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# SUMARIO

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## ORIGINALES



## ARTÍCULOS ESPECIALES



## CASE REPORT

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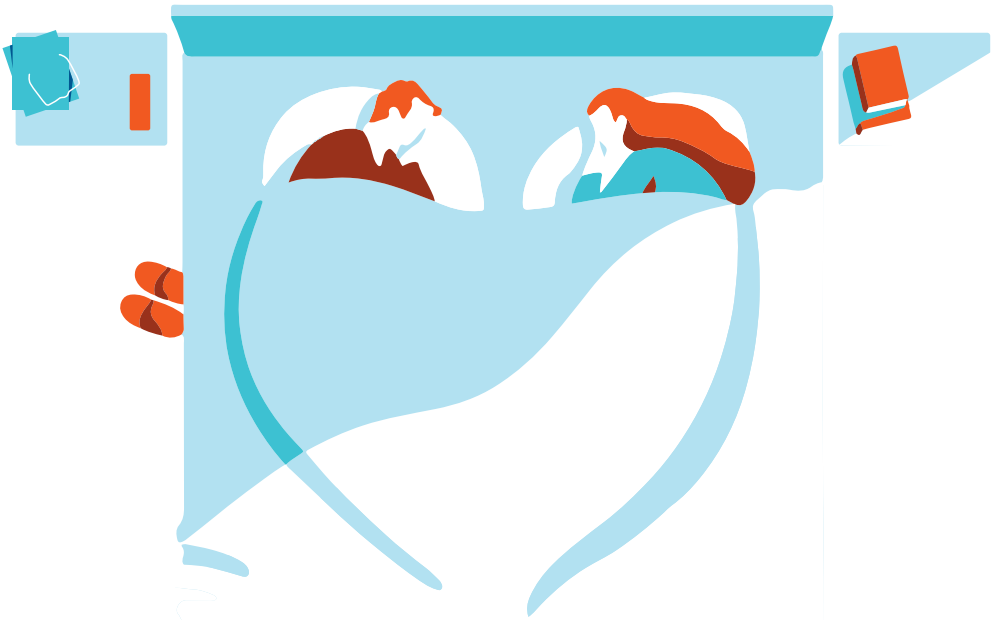

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ORIGINAL

# Association between atherogenic dyslipidemia and lipid triad with cardiovascular risk scales in 418.343 Spanish workers

*Asociación entre dislipemia aterogénica y tríada lipídica con escalas de riesgo cardiovascular en 418.343 trabajadores españoles*

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## Abstract

***Introduction and objectives:*** Cardiovascular diseases in their genesis generally present an anatomopathological process such as atherosclerosis. Atherogenic dyslipidemia (AD) and lipid triad (TL) are parameters that can predict the appearance of atherosclerosis. The aim of this study is to assess the relationship between AD and LT with different cardiovascular risk (CVR) scales.
***Material and methods:*** A descriptive, cross-sectional study was carried out in a large sample of Spanish workers, specifically 418343, in which the presence or absence of AD and TL was assessed. Different CVR scales such as REGICOR, SCORE 2, ERICE and vascular age were also determined using the Framingham and SCORE criteria.
***Results:*** The mean values of all CVR scales and the prevalence of elevated values of these scales are higher in both AD and TL. The scale that most increases the risk of presenting both AD and TL is ALLY of Framingham vascular age. The CVR scales, in general, have a low predictive power for both AD and TL.
***Conclusions:*** There is a good association between the CVR scales analyzed and AD and TL. The value of these CVR scales for predicting AD and TL is low, with the exception of ALLY with the Framingham criteria.

*Key words:* Atherogenic dyslipidemia, cardiovascular disease, cardiovascular risk, atherosclerosis.

## *Resumen*

***Introducción y objetivos:*** Las enfermedades cardiovasculares en su genesis presentan generalmente un proceso anatomopatológico como es la atherosclerosis. La dislipemia aterogénica (DA) y la triada lipídica (TL) son parámetros que pueden predecir la aparición de atherosclerosis. El objetivo de este estudio es valorar la relación que existe entre la DA y TL con diferentes escalas de riesgo cardiovascular (RCV).
***Material y métodos:*** Estudio descriptivo y transversal realizado en una amplia muestra de trabajadores españoles, concretamente 418343, en los que se valora la presencia o no de DA y TL. También se determinan diferentes escalas de RCV como REGICOR, SCORE 2, ERICE y edad vascular con los criterios de Framingham y SCORE.
***Resultados:*** Los valores medios de todas las escalas de RCV y la prevalencia de valores elevados de estas escalas son superiors tanto en la DA como en la TL. La escala que más incrementa el riesgo de presentar tanto DA como TL es ALLY de edad vascular Framingham. Las escalas de RCV, en general, tienen un bajo poder de predicción tanto de DA como de TL.
***Conclusiones:*** Existe una buena asociación entre las escalas de RCV analizadas y la DA y TL. El valor de estas escalas de RCV para predecir DA y TL es bajo, a excepción de ALLY con los criterios de Framingham.

*Palabras clave:* Dislipidemia aterogénica, enfermedad cardiovascular, riesgo cardiovascular, aterosclerosis.

## Introduction

Cardiovascular diseases (CVD) are currently responsible for a high morbidity and mortality rate in the vast majority of countries[1] and are considered by all to be the leading cause of death worldwide. There are many diseases that can be included in this concept, from diseases of the heart itself such as coronary heart disease to conditions of the vascular tree such as arterial hypertension[2].

There are direct methods for evaluating CVD[3,4] (analytical, imaging, etc.) and indirect methods based mainly on the determination, using scales[5], of the risk of presenting a cerebrovascular event in a given period, which is generally established as ten years.

In the vast majority of these health problems, one element that is always present is atherosclerosis[6]. This condition occurs when fatty elements build up on the walls of the blood vessel (artery). This accumulation of fat gives rise to what is called plaque[7]. This causes problems in different organs of our body. If an artery becomes clogged, it can lead to the occurrence of different cerebrovascular events.

Atherogenic dyslipidemia and lipid triad8 are two clinical entities characterized by the coexistence of pathological values of different lipid parameters such as triglycerides and HDL, in the case of dyslipidemia, and these two and LDL in the case of the triad. These two parameters are early predictors of atherosclerosis, hence their clinical importance.

Based on the above, the aim of this study is to determine the relationship of atherogenic dyslipidemia and the lipid triad with different scales that determine cardiovascular risk in a group of Spanish workers from different regions and work groups.

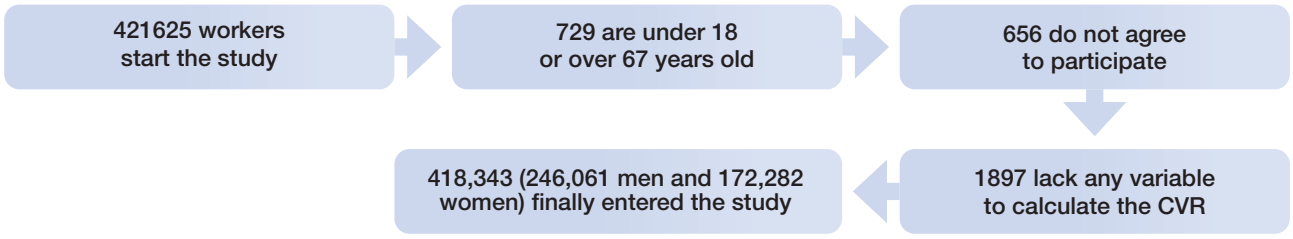
## Methods

In a group of 418,343 Spanish workers (172,282 women and 246,061 men), a cross-sectional descriptive study was carried out using data from occupational medical examinations performed between January 2019 and June 2020. The workers belonged to the primary, secondary and tertiary sectors.

Inclusion criteria were established as follows:
- Age between 18 and 69 years.
- Working in one of the companies included in the study.
- Agreeing to participate in the study.

The flow diagram is presented in **figure 1**.

**Figure 1:** Flowchart of participants.




### *Determination of variables*

The responsibility for identifying the clinical, analytical, and anthropometric variables required to calculate the various scales included in the study fell on the health workers of the participating companies. The measurements were standardized to reduce interobserver bias.

Using the subject upright and the abdomen relaxed, the waist circumference was measured using a tape measure at the level of the last rib.

With the patient seated and after at least 10 minutes of rest, blood pressure was measured using an OMRON M3 sphygmomanometer. The mean blood pressure was calculated from three measurements.

After fasting for at least 12 hours, the analytical parameters were collected using precipitation methods for HDL cholesterol and enzymatic methods for glucose, triglycerides, and cholesterol. Using the Friedewald formula (valid only for triglyceride amounts under 400), LDL-cholesterol was calculated. In mg/dL, all analytical parameters were presented.

Different cardiovascular risk scales were calculated:

- Registro Gironí del Cor (REGICOR)[9,10].

The likelihood of having a fatal or non-fatal cerebrovascular incident over the following ten years is determined by this scale. It can be computed for ages between 35 and 74. It is divided into four categories: low less than 5%,

moderate, high between 10% and 14% high, and very high more than 15%.

- Systematic Coronary Risk Evaluation 2 (SCORE2)[11]
Assesses the probability of a cerebrovascular event occurring in the next decade. It can be calculated between 40 and 69 years of age. Its classification varies according to age group (under 50 years and over 50 years) so that in the first group we will consider low or moderate risk if it is less than 2.5%, high between 2.5-7.5% and very high above 7.5%, while in the second group it will be low or moderate risk if it is less than 5%, high between 5-10% and very high above 10%.

- Framingham and SCORE vascular age[12].
Both vascular age scales are based on cardiovascular risk scales with the same name and both are calculated from tables. In both cases, the concept of ALLY[13] (avoidable lost life years) can be applied, which is calculated by subtracting the vascular age from the chronological age. Our group established 10 years as moderate ALLY values and 18 years as high values[14].

- ERICE score[15].
The Spanish Cardiovascular Risk Equation (ERICE) is based on data from several epidemiological studies in different regions of Spain. It assesses the probability of a fatal cerebrovascular event occurring in the next ten years and can be calculated between the ages of thirty and eighty. Total cholesterol, age, smoking, diabetes, sex, systolic blood pressure and the presence or absence of antihypertensive drug treatment are the factors used to calculate it.

Low (less than 5%), mild (5-9%), moderate (10-14%), moderate-high (15-19%), high (20-29%), and extremely high (greater than 30%) are the five categories.

If the combination of high triglyceride levels, low HDL cholesterol levels (less than 50 mg/dL for women and less than 40 mg/dL for males), and normal LDL cholesterol levels was present, atherogenic dyslipidemia[16] was evaluated. A lipid triad[17] was deemed to exist if LDL cholesterol also surpassed 160 mg/dL.

Diabetes was defined as having fasting blood glucose levels greater than 125 mg/dL or using hypoglycemic medications.

A smoker was defined as someone who had smoked one or more cigarettes per day for the previous 30 days, or the equivalent in another mode of consumption, or someone who had quit smoking within the previous 12 months.

The workers were divided into three social groups using the 2011 National Classification of Occupations (CNO-11) and the Spanish Society of Epidemiology standards[18]. I. Managers, college employees, athletes, and creatives. Unskilled employees, part two.

### Ethical considerations and aspects

The study adhered to the 2013 Declaration of Helsinki as well as the institutional research committee's ethical requirements. The obtained data's confidentiality and anonymity could always be maintained. The Research Ethics Committee of the Balearic Islands (CEI-IB) gave the study their blessing with IB 4383/20. Only the person in charge of the study was able to decode the data used to identify each of the workers who were participating in the study. The research team committed to carefully upholding Organic Law 3/2018, of December 5, on the protection of personal data and guarantee of digital rights, ensuring that each participant in this study could exercise their right to access, rectification, erasure, and opposition to the use of their data for any purpose.

### Statistical analysis

For quantitative data, the t-student test was used to calculate the mean and standard deviation. The chi-square test was used to calculate prevalence for qualitative variables. ROC curves were used to evaluate how well the cardiovascular risk scales predicted the presence of atherogenic and triadic dyslipidemia. Calculations were made for the area under the curve (AUC), the cut-off points' sensitivity, specificity, and Youden index. Multinomial logistic regression was used to do the multivariate analysis. To conduct the statistical analysis, SPSS 28.0 was employed. p0.05 was the accepted cutoff for statistical significance.

## Results

The characteristics of the study participants are shown in **table I**. Men made up more than 58%. The majority group was between the ages of 30 and 49, with a mean age of 40. Over 75% were from socioeconomic class III, and over 33% smoked. In women, all variables had more favorable values.

**Table II** demonstrates that people of both sexes with atherogenic dyslipidemia and lipid triad have higher mean values on all evaluated cardiovascular risk scales.

When the prevalence of elevated values for each of the cardiovascular risk measures included in the study is evaluated, **table III** exhibits the similar tendency.

The outcomes of the multinomial logistic regression analysis are displayed in **table IV**. As the scores on the cardiovascular risk scales rise, so does the risk of atherogenic dyslipidemia and the lipid triad. The ALLY Framingham vascular age was shown to have the greatest OR values.

The areas under the curve of the various cardiovascular risk measures for predicting atherogenic dyslipidemia and the lipid triad are shown in **table V** and **figure 2**. The results for ALLY Framingham vascular age show the highest values.

**Table I:** Characteristics of the population.

| | Women n=172,282<br>Mean (SD) | Men n=246,061<br>Mean (SD) | Total n=418,343<br>Mean (SD) | p-value |
|---|---|---|---|---|
| **Age (years)** | 39.6 (10.8) | 40.6 (11.1) | 40.2 (11.0) | <0.0001 |
| **Height (cm)** | 161.8 (6.5) | 174.6 (7.0) | 169.4 (9.3) | <0.0001 |
| **Weight (kg)** | 66.2 (14.0) | 81.4 (14.7) | 75.1 (16.2) | <0.0001 |
| **Waist circumference (cm)** | 74.8 (10.6) | 86.2 (11.1) | 81.5 (12.2) | <0.0001 |
| **SBP (mmHg)** | 117.4 (15.7) | 128.2 (15.5) | 123.7 (16.5) | <0.0001 |
| **DBP (mmHg)** | 72.6 (10.4) | 77.8 (11.0) | 75.6 (11.0) | <0.0001 |
| **Total colesterol (mg/dL)** | 190.6 (35.8) | 192.6 (38.9) | 191.8 (37.7) | <0.0001 |
| **HDL-c (mg/dL)** | 56.8 (8.7) | 50.3 (8.5) | 53.0 (9.1) | <0.0001 |
| **LDL-c (mg/dL)** | 116.1 (34.8) | 118.0 (36.7) | 117.2 (35.9) | <0.0001 |
| **Triglycerides (mg/dL)** | 89.1 (46.2) | 123.7 (86.4) | 109.5 (74.6) | <0.0001 |
| **Glycaemia** | 87.8 (15.1) | 93.3 (21.3) | 91.0 (19.2) | <0.0001 |
| **ALT (U/L)** | 20.2 (13.6) | 31.0 (20.2) | 26.6 (18.6) | <0.0001 |
| **AST (U/L)** | 18.2 (7.9) | 24.4 (13.3) | 21.7 (11.7) | <0.0001 |
| **GGT (U/L)** | 20.4 (19.7) | 35.8 (39.3) | 29.6 (33.6) | <0.0001 |
| | % | % | % | p |
| **18-29 years** | 20.7 | 18.8 | 19.6 | |
| **30-39 years** | 29.7 | 27.6 | 28.4 | |
| **40-49 years** | 29.6 | 30.1 | 29.9 | |
| **50-70 years** | 20.0 | 23.6 | 22.2 | |
| **Social class I** | 6.9 | 4.9 | 5.7 | |
| **Social class II** | 23.4 | 14.9 | 18.4 | |
| **Social class III** | 69.7 | 80.3 | 75.9 | |
| **Non-smokers** | 67.2 | 66.6 | 66.9 | |
| **Smokers** | 32.8 | 33.4 | 33.2 | |

SBP systolic blood pressure. DBP diastolic blood pressure. HDL-c high density lipoprotein-cholesterol. LDL-c low density lipoprotein-cholesterol. ALT aspartate transaminase. ALT alanine transaminase GGT gammaglutamyl transferase.

**Table II:** Mean values of cardiovascular risk scales according presence or absence of atherogenic dyslipidemia and lipid triad by sex.

| | Women | | | | | Men | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Non AD | | Yes AD | | | Non AD | | Yes AD | | |
| | n | Mean (SD) | n | Mean (SD) | p-value | n | Mean (SD) | n | Mean (SD) | p-value |
| **ALLY VA SCORE2** | 80164 | 4.1 (5.1) | 5132 | 6.5 (5.4) | <0.0001 | 116929 | 7.4 (6.8) | 14611 | 10.0 (7.2) | <0.0001 |
| **SCORE** | 80164 | 0.4 (0.9) | 5132 | 1.0 (1.4) | <0.0001 | 116929 | 1.7 (2.2) | 14611 | 2.2 (2.7) | <0.0001 |
| **ALLY VA Framingham** | 130226 | 0.2 (11.5) | 6395 | 14.0 (13.8) | <0.0001 | 181651 | 5.7 (10.0) | 18178 | 16.5 (10.8) | <0.0001 |
| **REGICOR** | 126345 | 2.9 (2.2) | 6318 | 3.5 (2.3) | <0.0001 | 177759 | 3.3 (2.2) | 18168 | 3.8 (2.7) | <0.0001 |
| **ERICE** | 130226 | 2.6 (3.2) | 6395 | 4.4 (4.6) | <0.0001 | 181644 | 4.4 (5.1) | 18178 | 6.8 (6.7) | <0.0001 |
| | n | Non LT | n | Non LT | p-value | n | Non LT | n | Non LT | p-value |
| **ALLY VA SCORE2** | 83852 | 4.1 (5.2) | 1444 | 8.0 (5.6) | <0.0001 | 127158 | 7.5 (6.9) | 4382 | 11.7 (7.4) | <0.0001 |
| **SCORE** | 83852 | 0.5 (1.0) | 1444 | 1.3 (1.6) | <0.0001 | 127158 | 1.7 (2.2) | 4382 | 2.4 (2.9) | <0.0001 |
| **ALLY VA Framingham** | 134969 | 0.6 (11.7) | 1652 | 19.3 (12.9) | <0.0001 | 194562 | 6.3 (10.3) | 5267 | 19.9 (10.4) | <0.0001 |
| **REGICOR** | 131035 | 2.9 (2.2) | 1628 | 3.8 (2.6) | <0.0001 | 190723 | 3.3 (2.2) | 5204 | 4.4 (3.2) | <0.0001 |
| **ERICE** | 134969 | 2.6 (3.3) | 1652 | 5.1 (4.5) | <0.0001 | 194555 | 4.6 (5.2) | 5267 | 6.7 (6.3) | <0.0001 |

ALLY VA Avoidable lost life years vascular age. SCORE Systematic Coronary Risk Evaluation. REGICOR Registro Gironi del Corazón. ERICE Ecuación de riesgo cardiovascular española. AD atherogenic dyslipidemia. LT lipid triad.

**Table III:** Prevalence of high values of cardiovascular risk scales according presence or absence of atherogenic dyslipidemia and lipid triad by sex.

| | Women | | | | | Men | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Non AD | | Yes AD | | | Non AD | | Yes AD | | |
| | n | % | n | % | p-value | n | % | n | % | p-value |
| **ALLY VA SCORE >10** | 80164 | 15.0 | 5132 | 28.1 | <0.0001 | 116929 | 33.5 | 14611 | 48.6 | <0.0001 |
| **SCORE high-very high** | 80164 | 1.1 | 5132 | 3.0 | <0.0001 | 116929 | 10.5 | 14611 | 17.8 | <0.0001 |
| **ALLY VA Framingham >10** | 130226 | 17.8 | 6395 | 57.3 | <0.0001 | 181651 | 29.4 | 18178 | 69.4 | <0.0001 |
| **REGICOR high-very high** | 126345 | 1.5 | 6318 | 2.3 | <0.0001 | 177759 | 1.9 | 18168 | 3.5 | <0.0001 |
| **ERICE high-very high** | 130226 | 0.2 | 6395 | 3.1 | <0.0001 | 181644 | 2.2 | 18178 | 5.2 | <0.0001 |
| | n | % | n | % | p-value | n | % | n | % | p-value |
| **ALLY VA SCORE >10** | 83852 | 15.4 | 1444 | 37.5 | <0.0001 | 127158 | 34.5 | 4382 | 57.7 | <0.0001 |
| **SCORE2 high-very high** | 83852 | 1.1 | 1444 | 4.8 | <0.0001 | 127158 | 10.9 | 4382 | 22.1 | <0.0001 |
| **ALLY VA Framingham >10** | 134969 | 19.0 | 1652 | 74.8 | <0.0001 | 194562 | 31.7 | 5267 | 82.1 | <0.0001 |
| **REGICOR high-very high** | 131035 | 1.6 | 1628 | 3.0 | <0.0001 | 190723 | 2.0 | 5204 | 6.0 | <0.0001 |
| **ERICE high-very high** | 134969 | 0.2 | 1652 | 0.7 | <0.0001 | 194555 | 2.4 | 5267 | 4.4 | <0.0001 |

ALLY VA Avoidable lost life years vascular age. SCORE Systematic Coronary Risk Evaluation. REGICOR Registro Gironi del Corazón. ERICE Ecuación de riesgo cardiovascular española. AD atherogenic dyslipidemia. LT lipid triad.

**Table IV:** Multinomial logistic regression.

| | Atherogenic dyslipidemia | Lipid triad |
|---|---|---|
| | OR (95% CI) | OR (95% CI) |
| ALLY VA SCORE <10 | 1 | 1 |
| ALLY VA SCORE ≥10 | 2.17 (2.11-2.24) | 3.03 (2.87-3.19) |
| ALLY VA Framingham <10 | 1 | 1 |
| ALLY VA Framingham ≥10 | 6.01 (5.85-6.18) | 11.34 (10.68-12.04) |
| SCORE2 low | 1 | 1 |
| SCORE2 moderate | 1.29 (1.22-1.36) | 1.48 (1.35-1.62) |
| SCORE high-very high | 2.51 (2.40-2.63) | 3.26 (3.04-3.50) |
| REGICOR low | 1 | 1 |
| REGICOR moderate | 1.25 (1.15-1.36) | 1.61 (1.42-1.82) |
| REGICOR high-very high | 1.97 (1.82-2.14) | 3.26 (2.88-3.68) |
| ERICE low | 1 | 1 |
| ERICE moderate | 1.21 (1.12-1.31) | 1.19 (1.14-1.24) |
| ERICE high-very high | 3.41 (3.18-3.66) | 2.65 (2.33-3.02) |

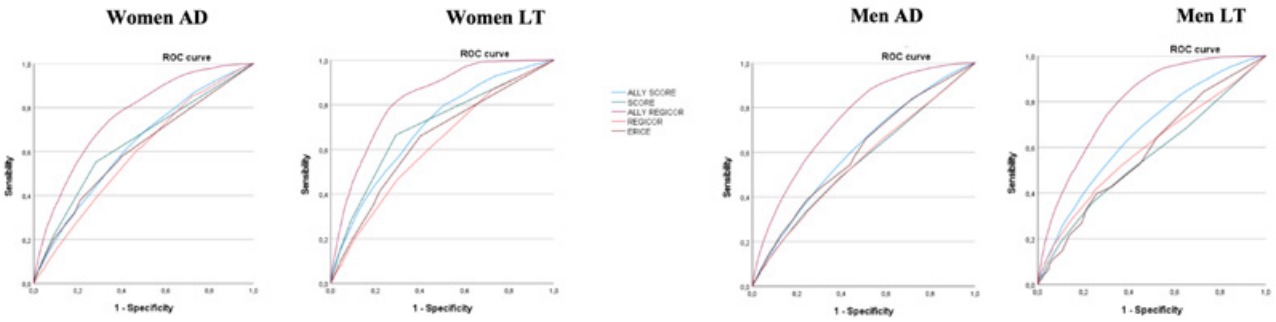
ALLY VA Avoidable lost life years vascular age. SCORE Systematic Coronary Risk Evaluation. REGICOR Registro Gironi del Corazón. ERICE Ecuación de riesgo cardiovascular española. AD atherogenic dyslipidemia. LT lipid triad.

**Table V:** Areas under the curve and cutoff points of the different cardiovascular risk scales for predicting atherogenic dyslipidemia and lipid triad.

| | AD Women | LT Women |
|---|---|---|
| | AUC (95% ci) | AUC (95% ci) |
| ALLY VA SCORE | 0.628 (0.620-0.636) | 0.698 (0.685-0.711) |
| SCORE2 | 0.641 (0.633-0.649) | 0.6978 (0.684-0.713) |
| ALLY VA Framingham | 0.762 (0.756-0.769) | 0.826 (0.817-0.835) |
| REGICOR | 0.592 (0.584-0.599) | 0.616 (0.602-0.630) |
| ERICE | 0.607 (0.598-0.615) | 0.641 (0.627-0.656) |
| | AD Men | LT Men |
| ALLY VA SCORE | 0.609 (0.604-0.614) | 0.663 (0.655-0.671) |
| SCORE | 0.555 (0.550-0.560) | 0.558 (0.548-0.567) |
| ALLY VA Framingham | 0.748 (0.744-0.752) | 0.795 (0.789-0.801) |
| REGICOR | 0.556 (0.551-0.562) | 0.594 (0.585-0.603) |
| ERICE | 0.601 (0.596-0.606) | 0.584 (0.575-0.592) |

ALLY VA Avoidable lost life years vascular age. SCORE Systematic Coronary Risk Evaluation. REGICOR Registro Gironi del Corazón. ERICE Ecuación de riesgo cardiovascular española. AD atherogenic dyslipidemia. LT lipid triad.

**Figure 2:** ROC curve.




## Discussion

The prevalence of elevated values and the mean values of all the cardiovascular risk scales used in this investigation are higher in persons with lipid triad and atherogenic dyslipidemia.

With the exception of the ALLY Framingham, the ROC curves have moderate values for the areas under the curve, making them ineffective as predictors of AD and LT.

We have not been able to find studies that relate either atherogenic dyslipidemia or the lipid triad to any scale that assesses cardiovascular risk, so we will focus this discussion on the relationship of cardiovascular disease

to atherosclerosis and on the relationship of dyslipidemia to scales that predict cardiovascular risk.

Alterations in the plasma lipid profile that are often associated with clinical conditions are known as dyslipidemias. Dyslipidemias, particularly elevated plasma levels of LDL cholesterol, are important risk factors for cardiovascular disease, but some forms, such as hypertriglyceridemia, are associated with serious diseases in other organ systems, such as nonalcoholic fatty liver disease and acute pancreatitis.

An investigation carried out by our group in 610 Spanish veterinarians[19] concluded that the level of cardiovascular risk determined with different scales, most of which were included in this study, correlated very well with the values of the different lipid parameters and was much higher in those veterinarians who had dyslipidemia. Similar results were obtained in a Bolivian study[20] carried out in 1094 miners and in another by the same group in 5370 farmers[21]. Another study carried out in more than 59000 workers[22] also found this association.

As indicated above, although atherosclerosis is a physiological process, in certain situations it will accelerate and can cause certain cardiovascular diseases[23]. Atherogenic dyslipidemia and the lipid triad are parameters that predict the appearance of atherosclerosis.

Lipoprotein a is a complex circulating lipoprotein, and there is ample scientific evidence of its important role as a risk factor for atherosclerotic cardiovascular disease[24]. Lipoprotein a has many similarities with low-density lipoprotein (LDL), but differs from LDL in that it has an additional apolipoprotein called apo(a)[25].

### Strengths and limitations

The study's biggest advantages are its massive sample size—more than 418 000 workers—and the extensive use of cardiovascular risk assessments.

The primary drawback is that results may not be extrapolated to other groups because the cardiovascular risk measures utilized were designed for the Spanish population.

## Conclusions

For all of the assessed cardiovascular risk scales, atherogenic dyslipidemia and the lipid triad are associated with greater mean values and higher prevalence of elevated values.

In the multivariate analysis, ALLY Framingam is the scale that significantly raises the risk of presenting AD and LT.

With the exception of ALLY Framingham, we noticed in the ROC curves that the cardiovascular risk scales do not accurately classify the existence of atherogenic dyslipidemia and lipid triad.

### Conflict of Interest

The authors declare that there is no conflict of interest.

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ORIGINAL

# Relationship between heart age and insulin resistance risk scales in 139634 Spanish workers

*Relación entre la edad del corazón y escalas de riesgo de resistencia a la insulina en 139634 trabajadores españoles*

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## Abstract

***Introduction:*** Insulin resistance is a key factor in the development of type 2 diabetes, which is one of the most prevalent cardiometabolic disorders. Heart age is a new tool for assessing cardiovascular risk. The aim of this study is to assess the association between heart age and different insulin resistance risk scales.
***Material and methods:*** Descriptive and cross-sectional study in 139634 Spanish workers in which both heart age and different insulin resistance risk scales such as TyG index, METS-IR and triglycerides/HDL were determined.
***Results:*** Heart age values increase as do the values of the insulin resistance risk scales. The risk of presenting elevated heart age values increases in those with high values of the insulin resistance scales, with the highest odds ratios being found for TyG index. The value of the insulin resistance risk scales for predicting the occurrence of moderate or high ALLY heart age values is not high.
***Conclusions:*** There is a good relationship between heart age values and the values of the insulin resistance risk scales, however the predictive value of these insulin resistance scales for predicting elevated ALLY heart age values is low.

*Key words:* heart age, insulin resistance, risk scales.

## *Resumen*

***Introducción:*** La resistencia a la insulina es un factor clave para que aparezca diabetes tipo 2 que es una de las alteraciones cardiometabólicas más prevalentes. La edad del corazón es una nueva herramienta para valorar el riesgo cardiovascular. El objetivo de este estudio es valorar la asociación que existe entre la edad del corazón y diferentes escalas de riesgo de resistencia v la insulina.
***Material y métodos:*** Estudio descriptivo y transversal en 139634 trabajadores españoles en los que se determinan tanto la edad del corazón como distintas escalas de riesgo de resistencia a la insulina como TyG index, METS-IR y triglicéridos/HDL.
***Resultados:*** Los valores de edad del corazón se incrementan a medida que lo hacen los valores de las escalas de riesgo de resistencia a la insulina. El riesgo de presentar valores elevados de edad del corazón se incrementa en aquellas personas con valores altos de las escalas de resistencia a la insulina, siendo las odds ratio más elevadas las encontradas para TyG index. El valor de las escalas de riesgo de resistencia a la insulina para predecir la aparición de valores moderados o altos de edad cardiaca ALLY no es elevado.
***Conclusiones:*** Existe buena relación entre los valores de edad del corazón y los valores de las escalas de riesgo de resistencia a la insulina, sin embargo el valor predictivo de estas escalas de resistencia a la insulina para predecir valores elevados de ALLY edad del corazón es bajo.

*Palabras clave:* edad del corazón, resistencia a la insulina, escalas de riesgo.

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## Introduction

Cardiovascular diseases are currently considered to be one of the main public health problems in practically all countries of the world, due to their high prevalence and high morbidity and mortality[1].

Many cardiovascular disease risk scales have been developed in recent decades, most of them assessing the probability of presenting a cerebrovascular event, fatal or non-fatal, in a given period of time, generally established as ten years[2]. For some, these scales give a false sense of security, since the values obtained are in most cases low despite the coexistence of different risk factors. To resolve this situation, scales have appeared in recent years that assess the aging of the heart or vascular tree and that are also expressed as an absolute number and not as a percentage, a situation that for some authors makes it easier to understand the level of risk to which the person is exposed[3].

Insulin resistance appears when different cells (muscle cells, adipocytes or hepatocytes) do not respond adequately to the action of insulin, so that blood glucose absorption cannot take place. To compensate for this situation, there is an increase in insulin production to allow glucose to enter the cells[4]. As long as the pancreas is able to produce sufficient insulin, blood glucose levels will remain normal, but as insulin production decreases, blood glucose levels will rise, which can lead to the onset of prediabetes[5] and later diabetes[6].

The aim of this study is to determine the relationship between the values of different insulin resistance risk scales and the values of the heart age scale.

## Methods

A cross-sectional descriptive study was carried out on 139634 workers attending medical check-ups, and belonging to different work sectors and different Spanish regions. The study was carried out between January 2019 and June 2020.

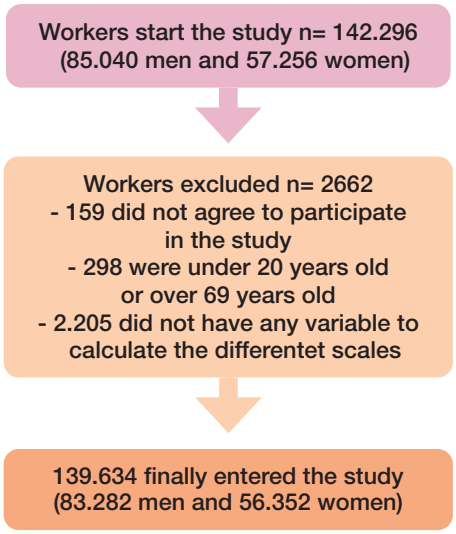
Inclusion criteria were: age between 18 and 69 years.
- Working in the companies included in the study.
- Accepting participation in the study and the transfer of data.

The flow chart is presented in **figure 1**.

### *Determination of variables*

The health professionals from the different companies that participated in the study were responsible for carrying out the analytical determinations and the anthropometric and clinical measurements necessary to obtain the variables included in this study. To avoid possible interobserver bias, all measurements were standardized.

**Figure 1:** Flow chart of the participants.




To obtain the waist circumference, a tape measure was placed parallel to the floor and at the level of the last floating rib while the patient was in a standing position and with the abdomen relaxed.

To obtain blood pressure, the patient had to rest for at least 10 minutes beforehand. The person was seated and three measurements were taken, calculating the mean value of the three.

Blood tests were obtained after a minimum fasting period of 12 hours using enzymatic processes for blood glucose, cholesterol and triglycerides and precipitation for HDL-cholesterol. LDL-cholesterol was obtained using the Friedewald formula. All the results of all the variables were expressed in mg/dL.

Cardiac age is a new instrument that is calculated on the basis of the classic Framingham cardiovascular risk scale. While the classic cardiovascular risk scales assess the probability of a cerebrovascular event in the next decade, whether fatal or non-fatal, Heart Age assesses the aging of the heart.

Different variables are used to calculate heart age, such as age, sex, height, weight, abdominal circumference, family history of cardiovascular disease, diabetes, tobacco use, lipid profile, systolic blood pressure and consumption of antihypertensive drugs[7]. A calculator is used to obtain the age of the heart, which is available at: www.heartage.me. This calculator can be applied to people between 20 and 80 years of age. The range of values varies between minus 20 and plus 20 years, the limits being 18 and 80 years.

An important concept is the so-called ALLY[8] (avoidable years of life lost), which is the result of subtracting the age of the heart from the chronological age. A publication by our group established the cut-off points, with moderate

ALLY being considered moderate from 11 years of age and high ALLY from 17 years of age onwards[9].

Blood glucose was classified according to the indications of the American Diabetes Association10, which establishes that a person is diabetic if: blood glucose values exceed 125 mg/dL in two different determinations, or if the HbA1c ≥ 6.5% or when the person consumes hypoglycemic agents.

Determination of the percentage of the body's insulin resistance was analysed with the following scales:

Different scales are calculated to assess the risk of insulin resistance:

- Metabolic Insulin Resistance Score (METS-IR)[11]. METS-IR = Ln [(2FPG) + TG] BMI)/(Ln[HDLc]). High values are considered from 50
- The triglyceride and glucose index (TyG index) and some of its variants:
  - TyG = Ln [fasting TG (mg/dL) FPG (mg/dL)/2][12]. High values are considered from 8.8
  - The triglyceride glucose-body mass index (TyG-BMI)[13]
  - TyG - waist circumference (TyG-WC)[13]
- Triglycerides/HDL[14] High values are considered from 2.4

A smoker is a person who has consumed at least one cigarette a day (or the equivalent in other tobacco modalities) in the last 30 days or who has quit smoking less than 1 year ago.

Heart-healthy eating habits were determined by means of the questionnaire on adherence to the Mediterranean diet[15]. This questionnaire consists of 14 questions that are scored with 0 or 1 point, with adherence being considered high if the final score is 9 or higher.

Physical activity was assessed by applying the IPAQ[16] (International Physical Activity Questionnaire). Alcohol intake was quantified in alcohol units (AU). In Spain, one AU is equivalent to 10 grams of pure ethanol. High consumption was considered to be higher if it exceeded 14 AU in women and 21 in men.

The determination of social class is obtained from the National Classification of Occupations 2011[17] and following the criteria established by the Spanish Society of Epidemiology. According to the CNO-11, workers were classified into three social classes: I. Managers, university professionals, athletes and artists. II. Intermediate occupations and skilled self-employed workers. III. Unskilled workers.

### *Ethical considerations and aspects*

In our research, the ethical norms and the Declaration of Helsinki of the year 2013 have been respected at all times. The anonymity and confidentiality of all people is guaranteed. The research received the approval of the Research Ethics Committee of the Balearic Islands (CEI-IB): IB 4383/20. The information of each participant was coded and only the person responsible for the study could know their identity. All researchers complied with Organic Law 3/2018, of December 5, on the protection of personal data and guarantee of digital rights, which guarantees the right of access, rectification, cancellation and opposition of the data collected at all times.

### *Statistical analysis*

Student's t test was used to analyze the quantitative variables, calculating the means and standard deviations. The chi-square test was applied for the qualitative variables, calculating the prevalence. ROC curves were calculated by determining the areas under the curve (AUC). A multinomial logistic regression analysis was performed, calculating the odds ratio. Statistical analysis was performed with the SPSS 28.0 program. The accepted level of statistical significance was $p<0.05$.

## Results

**Table I** shows the anthropometric, clinical, analytical, sociodemographic and healthy habits characteristics of the 139,634 workers who entered the study (83,282 men 59.6% and 56,352 women 40.4%). The mean age of the sample was slightly over 40 years, with the majority of people between the ages of 30 and 49. All the variables showed more favorable values in women. Most of the workers belonged to social class III and their educational level was elementary. The prevalence of high physical activity and high adherence to the Mediterranean diet were lower in men. Approximately one in three people included in the study were a smoker. One third of the people smoked.

The mean values of ALLY heart age according to the values of the different risk scales for insulin resistance are presented in **table II**. The mean values of ALLY increase at the same time as the values of the risk scales of insulin resistance. In all cases the differences observed are statistically significant.

The prevalence of elevated values increases as do the values of the different insulin resistance risk scales. In all cases the observed differences are also statistically significant. The complete data is presented in **table III**.

**Table IV** presents the results of the multinomial logistic regression analysis. The risk of presenting either moderate or high values of ALLY heart age increases in parallel with the increase in the values of the insulin resistance risk scales. The highest OR values were those found for the TyG index.

**Figure 2** and **table V** present the results of the ROC curves. The areas under the curve of all the insulin resistance risk scales to predict the presence of moderate values of ALLY heart age are low, while for ALLY high heart age it is considered moderate.

