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Original article

Physical activity and urinary metabolomics in an adult population: an observational study in Getxo

[*Actividad física y metabolómica urinaria en población adulta: estudio observacional en Getxo*]

[*Atividade física e metabolómica urinária na população adulta: estudo observacional em Getxo*]

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ABSTRACT

Introduction: Metabolic syndrome and its associated cardiometabolic disorders currently represent one of the major challenges to global public health. Among the modifiable factors related to its development, physical activity plays a significant role due to its influence on multiple physiological and metabolic processes. In recent years, urinary metabolomics based on nuclear magnetic resonance has emerged as a useful tool for studying metabolic modifications related to lifestyle habits and health status.

Objective: To analyze the relationship between the level of physical activity and the urinary metabolomic profile in a physically active adult population in the municipality of Getxo.

Materials and methods: An observational, descriptive, and correlational study was conducted with adults aged 17 years and older participating in organized physical activities in Getxo. The sample consisted of 189 participants. Sociodemographic, anthropometric, and lifestyle variables were collected using structured questionnaires. Physical activity levels were assessed using a composite index (PA_score) derived from exercise frequency, occupational activity, and the type of sport practiced. The urinary metabolomic profile was obtained using proton nuclear magnetic resonance spectroscopy (^{1}H-NMR). The metabolomic data underwent quality control procedures, normalization, logarithmic transformation, and multivariate and univariate statistical analysis.
Results: The cohort exhibited a predominantly active profile, with a high weekly frequency of exercise and a predominance of strength training and aerobic components. Exploratory PCA analysis showed partial clustering trends according to physical activity level. Nominal associations were identified between PA_score and certain urinary metabolites related to energy pathways and oxidative metabolism, although with moderate effect sizes. Adjusted models suggested independent metabolic associations linked to the level of habitual physical activity.
Conclusions: The results showed the existence of urinary metabolomic variations associated with the level of physical activity in a physically active adult population. Although the associations detected were moderate and exploratory, the findings support the potential of urinary metabolomics as a complementary tool for studying the relationship between physical activity and metabolic health.

Keywords : physical activity; nuclear magnetic resonance spectroscopy; urinary metabolomics; adult population; metabolic syndrome.

RESUMEN

Introducción: el síndrome metabólico y las alteraciones cardiometabólicas asociadas representan actualmente uno de los principales desafíos para la salud pública mundial. Entre los factores modificables relacionados con su desarrollo, la actividad física desempeña un papel relevante debido a su influencia sobre múltiples procesos fisiológicos y metabólicos. En los últimos años, la metabolómica urinaria basada en resonancia magnética nuclear ha emergido como una herramienta útil para estudiar modificaciones metabólicas relacionadas con los hábitos de vida y el estado de salud.
Objetivo: analizar la relación entre el nivel de actividad física y el perfil metabolómico urinario en población adulta físicamente activa del municipio de Getxo.

Materiales y métodos: se realizó un estudio observacional, descriptivo y correlacional en personas adultas mayores de 17 años vinculadas a actividades físicas organizadas en Getxo. La muestra estuvo constituida por 189 participantes. Se recogieron variables sociodemográficas, antropométricas y relacionadas con hábitos de vida mediante cuestionarios estructurados. El nivel de actividad física fue evaluado mediante un índice compuesto (PA_score) elaborado a partir de la frecuencia de ejercicio, actividad ocupacional y modalidad deportiva practicada. El perfil metabolómico urinario se obtuvo mediante espectroscopía de resonancia magnética nuclear de protones (^1H-RMN). Los datos metabolómicos fueron sometidos a procedimientos de control de calidad, normalización, transformación logarítmica y análisis estadístico multivariante y univariante.

Resultados: la cohorte presentó un perfil predominantemente activo, con elevada frecuencia semanal de ejercicio y predominio de actividades de fuerza y componentes aeróbicos. El análisis exploratorio mediante PCA mostró tendencias de agrupación parcial según el nivel de actividad física. Se identificaron asociaciones nominales entre el PA_score y determinados metabolitos urinarios relacionados con rutas energéticas y metabolismo oxidativo, aunque con tamaños de efecto moderados. Los modelos ajustados sugirieron asociaciones metabólicas independientes vinculadas al nivel de actividad física habitual.

Conclusiones: los resultados evidenciaron la existencia de variaciones metabolómicas urinarias asociadas al nivel de actividad física en población adulta físicamente activa. Aunque las asociaciones detectadas fueron moderadas y de carácter exploratorio, los hallazgos respaldan el potencial de la metabolómica urinaria como herramienta complementaria para el estudio de la relación entre actividad física y salud metabólica.

Palabras clave: actividad física; espectroscopía de resonancia magnética nuclear; metabolómica urinaria; población adulta; síndrome metabólico.

