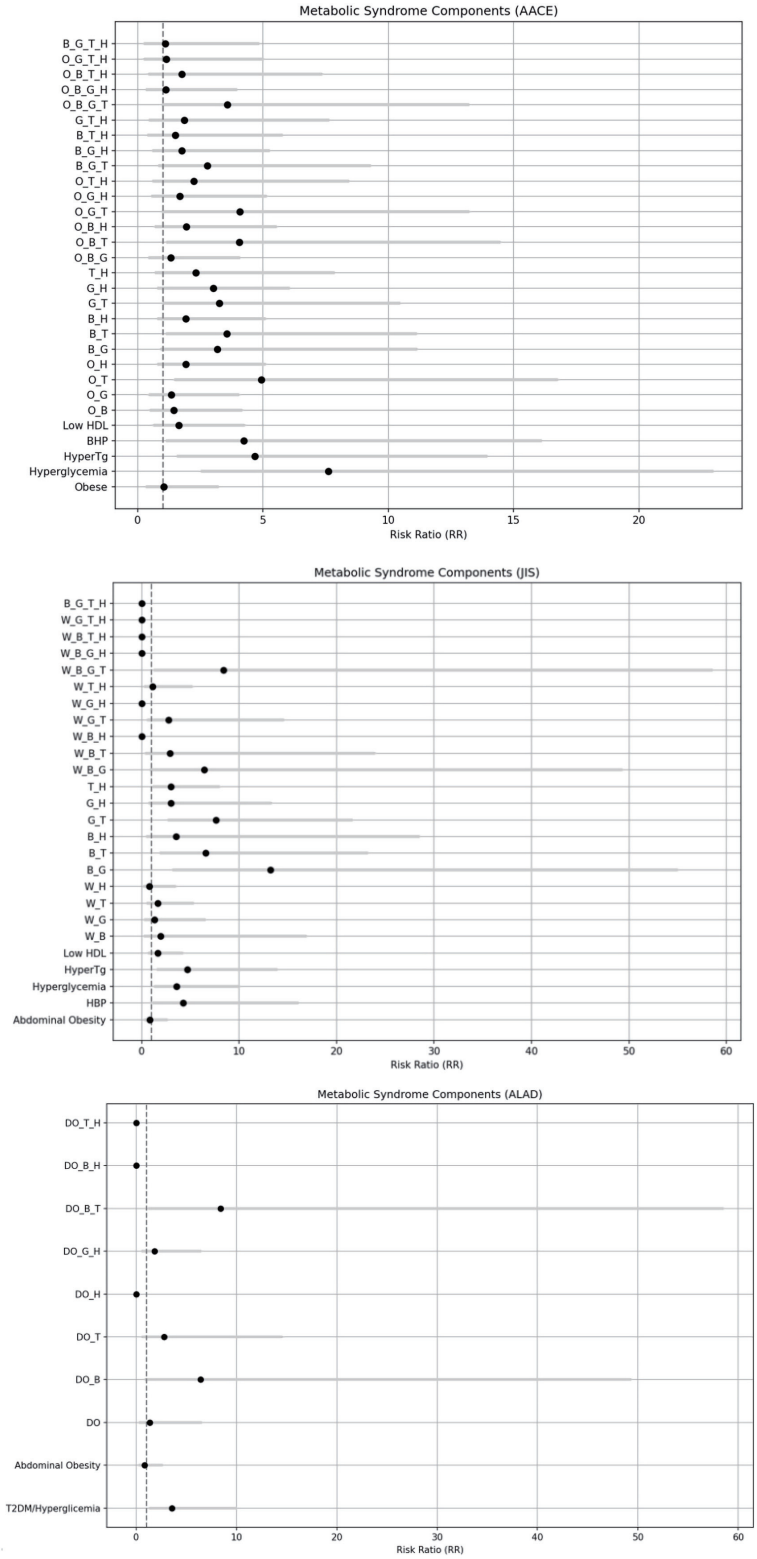


**Figure 3.** Different combinations of each MetS definition as CVD risk. For individual data the indicators were: low HDL, HyperTg = hypertriglyceridemia, hyperglycemia, HBP= high blood pressure and abdominal obesity. For the data as a whole: W = altered waist circumference, G = hyperglycemia, T = hypertriglyceridemia, H = low HDL, B = elevated blood pressure, D = T2DM/hyperglycemia, O = obesity, T = triglycerides, DO = diabetes and obesity. MetS: metabolic syndrome; CVD: cardiovascular diseases; T2DM: type 2 diabetes mellitus; HDL: high-density lipoprotein.