**Table I:** Characteristics of the population.

| | Men n=83,282<br>Mean (SD) | Women n=56,352<br>Mean (SD) | p-value |
|---|---|---|---|
| Age (years) | 41.4 (10.7) | 40.1 (10.4) | <0.0001 |
| Height (cm) | 173.8 (7.1) | 161.2 (6.5) | <0.0001 |
| Weight (kg) | 83.2 (14.6) | 66.3 (13.9) | <0.0001 |
| Body mass index (kg/m²) | 27.5 (4.5) | 25.5 (5.3) | <0.0001 |
| Waist circumference (cm) | 90.2 (10.3) | 76.3 (10.5) | <0.0001 |
| Waist to height ratio | 0.52 (0.06) | 0.47 (0.07) | <0.0001 |
| Systolic blood pressure (mmHg) | 126.2 (15.9) | 115.6 (15.7) | <0.0001 |
| Diastolic blood pressure (mmHg) | 76.6 (10.9) | 71.1 (10.7) | <0.0001 |
| Total cholesterol (mg/dl) | 199.6 (38.6) | 194.6 (36.9) | <0.0001 |
| HDL-cholesterol (mg/dl) | 50.0 (7.7) | 54.7 (9.2) | <0.0001 |
| LDL-cholesterol (mg/dl) | 122.6 (37.4) | 121.5 (37.1) | <0.0001 |
| Triglycerides (mg/dl) | 133.8 (95.6) | 90.8 (49.7) | <0.0001 |
| Glycaemia (mg/dl) | 93.0 (25.4) | 86.8 (18.1) | <0.0001 |
| n (%) | n (%) | p-value | |
| 18-29 years | 12558 (15.1) | 10110 (18.0) | <0.0001 |
| 30-39 years | 24648 (29.6) | 17460 (31.0) | |
| 40-49 years | 25178 (30.2) | 17094 (30.3) | |
| 50-59 years | 17370 (20.9) | 9984 (17.7) | |
| 60-70 years | 3528 (4.2) | 1704 (3.0) | |
| Social class I | 6234 (7.5) | 7632 (13.6) | <0.0001 |
| Social class II | 19856 (23.8) | 18112 (32.1) | |
| Social class III | 57192 (68.7) | 30608 (54.3) | |
| Primary school | 55306 (66.4) | 27086 (48.1) | |
| Secondary school | 22408 (26.9) | 22574 (40.0) | |
| University | 5568 (6.7) | 6692 (11.9) | |
| Non-smokers | 55618 (66.8) | 38252 (67.9) | <0.0001 |
| Smokers | 27664 (33.2) | 18100 (32.1) | |
| Non physical activity | 51984 (62.4) | 28962 (51.4) | <0.0001 |
| Yes physical activity | 31298 (37.6) | 27390 (48.6) | |
| Non healthy food | 54792 (65.8) | 29764 (52.8) | <0.0001 |
| Yes healthy food | 28490 (34.2) | 26588 (47.2) | |
| Non alcohol consumption | 56022 (67.3) | 47536 (84.4) | <0.0001 |
| Yes alcohol consumption | 27260 (32.7) | 8816 (15.6) | |

HDL high density lipoprotein. LDL Low density lipoprotein

**Table II:** Mean values of heart age according different insulin resistance risk scales by sex.

| ALLY HA | n | Men<br>Mean (SD) | p-value | n | Women<br>Mean (SD) | p-value |
|---|---|---|---|---|---|---|
| METS-IR normal | 72302 | 5.9 (7.8) | <0.0001 | 52206 | 1.0 (9.4) | <0.0001 |
| METS-IR high | 10980 | 12.6 (7.4) | | 4146 | 10.3 (9.0) | |
| TyG index normal | 52484 | 4.4 (7.3) | <0.0001 | 48696 | 0.4 (9.1) | <0.0001 |
| TyG index high | 30798 | 10.7 (7.7) | | 7656 | 9.7 (9.5) | |
| TyG-BMI normal | 57476 | 5.1 (7.6) | <0.0001 | 47070 | 0.3 (9.1) | <0.0001 |
| TyG-BMI high | 25806 | 10.4 (7.8) | | 9282 | 8.4 (9.5) | |
| TyG-waist normal | 59594 | 5.3 (7.7) | <0.0001 | 53166 | 1.2 (9.4) | <0.0001 |
| TyG-waist high | 23688 | 10.4 (7.9) | | 3186 | 10.2 (9.3) | |
| TG/HDL normal | 60208 | 5.0 (7.6) | <0.0001 | 44594 | -0,1 (8.9) | <0.0001 |
| TG/HDL high | 23074 | 11.4 (7.5) | | 11758 | 8.4 (9.3) | |

METS-IR Metabolic score for insulin resistance. TyG Triglyceride glucosa index BMI Body mass index
WtHR Waist to heigh ratio. TG Triglyceride HDL High density Lipoprotein. ALLY HA Avoidable lost life life years heart age

**Table III:** Prevalence of high values of heart age according different insulin resistance risk scales by sex.

| ALLY HA | Men | | | | | Women | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Normal<br>% | Moderate<br>% | High<br>% | p-value | n | Normal<br>% | Moderate<br>% | High<br>% | p-value |
| METS-IR normal | 72302 | 75,6 | 10,5 | 14,0 | <0.0001 | 52206 | 83,6 | 10,2 | 10,2 | <0.0001 |
| METS-IR high | 10980 | 40,8 | 16,2 | 43,1 | | 4146 | 51,2 | 37,7 | 37,7 | |
| TyG index normal | 52484 | 82,1 | 8,9 | 9,1 | <0.0001 | 48696 | 86,0 | 8,3 | 8,3 | <0.0001 |
| TyG index high | 30798 | 52,0 | 15,2 | 32,8 | | 7656 | 51,1 | 36,9 | 36,9 | |
| TyG-BMI normal | 57476 | 78,8 | 9,7 | 11,6 | <0.0001 | 47070 | 85,8 | 8,6 | 8,6 | <0.0001 |
| TyG-BMI high | 25806 | 53,6 | 14,6 | 31,8 | | 9282 | 58,2 | 30,2 | 30,2 | |
| TyG-waist normal | 59594 | 77,8 | 9,9 | 12,3 | <0.0001 | 53166 | 83,1 | 10,7 | 10,7 | <0.0001 |
| TyG-waist high | 23688 | 53,7 | 14,5 | 31,8 | | 3186 | 49,6 | 37,6 | 37,6 | |
| TG/HDL normal | 60208 | 79,3 | 9,5 | 11,1 | <0.0001 | 44594 | 87,3 | 7,6 | 7,6 | <0.0001 |
| TG/HDL high | 23074 | 49,2 | 15,6 | 35,2 | | 11758 | 58,3 | 29,7 | 29,7 | |

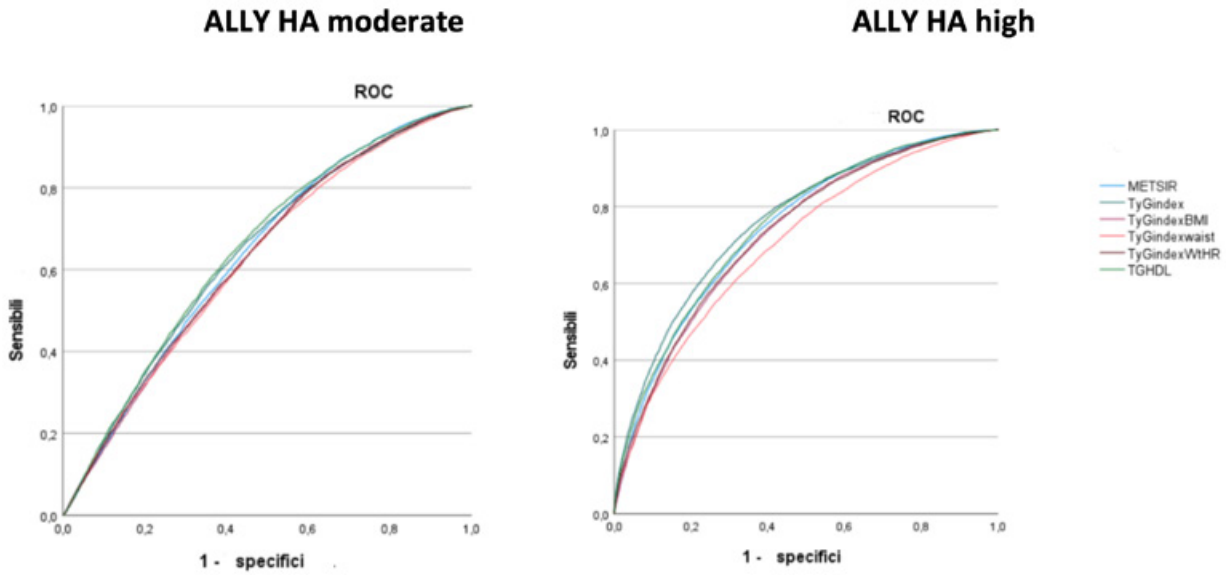
METS-IR Metabolic score for insulin resistance. TyG Triglyceride glucosa index BMI Body mass index
WtHR Waist to heigh ratio. TG Triglyceride HDL High density Lipoprotein. ALLY HA Avoidable lost life life years heart age

**Table IV:** Binomial logistic regression.

| | ALLY HA moderate | | ALLY HA high | |
|---|---|---|---|---|
| | OR (95% CI) | p-value | OR (95% CI) | p-value |
| **METS-IR normal** | 1 | | 1 | |
| **METS-IR high** | 1.91 (1.82-2.00) | <0.0001 | 1.99 (1.89-2.09) | <0.0001 |
| **TyG index normal** | 1 | | 1 | |
| **TyG index high** | 2.42 (2.33-2.52) | <0.0001 | 2.59 (2.47-2.71) | <0.0001 |
| **TyG-BMI normal** | 1 | | 1 | |
| **TyG-BMI high** | 1.49 (1.43-1.55) | 0.005 | 1.49 (1.42-1.55) | <0.0001 |
| **TyG-waist normal** | 1 | | 1 | |
| **TyG-waist high** | 1.06 (1.02-1.10) | <0.0001 | 1.09 (1.05-1.13) | <0.0001 |
| **TG/HDL normal** | 1 | | 1 | |
| **TG/HDL high** | 1.71 (1.65-1.78) | <0.0001 | 1.73 (1.66-1.81) | <0.0001 |

METS-IR Metabolic score for insulin resistance. TyG Triglyceride glucosa index BMI Body mass index WtHR Waist to heigh ratio. TG Triglyceride HDL High density Lipoprotein. ALLY HA Avoidable lost life life years heart age.

**Figure 2:** ROC curve.




ALLY HA Avoidable lost life life years heart age

**Table V:** Area under the curve (ROC curve).

| | ALLY HA moderate AUC (95% CI) | ALLY HA high AUC (95% CI) |
|---|---|---|
| **METS-IR** | 0.637 (0.632-0.642) | 0.746 (0.743-0.750) |
| **TyG index** | 0.640 (0.635-0.645) | 0.763 (0.759-0.766) |
| **TyG-BMI** | 0.627 (0.622-0.632) | 0.731 (0.728-0.734) |
| **TyG-waist** | 0.623 (0.618-0.627) | 0.705 (0.701-0.709) |
| **TyG-WtHR** | 0.629 (0.624-0.633) | 0.733 (0.730-0.737) |
| **TG/HDL** | 0.649 (0.644-0.654) | 0.752 (0.749-0.756) |

METS-IR Metabolic score for insulin resistance. TyG Triglyceride glucosa index BMI Body mass index WtHR Waist to heigh ratio. TG Triglyceride HDL High density Lipoprotein. AUC Area under the curve

## Discussion

The mean value and the prevalence of moderate or high values of ALLY cardiac age increase parallel to the values of the different insulin resistance risk scales used in this study. The results of the multinomial logistic regression analysis show that the insulin resistance risk scale with the highest odds ratio is the TyG index.

An exhaustive review of the literature, in different databases, has only allowed us to find a few articles that relate, albeit tangentially, the age of the heart with insulin resistance, for this reason it will not be possible to compare our results with those obtained by other authors.

A study carried out in 501 individuals without cardiovascular disease, with a mean age of 55.9 years, aimed at assessing the relationship between healthy vascular aging, lifestyle and the components of the metabolic syndrome found that vascular age was associated with

smoking, blood pressure, waist circumference and altered basal glycemia[18]. 18 This same group, in another study[19] found that healthy vascular aging was closely related to insulin resistance.

In an investigation carried out in 18,490 participants of the MARE[20] global consortium, without cardiovascular pathologies, in which healthy vascular aging was assessed, it was observed that the prevalence of metabolic syndrome, the genesis of which is insulin resistance, was lower in this group.

A Taiwanese study[21] of 4881 persons found that the risk of atherosclerotic cardiovascular disease, which is related to vascular aging, was higher in persons with metabolic syndrome, persons with elevated glycemia or glycosylated hemoglobin, that is, in persons with possible insulin resistance.

A Russian study[22] conducted in 750 patients with metabolic syndrome aged 35 to 80 years concluded that the presence of type 2 diabetes and insulin resistance was associated with an increased risk of early vascular aging.

### Strengths and limitations

The strengths of the study include the large sample size, which exceeds 139,000 participants, the wide variety of insulin resistance risk scales used, and the fact that we can consider this study as a benchmark with which to compare the results found in subsequent studies.

The main limitation is that insulin resistance has been determined using risk scales and not objective methods.

## Conclusions

Both the means and the prevalence of moderate and high values of ALLY heart age increase in parallel with the increase in the values of the different insulin resistance risk scales included in this study. The value of the insulin resistance risk scales to predict the appearance of moderate or high values of ALLY heart age is low in the first case and moderate in the second.

### Conflict of Interest

The authors declare that there is no conflict of interest.

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ORIGINAL

# How does ChatGPT perform on the European Board of Pediatric Surgery examination? A randomized comparative study

*¿Cuál es el rendimiento de ChatGPT en el examen del Consejo Europeo de Cirugía Pediátrica? Un estudio comparativo aleatorizado*

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## Abstract

***Purpose:*** The purpose of this study was to conduct a detailed comparison of the accuracy and responsiveness of GPT-3.5 and GPT-4 in the realm of pediatric surgery. Specifically, we sought to assess their ability to correctly answer a series of sample questions of European Board of Pediatric Surgery (EBPS) exam.
***Methods:*** This study was conducted between 20 May 2023 and 30 May 2023. This study undertook a comparative analysis of two AI language models, GPT-3.5 and GPT-4, in the field of pediatric surgery, particularly in the context of EBPS exam sample questions. Two sets of 105 (total 210) sample questions each, derived from the EBPS sample questions, were collated.
***Results:*** In General Pediatric Surgery, GPT-3.5 provided correct answers for 7 questions (46.7%), and GPT-4 had a higher accuracy with 13 correct responses (86.7%) (p=0.020). For Newborn Surgery and Pediatric Urology, GPT-3.5 correctly answered 6 questions (40.0%), and GPT-4, however, correctly answered 12 questions (80.0%) (p= 0.025). In total, GPT-3.5 correctly answered 46 questions out of 105 (43.8%), and GPT-4 showed significantly better performance, correctly answering 80 questions (76.2%) (p<0.001). Given the total responses, when GPT-4 was compared with GPT-3.5, the Odds Ratio was found to be 4.1. This suggests that GPT-4 was 4.1 times more likely to provide a correct answer to the pediatric surgery questions compared to GPT-3.5.
***Conclusion:*** This comparative study concludes that GPT-4 significantly outperforms GPT-3.5 in responding to EBPS exam questions.

*Key words:* ChatGPT, Pediatric Surgery, exam, questions, artificial intelligence.

## *Resumen*

***Introducción:*** El propósito de este estudio fue realizar una comparación detallada de la precisión y capacidad de respuesta de GPT-3.5 y GPT-4 en el ámbito de la cirugía pediátrica. En concreto, pretendíamos evaluar su capacidad para responder correctamente a una serie de preguntas de muestra del examen del European Board of Pediatric Surgery (EBPS).
***Métodos:*** Este estudio se llevó a cabo entre el 20 de mayo de 2023 y el 30 de mayo de 2023. Este estudio llevó a cabo un análisis comparativo de dos modelos de lenguaje de IA, GPT-3.5 y GPT-4, en el campo de la cirugía pediátrica, particularmente en el contexto de las preguntas de muestra del examen EBPS. Se cotejaron dos conjuntos de 105 (210 en total) preguntas de muestra cada uno, derivadas de las preguntas de muestra del EBPS.
***Resultados:*** En Cirugía Pediátrica General, la GPT-3.5 proporcionó respuestas correctas para 7 preguntas (46,7%), y la GPT-4 tuvo una mayor precisión con 13 respuestas correctas (86,7%) (p=0,020). Para Cirugía neonatal y Urología pediátrica, la GPT-3.5 respondió correctamente a 6 preguntas (40,0%), y la GPT-4, sin embargo, respondió correctamente a 12 preguntas (80,0%) (p= 0,025). En total, la GPT-3.5 respondió correctamente a 46 preguntas de 105 (43,8%), y la GPT-4 mostró un rendimiento significativamente mejor, respondiendo correctamente a 80 preguntas (76,2%) (p<0,001). Teniendo en cuenta el total de respuestas, cuando se comparó la GPT-4 con la GPT-3.5, se observó que la Odds Ratio era de 4,1. Esto sugiere que la GPT-4 era 4,2 veces más eficaz que la GPT-3.5. Esto sugiere que GPT-4 tenía 4,1 veces más probabilidades de proporcionar una respuesta correcta a las preguntas de cirugía pediátrica en comparación con GPT-3.5.
***Conclusiones:*** Este estudio comparativo concluye que GPT-4 supera significativamente a GPT-3.5 a la hora de responder a las preguntas del examen EBPS.

*Palabras clave:* ChatGPT, Cirugía Pediátrica, examen, preguntas, inteligencia artificial.

**Cite as:** U

## Introduction

The Chat Generative Pre-trained Transformer (ChatGPT) is a natural language processing tool that was trained on massive amounts of data and is driven by artificial intelligence (1). Due to its extraordinary capacity to generate human-like responses in response to text input within a conversation, ChatGPT has been gaining significant attention ever since it was first made available to the public in November 2022. GPT-3.5 was the foundational large language model that was used to support ChatGPT when it first launched. In March of 2023, an improved version known as GPT-4 was made available to the public with the promise of increased precision. Although there is a lot of interest in the use of ChatGPT, there is some debate about whether or not it should be used in medical practice[1-3].

The advent and progression of Artificial Intelligence (AI) in various fields have redefined the way we understand and implement knowledge[4]. AI's integration into medicine, particularly the field of pediatric surgery, offers an innovative lens to examine, decode, and provide solutions to complex surgical problems. The AI language models GPT-3.5 and GPT-4, developed by OpenAI, have demonstrated promising applications in diverse fields, including medicine. Yet, a comprehensive understanding of their capacity to accurately respond to professional, field-specific queries remains to be thoroughly explored[5,6].

The purpose of this study was to conduct a detailed comparison of the accuracy and responsiveness of GPT-3.5 and GPT-4 in the realm of pediatric surgery. Specifically, we sought to assess their ability to correctly answer a series of sample questions of EBPS exams.

## Materials and methods

This study was conducted between 20 May 2023 and 30 May 2023. This study undertook a comparative analysis of two AI language models, GPT-3.5 and GPT-4, in the field of pediatric surgery, particularly in the context of EBPS exam sample questions. Two sets of 105 (total 210) sample questions each, derived from the EBPS sample questions, were collated. These questions spanned a broad range of pediatric surgical knowledge and were structured in a variety of formats to best assess the capabilities of the AI models.

Both GPT-3.5 and GPT-4 models were set up for the study. The testing was conducted on a computer with an internet connection, and responses from the models were recorded on a digital platform for further analysis. Each model was independently presented with a set of 105 questions in the same sequence which are selected randomly (General Pediatric Surgery, Newborn Surgery, Thoracic Surgery, Pediatric Urology, Traumatology, Hepatopancreatobiliary Surgery, Pediatric Oncological Surgery; each one 15 questions per group). Each question was input individually, and the generated response was recorded (Sample; **Figure 1, 2, 3**). The responses from both AI models were carefully reviewed by experts in pediatric surgery. The responses were scored based on their correctness and relevance to the question.

**Figure 1:** Sample question in Newborn Surgery section.

**Figure 2:** Sample question in Hepatopancreatobiliary Surgery section.

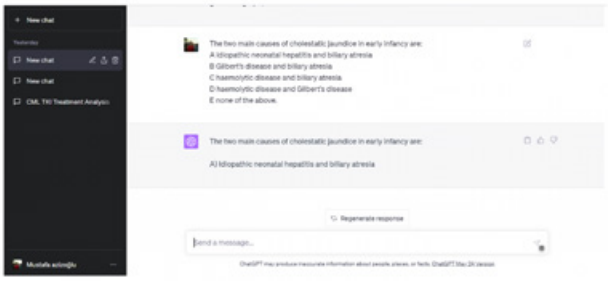
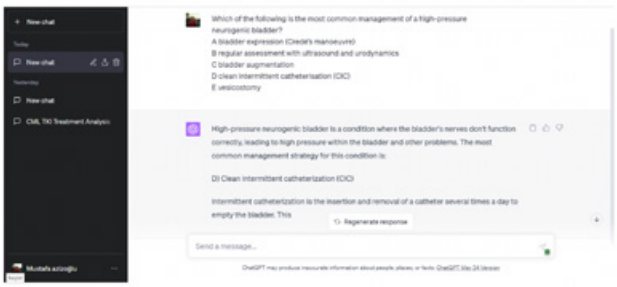


**Figure 3:** Sample question in Pediatric Urology section.



Following the review and scoring process, the number of correct answers provided by each model was summed up. The total correct answers were then expressed as a percentage of the total questions, giving an accuracy score for each model. The accuracy scores of GPT-3.5 and GPT-4 were compared to determine which model demonstrated superior performance in answering the EBPS sample questions.

### Inclusion criteria
Randomly selected questions from the EBPS study questions have been included in the study.

### Exclusion criteria
Questions containing images were excluded from the study as the GPT program does not accept images.

### Statistical analysis
For all items, descriptive statistics, frequency, and other characteristics were used in the statistical analysis of the data. The Chi-square test was used to evaluate the categorical variables, and when necessary, Fisher exact test was used on some of the data. SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA) was used to conduct the analyses. P values were all two-sided, and p values below 0.05 were regarded as statistically significant.

## Results

In this comparative study, the GPT-3.5 and GPT-4 language models were tested on a range of topics within pediatric surgery. Each topic was assessed for accuracy, with results indicating significant differences in performance between the two models.

A total of 210 questions were included in the study, 105 questions from each group. In General Pediatric Surgery, GPT-3.5 provided correct answers for 7 questions (46.7%) and incorrect answers for 8 questions (53.3%). In contrast, GPT-4 had a higher accuracy with 13 correct responses (86.7%) and only 2 incorrect responses (13.3%). This difference was found to be statistically significant (p= 0.020). For Newborn Surgery and Pediatric Urology, GPT-3.5 correctly answered 6 questions (40.0%) and incorrectly answered 9 questions (60.0%) for both topics. GPT-4, however, correctly answered 12 questions (80.0%) and incorrectly answered 3 questions (20.0%) for both categories, with the difference also being statistically significant (p= 0.025). In Thoracic Surgery, GPT-3.5 had a slightly higher accuracy, correctly answering 8 questions (53.3%) and incorrectly answering 7 questions (46.7%). GPT-4 had better performance in this category, with 12 correct responses (80.0%) and 3 incorrect responses (20.0%). However, the difference was not statistically significant (p= 0.121). The Traumatology category had GPT-3.5 correctly answering 7 questions (46.7%) and incorrectly answering 8 questions (53.3%). GPT-4 managed to correctly answer 11 questions (73.3%) while incorrectly answering 4 questions (26.7%). This difference was not statistically significant (p= 0.136). For Hepatopancreatobiliary Surgery and Pediatric Oncological Surgery, GPT-3.5 correctly answered 6 questions (40.0%) and incorrectly answered 9 questions (60.0%) in each category. On the other hand, GPT-4 correctly answered 10 questions (66.7%) and incorrectly answered 5 questions (33.3%) in both categories, with no statistically significant difference (p= 0.143). In total, GPT-3.5 correctly answered 46 questions out of 105 (43.8%), and incorrectly answered 59 questions (56.2%). GPT-4 showed a significantly improved performance, correctly answering 80 questions (76.2%) and incorrectly answering 25 questions (23.8%). The overall difference in performance was found to be statistically significant (p<0.001) (**Table I** and **figure 4**).

Given the total responses, when GPT-4 was compared with GPT-3.5, the Odds Ratio was found to be 4.1. This suggests that GPT-4 was 4.1 times more likely to provide a correct answer to the pediatric surgery questions compared to GPT-3.5.

**Figure 4:** Comparison of the frequency of the answers.

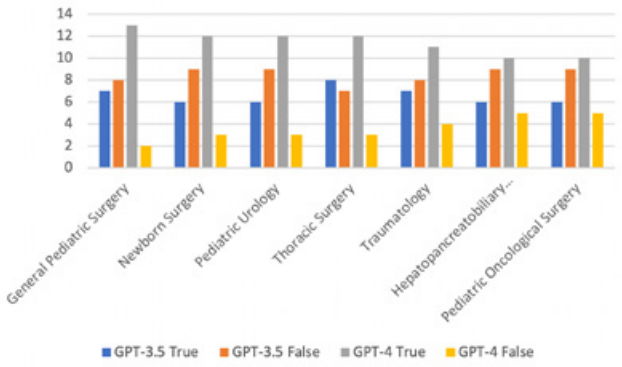



**Table I:** Comparison of GPT-3.5 and GPT-5 in terms of correct answers number.

| | GPT-3.5 | | | | GPT-4 | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | True | | False | | True | | False | | |
| | N | % | N | % | N | % | N | % | p-value |
| General Pediatric Surgery | 7 | 46,7 | 8 | 53,3 | 13 | 86,7 | 2 | 13,3 | 0.020 |
| Newborn Surgery | 6 | 40,0 | 9 | 60,0 | 12 | 80,0 | 3 | 20,0 | 0.025 |
| Pediatric Urology | 6 | 40,0 | 9 | 60,0 | 12 | 80,0 | 3 | 20,0 | 0.025 |
| Thoracic Surgery | 8 | 53,3 | 7 | 46,7 | 12 | 80,0 | 3 | 20,0 | 0.121 |
| Traumatology | 7 | 46,7 | 8 | 53,3 | 11 | 73,3 | 4 | 26,7 | 0.136 |
| Hepatopancreatobiliary Surgery | 6 | 40,0 | 9 | 60,0 | 10 | 66,7 | 5 | 33,3 | 0.143 |
| Pediatric Oncological Surgery | 6 | 40,0 | 9 | 60,0 | 10 | 66,7 | 5 | 33,3 | 0.143 |
| Total | 46 | 43,8 | 59 | 56,2 | 80 | 76,2 | 25 | 23,8 | <0.001 |

## Discussion

To our knowledge, this represents the inaugural comparative analysis of GPT-3.5 and GPT-4 in the context of responding to EBPS examination questions. The results from this study demonstrate the significant differences in the accuracy and responsiveness of GPT-3.5 and GPT-4 to field-specific queries within the realm of pediatric surgery. In particular, GPT-4 showed a statistically significant improvement in answering questions related to pediatric surgery as compared to its predecessor, GPT-3.5.

Previous work in the field of medical question-answering research has frequently concentrated on more specific tasks with the intention of improving model performance at the expense of their generalizability[7,8]. For instance, Jin et al.[9] were able to achieve an accuracy of 68.1% with their model that responds to yes-or-no questions, the answers to which can be found in the corpus of abstracts that are available through PubMed. The pursuit of more generalizable models has been met with an increasing number of obstacles. On a data set consisting of 12,723 questions taken from Chinese medical licensing exams, a different Jin et al[10] achieved an accuracy of 36.7%. In a similar, Ha et al.[11] reported only a 29% accuracy on 454 USMLE Step 1 and Step 2 questions in the year 2019. Gilson and colleagues found that when posing questions from the United States Medical Licensing Examination Step 1 and Step 2 exams to ChatGPT, the correct response rate was determined to be 58%[12-14]. However in our study, In total, GPT-3.5 correctly answered 46 questions out of 105 (43.8%), and incorrectly answered 59 questions (56.2%). GPT-4 showed a significantly improved performance, correctly answering 80 questions (76.2%) and incorrectly answering 25 questions (23.8%). The overall difference in performance was found to be statistically significant ($p<0.001$). In this study, the highest accuracy rate was observed in the General Pediatric Surgery section (86.7%).

This study has several limitations. To begin, the ChatGPT algorithm was initially trained on a corpus that was constructed using data that was produced on or before the year 2021. Because of this restriction, the model's prompts can only contain information that was discovered before that date. Second, because this model is closed and does not have a public application programming interface (API), we are unable to fine-tune it using data that is specific to a task and investigate the extent of the inherent stochasticity that it possesses. The fact that this work investigates ChatGPT's performance in context on the EBPS exam, however, means that these limitations did not hinder our analysis in any way. Third, updates to ChatGPT are being released on a regular basis. It is believed that these updates are the result of training on inputs provided by users as they are received. The version of ChatGPT that was used in this research was an older model than the one that was published at the time of the study's completion. When everything is taken into consideration, it is reasonable to hypothesize that the performance of the model will not suffer a significant decline with each new iteration of the model when it is applied to the task that we have outlined, and that the performance may even improve.

In conclusion, this comparative study concludes that GPT-4 significantly outperforms GPT-3.5 in responding to EBPS exam questions, showing a 76.2% accuracy rate compared to 43.8%. Thus, newer iterations of ChatGPT models may offer promising applications for professional, field-specific inquiries in medicine and pediatric surgery. Further studies are needed to evaluate the effectiveness of the GPT for EBPS exam preparation.

### Conflict of Interest

The authors declare that there is no conflict of interest.

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ORIGINAL

# Influence of sociodemographic variables and healthy habits on the values of overweight and obesity scales in 386,924 Spanish workers

*Influencia de variables sociodemográficas y hábitos saludables en los valores de escalas de sobrepeso y obesidad en 386,924 trabajadores españoles*

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## Abstract

***Introduction:*** Obesity is a highly prevalent chronic and multifactorial disease that is generally associated with an increased cardiometabolic risk.
***Objective:*** In this study we are interested in assessing the effect of different sociodemographic variables and healthy habits on the values of different scales that assess overweight and obesity.
***Methodology:*** A descriptive, cross-sectional study was carried out in 386,924 Spanish workers to assess the effect of different sociodemographic variables (age, sex, social class, level of education) and healthy habits (physical activity, Mediterranean diet and tobacco consumption) on the values of scales that determine overweight and obesity on the basis of different criteria.
***Results:*** All the variables analyzed increased the risk of presenting obesity with any of the criteria except educational level. The most influential variables were physical activity and Mediterranean diet.
***Conclusions:*** The risk profile of presenting obesity corresponds to that of an elderly male, with a low socioeconomic level, sedentary, with low adherence to the Mediterranean diet and a smoker.

*Key words:* Obesity, physical activity, Mediterranean diet, sociodemographic variables, smoking.

## *Resumen*

***Introducción:*** La obesidad es una enfermedad crónica y multifactorial altamente prevalente y que generalmente se asocia a un incremento del riesgo cardiometabólico.
***Objetivo:*** En este estudio nos interesa valorar el efecto de diferentes variables sociodemográficas y hábitos saludables en los valores de diferentes escalas que valoran sobrepeso y obesidad. Metodología. Se realiza un estudio descriptivo y transversal en 386,924 trabajadores españoles en los que se valora el efecto de distintas variables sociodemográficas (edad, sexo, clase social, nivel de estudios) y hábitos saludables (actividad física, dieta mediterránea y consumo de tabaco) en los valores de escalas que determinan sobrepeso y obesidad en base a diferentes criterios.
***Resultados:*** Todas las variables analizadas incrementan el riesgo de presentar obesidad con cualquiera de los criterios excepto el nivel de estudios. Las variables que más influyen son la actividad física y la dieta mediterránea.
***Conclusiones:*** El perfil de riesgo de presentar obesidad responde al de un varón de edad avanzada, con un nivel socioeconómico bajo, sedentario, con baja adherencia a la dieta mediterránea y fumador.

*Palabras clave:* Obesidad, actividad física, dieta mediterránea, variables sociodemográficas, tabaco.

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## Introduction

Obesity is considered a progressive and chronic pathology[1] that can have biological[2], psychological[3] and even social[4] repercussions on the life course of individuals. This disease is associated with an increase in the risk of suffering cardiovascular disorders[5], and also with an increase in mortality[6] and a decrease in the quality of life[7].

The World Health Organization (WHO) considers obesity to be an excessive or abnormal accumulation of fatty tissue that can cause health problems[8].

There are different factors that have been associated with the appearance of obesity, including sedentary lifestyle[9], poor diet[10], stress[11], poor quality[12] or insufficient number of hours of sleep[13], genetic causes[14], consumption of certain drugs (antidepressants[15], antipsychotics[16] or corticoids[17]) or pathologies such as polycystic ovary disease[18] among others.

Many scales have been used to classify obesity, some of which evaluate anthropometric parameters such as height and weight (body mass index BMI[19]), waist circumference (waist/height index[20]), or hip circumference (body adiposity index BAI[21]). Others are based on the estimation of body fat (Clínica Universitaria de Navarra body fat estimator CUN BAE[22]) or visceral fat (visceral fat metabolic score METS-VF[23]).

## Methods

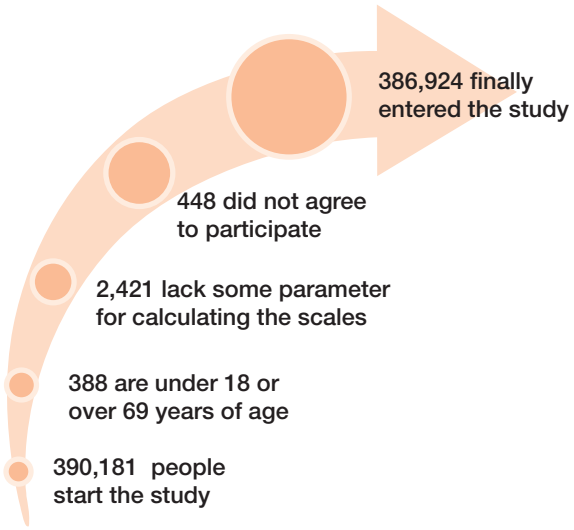
This work is based on an observational, cross-sectional and descriptive study carried out on 386,924 workers from different Spanish autonomous communities. The 60.2% (232,814 people) are men and 39.8% (154,110 people) are women. The workers included in this study are derived from those who attend the medical check-ups carried out periodically in all the participating companies. The study period covers the period January 2019 and June 2020.

In order to make the final selection of the sample, some inclusion criteria are established:

- To be between 18 and 69 years of age.
- To have an employment contract in one of the participating companies.
- Accept to be included in the study.
- Accept the transfer of the use of the data for epidemiological purposes.

The data flow diagram of the workers, after applying the inclusion criteria, is shown in **figure 1**.

**Figure 1:** Flow-chart of participants in the study.




### *Determination of variables*

The people who are part of the occupational health units of the participating companies were in charge of obtaining the data necessary to carry out this study. The data were collected by means of:

- Anamnesis. An exhaustive clinical history was used to collect data on sociodemographic variables (age, sex, social class and level of education) and healthy habits (tobacco, alcohol, Mediterranean diet and physical activity).
- Anthropometric and clinical determinations. These included height, weight, waist circumference, systolic and diastolic blood pressure.
- Analytical determinations. Lipid profile and glycemia were determined.

In an attempt to avoid possible biases in the study, the techniques used to measure the variables were standardized.

Height and weight were determined with the person standing and in underwear, arms hanging and thorax and head aligned. We used a SECA model scale-measuring device and the data are expressed in centimeters and kilograms.

To assess the abdominal waist circumference we use a SECA model measuring tape placed at the level of the last floating rib and parallel to the floor. The person is standing with the abdomen relaxed. The hip circumference is also measured in this position and placing the tape measure also parallel to the floor at the level of the widest part of the buttocks.

Blood pressure is obtained with an OMROM-M3 blood pressure monitor. For a correct assessment the person is seated and must be at rest for at least 10 minutes. The

cuff is placed around the arm until it fits snugly without being too tight, which is why cuffs of different sizes are available. We perform 3 consecutive determinations separated by one minute. The figure that is evaluated is an average of the three.

Blood determinations are obtained by venipuncture and after a previous fasting of 12 hours. The samples are processed and stored refrigerated for proper preservation for a period never exceeding 48-72 hours. The analysis of the samples is performed in reference laboratories that use similar methodology. Triglycerides, total cholesterol and blood glucose are determined by enzymatic techniques, while HDL cholesterol is determined by precipitation techniques. LDL cholesterol is estimated indirectly by applying the Friedewald formula, which is valid as long as triglycerides do not exceed 400 mg/dL. If the figure is higher than 400 mg/dL, LDL is determined directly. All analytical variables are expressed in mg/dL.

Sex is established as a dichotomous variable: male and female.

Age is calculated by subtracting the date of birth from the date of the medical examination.

The educational level considered is the highest of those that have been carried out in their entirety. Three levels are established: primary studies, secondary studies and university studies.

Social class will be determined by applying the criteria of the Spanish Society of Epidemiology and based on the type of work included in the 2011 national classification of occupations (CNO-11)[24]. Three levels are established:

- Social class I. This includes management personnel, professionals with university education, professional athletes and artists.
- Social class II. Includes intermediate professions and skilled self-employed workers.
- Social class III. Includes workers with low qualifications.

In our study, we consider that a person is a smoker if he or she has consumed any type of tobacco at least once a day in the last 30 days or if he or she has quit smoking less than 12 months ago.

Adherence to the Mediterranean diet was determined by applying a questionnaire[25] consisting of 14 questions scored with 0 or 1 point. Values of 9 or more points indicate high adherence[26].

The level of physical activity is determined by means of the International Physical Activity Questionnaire (IPAQ)[27]. This self-administered questionnaire quantifies the physical activity performed in the last seven days.

The overweight and obesity scales determined are:

- Body Mass Index (BMI). It is calculated by dividing the weight expressed in kilograms by the squared height expressed in meters.

It is stratified into underweight (less than 18.5 kg/m$^2$), normal weight (between 18.5 and 24.9 kg/m$^2$), overweight (between 25 and 29.9 kg/m$^2$) and obese (over 30 kg/m$^2$).

- Body adiposity index[28] (BAI)

BAI = (Hip Circumference in centimetres / Height in metres ^ 1.5) – 18

- Clínica Universitaria de Navarra body adiposity estimator[29] (CUN BAE)

-44.988 + (0.503 × age) + (10.689 × sex) + (3.172 × BMI) - (0.026 × BMI2) + (0.181 × BMI × sex) - (0.02 × BMI × age) - (0.005 × BMI2 × sex) + (0.00021 × BMI2 × age).

Male =0 Female =1.

- Metabolic score for visceral fat[30] (METS-VF)

$$METS\text{-}VF = 4.466 + 0.011*(Ln(METS\text{-}IR))^3 + 3.239*(Ln(WHtr))^3 + 0.319*(Sex) + 0.594*(Ln(Age))$$

where

Metabolic Score for Insulin Resistance (METS-IR)[31] is obtained using the formula:

METS-IR = Ln (2 x glycaemia + triglycerides) x BMI/Ln HDL-c

### *Considerations and ethical aspects*

In this study, the ethical rules that should govern research and the 2013 Declaration of Helsinki have been fully respected. The anonymity and confidentiality of the participants has always been guaranteed. The study received the approval of the Balearic Islands Research Ethics Committee (CEI-IB), which granted its consent under number IB 483/20.

The data of each participant are coded and only the principal investigator knows who they are. Most of the researchers who participated in this study complied with Organic Law 3/2018, enacted on December 5, 2018, on the protection of personal data and guarantee of digital rights, which allows and guarantees that study participants can access, rectify, cancel, and oppose the use of the data collected at any time.

### *Statistical analysis*

Student's t-test was used to analyze the quantitative data, which determined the means and standard deviations. When the variables were quantitative, the chi2 test was used to calculate prevalence. Multinomial logistic regression analysis was performed and odds ratios with 95% confidence intervals were calculated. Statistical analysis was performed with SPSS 28.0 software. The accepted level of statistical significance was $p<0.05$.

## Results

The anthropometric, clinical, analytical, sociodemographic and healthy habits data of the 386924 workers in the study are shown in **table I**. The mean age of the participants is slightly over 39 years. With the exception of LDL cholesterol, the variables show more negative values in the group of men. A total of 60.2% are men, while 39.8% are women. The majority of the population is between 30 and 49 years old. Most belong to socioeconomic class III and have primary education. 45.5% of the men and 52.2% of the women practice physical activity regularly, and 51.4% of the women have a high adherence to the Mediterranean diet, and 41% of the men. Thirty-three percent of the women and slightly more than 37% of the men smoke.

**Tables II** and **III** show the mean values of the four scales that assess overweight and obesity, and it can be seen that these mean values increase in parallel with increasing age and decreasing social class and level of education. Higher values are also observed in sedentary people and those with low adherence to the Mediterranean diet. Smokers present lower mean values. All the differences observed are statistically significant. In all the scales the values are higher in men except CUN BAE.

**Tables IV** and **V** show the prevalence of high values for the four overweight and obesity scales in both sexes. The trend is the same as that seen for the mean values, i.e. an increase in the prevalence of high values as age increases and socioeconomic level decreases, as well as in sedentary people and those with low adherence to the Mediterranean diet. In smokers the prevalences are also lower. In all cases the differences found are also statistically significant.

**Table VI** presents the results of the multivariate analysis using multinomial logistic regression. In the four scales a similar pattern is followed, all the sociodemographic variables and healthy habits influence the increase in the risk of presenting high values of the different overweight-obesity scales. This risk increases with age, as one descends in social class, in people who do little physical activity and have low adherence to the Mediterranean diet, and in non-smokers.

**Table I:** Characteristics of the population.

| | Men n=232,814<br>Mean (SD) | Women n=154,110<br>Mean (SD) | p-value |
|---|---|---|---|
| **Age (years)** | 39.8 (10.3) | 39.2 (10.2) | <0.001 |
| **Height (cm)** | 173.9 (7.0) | 161.2 (6.6) | <0.001 |
| **Weight (kg)** | 81.1 (13.9) | 65.3 (13.2) | <0.001 |
| **Waist circumference (cm)** | 87.7 (9.1) | 73.9 (7.9) | <0.001 |
| **Hip circumference (cm)** | 100.0 (8.4) | 97.2 (8.9) | <0.001 |
| **Systolic blood pressure (mmHg)** | 124.4 (15.1) | 114.4 (14.8) | <0.001 |
| **Diastolic blood pressure (mmHg)** | 75.4 (10.6) | 69.7 (10.3) | <0.001 |
| **Total cholesterol (mg/dl)** | 195.9 (38.9) | 193.6 (36.4) | <0.001 |
| **HDL-c (mg/dl)** | 51.0 (7.0) | 53.7 (7.6) | <0.001 |
| **LDL-c (mg/dl)** | 120.5 (37.6) | 122.3 (37.0) | <0.001 |
| **Triglycerides (mg/dl)** | 123.8 (88.0) | 88.1 (46.2) | <0.001 |
| **Glycaemia (mg/dl)** | 88.1 (12.9) | 84.1 (11.5) | <0.001 |
| | **%** | **%** | **p-value** |
| **20-29 years** | 17.9 | 19.5 | <0.001 |
| **30-39 years** | 33.1 | 33.3 | |
| **40-49 years** | 29.7 | 29.4 | |
| **50-59 years** | 16.3 | 15.3 | |
| **60-69 years** | 3.0 | 2.5 | |
| **Primary school** | 61.2 | 51.8 | <0.001 |
| **Secondary school** | 34.0 | 40.7 | |
| **University** | 4.8 | 7.5 | |
| **Social class I** | 5.3 | 7.2 | <0.001 |
| **Social class II** | 17.4 | 33.2 | |
| **Social class III** | 77.3 | 59.8 | |
| **Non physical activity** | 54.5 | 47.8 | <0.001 |
| **Yes physical activity** | 45.5 | 52.2 | |
| **Non healthy food** | 59.0 | 48.6 | <0.001 |
| **Healthy food** | 41.0 | 51.4 | |
| **Non smokers** | 62.9 | 67.0 | <0.001 |
| **Smokers** | 37.1 | 33.0 | |

HDL-c High density lipoprotein cholesterol. LDL Low density lipoprotein cholesterol

**Table II:** Mean values of overweight-obesity scales according to sociodemographic variables and healthy habits in men.

| Men | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | BMI | | BAI | | CUN BAE | | METS-VF | |
| | n | Mean (SD) | p-value | Mean (SD) | p-value | Mean (SD) | p-value | Mean (SD) | p-value |
| **20-29 years** | 41,742 | 25.0 (4.1) | <0.001 | 24.4 (3.7) | <0.001 | 21.1 (6.3) | <0.001 | 5.9 (0.5) | <0.001 |
| **30-39 years** | 76,96 | 26.5 (4.1) | | 25.2 (3.7) | | 24.6 (5.8) | | 6.3 (0.5) | |
| **40-49 years** | 69,068 | 27.4 (4.1) | | 26.1 (3.8) | | 27.1 (5.4) | | 6.6 (0.5) | |
| **50-59 years** | 38,028 | 27.9 (4.0) | | 27.0 (3.8) | | 28.9 (5.0) | | 6.8 (0.5) | |
| **60-69 years** | 7,016 | 28.3 (3.9) | | 27.9 (4.0) | | 30.3 (4.5) | | 6.9 (0.4) | |
| **Primary school** | 142,494 | 26.8 (4.3) | <0.001 | 25.9 (3.9) | <0.001 | 25.6 (6.4) | <0.001 | 6.4 (0.6) | <0.001 |
| **Secondary school** | 79,226 | 26.8 (4.1) | | 25.4 (3.7) | | 25.6 (6.0) | | 6.4 (0.6) | |
| **University** | 11,094 | 26.6 (3.8) | | 25.1 (3.6) | | 25.5 (5.6) | | 6.4 (0.5) | |
| **Social class I** | 12,262 | 26.6 (3.8) | <0.001 | 25.1 (3.6) | <0.001 | 25.5 (5.7) | <0.001 | 6.4 (0.5) | <0.001 |
| **Social class II** | 40,65 | 26.7 (4.0) | | 25.2 (3.7) | | 25.5 (5.9) | | 6.4 (0.5) | |
| **Social class III** | 179,902 | 26.8 (4.3) | | 25.8 (3.9) | | 25.6 (6.3) | | 6.4 (0.6) | |
| **Non physical activity** | 126,808 | 29.1 (4.1) | <0.001 | 27.1 (3.8) | <0.001 | 29.2 (5.4) | <0.001 | 6.7 (0.5) | <0.001 |
| **Yes physical activity** | 106,006 | 24.0 (2.2) | | 23.9 (3.1) | | 21.3 (4.1) | | 6.1 (0.5) | |
| **Non healthy food** | 137,464 | 28.7 (4.2) | <0.001 | 26.9 (3.9) | <0.001 | 28.6 (5.7) | <0.001 | 6.7 (0.5) | <0.001 |
| **Healthy food** | 95,35 | 24.0 (2.2) | | 23.9 (3.1) | | 21.2 (4.1) | | 6.1 (0.5) | |
| **Non smokers** | 146,48 | 27.1 (4.1) | <0.001 | 25.9 (3.9) | <0.001 | 26.2 (6.0) | <0.001 | 6.4 (0.6) | <0.001 |
| **Smokers** | 86,334 | 26.2 (4.3) | | 25.4 (3.8) | | 24.6 (6.4) | | 6.4 (0.6) | |

BMI Body mass index. BAI Body adiposity index. CUN BAE Clinica Universitaria de Navarra Body Adiposity Estimator. METS-VF Metabolic Score for Visceral Fat.