RESUMO

Introdução: A síndrome metabólica e as alterações cardiometabólicas associadas representam atualmente um dos principais desafios para a saúde pública mundial. Entre os fatores modificáveis associados ao seu desenvolvimento, a atividade física desempenha um papel relevante devido à sua influência sobre múltiplos processos fisiológicos e metabólicos. Nos últimos anos, a metabolómica urinária baseada em ressonância magnética nuclear (RMN) tem

emergido como uma ferramenta útil para estudar alterações metabólicas associadas aos hábitos de vida e ao estado de saúde.

Objetivo: Analisar a relação entre o nível de atividade física e o perfil metabolómico urinário numa população adulta fisicamente ativa do município de Getxo.

Materiais e métodos: Foi realizado um estudo observacional, descritivo e correlacional em adultos com idade superior a 17 anos participantes em atividades físicas organizadas no município de Getxo. A amostra foi constituída por 189 participantes. Foram recolhidas variáveis sociodemográficas, antropométricas e relacionadas com os hábitos de vida através de questionários estruturados. O nível de atividade física foi avaliado através de um índice composto (PA_score), elaborado com base na frequência de exercício, na atividade física ocupacional e na modalidade desportiva praticada. O perfil metabolómico urinário foi obtido por espectroscopia de ressonância magnética nuclear de protão (^1H-RMN). Os dados metabolómicos foram submetidos a procedimentos de controlo de qualidade, normalização, transformação logarítmica e análises estatísticas multivariadas e univariadas.

Resultados: A coorte apresentou um perfil predominantemente ativo, caracterizado por uma elevada frequência semanal de exercício e pelo predomínio de atividades de força e componentes aeróbios. A análise exploratória por análise de componentes principais (PCA) revelou tendências de agrupamento parcial em função do nível de atividade física. Foram identificadas associações nominais entre o PA_score e determinados metabolitos urinários relacionados com vias energéticas e metabolismo oxidativo, embora com magnitudes de efeito moderadas. Os modelos ajustados sugeriram associações metabólicas independentes relacionadas com o nível habitual de atividade física.

Conclusões: Os resultados evidenciaram a existência de variações metabolómicas urinárias associadas ao nível de atividade física numa população adulta fisicamente ativa. Embora as associações observadas tenham sido moderadas e de natureza exploratória, os resultados sustentam o potencial da metabolómica urinária como uma ferramenta complementar para o estudo da relação entre a atividade física e a saúde metabólica.

Palavras-chave: Atividade física; espectroscopia de ressonância magnética nuclear; metabolómica urinária; população adulta; síndrome metabólica.

INTRODUCTION

Metabolic syndrome is one of the most clinically and epidemiologically relevant metabolic disorders today due to its close association with cardiovascular disease, type 2 diabetes mellitus, and increased premature mortality. This disorder is characterized by the coexistence of several cardiometabolic risk factors, including abdominal obesity, impaired glucose metabolism, hypertension, and dyslipidemia. The high prevalence observed in recent decades has made metabolic syndrome a major public health problem internationally (Fragozo-Ramos, 2022; Martínez, 2021; Ibarra *et al.,* 2021; Espinoza-Rivera *et al.,* 2023).

Several studies have indicated that changes in modern lifestyles have contributed to a progressive increase in factors related to the development of metabolic disorders. Among these, sedentary behavior and decreased levels of physical activity are some of the most relevant modifiable determinants. Increased time spent on sedentary activities, along with less active behavior patterns, has been associated with a higher cardiometabolic risk and physiological changes capable of altering multiple metabolic pathways (Moscoso, 2020; Ugarriza, 2022; Arsentales-Montalva *et al.,* 2019; Cristi-Montero *et al.,* 2019).

In contrast, regular physical activity has shown beneficial effects on various parameters related to metabolic health. Available scientific evidence indicates that physical exercise contributes to improved glycemic regulation, lipid metabolism, cardiovascular function, and overall energy balance. Furthermore, physical activity has been described as a protective factor against the development of metabolic and cardiovascular diseases, independent of other sociodemographic and behavioral factors (González-Chávez *et al.,* 2019; Ugarriza, 2022; Carrera *et al.,* 2020; Arsentales -Montalva *et al.,* 2019; Ramírez *et al.,* 2012).

In recent years, the development of omics techniques has expanded the study of the biological mechanisms involved in the relationship between physical activity and metabolic health. In this context, metabolomics has emerged as a valuable tool for identifying metabolic changes associated with different physiological and behavioral

states. Urinary metabolomics, in particular, allows for an integrated view of systemic metabolism through the simultaneous analysis of multiple low-molecular-weight metabolites present in urine (Aguilar & Carballo, 2020; López, 2021).