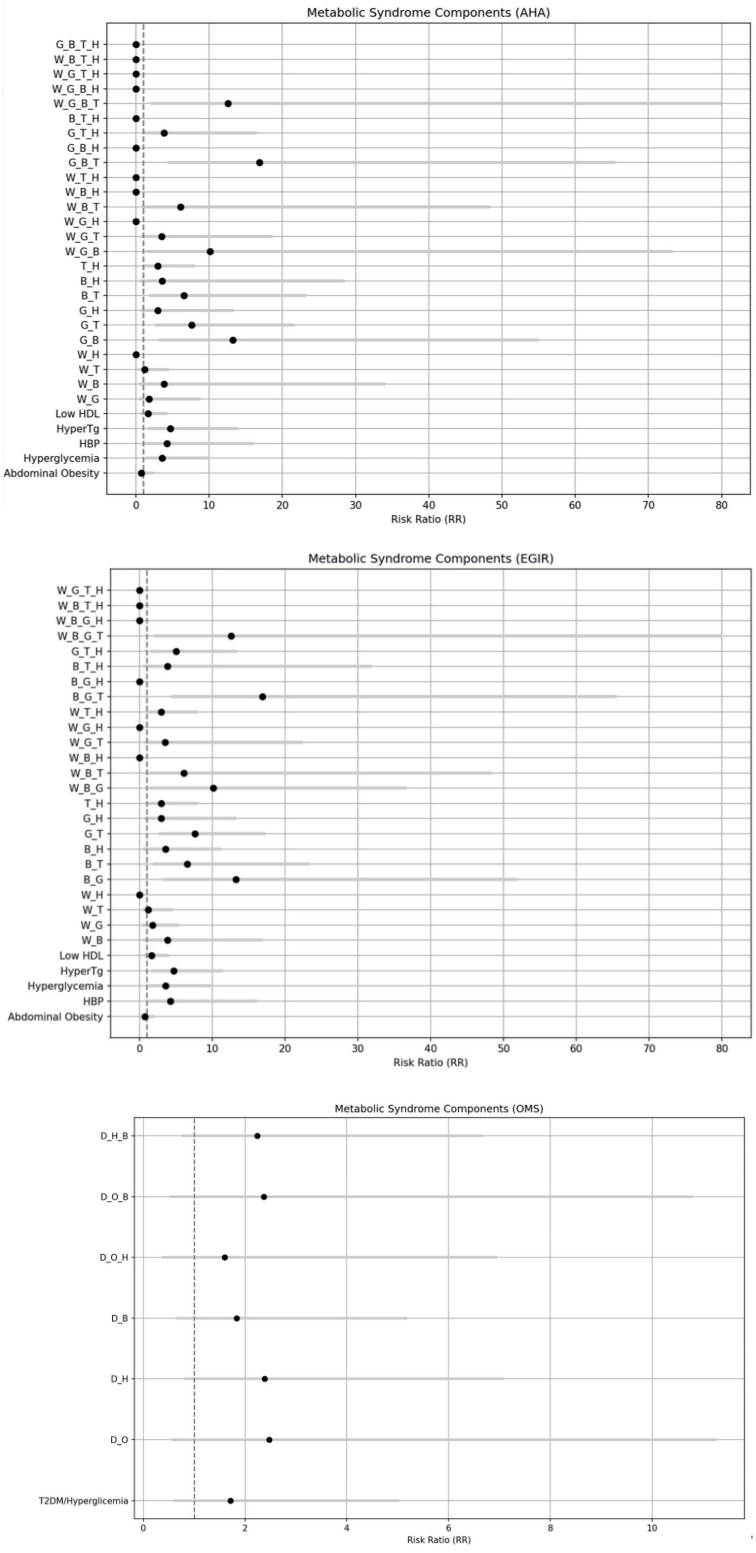


**Figure 3.** *(continued)* Different combinations of each MetS definition as CVD risk. For individual data the indicators were: low HDL, HyperTg = hypertriglyceridemia, hyperglycemia, HBP= high blood pressure and abdominal obesity. For the data as a whole: W = altered waist circumference, G = hyperglycemia, T = hypertriglyceridemia, H = low HDL, B = elevated blood pressure, D = T2DM/hyperglycemia, O = obesity, T = triglycerides, DO = diabetes and obesity. MetS: metabolic syndrome; CVD: cardiovascular diseases; T2DM: type 2 diabetes mellitus; HDL: high-density lipoprotein.