**Table III:** Mean values of overweight-obesity scales according to sociodemographic variables and healthy habits in women.

| Women | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | BMI | | BAI | | CUN BAE | | METS-VF | |
| | n | Mean (SD) | p-value | Mean (SD) | p-value | Mean (SD) | p-value | Mean (SD) | p-value |
| **20-29 years** | 29,978 | 23.8 (4.8) | <0.001 | 28.4 (4.7) | <0.001 | 31.3 (6.9) | <0.001 | 5.0 (0.7) | <0.001 |
| **30-39 years** | 51,392 | 24.6 (4.9) | | 28.9 (4.9) | | 33.8 (6.6) | | 5.3 (0.7) | |
| **40-49 years** | 45,296 | 25.7 (4.8) | | 30.1 (4.8) | | 36.7 (6.0) | | 5.6 (0.7) | |
| **50-59 years** | 23,516 | 26.8 (4.8) | | 31.5 (4.8) | | 39.3 (5.4) | | 5.9 (0.6) | |
| **60-69 years** | 3,928 | 27.5 (4.5) | | 32.7 (4.7) | | 41.2 (4.8) | | 6.1 (0.6) | |
| **Primary school** | 79,810 | 25.9 (5.1) | <0.001 | 30.7 (4.9) | <0.001 | 36.3 (7.0) | <0.001 | 5.6 (0.7) | <0.001 |
| **Secondary school** | 62,690 | 24.5 (4.6) | | 28.6 (4.7) | | 34.1 (6.5) | | 5.3 (0.8) | |
| **University** | 11,610 | 23.9 (4.4) | | 27.9 (4.6) | | 33.1 (6.3) | | 5.3 (0.7) | |
| **Social class I** | 10,744 | 23.8 (4.3) | <0.001 | 27.8 (4.6) | <0.001 | 33.1 (6.2) | <0.001 | 5.2 (0.7) | <0.001 |
| **Social class II** | 51,230 | 24.1 (4.4) | | 28.3 (4.6) | | 33.6 (6.3) | | 5.3 (0.7) | |
| **Social class III** | 92,136 | 25.9 (5.1) | | 30.6 (4.9) | | 36.3 (7.0) | | 5.6 (0.7) | |
| **Non physical activity** | 73,684 | 28.3 (5.1) | <0.001 | 31.7 (5.1) | <0.001 | 39.8 (6.3) | <0.001 | 5.9 (0.6) | <0.001 |
| **Yes physical activity** | 80,426 | 22.3 (2.3) | | 27.7 (3.9) | | 30.9 (4.2) | | 5.1 (0.6) | |
| **Non healthy food** | 74,828 | 28.0 (5.3) | <0.001 | 31.6 (5.2) | <0.001 | 39.4 (6.6) | <0.001 | 5.8 (0.7) | <0.001 |
| **Healthy food** | 79,282 | 22.4 (2.4) | | 27.8 (3.9) | | 31.2 (4.3) | | 5.1 (0.6) | |
| **Non smokers** | 103,300 | 25.5 (5.0) | <0.001 | 29.9 (5.0) | <0.001 | 35.7 (6.9) | <0.001 | 5.5 (0.7) | <0.001 |
| **Smokers** | 50,810 | 24.5 (4.8) | | 29.2 (4.7) | | 34.1 (6.8) | | 5.4 (0.8) | |

BMI Body mass index. BAI Body adiposity index. CUN BAE Clinica Universitaria de Navarra Body Adiposity Estimator. METS-VF Metabolic Score for Visceral Fat.

**Table IV:** Prevalence of high values of overweight-obesity scales according to sociodemographic variables and healthy habits in men.

| Men | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | BMI obesity | | BAI obesity | | CUN BAE obesity | | METS-VF high | |
| | n | % (CI 95%) | p-value | % (CI 95%) | p-value | % (CI 95%) | p-value | % (CI 95%) | p-value |
| **20-29 years** | 41,742 | 10,9 (10.7-11.1) | <0.001 | 38,5 (38.3-38.7) | <0.001 | 23,0 (22.8-23.2) | <0.001 | 0,7 (0.5-0.9) | <0.001 |
| **30-39 years** | 76,960 | 16,7 (16.6-16.8) | | 48,8 (48.7-48.9) | | 43,6 (43.5-43.7) | | 3,5 (3.4-3.6) | |
| **40-49 years** | 69,068 | 22,7 (22.6-22.8) | | 38,2 (38.1-38.3) | | 63,5 (63.4-63.6) | | 11,3 (11.2-11.4) | |
| **50-59 years** | 38,028 | 27,1 (26.8-27.3) | | 45,9 (45.7-46.2) | | 78,6 (78.3-78.9) | | 20,3 (20.0-20.5) | |
| **60-69 years** | 7,016 | 29,8 (28.9-30.7) | | 35,3 (34.4-36.2) | | 88,8 (87.9-89.7) | | 30,1 (29.2-31.0) | |
| **Primary school** | 142,494 | 20,3 (20.3-20.3) | <0.001 | 45,6 (45.6-45.6) | <0.001 | 52,8 (52.8-52.8) | <0.001 | 9,3 (9.3-9.3) | <0.001 |
| **Secondary school** | 79,226 | 18,6 (18.5-18.7) | | 39,1 (39.0-39.2) | | 53,1 (53.0-53.2) | | 8,3 (8.2-8.4) | |
| **University** | 11,094 | 16,4 (15.6-17.2) | | 35,6 (34.8-36.4) | | 52,1 (51.4-52.9) | | 6,9 (6.1-7.7) | |
| **Social class I** | 12,262 | 17,1 (16.3-17.9) | <0.001 | 35,2 (34.4-36.0) | <0.001 | 52,4 (51.6-53.2) | <0.001 | 7,2 (6.4-8.0) | <0.001 |
| **Social class II** | 40,650 | 17,6 (17.3-17.8) | | 37,3 (37.0-37.5) | | 51,7 (51.4-52.0) | | 7,9 (7.6-8.1) | |
| **Social class III** | 179,902 | 20,2 20.2-20.2) | | 44,7 (44.7-44.7) | | 53,2 (53.2-53.2) | | 9,2 (9.2-9.2) | |
| **Non physical activity** | 126,808 | 35,9 (35.9-35.9) | <0.001 | 56,5 (56.5-56.5) | <0.001 | 80,8 (80.8-80.8) | <0.001 | 16,2 (16.2-16.2) | <0.001 |
| **Yes physical activity** | 106,006 | 0,1 (0.1-0.1) | | 26,7 (26.7-26.7) | | 19,5 (19.5-19.5) | | 0,1 (0.1-0.1) | |
| **Non healthy food** | 137,464 | 33,1 (33.1-33.1) | <0.001 | 54,1 (54.1-54.1) | <0.001 | 76,2 (76.2-76.2) | <0.001 | 14,9 (14.9-14.9) | <0.001 |
| **Healthy food** | 95,350 | 0,1 (0.1-0.1) | | 26,8 (26.8-26.8) | | 19,2 (19.2-19.2) | | 0,1 (0.1-0.1) | |
| **Non smokers** | 146,480 | 21,2 (21.2-21.2) | <0.001 | 44,1 (44.1-44.1) | <0.001 | 56,8 (56.8-56.8) | <0.001 | 8,9 (8.9-8.9) | <0.001 |
| **Smokers** | 86,334 | 16,7 (16.6-16.8) | | 40,8 (40.7-40.9) | | 46,3 (46.2-46.4) | | 8,8 (8.7-8.9) | |

BMI Body mass index. BAI Body adiposity index. CUN BAE Clinica Universitaria de Navarra Body Adiposity Estimator. METS-VF Metabolic Score for Visceral Fat.

**Table V:** Prevalence of high values of overweight-obesity scales according to sociodemographic variables and healthy habits in women.

| | Women | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | BMI | | BAI | | CUN BAE | | METS-VF | |
| | n | % (CI 95%) | p-value | % (CI 95%) | p-value | % (CI 95%) | p-value | % (CI 95%) | p-value |
| **20-29 years** | 29,978 | 10,5 (10.1-10.9) | <0.001 | 2,3 (1.9-2.7) | <0.001 | 24,7 (24.3-25.1) | <0.001 | 0,03 (0.01-0.05) | <0.001 |
| **30-39 years** | 51,392 | 12,8 (12.6-13.0) | | 2,9 (2.7-3.1) | | 35,8 (35.6-36.0) | | 0,3 (0.1-0.5) | |
| **40-49 years** | 45,296 | 16,7 (16.5-16.9) | | 3,4 (3.2-3.6) | | 55,2 (55.0-55.4) | | 0,5 (0.3-0.7) | |
| **50-59 years** | 23,516 | 21,7 (21.3-22.1) | | 4,2 (3.8-4.6) | | 77,6 (77.2-78.0) | | 1,5 (1.1-1.9) | |
| **60-69 years** | 3,928 | 25,5 (24.4-26.6) | | 3,7 (2.6-4.8) | | 90,6 (89.5-91.7) | | 1,8 (0.7-2.9) | |
| **Primary school** | 79,810 | 19,0 (18.9-19.1) | <0.001 | 4,2 (4.1-4.3) | <0.001 | 55,3 (55.2-55.4) | <0.001 | 0,7 (0.6-0.8) | <0.001 |
| **Secondary school** | 62,690 | 11,4 (11.3-11.5) | | 2,1 (2.0-2.2) | | 39,4 (39.3-39.5) | | 0,3 (0.2-0.4) | |
| **University** | 11,610 | 9,1 (8.5-9.7) | | 1,7 (1.1-2.3) | | 33,1 (32.5-33.7) | | 0,3 (0.0-0.9) | |
| **Social class I** | 10,744 | 9,2 (8.6-9.8) | <0.001 | 1,6 (1.0-2.2) | <0.001 | 33,1 (32.5-33.7) | <0.001 | 0,1 (0.0-0.7) | <0.001 |
| **Social class II** | 51,230 | 9,8 (9.6-10.0) | | 1,7 (1.5-1.9) | | 36,0 (35.8-36.2) | | 0,3 (0.1-0.5) | |
| **Social class III** | 92,136 | 18,9 (18.8-19.0) | | 4,1 (4.0-4.2) | | 54,9 (54.8-55.0) | | 0,7 (0.6-0.8) | |
| **Non physical activity** | 73,684 | 31,7 (31.6-31.8) | <0.001 | 6,5 (6.4-6.6) | <0.001 | 78,8 (78.7-78.9) | <0.001 | 1,1 (1.0-1.2) | <0.001 |
| **Yes physical activity** | 80,426 | 0,05 (0.0-0.2) | | 0,2 (0.1-0.3) | | 18,2 (18.1-18.3) | | 0,02 (0.0-0.2) | |
| **Non healthy food** | 74,828 | 31,2 (31.1-31.3) | <0.001 | 6,4 (6.3-6.5) | <0.001 | 74,4 (74.3-74.5) | <0.001 | 1,0 (0.9-1.1) | <0.001 |
| **Healthy food** | 79,282 | 0,1 (0.0-0.2) | | 0,2 (0.1-0.3) | | 21,4 (21.3-21.5) | | 0,04 (0.0-0.1) | |
| **Non smokers** | 103,300 | 16,8 (16.8-16.8) | <0.001 | 3,5 (3.5-3.5) | <0.001 | 50,3 (50.3-50.3) | <0.001 | 0,5 (0.5-0.5) | <0.001 |
| **Smokers** | 50,810 | 12,0 (11.8-12.2) | | 2,5 (2.3-2.7) | | 40,7 (40.5-40.7) | | 0,4 (0.2-0.6) | |

BMI Body mass index. BAI Body adiposity index. CUN BAE Clinica Universitaria de Navarra Body Adiposity Estimator. METS-VF Metabolic Score for Visceral Fat

**Table VI:** Multinomoal logistic regression.

| | BMI obesity OR (95% CI) | BAI obesity OR (95% CI) | CUN BAE obesity OR (95% CI) | METS-VF high OR (95% CI) |
|---|---|---|---|---|
| **Female** | 1 | 1 | 1 | 1 |
| **Male** | 1.07 (1.05-1.09) | 25.01 (24.26-25.78) | 1.02 (1.00-1.04) | 18.28 (17.00-19.66) |
| **20-29 years** | 1 | 1 | 1 | 1 |
| **30-39 years** | ns | ns | 2.47 (2.30-2.65) | 1.72 (1.62-1.83) |
| **40-49 years** | ns | ns | 5.21 (4.86-5.59) | 3.12 (2.94-3.31) |
| **50-59 years** | ns | ns | 10.10 (9.42-10.83) | 8.39 (7.86-8.97) |
| **60-69 years** | 1.07 (1.02-1.12) | ns | 19.30 (17.96-20.73) | 28.95 (25.52-32.85) |
| **Social class I** | 1 | 1 | 1 | 1 |
| **Social class II** | 1.31 (1.25-1.37) | 1.24 (1.21-1.28) | 1.32 (1.27-1.37) | 1.11 (1.05-1.17) |
| **Social class III** | 1.34 (1.30-1.38) | 1.59 (1.53-1.65) | 1.51 (1.47-1.55) | 1.26 (1.17-1.36) |
| **Yes physical activity** | 1 | 1 | 1 | 1 |
| **Non physical activity** | 24.33 (18.32-32.32) | 3.39 (3.27-3.51) | 10.26 (9.97-10.56) | 41.84 (33.19-52.74) |
| **Yes healthy food** | 1 | 1 | 1 | 1 |
| **Non healthy food** | 14.80 (10.45-20.96) | 1.39 (1.34-1.44) | 1.62 (1.57-1.67) | 6.28 (5.02-7.86) |
| **Non smokers** | 1 | 1 | 1 | 1 |
| **Smokers** | 0.74 (0.72-0.75) | 0.82 (0.81-0.83) | 0.63 (0.62-0.64) | 1.19 (1.15-1.23) |

BMI Body mass index. BAI Body adiposity index. CUN BAE Clinica Universitaria de Navarra Body Adiposity Estimator. METS-VF Metabolic Score for Visceral Fat.

## Discussion

All the variables analyzed, sociodemographic and healthy habits, influence the mean values and the prevalence of high values of all the overweight and obesity scales.

In the multivariate analysis, the variables that most increase the risk of presenting obesity are physical exercise and Mediterranean diet. The only variable that shows no effect is educational level.

In our study, we found a higher prevalence of overweight-obesity with the four scales in men; these data contradict the majority of studies consulted where this prevalence is higher in women[32]. Some authors attribute this higher prevalence in women to gender inequalities, so that it is gender and not sex that is responsible[33-34].

In our study, as in practically all the other studies consulted, the prevalence of obesity increases with age[35]. Some authors have observed that excess weight and aging share a similar spectrum of phenotypes, such as compromised genome integrity, impaired mitochondrial function, accumulation of macromolecules within the cell, weakened immunity, altered tissue and body composition, and inflammatory processes[36].

The low socioeconomic level, represented by social class III, in our study is related to a higher prevalence of overweight-obesity. These data are similar to those found by different authors[37-40].

Various researchers have established nine potential

mechanisms to explain the existing disparities in obesity. These mechanisms can be grouped into three groups: health behaviors, biological factors and the socioeconomic environment[41].

A high level of physical activity is the most important protective factor against obesity, with the different scales studied in our study. This protective effect is also found in different studies.

A systematic review in 2020[42] that evaluated, among other things, the effect of physical exercise on obesity concluded that the prevalence of obesity was lower in non-sedentary persons and that physical exercise was fundamental in both preventive and intervention strategies for obesity. In the same sense, the authors of a 2021 study expressed the opinion that at least 150 minutes of moderate aerobic exercise or 75 minutes of vigorous aerobic exercise each week, and resistance and/or strengthening exercises of all muscle groups twice a week[43] are necessary to avoid obesity. Similar recommendations are stated in a systematic review[44] from 2021.

All organ systems of the body are influenced by regular physical activity and it has a number of overall health benefits. Physical activity alone does not work for weight loss; however, it is essential for maintaining weight loss. Exercise can help maintain a stable body weight, but it can also help better control appetite and food preference[45].

A 2023 review evaluating the role of exercise, either alone or combined with other treatments, in the prevention and management of obesity concludes that, although bariatric surgery and pharmacotherapy are the most effective therapies in severe obesity, physical exercise has an important role in facilitating and improving weight loss in combination with other methods[46].

Low adherence to the Mediterranean diet has been found in our study to be a predisposing factor for obesity. These data are similar to those found by other authors.

A review that evaluated four meta-analyses, which included 16 randomized controlled trials, found a greater decrease in BMI in persons with high adherence to the Mediterranean diet compared to other types of diet. In the same review, a meta-analysis of 7 prospective cohort studies found a lower risk of obesity in persons with greater adherence to the Mediterranean diet[47].

A study carried out in 268 obese persons, comparing the Mediterranean diet with the ketogenic diet, evaluated the time required to achieve a loss of 5% of initial body weight and the effect on body composition, observing that both were effective in reducing weight and fat mass, although the Mediterranean diet achieved a greater decrease in waist circumference and body fat and a greater increase in body water[48].

### Strengths and limitations

The strengths of the study include, on the one hand, the enormous size of the sample, which exceeds 386,000 workers, which gives great power to the results obtained, and on the other hand, the wide variety of obesity scales used.

The main limitation is that the study was carried out in the working population, which excludes people under 18 years of age and those over 69 years of age, a situation that may prevent extrapolation of the results to the general population.

## Conclusions

All the sociodemographic variables and healthy habits, especially physical activity and the Mediterranean diet, will influence the values of the overweight and obesity scales.

### Conflict of Interest

The authors declare that there is no conflict of interest.

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ORIGINAL

# Intervención en salud psicofísica y deterioro cognitivo en trabajadores. Repercusión del tipo de trabajo y la turnicidad

*Intervention in psychophysical health and cognitive impairment in workers. Impact of type of work and shift work*

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## Resumen

***Introducción:*** El envejecimiento de la población laboral plantea actuaciones preventivas desde los centros de trabajo para minimizar su repercusión en salud. Es objetivo de este estudio conocer el impacto de un programa de intervención en prevención del envejecimiento psicofísico y cognitivo de una población laboral y su relación con el tipo de trabajo y la turnicidad.
***Metodología:*** Estudio comparativo longitudinal y prospectivo en 273 trabajadores de la industria química de la Comunidad Autónoma de Murcia tras intervención mediante un programa de formación, información, control y seguimiento desde enero de 2019 hasta septiembre de 2021, valorando: prensión manual, circunferencia del gemelo, Fragilidad-Frail, depresión-Beck, Ansiedad-Estado-Rasgo, deterioro cognitivo-Pfeiffer y reserva cognitiva -Escala de Reserva Cognitiva y la relación de estas variables con el tipo de trabajo (manual y no manual) y la turnicidad. Se analizan los resultados con el programa SPSS 28.0 considerando significativo un valor $p < 0,05$.
***Resultados:*** Se observan mejores resultados en postintervención en depresión de Beck en trabajadores manuales y no manuales y en todos los turnos ($p<0,001$) y en fragilidad-Frail en trabajadores no manuales y en los que no trabajan a turnos ($p<0,001$). No se observan diferencias significativas con el resto de variables ni relación con el tipo de trabajo y turnicidad ($p>0,05$).
***Conclusiones:*** La intervención en prevención primaria mediante un programa de prevención en envejecimiento consigue mejorar los resultados, especialmente en fragilidad y en depresión. La intervención precoz puede ayudar a evitar la aparición del deterioro psicofísico o, si esto no es posible facilitar actuaciones tempranas que retarden su evolución.

*Palabras clave:* Fragilidad, depresión, deterioro cognitivo, turnicidad, tipo de trabajo, prevención del envejecimiento, salud laboral.

## *Abstract*

***Introduction:*** The aging of the workforce necessitates preventive measures within the workplace to minimize its impact on health. The objective of this study is to assess the impact of an intervention program aimed at preventing psychophysical and cognitive aging in a working population and its relationship with the type of work and shift work.
***Methodology:*** A longitudinal and prospective comparative study was conducted on 273 workers in the chemical industry of the Autonomous Community of Murcia. The intervention consisted of a training, information, control, and monitoring program conducted from January 2019 to September 2021. The following parameters were assessed: manual grip strength, calf circumference, Frailty-Frail assessment, Beck Depression Inventory, State-Trait Anxiety Inventory, Pfeiffer Cognitive Impairment Test, and Cognitive Reserve measured with the Cognitive Reserve Scale. The relationship of these variables with the type of work (manual and non-manual) and shift work was also examined. Data analysis was performed using SPSS 28.0, with significance set at $p < 0.05$.
***Results:*** Post-intervention, significant improvements were observed in Beck Depression Inventory scores among both manual and non-manual workers in all shifts ($p < 0.001$), as well as in Frailty-Frail scores among non-manual workers and those not working shifts ($p < 0.001$). No significant differences were observed in the remaining variables, and there was no significant relationship with type of work or shift work ($p > 0.05$).
***Conclusions:*** Primary prevention intervention through an aging prevention program leads to improved outcomes, especially in the case of frailty and depression. Early intervention may help prevent the onset of psychophysical deterioration or, if not possible, facilitate early interventions that delay its progression.

*Key words:* Frailty, depression, cognitive impairment, shift work, type of work, aging prevention, occupational health.

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## Introducción

El envejecimiento de la población general y laboral en el mundo industrializado plantea nuevos objetivos para las organizaciones sobre la protección y cuidado de la salud de los trabajadores[1], con el fin de conseguir un enlentecimiento del proceso de deterioro físico y cognitivo[2]. Se trata de reducir el riesgo de fragilidad, entendida como *un síndrome biológico en el que se produce una disminución de la reserva y resistencia a factores estresantes, resultantes de una acumulación de disminución de múltiples sistemas fisiológicos aumentando la vulnerabilidad a resultados adversos*[3] y de mantener en buen estado las aptitudes psicofísicas de los trabajadores que prolongan su vida laboral.

En la actualidad, ya es un hecho que la introducción en los centros de trabajo de planes de salud específicos y dirigidos por equipos multidisciplinares tiene un impacto positivo en la salud de las personas que trabajan, a la vez que se consiguen mejores resultados desde otras perspectivas como: mayor satisfacción laboral, mejora del rendimiento, reducción del absentismo y/o aumento de la productividad[4].

Para obtener resultados exitosos es necesario diseñar programas individualizados según las características específicas de cada población, buscando un equilibrio entre las áreas física[5], emocional y cognitiva[6], de forma que se consiga un abordaje integral de la salud del trabajador.

Para la implementación de estos programas se hace imprescindible valorar las condiciones de trabajo y de los riesgos a las que están expuestos los trabajadores y que pueden suponer un daño para su salud psicofísica y cognitiva[7], esto ocurre de forma especial en trabajos que conllevan turnicidad[8] o que suponen esfuerzos con carga física[9,10]. Los programas de intervención, su seguimiento prospectivo y la evaluación al final de los resultados permitirá conocer la eficacia de la implantación de estas actividades en los centros de trabajo[11] y poder extrapolarlo a otras organizaciones a través de los Servicios de Prevención de Riesgos Laborales, contribuyendo de esta manera a la introducción del concepto de entornos laborales saludables que recomienda la Organización Mundial de la Salud[12].

Es objetivo de este estudio conocer el impacto de un programa de intervención en prevención del envejecimiento psicofísico y cognitivo de una población laboral considerando el tipo de trabajo desempeñado y la turnicidad. Se valora la fragilidad física, el estado ansioso-depresivo y reserva y deterioro cognitivos.

## Metodología

Estudio comparativo longitudinal y prospectivo en una población laboral española del sector de la industria química de la Comunidad Autónoma de la Región de Murcia, con muestra representativa de 273 trabajadores (231 hombres y 42 mujeres) de edades comprendidas entre los 18 y 65 años. Los datos se recogieron durante los exámenes de salud realizados en la empresa desde enero de 2019 hasta septiembre de 2021, con participación voluntaria y consentimiento informado para el uso epidemiológico de los resultados, como especifica la legislación española[13,14]. Son criterios de inclusión no estar en incapacidad temporal en el momento del examen de salud y completar los datos de todas las variables incluidas en el estudio. Son criterios de exclusión el abandono del programa y no completar con los datos requeridos.

Las mediciones se realizaron en dos momentos temporales: en la primera visita y previo a la puesta en marcha del programa de salud específico en prevención del envejecimiento en la empresa y, la segunda visita durante el control evolutivo, tras su inclusión en el programa.

El estudio fue aprobado por el Comité Ético de Investigación Clínica del Área de Salud de Baleares (IB 4383/20).

***Variables incluidas en el estudio:***

Edad estratificada en rangos: 18-30 años, 31-45 años, 46-60 años, > 60 años; Sexo: hombre o mujer; Estado civil: casado, separado o soltero; Tipo de convivencia: familiar o en solitario; Clase social y tipo de trabajo: a partir de la Clasificación Nacional de Ocupaciones del año 2011[15], tomando como referencia la propuesta del grupo de determinantes sociales de la Sociedad Española de Epidemiología[16]. Esta clasificación incluye seis grupos reducidos a tres para este trabajo: Clase I. Directores/gerentes, profesionales universitarios, deportistas y artistas; Clase II. Ocupaciones intermedias y trabajadores por cuenta propia sin asalariados; y Clase III. Trabajadores no cualificados. La CNO permite también dividir a los trabajadores en manuales (blue collar) y no manuales (white collar); Turno de trabajo: trabajo nocturno/rotativo o trabajo en turno fijo y sin nocturnidad.

Las variables recogidas como hábitos de vida en el estudio han sido antes de la intervención (cuestionarios de situación basal) y al finalizar el programa (cuestionarios post-intervención):

Para la valoración de hábitos de vida en alimentación se utilizó la encuesta validada PREDIMED, de adherencia a la dieta mediterránea y se consideró buena adherencia (alimentación saludable) a partir de 9 puntos[17].

Para la valoración de hábitos de vida saludable en actividad física se utilizó la encuesta validada IPAQ-reducida. Clasifica en 3 categorías: Baja. No registran actividad física o la registra, pero no alcanza las categorías media y alta; Media. Considera los siguientes criterios: 3 o más días de actividad física vigorosa por

lo menos 20 min por día, 5 o más días de actividad física de intensidad moderada o caminar por lo menos 30 min, 5 o más días de cualquier combinación de actividad física leve, moderada o vigorosa que alcancen un registro de 600 METs-min/semana; Alta. Es una categoría que cumple los siguientes requerimientos: 3 o más días de actividad física vigorosa o que acumulen 1.500 METs-min-semana, 7 o más días de cualquier combinación de actividad física leve, moderada o vigorosa que alcance un registro de 3.000 METs-min/semana[18]. Para este estudio se ha considerado no realizar actividad física a la categoría baja y sí realizarla en las personas incluidas en las categorías media y alta.

Tabaquismo: fumador actual y no fumador (incluye nunca fumadores y exfumadores de más de un año).

El contenido del programa de intervención preventiva implantado en la empresa se muestra en la **tabla I**.

***Variables laborales:***
El comparativo de envejecimiento psicofísico y deterioro cognitivo se valoró, teniendo en cuenta el tipo de trabajo (manual/no manual)

Se consideró la turnicidad (no turnicidad/si turnicidad o nocturnidad)

Ambas en dos momentos temporales (antes y después de la implantación del programa de salud)

***Análisis estadístico:***
Para analizar los datos cuantitativos se utilizó la prueba t de Student, que determinó las medias y desviaciones típicas. El análisis estadístico se llevó a cabo con el programa informático SPSS 28.0. El nivel de significación estadística aceptado fue p<0,05.

## Resultados

Las características de la población estudiada se muestran en la **tabla II**, edad media algo superior en los hombres que en las mujeres (47/43 años). En las variables sociodemográficas y laborales se observan

**Tabla I:** Programa de Intervención Preventiva.

| Componentes | Actividades incluidas | Responsable de la actividad-colaboradores | Medidas y Cuestionarios utilizados |
|---|---|---|---|
| Hábitos de vida: Nutrición saludable basada en dieta mediterránea | Comunicaciones orales online de alimentación equilibrada, soporte digital de hábitos alimentarios y calorías, consulta presencial mensual control de peso | Médico/Enfermero del trabajo y dietista/ nutricionista | - Cuestionario Predimed[17]<br>Puntuación:<br>• ≤9 No saludable<br>• >9 Saludable |
| Hábitos de vida: Actividad física | Soporte digital de videos sobre planes de ejercicio físico centrados en trabajo de fuerza y resistencia. | Médico/Enfermero del trabajo y preparador físico especialista en salud y prevención de lesiones | - Cuestionario IPAC-reducido[6]<br>Puntuación:<br>• No actividad física = Categoría baja<br>• Sí actividad física = Categorías media y alta |
| Estado físico | Clases semanales online de activación muscular en el puesto de trabajo y consulta presencial mensual de recuperación de lesiones en trabajadores con patología | Médico/Enfermero del trabajo y preparador físico especialista en salud y prevención de lesiones | - Prensión manual brazo dominante[27,28,29]<br>Puntuación:<br>• Hombre <30 baja<br>• Mujer <20 baja<br>- Circunferencia gemelo[30,31]<br>Puntuación:<br>• Hombre <34 bajo<br>• Mujer <33 bajo<br>- Cuestionario de Frail[32]<br>Puntuación:<br>• ≥1 prefrágil<br>• ≥2 frágil |
| Bienestar emocional | Sesiones semanales online de técnicas de relajación, mindfulness y ejercicios de estiramientos | Médico/Enfermero del trabajo, psicólogo y especialista en mindfullnes | - Cuestionario Depresión (Beck)[33]<br>Puntuación:<br>• ≥17 depresión clínica<br>- Cuestionario Ansiedad (E-R)[34]<br>Puntuación:<br>• Ansiedad baja< 30<br>• Ansiedad media 30-44 Ansiedad alta>44 |
| Deterioro cognitivo | Sesiones mensuales online de motivación, ansiedad, estrés, resiliencia, empatía, sueño y descanso | Médico/Enfermero del trabajo, psicólogo especialista en mindfullnes | - Cuestionario de Pfeiffer[35]<br>Puntuación:<br>• Deterioro leve 3-4<br>• Deterioro moderado 5-7<br>• Deterioro grave 8-10<br>- Cuestionario Escala de Reserva Cognitiva (ERC)[36]<br>Puntuación: 0-96 puntos: a >puntuación, >reserva |

diferencias significativas entre ambos sexos para: estado civil, en ambos sexos mayoritariamente casados; nivel de estudios, secundarios y tipo de alimentación, saludable, más en las mujeres (p<0,05). Las diferencias no son significativas para el resto de variables: en ambos casos conviven con otras personas, pertenecen mayoritariamente a clase II y con trabajo manual y turnicidad, realizan actividad física y no son fumadores (p>0,05). En las variables asociadas a envejecimiento se observan diferencias significativas (p<0,05) en prensión manual de brazo dominante y circunferencia de gemelo, en ambos casos mayor en los hombres.

Los resultados del comparativo pre y post intervención muestran en todos los casos valores de normalidad, con pequeñas variaciones tras la intervención.

El comparativo en función del tipo de trabajo muestra diferencias significativas (p<0,001) en los resultados del cuestionario de depresión de Beck y en ambos tipos de trabajo manual (pre 4,68/post 3,66) y no manual (pre 4,48/post 3,32), con valores más favorables post-intervención. En los resultados del cuestionario de fragilidad-Frail solo se observan resultados con significación estadística (p<0,001) en los trabajadores no manuales comparando la pre y post intervención (pre 0,16/post 0,07), en todos los casos con valores dentro de la normalidad (**Tabla III**) (**Figuras 1** y **2**).

El comparativo en función del trabajo a turnos/nocturno muestra diferencias significativas (p<0,001) en los resultados del cuestionario de depresión de Beck y en ambos turnos de trabajo sin turnicidad/nocturnidad (pre 4,68/post 3,66) y con turnicidad/nocturnidad (pre 4,59/ post 3,50), con valores más favorables post-intervención.

En fragilidad valorada con el cuestionario Frail se observan diferencias significativas (p<0,001) solo en trabajadores que no realizan turnos, con ligeras mejoras post intervención (pre 0,15/post 0,10), si bien dentro de parámetros de normalidad en todos los casos (**Tabla IV**) (**Figuras 3** y **4**).

**Tabla II:** Características de la muestra poblacional.

| **Variables sociodemográficas y laborales** | | **Hombres n=231 n (%)** | **Mujeres n=42 n (%)** | **p** |
|---|---|---|---|---|
| **Edad (años)** | 18-30<br>31-45<br>46-60<br>>61 | 1 (0,43%)<br>73 (31,60%)<br>150 (64,93%)<br>7 (3,03%) | 0 (0%)<br>22 (52,38%)<br>20 (47,61%)<br>0(0%) | >0,05 |
| **Estado Civil** | Casado<br>Separado<br>Soltero | 192 (83,11%)<br>15 (11,36%)<br>24 (10,38%) | 28 (66,66%)<br>5 (11,90%)<br>9 (21,42%) | <0,05 |
| **Convivencia** | No<br>Si | 20 (8,65%)<br>211 (91,34%) | 3 (7,14%)<br>39 (92,85%) | >0,05 |
| **Clase social** | I<br>II<br>III | 35 (15,15%)<br>24 (10,38%)<br>172 (74,45%) | 10 (23,80%)<br>6 (14,28%)<br>26 (61,90%) | >0,05 |
| **Tipo de Trabajo** | Trabajo manual<br>Trabajo no manual | 172 (74,45%)<br>59 (25,54%) | 26 (61,90%)<br>16 (38,09%) | >0,05 |
| **Nivel de estudios** | Primarios<br>Secundarios<br>Universitarios | 5 (2,16%)<br>168 (72,72%)<br>58 (25,10%) | 0(0%)<br>24 (57,14%)<br>18 (42,85%) | <0,05 |
| **Trabajo a turnos** | No<br>Si | 90 (38,96%)<br>141 (61,03%) | 19 (45,23%)<br>23 (54,76%) | >0,05 |
| **Variables hábitos de vida** | | **Hombres n= n (%)** | **Mujeres n= n (%)** | **p** |
| **Alimentación saludable** | No<br>Si | 75 (32,46%)<br>156 (67,53%) | 6 (14,28%)<br>36 (85,71%) | <0,05 |
| **Actividad física** | No<br>Si | 73(31,60%)<br>158 (68,39%) | 19 (45,23%)<br>23 (54,76%) | >0,05 |
| **Consumo de tabaco** | No<br>Si | 197 (85,28%)<br>34 (14,71%) | 36 (85,71%)<br>6 (14,28%) | >0,05 |
| **Variables asociadas a envejecimiento** | | **Hombres n= Media (dt)** | **Mujeres n= Media (dt)** | **p** |
| **Edad** | | 47,41 (6,7) | 43,04 (6,44) | >0,05 |
| **Fragilidad física** | Prensión manual<br>Circunferencia de gemelo<br>Cuestionario Frail | 49,89 (8,01)<br>38,62 (3,34)<br>0,104 (0,32) | 31,42 (9,19)<br>36,9 (3,17)<br>0,21 (0,41) | <0,05<br><0,05<br>>0,05 |
| **Situación cognitivo-emocional** | Cuestionario depresión (Beck)<br>Cuestionario Ansiedad E-R<br>Cuestionario Pfeiffer<br>ERC18-35<br>ERC36-64 | 4,61 (4,4)<br>47,88 (6.67)<br>1,7 (1,02)<br>52,73 (11,62)<br>54,01 (10,07) | 4,95 (5,77)<br>49,5 (6,1)<br>1,28 (0,94)<br>58,02 (9,6)<br>56,97 (11,06) | >0,05<br>>0,05<br>>0,05<br>>0,05<br>>0,05 |

**Tabla III:** Comparativo pre-intervención y post-intervención en salud psicofísica y cognitiva y su relación con el tipo de trabajo desarrollado.

| | | Manual n= 198 media (dt) | p | No manual n=75 media (dt) | p |
|---|---|---|---|---|---|
| **Prensión manual dominante** | pre-intervención<br>post-intervención | 48,57 (10,58)<br>46,71 (9,59) | <0.001 | 43,04 (9,48)<br>42,16 (9,56) | >0.05 |
| **Circunferencia gemelo** | pre-intervención<br>post-intervención | 38,58 (3,55)<br>38,86 (3,14) | >0.05 | 37,77 (2,78)<br>38,06 (2,98) | >0.05 |
| **Depresión Beck** | pre-intervención<br>post-intervención | 4,68 (4,75)<br>3,66 (4,24) | <0.001 | 4,48 (4,15)<br>3,32 (3,01) | <0.001 |
| **Ansiedad Estado-Rasgo** | pre-intervención<br>post-intervención | 48,09 (6,13)<br>48,26 (6,10) | >0.05 | 48,62 (5,64)<br>48,77 (5,98) | >0.05 |
| **Deterioro cognitivo-Pfeiffer** | pre-intervención<br>post-intervención | 1,63 (1,04)<br>1,65 (1,03) | >0.05 | 1,65 (0,97)<br>1,64 (0,98) | >0.05 |
| **Fragilidad-Frail** | pre-intervención<br>post-intervención | 0,11 (0,33)<br>0,13 (0,42) | >0.05 | 0,16 (0,37)<br>0,07 (0,30) | <0.001 |
| **Reserva cognitiva-ERC-18-35** | pre-intervención<br>post-intervención | 53,52 (11,79)<br>54,82 (11,34) | >0.05 | 54,44 (10,42)<br>55,16 (11,30) | >0.05 |
| **Reserva cognitiva-ERC-36-64** | pre-intervención<br>post-intervención | 53,95 (10,67)<br>55,74 (10,56) | >0.05 | 56,20 (9,25)<br>56,88 (7,58) | >0.05 |

Se considera: prensión manual baja hombres <30 y mujeres <20; contorno de gemelo bajo hombres <34 mujeres <33; fragilidad-Frail-No frágil 0/Prefrágil 1/Frágil 2-5; depresión-Beck: -normal 0-10/ligero trastorno emocional 11-16/depresión clínica borderline 17-20/depresión moderada 21-30/severa 31-40; ansiedad-cuestionario estado-rasgo (E-R)-bajo<30/medio 30-44/alto>44; deterioro cognitivo-Pfeiffer: -normal 0-2/deterioro leve 3-4/deterioro moderado 5-7/ deterioro grave 8-10; reserva cognitiva-escala de Reserva Cognitiva (ERC) puntuación 0-96, >puntuación >reserva cognitiva, se considera significativo un valor de p<0,05.

**Figura 1:** Comparación depresión de Beck pre y post intervención según el tipo de trabajo.

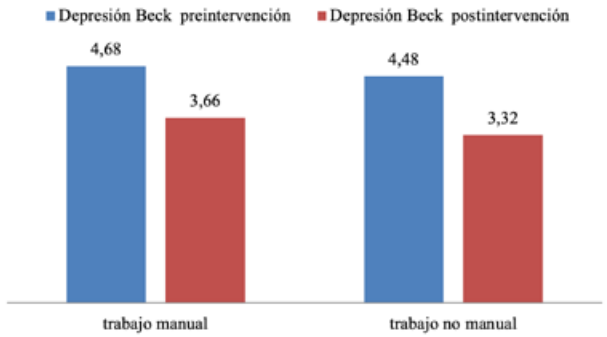
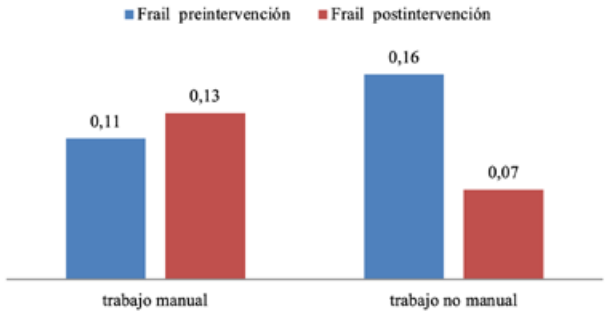



**Figura 2:** Comparación cuestionario de Frail pre y post intervención según el tipo de trabajo.




## Discusión

En este artículo se analiza el efecto de la implantación de un programa de salud desde los servicios de prevención de las empresas dirigido a la prevención del envejecimiento psicofísico de los trabajadores. El objetivo es actuar en el primer nivel, prevención primaria y en promoción de la salud. En nuestro trabajo, se trata de un colectivo de trabajadores jóvenes, con predominancia de hombres, estilo de vida saludable en alimentación, práctica de actividad física regular y bajo consumo de tabaco. Se valora el impacto del programa de prevención del envejecimiento en relación al tipo de trabajo y a la turnicidad/nocturnidad.

Los resultados de nuestro estudio presentan resultados de normalidad al tratarse de una población joven, sin embargo, se observa una mejor respuesta y con significación estadística en el cuestionario de depresión-Beck tras la intervención, tanto en trabajos manuales, como no manuales. No encontramos en la bibliografía comparativa con intervenciones similares a la nuestra y en actuaciones tan tempranas. Los estudios previos realizados sobre depresión en población laboral demuestran que la combinación de la intervención en el trabajo mediante la adaptación de puestos y horarios en personas depresivas, la intervención clínica, el ejercicio físico y la dieta puede disminuir los síntomas depresivos y reducir ligeramente el absentismo aunque no aumente al final del año el número de personas activas laboralmente[19]. A diferencia con nuestro trabajo estos estudios no contemplan la relación entre estado depresivo con el tipo de trabajo desempeñado.

Según algunos autores las condiciones de trabajo como son las exigentes demandas físicas y/o psicológicas, la jornada laboral, el horario de trabajo, la precariedad laboral, el reconocimiento o la promoción laboral pueden empeorar el estado depresivo del trabajador, recomendando actuaciones preventivas en los centros de trabajo para disminuir esta prevalencia[20].

**Tabla IV:** Comparativo pre-intervención y post-intervención en salud psicofísica y cognitiva y su relación con el trabajo a tunos y nocturno.

| | | No turnos n=109 media (dt) | p | Si turnos n=164 media (dt) | p |
|---|---|---|---|---|---|
| **Prensión manual dominante** | pre-intervención<br>post-intervención | 45,47 (10,31)<br>44,19 (9,71) | >0.05 | 48,11 (10,63)<br>46,31 (9,75) | >0.05 |
| **Circunferencia gemelo** | pre-intervención<br>post-intervención | 37,98 (2,78)<br>38,35 (2,96) | >0.05 | 38,60 (3,70)<br>38,83 (3,20) | >0.05 |
| **Depresión Beck** | pre-intervención<br>post-intervención | 4,68 (4,61)<br>3,66 (3,49) | <0.001 | 4,59 (4,58)<br>3,50 (4,22) | <0.001 |
| **Ansiedad Estado-Rasgo** | pre-intervención<br>post-intervención | 48,42 (5,77)<br>48,33 (5,78) | >0.05 | 48,12 (6,14)<br>48,44 (6,26) | >0.05 |
| **Deterioro cognitivo-Pfeiffer** | pre-intervención<br>post-intervención | 1,69 (1,02)<br>1,70 (1,01) | >0.05 | 1,60 (1,02)<br>1,61 (1,02) | >0.05 |
| **Fragilidad-Frail** | pre-intervención<br>post-intervención | 0,15 (0,36)<br>0,10 (0,36) | <0.001 | 0,10 (0,33)<br>0,12 (0,41) | >0.05 |
| **Reserva cognitiva-ERC-18-35** | pre-intervención<br>post-intervención | 52,88 (11,31)<br>54,23 (11,08) | >0.05 | 54,40 (11,48)<br>55,40 (11,47) | >0.05 |
| **Reserva cognitiva-ERC-36-64** | pre-intervención<br>post-intervención | 55,14 (9,72)<br>56,54 (7,91) | >0.05 | 54,14 (10,76)<br>55,70 (11,00) | >0.05 |

Se considera: prensión manual baja hombres <30 y mujeres <20; contorno de gemelo bajo hombres <34 mujeres <33; fragilidad-Frail-No frágil 0/Prefrágil 1/Frágil 2-5; depresión-Beck: -normal 0-10/ligero trastorno emocional 11-16/depresión clínica borderline 17-20/depresión moderada 21-30/severa 31-40; ansiedad-cuestionario estado-rasgo (E-R)-bajo<30/medio 30-44/alto>44; deterioro cognitivo-Pfeiffer: -normal 0-2/deterioro leve 3-4/deterioro moderado 5-7/ deterioro grave 8-10; reserva cognitiva-escala de Reserva Cognitiva (ERC) puntuación 0-96, >puntuación >reserva cognitiva, se considera significativo un valor de p<0,05.