The use of proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy has facilitated the reproducible and non-invasive characterization of complex metabolomic profiles. This analytical approach allows the detection of variations related to energy processes, amino acid metabolism, oxidative stress, and other biochemical pathways potentially modulated by habitual physical activity. Therefore, the integration of behavioral variables and metabolomic profiles currently represents a relevant line of research within the field of cardiometabolic health and exercise physiology (López, 2021).

Despite the growing number of studies on physical activity and metabolic risk, limitations remain regarding the study of specific populations and the identification of metabolic biomarkers associated with lifestyle habits in specific local contexts. At the municipal and community levels, the available evidence remains limited, especially in studies that integrate epidemiological information and urinary metabolomics analyses in physically active adults (Torres *et al.,* 2021; García *et al.,* 2022; Pacheco & Altamirano, 2023; Flores & Ureta, 2023; Ramírez *et al.,* 2020).

In this context, the present study aimed to analyze the relationship between the level of physical activity and the urinary metabolomic profile in the adult population of the municipality of Getxo, using nuclear magnetic resonance spectroscopy and multivariate statistical analysis tools.

MATERIALS AND METHODS

Studio design

An observational, descriptive, and correlational study with a quantitative approach was conducted to analyze the relationship between habitual physical activity and the urinary metabolomic profile in an adult population. The study had a cross-sectional design and was carried out over a period of approximately eight months.

Participants and study context

The study population consisted of adults involved in organized physical activities in the municipality of Getxo. Participants were men and women over 17 years of age who regularly engaged in physical activity in various sports and recreational settings within the municipality.

The final sample consisted of 189 participants, selected through a voluntary inclusion procedure. All participants were informed beforehand about the general characteristics of the study and agreed to participate voluntarily.

Study variables

The main variables analyzed were the level of physical activity and the urinary metabolomic profile. Additionally, sociodemographic, anthropometric, and lifestyle-related variables were collected.

The variables recorded included sex, age, body weight, height, smoking status, alcohol consumption, employment status, and frequency of weekly physical activity. Data related to the sport practiced by each participant were also collected.

Evaluation of physical activity

The characterization of physical activity was carried out using structured questionnaires aimed at collecting information on weekly frequency of exercise, occupational activity and sports modalities practiced.

Due to the lack of variability in the dichotomous variable of physical activity, a composite index called PA_score was developed, designed to more accurately represent the behavioral phenotype associated with habitual physical activity. This index integrated information regarding weekly exercise frequency, occupational physical activity level, and the type of sport activity performed.

The PA_score had a mean of 3.80 with a standard deviation of 1.18 and a median of 4, indicating a moderate to vigorous overall physical activity profile in the cohort. The detected range was 2 to 6, with the first quartile (Q1) being 3 and the third quartile (Q3)

5, indicating significant variability and a wide distribution of the physical phenotype among the participants.

Obtaining and processing biological samples

Urine samples were collected from all participants following standardized storage and preservation procedures. Urinary metabolomics analysis was performed using proton nuclear magnetic resonance spectroscopy (^{1}H-NMR).

The metabolomics panel included approximately 150 urinary metabolites corresponding to different functional groups and metabolic pathways. The concentrations obtained were previously normalized using creatinine to reduce variability associated with urinary dilution and improve comparability between samples.

Preprocessing of metabolomic data

Prior to statistical analysis, metabolomic data underwent quality control and analytical cleaning procedures. Metabolites with a high proportion of missing values were excluded from the analysis.

The remaining missing values were imputed using relative minimum value procedures. Subsequently, the metabolomic concentrations were transformed using base-10 logarithms to reduce skewness in the distributions and stabilize variance.

autoscaling procedure was applied to center the variables and standardize the scale differences between metabolites before performing the multivariate analyses.

Statistical analysis

Statistical analysis was performed using descriptive statistics, inferential analysis, and multivariate techniques. Continuous variables were expressed as mean and standard deviation, while categorical variables were presented as absolute frequencies and percentages.

The distribution of the PA_score between groups was assessed using non-parametric tests after verifying the lack of normality using the *Shapiro-Wilk test.* Contingency tables and χ^2 tests were used for comparisons between categorical variables.

Exploratory metabolomics analysis was performed using principal component analysis (PCA) with pre-transformed and standardized matrices. Subsequently, simple linear regression models were applied to study the association between individual urinary metabolites and the PA score.

Statistical significance values were corrected for multiple comparisons using the Benjamini-Hochberg method to control for false discovery rate (FDR). In addition, multivariate models were fitted incorporating potentially confounding covariates such as age, sex, body mass index, smoking, and alcohol consumption.

Statistical and metabolomic processing was performed using specialized statistical software and electronic spreadsheets for data organization and traceability.