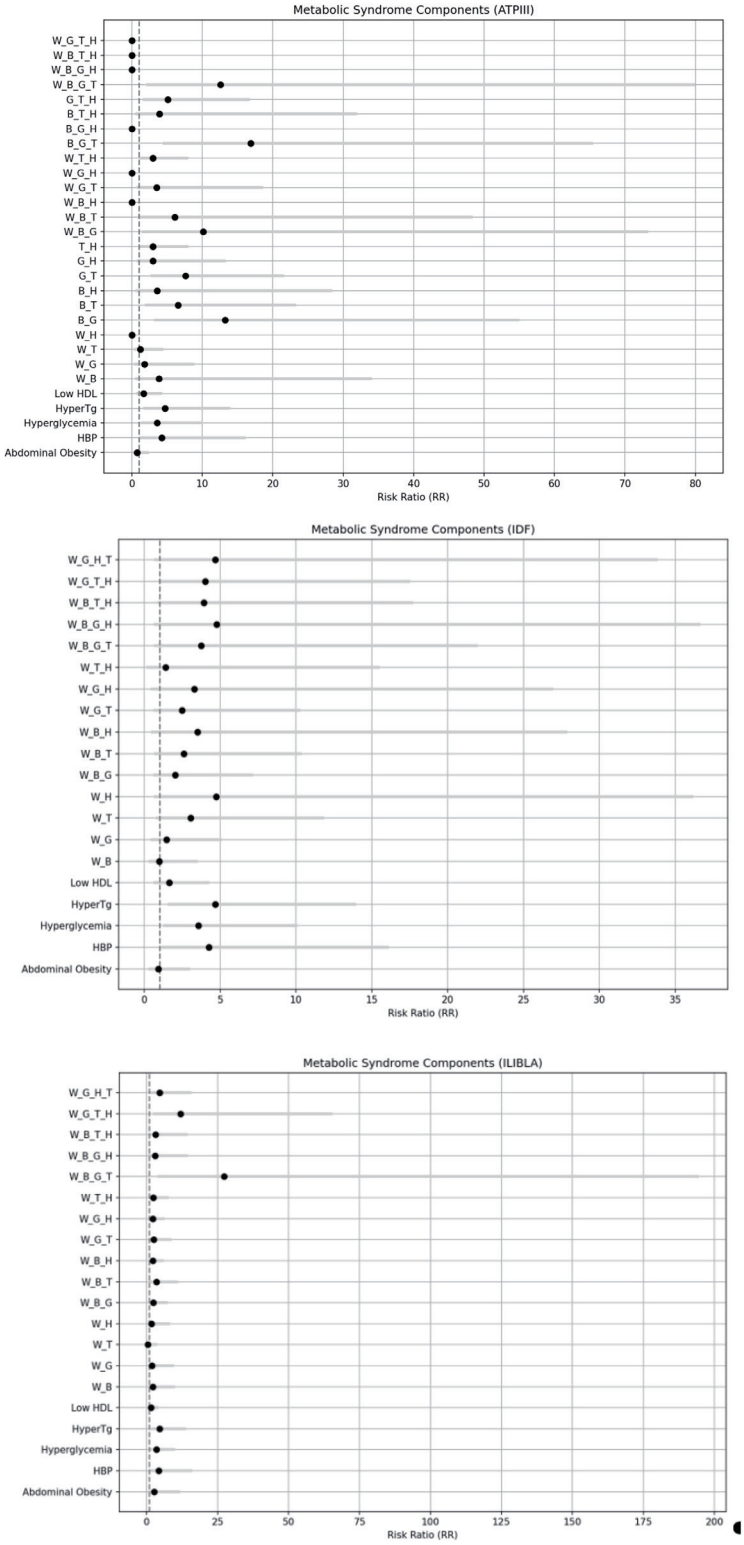


**Figure 3.** *(continued)* Different combinations of each MetS definition as CVD risk. For individual data the indicators were: low HDL, HyperTg = hypertriglyceridemia, hyperglycemia, HBP= high blood pressure and abdominal obesity. For the data as a whole: W = altered waist circumference, G = hyperglycemia, T = hypertriglyceridemia, H = low HDL, B = elevated blood pressure, D = T2DM/hyperglycemia, O = obesity, T = triglycerides, DO = diabetes and obesity. MetS: metabolic syndrome; CVD: cardiovascular diseases; T2DM: type 2 diabetes mellitus; HDL: high-density lipoprotein.