**Figura 3:** Comparación depresión de Beck pre y post intervención según turnicidad.

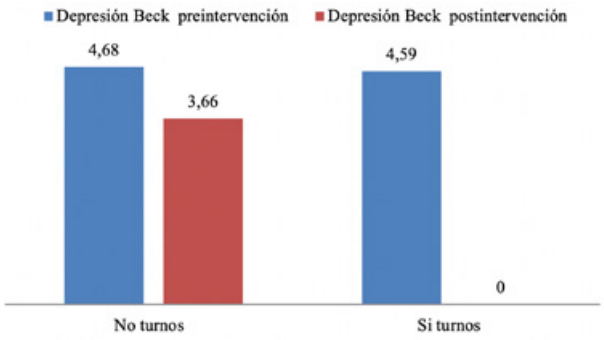
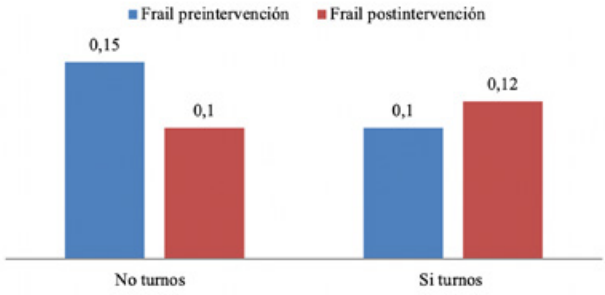



**Figura 4:** Comparación cuestionario de Frail pre y post intervención según turnicidad.




Los resultados de nuestro trabajo en el cuestionario de depresión de Beck, comparando pre y postintervención en relación con el trabajo a turnos y nocturno muestran, dentro de los valores de normalidad, unos mejores resultados en la postintervención y con significación estadística. Los estudios realizados en países como Estados Unidos en envejecimiento saludable y su relación con el trabajo nocturno o a turnos rotativos establecen una relación con una menor probabilidad de envejecimiento saludable en colectivos sanitarios como las enfermeras y respaldan la idea de que el exceso de trabajo en turnos nocturnos es un problema de salud importante que también puede conducir a un deterioro de la salud general entre las personas mayores, considerando como tales a los mayores de 70 años[21]. En nuestro trabajo la edad de la población participante en el estudio es claramente menor, no superando de media los 50 años y, por ello los resultados son de normalidad, sin embargo, permiten intuir que la actuación temprana en intervención preventiva puede retrasar el deterioro cognitivo y muestra clara mejoría en aspectos como los procesos psicoafectivos como los depresivos.

Nuestros resultados en fragilidad cuantificada con el cuestionario de Frail muestran en todos los casos valores normales, pero con mejoría postintervención en trabajadores no manuales y que no realizan turnos rotativos nocturnos. En este tema, la bibliografía científica evidencia que la fragilidad asociada al envejecimiento alcanza a la población laboral actual más envejecida y esto supone alteraciones de las capacidades laborales como bajo rendimiento, menor productividad y mayores ausencias en el trabajo, surge la necesidad imperiosa por revertir este problema que cada vez afecta a mayor número de trabajadores en todo el mundo[22]. Actualmente no existe un consenso científico unificado para medir fragilidad, pero en la bibliografía revisada encontramos varias herramientas entre ellas el cuestionario de Frail que es el utilizado en nuestro trabajo y que aporta la suficiente información

para la realización de un diagnóstico respecto a este estado tan complejo[23].

Respecto al abordaje en prevención de fragilidad existen ya programas específicos dentro de las guías de la Organización Mundial de la salud que promueven actividades multicomponente individualizadas dirigidos a adultos mayores con resultados positivos tanto a nivel funcional como cognitivo[24]. En estudios realizados en personas mayores que presentaban deterioro cognitivo y demencia, la implementación de programas multicomponente con valoraciones prospectiva muestran mejoría en la capacidad funcional, cognición y estado de ánimo[25] e incluso en algunos casos se ha logrado revertir la fragilidad hasta en un 36% de las personas[26]. En todos los casos estos programas se han realizado en población de mayor edad que la de nuestro estudio e institucionalizada, por lo que no es posible hacer una comparativa con nuestros resultados.

En consecuencia, al incremento del envejecimiento de la población laboral y teniendo en cuenta que, las empresas contarán en unos años con mayor número de trabajadores de edad más avanzada es necesario extrapolar este tipo de programas de prevención del envejecimiento a población laboral joven desde los servicios de prevención y estudiar su impacto mediante la implantación, seguimiento y evaluación con la finalidad de establecer protocolos de salud que logren mejorar la calidad de vida de la población laboral al llegar a edades avanzadas, si es posible anticipándose a la aparición de patologías o deterioro psico-físico, o si esto no es posible enlentecer su progresión en el tiempo.

Son fortalezas de este trabajo la implantación desde un servicio de prevención de un programa de prevención del envejecimiento en población laboral y la medición de variables concretas para cuantificar el estado físico, emocional y cognitivo antes y después de la puesta en marcha del programa valorando así su impacto en la salud de la población del estudio. Además, la validez, el bajo coste económico y el fácil manejo de cuestionarios y herramientas validadas hace que sean una buena elección para la práctica profesional de la medicina y la enfermería del trabajo.

Son debilidades del estudio el tamaño muestral, su desigualdad por sexos, la edad joven de la población estudiada y el no realizar un acompañamiento por parte del profesional en la realización de las actividades que puedan certificar el cumplimiento de éstas por parte de los participantes. Por todo ello no es posible extrapolar estos resultados a otras poblaciones laborales y se necesitan estudios posteriores que soslayen estos sesgos y permitan valorar de forma precisa su utilidad preventiva.

## Conclusiones

1. El programa preventivo en envejecimiento saludable implantado muestra mejoría significativa en fragilidad-cuestionario Frail en trabajadores no manuales y en trabajadores sin turnicidad rotativa.
2. El programa preventivo en envejecimiento saludable implantado muestra mejoría significativa en los resultados del cuestionario de depresión de Beck en trabajadores tanto manuales como no manuales y en trabajadores con y sin turnicidad.
3. La prensión manual, la circunferencia del gemelo, la estimación de ansiedad y deterioro cognitivo con los cuestionarios de Ansiedad E-R, de Pfeiffer y de ERC no muestran mejoría significativa en la población laboral estudiada relacionándolos con el tipo de trabajo ni con la turnicidad rotativa tras la implantación del programa de prevención del envejecimiento saludable.

### Conflicto de intereses

Los autores declaran no tener ningún conflicto de intereses.

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ORIGINAL

# The Impact of Fast Food Consumption on the Development of General and Central Obesity

*El impacto del consumo de comida rápida en el desarrollo de la obesidad general y central*

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## Abstract

***Background and objectives:*** Fast food consumption among adolescents and young people is increasing. Consumption of these foods is associated with a high intake of energy and fat resulting in overweight and obesity. This study aimed to investigate the relationship between fast food consumption and general and central obesity among Zahedan University of Medical Sciences students.
***Materials and methods:*** A cross-sectional study was carried out on a simple random sampling method on 351 students of Zahedan University of Medical Sciences (151 boys and 200 girls). Demographic data and fast food consumption were completed through interviews with students, and Body mass index and waist circumference were used as indicators of general and central obesity in students, respectively.
***Results:*** The prevalence of general and central obesity among students was 18.5% (28.5% boys and 11% girls) and 7.7% (8.6% boys and 7% girls), 47.6% (51.7% boys and 44.5% girls) more than 2 times a week and 48.1% occasionally (45% boys and 50.5% girls) consumed at least one type of fast food. There was a significant relationship between fast food consumption with both general types of obesity (p = 0.028) and central (P = 0.014).
***Conclusions:*** Findings of the study indicated that fast food consumption and consequently general and central obesity were high. Therefore, the necessity of interventions such as continuous nutrition education programs to improve the nutritional literacy of young people and students is required.

*Key words:* Fast food, students, general obesity, central obesity, nutrition .

## *Resumen*

***Antecedentes y objetivos:*** El consumo de comida rápida entre adolescentes y jóvenes está aumentando. El consumo de estos alimentos se asocia a una ingesta elevada de energía y grasas que provoca sobrepeso y obesidad. Este estudio tenía como objetivo investigar la relación entre el consumo de comida rápida y la obesidad general y central entre los estudiantes de la Universidad de Ciencias Médicas de Zahedan.
***Materiales y métodos:*** Se realizó un estudio transversal con un método de muestreo aleatorio simple sobre 351 estudiantes de la Universidad de Ciencias Médicas de Zahedan (151 chicos y 200 chicas). Los datos demográficos y el consumo de comida rápida se completaron mediante entrevistas con los estudiantes, y se utilizaron el índice de masa corporal y el perímetro de cintura como indicadores de obesidad general y central en los estudiantes, respectivamente.
***Resultados:*** La prevalencia de obesidad general y central entre los estudiantes fue del 18,5% (28,5% chicos y 11% chicas) y del 7,7% (8,6% chicos y 7% chicas), el 47,6% (51,7% chicos y 44,5% chicas) más de 2 veces por semana y el 48,1% ocasionalmente (45% chicos y 50,5% chicas) consumían al menos un tipo de comida rápida. Se observó una relación significativa entre el consumo de comida rápida y los tipos generales de obesidad (p = 0,028) y central (p = 0,014).
***Conclusiones:*** Los resultados del estudio indicaron que el consumo de comida rápida y, en consecuencia, la obesidad general y central eran elevados. Por lo tanto, se requiere la necesidad de intervenciones tales como programas continuos de educación nutricional para mejorar los conocimientos nutricionales de jóvenes y estudiantes.

*Palabras clave:* Comida rápida, estudiantes, obesidad general, obesidad central, nutrición.

**Cite as:** M

## Introduction

Convenience food can be defined as food that is prepared quickly and is usually consumed outside the home[1], which includes different kinds of sandwiches: hamburgers, cheeseburgers, fried shrimp, hot dogs, chicken nuggets, French fries, pizzas, sausages and hot dogs[2]. Reasons for eating convenience food include easy and fast access, low cost, good taste, and dietary diversity[3]. Consumption of convenience foods has increased worldwide over the past decades. In Iran, 2% of household income is spent on convenience foods[4].

Studies have shown that most teenagers and youth have improper nutritional patterns and consumption of high-fat, high-salt, sweet and fried foods have increased among them. Increasing consumption of these foods is associated with receiving high energy and fat which leads to increased body fat percentage, overweight, and obesity[5,6].

The prevalence of obesity in the world is increasing rapidly so it has become a serious epidemic disease and it is estimated to be the fifth leading cause of death in the world[7]. Based on the report of WHO in 2016, 15% of people over the age of 18 are overweight (39% women and 40% men) and 13% suffer from obesity (15% women and 11% men). In general, the global prevalence of obesity has almost tripled between 1976 and 2016. The main cause of overweight and obesity is an energy imbalance between calories received and calories consumed; this imbalance is due to increasing consumption of high-energy and high-fat foods, increasing sedentary lifestyle, and urbanization[8]. Obesity is a risk factor for diseases such as specific cancers, high blood pressure, type 2 diabetes, changes in blood lipid levels, metabolic syndrome, cardiovascular disease, respiratory problems, and stroke[7]. One of the main causes of obesity can be a change in the diet, one of which is an increase in the use of convenience foods[7].

Evidence shows that students are more prone to unhealthy dietary habits due to replacing fruits and vegetables with convenience food and non-alcoholic beverages(9), especially medical students consume more convenience foods due to higher educational occupations and as a result, they are prone to overweight and obesity[10]. In studies conducted in Iran; 52.6% of medical students of Shahid Beheshti University ate 1-2 times a week and 72.4% of Qom students ate at least one type of convenience food per week or month [18]. Among medical students in India, more than 90% of students ate convenience foods, and among them, 34.05% suffered from overweight and obesity[11]. In the Michigan-US study on adults over 18 years of age; the risk of obesity was 60% among those who ate convenience foods 2 to 3 times a week and 81% among those who ate 3 or more meals[12].

Due to the increasing tendency of teenagers and youth, especially students, to eat convenience food and its relationship with overweight, obesity, and subsequent diseases, efforts for identifying nutritional behaviors associated with overweight and obesity, including the frequency of consumption of convenience foods in this stratum of society can help control and prevent general and central obesity, and other related diseases caused by their consumption[9,13]. Therefore, in the current study, the relationship between convenience food consumption and general and central obesity in students of Zahedan University of Medical Sciences was investigated and solutions were provided to improve the diet of students.

## Materials and methods

The current study is a cross-sectional (descriptive-analytical) study that was conducted on 351 students of different faculties of Zahedan University of Medical Sciences (200 girls and 151 boys) by a simple random sampling method. In this way that 111 students from the medical faculty (50 boys and 61 girls), 48 from dentistry (26 boys and 22 girls), 57 from paramedical (25 boys and 32 girls), 45 from health (15 boys and 30 girls), 32 from rehabilitation (15 boys and 17 girls) and 58 from Nursing and Midwifery students (20 boys and 38 girls) of Zahedan university were selected based on the list of students in each faculty according to the population of the faculties and separately for girls and boys. After satisfying the students, the information form including demographic information (age, sex, residence status, marital status, field of study), anthropometrics, and eating convenience food was completed through interviews with students. In preparing the convenience food questionnaire, a questionnaire whose validity and reliability had been previously confirmed in a study was used[6]. The sample size was calculated at 351 people using the Morgan table.

For determining anthropometric indices; Weighing was done using a standard scale with the least possible coverage and without shoes, with an accuracy of 0.1 kg, and measuring height was done with a stature meter with an accuracy of 0.1 cm, while the person is barefoot and he/she was placed next to the stature meter so that the back of his/her legs, buttocks, shoulders and back of his/her head was completely tangential to the stature meter.

Waist circumference was measured in its narrowest area and in the position where the person was at the end of his normal exhalation and the abdominal muscle was without contraction using an inelastic tape meter with an accuracy of 0.1 cm. Body mass index (BMI) was calculated by dividing weight (kg) by height squared ($m^2$). BMI classification was determined according to the WHO recommended grouping as follows: BMI <18.5 was low weight, 18.5-24.9 had normal weight, and BMI > 25 kg/$m^2$ was overweight and obese(9). Waist circumference according to WHO criteria were considered central obesity for men and women as >102 and >88, respectively.

SPSS-16 software was used for statistical analysis. Descriptive and analytical statistical methods (Chi-square tests and one-way analysis of variance) were used for data description.

This study has been approved by the Research Council of Zahedan University of Medical Sciences with the code of ethics committee code IR.ZAUMS.REC.1397.76.

## Results

The present study was conducted on 351 male and female students that quantitative and qualitative findings of the study and the relationship between the data and anthropometric variables and consumption of convenience food are shown in the below tables. **Table I** shows the mean and standard deviation of the variables of age, weight, height, BMI, and waist circumference.

The frequency of eating convenience food and BMI and waist circumference in male and female students was determined and the findings have been shown in **tables II** and **III**. There was a significant relationship between eating convenience food and demographic characteristics such as residential status (p=0.01) and mother's education (p=0.014), while there was no significant relationship between eating convenience food with gender, marital status, and father's education educational grade (p>0.05). It was observed that 49.3% of the students living in dormitories ate convenience food permanently and 48.9% of them sometimes ate convenience food. 49.06% of students who had mothers with higher education (diploma and higher grades) ate convenience food permanently and 47.4% of them sometimes ate convenience food.

The highest frequency of convenience food foods in students is related to pizza (18.3%), hamburgers (9.2%), fried potatoes (5%), sausages (4.7%), fried chicken (4.4%), and (36.9%) was also a combination of 2 or 3 convenience food.

The relationship between eating convenience food and students' anthropometric indices was determined by the Chi-square test. According to (**Table IV**) there was a significant statistical relationship between the consumption of convenience food and waist circumference (p = 0.014) and body mass index (*p* = 0.028).

**Table I:** Demographic and anthropometric characteristics of students of Zahedan University of Medical Sciences (n =351).

| Variable | M ± SD | Variation range |
|---|---|---|
| **Age (year)** | 21.48±2.76 | 17-40 |
| **Height (cm)** | 167.91±9.32 | 149-197 |
| **Weight (Kg)** | 61.73±13.9 | 3-35.130 |
| **Body mass index (kg /m²)** | 21.77±3.91 | 14.39-19.68 |
| **Waist (cm)** | 77.37±11.06 | 57-122 |

**Table II:** Frequency distribution of eating convenience food among Students of Zahedan University of Medical Sciences by gender.

| Consume ready meals | Women | Men | Total |
|---|---|---|---|
| **Permanently** | 89 (25.4%) | 80 (22.8%) | 169 (48.1%) |
| **Sometimes** | 101 (28.8%) | 66 (18.8%) | 167 (47.6%) |
| **Not consume** | 10 (2.8%) | 5 (1.4%) | 15 (4.3%) |
| **Total** | 200 (57%) | 151 (43%) | 351 (100%) |

**Table III:** Frequency distribution of Body Mass Index (BMI) and waist circumference in students of Zahedan University of Medical Sciences by gender.

| Body mass index | Women | Men | Total | *p*. value |
|---|---|---|---|---|
| Lightweight | 55 (27.5 %) | 18 (11.9%) | 73 (20.8%) | 0.0001 |
| Normal | 123 (61.5%) | 90 (59.6%) | 213 (60.7%) | |
| Overweight and obesity | 22 (11%) | 43 (28.5%) | 65 (18.5%) | |
| Total | 200 (100%) | 151 (100%) | 351 (100%) | |
| **Waist** | | | | |
| Normal | 186 (93%) | 138 (91.4%) | 324 (92.3%) | 0.358 |
| Central obesity | 14 (7%) | 13 (8.6%) | 27 (7.7%) | |
| Total | 200 (100%) | 151 (100%) | 351 (100%) | |

**Table IV:** Frequency distribution of BMI and waist circumference by eating convenience food in students of Zahedan University of Medical Sciences.

| Body mass index | Permanently | Sometimes | Not consume | Total | p. value |
|---|---|---|---|---|---|
| Lightweight | 28 (8%) | 40 (11.4%) | 5 (1.4%) | 73 (20.8%) | 0.028 |
| Normal | 100 (28.5%) | 103 (29.3%) | 10 (2.8%) | 213 (60.6%) | |
| Overweight and obesity | 41 (11.7%) | 24 (6.8) | 0 | 65 (18.5%) | |
| Total | 169 (48.2%) | 167 (47.5%) | 15 (4.3%) | 351 (100%) | |
| **Waist** | | | | | |
| Normal | 147 (41.9%) | 162 (46.2%) | 15 (4.3%) | 324 (92.3%) | 0.014 |
| Overweight and obesity | 20 (5.7%) | 7 (2%) | 0 | 27 (7.7) | |
| Total | 167 (47.6%) | 169 (48.2%) | 15 (4.3%) | 351 (100%) | |

## Discussion

The results of this study showed that 47.6% of students ate at least one type of convenience food more than 2 times a week and 48.1% of them sometimes (monthly or every few months). The prevalence of eating convenience food did not show a statistically significant difference between the two sexes, but eating convenience food was higher in male students (22.8% permanently and 18.8% sometimes) than in female students (25.4% permanently and 28.8% sometimes).

The prevalence of eating convenience food in the studied students was higher than that eating convenience food in the students studied by Asadi et al in Tehran with a prevalence of 18% in boys and 11% in female students[14] and it was less than the consumption in students of Qom universities with a frequency of 72.4%[15]. In the study of Saudi female students, 74.5% of students ate convenience food 1-2 times a week[8], which is more common than the prevalence of consumption in Zahedan students.

There was a statistically significant relationship between students' living status (dormitory or non-dormitory) with eating convenience food so eating convenience food was more prevalent among students living in dormitories. Also, there was a significant relationship between eating convenience food and mother's education, so with the increase in maternal education, the prevalence of eating convenience food among students increased. It seems that the increasing the level of the mother's education is associated with the possible employment of the mother outside the home; as a result, lack of enough opportunity to prepare and cook food at home, and also due to the mother's employment, the higher income of the family increases the possibility and desire to eat convenience food in the family[16].

The main reasons for eating convenience food among students include easy access to these foods, lack of sufficient skills in preparing food, and the desired taste of convenience food[1,9]. It seems that the above reasons have been effective in eating fast food in the students of the present study.

Convenience foods are low in micronutrients, low in fiber, high in energy density, high in glycemic response, and high in sugar[14], which can increase daily energy intake and thus lead to overweight and obesity. Numerous studies have shown that eating convenience food is directly related to obesity and overweight due to high energy intake[14,17]. Excessive consumption of convenience food is associated with increasing the risk of chronic diseases. Obesity is a risk factor for many chronic diseases such as diabetes, cardiovascular disease, hypertension, etc[17].

Obesity, especially central obesity has also a high prevalence in different age and sex groups in Iran. In Tehran, the prevalence of central obesity between the years 1999-and 2001 increased from 63.1% to 79.5% in men and from 67.1% to 82.1% in women, respectively[18].

In the study of Mortazavi and Shahrakipour in 2003-2004, the prevalence of overweight and obesity in students of Zahedan University of Medical Sciences was 12.9% and 1.3%, respectively, and the prevalence of central obesity in male students was 3.1% and in female students was 39.5%. Was[19]. In the current study, the prevalence of overweight and general obesity in students of this university was 18.5%, respectively, and the prevalence of central obesity in male and female students was 8.6% and 7%, respectively, which shows an increase in prevalence compared to the previous study.

In the current study, there was a statistically significant relationship between convenience food and general and central obesity, which was in line with the study of Shah Tahir et al. in terms of the relationship with general obesity(19), which showed a significant relationship between eating convenience food and general obesity and in terms of the relationship with central obesity, it is consistent with the study of Francis et al in Jamaica[20] that a statistically significant relationship was observed between the eating convenience food and central obesity.

The findings of the current study show high consumption of convenience food and consequently overweight and general and central obesity in students. It seems that by teaching appropriate nutritional patterns and emphasizing the consumption of healthy foods instead of eating convenience food we can be effective in controlling and preventing overweight and obesity in different age and sex groups[21].

It is recommended that nutrition interventions and education in the universities and schools of the country should be performed at different times and continuously, in this way, it can be effective in institutionalizing healthy eating habits that are effective in preventing many non-communicable diseases related to nutrition including obesity and obesity-related diseases.

## Conclusion

The findings of the present study showed that the prevalence of general and central obesity among students was 18.5%, 7.7%, and 47.6%. Findings of the study indicated that fast food consumption and consequently general and central obesity were high. Therefore, the necessity of interventions such as continuous nutrition education programs to improve the nutritional literacy of young people and students is required. It is recommended that nutrition interventions and education in the universities and schools of the country should be performed at different times and continuously, in this way, it can be effective in institutionalizing healthy eating habits that are effective in preventing many non-communicable diseases related to nutrition including obesity and obesity-related diseases.

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## Declaration of competing interest
The authors declared no potential conflicts of interest to the research, authorship, and/or publication of this article.

## Availability of data
Data is available from the authors on reasonable request.

## Authors contributions
Study concept and design: MN(Mehrdad Naghizadeh); acquisition of data: MA(Mehdi Ahmadi) and MN; analysis and interpretation of data: MA, MN ; drafting of the manuscript:MN and SJ(Saber Jafari maskouni); ; critical revision of the manuscript: ZM(Zinat Mortazavi) and MN; statistical analysis: SJ; and study supervision: ZM, MNand MA.

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ORIGINAL

# An unusual adverse effect of the clozapine - appendicitis: A meta-analysis

*Un efecto adverso inusual de la clozapina - apendicitis: Un meta-análisis*

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## Abstract

***Objective:*** This meta-analysis aimed to compare the risk of appendicitis between clozapine and other antipsychotic medications.
***Methods:*** Using the databases EMBASE, PubMed, SCOPUS, and Cochrane, we carried out a thorough literature search up to May 2023. Studies comparing Clozapine and Other antipsychotics in terms of occurrence of the appendicitis were included. We applied a random effect model using Rev-Man 5.4 software.
***Results:*** Four studies were included in the analysis, involving a total of 4,685 patients on clozapine and 15,777 patients on other antipsychotics. Results consistently showed a higher incidence of appendicitis among patients treated with clozapine across all four studies, with incidence rates ranging from 2,086 to 2,726 per 100,000. A significantly higher incidence of appendicitis was observed in the clozapine group (OR: 45.76, 95% CI 8.03 to 260.75; P<0.0001), despite the considerable heterogeneity across the studies (I2=81%).
***Conclusions:*** This meta-analysis highlights the importance of monitoring patients treated with clozapine for the occurrence of appendicitis. Clinicians should be aware of this potential risk and consider it when prescribing antipsychotic treatments.

*Key words:* Clozapine, appendicitis, schizophrenia, antipsychotics.

## *Resumen*

***Objetivo:*** Este meta-análisis tuvo como objetivo comparar el riesgo de apendicitis entre clozapina y otros medicamentos antipsicóticos.
***Métodos:*** Utilizando las bases de datos EMBASE, PubMed, SCOPUS y Cochrane, se realizó una búsqueda bibliográfica exhaustiva hasta mayo de 2023. Se incluyeron estudios que comparaban Clozapina y Otros antipsicóticos en cuanto a la aparición de la apendicitis. Se aplicó un modelo de efectos aleatorios utilizando el software Rev-Man 5.4.
***Resultados:*** Se incluyeron cuatro estudios en el análisis, con un total de 4.685 pacientes con clozapina y 15.777 pacientes con otros antipsicóticos. Los resultados mostraron sistemáticamente una mayor incidencia de apendicitis entre los pacientes tratados con clozapina en los cuatro estudios, con tasas de incidencia que oscilaban entre 2.086 y 2.726 por 100.000. La incidencia de apendicitis fue significativamente mayor entre los pacientes tratados con clozapina que entre los tratados con otros antipsicóticos. Se observó una incidencia significativamente mayor de apendicitis en el grupo de clozapina (OR: 45,76; IC 95%: 8,03 a 260,75; P<0,0001), a pesar de la considerable heterogeneidad entre los estudios (I2=81%).
***Conclusiones:*** Este metaanálisis destaca la importancia de monitorizar a los pacientes tratados con clozapina para detectar la aparición de apendicitis. Los clínicos deben ser conscientes de este riesgo potencial y tenerlo en cuenta a la hora de prescribir tratamientos antipsicóticos.

*Palabras clave:* Clozapina, apendicitis, esquizofrenia, antipsicóticos.

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## Introduction

Clozapine is an atypical antipsychotic medication that is primarily used to treat schizophrenia, especially in individuals who do not respond well to other antipsychotic medications. It is known for its efficacy in reducing both positive and negative symptoms of the disorder. However, despite its therapeutic benefits, clozapine has several adverse effects that can be concerning for patients and healthcare providers alike[1].

One of the most serious side effects of clozapine is agranulocytosis, a potentially life-threatening condition characterized by a significant reduction in the number of white blood cells, particularly neutrophils[2]. This can leave the patient susceptible to infections and sepsis. As a result, patients on clozapine are required to undergo regular blood tests to monitor their white blood cell count. Clozapine is associated with significant weight gain, which can lead to obesity, diabetes, and other metabolic disturbances. Clozapine can cause sedation, dizziness, and lightheadedness, especially during the initial phase of treatment or upon dosage adjustment. Orthostatic hypotension, a sudden drop in blood pressure upon standing, is another common side effect of clozapine[3-5].

Clozapine may cause constipation and other gastrointestinal issues, such as nausea, vomiting, and abdominal pain. These side effects can be managed with dietary adjustments, increased fluid intake, and over-the-counter laxatives, if necessary. In rare cases, severe constipation may lead to more serious complications, such as bowel obstruction or paralytic ileus and appendicitis[6].

In this meta-analysis, we investigate whether, in comparison to other antipsychotics, clozapine use is associated with an increased risk of appendicitis.

## Materials and methods

### Search strategy

We did a comprehensive literature search up to May 2023 using EMBASE, PubMed, SCOPUS, and Cochrane databases. The keywords used for the searches were "clozapine, clozapine and side effects, clozapine and appendicitis, clozapine and other antipsychotics". Moreover, manual searches of references and reviews were done for additional relevance.

### Study selection

Studies comparing the incidence of appendicitis during clozapine and other antipsychotics treatment were included. The reviews, case reports, and irrelevant confounding articles were excluded.

### Data extraction

Four authors independently reviewed the included studies (FBA, SIA, HŞB, HMA, and OG). We extracted information on sample size, study design, and year of publication. The studies' participants' ages and genders, the additional antipsychotic medications they took, their diagnoses, and the length of time they had been taking antipsychotics were all reviewed.

### Risk of bias assessment

The Newcastle-Ottawa Scale (NOS), designed especially for observational studies, was chosen to assess the level of quality of the selected studies. Four authors (OG, SIA, HMA, and HŞB) independently analyzed the included studies, and any disagreements were resolved through discussion with the other reviewers. Thanks to the efforts of four different authors (OG, SIA, HMA, and HŞB), who used a predetermined meta-analysis form to extract pertinent data from each study, interobserver agreement was found to be high and satisfactory.

### Statistical analysis

The Review Manager (RevMan) software, version 5.4, was used to analyze the statistical data. Risk ratios and measured mean differences were used to evaluate both continuous and dichotomous variables. The amount of statistical heterogeneity was assessed using the Chi-square test and the I2 statistic, which both quantify statistical heterogeneity. The significance level was set at $p<0.05$. To analyze the data, we used a model with random effects.

### Reporting

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) was used to report the findings of this meta-analysis.

## Results

Four studies comparing clozapine (n=4685) and other antipsychotics (n=15777) were determined to be appropriate for meta-analysis during the screening process of studies (PRISMA), as shown in **figure 1**. These four studies included three retrospective studies and one case series. The New-Castle Ottawa scores, type and year of the studies were summarized in **table I**.

The results presented in this article are based on four studies investigating the incidence and onset of appendicitis in patients treated with Clozapine and other antipsychotics (AP) (**Table II**).

In the study conducted by Kawakita et al.[7] (study period: 2009-2021), among 65 patients on Clozapine (21 males and 44 females, mean age 32.3 years, range 23.1-50.4 years), 5 cases of appendicitis were reported, yielding an incidence rate of 2,086 per 100,000. The average age at the onset of appendicitis in this group was 23 years (range 16.7-28.6 years). In the comparison group treated with other APs (400 patients, 171 males and 229 females), 5 cases of appendicitis were reported. The average age at the onset of appendicitis was 30.7 years (range 24.1-59.9 years).

**Figure 1:** PRISMA flow diagram of study selection.

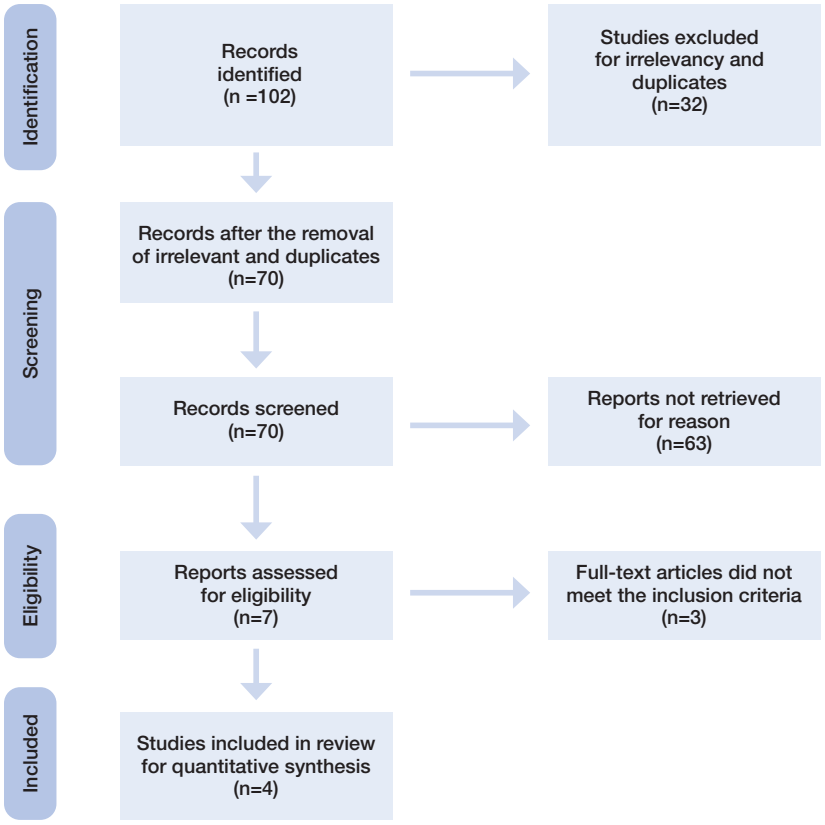


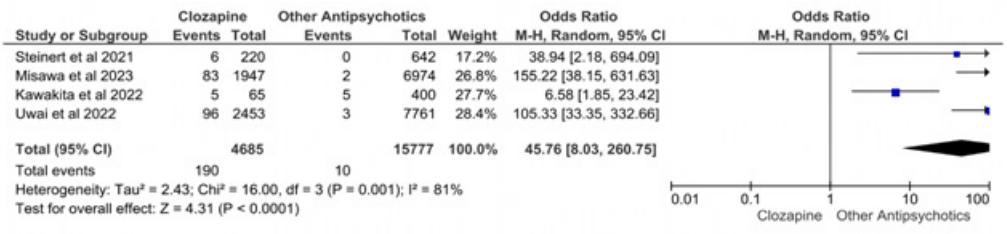

**Table I:** Summary of the included studies.

| No | Author | Region | Year | Clozapine (n=4685) | Other antipsychotics (n=15777) | Type of Study | NOS score |
|---|---|---|---|---|---|---|---|
| 1 | Kawakita et al | Japan | 2022 | 65 | 400 | Retrospective | 5 |
| 2 | Uwai et al | Japan | 2022 | 2453 | 7761 | Retrospective | 5 |
| 3 | Misawa et al | Japan | 2023 | 1947 | 6974 | Retrospective | 6 |
| 4 | Steinert et al | Germany | 2021 | 220 | 642 | Case series | 4 |

**Table I:** Characteristics of the studies.

| No | Author | Study Period | Group | N | Sex, M/F | Age | Appendicitis (n) | Incidence (per 100,000) | Age at onset of appendicitis | Time to onset appendicitis |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Kawakita et al | 2009-2021 | Clozapine<br>Other AP | 65<br>400 | 21/44<br>171/229 | 32.3(23.1-50.4)<br>NA | 5<br>5 | 2,086<br>NA | 23(16.7-28.6)<br>30.7(24.1-59.9) | NA<br>NA |
| 2 | Uwai et al | 2004-2021 | Clozapine<br>Other AP | 2453<br>7761 | NA<br>NA | NA<br>NA | 96<br>3 | NA<br>NA | NA<br>NA | 445(245-675)<br>NA |
| 3 | Misawa et al | 2004-2021 | Clozapine<br>Other AP | 1947<br>6974 | 1086/835<br>3211/3763 | NA<br>NA | 83<br>2 | NA<br>NA | NA<br>NA | 674(314-1096)<br>NA |
| 4 | Steinert et al | NA (14 years) | Clozapine<br>Other AP | 220<br>642 | NA<br>NA | NA<br>NA | 6<br>0 | 2,726<br>130 | NA<br>NA | NA<br>NA |

**Figure 2:** Meta-analysis of the included studies in terms of occurrence of the appendicitis rate.



In the Uwai et al.[8] study (study period: 2004-2021), 96 cases of appendicitis were reported among 2,453 patients on Clozapine. The median time to the onset of appendicitis in this group was 445 days (range 245-675 days). In the comparison group of 7,761 patients treated with other APs, there were 3 cases of appendicitis.

The study by Misawa et al.[9] (study period: 2004-2021) involved 1,947 patients on Clozapine (1,086 males and 835 females). Here, 83 cases of appendicitis were reported, with a median time to onset of 674 days (range 314-1096 days). In the comparison group of 6,974 patients on other APs (3,211 males and 3,763 females), 2 cases of appendicitis were identified.

In the final study by Steinert et al. (10) spanning 14 years, 6 cases of appendicitis were reported among 220 patients on Clozapine, yielding an incidence rate of 2,726 per 100,000. In the comparison group of 642 patients on other APs, no cases of appendicitis were reported, and the incidence rate was estimated at 130 per 100,000.

### Meta-analysis

Four studies[7-10] have discussed appendicitis rates in patients who received clozapine and other AP. The Clozapine group had a significantly higher incidence of appendicitis compared to other AP (I2=81%), (OR: 45.76, 95% CI 8.03 to 260.75; P<0.0001) (**Figure 2**).

## Discussion

We will discuss the adverse effects associated with the use of clozapine and other antipsychotic medications. It is crucial to keep in mind that these medications, while effective in managing psychotic symptoms, also carry a risk of adverse reactions. Therefore, the benefits must be carefully weighed against these potential risks.

Clozapine, despite being one of the most effective antipsychotics for treatment-resistant schizophrenia, is associated with several adverse effects[6]. These range from relatively common but mild side effects such as salivation, sedation, and constipation to serious, potentially life-threatening conditions such as neutropenia, agranulocytosis, myocarditis, and seizures. The risk of agranulocytosis, in particular, has led to mandatory blood monitoring protocols for patients on clozapine. Additionally, the metabolic disturbances caused by clozapine, such as weight gain, hyperlipidemia, and diabetes mellitus, are concerning due to their long-term implications on patients' cardiovascular health[11-15]. In recent years, there have been publications suggesting an increased risk of appendicitis associated with the use of clozapine[7-10,16,17, 18]. This meta-analysis was conducted to compare the risk of appendicitis between clozapine and other antipsychotic medications.

The higher incidence of appendicitis among patients treated with Clozapine, compared to other APs, was consistently observed across all four studies. In the study by Kawakita et al.[7] the incidence rate among patients on Clozapine was remarkably high (2,086 per 100,000). This was corroborated by the findings of Steinert et al. (10) where the incidence rate for Clozapine patients was even higher (2,726 per 100,000), while no cases of appendicitis were reported in the comparison group.

Furthermore, Uwai et al.[8] and Misawa et al.[9] reported median times to onset of appendicitis of 445 days and 674 days, respectively, for patients treated with Clozapine. These figures suggest a relatively quick onset of appendicitis following the initiation of Clozapine treatment, as compared to other APs.

The results of the meta-analysis further substantiated these findings. A significantly higher incidence of appendicitis was observed in the Clozapine group (OR: 45.76, 95% CI 8.03 to 260.75; P<0.0001), despite the considerable heterogeneity across the studies (I2=81%). The reasons for this increased risk of appendicitis with Clozapine remain to be clarified[7]. It may be related to the unique pharmacological properties of Clozapine, which could potentially impact gut motility or the immune response. Further research is needed to elucidate the underlying mechanisms and to develop strategies for mitigating this risk.

## Conclusions

The findings of this meta-analysis highlight the importance of monitoring for symptoms of appendicitis in patients treated with Clozapine. Clinicians should be aware of this potential risk and consider it in their decision-making when prescribing antipsychotic treatments.

### Conflict of interest

No

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ORIGINAL

# Índices de adiposidad corporal (BAI) y volumen abdominal (AVI). Relación con hábitos de vida en población laboral

*Corporal body adiposity (BAI) and abdominal volume (AVI) indices. Relationship with lifestyle in the working population*

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## Resumen

***Introducción:*** La obesidad es un problema global de prevalencia creciente. La patogenia de las enfermedades cardiovasculares comienza mucho antes de la presentación del evento cardiovascular. Es objetivo de este trabajo valorar la adiposidad relacionada con obesidad con los índices de volumen abdominal (AVI) y de adiposidad corporal(BAI), las diferencias por sexo y su relación con parámetros de obesidad y variables socio-culturales.

***Método:*** Estudio transversal en trabajadores españoles de diversos sectores desde enero 2019 a septiembre 2021. Se calcularon los valores de AVI y BAI mediante sus fórmulas específicas y su relación con índice de masa corporal (IMC), perímetro de cintura (IC)índice cintura altura (ICA) e índice cintura cadera (ICC). Se estudió la relación de ambos índices con estilo de vida saludable: alimentación-PREDIMED y actividad física-IPAC-reducido. Se utilizó el programa SPSS 27.0, considerando significación estadística p< 0,05.

***Resultados:*** Estudio realizado en 193.462 trabajadores (116.407 hombres y 77.055 mujeres) con edad media 39,2 años las mujeres y 39,8 años los hombres; índice de masa corporal en sobrepeso: 25,2 las mujeres, 26,8 los hombres; mayor actividad física (54,5%) y alimentación saludable (59,1%) en las mujeres. Los valores medios de AVI y BAI aumentan en ambos sexos con la edad, especialmente a partir de los 50 años, en mujeres con estudios primarios y clase social III y en hombres con estudios primarios/secundarios y clase social III. En ambos sexos son más altos cuando no se realiza actividad física o no hay adherencia a dieta mediterránea. En ambos sexos son más altos en personas no fumadoras. (p<0.0001). Son más elevados, en ambos sexos cuando ICA, ICC están en valores altos y el IMC en valores de obesidad. Los valores medios de AVI son más altos en hombres y los de BAI en mujeres (p<0.0001).

***Conclusiones:*** Los índices de adiposidad corporal (BAI) y de volumen abdominal (AVI) muestran diferencias entre hombres y mujeres, aumentan sus valores medios con la edad, muestran relación con la situación social y cultural y con los hábitos de vida saludables. Los valores medios de AVI y BAI aumentan según lo hacen los parámetros de obesidad en ambos sexos: ICA, ICC e IMC.

*Palabras clave:* Adiposidad corporal, volumen abdominal, riesgo cardiovascular, salud laboral.

## *Abstract*

***Introduction:*** Obesity is a global problem of increasing prevalence. The pathogenesis of cardiovascular disease begins long before the onset of a cardiovascular event. The aim of this work is to assess obesity-related adiposity with abdominal volume index (AVI) and body adiposity index (BAI), sex differences and their relationship with obesity parameters and socio-cultural variables.

***Methods:*** Cross-sectional study in Spanish workers from different sectors from January 2019 to September 2021. AVI and BAI values were calculated using their specific formulas and their relationship with body mass index (BMI), waist circumference (WC), waist height index (WHI) and waist hip index (WHI). The relationship of both indexes with healthy lifestyle was studied: diet-PREDIMED and physical activity-IPAC-reduced. The SPSS 27.0 program was used, considering statistical significance p<0.05.

***Results:*** Study conducted on 193,462 workers (116,407 men and 77,055 women) with mean age 39.2 years for women and 39.8 years for men; overweight body mass index: 25.2 for women, 26.8 for men; greater physical activity (54.5%) and healthy eating (59.1%) in women. The mean values of AVI and BAI increase in both sexes with age, especially after 50 years of age, in women with primary education and social class III and in men with primary/secondary education and social class III. In both sexes they are higher when there is no physical activity or no adherence to the Mediterranean diet. In both sexes they are higher in non-smokers (p<0.0001) and are higher in both sexes when ICA, ICC are high and BMI is obese. The mean values of AVI are higher in men and those of BAI in women (p<0.0001).

***Conclusions:*** Body adiposity indexes (BAI) and abdominal volume index (AVI) show differences between men and women, increase their mean values with age, show relationship with social and cultural situation and with healthy life habits. The mean values of AVI and BAI increase as do the parameters of obesity in both sexes: ICA, ICC and BMI.

*Key words:* Body adiposity, abdominal volume, cardiovascular risk, occupational health.