Ethical considerations

The research was conducted in accordance with the ethical principles applicable to studies involving human subjects and ensuring the confidentiality of the information collected. Participation was voluntary, and the data obtained were anonymized and used exclusively for scientific and academic purposes.

RESULTS AND DISCUSSION

General characterization of the sample and physical activity profile

The cohort analyzed consisted of 189 physically active adult participants, with representation of both sexes and a wide age distribution. From a descriptive point of view, the sample presented a predominantly active profile, characterized by a high weekly frequency of physical activity and significant participation in sports related to both strength training and aerobic activities.

Most participants reported engaging in physical activity two or three times a week or almost daily, and a notable diversity of sports modalities was observed. Among the most frequent activities were strength training, swimming, running, cycling, and walking,

reflecting the coexistence of different patterns of physical behavior within the studied population.

Regarding lifestyle habits, the majority of participants were non-smokers and consumed alcohol in social settings. A considerable proportion of participants also had predominantly sedentary work, coexisting with a subgroup that engaged in occupational activities involving moderate to high levels of physical exertion (Tables 1 and 2).

Table 1. *- Descriptive sociodemographic and habit characteristics of the study sample*

Variable.1	level	Overall
n		189
gender (%)	Female	83 (43.9)
	Male	106 (56.1)
age (mean (SD))		39.00 (11.77)
weight (mean (SD))		70.82 (12.84)
height (mean (SD))		171.70 (9.00)
smoker (%)	No	173 (91.5)
	Yes	16 (8.5)
cigarettes_day (%)	Between 11 and 20	2 (12.5)
	Between 21 and 30	1 (6.2)
	Less than 10	13 (81.2)
work_activity (%)	Medium- high physical effort	57 (30.2)
	Sedentary	132 (69.8)
physical_activity (%)	Yes	189 (100.0)
frequency_activity (%)	Almost every day	84 (44.4)
	Once a week	12 (6.3)
	Two or three times a week	93 (49.2)
drink_alcohol (%)	Every day	2 (1.1)
	Never	33 (17.5)
	Several times a day	1 (0.5)
	Social drinker	153 (81.0)

Table 2. *- Description of the sample based on physical activity and related variables*

Variable	level	Overall	Total
n		189	
age (mean (SD))		39.00 (11.77)	
gender (%)	Female	83 (43.9)	
	Male	106 (56.1)	
work_activity (%)	Medium- high physical effort	57 (30.2)	
	Sedentary	132 (69.8)	
physical_activity (%)	Yes	189 (100.0)	
frequency_activity (%)	Almost every day	84 (44.4)	
	Once a week	12 (6.3)	
	Two or three times a week	93 (49.2)	
Type of activity (multiple response)			
Type of activity: strength training			114 (60.3%)
Type of activity: swimming			34 (18%)
Type of activity: running			32 (16.9%)
Type of activity: cycling			29 (15.3%)
Type of activity: walking			29 (15.3%)
Type of activity: rugby			23 (12.2%)
Type of activity: padel			13 (6.9%)
Type of activity: Pilates			10 (5.3%)
Type of activity: volleyball			7 (3.7%)
Type of activity: yoga			7 (3.7%)
Type of activity: field hockey			6 (3.2%)
Type of activity: spinning			6 (3.2%)
Type of activity: athletics			5 (2.6%)
Type of activity: surfing			5 (2.6%)
Type of activity: basketball			4 (2.1%)
Type of activity: ping-pong			4 (2.1%)
Type of activity: ultimate frisbee			4 (2.1%)
Type of activity: climbing			3 (1.6%)
Type of activity: mountaineering			3 (1.6%)
Type of activity: soccer			3 (1.6%)
Type of activity: tennis			3 (1.6%)
Type of activity: water polo			3 (1.6%)
Type of activity: hiking			2 (1.1%)
Type of activity: Hockey			2 (1.1%)
Type of activity: indoor soccer			2 (1.1%)
Type of activity: trail			2 (1.1%)
Type of activity: trail running			2 (1.1%)
Type of activity: Zumba			2 (1.1%)