showed no significant association. This variability in CVD risk can be attributed to differences in the specific components of each MetS definition. For example, some definitions place greater emphasis on abdominal obesity or hyperglycemia [9, 10, 14]. On the other hand, a recent study comparing the prevalence of MetS in patients with diabetes mellitus using JIS, IDF, and NCEP-ATPIII criteria found differences in prevalence according to the criteria used [32]. Additionally, the clinical utility of MetS about sudden cardiac death showed that WHO, IDF, and JIS definitions were strong predictors, while the ATP III definition was not associated with risk [33].

This can be translated as the variability in diagnostic criteria influencing the identification of populations with different risk profiles. These observations align with recent studies that also report variations in CVD risk according to the type of MetS diagnosed [34-36]. Understanding these differences is crucial for developing more effective and personalized prevention and treatment strategies for MetS and associated complications.

Analyzing MetS subtypes and their relationship to CVD risk yields intriguing findings. Initially, one might expect that all defining criteria of MetS would have a significant impact on CVD risk independently, considering that most definitions give similar weight to these criteria. However, our results reveal a more nuanced reality. It was observed that only specific components of MetS are independently associated with an elevated risk of CVD, while others did not demonstrate such an association. This difference highlights the inherent heterogeneity of the MetS criteria. It suggests an underlying complexity in the interaction between the different components of the syndrome and their contribution to CVD risk. This could underscore the importance of a detailed and differentiated assessment of MetS components in the context of CVD risk rather than assuming a uniform equivalence in their impact.

Hyperglycemia emerges as an isolated CVD factor in various MetS definitions, highlighting its critical role as an independent risk indicator. High blood glucose, indicative of prediabetes and diabetes, underscores its crucial importance in MetS and its relation to CVD risk. A thorough examination of the abundant research on the micro and macrovascular problems related to diabetes and prediabetes corroborates the importance of elevated blood sugar as a meaningful autonomous threat for the genesis of cardiovascular disorders. As studies have revealed, chronic hyperglycemia's contribution to endothelial harm and heightened arterial stiffness hastens the damaging process of atherosclerosis [37, 38]. This link between hyperglycemia and cardiovascular risk underscores the need for careful blood glucose management in MetS patients to control their glycemic state and as a crucial strategy in reducing the risk of cardiovascular complications.

Similarly, most definitions concur that an autonomous relationship exists between elevated triglyceride levels and CVD. High triglyceride levels, a precursor of dyslipidemia's troubling presence, have for years been thought to encourage the troubling genesis of atherosclerosis and later cardiovascular complications, strongly emphasizing the need to carefully consider dyslipidemia's role when attempting to assess looming cardiovascular dangers accurately. Furthermore, as has been underscored in light of the seminal Framingham study, it continues to be incorporated into cardiovascular risk appraisal as a notable determinant. Elevated triglyceride levels have been shown to correlate with an increased likelihood of atherosclerosis progression, the defining mechanism implicated in the pathogenesis of various cardiovascular disorders. According to multiple studies referenced in the literature, not only has dyslipidemia been found to contribute to the process of atherosclerotic plaque development, especially in the form of hypertriglyceridemia, but it has also been linked to an increased risk of cardiovascular complications [39, 40]. The incorporation of triglyceridemia into predictive formulas estimating cardiovascular hazard, such as the widely used Framingham risk prediction tool, underscores the necessity of accounting for dyslipidemia as a pivotal factor when evaluating total risk in patients with MetS, highlighting the significance of its administration for the avoidance of CVD [41].