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## Introducción

La obesidad es un problema global. Se estima que más de 4.000 millones de personas en el mundo, el 51% de la población global, sufrirán sobrepeso u obesidad en 2035. Es uno de los principales factores de riesgo para numerosas enfermedades no transmisibles crónicas, entre las que se incluyen: diabetes, enfermedades cardiovasculares, hipertensión, accidentes cerebrovasculares e incluso algunos tipos de cánceres[1].

La regulación de la distribución del tejido adiposo es un factor clave en obesidad, si consideramos las estrechas asociaciones epidemiológicas y metabólicas entre la acumulación de grasa centralizada y el riesgo de enfermedad[2]. En los últimos años, se ha enfatizado la importancia de identificar de forma temprana el riesgo, para ello, se han utilizados diversos índices como: el de grasa visceral (VAI), grasa disfuncional (DAI) índice de forma corporal A (ABSI), producto de acumulación de lípidos (LAP), índice de redondez corporal (BRI), glucosa, biomarcadores de lípidos y presión arterial (PA)quepueden ser útiles en la prevención de complicaciones[3]. La estabilización de la placa aterosclerótica puede ser un objetivo terapéutico preventivo para reducir el riesgo de enfermedad coronaria en pacientes con obesidad visceral[4].

Aspecto clave en las intervenciones preventivas son las actuaciones en el estilo de vida. Tanto la obesidad como la diabetes tipo 2 son consecuencias comunes del aumento del sedentarismo y de la densidad energética de las dietas. Ambos son potencialmente prevenibles, pero necesitan de planes globales y nacionales para su manejo adecuado en la población[5].

Intervenciones en hábitos alimenticios como PREDIMED-Plus han mostrado su eficacia para disminuir la adiposidad y mejorar los factores de riesgo cardiovascular en adultos mayores con sobrepeso/obesidad y síndrome metabólico, así como en individuos con o en riesgo de diabetes[6].

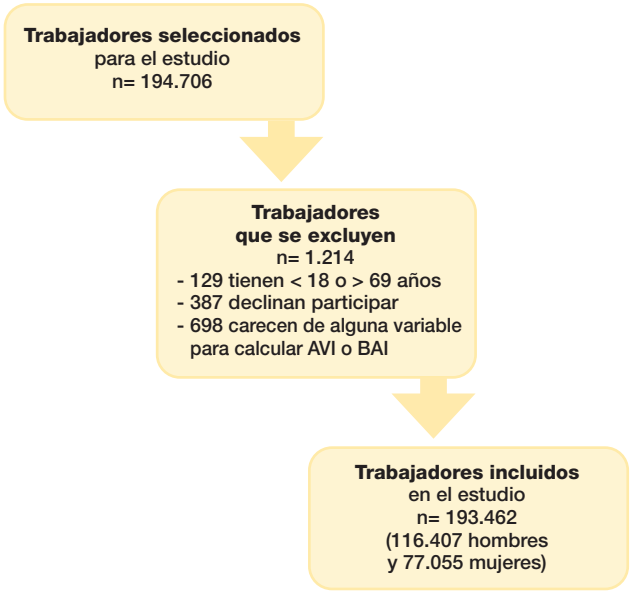
El efecto perjudicial de las conductas sedentarias sobre los rasgos cardiometabólicos y relacionados con la obesidad ha mostrado ser independiente de los niveles de actividad física. Por lo tanto, la reducción del tiempo sedentario debe ser un objetivo de la población además de aumentar sus niveles de actividad física[7].

Es objetivo de este trabajo es estimar la relación de los índices de adiposidad corporal (BAI) y de volumen abdominal (AVI) con variables sociales, culturales, establecer las diferencias por sexo y estimar la relación de los valores medios de ambos índices con parámetros de obesidad en la población laboral objeto de estudio.

## Método

Estudio transversal realizado en 193.462 trabajadores (116.407 hombres y 77.055 mujeres) de nueve comunidades autónomas en España (Islas Baleares, Andalucía, Canarias, Comunidad Valenciana, Cataluña, Madrid, Castilla-La Mancha, Castilla y León, y País Vasco) y con ocupaciones laborales diversas como: hostelería, construcción, comercio, sanidad, administración pública, transporte, educación, industria y limpieza. El estudio se realizó durante los exámenes de salud efectuados en los Servicios de Prevención de Riesgos Laborales (SPRL) de las empresas participantes durante el periodo comprendido entre enero de 2019 hasta septiembre de 2021. Son criterios de inclusión: edad entre 18 y 67 años, ser trabajador en activo y aceptación voluntaria de participación en el estudio. (**Figura 1**).

**Figura 1:** Diagrama de flujo de los participantes en el estudio.




La recogida de datos sobre antecedentes clínicos y familiares se realiza por el personal sanitario durante los exámenes de salud mediante entrevista, registrando los datos en base informatizada y con riguroso cumplimiento de lo estipulado en la Ley Orgánica de Protección de Datos Personales y garantía de los derechos digitales 2018 (LOPD)[8].

### Variables recogidas:

Edad-rangos: 18-29 años, 30-39, 40-49 años, 50-59años, 60-69 años.

Las medidas antropométricas de talla, peso, índice de masa corporal (IMC), circunferencia de cintura (CC), índice cintura/cadera (ICC), presión arterial (PA) y parámetros analíticos, fueron realizadas por el personal sanitario de las diferentes unidades de salud laboral participantes en el estudio, previa homogeneización de las técnicas de

medición. El laboratorio concertado para analíticas era común a todos ellos y de implantación nacional.

Índice de Masa Corporal (IMC) -índice de Quetelet (IMC=peso (kg)/altura$^2$ (metros) y clasifica (OMS-2023): normopeso <25; sobrepeso >25-<30; obesidad grado 1 >30-<40; obesidad grado 2 >40 9.

Los perímetros de cadera y cintura fueron determinados con la cinta métrica modelo SECA 20, con un rango de medida que va desde 1 cm hasta los 200 cm, divididos a escala milimétrica. Los rangos considerados fueron: perímetro de cintura normal en el hombre <94 cm y en la mujer <80 cm. El Índice cintura/cadera, normal en hombres <0,94 y en mujeres<0,84. El Índice cintura/altura normal <0,5.

La clase social y el tipo de trabajo se codificaron de acuerdo a la Clasificación Nacional de Ocupaciones vigente desde el año 2011 (CNO-11)10. Se tomó como referencia la propuesta del grupo de determinantes sociales de la Sociedad Española de Epidemiologia. Esta clasificación incluye seis grupos que se han reducido a tres para este trabajo: Clase I directores/gerentes, profesionales universitarios, deportistas y artistas; Clase II ocupaciones intermedias y trabajadores por cuenta propia sin asalariados; y Clase III trabajadores no cualificados[11].

El nivel de estudios categoriza a los participantes en tres niveles educativos, de acuerdo con el sistema educativo vigente en España:

- Primarios-Elementales: Si el participante realizó los seis niveles, desde primero a sexto de primaria.
- Secundarios-Medios: En el caso de haber cursado los siguientes ciclos, el primero formado por los cursos que van de primero a tercero de la educación secundaria obligatoria (E.S.O) y el segundo ciclo que consta sólo de un curso que es cuarto de la E.S.O. Si los estudios se cursaron antes del 2010, se clasificó en este grupo a todos aquellos que hubieran cursado séptimo y octavo de primaria, así como primero y segundo del Bachillerato Unificado Polivalente (B.U.P.)
- Universitarios-Superiores: Donde se incluyen todos aquellos que hubieran realizado alguna enseñanza universitaria en cualquiera de las estructuras establecidas y de acuerdo con la legislación vigente en el momento de haber sido cursadas.

La tensión arterial se determinó en decúbito supino con un esfigmomanómetro automático OMRON M3 calibrado tras 10 minutos de reposo (tamaño del manguito ajustado a la circunferencia del brazo). Se realizaron tres mediciones a intervalos de 1 minuto y se calculó la media de las tres.

Las muestras de sangre se obtuvieron por venopunción periférica tras un ayuno de 12 horas y se enviaron al laboratorio de referencia donde se procesaron en un plazo de 48-72 horas. La glucemia, el colesterol total y los triglicéridos se determinaron por métodos enzimáticos automatizados, expresando los valores en miligramo/decilitro (mg/Dl). Las lipoproteínas de alta densidad (HDL) se calcularon por precipitación con dextranosulfato Cl2Mg, y los valores se expresaron en mg/dL. Las lipoproteínas de baja densidad (LDL) se estimaron mediante la fórmula de Friedewald LDL= (colesterol total -HDL- triglicéridos/5), siempre que los triglicéridos fueran inferiores a 400 mg/dl, y se expresaron en mg/dl. En caso contrario, no se calculó el LDL.

Las variables de hábitos de vida incluidas en el estudio han sido:

Para la valoración de hábitos de vida en alimentación se utilizó la encuesta validada PREDIMED, de adherencia a la dieta mediterránea y se consideró buena adherencia a partir de 9 puntos[12,13].

Para la valoración de hábitos de vida saludable en actividad física se utilizó la encuesta validada IPAQ-reducida. Clasifica en 3 categorías: Baja. No registran actividad física o la registra, pero no alcanza las categorías media y alta; Media. Considera los siguientes criterios: 3 o más días de actividad física vigorosa por lo menos 20 min por día, 5 o más días de actividad física de intensidad moderada o caminar por lo menos 30 min, 5 o más días de cualquier combinación de actividad física leve, moderada o vigorosa que alcancen un registro de 600 METs-min/semana;. Alta. Es una categoría que cumple los siguientes requerimientos: 3 o más días de actividad física vigorosa o que acumulen 1.500 METs-min-semana, 7 o más días de cualquier combinación de actividad física leve, moderada o vigorosa que alcance un registro de 3.000 METs-min/semana[14,15]. Para este estudio se ha considerado no realizar actividad física a la categoría baja y sí realizarla en las personas incluidas en las categorías media y alta.

El índice de volumen abdominal- abdominal volume index (AVI): utiliza la fórmula propuesta por Guerrero-Romero et al: AVI = [2 x (cintura-cm)$^2$+0,7 (cintura-cadera-cm)$^2$]/1.000[16].

El índice de adiposidad corporal-body adiposity index (BAI). Utiliza la fórmula propuesta por Bergman RN et al: BAI = (circunferencia de la cadera)/(altura)(1.5)-18)[17].

**Análisis estadístico:**

Para el estudio estadístico se realizó un análisis univariante empleando la t-student y la chi cuadrado. El análisis estadístico se realizó con el programa SPSS 29.0, siendo el nivel de significación estadística aceptado de 0,05.La correlación entre las diferentes escalas se obtuvo aplicando el coeficiente de Pearson.

El estudio fue aprobado por el Comité Ético de Investigación Clínica del Área de Salud de Baleares (IB 4383/20).

## Resultados

Estudio descriptivo transversal en una población laboral de 193.462 personas (116.407 hombres y 77.055 mujeres);edad media de 39,2 años en mujeres y 39,8 años en hombres; en ambos sexos mayoritariamente de estudios primarios y clase social III, IMC 25,2 en mujeres y 26,8 en hombres, valores de presión arterial, circunferencia de cintura y de cadera en valores de normalidad, más altos en hombres que en mujeres; presión arterial, glucemia y lípidos en rangos de normalidad, más altos en hombres que en mujeres. Los hábitos de vida con mayor porcentaje de mujeres que realizan actividad física y mayor adherencia a dieta mediterránea. En ambos sexos son mayoritariamente no fumadores. Los resultados se muestran en la **tabla I** y son estadísticamente significativos (p<0.0001).

Los valores medios de AVI y BAI aumentan en ambos sexos con la edad, en mujeres con estudios primarios y clase social III y en hombres con estudios primarios/ secundarios y clase social III. En ambos sexos son más altos cuando no se realiza actividad física o no hay adherencia a dieta mediterránea. En ambos sexos son más altos en personas no fumadoras. En todos los casos las diferencias son significativas estadísticamente (p<0.0001). (**Tabla II**).

Los valores medios de AVI y BAI son más elevados, tanto en hombres como en mujeres en personas con ICA alto, ICC alto e IMC en valores de obesidad. Los valores medios de AVI son más altos en hombres y los de BAI en mujeres. En todos los casos las diferencias son significativas estadísticamente (p<0.0001). (**Tabla III**). (**Figuras 2** y **3**).

El coeficiente de correlación de Pearson muestra,en ambos sexos buena correlación (0.61 - 0.80) del IMC con los parámetros de obesidad (PC,PCAD, ICA) y de AVI y BAI con IMC y PCAD.

En mujeres muy buena correlación (0.81-1.00)de AVI con PC e ICA y de BAI con PCAD.

En hombres muy buena correlación (0.81-1.00)de AVI con PC e ICA y buena (0.61-0.80)con ICC y de BAI buena correlación con PCAD. (**Tabla IV**).

**Tabla I:** Características de la muestra poblacional.

| VARIABLES | | VALORES MEDIOS | | |
|---|---|---|---|---|
| | | Mujeres=77055 | Hombres=116407 | |
| | | Mean (Sd) | Mean (Sd) | p-valor |
| **Parámetros somatométricos** | Edad (años)) | 39.2 (10.2) | 39.8 (10.3) | <0.0001 |
| | Altura (cm.) | 161.2 (6.6) | 173.9 (7.0) | <0.0001 |
| | Peso (Kg.) | 65.3 (13.2) | 81.1 (13.9) | <0.0001 |
| | IMC (kg/m²) | 25.2 (4.9) | 26.8 (4.2) | <0.0001 |
| | Circunferencia de cintura (cm) | 73.9 (7.9) | 87.7 (9.1) | <0.0001 |
| | Circunferencia de cadera (cm) | 97.2 (8.9) | 100.1 (8.4) | <0.0001 |
| **Presión arterial** | Sistólica (mmHg) | 114.4 (14.8) | 124.4 (15.1) | <0.0001 |
| | Diastólica (mmHg) | 69.7 (10.3) | 75.4 (10.6) | <0.0001 |
| **Parametros analíticos** | Colesterol Total (mg/dL) | 193.6 (36.4) | 195.9 (38.9) | <0.0001 |
| | HDL-c colesterol (mg/dL) | 53.7 (7.6) | 51.0 (7.0) | <0.0001 |
| | LDL-colesterol (mg/dL) | 122.2 (37.0) | 120.5 (37.6) | <0.0001 |
| | Triglicéridos (mg/dL) | 88.1 (46.2) | 123.8 (88.0) | <0.0001 |
| | Glucemia mg/dL) | 84.1 (11.5) | 88.1 (12.9) | <0.0001 |
| **VARIABLES** | | **PORCENTAJES** | | |
| | | % (CI 95%) | % (CI 95%) | p-valor |
| **Edad** | 18-29 años | 19.5 | 17.9 | <0.0001 |
| | 30-39 años | 33.3 | 33.1 | |
| | 40-49 años | 29.4 | 29.7 | |
| | 50-59 años | 15.3 | 16.3 | |
| | 60-69 años | 2.5 | 3.0 | |
| **Nivel de estudios** | Primarios | 51.8 | 61.2 | <0.0001 |
| | Secundarios | 40.7 | 34.0 | |
| | Universitarios | 7.5 | 4.8 | |
| **Clase social** | Clase social I | 7.0 | 5.3 | <0.0001 |
| | Clase social II | 33.2 | 17.5 | |
| | Clase social III | 59.8 | 77.3 | |
| **Actividad física** | Sí | 54.5 | 47.8 | <0.0001 |
| | No | 45.5 | 52.2 | |
| **Alimentación saludable** | Sí | 59.1 | 48.6 | <0.0001 |
| | No | 41.0 | 51.4 | |
| **Tabaquismo** | No Fumador | 67.0 | 62.9 | <0.0001 |
| | Fumador | 33.0 | 37.1 | |

Alimentación saludable-cuestionario PREDIMEDconsidera buena adherencia a partir de 9 puntos. Actividad física-cuestionario IPAC reducido. Se considerano realizar actividad física a la categoría baja y sí actividad física en las personas incluidas en las categorías media y alta.Se considera significativo un valor de p<0,005. Sd=desviación estándar; CI= intervalo de confianza

**Tabla II:** Valores medios de AVI y BAI según variables sociodemográficas y hábitos de vida. Diferencias mujeres /hombres.

| **Mujeres** | | | | | | |
|---|---|---|---|---|---|---|
| **VARIABLES** | | **n** | **AVI** | **p** | **BAI** | **p** |
| | | | **Media (dt)** | | **Media (dt)** | |
| **Edad** | 20-29 años | 14989 | 11,13 (2,34) | <0.0001 | 28,38 (4,70) | <0.0001 |
| | 30-39 años | 25896 | 11,33 (2,46) | | 28,87 (4,91) | |
| | 40-49 años | 22648 | 11,62 (2,40) | | 30,09 (4,81) | |
| | 50-59 años | 11758 | 11,88 (2,41) | | 31,46 (4,79) | |
| | 60-69 años | 1964 | 11,91 (2,20) | | 32,70 (4,68) | |
| **Nivel de estudios** | Primarios | 39905 | 11,67 (2,47) | <0.0001 | 30,68 (4,92) | <0.0001 |
| | Secundarios | 31345 | 11,29 (2,36) | | 28,60 (4,75) | |
| | Universitarios | 5805 | 11,11 (2,28) | | 27,92 (4,55) | |
| **Clase social** | Clase social I | 5372 | 11,09 (2,23) | <0.0001 | 27,84 (4,57) | <0.0001 |
| | Clase social II | 25615 | 11,21 (2,37) | | 28,29 (4,60) | |
| | Clase social III | 46068 | 11,67 (2,45) | | 30,58 (4,95) | |
| **Actividad física** | No | 36842 | 12,56 (2,73) | <0.0001 | 31,74 (5,07) | <0.0001 |
| | Sí | 40213 | 10,48 (1,53) | | 27,69 (3,94) | |
| **Alimentación saludable** | No | 37414 | 12,51 (2,75) | <0.0001 | 31,57 (5,16) | <0.0001 |
| | Sí | 39641 | 10,50 (1,52) | | 27,79 (3,94) | |
| **Tabaquismo** | No fumador | 51650 | 11,54 (2,40) | <0.0001 | 29,85 (5,03) | <0.0001 |
| | Fumador | 25405 | 11,35 (2,46) | | 29,16 (4,75) | |
| **Hombres** | | | | | | |
| **VARIABLES** | | **n** | **AVI** | **p** | **BAI** | **p** |
| | | | **Media (dt)** | | **Media (dt)** | |
| **Edad** | 20-29 años | 20871 | 14,80 (3,00) | <0.0001 | 24,35 (3,70) | <0.0001 |
| | 30-39 años | 38480 | 15,59 (3,23) | | 25,21 (3,68) | |
| | 40-49 años | 34534 | 16,14 (3,39) | | 26,08 (3,79) | |
| | 50-59 años | 19014 | 16,08 (3,33) | | 26,96 (3,80) | |
| | 60-69 años | 3508 | 16,10 (3,04) | | 27,86 (4,04) | |
| **Nivel de estudios** | Primarios | 71247 | 15,69 (3,34) | 0.013 | 25,89 (3,93) | <0.0001 |
| | Secundarios | 39613 | 15,75 (3,21) | | 25,38 (3,74) | |
| | Universitarios | 5547 | 15,69 (3,04) | | 25,11 (3,58) | |
| **Clase social** | Clase social I | 6131 | 15,74 (3,09) | 0.659 | 25,08 (3,61) | <0.0001 |
| | Clase social II | 20325 | 15,71 (3,17) | | 25,22 (3,71) | |
| | Clase social III | 89951 | 15,70 (3,32) | | 25,83 (3,90) | |
| **Actividad física** | No | 63404 | 17,07 (3,52) | <0.0001 | 27,14 (3,82) | <0.0001 |
| | Sí | 53003 | 14,08 (2,00) | | 23,94 (3,11) | |
| **Alimentación saludable** | No | 68732 | 16,84 (3,51) | <0.0001 | 26,89 (3,87) | <0.0001 |
| | Sí | 47675 | 14,07 (2,00) | | 23,92 (3,10) | |
| **Tabaquismo** | No fumador | 73240 | 15,82 (3,20) | <0.0001 | 25,86 (3,86) | <0.0001 |
| | Fumador | 43167 | 15,52 (3,41) | | 25,37 (3,84) | |

AVI=Índice de volumen abdominal- Abdominal volumeindex, BAI= Índice de adiposidad corporal-bodyadiposity índex. Alimentación saludable-cuestionario PREDIMEDconsidera buena adherencia a partir de 9 puntos. Actividad física-cuestionario IPAC reducido. Se considerano realizar actividad física a la categoría baja y sí actividad física en las personas incluidas en las categorías media y alta.dt=desviación típica. Se considera significativo un valor de p<0,005.

**Tabla III:** Valores medios de AVI y BAI según parámetros de sobrepeso y obesidad. Diferencias mujeres /hombres.

| **Mujeres** | | | | | | |
|---|---|---|---|---|---|---|
| **Variables** | | **n** | **AVI** | **p** | **BAI** | **p** |
| | | | **Media (dt)** | | **Media (dt)** | |
| **ICA** | normal | 64646 | 10,75 (1,52) | <0.0001 | 28,69 (4,20) | <0.0001 |
| | alto | 12409 | 15,23 (2,74) | | 34,52 (5,62) | |
| **ICC** | normal | 74715 | 11,26 (2,06) | <0.0001 | 29,46 (4,82) | <0.0001 |
| | alto | 2340 | 18,23 (3,29) | | 34,81 (6,10) | |
| **IMC** | bajo peso | 1944 | 9,38 (1,42) | <0.0001 | 23,21 (2,88) | <0.0001 |
| | normopeso | 42025 | 10,46 (1,57) | | 27,64 (3,86) | |
| | sobrepeso | 21393 | 11,98 (1,75) | | 30,52 (3,21) | |
| | obesidad | 11693 | 14,55 (3,07) | | 36,19 (4,70) | |
| **Hombres** | | | | | | |
| **ICA** | normal | 60770 | 13,52 (1,58) | <0.0001 | 24,11 (3,21) | <0.0001 |
| | alto | 55637 | 18,10 (2,98) | | 27,40 (3,77) | |
| **ICC** | normal | 104536 | 15,06 (2,61) | <0.0001 | 25,42 (3,76) | <0.0001 |
| | alto | 11871 | 21,45 (3,03) | | 28,01 (3,96) | |
| **IMC** | bajo peso | 680 | 12,10 (1,45) | <0.0001 | 19,49 (2,66) | <0.0001 |
| | normopeso | 40979 | 13,28 (1,67) | | 23,24 (2,92) | |
| | sobrepeso | 51999 | 16,21 (2,59) | | 25,92 (2,94) | |
| | obesidad | 22749 | 19,03 (3,49) | | 29,73 (3,53) | |

AVI=Índice de volumen abdominal- Abdominal volumeindex, BAI= Índice de adiposidad corporal-bodyadiposity índex. ICA= Índice Cintura/altura; ICC= Índice Cintura/cadera; IMC= Índice de Masa Corporal; dt= desviación típica.Se considera significativo un valor de p<0,005.

**Figura 2:** Comparativa hombres vs mujeres. Valores medios de AVI y BAI según IMC.

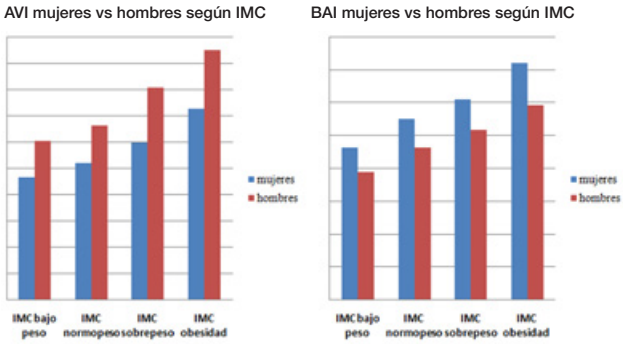



**Figura 3:** Comparativa hombres vs mujeres. Valores medios de AVI y BAI según parámetros de obesidad.

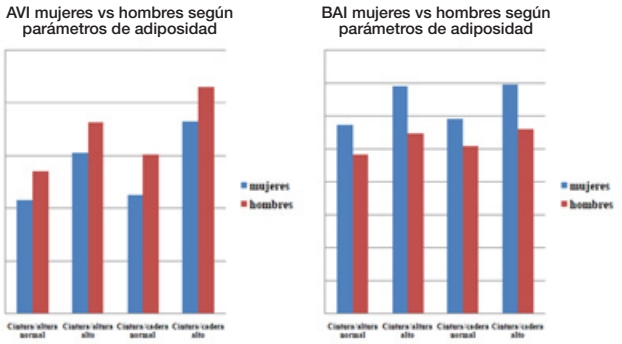



**Tabla IV:** Coeficiente de correlación de Pearson entre BAI y AVI con IMC. Indicadores de adiposidad.

| **Mujeres** | | | | | | | |
|---|---|---|---|---|---|---|---|
| | **IMC** | **PC** | **PCAD** | **I CA** | **ICC** | **AVI** | **BAI** |
| **IMC** | 1 | ,663** | ,719** | ,701** | ,048** | ,696** | ,720** |
| **PC** | | 1 | ,558** | ,925** | ,586** | ,987** | ,421** |
| **PCAD** | | | 1 | ,498** | -,340** | ,645** | ,806** |
| **ICA** | | | | 1 | ,559** | ,907** | ,593** |
| **ICC** | | | | | 1 | ,484** | -,309** |
| **AVI** | | | | | | 1 | ,487** |
| **BAI** | | | | | | | 1 |
| **Hombres** | | | | | | | |
| | **IMC** | **PC** | **PCAD** | **I CA** | **ICC** | **AVI** | **BAI** |
| **IMC** | 1 | ,658** | ,658** | ,681** | ,139** | ,665** | ,679** |
| **PC** | | 1 | ,530** | ,919** | ,635** | ,995** | ,377** |
| **PCAD** | | | 1 | ,405** | -,313** | ,559** | ,749** |
| **ICA** | | | | 1 | ,661** | ,913** | ,533** |
| **ICC** | | | | | 1 | ,602** | -,252** |
| **AVI** | | | | | | 1 | ,404** |
| **BAI** | | | | | | | 1 |

Valoración del Índice Kappa (Fuerza de la concordancia): < 0.20 Pobre; 0.21 – 0.40 Débil; 0.41 – 0.60 Moderada; 0.61 – 0.80 Buena; 0.81 – 1.00 Muy buena
IMC=índice de masa corporal; PC=perímetro de cintura; PCAD=perímetro de cadera;ICA=índice cintura/altura;ICC= índice cintura/cadera; AVI= Índice de volumen abdominal- Abdominal volumeindex, BAI= Índice de adiposidad corporal-bodyadiposity índex.

## Discusión

Los resultados de nuestro estudio muestran una población con claras diferencias somatométricas, en factores de riesgo y estilo de vida entre hombres y mujeres, con valores más desfavorables para los hombres. Coinciden con lo recogido en otros trabajos previosy con distintas formas de obesidad, donde en las mujeres existe mayor proporción de grasa corporal y en los hombres de grasa abdominal, lo que conlleva envarones mayores riesgos para la salud en presión arterial y parámetros lipídicos como se observa también en nuestro trabajo[18].

En estilo de vida: actividad física y dieta observamos diferencias entre hombres y mujeres, con mayor adherencia a dieta saludable y mayor actividad física en mujeres. Estos resultados difieren de los obtenidos en estudios previos realizados también en población laboral durante el periodo de pandemia COVID-19 en los que se valoraba, al igual que en éste, la adherencia a la dieta mediterránea con cuestionario PREDIMED con mayor adherencia en las mujeres, mientras que la actividad física valorada con el cuestionario IPAQ mostraba mayores niveles de actividad de moderada/alta en varones. En nuestro estudio la actividad moderada-alta se ha unificado y esto puede significar un sesgo en la comparativa. También en este estudio, al igual que en el nuestro, se observa la influencia de la clase social y el nivel formativo en la actividad física aunque no ocurre lo mismo con la adherencia a dieta mediterránea[19].

Las tendencias en este tema se van modificando y así lo muestra el estudio prospectivo realizado durante diez años (1999-2010) entre la población adulta de las Illes Balears que observó diferencias significativas en función de sexo, edad (26-45 y 46-65 años), nivel educativo (nivel medio y alto) y nivel socioeconómico (nivel ocupacional medio). En dicho estudio, durante el período de la entrevista 2009-2010, las personas con mayor adherencia tenían más probabilidades de ser

mayores (entre 46 y 65 años) y menos probabilidades de tener un nivel ocupacional bajo, lo que muestra una tendencia cambiante en estilo de vida en los últimos años[20].

La ingesta de alimentos poco saludables y la actividad física insuficiente están relacionadas con la obesidad o las enfermedades del estilo de vida, pudiendo causar enfermedades cardiovasculares e incrementar una mortalidad más temprana. Para prevenir la progresión de la obesidad o las enfermedades relacionadas con el estilo de vida, la nutrición y el ejercicio son aspectos importantes, antes y después del desarrollo de patología cardiovascular y, son especialmente útiles para implementar estrategias preventivas primarias que revelan de forma precoz los riesgos detectables para el posterior desarrollo de las enfermedades cardiovasculares[21].

En la práctica clínica, las medidas antropométricas distintas del IMC rara vez se evalúan, pero pueden ser más predictivas del riesgo cardiovascular. Los hallazgos más recientes indican la necesidad de medidas antropométricas que consideren la distribución de la grasa corporal al evaluar el riesgo cardiovascular[22]. Cobran importancia nuevas medidas antropométricas de adiposidad corporal y la relación cintura-altura, así como CC y ICC, junto con medidas tradicionales como el IMC, para reducir el riesgo de mortalidad por causa específica. Estas nuevas medidas parecen ser válidas como predictores de riesgo de mortalidad por todas las causas y, especialmente por ECV en hombres, pero no tanto en mujeres. De igual forma, existen marcadas diferencias por sexo en cuanto al riesgo de mortalidad para las diferentes medidas antropométricas[23].

En nuestro trabajo hemos utilizado dos índices de adiposidad, AVI y BAI, cuyos resultados han reflejado un aumento con la edad en ambos sexos, con diferencias según la clase social y el nivel educacional.

La asociación entre el nivel socioeconómico y la obesidad, así como las diferencias entre hombres y mujeres ya se había puesto de manifiesto en diversos trabajos previos, desde la evidencia sobre el tema mostrada ya en 2004 y actualizada en las posteriores revisiones destaca que, en países de bajos ingresos o en países subdesarrollados, la asociación del riesgo de complicaciones con la obesidad parece ser positiva para ambos, hombres y mujeres. Las personas con mayor nivel social y económico y/o aquellos con mayor nivel educativo tienden a tener más probabilidades de ser obesos. Sin embargo, en países de ingresos medios o en países con un nivel social medio, esta asociación se vuelve en gran medida mixta para los hombres y principalmente negativa para las mujeres[24].

El índice de adiposidad corporal (BAI) está avalado por estudios previos predictivos de la mortalidad por enfermedad cardiovascular y enfermedad coronaria, en comparación con el obtenido con el IMC, la circunferencia de la cintura y el índice cintura-cadera. Un estudio de seguimiento prospectivo a 15 años de 4175 hombres australianos, sin enfermedad cardíaca, diabetes ni accidente cerebrovascular mostró que BAI parecía tener un interés potencial como medida del porcentaje de grasa corporal y de obesidad, pero no fue eficaz para predecir enfermedades cardiovasculares y cardiopatías coronarias[25]. Igualmente en otros trabajos se afirma que, si bien el BAI está significativamente relacionado con la grasa corporal medida por impedancia bioeléctrica, parece ser de menor interés que otros marcadores de adiposidad más establecidos con respecto a su asociación con factores de riesgo CV o marcadores inflamatorios. Es por ello que sugieren realizar más estudios para evaluar con mayor profundidad la utilidad clínica del BAI y su relación con los factores de riesgo CV y con otros parámetros de salud, particularmente en diversas poblaciones[26].

En Salud Laboral BAI parece un índice de utilidad preventiva en obesidad que permitiría actuar de forma precoz en la aparición de complicaciones cardiovasculares, tanto más cuando se relaciona directamente con actividades de promoción de la salud, muy implantadas ya en las empresas en cuanto a hábitos de vida saludables, especialmente alimentación saludable y actividad física. En nuestro trabajo, en ambos sexos los valores medios tanto de BAI como de AVI son más elevados en personas que no muestran adherencia a alimentación saludable ni realizan actividad física regular y en no fumadores.

En un estudio realizado en población española se constata la relación entre estilos de vida y hábitos alimentarios y su relación con la prevalencia de sobrepeso y obesidad en población adulta. En él, los factores de estilos de vida asociados al sobrepeso y la obesidad presentan patrones diferentes en hombres y mujeres. Es por ello necesario comprenderlos para identificar áreas de intervención conductual en pacientes con sobrepeso y obesidad considerando estos diferentes patrones entre hombres y mujeres y considerar también las diferencias sociales, económicas y culturales[27].

No está claro si un estilo de vida saludable afecta a la longevidad en presencia de multimorbilidad En el análisis de datos del Biobanco del Reino Unido se muestra que, independientemente de la presencia de multimorbilidad, adoptar un estilo de vida más saludable se asocia con hasta 6,3 años más de vida para los hombres y 7,6 años para las mujeres; sin embargo, no todos los factores de riesgo relacionados con el estilo de vida se correlacionan por igual con la esperanza de vida, siendo el tabaquismo significativamente peor que otros[28]. En nuestro trabajo el tabaco no muestra relación con los índices AVI y BAI, no se correlaciona con el incremento de los valores medios de estos índices y, por ello con la adiposidad ligada a obesidad.

Por su parte AVI es una herramienta antropométrica confiable y fácil de calcular para la estimación del volumen abdominal total que se muestra fuertemente relacionado con la intolerancia a la glucosa y la diabetes mellitus tipo 229. Muestra ser, además de una medida indirecta de obesidad abdominal junto con la circunferencia de la cintura, un índice de utilidad predictiva en otras patologías, destacando la relación entre la obesidad y depresión/ansiedad[30].

Nuestros resultados muestran coincidencia en la relación entre AVI y BAI y la obesidad estimada atendiendo al índice de masa corporal y a los parámetros tradicionales de IC, ICA e ICC, especialmente en hombres con BAI y en mujeres con AVI y, por ello se consideran de utilidad en ámbito laboral en prevención primaria y dirigidas a campañas de promoción dela salud implementadas desde las empresas. Estudios previos en ámbito laboral muestran que, la actividad física y la alimentación cardiosaludable mejoran las escalas relacionadas con el sobrepeso y la obesidad[31]y disminuyen el riesgo de síndrome metabólico, fenotipo de cintura hipertrigliceridémica y cintura hipertensiva en la población mediterránea española[32].

La actividad física baja y el sedentarismo y la ingesta excesiva de alimentos afectan la circunferencia de cintura y el IMC en adultos; sin embargo, la relación no está clara. Algunos autores afirman que, con la escasa actividad física, la prevalencia de obesidad se mantiene significativa solo entre los hombres y mejora con la inclusión de la actividad física, pero que se necesitan más estudio que contemplen las diferencias entre hombres y mujeres en cuanto a la forma en que la actividad física, el sedentarismo y el consumo de alimentos se asocian con la obesidad[33]. Se destaca la importancia de considerar conjuntamente la actividad física ocupacional y no ocupacional en los estudios que buscan comprender la asociación entre la actividad física y la adiposidad abdominal[34].

AVI y BAI son herramientas antropométricas confiables y fáciles de calcular, de utilidad en salud laboral considerando que la acumulación excesiva de tejido adiposo intraabdominal denominada obesidad visceral, es parte de un fenotipo que incluye la expansión disfuncional del tejido adiposo subcutáneo y el almacenamiento ectópico de triglicéridos estrechamente relacionados con la agrupación de factores de riesgo cardiometabólicos. En la práctica clínica, junto con la medición de la circunferencia de la cintura además del índice de masa corporal podrían ser de utilidad para la identificación temprana de las personas con mayor riesgo y el manejo posterior de un subgrupo de pacientes con sobrepeso u obesidad y con alto riesgo cardiometabólico[35].

Se considera fortaleza de este trabajo el tamaño de la muestra poblacional estudiada y la precisión que se logra al utilizar índices de adiposidad como el BAI y el AVI, reconocidos por su capacidad predictiva de adiposidad y en obesidad y sus complicaciones posteriores en patologías cardiovasculares y de otro tipo, como el cáncer.

Se considera una limitación de este trabajo la falta de datos para comparar entre diferentes sectores laborales en esta amplia muestra de población. Además, se han excluido las personas menores de 18 y mayores de 66 años. Por ello, se debe tener precaución al interpretar los resultados y aplicarlos a la población general. En resumen, no se puede establecer una relación temporal con este diseño transversal y, sería necesario realizar un estudio prospectivo posterior para evaluar la efectividad de los índices AVI y BAI como herramientas predictivas en diferentes poblaciones laborales y sectores profesionales y, por ello también en población general no laboral.

La patogenia de las enfermedades cardiovasculares asociadas a la obesidad comienza mucho antes de la presentación de un evento cardiovascular y, es por esto que las actuaciones preventivas llevadas a cabo en las empresas son de gran importancia, anticipándose al daño en la salud, lo que constituye uno de los principios básicos en Medicina del Trabajo y en las actuaciones preventivas realizadas en los Servicios de Prevención de Riesgos Laborales y en las Unidades Básicas de Salud.

## Conclusiones

Los índices de adiposidad corporal (BAI) y de volumen abdominal (AVI) muestran diferencias entre hombres y mujeres y aumentan sus valores medios con la edad, situación social y cultural y con los hábitos de vida de la población laboral objeto de estudio: alimentación y actividad física, pero no así con el tabaquismo.

Los valores medios de AVI y BAI aumentan según lo hacen los parámetros de obesidad y son más elevados en ambos sexos según aumenta el ICA, ICC e IMC.

Existe una buena o muy buena correlación entre los índices AVI y BAI y el IMC y con los parámetros de obesidad (perímetro de cintura, índice cintura/altura e índice cintura/cadera).

### Conflicto de intereses

Los autores declaran no tener ningún conflicto de intereses.

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ORIGINAL

# Analysis of studies on disaster management in health with science mapping technique

*Análisis de estudios sobre gestión de desastres en Salud con técnica de mapeo científico*

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## Abstract

***Background:*** Resilience of disaster management is expressed as the ability to meet the needs of the population and to reduce the potential impact of disasters. Particularly, the recent Covid-19 pandemic process all over the world has spoiled all plans and forecasts, once again revealing the necessity and importance of disaster management.
***Methods:*** This research was carried in order to analyze scientific publications on disaster management in the field of health by using science mapping technique. The search engine of the Web of Science database was searched by selecting all publications scanned in the Web of Science Core Collection and database by typing the keywords "disaster management" and "health" with the "topic" option. As a result of the search, 1290 publications indexed between 1977 and April 2023 were reached and analyzed.
***Results:*** According to the results of the analysis, the highest production was made in 2022 with 163 publications; the publication with the highest number of citations with 895 citations was "Telehealth for global emergencies: Implications for coronavirus disease 2019 (Covid-19)".
***Conclusion:*** In addition, it is seen that studies focusing on disaster management in health are increasing day by day, especially with the recent Covid-19 pandemic that has affected the whole world. Especially in this process, it is expected that scientific studies in this field will guide decision makers.

*Key words:* Health Disaster Management, Health Management, Science Mapping Analysis.

## *Resumen*

***Antecedentes:*** La resiliencia de la gestión de desastres se expresa como la capacidad de satisfacer las necesidades de la población y reducir el impacto potencial de los desastres. En particular, el reciente proceso de pandemia de Covid-19 en todo el mundo ha echado a perder todos los planes y pronósticos, revelando una vez más la necesidad e importancia de la gestión de desastres.
***Métodos:*** Esta investigación se llevó a cabo con el fin de analizar las publicaciones científicas sobre la gestión de desastres en el campo de la salud mediante el uso de la técnica de mapeo científico. Se buscó en el motor de búsqueda de la base de datos de Web of Science seleccionando todas las publicaciones escaneadas en la colección principal y la base de datos de Web of Science escribiendo las palabras clave "gestión de desastres" y "salud" con la opción "tema". Como resultado de la búsqueda se alcanzaron y analizaron 1290 publicaciones indexadas entre 1977 y abril de 2023.
***Resultados:*** Según los resultados del análisis, la mayor producción se realizó en 2022 con 163 publicaciones; la publicación con mayor número de citas con 895 citas fue "Telesalud para emergencias globales: implicaciones para la enfermedad por coronavirus 2019 (Covid-19)".
***Conclusión:*** Además, se ve que los estudios enfocados en la gestión de desastres en salud se incrementan día a día, especialmente con la reciente pandemia del Covid-19 que ha afectado a todo el mundo. Especialmente en este proceso, se espera que los estudios científicos en este campo guíen a los tomadores de decisiones.

*Palabras clave:* Gestión de Desastres en Salud, Gestión en Salud, Análisis de Mapeo Científico.

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## Introduction

Disasters are human events that can cause great damage to living and non-living beings in the environment[1]. Disasters usually result in death or damage. The word disaster is of Arabic origin and means great destruction, catastrophe and calamity[2]. There is always a risk of disaster[3] and disasters create anxiety on people. Natural disasters, weather events, epidemics (especially the recent coronavirus pandemic), many dangerous events that people are exposed to are within the scope of disasters[4].

Disasters can be man-made or natural disasters. The damage caused by disasters to the natural, economic and social environment is a fact known by everyone. Against this risk, everyone should be prepared for disasters. This can only be achieved through good disaster management. The concept of disaster management emerges with a holistic and systematic management approach[5,3]. Disaster management is the activity of preparing for and responding to a disaster before it occurs. Disaster management is a form of management that will minimize the consequences.

Disaster management consists of four phases. These stages consist of mitigation, preparedness, response and recovery[6,7]. The mitigation stage consists of actions and strategies created to limit or mitigate the effects of a disaster that may occur. The second stage in the disaster management process is the preparation stage. At this stage, it is the part that includes special capacity and information required for the hazard that will occur by experts or governments. The response phase covers the emergency needs and assistance required during or after the disaster and includes the rescue of the victims. The final phase is recovery, which involves providing the necessary professional support to improve living conditions[6]. Considering the four implementation phases of disaster management, it is considered that the most important component is the risk reduction phase. Because with risk reduction, loss of life and property is minimized and the risks that may be caused by the disaster are identified and reduced before the disaster occurs[8]. Well-planned disaster management plans in a society contribute to raising the awareness of individuals and play an important role in warning societies about how to cope with the consequences of major disasters. Especially in recent times, disasters can be responded to quickly and this has led to a significant decrease in the number of lives lost by reducing the destructive consequences of disasters[9].

One of the prominent sectors in the fight against disasters is the health service sector. As the destructiveness of disasters increases, the demand for health services may increase and the problems that may be experienced accordingly increase. In this context, health institutions are among the critical organizations in terms of disasters. Because these institutions are considered as medical service centers during the disaster process. Therefore, in order to reduce the effects of disasters in an emergency, it is necessary to establish an applicable disaster management process especially for these institutions.

In disaster situations, health systems sometimes fail to perform adequately and therefore systems may be interrupted. Since there will be some problems arising from the demand for medical services in disaster situations, it becomes very important to manage the disaster in these situations10. Many disasters, especially the Covid-19 pandemic in recent years, have caused some disruptions, shortages and changes in health services[11]. Therefore, disaster management is very important especially in health services.