Type of activity: mountaineering			1 (0.5%)
Type of activity: aquagym			1 (0.5%)
Type of activity: badminton			1 (0.5%)
Type of activity: ballet			1 (0.5%)
Type of activity: beach volleyball			1 (0.5%)
Type of activity: beach volleyball			1 (0.5%)
Type of activity: boxing			1 (0.5%)
Type of activity: calisthenics			1 (0.5%)
Type of activity: capoeria			1 (0.5%)
Type of activity: CrossFit			1 (0.5%)
Type of activity: dance			1 (0.5%)
Type of activity: fitboxing			1 (0.5%)
Type of activity: functional training			1 (0.5%)
Type of activity: hitt			1 (0.5%)
Type of activity: martial arts			1 (0.5%)
Type of activity: paddle tennis			1 (0.5%)
Type of activity: race walking			1 (0.5%)
Type of activity: skateboarding			1 (0.5%)
Type of activity: skating			1 (0.5%)
Type of activity: ski mountaineering			1 (0.5%)
Type of activity: skiing			1 (0.5%)
Type of activity: strength training			1 (0.5%)
Type of activity: strength			1 (0.5%)
Type of activity: strength training			1 (0.5%)
Type of activity: swimming			1 (0.5%)
Type of activity: tai chi			1 (0.5%)

The construction of the composite physical activity index (PA_score) allowed for the integration of different behavioral dimensions related to exercise frequency, occupational activity, and the sports practiced. The observed distribution of the index showed sufficient interindividual variability to allow for the stepwise analysis of physical activity levels and their association with the urinary metabolomic profile.

The absence of statistically significant differences between men and women in the distribution of the PA_score suggested a relative homogeneity of physical behavior between both groups within this cohort. This finding is methodologically relevant because it reduces the possibility of significant sex-related behavioral biases in subsequent metabolomic analyses.

Stratifying the PA_score into quartiles also allowed for the identification of consistent behavioral gradients related to the frequency of physical activity and the level of occupational effort. Participants with higher index values exhibited greater frequency of weekly exercise and a higher proportion of physically demanding work activity, supporting the internal consistency of the constructed index.

These descriptive results show that the studied cohort presented a physically active and heterogeneous behavioral phenotype, suitable for the exploratory analysis of metabolomic associations related to habitual physical activity.

From an interpretive perspective, the findings are consistent with previous research that describes physical activity as a complex and multidimensional behavior, influenced by occupational, recreational, and behavioral factors. Furthermore, the high prevalence of strength training and aerobic activities observed in the cohort aligns with current patterns of physical activity described in urban adult populations.

The existence of interindividual variability in levels of physical activity is of particular importance in the metabolomic context, because the physiological adaptations induced by exercise do not usually manifest themselves in a dichotomous way, but as a biological continuum dependent on the intensity, frequency and regularity of physical practice.

In this regard, the use of a composite index such as the PA_score represents a useful methodological approach for more accurately capturing the complexity of the physical activity phenotype, avoiding limitations associated with traditional binary classifications. This strategy allowed for the establishment of a more suitable analytical basis for studying possible metabolic modulations associated with different levels of habitual physical exposure (Figures 1 and 2).

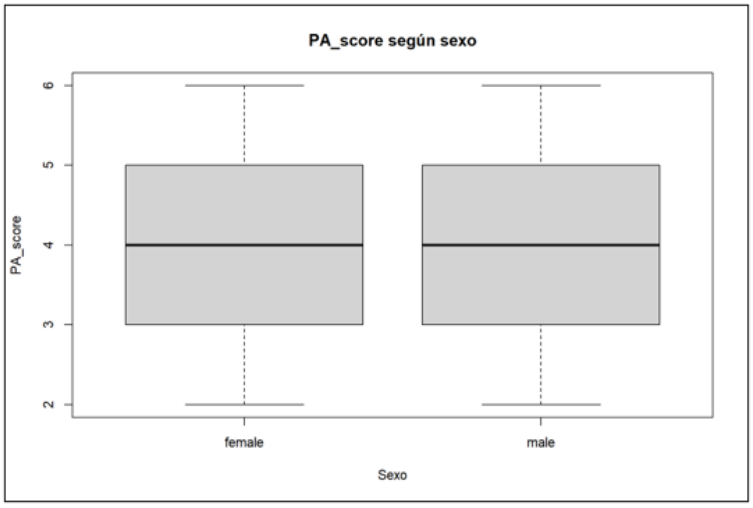


Figure 1. *- Distribution of the composite physical activity index (PA_score) by gender*