In the case of high blood pressure (HBP), despite being a known risk factor for CVD, it shows a less consistent association as an isolated element within MetS in our analysis. This observation might indicate that the influence of HBP as an independent risk factor may be more limited or less direct in the context of MetS compared to its recognized impact in general populations. Research into the prolonged effects of hypertension has likewise revealed connections to how cardiovascular illnesses may evolve over the long run. HBP consistently forecasts future cardiovascular troubles independently over longitudinal research. However, its interplay with additional metabolic elements is often more intricate and less directly proportional, as demonstrated through its combined impacts with other health determinants in wide-ranging studies over time [42, 43]. The simultaneous presence of additional metabolic risk factors, such as abnormal lipid levels, IR, or being overweight, may further or compound HBP's impact on CVD risk when MetS is already a contributing element. This multifactorial interaction underscores the importance of a comprehensive approach in assessing and managing cardiovascular risk, considering the presence of hypertension and the broader metabolic context in which it occurs.

However, while several studies have recognized WC as an indicator of abdominal obesity, it has been recognized in several studies for its role in increasing CVD risk. However, controversies persist about its level of risk in the context of MetS. Although specific investigations underscore WC as a dependable forecaster of CVD, accentuating its association with visceral fat accumulation and systemic inflammation, other studies propose that WC does not consistently manifest as an autonomous risk factor independent of other health or lifestyle elements [44, 45]. This discrepancy could reflect the complexity of the relationship between abdominal obesity and other MetS components, suggesting that its impact on CVD risk might be more significant in combination with other risk factors, such as dyslipidemia or hyperglycemia.

As for low HDL levels, their role in CVD risk is equally debated. While specific investigations have discerned a definite part of low HDL as a peril for CVD, emphasizing its significance in endothelial performance and safeguarding against atherosclerosis [46, 47], other studies have not found such an unambiguous relationship [48]. While there could be various justifications for the inconsistencies observed, such as diver-

 

gences in the sizes of the groups scrutinized, dissimilarities in the cohorts evaluated, or potentially the dangers linked to low HDL levels manifesting over a more prolonged period extending beyond our group's 5-year follow-up, further exploration is needed to elucidate possible reasons for the discrepant results observed fully. The interrelationships among low HDL cholesterol heightened cardiovascular risk as a feature of MetS, and their combined implications for health outcomes have a more elaborate character than envisioned in past conceptualizations.

In our study, the role demonstrated by both HDL and WC was reflected in the combinations of three or four-factor criteria. This may mean that WC, despite not consistently manifesting as an independent risk factor, appears to have a synergistic relationship with other MetS components, suggesting that its impact on CVD risk is magnified by other factors such as hyperglycemia or hypertension [49, 50]. Similarly, although not robust predictors of CVD alone, low HDL levels may potentiate the effect of other risk factors when presented in combination [51, 52]. This observation suggests that the CVD risk associated with these combinations of factors may be more pronounced in a medium-term follow-up, like the 5 years of our cohort. These complex interactions underscore the importance of a comprehensive approach in assessing cardiovascular risk in MetS patients, where multiple risk factors must be considered to evaluate their cardiovascular risk accurately.

## Public health implications of the study

Given the complexity and heterogeneity in the diagnostic criteria for MetS, we propose a more global and inclusive approach. This approach would consider an individual affected by MetS if they meet any of the nine diagnostic criteria types. This global strategy would increase the sensitivity of the diagnosis and facilitate the identification of at-risk individuals, who could benefit from preventive and therapeutic interventions. Furthermore, implementing technological applications could play a crucial role in this process. These applications, designed to be intuitive and accessible, could enable a quick and efficient assessment of MetS risk based on various diagnostic criteria. This would improve diagnostic efficiency and allow for greater personalization in health management. Such a technological approach could revolutionize how MetS is managed, making diagnosis and monitoring more accessible and accurate.

On the other hand, the finding that different MetS criteria are unevenly associated with CVD risk is intriguing and concerning. This variability suggests that the mere presence of MetS, diagnosed according to a specific criterion, does not uniformly imply an elevated risk of CVD. This situation could lead to significant diagnostic and therapeutic confusion. For example, a patient could be diagnosed with MetS according to a criterion not strongly associated with CVD, which could lead to a misperception of low cardiovascular risk. Existing literature indicates that some MetS components, such as hyperglycemia, hypertriglyceridemia, and elevated pressure, have a stronger correlation with CVD risk than others. Hence, whether the MetS standard applied in everyday medical care ought to be founded solely on whether the condition is current in itself but, moreover, on a complete evaluation of the individual's danger to cardiovascular well-being. This highlights the need for more nuanced and personalized diagnostic approaches in evaluating MetS and its relation to CVD risk, which can have significant implications in preventing and managing these conditions.