Disaster management process starts with the identification of possible risks that may affect individuals, communities and hospitals and its effects can be reduced by people taking precautions. Inappropriate execution of disaster management processes creates an ineffective and complex chaos environment. Especially hospital disaster management should have a holistic approach that includes not only response processes but also policies and plans that will cover all processes of the disaster[12]. Crowe et al. (2014) stated that disaster management should be sufficiently resilient[13]. This resilience covers the objectives set during the disaster preparedness phase. Resilience of disaster management is expressed as the ability to meet the needs of the population and reduce the potential impact of disasters. Especially the Covid-19 Pandemic process experienced all over the world in the recent period has disrupted all plans and forecasts and once again revealed the need and importance of disaster management.

With Covid 19, great increases have occurred in disaster management studies. To examine these studies, bibliometric analysis has been essential. The science mapping method, which is one of the bibliometric analysis methods, is generally a visual representation of the knowledge and understanding available in a science branch. These maps provide a visual arrangement of the knowledge, concepts, theories, relationships, and methods found in that field. Science maps are used to gain a better understanding of a subject, to discover new relationships and patterns, or to make complex knowledge structures more understandable.

## Methodology

### Aim

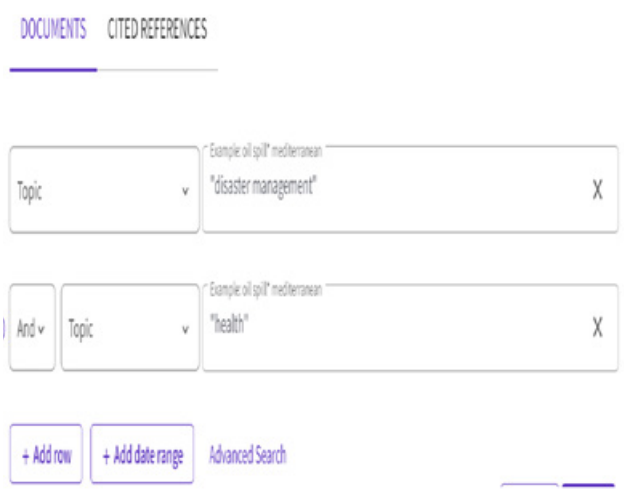
The aim of this research is to examine scientific studies in the field of disaster management in health by using science mapping technique. By using the science mapping technique in the research, it is aimed to better communicate the basic findings of bibliometric

visualization and to better reflect the studies in the literature by providing rich information to the readers.

### Data Analysis

The WoS database was used in the research because it contains many scientific studies and is supported by various indexes. In the research, all studies in the field of disaster management in health were included in the research, regardless of the index (SSCI, SCI, AHCI) in the WoS database. The data obtained in the research were analyzed in terms of various parameters such as citations, authors, countries of publication, keywords, and year of publication. Co-citation analysis was also conducted in this research. In the research, the keywords "disaster management" and "health" were searched in the WoS database by selecting the Web of Science Core Collection and all scanned publications with the "topic" option. Since the analyzes were made on 05.04.2023, works published between 1977-2023 (April) were included in the research. The research is a descriptive survey model. Ethics committee permission was not obtained since the research was not experimental and was not conducted on humans. R-Bibliomterix program was used for scientific mapping in the research. This package program is a bibliometrix package developed using R Studio software. From this perspective, bibliometrix has a powerful function in terms of creating co-citation networks, bibliographic link networks, co-authorship and co-creation networks. Bibliometrix meets the needs of bibliometric analysis with scientific visualization and data analysis[14].

**Figure 1:** Screening strategy of the research.




## Results

In this research, Web of Science (WoS) database was used for bibliometric analysis. In the research, firstly, publications related to the relevant topic were tried to be identified and a search strategy was created. Search strategy for the subject is presented in **figure 1**.

The search strategy of the research is shown in **figure 1**. On 05.04.2023, "disaster management" and "health" keywords were searched from the WOS database by selecting all publications in the Web of Science Core Collection (SSCI, SCI, AHCI, SCI-E, etc.) with the "topic" option. As a result of the search, 1290 publications were reached and these publications were analyzed.

The top 3 most cited studies among the publications obtained by searching the WoS database of publications on disaster management in health are shown in **table I**. When the most cited studies are analyzed, the research by Smith et al. (2020) titled "Telehealth for global emergencies: Implications for coronavirus disease 2019 (Covid-19)" by Smith et al. In this research, the importance of using telehealth to provide care in the Covid-19 pandemic, especially as a way to reduce the risk of cross-contamination caused by close contact, was emphasized. For telehealth to be effective as part of emergency response, it must first become a routine part of the health system. The research also provides basic solutions for the widespread use of telehealth. The second most cited research is "A Social Vulnerability Index for Disaster Management" by Flanagan et al. In the research, it is emphasized that socially vulnerable people are more likely to be negatively affected, less likely to recover and more likely to die in disaster events[12,15,16].

**Figure 2** shows the publication years of the scientific studies published on the subject.

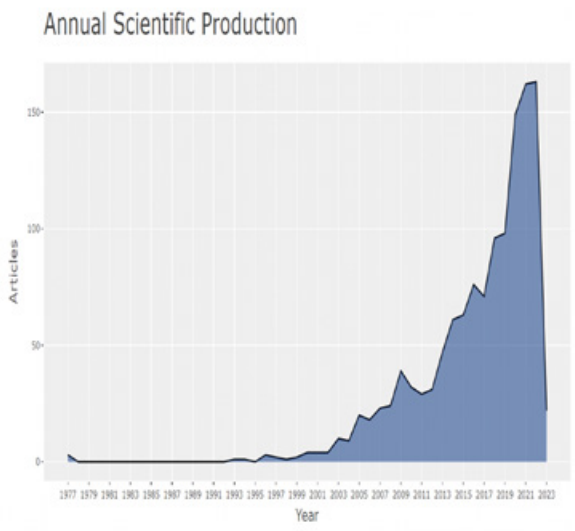
The publication years of related studies on disaster management in health according to years are given in **figure 3**. Accordingly, the highest number of publications was realized in 2022 with 163 publications. This was followed by 2021 with 162 publications. Especially the studies published in 2019 showed an increase of 52%, reaching 149 publications from 98 publications.

The co-occurrence map of plus keywords are presented in **figure 3**.

**Table I:** Information on the most cited publications on disaster management in health.

| Research | Author(s) | Journal | Cite |
|---|---|---|---|
| Telehealth for global emergencies: Implications for coronavirus disease 2019 (Covid-19) | Smith et al., 2020 | Journal Of Telemedicine and Telecare | 895 |
| A Social Vulnerability Index for Disaster Management | Flanagan ve diğerleri, 2011 | Journal Of Homeland Security and Emergency Management | 596 |
| Pandemics, transformations and tourism: be careful what you wish for | Hall ve diğerleri, 2020 | Tourism Geographies | 512 |

**Figure 2:** Publication Years of Scientific Studies on Disaster Management in Health.




When interpreting visual networks, the colors of the clusters indicate how many different themes they are divided into, and the fonts and sizes of the clusters indicate the size of the number of occurrences. When interpreting the relationship between clusters, the distance between two circles is taken as the basis[17]. Keywords are divided into 4 clusters. The red cluster represents the theme "health" and is the most frequently used theme. The purple cluster is "management and emergency", the blue cluster is "disaster management" and the green cluster is "post-disaster trauma".

**Figure 4** shows the co-occurrence map of the words in the titles of the publications.

Looking at the co-occurrence map of the words in the titles of the publications, the words are divided into 5 clusters. The red cluster represents "disaster management" and is the most frequently used theme. Blue cluster represents "health", green cluster represents "pandemic", purple cluster represents "earthquake" and orange cluster represents "risk and assessment".

**Figure 3:** Co-occurrence map of plus keywords.


**Figure 5** shows the co-occurrence map of the words in the abstracts of the studies.

According to **figure 5**, the words are divided into 3 clusters. The blue cluster represents "disaster management" and is the most frequently used theme. The red cluster represents "pre-disaster preparations" and the green cluster represents "pandemic".

**Figure 6** shows the co-occurrence map of the words in the author keywords of the publications. According to this, the words are divided into 3 clusters. The blue cluster represents "Covid-19 and disaster management" and is the most frequently used theme. The red cluster represents "pre-disaster preparations", the green cluster represents "disaster nursing" and the purple cluster represents "disaster education".

Co-citation analysis was conducted in the research and the findings related to the analysis are given below. While creating network visuals in co-citation data, relationships between influential publications are taken as a basis and potentially indicate disciplinary contributions in an interdisciplinary field[18].

**Figure 4:** Co-occurrence map of words in publication titles.

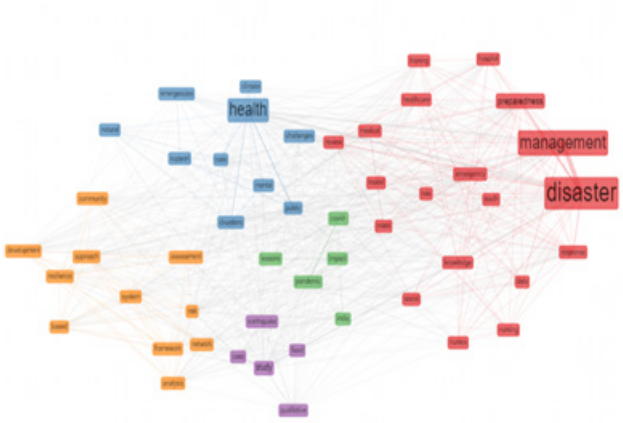



**Figure 5:** Co-occurrence map of words in publication abstract.

The co-citation map of the publications are presented in **figure 7**.

As a result of the relevant analysis, publications were grouped around 9 clusters. The pink cluster is represented by "world health" and is the most frequently used theme. The purple cluster is represented by "al kalaileh, 2012", the aqua green cluster by "subbarao I, 2008" and the orange cluster by "Norris Fh, 2008". While the brown and green clusters are clustered by two publications in a different theme, one publication is clustered in the red, blue and gray clusters.

The co-citation map of the journals are presented in **fig. 8**.

According to the co-citation analysis, the publications are grouped around 3 clusters. The most frequently used red cluster is represented by prehosp disaster med, disaster med public and lancet journals, while the main themes of the cluster are disaster management and public health. The blue cluster is represented by international disaster risk re, disasters and natural hazards journals and the main themes of the cluster are disaster management and governance. The green cluster consists of the least preferred journals and its main themes are disaster management and nursing.

**Figure 6:** Co-occurrence map of author keywords.


**Figure 8:** Co-Citation Analysis of Journals.


**Figure 9** shows the network map of researchers in their own countries and in collaboration network with other countries.

**Figure 9** shows a map of countries' collaboration network. Countries working on different topics are divided into 10 clusters. The blue cluster is represented by "United States of America (USA)", which is the most frequently cooperating country. "Australia" represents the red cluster, "India" the green cluster and "South Africa" the purple cluster. Apart from these, Ethiopia, Czech Republic, Egypt, Greece, Ecuador and Cuba individually represent different clusters. At the same time, the USA (870 publications 4413 citations) Australia (296 publications 2431 citations) has the highest number of publications and citations on health disaster management. This is followed by Iran (222), China (217) and India (217).

Keywords are analyzed under four headings. These are plus keywords, keywords used by the author, keywords in the abstract and words in the title. Plus keywords refer to extra keywords used to further specialize a word[19]. In this research, only author keywords were analyzed.

**Figure 7:** Co-Citation Analysis of Publications.


**Figure 9:** Collaboration Network map of countries.

**Figure 10** shows the thematic map of studies on disaster management in health. Accordingly, it shows how the intensity of the themes changes when moving up and down on a vertical line. As we move upwards, it is seen that the density of themes increases and the frequency of research is high. In the upper right part of the diagram are the themes that have high centrality and intensity and form the foundation of the research area. These themes are the areas that researchers have studied and shown the most interest in. At the same time, these themes have strong links with other thematic areas and form the cornerstones of the research area. The themes in the upper left part are those that have been studied a lot before, but have become less relevant over time and their links with other thematic areas have weakened. This includes topics of research where there is over-specialization and where relationships with other themes are not established or are weak. The themes in the lower left part of the diagram represent emerging or emerging themes. These themes are areas of work that are understudied and have weak links to other thematic areas. Finally, the themes in the lower right part of the diagram represent themes that have not been sufficiently studied, although they are important for the development of the relevant research area[27].

**Figure 11** shows the sections of the thematic map, which are categorized according to centrality and intensity ranking values using two special tools.

Motor themes: The themes in this quadrant are related to developing and structuring the research field. As they offer strong centrality and high intensity, they are treated as motor themes of the field. The motor themes of the author keywords are disaster and disaster preparedness.

They are highly developed and isolated themes: These are strongly related, highly specialized and secondary, but do not have the appropriate back ground or importance for the field. the Very advanced and isolated themes of the author keywords are wireless sensor networks and climate change.

Emerging or declining themes: These themes are relatively weak and have low density and centrality. They mainly represent emerging or disappearing themes. The emerging or declining themes of the author keywords are Covid-19, disasters and climate change.

Fundamental and transformational themes: These themes are relevant to the research area. However, they are not well developed. This quadrant includes transversal and general core themes[20]. The core themes of the author keywords are disasters and disaster management.

**Figure 12** shows the trending topics of studies on disaster management in health. When the author keywords were analyzed, it was seen that the most used topic was "disaster preparedness" in 2019 (57) and public health in 2018 (57). This is followed by earthquake, medical disasters, and resilience. As of 2019, "Covid-19" is also among the most frequently used topics.

**Figure 13** shows the dynamics of author keywords of studies on disaster management in health. According to this, disaster management, which has gained momentum since 2003, has been the most used keyword with a steady increase. This is followed by "Covid-19", which gained momentum rapidly in 2020.

**Figure 10:** Thematic map.


**Figure 11:** Thematic map.

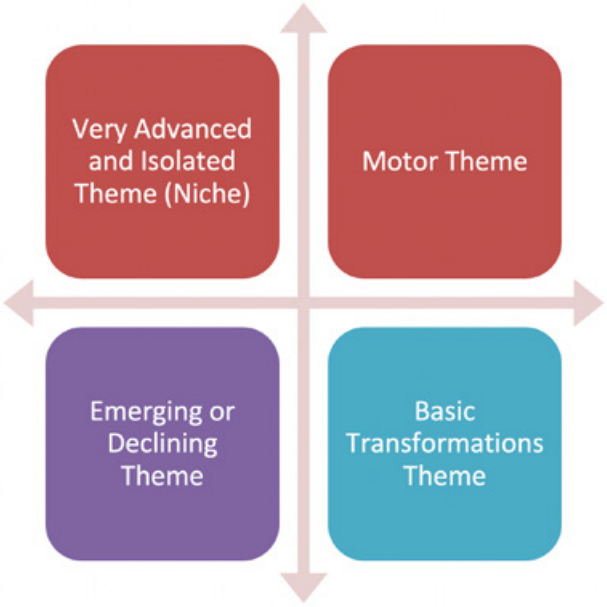
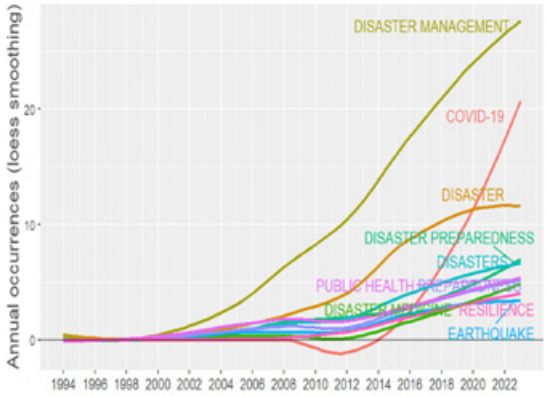


**Figure 12:** Trending topics of publications on disaster management in health.


**Figure 13:** 13 Word dynamics of publications on disaster management in health.




## Discussion

This research reveals the effective aspects of the studies on disaster management in health through science mapping analysis. With science mapping analysis, various information, patterns, relationships and visuals specific to the researched topic can be displayed. In this context, 1290 scientific studies published between 1977 and 2023 (April) on disaster management in health were analyzed. There has been a significant increase in the number of scientific publications in the field of disaster management in health, especially after the 2000s. Especially the year 2022 is the year with the highest number of publications. Interest in disaster management in health has increased significantly after 2019. The most important reason for this is thought to be the Covid-19 that occurred in Wuhan, the capital of China's Hubei region, on November 17, 2019. "aTelehealth for global emergencies: Implications for coronavirus disease 2019 (Covid-19)" is the most cited work with 895 citations.

Results showed that the collaborations between the authors were mostly in the USA and Australia. The fact that studies published by researchers in many different countries are included in the literature draws attention to the importance of disaster management in health.

Authors who want to address the most important areas of disaster management in health can prioritize the motor themes of disasters and disaster preparedness. Authors who want to work on marginal topics; wireless sensor networks and climate change, authors who want to work on current issues; Covid-19, disasters and climate change, and authors who want to work on the most basic areas can conduct studies based on the themes of disasters and disaster management. The concept of disaster management is mostly used with the concept of disaster preparedness and the most frequently used keywords in the publications in the literature are seen to contain the phrase "health". In the results of the co-citation analysis, the concept of "world health" was found to be prominent.

In a study conducted by Palteki et al. (2023), bibliometric analysis of Hospital Disaster Plans between 2002 and 2021 was examined. It was observed that only hospitals were focused on disaster[21]. In another study by Gurpur et al. (2021), a bibliometric analysis of 1649 publications in the Scopus database of studies on the relationship between laws and disaster management was conducted and as a result of the study, it was determined that the publications related to these two concepts were not sufficient[22]. Barnes et al. (2019) conducted a bibliometric analysis of publications containing the themes of "simulation techniques", "natural disasters" and "disaster management" and associated the results with government policy[23]. Jiang et al. (2019) analyzed the visuality of publications on disaster management and tourism crisis using CiteSpace. As a result of the study, it was found that publications in the USA and Australia collaborated better than others[24]. Sweileh (2019) conducted a bibliometric analysis of health-related natural disasters between 1900 and 2017. As a result of the study, based on the information in the literature on natural disasters in health, he determined that this field is growing rapidly, but he argued that research collaborations are insufficient in terms of internationalization[25]. Zhou et al. (2019) analyzed the publications on "medical disaster" in the Wos database and found that there were 564 publications on this subject[26].

It has been seen in the literature review that studies on bibliometric analysis have not been carried out after certain years. In addition, it has been determined that studies on bibliometric analysis are limited to "medical disaster", "disaster management", "natural disaster" and limited bibliometric analysis has been carried out in the field of health.

## Conclusions and limitations

In conclusion, this research is a valuable tool for understanding the scientific productivity and impact of studies in the field of disaster management in

health through science mapping. With the covid 19, the tendency to disaster management in health has increased, however, it has been necessary to examine these studies in depth. This analysis can be used to follow the development of the field, identify popular topics and recognize important researchers. In this research, data on publications related to disaster management in health were scanned in the WOS database and analyzed in this context. Therefore, the use of only one database for analysis constitutes the limitations of the research. For this reason, it is thought that the scope of the research can be expanded by evaluating many studies published through different programs (Citespace, SciMAT) by using different databases. In this context, the sources used in the period when the research was conducted should be carefully selected.

## Competing interests
All authors declare no competing interest.

## Funding
Not applicable

## Authors' contributions
İlknur Arslan Aras performed the data collection and analysis. Gülizar Gülcan Şeremet wrote the introduction, discussion, and conclusion sections and carefully checked the manuscript.

## Ethical Approval
Ethics committee approval is not required because secondary data has been used in the study.

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ORIGINAL

# Association between PAI-1 4G/5G polymorphism and COVID-19 patients with different SARS-CoV-2 variants

*Asociación entre el polimorfismo PAI-1 4G/5G y los pacientes COVID-19 con diferentes variantes de SARS-CoV-2*

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## Abstract

***Introduction:*** Previous studies revealed that plasma PAI-1 level increases during SARS-CoV-2 infection and as a result, the probability of coagulation abnormalities during the course of infection increases. To our knowledge, there is no scientific investigation that evaluates the association between PAI-1 4G/5G polymorphism and SARS-CoV-2 variants of concern.
***Methods:*** Total number of 408 individuals were included in the study (204 control and 204 patients). PAI-1 gene 4G/5G (rs1799889 A>G) polymorphism were genotyped by PCR-RFLP. The Ct values of COVID-19 patients were recorded to analyze the association with PAI-1 4G/5G gene polymorphism and viral load.
***Results:*** The PAI-1 4G/4G, 4G/5G, and 5G/5G genotype frequencies were, 24.5%, 40.2% and 35.3% in cases versus 1%, 2% and 97% in controls, respectively. The 4G allele has significant distribution between Delta variant cases and control, but not for the Omicron variant. The distribution of PAI-1 4G/5G + 4G/4G and 5G/5G genotype frequencies were, 79% and 21% in the Delta variant versus 51% and 49% in the Omicron variant, respectively. Carriers of the 4G allele had higher viral loads and lower Ct values as well.
***Conclusion:*** Ct values in the distribution of PAI-1 4G/5G + 4G/4G and 5G/5G genotype frequencies were, 21 and 25 in the Delta variant versus 26 and 28 in the Omicron variant.

*Key words:* PAI-1, polymorphism, COVID-19, SARSCoV-2 VoCs, coagulation.

## *Resumen*

***Introducción:*** Estudios previos revelaron que el nivel plasmático de PAI-1 aumenta durante la infección por SARS-CoV-2 y, como resultado, aumenta la probabilidad de anomalías de la coagulación durante el curso de la infección. Hasta donde sabemos, no existe ninguna investigación científica que evalúe la asociación entre el polimorfismo 4G/5G del PAI-1 y las variantes preocupantes del SARS-CoV-2.
***Métodos:*** Se incluyó en el estudio a un total de 408 individuos (204 controles y 204 pacientes). El polimorfismo 4G/5G (rs1799889 A>G) del gen PAI-1 se genotipificó mediante PCR-RFLP. Se registraron los valores Ct de los pacientes COVID-19 para analizar la asociación con el polimorfismo 4G/5G del gen PAI-1 y la carga viral.
***Resultados:*** Las frecuencias de los genotipos PAI-1 4G/4G, 4G/5G y 5G/5G fueron, 24,5%, 40,2% y 35,3% en los casos frente a 1%, 2% y 97% en los controles, respectivamente. El alelo 4G tiene una distribución significativa entre los casos de la variante Delta y el control, pero no para la variante Omicron. La distribución de las frecuencias de los genotipos PAI-1 4G/5G + 4G/4G y 5G/5G fueron, respectivamente, 79% y 21% en la variante Delta frente a 51% y 49% en la variante Omicron. Los portadores del alelo 4G también presentaron cargas virales más elevadas y valores Ct más bajos.
***Conclusiones:*** Los valores de Ct en la distribución de frecuencias de genotipos PAI-1 4G/5G + 4G/4G y 5G/5G fueron, 21 y 25 en la variante Delta frente a 26 y 28 en la variante Omicron.

*Palabras clave:* PAI-1, polimorfismo, COVID-19, SARSCoV-2 VoCs, coagulación.

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## Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the RNA virus causing the COVID-19 pandemic, and it has a high mutation rate. So far, five different variants have been deemed variants of concern (VOCs) by the World Health Organization due to increased transmissibility, morbidity and, decreased susceptibility to antiviral drugs and neutralizing antibodies, and ability to evade natural immunity and infect vaccinated individuals[1]. These VOCs are Alpha (B.1.1.7, United Kingdom), Beta (B.1.351 South Africa), Gamma (P.1, Brazil), Delta (B.1.617.2, India), and Omicron (B.1.1.529, South Africa). According to the data which were published by Near East University DESAM Research Institute, the SARS-CoV-2 Omicron variant has been the most rampant variant after Delta variant in Northern Cyprus since the 17th of December 2021 when the first case was seen in Northern Cyprus.

A wide range of symptoms (from mild to severe) was reported for patients with exposure to COVID-19. While most infected individuals have had mild symptoms and recovered without any treatment, some cases were showed a variety of severe phenotypes with multiple symptoms, such as fever, tiredness, cough and loss of taste or smell. Recent published case data suggested that out of all hospitalized patients, 20-30% of them suffer from endothelial injury caused by coagulation and 10% of the hospitalized patients have thrombotic complications[12;14]. Additionally, it is observed that 79% of the patients who have died from COVID-19 developed pulmonary artery thrombosis with coagulation and thrombosis being the main forces behind endothelial cell injury[2;17].

The mechanism of infect to humans of SARS-CoV-2; it binds the host cellular angiotensin-converting enzyme-2 (ACE2) receptor, which the virus has strong binding affinity, and entries the host cell, and replicate its viral genome[2;21]. ACE2 is an angiotensin-converting enzyme, and the virus halts the production of angiotensin when it binds to the ACE2 receptor. Without angiotensin, antithrombotic and anti-inflammatory activities in the endothelial cells decrease, thus coagulation and thrombosis could be observed in some of the hospitalized COVID-19 patients[2]. In hospitalized COVID-19 patients, coagulation markers are regularly observed and antithrombotic drugs such as Clexane or Enoxaparin are administered if the need arises[9]. Thrombosis and coagulation are also symptoms of a weakened fibrinolytic activity, and it can be described as the result of multiple plasminogen inhibitors' interaction with multiple plasminogen activators[3;7]. Transformation of plasmin into plasminogen is achieved by plasminogen activators[8]. Plasminogen is mainly synthesized by the liver and can be found in the plasma and its activation from plasmin is mediated by tissue-type (t-PA) and urokinase-type (u-PA) plasminogen activators. Both mentioned activators are tightly regulated by plasminogen activator inhibitors (PAIs), but the main inhibitor of fibrinolysis is *PAI-1*[6]. Increased *in vivo* expression of PAI-1 decreases the fibrinolytic activity and decreased fibrinolytic activity could lead to thrombosis and coagulation in COVID-19 infected hospitalized patients[7]. Furthermore, higher plasma levels of PAI-1 also are linked with increased clot lysis time and it could be an indicator of COVID-19 severity in hospitalized patients in order to prevent poor end results[4;10;22].

The 4G/5G polymorphism is the single guanosine insertion/deletion variation (5G or 4G) in the PAI-1 gene promoter region, situated 675 base pairs upstream from the transcriptional start site. And the transcription factors have access to a supplemental binding site in the 5G allele, while is absent in the 4G allele[18]. Furthermore, plasma PAI-1 levels are genetically determined to a certain degree[7]. A study in Western populations showed that, 5G homozygotes have the lowest PAI-1 concentrations, while 4G homozygotes have the highest PAI-1 concentrations[7]. A recent study showed that a link between PAI-1 4G/5G polymorphism and COVID-19 and they reported that 4G homozygote patients have the highest plasma PAI-1 concentrations followed by 4G/5G heterozygotes and the least amount of plasma concentration was found in patients with 5G homozygote also the polymorphism associated with severity of the disease[19]. Abdullaev and colleagues also support previous findings, and they have observed that of all COVID-19 patients identified with PAI-1 4G/5G polymorphism have showed thrombotic events[1]. The postmortem examinations have also done in the same study and they revealed that the thrombotic events were mainly raised from pulmonary artery thrombosis or pulmonary embolism with deep vein thrombosis[1]. In addition, the ratio of women who have suffered from pulmonary embolism was twice as much compared to men[1].

Furthermore, Behling et al. have reported a four-day-old fetal autopsy that has shown signs of placental injury caused by coagulation alteration due to fetal SARS-CoV-2 infection, which the mother who had infected in the last trimester of pregnancy and she had homozygote in the 4G allele[11]. They conclude that SARS-CoV-2 passed the placental barrier from the mother who is carried the *PAI-1* 4G/5G polymorphism to infect the fetus and the polymorphism could increase the damage of the SARS-CoV-2 infection[11].

Even though there have been a few studies about the interaction between the *PAI-1* 4G/5G polymorphism and SARS-CoV-2, the effects of different SARS-CoV-2 variants of concern on the individuals with this polymorphism have yet to be researched. Thus, this study aimed to investigate the association between SARS-COV-2 Delta and Omicron (B.1) variants, viral loads and the *PAI-1* 4G/5G polymorphism.

## Materials and methods

***Sample Collection:*** A total number of 408 individuals who admitted to Near East University Hospital COVID-19

PCR Diagnosis Laboratory for routine SARS-CoV-2 RT-PCR test were used in this study. The control group consisted of 204 individuals who were SARS-CoV-2 RT-qPCR negative. On the other hand, the case group consisted of 204 patients whom 100 of them were SARS-CoV-2 RT-qPCR positive, infected with SARS-CoV-2 Delta variant and 104 of them were SARS-CoV-2 RT-qPCR positive, infected with SARS-CoV-2 Omicron (BA.1) variant.

***Detection of SARS-CoV-2 and identification of VoCs:*** The 204 patients, who detected of SARS-CoV-2 with Real-Time Polymerase Chain Reaction (RT-qPCR) approach using UNIPLEX SARS-CoV-2 RT-qPCR Detection Kit (Nicosia, Northern Cyprus), included to variants identification analysis by the use of the Multiplex SARS-CoV-2 VoC RT-qPCR detection kit (Nicosia, Northern Cyprus). The samples were analyzed for H69-70 deletion, N501Y, K417N, T478K, Y144del, and P681R mutations for segregation of the VoCs of SARS-CoV-2 between Delta (B.1.617.2) and Omicron (BA.1).

The segregation was done as follow:

- Delta variant: the sample was negative for the mutation H69-70 deletion, N501Y, K417N, Y144del mutations and positive for the Spike T478K and P681R mutations.
- Omicron variant: the sample was negative for the P681R mutation and positive for the H69-70 deletion, N501Y, T478K, K417N, and Y144del mutations.

The whole-genome sequencing analysis was done for confirmations of the VoCs denotations of samples (GISAID reference numbers EPI_ISL_12574367, EPI_ISL_12574374, EPI_ISL_12574370, EPI_ISL_12574375,EPI_ISL_12574368,EPI_ISL_12574373, EPI_ISL_12574369, EPI_ISL_12574371, EPI_ISL_12574372, EPI_ISL_12574000).

***PAI-1 4G/5G Gene Polymorphism Genotyping:*** The human genomic DNA was extracted from volunteered SARS-CoV-2 RT-qPCR positive and negative (control) cases using Uniplex RT-qPCR SARS-CoV-2 RT-qPCR Detection Kit (IKAS Medical, Nicosia, Northern Cyprus). *PAI-1* gene polymorphism (rs1799889 A>G) was genotyped by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Genotypes were determined according to the presence and absence of the restriction sites that were analyzed and alleles were designated with respect to actual base change according to the Ensemble (http://www.ensembl.org/) genome browser and NCBI SNP database (https://www.ncbi.nlm.nih.gov/SNP/, dbSNP).

***Viral load calculation:*** The cycle threshold (Ct), that is defined the value of the first PCR cycle detected of the viral RNA amplification, is negatively correlated with the viral load. The Ct value of the viral amplification provides to assess semi-quantitatively of the viral load in the host.

Low Ct value represents high level of viral load and high Ct value represents low level of viral load in the host[16;20]. The viral load was grouped according to Ct value as follows:

- 20>Ct value>30 was defined high viral load
- 30>Ct value>35 was defined as low viral load.

***Statistical Analysis:*** Data statistics was done by utilizing SPSS software (Statistical Package for the Social Sciences, SPSS Inc, Chicago, IL, USA, and version 25). Descriptive data and genotype data of the study group were expressed as mean ± standard deviation (SD) or number and frequency, where applicable. Normal and non-normal distributed quantitative variables were differentiated with Student's t-test and Mann–Whitney U test between two groups, respectively. The genotype and allelic frequency distributions of PAI-1 675 4G/5G polymorphisms between the study groups were compared using Chi square ($\chi^2$). Pearson's chi-square test or the Fisher's exact test were used to verify the association of the categorical variables between study groups, when the conditions for using the chi-square test were not verified. Hardy-Weinberg equilibrium (HWE) was assessed by Fischer's exact test. OR and 95 % CI were estimated by binary logistic regression analysis adopting codominant, dominant, recessive and additive inheritance models. Akaike's information criterion (ACI) was utilized in the selection of the most suitable inheritance model for the data available. To assess the differences between groups, the data were log transformed to meet ANOVA criteria and then subjected to one-way ANOVA with Tukey's post-hoc analysis. Relative risks were assessed of PAI-1 675 4G/5G polymorphism in COVID-19 Delta and Omicron (BA.1) variant patients by calculating odds ratios (ORs) and 95% confidence intervals (CIs) that were considered separate outcomes. In all cases differences were considered significant at $p < 0.05$.

## Results

### General characteristics of the study group

The study group includes 204 COVID-19 patients (100 patients who are infected by the SARS-CoV-2 Delta variant and 104 patients who are infected by the SARS-CoV-2 Omicron (BA.1) variant) and 204 non-infected patients as a control group. The mean age of COVID-19 patient's ± SD was 48.49±11.54 and control group 47.24±12.34 (p=0.290). The gender distribution of the patients' group is 114 (55.9%) female and 90 (44.1%) male for control group 94 (46.1%) female and 110 (53.9%) (p=0.060).

### Allelic and genotypic distribution frequency of PAI-1 -675 4G/5G polymorphism in study group.

The genotypic and allelic frequency distributions of PAI-

1 -675 4G/5G polymorphism in COVID-19 patients who are infected by the SARS-CoV-2 Delta and Omicron BA.1variants and the control group are presented in **table I**.

Notable differences were observed in genotype frequencies of *PAI-1* -675 4G/5G polymorphism between SARS-CoV-2 patients and control group (***p=0.001***).

Furthermore, the risk allele of *PAI-1* -675 4G/5G polymorphism was found to be statistically significant (OR=39.05, 95% CI=/18.88-80.78, ***p=0.001***) in SARS-CoV-2 Delta and Omicron BA.1 variants infected patients compared to controls (**Table I**).

The study group includes 204 COVID-19 patients who are infected by the SARS-CoV-2 Delta and Omicron BA.1 variants and 204 non-infected patients as a control group. OR: Odds Ratio, CI: Confidence Interval. $\chi^2$ and HWE tests were used to compare the genotypic and allelic frequency distributions of polymorphisms between the groups. In all cases, differences were considered significant at $p < 0.05$.

Mutation analysis of *PAI-1 -675 4G/5G* polymorphism showed that 64.7% of SARS-CoV-2 positive patients (case group) were carried at least one mutant allele (homozygous or heterozygous), while the control group has consisted of 3% were carried mutation at least one allele. The differences in the distribution of the PAI-1 6754G/5G polymorphism between the two groups were statistically significant (OR=0.17, 95% CI=0.07-0.4, ***p=0.001***) (**Figure 1**).

## The distribution of PAI-1 6754G/5G polymorphism in the patients with SARS-CoV-2 Delta and Omicron BA.1 variants

Furthermore, we also investigated of the distribution of PAI-1 6754G/5G polymorphism in SARS-CoV-2 patients who were infected with Delta and Omicron BA.1 variants. We observed that 21% of SARS-CoV-2 Delta variant infected patients had the 5G/5G (wild type) genotype, while 79% of SARS-CoV-2 Delta variant infected patients carried at least one mutant allele (homozygous or heterozygous). However, the 5G/5G genotype was more prevalent in the SARS-CoV-2 patients who were infected with Omicron BA.1 variant (49%), and the frequency of the mutant genotypes (homozygous or heterozygous) was lower (51%) compared to the patients infected with SARS-CoV-2 Delta variant group (OR=3.62, 95% CI=1.95-6.70, ***p=0.001***) (**Figure 2**).

## Analysis of PAI-1 675 4G/5G polymorphism based on the four genetic inheritance models in the patients with SARS-CoV-2 Delta and Omicron BA.1 variants

The genotype frequencies were analyzed by four genetic models: additive, co-dominant, dominant, and recessive models in COVID-19 cases. The PAI-1 -675 4G/5G

**Table I:** The genotypic and allelic frequency distributions of PAI-1 -675 4G/5G SNP in the study group.

| SNP | Genotypic Frequencies n (%) | | | Allelic Frequencies | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Genotype | Cases (n=204) | Control (n=204) | P-Value | Allele | Cases (n=204) | Control (n=204) | $\chi^2$ | OR/CI(95%) | P-Value |
| PAI-1 675-4G/5G | | | | | | | | | |
| 5G/5G<br>4G/5G<br>4G/4G | 72(35.3)<br>82(40.2)<br>50(24.5) | 192(97)<br>4(2)<br>2(1) | ***0.001*** | 4G/5G | 0.55/0.45 | 0.98/0.02 | 201.96 | 39.05/18.88-80.78 | ***0.001*** |

**Figure 1:** *PAI-1 675 4G/5G* polymorphism genotype distribution. 5G/5G (Wild Type), 4G/5G (Heterozygote), 4G/4G (Homozygote).

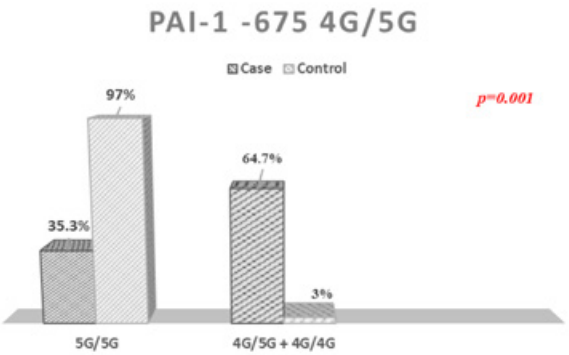
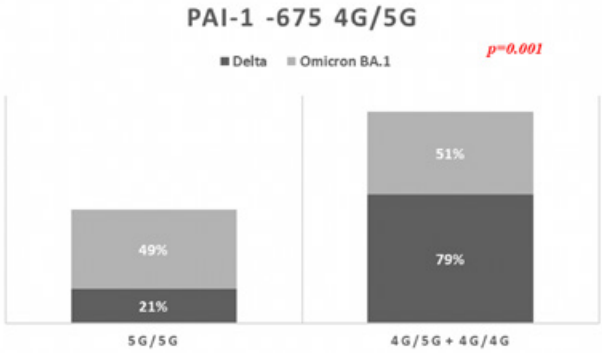



**Figure 2:** The distribution of PAI-1 6754G/5G polymorphism in the patients with SARS-CoV-2 Delta and Omicron BA.1 variants. *PAI-1* polymorphism genotype distribution 5G/5G (Wild Type), 4G/5G (Heterozygote), 4G/4G (Homozygote).



polymorphism, a significant association between this polymorphism and increased risk of SARS-CoV-2 Delta variant compared to Omicron BA.1 variants cases, and the analysis showed that in all four models, co-dominant genotype (5G/5G) vs (4G/4G) (OR=2.85, 95% CI.=1.34-6.05, p=0.005); co-dominant genotype (4G/4G) vs (5G/5G) (OR=0.35, 95% CI.=0.16-0.74, ***p=0.005***); dominant (OR=3.62, 95% CI.=1.95-6.70, ***p=0.001***); recessive (OR=0.76, 95% CI.=0.40-1.45, ***p=0.417***); additive (OR=0.57, 95% CI=0.11-1.66, ***p=0.002***) (**Table II**).

### Associations of the PAI-1 6754G/5G polymorphism and viral load of SARS-CoV-2

To better understand the relationship between *PAI-1 -675 4G/5G* polymorphism and severity of COVID-19, we next evaluated the potential effects of *PAI-1 -675 4G/5G* polymorphism on the viral load of SARSCoV-2. We observed that heterozygote (4G/5G) and homozygote (4G/4G) genotypes carriers of *PAI-1 -675 4G/5G* polymorphism had high viral load in SARS-CoV-2 patients compared to wild type carriers (5G/5G) (*p=0.001*, respectively) (**Figure 3A**).

Also, the low Ct value that means high viral load was found in SARS-CoV-2 Delta and Omicron (BA.1) variants infected patients carried at least one mutant allele carriers (homozygous and heterozygous; 4G/5G+4G/4G) of *PAI-1 -675 4G/5G* polymorphism compared to wild type carriers (5G/5G) (*p=0.001* and *p=0.001*, respectively) (**Figure 3B** and **figure 3C**).

## Discussion

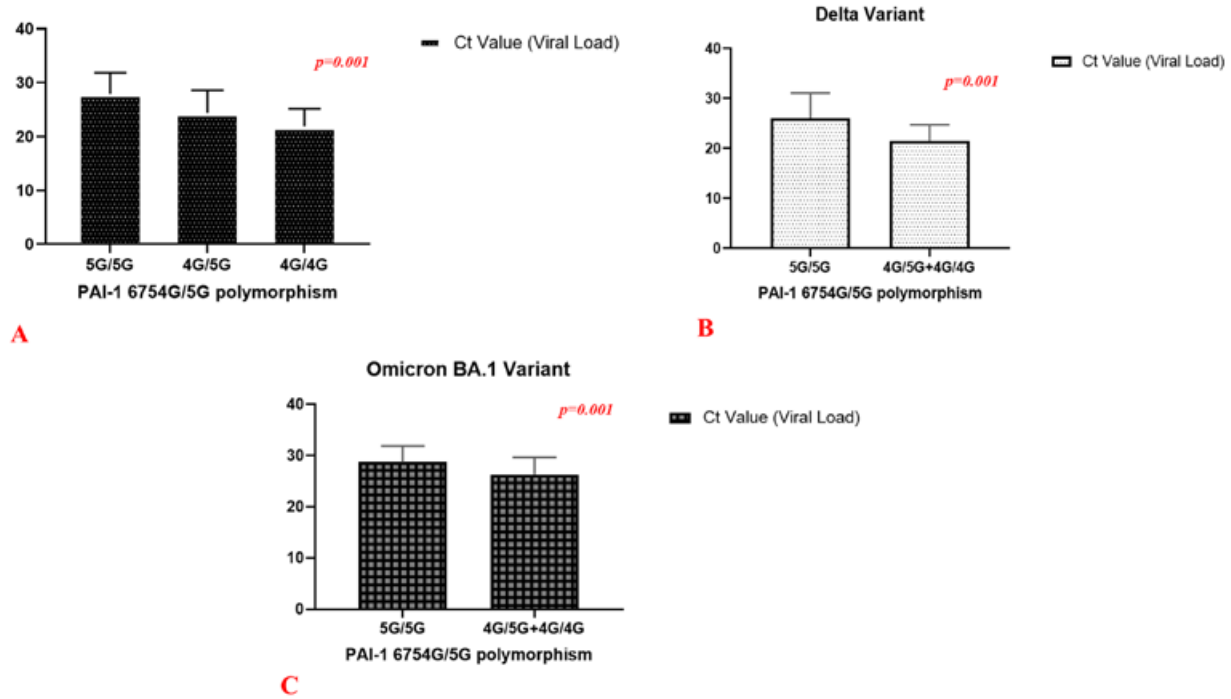
In our study, we have found that the COVID-19 patients who have the 4G allele of the *PAI-1 4G/5G* polymorphism were mainly infected with the Delta variant of the SARS-CoV-2 compared to the Omicron (BA.1) variant.

**Table II:** Analysis of SNPs based on the four genetic inheritance models.

| SNP | Model of Inheritance | OR (95 % CI) | p-Value | AIC[a] |
|---|---|---|---|---|
| PAI-1 -675 4G/5G | **Co-dominant**<br>5G/5G vs 4G/4G<br>4G/4G vs 5G/5G | <br>2.85 (1.34-6.05)<br>0.35 (0.16-0.74) | <br>0.005<br>0.005 | - |
| | **Dominant**<br>5G/5G vs 4G/5G+4G/4G | 3.62 (1.95-6.70) | 0.001 | 13.15 |
| | **Recessive**<br>4G/4G vs 4G/5G +5G/5G | 0.76 (0.40-1.45) | 0.417 | 15.39 |
| | **Additive**<br>4G/4G vs 4G/5G vs 5G/5G | 0.57 (0.11-1.66) | 0.002 | 16.32 |

The AIC: the preferred inheritance model is the one with the minimum AIC value. OR; Odds ratio, CI; Confidence interval, AIC; Akaike's information criterion. p-value≤0.05 considered statistically significant. p-values in bold remained significant after Bonferroni correction.