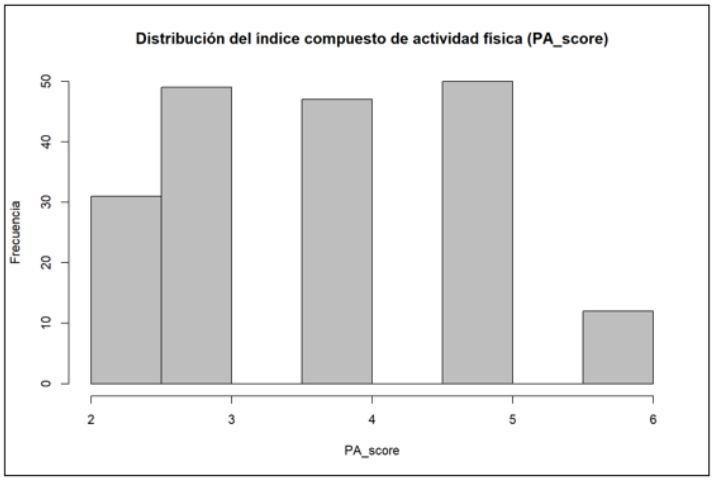


Figure 2. *- Distribution of the composite physical activity index (PA_score)*

Urinary metabolomic profile and multivariate exploratory analysis

Urinary metabolomics analysis performed using nuclear magnetic resonance spectroscopy allowed for the characterization of a broad set of metabolites related to different biochemical pathways and physiological processes. The metabolomics panel included approximately 150 metabolites belonging to diverse functional groups, including amino acids and derivatives, organic acids, carbohydrates, nitrogenous compounds, energy metabolites, and substances related to oxidative metabolism (Table 3).

Table 3. *- Approximate functional classification of the urinary metabolomics panel*

Metabolomic Panel Classification Table	
Class	**Number of metabolites**
Organic acids	69
Amino acids and derivatives	47
Others	19
Carbohydrates and polyols	8
Exogenous metabolites	4
Purines and pyrimidines	2

The breadth of the analyzed panel provided a global representation of the participants' systemic metabolism, allowing the exploration of possible associations between usual levels of physical activity and detectable changes in the urinary metabolome.

From a descriptive standpoint, the quantified metabolites showed considerable interindividual heterogeneity, both in their absolute values and in the observed measures of dispersion. This behavior is common in population metabolomics studies due to the simultaneous influence of multiple physiological, behavioral, nutritional, and environmental factors on urinary metabolite concentrations.

To minimize the impact of technical sources of variability, the data underwent quality control procedures, creatinine normalization, logarithmic transformation, and *autoscaling* before statistical analysis. The application of these methodological strategies improved comparability between samples and reduced the disproportionate effect of highly abundant metabolites on multivariate models.

Exploratory analysis using principal component analysis (PCA) allowed us to evaluate the overall structure of the metabolomic data and explore possible clustering patterns associated with physical activity levels. The representation of individuals in the multivariate space defined by the first principal components showed a continuous distribution of metabolomic profiles, with no completely distinct clustering observed between physical activity levels (Figure 3).

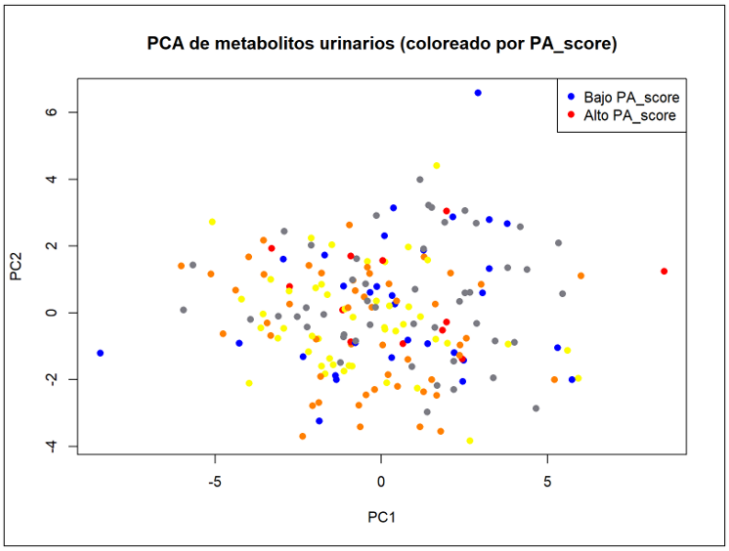


Figure 3. *- Principal component analysis (PCA) of urinary metabolites colored according to the composite physical activity index (PA_score)*

However, when the PA_score was incorporated as a color gradient within the multivariate representation, partial trends in metabolic organization related to habitual physical activity levels were identified. Participants with similar index values tended to be located relatively close together within the metabolomic space, suggesting the existence of gradual metabolic modulations associated with physical activity.

The absence of clearly defined separations between groups is consistent with the physiological nature of physical activity as a continuous and multifactorial exposure. Unlike certain metabolic diseases or intensive clinical interventions, the effects of habitual physical activity are usually manifested through discrete metabolic modifications distributed across multiple biochemical pathways, rather than through extreme alterations in a small number of metabolites.

From a methodological perspective, the relative homogeneity observed in the overall distribution of the cohort may also be related to the characteristics of the sample studied, which is composed exclusively of physically active individuals. The absence of a clearly sedentary group limits the possibility of detecting extreme metabolic contrasts, although it allows for the exploration of internal variations within different levels of habitual physical activity.