By tracking specific metabolic markers, including hyperglycemia, hypertriglyceridemia, and blood pressure levels, our investigation underscores the utility of these physiological indicators in strongly predicting the likelihood of CVD for participants over the ensuing half-decade. Based on these results, it is proposed that focusing clinical efforts on addressing such determinants may prove uniquely successful in mitigating CVD hazards in the near and intermediate future. For example, optimizing glycemic control, working triglyceride levels, and effective hypertension management should be considered key elements in treatment strategies for MetS patients. However, these findings should not lead to underestimating the importance of other factors, such as WC and HDL levels. Although these factors were not as strongly associated with CVD risk at 5 years in our study, they could represent more significant long-term risks. Therefore, it is crucial to maintain a holistic approach to managing MetS, including strategies for weight reduction and maintaining healthy HDL levels, as part of a comprehensive plan for CVD prevention.

## Study limitations

Despite the valuable findings of our study, it is essential to recognize its limitations to contextualize the results correctly. First, the 5-year follow-up duration, although providing significant information on the medium-term effects of MetS risk factors on CVD, may not fully capture the long-term manifestations of these risks. Second, the generalization of the results may be limited by the specificity of the study population, which might have unique characteristics in terms of genetics, lifestyle, and environmental factors. Additionally, although we have analyzed several risk factors and their combinations, other unmeasured or not included factors in the study could also influence CVD risk. Finally, the study's observational nature prevents establishing definitive causal relationships between MetS risk factors and the development of CVD. These limitations suggest additional studies, with longer follow-ups and in diverse populations, to deepen the understanding of the relationship between MetS and CVD.

## Conclusions

This study unveils significant variations in the prevalence of MetS depending on the definition used and notable differences in the risk of CVD associated with various types of MetS. We have identified that while some components of MetS are linked with an increased risk of CVD, others do not show such

a direct relationship. These findings emphasize the complexity of MetS and the need for a differentiated approach in cardiovascular risk assessment. This study also highlights the importance of certain factors, such as hyperglycemia, hypertriglyceridemia, and HBP, in determining short- and medium-term CVD risk. In contrast, other factors, like WC and HDL levels, may have a more significant impact in the long term.

In light of these findings, we recommend the consideration of all available definitions of MetS in clinical practice for a more comprehensive risk assessment. Additionally, future studies with larger sample sizes and extended follow-up periods are suggested to corroborate and expand these results. This would enable a deeper understanding of how different components of MetS interact and contribute to long-term CVD risk. Focusing on the comprehensive management of the most prominent risk factors identified, such as hyperglycemia, hypertriglyceridemia, and hypertension, without neglecting the management of other factors that might have cumulative or long-term effects on cardiovascular health is also crucial. Finally, we recommend that future research explore the possibility of using multiple MetS criteria to assess cardiovascular risk more accurately, which could significantly enhance prevention and treatment strategies for patients with MetS.

## Supplementary Material

**Suppl 1.** Bivariate analysis of the characteristics associated with cardiovascular disease.

## Acknowledgments

A special thanks to the members of Tropical Diseases Research Institute, Universidad Nacional Toribio Rodríguez de Mendoza de Amazonas (UNTRM), Amazonas, Peru for their support and contributions throughout the completion of this research.

## Financial Disclosure

This study is self-financed.

## Conflict of Interest

The authors declare no conflict of interest.

## Informed Consent

It was not necessary to obtain informed consent in this study

## Author Contributions

VIctor Juan Vera-Ponce: methodology, validation, writing - review and editing. Fiorella E. Zuzunaga-Montoya: conceptualization, data analysis, writing - review and editing. Joan A. Loayza-Castro: data analysis, methodology, validation, writing - original draft. Luisa Erika Milagros Vasquez Romero: data analysis, methodology, validation, writing - original draft. Eder Jesus Orihuela Manrique: supervision, project administration, writing - review and editing. Mario J. Valladares-Garrido: project administration, funding acquisition, writing - review and editing. Enrique Vigil-Ventura: supervision, methodology, writing - review and editing. Rafael Tapia-Limonchi: supervision, writing - review and editing.

## Data Availability

The data supporting the findings of this study can be accessed by the original research paper at the follow link: https://figshare.com/articles/dataset/PERU_MIGRANT_Study_Baseline_and_5yr_follow-up_dataset/4832612.

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