**Figures 3 A, B, C:**



Our study associated how many COVID-19 patients have which type of polymorphism with respect to whether they are infected with the Delta or the Omicron variant. One observation we made is that 4G homozygous and 4G/5G heterozygous individuals contracted the Delta variant more and 5G homozygous people contracted the Omicron variant more. A study which was done before the emergence of the Omicron and at the time when the Delta variant was the most dominant strain on the planet reported that COVID-19 patients with the 4G allele make up the most populated patient group of them all; a result that is in line with our findings[19].

These finding weren't the first time that *PAI-1 4G/5G* polymorphism has been correlated with a susceptibility increasing effect on certain diseases. Although the disease in question wasn't COVID-19, a study has found out that individuals who have the *PAI-1 4G/5G* polymorphism are more susceptible to T2DM which further supports our findings and the possibility of PAI-1 4G/5G polymorphism makes people vulnerable to COVID-19[15].

Two separate studies have associated the 4G allele with the thrombotic complications caused by coagulation alterations in severe COVID-19 patients and their findings supports ours in which the 4G allele could be used as an indicator of a unexpectedly more severe course of SARS-CoV-2 infection; especially if the patient was infected with the Delta variant of concern[1;11].

If a COVID-19 patient is infected by the Delta variant of SARS-COV-2, then the infection fares more severe compared to a COVID-19 infection caused by the Omicron (BA.1) variant. In terms of Delta variant caused COVID-19, our findings have shown that 4G homozygous patients show the lowest Ct values followed by heterozygote and 5G homozygote patients respectively. A recent study have shown the correlation between lower Ct values with increased chance of worse outcomes and this association further strengthens the idea of that the people who have the 4G allele are more susceptible to COVID-19 infection as well as the course of infection is more severe that those who are 5G homozygous[5]. Thus, both the viral load and the variant of infection could be utilized as an COVID-19 severity indicator.

## Conclusion

Our study has found a significant association between the 4G allele of *PAI-1 4G/5G* polymorphism and increased susceptibility to the Delta variant of SARS-CoV-2 whereas, the same association wasn't found with the Omicron variant. Our findings revealed a similar pattern in patients' Ct values as well. Patients who have the 4G allele show lower Ct values, meaning more severe infections, if they were infected by the Delta variant of concern rather than the Omicron (BA.1) variant. Thus, the 4G allele of this polymorphism has potential to be a predictor of infection severity in COVID-19 Delta variant infections.

### Ethical approval

All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (Approval number: YDU/2022/99-1486).

### Conflict of Interest

The authors do not have any conflict of interest to declare.

### Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

### Author Contribution

Conceived and designed the analysis: E.M., G.A., M.C.E.; Collected the data: E.M., G.A., A.T., G.T., E.U.E., H.E., K.S., M.C.E; Contributed data or analysis tools: E.M., G.A., A.T., G.T., E.U.E., H.E., K.S., M.C.E ; Performed the analysis: E.M., A.T.; Wrote the paper: E.M., G.A., M.C.E.; revised the paper: E.M., G.A., A.T., G.T., E.U.E., H.E., K.S., T.S., M.C.E; supervised the project: M.C.E

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ORIGINAL

# Refugee and suicide risk in Turkey: A single center cross-sectional study

*Refugiados y riesgo de suicidio en Turquía: un estudio transversal de un solo centro*

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## Abstract

***Objective:*** This article aims to examine the relationship between the psychiatric health status of refugees in Turkey and the Human Development Index (HDI) levels of the countries from which they originate.
***Materials and methods:*** This cross-sectional observational study was conducted to investigate potential correlations between suicide rates and demographic characteristics, diagnostic categories, alcohol/substance abuse, and HDI among individuals in Turkey.
***Results:*** In this study, 121 participants (mean age of 32.7 years, 52% male) with diagnoses of bipolar disorder (38%), psychotic disorders (43%), and depression (19%) were examined. Alcohol and substance abuse were present in 23% and 26% of participants, respectively. However, no significant demographic differences were found between those who had attempted suicide and those who hadn't. The only exception was the distribution of diagnoses (p=0.034). The depression group had the highest suicide rate (47.8%), followed by the bipolar group (26.09%), and the psychotic group (17.3%). A significant difference in substance abuse rates was found across diagnostic groups, with the depression group reporting the lowest rate. Despite these findings, regression analysis did not detect significant predictors of suicide attempts (p>0.05).
***Conclusions:*** This study underscores suicide risk factors among immigrants, emphasizing the need for comprehensive research and suicide prevention strategies targeting diverse populations.

*Key words:* Refugee, alcohol abuse, substance abuse, suicide risk.

## *Resumen*

***Objetivo:*** Este artículo pretende examinar la relación entre el estado de salud psiquiátrica de los refugiados en Turquía y los niveles del Índice de Desarrollo Humano (IDH) de los países de los que proceden.
***Materiales y métodos:*** Este estudio observacional transversal se llevó a cabo para investigar las posibles correlaciones entre las tasas de suicidio y las características demográficas, las categorías de diagnóstico, el abuso de alcohol/sustancias y el IDH entre los individuos en Turquía.
***Resultados:*** En este estudio se examinaron a 121 participantes (edad media de 32,7 años, 52% varones) con diagnósticos de trastorno bipolar (38%), trastornos psicóticos (43%) y depresión (19%). El alcohol y el abuso de sustancias estaban presentes en el 23% y el 26% de los participantes, respectivamente. Sin embargo, no se encontraron diferencias demográficas significativas entre los que habían intentado suicidarse y los que no. La única excepción fue la distribución de los diagnósticos (p=0,034). El grupo con depresión tuvo la tasa de suicidio más alta (47,8%), seguido del grupo bipolar (26,09%) y el grupo psicótico (17,3%). Se encontró una diferencia significativa en las tasas de abuso de sustancias entre los grupos de diagnóstico, siendo el grupo de depresión el que registró la tasa más baja. A pesar de estos hallazgos, el análisis de regresión no detectó predictores significativos de intentos de suicidio (p>0,05).
***Conclusiones:*** Este estudio subraya los factores de riesgo de suicidio entre los inmigrantes, enfatizando la necesidad de una investigación exhaustiva y de estrategias de prevención del suicidio dirigidas a poblaciones diversas.

*Palabras clave:* Refugiado, abuso de alcohol, abuso de sustancias, riesgo de suicidio.

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## Introduction

In 2021 globally, a staggering 89.3 million people have been forcibly displaced, with 6.8 million of them being refugees from the Syrian Arab Republic. Türkiye was the largest refugee-hosting country in the world in 2021, with nearly 3.8 million seeking refuge there[1].

Stateless individuals frequently face significant obstacles in accessing critical services like education or healthcare, formal employment, and the freedom to travel[1]. Research has indicated that displaced persons generally experience a lower quality of life than the residents of the countries where they seek asylum. However, there are numerous variables that can impact the quality of life of asylum seekers and refugees, either positively or negatively. Factors such as low socio-economic status, limited education, trauma, intense mental stress, adverse life events after migration, lengthy refugee status procedures, psychopathology, and aging can all contribute to a poor quality of life[2]. Refugees frequently struggle to have their basic needs met, including security, food, housing, and other social requirements. Health security is a significant challenge for refugees in transit from war-torn low-income countries to those with little social and economic development. The millions of Syrian refugees in Turkey, Lebanon, and Jordan have posed extreme challenges to their health and social care systems[3].

Refugees are particularly vulnerable to experiencing mental health problems[4]. Due to the traumas they have experienced, the challenging travel conditions, and the difficulties they face during the adaptation process, refugees may be more prone to emotional disorders, anxiety disorders, and post-traumatic stress disorder. The purpose of this study is to examine the relationship between the Human Development Index (HDI) of the country of origin and psychiatric disorders in refugees in Turkey. In this context, the prevalence of psychiatric disorders among refugees from countries with different HDI levels will be compared, and the underlying reasons for this relationship will be determined[5,6].

It is known that the traumas and stresses experienced by refugees can lead to psychiatric disorders. However, the depth and scope of this problem may vary depending on the HDI levels of the countries from which the refugees originate. HDI is a comprehensive indicator evaluated based on factors such as life expectancy, education level, and per capita income of a country. This indicator reflects a country's overall quality of life and the living conditions of its citizens. Therefore, it can be thought that HDI may have a decisive impact on the psychiatric health status of refugees[7].

This article aims to examine the relationship between the psychiatric health status of refugees in Turkey and the HDI levels of the countries from which they originate. This topic has not been adequately addressed in the current literature, and this study aims to fill this gap. This study aims to provide important results and recommendations for the creation and implementation of policies and interventions for the psychiatric health of refugees.

## Material and methods

### Participants and groups

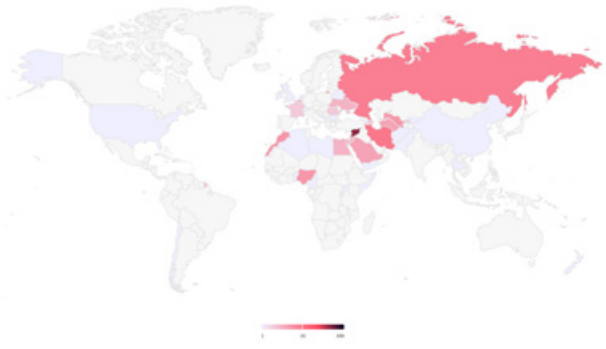
This study included 121 foreign patients who were hospitalized at Başakşehir Çam and Sakura City Hospital. This cross-sectional observational study was conducted to investigate potential correlations between suicide rates and demographic characteristics, diagnostic categories, alcohol/substance abuse, and Human Development Index (HDI) among individuals in Turkey. The demographic data collected included age, gender, marital status, and employment status. Clinical data included diagnosis, alcohol abuse status, substance abuse status, and duration of stay in Turkey. The Human Development Index (HDI) of each participant was also recorded. Participants were further divided into two groups: those who had attempted suicide (Suicide group) and those who had not (No-suicide group). The data was analyzed separately for these two groups and compared to identify any significant differences.

### Measurements

The HDI indices, hospitalization rates, diagnoses, and alcohol and substance use rates of the participants were recorded in this study. The HDI indices were calculated using data published by the United Nations Development Programme in 2019 (United Nations Development Programme, 2019). The number of hospitalizations, diagnoses and substance-alcohol use were obtained from the hospital records of the participants.

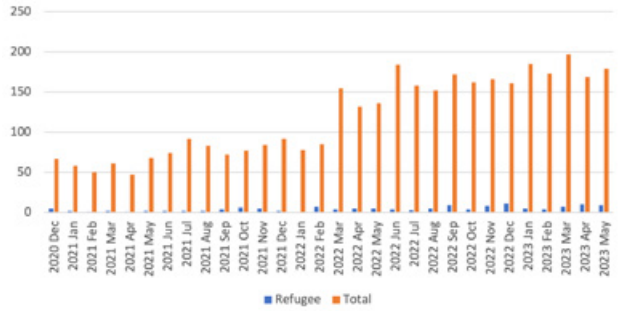
121 of the 3554 patients admitted to our hospital in the last 2 years (December 2020-May 2023) and admitted to our hospital were foreign nationals (**Figure 1**).

**Figure 1:** Country of origin.



The density distribution of these foreign nationals hospitalized according to the countries is schematized in **figure 2**.

**Figure 2:** Incidence of refugee and total admission.




### Inclusion criteria

Our study included patients aged 18 years and older who were hospitalized in the psychiatry clinic of Başakşehir Çam and Sakura Training Hospital, and patients whose file records and data were sufficient and regular in retrospective scanning.

### Exclusion criteria

Patients with insufficient and irregular patient records and data in the retrospective scan were excluded from the study. In addition, patients under the age of 18 and outpatients were not included in the study.

### Ethical approval

The ethics committee of this study was obtained from the ethics committee of Başakşehir Çam and Sakura Training Hospital.

### Limitations

- This study is limited to foreign patients who were hospitalized at Başakşehir Çam and Sakura City Hospital. Therefore, the generalizability of the results may be limited.
- The data used in this study was obtained from the participants' hospital records. Thus, there is a possibility of incomplete or inaccurate data.
- This study only considered specific factors, such as HDI indices, hospitalization rates, diagnoses, and alcohol and substance use rates. The exclusion of other factors or variables may limit the conclusions that can be drawn from the results.
- This study only conducted statistical analyses. Therefore, individual stories and experiences were not analyzed, and the conclusions are based solely on the researchers' interpretations.

### Statistical analysis

The data analysis was conducted using SPSS statistical software. Firstly, a bivariate correlation analysis was performed to determine the relationship between HDI indices, hospitalization rates, diagnoses, and alcohol and substance use rates. Then, participants were divided into low, medium, and high HDI categories, and an ANOVA analysis was conducted to determine the differences in hospitalization rates, diagnoses, and alcohol and substance use rates among these categories.

## Results

The analysis includes a total of 121 participants with a mean age of 32.7±12.5 years. Approximately 52% (n=63) of the participants were male. Regarding marital status, 45% (n=54) were single, 27% (n=33) were married, and 11% (n=13) were divorced. In the context of employment status, 19% (n=23) of the participants were working, and 43% (n=52) were not working. In terms of diagnosis, 38% (n=46) have been diagnosed with bipolar disorder, 43% (n=52) with psychotic disorders, and 19% (n=23) with depression. The data showed that 23% (n=28) of the participants had alcohol abuse issues, 60% (n=72) do not, and 17% (n=21). With respect to substance abuse, 26% (n=31) of the participants have issues with substance abuse, and 59% (n=71) do not. The average HDI for the sample was 697±35, and the average length of stay (LOS) in Turkey was 5.5±3.4 days (**Table I**).

**Table I:** Patients demographics.

| | N or mean | % or SD |
|---|---|---|
| **Age (year)*** | 32,70 | 12,50 |
| **Gender (M)** | 63,00 | 52,00% |
| **Marital status** | | |
| Single | 54,00 | 45,00% |
| Married | 33,00 | 27,00% |
| Divorced | 13,00 | 11,00% |
| NA | 21,00 | 17,40% |
| **Employment status** | | |
| Working | 23,00 | 19,00% |
| Not-working | 52,00 | 43,00% |
| NA | 46,00 | 38,00% |
| **Diagnosis** | | |
| Bipolar disorder | 46,00 | 38,00% |
| Psychotic disorders | 52,00 | 43,00% |
| Depression | 23,00 | 19,00% |
| **Alcohol abuse** | | |
| Yes | 28,00 | 23,00% |
| No | 72,00 | 60,00% |
| NA | 21,00 | 17,00% |
| **Substance abuse** | | |
| Yes | 31,00 | 26,00% |
| No | 71,00 | 59,00% |
| NA | 19,00 | 15,00% |
| **HDI*** | 697,40 | 135,10 |
| **Live in Turkey (year)*** | 5,50 | 3,40 |
| **LOS** | 21,80 | 15,10 |
| **Suicide** | | |
| Yes | 32,00 | 26,00% |
| No | 69,00 | 57,00% |
| NA | 20,00 | 17,00% |

*Mean, SD; LOS: Lenght of Stay, NA: Not available, HDI: Human developmental index

The mean age for the Suicide group was 32±13.1 while the No-suicide group had a mean age of 33.5±12.8 (p=0.590). Gender differences between the groups were not significant (p=0.336). There was

**Table II:** Comparison in terms of suicide attempt.

| | Suicide (n=32) | | No-suicide (n=69) | | p-value |
|---|---|---|---|---|---|
| | N or mean | % or SD | N or mean | % or SD | |
| **Age (year)*** | 32 | 13.1 | 33,50 | 12,8 | 0.590 |
| **Gender** | | | | | 0.336 |
| **Male** | 16 | 50% | 36,00 | 52,17% | |
| **Female** | 15 | 46.9% | 33,00 | 47,83% | |
| **Trans** | 1 | 3.1% | 0,00 | 0,00% | |
| **Marital status** | | | | | 0.564 |
| **Single** | 9 | 28.1% | 20,00 | 28,99% | |
| **Married** | 12 | 37.5% | 33,00 | 47,83% | |
| **Divorced** | 4 | 12.5% | 5,00 | 7,25% | |
| **Employment status** | | | | | 0.662 |
| **Working** | 5 | 15.6% | 14,00 | 20,29% | |
| **Not-working** | 14 | 43.7% | 30,00 | 43,48% | |
| **Diagnosis** | | | | | 0.034 |
| **Bipolar disorder** | 12 | 37.5% | 24,00 | 34,78% | |
| **Psychotic disorders** | 9 | 28.1% | 35,00 | 50,72% | |
| **Depression** | 11 | 34.4% | 10 | 14,49% | |
| **Alcohol abuse** | | | | | 0.676 |
| **Yes** | 21 | 65.6% | 41 | 59,42% | |
| **No** | 7 | 21.9% | 17 | 24,64% | |
| **Substance abuse** | | | | | 0.596 |
| **Yes** | 21 | 65.6% | 41 | 59,42% | |
| **No** | 7 | 21.9% | 18 | 26,09% | |
| **HDI*** | 693 | 127 | 696,10 | 137,1 | 0.909 |
| **Live in Turkey (year)*** | 5.5 | 3.3 | 5,9 | 3,5 | 0.741 |
| **LOS (days)*** | 22.4 | 14.65 | 22,8 | 16,4 | 0.905 |

* Mean, SD: independent T-test; LOS: Lenght of Stay, NA: Not available, HDI: Human developmental index.

no significant difference between groups in terms of marital status (p=0.564). In the context of employment status, the difference was not statistically significant between groups (p=0.662). In terms of diagnosis, the Suicide group had 12 (37.5%) individuals with bipolar disorder, 9 (28.1%) with psychotic disorders, and 11 (34.4%) with depression. The No-suicide group had 24 (34.8%) individuals with bipolar disorder, 35 (50.7%) with psychotic disorders, and 10 (14.5%) with depression. The distribution of diagnoses showed a significant difference between the two groups (p=0.034). Concerning alcohol abuse and substance abuse, the differences were not statistically significant (p=0.676, p=0.586, respectively). The average HDI was 693±127 for the Suicide group and 696±137 for the No-suicide group. The difference was not statistically significant (p=0.909). The mean duration of living in Turkey was not statistically significant (p=0.741). The average LOS was not statistically significant (p=0.905) (**Table II**).

No significant difference was found between groups in terms of age (p=0.145). The Bipolar group consisted of 23 (50%) males, 22 (47.8%) females, and 1 (2.2%) transgender individual. The Psychotic group included 29 (55.7%) males and 23 (44.2%) females, with no transgender individuals. The Depression group comprised 11 (47.8%) males and 12 (52.2%) females. Gender differences across groups were not significant (p=0.716). A significant difference was observed between groups (p=0.027) regarding marital status. The Bipolar group had a lower proportion of singles (19.6%) and a higher proportion of divorced individuals (17.4%) than the other groups. In the context of employment status, no significant differences were found between the groups (p=0.525). In terms of suicide rates, there was a significant difference (p=0.034). The Depression group had the highest rate of suicide at 47.8%, followed by the Bipolar group at 26.09%, and the Psychotic group at 17.3%. With respect to alcohol abuse, no significant differences were observed across the groups (p=0.236). However, substance abuse rates differed significantly between the groups (p=0.021), with the Depression group reporting the lowest rate (4.4%). The average HDI was similar across the groups, with no significant difference (p=0.777). The mean duration of living in Turkey differed between groups, but not significantly so (p=0.356). Lastly, the average length of stay (LOS) in the facility showed a trend toward significance (p=0.072), with the shortest stay observed in the Depression group (16.1 days) (**Table III**).

Regression analysis for suicide attempts was performed. Accordingly, no significant difference was detected among the items regarding suicide (p>0.05) (**Table IV**).

## Discussion

Research exploring suicidal tendencies among immigrants can be challenging to assimilate into a coherent theoretical model due to the multifaceted and complex nature of the findings[8]. Some studies indicate a higher prevalence of suicide attempts among immigrants compared to the indigenous population, while others find

**Table III:** Comparison in terms of diagnosis.

| | Bipolar disorders (n=46) | | Psychotic disorders (n=52) | | Depression (n=23) | | |
|---|---|---|---|---|---|---|---|
| | N or mean | % or SD | N or mean | % or SD | N or mean | % or SD | p-value |
| **Age (year)*** | 30,20 | 9,20 | 33,40 | 13 | 36,30 | 16,2 | 0,145 |
| **Gender** | | | | | | | 0.716 |
| **Male** | 23,00 | 50,00% | 29,00 | 55,77% | 11,00 | 47,83% | |
| **Female** | 22,00 | 47,83% | 23,00 | 44,23% | 12,00 | 52,17% | |
| **Trans** | 1,00 | 2,17% | 0,00 | 0,00% | 0,00 | 0,00% | |
| **Marital status** | | | | | | | 0,027 |
| **Single** | 9,00 | 19,57% | 20,00 | 38,46% | 4,00 | 17,39% | |
| **Married** | 21,00 | 45,65% | 22,00 | 42,31% | 11,00 | 47,83% | |
| **Divorced** | 8,00 | 17,39% | 1,00 | 1,92% | 4,00 | 17,39% | |
| **Employment status** | | | | | | | 0,525 |
| **Working** | 7,00 | 15,22% | 10,00 | 19,23% | 6,00 | 26,09% | |
| **Not-working** | 20,00 | 43,48% | 24,00 | 46,15% | 8,00 | 34,78% | |
| **Suicide** | | | | | | | 0,034 |
| **Yes** | 12,00 | 26,09% | 9,00 | 17,31% | 11,00 | 47,83% | |
| **No** | 24,00 | 52,17% | 35,00 | 67,31% | 10,00 | 43,48% | |
| **Alcohol abuse** | | | | | | | 0,236 |
| **Yes** | 14,00 | 30,43% | 10 | 19,23% | 4 | 17,39% | |
| **No** | 23,00 | 50,00% | 33 | 63,46% | 16 | 69,57% | |
| **Substance abuse** | | | | | | | 0,021 |
| **Yes** | 13,00 | 28,26% | 17 | 32,69% | 1 | 4,35% | |
| **No** | 25,00 | 54,35% | 27 | 51,92% | 19 | 82,61% | |
| **HDI*** | 708,60 | 136,90 | 690,60 | 134,8 | 690,40 | 136,1 | 0,777 |
| **Live in Turkey (year)*** | 5,10 | 2,80 | 4,9 | 3 | 6,7 | 4,2 | 0,356 |
| **LOS (days)*** | 21,30 | 12,00 | 24,8 | 17,1 | 16,1 | 14,2 | 0,072 |

* Mean, SD: independent T-test; LOS: Lenght of Stay, NA: Not available, HDI: Human developmental index.

**Table IV:** Regression analysis for Suicide attempt.

| | B | S.E. | Wald | df | Sig. | Exp(B) |
|---|---|---|---|---|---|---|
| **HDI** | ,000 | ,002 | ,039 | 1 | ,843 | 1,000 |
| **Age** | -,031 | ,023 | 1,750 | 1 | ,186 | ,970 |
| **Gender** | ,140 | ,489 | ,082 | 1 | ,774 | 1,150 |
| **Alcohol abuse** | -,223 | ,581 | ,147 | 1 | ,702 | ,800 |
| **Substance abuse** | -,346 | ,593 | ,340 | 1 | ,560 | ,708 |
| **Diagnosis** | ,180 | ,332 | ,293 | 1 | ,588 | 1,197 |
| **Constant** | ,197 | 1,588 | ,015 | 1 | ,901 | 1,218 |

no substantial difference[9,10]. (Shoval et al., 2007; Lipsicas et al., 2014). Furthermore, multiple trends and processes suggested by the data underscore the variance in suicide attempts and death rates among these groups[11,12].

Complicating the matter further, immigrants and ethnic minorities often face disparities in accessing mental health services following suicide attempts or when experiencing suicidal ideation. This inequality in care potentially exacerbates mental health conditions and raises suicide risk.

The demographics of the participants in this study underscore the complexity of mental health and the multivariate factors influencing it. The diverse backgrounds, conditions, and experiences of these individuals, ranging from their marital status to substance and alcohol abuse and suicide attempts, offer a rich tableau for further analysis. This diversity can also inform the development of targeted therapeutic interventions to improve mental health outcomes.

However, our comparative analysis between those who attempted suicide (n=32) and those who did not (n=69) revealed no statistically significant differences across several parameters such as age, gender, marital status, employment status, substance or alcohol abuse, and length of stay in the country or hospital. These factors may not play a decisive role in suicide attempts among these patients.

Conversely, the Standardized Mortality Ratio (SMR) highlighted several diagnoses, such as borderline personality disorder, depression, bipolar disorder, opioid use, schizophrenia, anorexia nervosa, and alcohol use disorder, as significant risk factors for suicide. This reinforces the idea that clinical factors, such as diagnosis, may be more influential in predicting suicidal behavior than demographic or social factors.

Moreover, research indicates a threefold increase in suicide risk among psychiatric patients with concurrent alcohol or substance use[13]. Acute alcohol consumption, especially at high doses, was linked to a higher likelihood of suicide attempts, suggesting the need for interventions targeting alcohol use among individuals at risk[14].

Early detection and intervention are pivotal in suicide prevention, yet mental health conditions are often

undiagnosed and under-treated, particularly in primary healthcare settings[15,16].

Notably, the distribution of diagnoses showed a statistically significant difference between the suicide and no-suicide groups, with depression more prevalent in the former (34.4%) than in the latter (14.49%). This suggests the necessity for rigorous psychiatric evaluations and robust strategies to manage depression, which could significantly reduce suicide attempts in this population.

This research study additionally exposes the substantial gaps in the treatment of mental health disorders globally. These gaps are particularly pronounced in the treatment of major depressive disorder, with only one in five individuals in high-income countries and one in 27 in low to lower-middle-income countries receiving adequate treatment[17,18]. The treatment gap for alcohol use and dependency is even more alarming at 78%. Large treatment gaps also exist for depression (56%), bipolar disorder (50%), and schizophrenia (32%).

The insights derived from the demographic data, coupled with the finding that clinical factors such as diagnosis may be more indicative of suicide risk than sociodemographic factors, underscore the urgent need for healthcare systems to enhance mental health services. These services should particularly focus on the diagnosis and treatment of depression and other psychiatric disorders that have been associated with an increased risk of suicide.

Further, in light of the high prevalence of substance abuse, including alcohol abuse among patients, integrated treatment approaches that simultaneously address both psychiatric disorders and substance use disorders may be more effective in mitigating suicide risks.

The multitude of trends highlighted in this study emphasize the complexity of suicide risk factors and the challenges faced in suicide prevention. The data underscore the need for multifaceted and individualized therapeutic approaches in addressing mental health needs and suicidal tendencies. This includes improved access to mental health services, early detection and intervention strategies, and the provision of tailored treatment plans that take into account the diverse characteristics and backgrounds of patients.

## Conclusions

While this study contributes to the existing body of literature on suicide risks among immigrants, it also highlights the gaps in understanding the multifaceted nature of suicide risk and the need for more comprehensive research. Future studies should strive to delve deeper into the interplay of sociodemographic and clinical factors influencing suicide risk, as well as to investigate effective strategies for suicide prevention, with a particular emphasis on mental health services and treatment access among diverse populations.

### Conflict of interest

No

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ORIGINAL

# Identificación de la variante polimórfica rs9939609 del gen *FTO* en población duranguense

*Identification of the polymorphic variant rs9939609 of the FTO gene in duranguense population*

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## Resumen

***Introducción:*** Los conocimientos derivados de la variabilidad genética permitirán proporcionar las herramientas para entender y controlar la epidemia mundial de enfermedades crónicas específicas, particularmente del sobrepeso, la obesidad, la enfermedad cardiovascular, la diabetes y las enfermedades neurodegenerativas.
***Objetivo:*** Identificar y establecer la frecuencia del polimorfismo rs9939609 del gen *FTO* en población.
***Materiales y métodos:*** Estudio de tipo descriptivo, donde se incluirán hombres y mujeres de la ciudad del Durango mayor de 18 años, nacidos en la ciudad de Durango, mujeres no embarazadas o lactando, tener transfusión sanguínea. Una vez obtenido el consentimiento firmado, se tomará una muestra de sangre capilar del dedo índice para el análisis de las variantes polimórficas que se realizaron por PCR punto final y PCR-HRM. El paquete informático que se ha utilizado para el análisis fue el SPSS para Windows Versión 15.0.
***Resultados:*** Se encontró una frecuencia del genotipo A/A 3.08%, el 31.38% corresponde a T/A y el 64.82% para T/T (EHW $X^2$=1.78; p<0.05).
***Conclusión:*** Se pudo establecer la identificación y frecuencia del polimorfismo rs9939609 del gen FTO en población duranguense, abriendo una pauta para el estudio de esta variante polimórfica y su relación con el desarrollo de enfermedades metabólicas.

*Palabras clave:* Variabilidad genética, enfermedad crónica, sobrepeso, obesidad, diabetes.

## *Abstract*

***Introduction:*** Knowledge derived from genetic variability will provide the tools to understand and control the global epidemic of specific chronic diseases, particularly overweight, obesity, cardiovascular disease, diabetes and neurodegenerative diseases.
***Objective:*** To identify and establish the frequency of the rs9939609 polymorphism of the *FTO* gene in population.
***Materials and methods:*** Descriptive study, which will include men and women of the city of Durango over 18 years old, born in the city of Durango, women not pregnant or breastfeeding, having blood transfusion. Once the signed consent was obtained, a capillary blood sample will be taken from the index finger for the analysis of polymorphic variants that were performed by endpoint PCR and PCR-HRM. The computer package used for the analysis was SPSS for Windows Version 15.0.
***Results:*** A frequency of genotype A/A 3.08% was found, 31.38% corresponded to T/A and 64.82% to T/T (EHW $X^2$=1.78; p<0.05).
***Conclusion:*** Through the present study it was possible to establish the identification and frequency of the rs9939609 polymorphism of the FTO gene in the population of Durango, opening a guideline for the study of this polymorphic variant and its relationship with the development of metabolic diseases.

*Key words:* Genetic variability, chronic disease, overweight, obesity, diabetes.

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## Introducción

En los últimos años, los estudios de asociación de genoma completo, conocidos como GWAs (por sus siglas en inglés), han permitido identificar muchos genes asociados enfermedades crónicas específicas, particularmente la obesidad, el cáncer, la enfermedad cardiovascular, la diabetes y las enfermedades neurodegenerativas, entre otras[1]. En este sentido, varios SNP (por sus siglas en ingles "single nucleotide polymorphisms") se han asociado con enfermedades crónicas comunes a través de interacciones con las ingestas de macro y micronutrientes, o con el consumo de determinados alimentos y patrones dietético. Por lo tanto, también se ha informado que las interacciones SNP-dieta están involucradas en las respuestas diferenciales a las intervenciones nutricionales destinadas a restringir el total de calorías ingesta o modificación de energía derivada de grasas, proteínas o carbohidratos. En ese sentido, los estudios realizados en una variedad de poblaciones han investigado los efectos de varias SNP sobre pérdida de peso, recuperación de peso y mejoras metabólicas relacionadas con los lípidos séricos niveles y resistencia a la insulina[2]. Estas investigaciones incluyen polimorfismos en o cerca de genes implicados en la regulación de la ingesta de alimentos, metabolismo de lípidos y lipoproteínas, insulina señalización, homeostasis de glucosa, respuesta inflamatoria, metabolismo de aminoácidos y circadiano ciclo[3].

El gen *FTO* se encuentra en el cromosoma 16 (16q12.2) y codifica la enzima dioxigenasa dependiente de alfa-cetoglutarato. El gen asociado a la masa grasa y la obesidad (*FTO*, por sus siglas en inglés) es un ejemplo probable de un gen regulador "interruptor maestro" que influye en el control epigenético sobre una serie de vías reguladoras clave en la regulación de la obesidad. Se ha correlacionado con el síndrome metabólico y el riesgo de diabetes[4]. Se ha estimado que la prevalencia de este polimorfismo es de 23% en americanos de ascendencia Mexicana. Estudios recientes indican que los individuos portadores del genotipo de riesgo AA del polimorfismo rs9939609 del gen *FTO* tenían niveles de leptina sérica significativamente más altos y niveles séricos de HDL-c más bajos en comparación con aquellos con genotipo TT; además se asoció el genotipo de riesgo AA con niveles más altos de leptina y niveles más bajos de HDL-c; por lo que es plausible que el alelo de riesgo *FTO* pueda aumentar el nivel de leptina sérica aumentando el índice de masa corporal (IMC)[5]. Otro estudio reciente en Mexicanos indico que los sujetos con al menos una copia del alelo de riesgo A del SNP rs9939609 de dicho gen tenían una mayor ingesta de alimentos que aquellos con dos copias del alelo de tipo salvaje (TT); por lo que hasta el momento es un SNP más fuertemente asociado con un aumento de IMC[6,7].

## Material y métodos

Previa aceptación por parte del comité de investigación de investigación de la Facultad de Medicina y Nutrición de la UJED con No. Reg. 024, se realizó un estudio descriptivo en el cual se incluyeron a 396 participantes. Dentro de los criterios de inclusión que cumplieron fue que sean hombres y mujeres mayores de 18 años nacidos en la ciudad de Durango, que aceptaran participar de manera voluntaria y firma de la carta de consentimiento informado. Dentro de los criterios de exclusión estuvieron estar embarazadas o lactando, haber recibido transfusión sanguínea. Posteriormente se invitó a una plática informativa acerca de las bondades y características del trabajo de investigación.

### Procedimientos

#### *Toma de Muestra Sanguínea*

Se procedió a la toma de muestra sanguínea para el polimorfismo genético, en donde se obtuvieron 10 µl de sangre capilar del dedo anular que se colecto en tubos foliados que contenían 100 µl de NaOH para someter la muestra a lisis alcalina, para ello las muestras fueron incubadas a una temperatura de 37ºC antes de su análisis acuerdo a la técnica establecida por Muñoz-Hernández et al[8].

#### *Análisis de polimorfismos genéticos*

El análisis de los polimorfismo se realizó en tres pasos por la amplificación del sitio polimórfico por PCR (Reacción en Cadena de la Polimerasa, Polymerase Chain Reaction por sus siglas en inglés). Acto seguido, por el análisis de fusión de los productos de amplificación. A continuación, se describe este: primero se realizó una amplificación por PCR convencional de punto final utilizando GoTaq Master Mix (Promega Inc. 29 Madison, WI) con el objetivo de obtener cantidades semejantes de productos de amplificación de cada una de las muestras.

La primera reacción de amplificación PCR punto final fue: Go Taq Master Mix 15 µl, agua 5.7µl, iniciador sentido 0.3 µl, iniciador antisentido 0.3 µl y lisado sanguíneo 1.2µl.

La segunda reacción de amplificación para cada muestra (15µl) fue preparada de la siguiente manera: Go Tag Master Mix 7.5 µl, agua 3.75 µl, iniciador sentido 0.35 µl, iniciador antisentido 0.35 µl y 0.75 µl del templado obtenido en la primera amplificación.

Luego se realizó el análisis de alta resolución de fusión (HRM por sus siglas en ingles high resolution melting), el cual se basa en la caracterización de los productos de PCR de acuerdo al comportamiento de disociación de las cadenas de ADN, ya que el método HRM es sensible incluso a un simple cambio de base, la temperatura de disociación se requiere para determinar inicialmente el punto de fusión para cada nuevo producto PCR- HRM, abarcando una gama de temperaturas de 55°C a 95°C, cubriendo todos los puntos de fusión de acuerdo al tipo de cambio de base.

Para ambas amplificaciones se utilizaron los siguientes iniciadores: sentido: GCT GGT TAT TCC TGA CCT ACT G, antisentido: GCC CAA GGA TGG TGT TTC TA diseñados en el programa Primer Quest Dising Tool de la compañía Integrated DNA Techonologies, utilizando las condiciones de amplificación anteriormente mencionadas.

Para el análisis de las curvas de fundido se utilizó un Termociclador Eco (Ilumina San Diego, Ca.) con canal para HRM. Como estándares se utilizaron muestras procesadas por reacción en cadena de la polimerasa del polimorfismo de la longitud de fragmentos de restricción correspondiente para rs9939609 (T/T) del gen *FTO*.

### Consideraciones éticas

Previa explicación del proyecto a los participantes seleccionados, acerca de sus beneficios, costos, riesgos y confidencialidad, se solicitó el consentimiento informado de acuerdo al Reglamento de la ley General de Salud de México, en materia de Investigación para la salud en su Título II, capítulo I, fracción II y a la declaración de Helsinki y salud publica vigente. Según el reglamento de la Ley General de Salud en materia de investigación capítulo I, referente a los Aspectos Éticos de la Investigación en Seres Humanos en el artículo 17 dicho estudio se clasifica como investigación con riesgo mínimo.

El capítulo II "La investigación que implique construcción y manejo de ácidos nucleicos recombinantes se trabajara en el marco de los artículos 86 y 87". En el presente estudio, se cumplió con la confidencialidad de los datos obtenidos del material genético, que se sustentan a partir del artículo 103bis, en materia de salubridad general del genoma humano.

### Análisis estadístico

Las frecuencias de los polimorfismos en estudio se determinaron por conteo directo, luego se realizó el análisis de genotipos a través del equilibrio Hardy-Weinberg por la prueba de X2. El paquete informático que se utilizara para el análisis es el SPSS para Windows Versión 15.0.

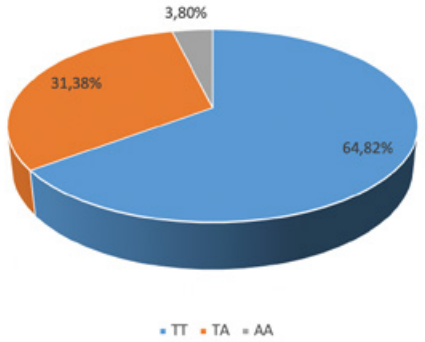
## Resultados

De la muestra total el mayor porcentaje corresponde al sexo masculino 49.6%, mientras que las mujeres representaron el 49.4% con una edad media de los participantes de 43.91 ± 8.67 años.

La distribución de los genotipos para esta población está representada de la siguiente forma: El 3.08% de la muestra presentan el homocigoto mutado A/A, el 31.38% corresponde a heterocigotos T/A y el 64.82% corresponde al homocigoto salvaje T/T (**Figura 1**). De acuerdo a lo que se muestra en las **figuras 2** y **3** de acuerdo a la distribución de los genotipos por sexo, se encontró que el sexo el homocigoto salvaje lo representa en mayor porcentaje el sexo femenino 65.14%, el heterocigoto se observó con mayor frecuencia en el sexo masculino 31.44%, el homocigoto mutado aumenta su frecuencia en el sexo femenino observándose una diferencia de un 3.81% con respecto al masculino.

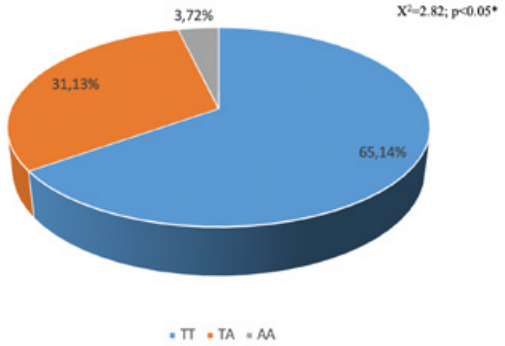
En cuanto a los alelos obtuvimos un 80.50% para T y un 19.49% para el alelo A, estas frecuencias alélicas no muestran diferencia en esta población de estudio por lo que se encuentra en equilibrio de Hardy-Weinberg ($X^2$= 1.78, *p>0.05*). Además también se encontró que no hay una correlación estadísticamente significativa entre la presencia del polimorfismo y el sexo ($X^2$=0.848, p=0.654).

**Figura 1:** Distribución de las frecuencias genotípicas en la población en estudio.



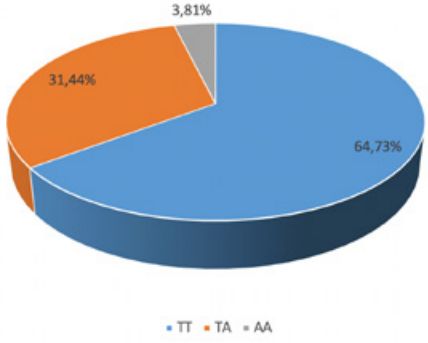

*Prueba del Equilibrio de Hardy- Weinberg

**Figura 2:** Distribución de las frecuencias genotípicas en mujeres de la población en estudio.




*Prueba del Equilibrio de Hardy- Weinberg.

**Figura 3:** Distribución de las frecuencias genotípicas en hombres de la población en estudio.




*Prueba del Equilibrio de Hardy- Weinberg.

## Discusión

En los recientes años la investigación a nivel molecular ha tomado un rol de importancia no solo clínica sino también para la salud pública; por el incremento de la prevalencia de afecciones no transmisibles como lo son los trastornos cardiometabólicos.

Es por este motivo que el objetivo del presente fue identificar y establecer la frecuencia del polimorfismo rs9939609 del gen *FTO* en población Duranguense. Al respecto se establece que la población duranguense se encuentra una alta frecuencia del polimorfismo homocigoto silvestre TT, los cual concuerda con lo reportado en poblaciones americanas en el Proyecto 1000 Genomas (referencia) y menor en poblaciones europeas. Así mismo en un estudio que incluyo muestras de personas con y sin y diabetes tipo 2 realizado en población guerrerense encontraron frecuencias similares a las de este estudio[9].

En el estado de Durango se ha establecido la multicausalidad que afectan la tasa de mortalidad en el estado, ya que las enfermedades de tipo metabólicas comparten factores de riesgo entre los que destacan el sobre peso y la obesidad, así como el tabaquismo, el colesterol elevado, la hipertensión arterial y la predisposición genética. Es por este motivo que es indispensable continuar fortaleciendo el primer nivel de atención, específicamente las acciones de prevención y promoción de los programas de salud orientados a reducir estos factores, así como modificar patrones alimenticios y a favorecer una vida saludable por medio de la actividad física y otras prácticas saludables[10].

En este sentido, un estudio nutrigenético realizado en la Universidad Nacional de La Plata en Argentina del que participaron 173 voluntarios se estableció que la frecuencia del alelo A fue de 0.27, además se estableció una de las contribución de la presencia del polimorfismo y la ingesta alimentaria comparando la ingesta de nutrientes y grupos de alimentos entre portadores y no portadores del alelo de riesgo A, encontrando que aquellos portadores del alelo A tienen una mayor ingesta de proteínas y de ácidos grasos saturados, y a su vez, se observó una tendencia no significativa a un mayor consumo de grasas totales y a un menor consumo de carbohidratos y azúcares en comparación con los individuos TT[11]. En conclusión, los resultados obtenidos de este estudio sugieren que se podría identificar un patrón de consumo de alimentos y nutrientes característico para cada genotipo, y estos hallazgos podrían ser utilizados como una nueva herramienta para mejorar la adherencia a las intervenciones nutricionales para la pérdida de peso.

Otro estudio realizado en población chilena estableció una alta prevalencia del alelo A (29.9%). Además demostraron la asociación entre el gen *FTO* con otros marcadores de adiposidad[12], considerando estos hallazgos como una oportunidad para la implementación de intervenciones personalizadas basadas en el genotipo *FTO* de la población, como ha sido demostrado por el estudio *Food4Me*[13].

Una limitación del estudio que realizamos es que únicamente se estableció la frecuencia del polimorfismo rs9939609 y no de alguna de sus otras regiones intrónicas. Sin embargo los resultados obtenidos permiten establecer la distribución de la variabilidad genética del gen FTO en población duranguense, abriendo así la posibilidad del desarrollo de nuevas investigaciones que incluyan variables de riesgo metabólico y nutrigenético.