Nevertheless, the PCA confirmed the existence of a metabolomic signal associated with the physical activity phenotype, supporting the hypothesis that habitual exercise can influence urinary metabolism even in relatively homogeneous populations from a behavioral point of view.

These findings are consistent with previous metabolomics research describing physical activity as a systemic modulator of energy metabolism, oxidative balance, and various pathways related to physiological adaptation to exercise. Recent studies have indicated that changes induced by physical activity are often reflected in subtle but coordinated modifications of multiple metabolites, especially those linked to mitochondrial processes, amino acid metabolism, and redox regulation.

Furthermore, the partial organization observed in the multivariate space supports the usefulness of non-targeted metabolomic approaches as complementary tools for the study of exercise physiology and the metabolic effects associated with different patterns of physical activity in the general population.

Overall, the exploratory multivariate analysis provided evidence of metabolomic modulation associated with habitual physical activity level, establishing a solid basis for further analysis of specific associations between individual urinary metabolites and the composite physical activity index.

Association between urinary metabolites and the composite physical activity index

With the aim of identifying urinary metabolites potentially associated with the usual level of physical activity, univariate analyses were performed using simple linear regression models, considering each metabolite as a dependent variable and the composite physical activity index (PA_score) as an independent variable.

The results showed that several metabolites exhibited nominal associations with the PA_score , with both positive and negative relationships observed. Although no robust associations of large magnitude were identified after strict correction for multiple comparisons, the overall pattern observed suggests the existence of subtle metabolic modulations related to habitual physical activity (Tables 4 and 5).

Table 4. *- Urinary metabolites associated with the composite physical activity index (PA_score) (p < 0.05)*

Significant metabolites_p005
metabolite,"beta"," pval "," fdr "
number_of_vaccines,0.128,0.037,0.319
Fumaric acid, -0.122, 0.045, 0.32
Oxypurinol, 0.138, 0.030, 0.32
Pantothenic acid, -0.15, 0.01, 0.32
Theobromine, -0.132, 0.03, 0.31

Table 5. *- Association between selected urinary metabolites and the composite physical activity index (PA_score) after multivariable adjustment.*

Adjusted Models _Metabolites_PA_score		
metabolite	**beta_PA**	**p_value**
number_of_vaccines	0.14	0.09
Fumaric acid	-0.11	0.15
Oxypurinol	0.23	0.01
Pantothenic acid	-0.14	0.07
Theobromine	-0.12	0.16

Among the metabolites with the most prominent associations were compounds involved in metabolic pathways related to energy metabolism, oxidative balance, purine metabolism, and the availability of metabolic cofactors.

In particular, some metabolites linked to mitochondrial metabolism and energy production showed consistent associations with the physical activity index. This finding is physiologically consistent, since regular exercise involves sustained bioenergetic adaptations, increased oxidative efficiency, and modifications in the utilization of energy substrates.

However, the magnitude of the associations observed in this study was relatively moderate. This can be explained by several methodological and biological factors. First, the cross-sectional nature of the study limits the ability to detect dynamic changes related to temporal shifts in physical activity. Second, the cohort analyzed had a

predominantly active profile, reducing the contrast between extreme groups of physical behavior.

Nevertheless, the existence of gradual and physiologically consistent associations lends internal consistency to the findings and supports the hypothesis that regular physical activity can partially modulate the urinary metabolomic profile.

The graphical representation using *volcano the plot* allowed for an integrated visualization of both the effect size and the statistical significance of the detected associations. The observed distribution confirmed that most metabolites had coefficients close to zero, while a small number of compounds showed more distant trends, reflecting possible biologically relevant associations (Figure 4).

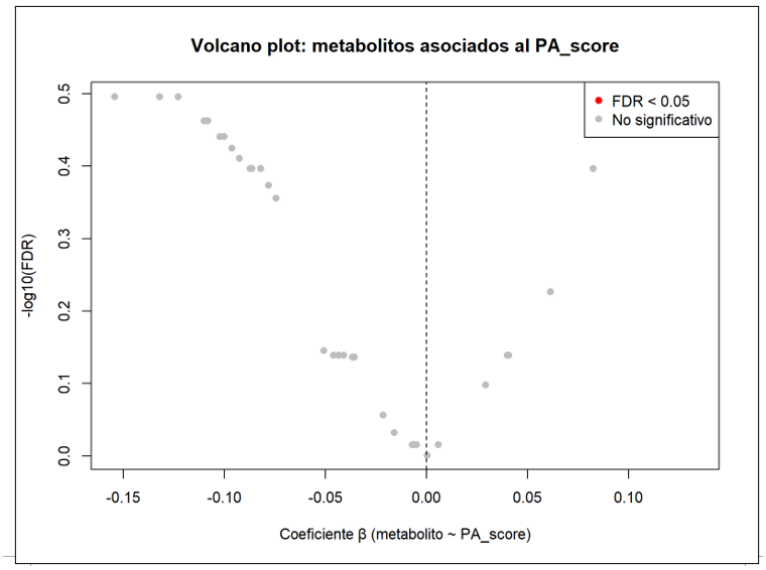


Figure 4. *- Volcano Plot of urinary metabolites associated with the composite physical activity index (PA_score)*

heatmap and hierarchical clustering analysis showed partial patterns of metabolic co-expression, suggesting that some metabolites associated with the PA_score tend to vary in a coordinated manner. This behavior reinforces the idea that physical activity does not act on a single isolated metabolic process, but rather on multiple interconnected biochemical pathways (Figure 5).

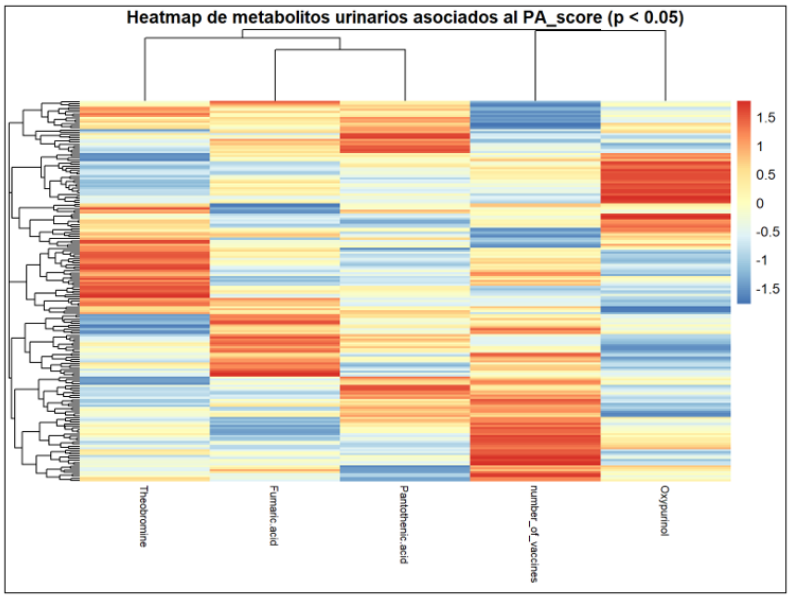


Figure 5. *- Heatmap of urinary metabolites associated with the composite physical activity index (PA_score) (p < 0.05)*

Multivariate models adjusted for age, sex, body mass index, smoking, and alcohol consumption allowed us to assess whether the observed associations were independent of potential confounding factors. After adjustment, some metabolites partially maintained their relationship with the PA_score , while others lost statistical consistency.

This behavior suggests that some of the observed metabolomic variability may be simultaneously influenced by demographic variables and coexisting lifestyle habits. However, the persistence of certain associations after adjustment supports the existence of an independent, albeit modest, effect of physical activity on urinary metabolism.

Taken together, the univariate and multivariate analyses conducted in this research suggest that habitual physical activity levels are associated with small but physiologically plausible urinary metabolomic changes. These results contribute to expanding the existing knowledge on the interaction between physical behavior and human metabolism, supporting the potential of urinary metabolomics as a complementary tool in the study of metabolic adaptations related to habitual physical exercise.

CONCLUSIONS

The conclusions presented below are derived directly from the objectives set and the results obtained in the research, allowing us to assess the fulfillment of the hypotheses formulated and the scientific contribution of the study.

Significant associations were observed between the PA_score and lifestyle-related variables, especially with the weekly frequency of physical activity and the level of occupational physical exertion, which provides internal consistency to the developed index and supports its methodological utility for future metabolomic analyses.

The results showed a trend towards a lower prevalence of smoking in the groups with higher levels of physical activity, suggesting the coexistence of healthier behavior patterns in individuals with high physical activity profiles.

Multivariate exploratory analysis using PCA revealed gradual patterns of metabolomic organization associated with the level of physical activity, although without observing completely differentiated groupings between individuals, suggesting a discrete and distributed metabolic modulation associated with habitual physical exercise.

The observed associations were of moderate magnitude and primarily exploratory in nature; however, they showed physiological coherence with previously described metabolic mechanisms related to physical activity and systemic adaptations induced by regular exercise.

Multivariate models adjusted for sociodemographic variables and lifestyle habits partially confirmed the persistence of some associations between physical activity and urinary metabolites, suggesting the existence of an independent, albeit discrete, effect of physical behavior on the metabolomic profile.

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***Conflict of interest*:**
The authors declare no conflicts of interest.

Authors' contribution:
The authors have participated in the writing of the work and analysis of the documents.



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