## Conclusión

A través del presente se pudo establecer la identificación y frecuencia del polimorfismo rs9939609 del gen *FTO* en población duranguense, abriendo una pauta para el estudio de esta variante polimórfica y su relación con el desarrollo de enfermedades metabólicas.

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### Conflicto de interés

“Los autores declaran que no tienen conflicto de interés”

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ORIGINAL

# Influence of tobacco consumption and other variables on the values of different cardiovascular risk factors in 418,343 spanish workers

*Influencia del consumo de tabaco y otras variables en los valores de diferentes factores de riesgo cardiovascular en 418.343 Trabajadores españoles*

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## Summary

***Introduction and objectives:*** Cardiovascular risk factors (CVRF) are understood to be the factors that increase the appearance of cardiovascular disease. There are many CVRF, particularly diabetes, arterial hypertension (AHT), dyslipidemia, obesity, sedentary lifestyle, and tobacco consumption. The aim of this study was to assess the influence of different sociodemographic variables and tobacco consumption on CVRF.

***Methods:*** A descriptive, cross-sectional study was carried out in a large group of Spanish workers from different regions in which three classic CVRF were assessed: diabetes, dyslipidemia, and arterial hypertension, along with their relationship with sociodemographic variables such as age, sex, social class, and tobacco consumption.

***Results:*** All the sociodemographic variables, but especially age, sex, and tobacco consumption, increased the risk of presenting these CVRF.

***Conclusions:*** The profile of the person at greatest risk for dyslipidemia, high blood glucose levels, and arterial hypertension would be an older male, with a low socioeconomic level, and a smoker.

*Key words:* hypertension, dyslipidemia, prediabetes, diabetes, smoking.

## *Resumen*

***Introducción y objetivos:*** Entendemos por factores de riesgo cardiovascular (FRCV) aquellos que incrementan la aparición de enfermedades cardiovasculares. Existen muchos FRCV entre los que podemos destacar la diabetes, la hipertensión arterial (HTA), las dislipemia, la obesidad, el sedentarismo o el consumo de tabaco. El objetivo de este estudio es valorar la influencia de diferentes variables sociodemográficas y el consumo de tabaco sobre los FRCV.

***Material y métodos:*** Se realiza un estudio descriptivo y transversal en un amplio colectivo de trabajadores españoles de distintas regiones en los que se valoran tres FRCV clásicos como la diabetes, la dislipemia y la hipertensión arterial y su relación con variables sociodemográficas como la edad, el sexo y la clase social y el consumo de tabaco.

***Resultados:*** Todas la variables sociodemográficas, pero especialmente la edad y el sexo, y el consumo de tabaco van a incrementar el riesgo de presentar estos FRCV.

***Conclusiones:*** El perfil de persona con mayor riesgo para presentar dislipemia, valores elevados de glucemia e hipertensión arterial sería un varón de edad avanzada, con un nivel socioeconómico bajo y fumador.

*Palabras clave:* Hipertensión arterial, dislipemia, prediabetes, diabetes, tabaco.

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## Introduction

Cardiovascular disease (CVD) is currently the leading etiological factor in morbidity and mortality worldwide[1]. Cardiovascular disease refers to a very broad term that encompasses problems of the heart[2,3] and blood vessels[4,5]. Atherosclerosis[6,7] is often the cause of these problems. This condition occurs when fats and cholesterol build up on the walls of the arteries[8]. This buildup is known as plaque[9]. Plaque can narrow blood vessels over time, causing problems throughout the body. A heart attack or stroke can occur if an artery becomes clogged[10].

The etiology of CVD is very diverse and usually multifactorial, therefore, using population-wide strategies, most CVD can be prevented by acting on behavioral risk factors, such as tobacco use[11], unhealthy diets[12], obesity[13], sedentary lifestyle[14], and harmful use of alcohol[15] or other drugs[16].

The aim of this study was to assess the influence of different sociodemographic variables such as age, sex, social class, and tobacco consumption on some factors that increase cardiovascular risk in a large group of Spanish workers.

## Methods

Between the months of January 2017 and December 2019, this descriptive, cross-sectional study was conducted in 418,343 Spanish workers from various autonomous communities and different productivity sectors. The participants in the research were selected from among those who attended the periodic health surveillance carried out in all the participating companies.

The criteria for inclusion in the study were: being at least 18 and no more than 69 years of age, having an employment contract with one of the companies participating in the study, not being in a situation of temporary incapacity at the time, and accepting by informed consent to participate in the study and the use of the data collected for epidemiological purposes.

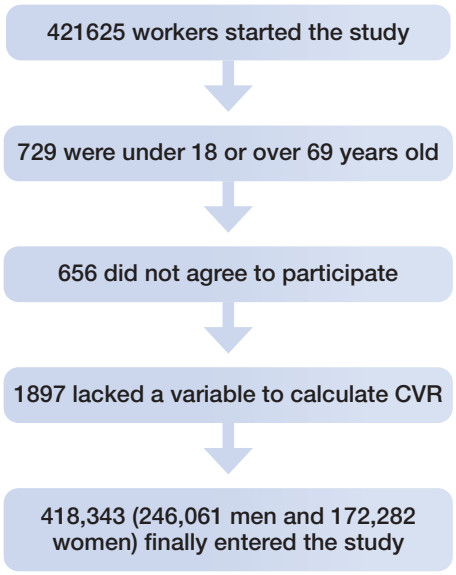
The flow chart of the workers who participated in the study is shown in **figure 1**.

**Table I** shows the characteristics of the population, with all anthropometric, clinical, and analytical variables revealing higher or less favorable values in men. The most frequent age was between 30 and 49 years. Most of the employees belonged to social class III. Approximately every third person in the study smoked.

### *Measurement and data collection*

Medical and nursing professionals from the companies included in the study were responsible for taking anthropometric (height, weight, and waist circumference), clinical, and analytical measurements with prior standardization of measurement techniques.

**Figure 1:** Flowchart.




Weight and height were obtained using a SECA 700 model measuring scale. A SECA model measuring tape was used while the person was standing upright, with the lower extremities together, the trunk erect, and the abdomen relaxed to determine the abdominal waist circumference. To obtain an accurate measurement, the tape measure was placed parallel to the floor at the level of the last floating rib.

Blood pressure was obtained with the worker seated and after a minimum rest period of 10 minutes using a calibrated OMRON M3 automatic sphygmomanometer. Three measurements were obtained 60 seconds apart and the mean was used. The different analytical values were obtained after a fasting period of no less than 12 hours. Total cholesterol, glycemia, and triglycerides were determined using automated enzymatic techniques. High-density lipoprotein (HDL) values were obtained using dextran sulfate-MgCl2 precipitation techniques. Low-density lipoproteins (LDL) were calculated indirectly by applying the Friedewald formula. All these analytical parameters are expressed in mg/dL.

Friedewald's formula: LDL = cholesterol - HDL - triglycerides/5

The following cardiovascular risk factors were determined:

- Arterial Hypertension

Blood pressure figures were classified according to the criteria of the seventh Joint National Committee for the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7)[17] as shown in **table I**.

**Table I:** Classification of blood pressure values according to the JNC-7.

| Category | Systolic (mmHg) | | Diastolic (mmHg) |
|---|---|---|---|
| Normal | <120 | and | <80 |
| Prehypertension | 120–139 | or | 80–89 |
| Hypertension | | | |
| Stage 1 | 140–159 | or | 90–99 |
| Stage 2 | >160 | or | >100 |

*Adapted from JNC 7 Express: The Seventh Report of the Joint National Committee

- Glycemia
Values were classified according to the criteria of the American Diabetes Association (ADA)[18] which considers values to be normal when they are less than 100mg/dL; altered basal glycemia or prediabetes if values are between 100 and 125 mg/dL; and diabetes if values exceed 125 mg/dL.

- Dyslipidemia
In order to classify the values of lipid parameters, the recommendations of the Spanish Heart Foundation[19] were used.

Total cholesterol is classified as:
- Normal values below 200 mg/dL
- Borderline values between 200-239 mg/dL
- High values when the figures exceed 239 mg/dL

LDL is classified as:
- Normal values below 100 mg/dL
- Borderline values between 100 and 159 mg/dL
- High values when they exceed 159 mg/dL

Triglycerides are classified as:
- Normal values when less than 150 mg/dL
- Borderline values between 100 and 199 mg/dL
- High values when above 200 mg/dL.

In this study we considered as smokers those persons who had consumed at least one cigarette daily (or the equivalent in other varieties of consumption) in the previous 30 days or who had quit smoking less than one year before.

The social determinants group of the Spanish Society of Epidemiology, based on the type of work included in the 2011 national classification of occupations (CNO-11)[20] established a classification of social classes. For this study we opted for classification in three categories:

- Social class I. Managers, sportsmen and artists, university professionals, and skilled self-employed workers.
- Social class II. Unskilled self-employed workers and so-called intermediate occupations.
- Social class III. Unskilled workers.

### *Statistical analysis*
The frequency and distribution of categorical variables were calculated, and a descriptive analysis of these variables was performed. The mean and standard deviation of the quantitative variables were calculated as they presented a normal distribution.

For independent samples, Student's t-test and Chi-squared test were used. When circumstances required it, Fisher's exact statistic was corrected. Calculation of odds ratios with their 95% confidence intervals was used to conduct multivariate analysis using multinomial logistic regression. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 28.0 for Windows, which had an accepted statistical significance level of 0.05.

### *Ethical aspects*
The study investigators were committed at all times to strict compliance with all the standards of ethics in health sciences research that are established both in Spain and internationally and that are included in the Declaration of Helsinki, paying special attention to the anonymity of the participants and the confidentiality of the data collected. The study was approved by the Ethics and Research Committee of the Balearic Islands (CEI-IB) with indicator IB 4383/20. Since participation in the research was voluntary, it was necessary to obtain oral and written consent after participants had received clear and sufficient information on the characteristics and content of the study, for which a model of informed consent and a sheet with information on the objectives of the research were provided.

The study data were identified by a code, and only the principal investigator was in a position to establish a connection between these and the participants. The identity of the participants cannot be revealed at any time during the research, since the investigators have the obligation and commitment not to divulge any information that could identify them. At all times, the researchers are committed to strict compliance with Organic Law 3/2018, of December 5, on the protection of personal data and guarantee of digital rights, ensuring that the people participating in the study have the right to access, rectify, cancel, and oppose the data collected.

## Results

**Table II** shows the anthropometric and clinical characteristics of the 418343 employees in the study (246061 men and 172282 women). The group had a mean age of 40.2 ± 11.0 years with most of the participants aged between 30 and 49 years. All variables had more negative values in men. One out of every three employees smoked, and three out of four belonged to social class III.

**Table II:** Characteristics of the population.

| | Women n=172.282 Mean (SD) | Men n=246.061 Mean (SD) | Total n=418.343 Mean (SD) | p-value |
|---|---|---|---|---|
| **Age** | 39.6 (10.8) | 40.6 (11.1) | 40.2 (11.0) | <0.0001 |
| **Height** | 161.8 (6.5) | 174.6 (7.0) | 169.4 (9.3) | <0.0001 |
| **Weight** | 66.2 (14.0) | 81.4 (14.7) | 75.1 (16.2) | <0.0001 |
| **Waist** | 74.8 (10.6) | 86.2 (11.1) | 81.5 (12.2) | <0.0001 |
| **SBP** | 117.4 (15.7) | 128.2 (15.5) | 123.7 (16.5) | <0.0001 |
| **DBP** | 72.6 (10.4) | 77.8 (11.0) | 75.6 (11.0) | <0.0001 |
| **Cholesterol** | 190.6 (35.8) | 192.6 (38.9) | 191.8 (37.7) | <0.0001 |
| **HDL-c** | 56.8 (8.7) | 50.3 (8.5) | 53.0 (9.1) | <0.0001 |
| **LDL-c** | 116.1 (34.8) | 118.0 (36.7) | 117.2 (35.9) | <0.0001 |
| **Triglycerides** | 89.1 (46.2) | 123.7 (86.4) | 109.5 (74.6) | <0.0001 |
| **Glycemia** | 87.8 (15.1) | 93.3 (21.3) | 91.0 (19.2) | <0.0001 |
| | % | % | % | p-value |
| **18-29 years** | 20.7 | 18.8 | 19.6 | <0.0001 |
| **30-39 years** | 29.7 | 27.6 | 28.4 | |
| **40-49 years** | 29.6 | 30.0 | 29.9 | |
| **50-59 years** | 16.8 | 19.7 | 18.5 | |
| **≥60 years** | 3.2 | 3.9 | 3.6 | |
| **Social class I** | 6.9 | 4.9 | 5.7 | <0.0001 |
| **Social class II** | 23.4 | 14.9 | 18.4 | |
| **Social class III** | 69.7 | 80.3 | 75.9 | |
| **Non-smokers** | 67.2 | 66.6 | 66.9 | <0.0001 |
| **Smokers** | 32.8 | 33.4 | 33.2 | |

**Table III:** Mean values of different cardiovascular risk factors according tobacco consumption by sex.

| | Men | | | Women | | |
|---|---|---|---|---|---|---|
| | Non-smokers n=163920 Mean (SD) | Smokers n=82141 Mean (SD) | p-value | Non-smokers n=115727 Mean (SD) | Smokers n=56555 Mean (SD) | p-value |
| **Age** | 40.2 (11.1) | 40.8 (11.0) | <0.0001 | 39.3 (10.8) | 39.7 (10.8) | <0.0001 |
| **SBP** | 128.0 (15.5) | 128.2 (15.5) | <0.0001 | 117.2 (15.7) | 117.5 (15.6) | <0.0001 |
| **DBP** | 77.6 (11.0) | 77.8 (10.9) | <0.0001 | 72.4 (10.4) | 72.7 (10.4) | <0.0001 |
| **Cholesterol** | 192.3 (39.2) | 192.7 (38.7) | 0.034 | 190.2 (35.9) | 190.9 (35.8) | <0.0001 |
| **HDL-c** | 50.2 (8.5) | 50.3 (8.5) | 0.003 | 56.7 (8.6) | 56.8 (8.7) | 0.034 |
| **LDL-c** | 117.8 (36.9) | 118.2 (36.6) | 0.008 | 115.7 (34.7) | 116.3 (34.8) | <0.0001 |
| **Triglycerides** | 124.4 (87.8) | 123.4 (85.7) | 0.007 | 89.2 (46.4) | 89.1 (46.1) | 0.835 |
| **Glycemia** | 93.1 (21.3) | 93.4 (21.2) | 0.003 | 87.7 (15.0) | 87.9 (15.2) | 0.052 |

**Table IV:** Prevalence of values of different cardiovascular risk factors according to tobacco consumption by sex.

| | Men | | | Women | | |
|---|---|---|---|---|---|---|
| | Non-smokers n=163920 % | Smokers n=82141 % | p-value | Non-smokers n=115727 % | Smokers n=56555 % | p-value |
| **Normal** | 21.7 | 21.1 | 0.006 | 51.2 | 50.6 | 0.017 |
| **Pre AHT** | 51.7 | 51.8 | | 37.1 | 37.4 | |
| **Hypertension 1** | 20.7 | 21.0 | | 9.2 | 9.6 | |
| **Hypertension 2** | 5.9 | 6.1 | | 2.4 | 2.5 | |
| **High Cholesterol** | 39.9 | 40.2 | 0.01 | 36.6 | 37.1 | 0.07 |
| **High LDL** | 35.7 | 36.3 | 0.003 | 31.5 | 32.2 | 0.002 |
| **High Triglycerides** | 23.8 | 24.1 | 0.041 | 7.9 | 8.0 | 0.039 |
| **Glycemia 100-125** | 18.5 | 18.9 | 0.007 | 10.1 | 10.1 | 0.001 |
| **Glycemia > 125** | 3.5 | 3.6 | | 1.3 | 1.3 | |

**Table V:** Multinomial logistic regression.

| | Hypertension OR (95% CI) | High Cholesterol OR (95% CI) | High LDL-c OR (95% CI) | High Triglycerides OR (95% CI) | Diabetes OR (95% CI) | Glycemia > 100 OR (95% CI) |
|---|---|---|---|---|---|---|
| **18-29 years** | 1 | 1 | 1 | 1 | 1 | 1 |
| **30-39 years** | 1.59 (1.54-1.65) | 1.33 (1.25-1.41) | 1.05 (1.01-1.09) | 1.07 (1.03-1.11) | 1.73 (1.63-1.83) | 1.56 (1.51-1.62) |
| **40-49 years** | 3.37 (3.26-3.50) | 1.61 (1.56-1.67) | 1.69 (1.63-1.75) | 1.40 (1.35-1.46) | 4.62 (4.33-4.92) | 3.03 (2.93-3.14) |
| **50-59 years** | 7.27 (7.01-7.55) | 3.28 (3.17-3.40) | 3.47 (3.35-3.59) | 2.11 (2.03-2.20) | 11.30 (10.45-12.22) | 5.74 (5.53-5.95) |
| **60-69 years** | 10.80 (10.37-11.24) | 8.03 (7.73-8.34) | 8.67 (8.34-9.00) | 4.17 (3.98-4.36) | 23.03 (20.62-25.73) | 10.07 (9.65-10.51) |
| **Female** | 1 | 1 | 1 | 1 | 1 | 1 |
| **Male** | 2.57 (2.53-2.62) | 1.09 (1.08-1.11) | 1.14 (1.13-1.16) | 3.53 (3.46-3.60) | 2.46 (2.35-2.58) | 2.14 (2.10-2.18) |
| **Social class I** | 1 | 1 | 1 | 1 | 1 | 1 |
| **Social class II** | 1.17 (1.15-1.20) | 1.06 (1.03-1.10) | 1.04 (1.02-1.06) | 1.15 (1.13-1.18) | 1.78 (1.60-1.98) | 1.44 (1.41-1.48) |
| **Social class III** | 1.40 (1.34-1.45) | 1.14 (1.11-1.17) | 1.07 (1.04-1.10) | 1.38 (1.33-1.44) | 1.83 (1.72-1.95) | 1.48 (1.42-1.54) |
| **Non-smokers** | 1 | 1 | 1 | 1 | 1 | 1 |
| **Smokers** | 1.02 (1.00-1.04) | 1.03 (1.01-1.05) | 1.07 (1.04-1.11) | 1.03 (1.01-1.06) | 1.08 (1.05-1.11) | 1.04 (1.01-1.07) |

**Table III** shows the mean values of the different cardiovascular risk factors analyzed in this study, according to smoking and sex. It can be observed that in all cases, in both women and men, these mean values we re higher in the group of smokers. The differences found were statistically significant in all cases.

**Table IV**, which shows the prevalence of elevated values of the different cardiovascular risk factors, reveals the same trend already described for the mean values, that is, a higher prevalence in smokers.

**Table V** shows the results of the multivariate analysis using multinomial logistic regression, revealing that all the sociodemographic variables –especially age, sex, and tobacco consumption– increased the risk of presenting elevated values of the different cardiovascular risk factors

In this analysis, the reference variables were younger age, female sex, social class I, and being a non-smoker.

## Discussion

The appearance of the different risk factors analyzed in this study were favored by all the sociodemographic variables studied, that is, age, sex, and social class, and also by smoking.

The prevalence of arterial hypertension in our study was around 27% in men and 12% in women; these figures are lower than those found in Di@bet.es, a national study seeking to measure the prevalence of diabetes mellitus and other cardiovascular risk factors in Spanish adults[21]. That study analyzed 5048 Spanish adults and calculated the prevalence of arterial hypertension at 49.9% in men and 37.1% in women; these higher figures could be explained by the fact that persons aged over 69 years were included in that study.

Data from the Spanish Ministry of Health[22] show an overall prevalence of diabetes of 7.5% in the year 2020, higher values than those found by us, which are 3.5% in men and 1.3% in women; this disparity in the figures could be due to the exclusion in our study of persons aged 70 years and older. The prevalence of prediabetes was 23.7% in a study of 616 Mexicans[23], figures somewhat higher than those obtained by us. A very recent meta-analysis[24] that included 7014 studies assessed the global prevalence of prediabetes in the world, estimating it at 5.8%, a lower figure than ours. Data from the Spanish national health survey of 2017[25] show a prevalence of hypercholesterolemia of 19.8%, figures well below those obtained by us.

Sex hormones and sex chromosomes have an impact on the regulation of blood pressure (BP) and the distribution of cardiovascular (CV) risk factors, which explains why the prevalence of arterial hypertension is higher in men, as seen in our study[26]. This higher prevalence in men has been observed in two studies carried out in the Spanish working population[27,28].

The China-PAR (Prediction for Atherosclerotic Cardiovascular Disease Risk in China) project, which included 53891 people, assessed the effect of socioeconomic level (classified in three levels) on the prevalence of arterial hypertension, observing that the lower the socioeconomic level, the higher the prevalence of arterial hypertension[29]. Similar data were found in the Jackson Heart Study carried out in 4761 people[30].

In our study, we found a negative effect of smoking on blood pressure, and these data are supported by the results obtained in the United Kingdom Biobank cohort, which included 98039 individuals (45457 men and 52582 women). Arterial stiffness levels and blood pressure figures were higher in men than in women and showed a stronger relationship with smoking[31]. Similar data were found in a study of US adults[32].

The risk of presenting diabetes in our study increased the lower the socioeconomic level; these data are similar to those obtained in a systematic review[33] in which the complications of diabetes were assessed but differ from those found in another review[34]. The prevalence of prediabetes and diabetes in a study conducted in Iran was higher in people with lower socioeconomic status[35].

According to the available evidence, smoking increases the risk of prediabetes and diabetes and all-cause mortality in the general population[36-39], along with aggravating chronic diabetic complications and glycemic control among people with diabetes.

Dyslipidemia in our study was higher in people of social class III, data that agree with a study conducted in China in almost 10000 adults[40]. A study conducted in poorly developed countries showed that dyslipidemia was more prevalent in people with a higher socioeconomic status[41].

Data from the Korean National Health and Nutrition Examination Survey for the years 2013 to 2019 including 8398 men showed a clear relationship between smoking and dyslipidemia[42].

As strengths of the study, it is worth highlighting the large sample size, over 418000 people, which gives great power to the results obtained.

The main limitation of the study is the exclusion of persons under 18 years of age and those aged 70 years and older, since the study was carried out in the working population, which could prevent extrapolation of the results to the general population, especially those over 69 years of age.

## Conclusions

All sociodemographic variables, including age, sex, and social class, have an impact on the increase in cardiovascular risk factors, especially age and sex. Tobacco use also increases these risk factors, although less significantly.

An older male, belonging to social class III, and a smoker has a high probability of presenting cardiovascular risk factors.

### Conflict of Interest

The authors declared that there is no conflict of interest.

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ORIGINAL

# Comparison of The Effects of Low Flow Desfluran and High Flow Desfluran on Oxidative Stress and DNA Damage in Anesthesia Applications

*Comparación de los efectos del desflurano de bajo flujo y del desflurano de alto flujo sobre el estrés oxidativo y el daño del ADN en aplicaciones anestésicas*

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## Abstract

***Background:*** Studies have reported that volatile anesthetics may affect genotoxic and oxidative stress in the present study, we aimed to compare low and high flow anesthesia techniques in terms of DNA damage and oxidative stress.
***Methods:*** We included 60 patients who underwent high and low flow desflurane anesthesia, and those who underwent low and high flow anesthesia were categorized in Groups I (n=31) and II (n=29), respectively. The hemodynamic and respiratory parameters of the patients were recorded and 8-OhdG (8-hydroxy deoxyguanosine) values for DNA (deoxyribonucleic acid) damage, MDA(Malondialdehyde), cystatin C, TAS (total antioxidant status), TOS (total oxidative status), and LPO (lıpıd peroxıd) values for oxidative stress were measured from the blood samples collected from the patients preoperatively, intraoperatively at the third hour and at the postoperative twenty-fourth hour.
***Results:*** Postoperative MDA value was significantly higher in the high flow group than in the low flow group ($p<0.05$). There was no significant intergroup difference in terms of TAS, TOS, cystatin C, LPO and 8 OhdG values ($p>0.05$).
***Conclusion:*** In conclusion, MDA values, an indicator for oxidative stress, increased significantly in high flow desflurane application. There was no intergroup difference in terms of DNA damage.

*Key words:* Low flow anesthesia, oxidative stress, DNA damage.

## *Resumen*

***Antecedentes:*** Estudios han reportado que los anestésicos volátiles pueden afectar el estrés genotóxico y oxidativo en el presente estudio, nos propusimos comparar técnicas de anestesia de bajo y alto flujo en términos de daño al ADN y estrés oxidativo.
***Métodos:*** Se incluyeron 60 pacientes sometidos a anestesia con desflurano de alto y bajo flujo, y los sometidos a anestesia de bajo y alto flujo se clasificaron en los grupos I (n=31) y II (n=29), respectivamente. Se registraron los parámetros hemodinámicos y respiratorios de los pacientes y los valores de 8-OhdG (8-hidroxi desoxiguanosina ) para el daño del ADN (ácido desoxirribonucleico), MDA (Malondialdehído), cistatina C, TAS (estado antioxidante total), TOS (estado oxidativo total), y LPO (lıpıd peroxıd) valores de estrés oxidativo se midieron a partir de las muestras de sangre recogidas de los pacientes preoperatoriamente, intraoperatoriamente a la tercera hora y en el postoperatorio de veinticuatro horas.
***Resultados:*** El valor postoperatorio de MDA fue significativamente mayor en el grupo de alto flujo que en el de bajo flujo ($p<0,05$). No hubo diferencias significativas entre los grupos en cuanto a los valores de TAS, TOS, cistatina C, LPO y 8 OhdG ($p>0,05$).
***Conclusiones:*** En conclusión, los valores de MDA, un indicador de estrés oxidativo, aumentaron significativamente en la aplicación de desflurano a alto flujo. No hubo diferencias intergrupales en cuanto al daño del ADN.

*Palabras clave:* Anestesia de bajo flujo, estrés oxidativo, daño en el ADN.

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## Introduction

low-flow anesthetic techniques are becoming more popular both here and abroad. The main drivers of this growth include benefits like increased economic output, a decrease in the ecosystem-damaging effects of greenhouse gases, and increased physiological heat and humidity loss[1]. Low-flow anesthesia applications have been made possible by high-standard anesthetic equipment and monitors.

The imbalance between insufficient antioxidant cell defense and the generation of reactive oxygen species (ROS), which results in molecule damage, is known as oxidative stress[2]. Oxidative stress is exacerbated by aging, inflammatory conditions, cancer, degenerative disorders, and drug exposure (including xenobiotics and anesthetics)[3]. Anesthesia-induced oxidative stress can have an impact on DNA, proteins, and lipids. Lipids are the ones that are most vulnerable to oxidation[4]. Plasma MDA levels are the most popular method used in investigations to assess the oxidative stress brought on by anesthetics[5]. TAS and TOS are additional oxidative stress indicators.

The majority and most mutagenic of the >20 oxidative base damage products produced by ROS in DNA is 8-OhdG (8-hydroxydeoxyguanosine)[6]. Most research[7] have relied solely on 8-OHdG as a measure of oxidative DNA damage.

There aren't many research on humans comparing the effects of low and high flow desflurane anesthesia on oxidative stress and DNA damage. In this study, desflurane was used as an inhaler agent to examine the effects of low flow and high flow anesthetic procedures on DNA damage and oxidative stress.

## Materials and methods

### Study Design, Population, and Data

This study was planned as a prospective randomized controlled trial. An informed consent form was signed by all patients included in the study. Approval was obtained from the Dicle University Ethics Committee dated 25.03.2021 and numbered 187. An informed consent form was signed by all patients included in the study Patients who did not want to participate in the study and who wanted to leave while the study was ongoing were excluded. The study was planned in accordance with the 2008 Declaration of Helsinki. All patients included in the study were provided detailed information related to the study, and their written informed consent was obtained. The randomization sequence was generated by a computerized random number generator and sealed in numbered envelopes.

Sixty patients with an ASA score of I–II and between the ages of 17-70 years, who were to undergo general anesthesia with desflurane, were included in the study. Patients aged <17 and >70 years, patients with liver and/or kidney failure, obese patients (BMI >30), trauma patients, ASA III-IV patients, patients with bleeding disorders, those using drugs that may affect the coagulation system, patients with cardiomyopathy, cerebrovascular disease, immobility, and malnutrition were excluded from the study.

### Preoperative and intraoperative routine

Blood samples were collected from the patients 30 minutes before the operation. After intravenous (i.v.) premedication with 1.5 mg midazolam, standard anesthesia monitoring (ECG, noninvasive blood pressure, peripheral $O_2$ saturation, temperature) was performed on the operating table. Before the induction of anesthesia, preoxygenation was applied at a rate of 4 L/min for 3 minutes to all patients. Furthermore, 1 mcg/kg fentanyl for anesthesia induction, 2 mg/kg propofol IV, and 0.6 mg/kg rocuronium bromide (Esmeron Organon, The Netherlands) i.v. as a neuromuscular blocker were administered within 20-30 seconds. All patients were manually ventilated with 100% $O_2$ until endotracheal intubation was performed after the drugs administered. Intubation was performed with a cuffed endotracheal tube of the appropriate diameter for the patient's age and body structure. After intubation, ventilation was performed in volume control mode with a Dräger Primus (Dräger, Medizintechnik, Germany) anesthesia device adjusted to tidal volume 6-8 ml/kg, respiratory frequency 12-16/min, PEEP 5-8 cm $H_2O$. Soda-lime (Sorbolime, Berkim, Turkey) was used as $CO_2$ absorbent in the anesthesia machine.

The patients were randomly divided into two groups. In both groups, the total gas flow (TGF) was set to 4L/min ($FiO_2$: 50%, air: 50%) and the desflurane volume was 7% until MAC (minimum alveolar concentration) was 1 in the maintenance of anesthesia.

In the low flow anesthesia group (Group I), TGF: 0.5 L/min ($FiO_2$: 70%, Air: 30%) was continued and the desflurane percent volume was set to MAC: 1.

In the high flow anesthesia group (Group II), TGF was continued at 4 L/min ($FiO_2$: 50, Air: 50%) and the desflurane volume was adjusted to to MAC: 1.

In both groups, blood was collected from the patients in the same way at the 3rd hour of the operation. In the last 30 minutes of the operation, Tramadol Hydrochloride 100 mg i.v, paracetamol 1 gr i.v and dexketoprofen 50 mg i.v were administered for postoperative analgesia. In the high flow anesthesia group, after the last skin suture was placed, the inhalation agent was turned off and 100% $O_2$ was started. The fresh gas flow was opened at 8 L/min. In the low flow anesthesia group, the inhalation agent was turned off 20 minutes before the end of the surgical period. The flow was continued at 0.5 L/

min until the last skin suture was placed, and then the fresh gas flow was turned on at 4 L/min. After starting spontaneous respiration, the patients in both groups were administered 0.03 mg/kg neostigmine and 0.01 mg/kg atropine intravenously and they were extubated. After the operation, the patients were collected to the postoperative care unit.

Blood was taken from the patients in both groups at the postoperative 24th hour with the same method. Respiratory parameters, hemodynamic data, and anesthesia durations of the patients included in the study were recorded. The blood taken from the patients in the perioperative period was centrifuged and was stored at -80°C.

In our study, lipid hydroperoxide (Catalogue No: 201-12-0727), cystatin C (Catalog No: 201-12-1105), 8-OHdG (Catalogue No: 201-12-1437) and MDA (Catalogue No: 201-12- 1372) levels were evaluated by ELISA method.

TAS levels were measured by automatic measurement method using 2,2'-Azinobis (3-ethylbenzothiazoline 6-sulfonic acid) in accordance with the method of Erel et al. The results were expressed as micromole Trolox® equiv./L[8].

TOS levels were measured using Erel's TOS method, which is based on the measurement of color change that occurs after the oxidants in the samples oxidize Fe+2 to Fe+3, and the amount of oxidant substances with the kits used by spectrophotometric methods. The results were expressed as micromoles of $H_2O_2$ equiv./L[9].

### Statistical Analysis

The necessary sample size was evaluated utilizing G-Power software. Assuming a one-tailed alpha error of 0.05, power of 0.80, an allocation ratio of N2/N1=1, and an effect size of 0.8, the minimum number of patients needed was 42 (21 in the Low Flow group and 21 in the High Flow group).

The statistical analysis was conducted using Windows-compatible SPSS 16.0 software. Categorical data are expressed as frequency and percentage, whereas continuous data are expressed as mean and standard deviation. The Fisher's exact test and the chi-square test were used to compare the category data. The distribution of the numerical data was examined using the Kolmogorov-Smirnov test. Data with a normal distribution were examined using the Student's t-test, while data with an abnormal distribution were examined using the Mann-Whitney U test. All comparisons were deemed significant if $P<0.05$.

## Results

A total of 62 patients were included in the study. Since 2 patients in group 2 were discharged early, their postoperative blood samples could not be taken. Therefore, these two patients were excluded from the study and the study was completed with 60 patients. The mean age of the patients enrolled in the study was 36.35±15.5 years. The demographic data of the patients are shown in **table I**. There was no significant intergroup difference in terms of age, BMI, sex, ASA score, preoperative and intraoperative hemodynamics and respiratory parameters ($p>0.05$).

**Table I:** Demographic data of patients.

| Characteristic | Group 1 (n = 31) | | Group 2 (n = 29) | | p value |
|---|---|---|---|---|---|
| | Frequency | Percent | Frequency | Percent | |
| **Sex** | | | | | **0.46** |
| **Female** | 11 | 35.5 | 13 | 44.8 | |
| **Male** | 20 | 65.5 | 16 | 55.2 | |
| **ASA*** | | | | | 0.62 |
| **I** | 13 | 41.9 | 14 | 48.3 | |
| **II** | 18 | 58.1 | 15 | 51.7 | |
| **Total** | 31 | 51.7 | 29 | 48.3 | |
| | Mean±Std | | Mean±Std | | |
| **Age** | 36.45 | 16.37 | 36.24 | 14.99 | 0.95 |
| **BMI**** | 23.31 | 2.82 | 25.03 | 3.82 | 0.052 |
| **AI0***** | 82.8 | 10.92 | 79.79 | 12.6 | 0.32 |
| **AI30** | 72.12 | 10.99 | 72.58 | 12.28 | 0.88 |
| **AI90** | 68.25 | 10.75 | 66.68 | 10.61 | 0.57 |
| **MAP0****** | 99.51 | 12.27 | 96.31 | 14.03 | 0.13 |
| **MAP30** | 74.86 | 15.84 | 77.1 | 15.26 | 0.5 |
| **MAP90** | 72 | 9.28 | 76.41 | 13.27 | 0.13 |
| **$SPO_2$0******* | 98.19 | 1.72 | 98.44 | 1.5 | 0.63 |
| **$SPO_2$30** | 98.54 | 1.12 | 98.37 | 2.07 | 0.49 |
| **$SPO_2$90** | 98.32 | 1.24 | 98.41 | 1.47 | 0.58 |
| **$ETCO_2$0******** | 32.93 | 3.8 | 33.14 | 4.84 | 0.54 |
| **$ETCO_2$30** | 31.74 | 2.7 | 30.85 | 2.46 | 0.19 |
| **$ETCO_2$90** | 32.38 | 2.87 | 30.51 | 3.57 | 0.032 |

*ASA:American Society of Anesthesiologist; **BMI:Body Mass Index; ***AI:Apical Impulse;
****MAP; Mean Arterial Pressure; *****$SPO_2$:Oxygen Saturation; ******$ETCO_2$:End Tidal Carbon Dioxide

When groups I and II were compared in terms of $ETCO_2$ values, $ETCO_2$ values at the 90th minute were found to be statistically significantly higher in group 1 (**Figure 1**) (p=0.032).

When groups I and II were compared in terms of preoperative, intraoperative, and postoperative TAS and TOS values, there was no statistically significant difference between the groups (p>0.05) (**Table II**). The TOS value measured at the third hour intraoperatively was higher in Group 2, but the difference was not statistically significant (p = 0.05).

When groups were compared on preoperative, intraoperative, and postoperative MDA values, there was no statistically significant difference between the groups on preoperative and intraoperative MDA values (p>0.05), but the MDA values at the postoperative 24th hour were statistically significantly higher in group 2 (p=0.048) (**Table III**).

When groups were compared on preoperative, intraoperative, and postoperative LPO and Cyt C values, there was no statistically significant difference (p>0.05) (**Table III**). In general, LPO and Cyt c values were higher in group 2, but the difference was not statistically significant.

When both groups were compared in terms of preoperative, intraoperative, and postoperative 8-OhdG values, there was no statistically significant difference (p>0.05) (**Table IV**). The 8-OhG values at the intraoperative 3rd hour were higher in group 2 but the difference was not statistically significant. (p=0.052)

**Figure 1:** Variation of Mean $ETCO_2$ Values Over Time According to the Given Flow.

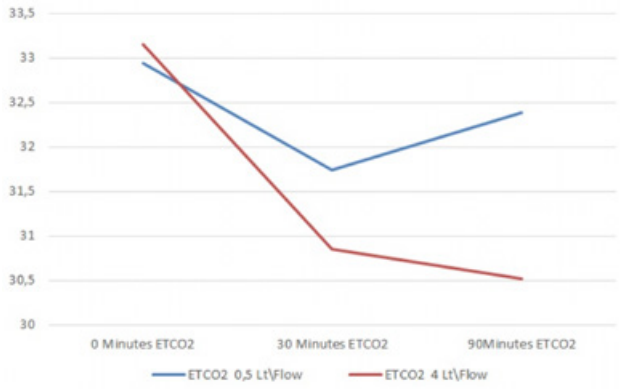


**Table II:** Comparison of groups in terms of total antioxidant status and total oxidant status values.

| Characteristic | Group 1 (n=31) Mean±Std | | Group 2 (n=29) Mean±Std | | p value |
|---|---|---|---|---|---|
| TAS* Preoperative | 1.55 | 0.27 | 1.52 | 0.32 | 0.66 |
| TAS Intraoperative | 1.59 | 0.4 | 1.60 | 0.22 | 0.13 |
| TAS Postoperative | 1.55 | 0.28 | 1.62 | 0.36 | 0.4 |
| TOS** Preoperative | 18.09 | 16.77 | 24.24 | 3.11 | 0.16 |
| TOS Intraoperative | 18.96 | 17.68 | 36.59 | 48.62 | 0.050 |
| TOS Postoperative | 20.54 | 25.59 | 62.33 | 119.56 | 0.14 |

*TAS:Total Antioxidant Status, **TOS:Total Oxidant Status

**Table III:** Comparison of groups in terms of lipid peroxide, malondialdehyde, and cystatin C values.

| Characteristic | Group 1 (n=31) Mean±Std | | Group 2 (n=29) Mean±Std | | p value |
|---|---|---|---|---|---|
| LPO* Preoperative | 24,57 | 23,47 | 35,34 | 32,75 | 0,41 |
| LPO Intraoperative | 24,52 | 24,28 | 37,52 | 32,91 | 0,13 |
| LPO Postoperative | 23,11 | 24,18 | 38,09 | 34,33 | 0,06 |
| MDA** Preoperative | 25,19 | 19,85 | 34,47 | 28,96 | 0,34 |
| MDA Intraoperative | 26,36 | 20,54 | 37,35 | 30,43 | 0,14 |
| MDA Postoperative | 23,21 | 19,95 | 35,79 | 28,98 | 0,048 |
| Cyt c*** Preoperative | 28,82 | 21,45 | 34,80 | 25,82 | 0,53 |
| Cyt c Intraoperative | 28,29 | 21,52 | 37,87 | 25,15 | 0,18 |
| Cyt c Postoperative | 25,33 | 18,76 | 35,64 | 26,48 | 0,33 |

*LPO: Lipid Peroxide, **MDA:Malondialdehyde and ***Cyt c:Cystatin C

**Table IV:** Comparison of groups in terms of 8-hydroxydeoxyguanosine values.

| Characteristic | Group 1 (n=31) Mean±Std | | Group 2 (n=29) Mean±Std | | p value |
|---|---|---|---|---|---|
| Preoperatif 8-OHdG | 23.25 | 22.13 | 33.88 | 30.16 | 0.12 |
| Intraoperative 8-OHdG | 24.27 | 22.56 | 36.51 | 30.55 | 0.052 |
| Postoperative 8-OHdG | 22.25 | 22.03 | 35.44 | 29.84 | 0.15 |

*8-OHdG: 8-hydroxydeoxyguanosine

## Discussion

In this work, we evaluated the effects of low flow and high flow desflurane anesthesia on oxidative stress and DNA damage. We discovered that the high flow desflurane group had considerably higher postoperative MDA levels than the low flow group. Although the hemodynamic characteristics of our patients were similar, we discovered that the low flow group had a considerably higher 90th minute $ETCO_2$ value. The two groups did not vary when we analyzed DNA damage and other oxidative stress indicators.

As is well known, membrane lipids are the components of cells that suffer the most harm from free oxygen radicals. MDA, a byproduct of lipid peroxidation, is utilized as a sign of damage brought on by oxidative stress[10] Allaouchiche et al. evaluated MDA levels after giving desflurane and propofol to pigs in their study. Animals treated with desflurane had considerably greater MDA concentrations than those treated with propofol, according to the researchers[11]. Desflurane and sevoflurane anesthesia were contrasted in laparoscopic cholecystectomy patients by Köksal et al. They noted that systemic and local lipid peroxidation as well as MDA levels were significantly greater in the desflurane administered group[12] Nevertheless, Kantekin et al. looked into how desflurane at various flow rates affected oxidative stress and free radicals in rats. The researchers separated the rats into three groups and found that the high flow desflurane group had considerably greater serum, brain, and liver MDA and SOD levels than the other groups[13]. We found results in our investigation that were comparable to those of Kantekin et al. Patients who underwent high flow desflurane anesthesia exhibited significantly greater MDA levels than the low flow desflurane group at the 24-hour postoperative mark.

The occurrence of hyperoxia in high flow anesthetic treatments is unavoidable. In cell culture and ischemia reperfusion experiments, hyperoxia results in an increase in ROS[14,15,16]. As a result, we believe that one of the reasons of oxidative stress is the high flow anesthetic approach. Because the increase in oxidative stress measures can be explained by high $FiO_2$ exposure, given that the desflurane MAC values in our study groups were equal. As the level of breathed oxygen declines as the fresh gas flow is lowered, the patient's risk of hypoxia rises. Obata et al. reported in their investigation that sufficient oxygen levels were given during maintenance with $FiO_2$ set at 30% to prevent hypoxia[17]. In our study, we determined that the minimum inspired oxygen concentration should be 32%. None of our patients experienced clinical hypoxia.

The study by Yüce et al., in which they analyzed individuals who were to have thyroid and parathyroid surgery, must be emphasized when the studies in the literature on TAS, Cyct-C, LPO, and TOS, which are other markers of oxidative stress, are examined. In this investigation, the patients were split into two groups and given desflurane at rates of 0.5 L/min and 1 L/min, respectively, to examine the preoperative, intraoperative, and postoperative oxidative stress markers. At the first postoperative hour, the TAS and Cyct-C were statistically significantly lower in the 0.5 L/flow group than in the 1 L/flow group. There was no discernible difference between the two groups' TAS and CYct-C levels at the postoperative 24th hour[18] The preoperative, intraoperative, and postoperative TAS, CYct-c, LPO, and TOS values in our investigation, however, did not show a statistically significant difference.

Desflurane-related genotoxicity has been noted in investigations on the production of DNA damage by anesthetics when cells are exposed to desflurane in vitro. Halothane, isoflurane, sevoflurane, and desflurane are volatile anesthetics that Kaymak et al. reported to cause DNA damage in cells in their in vitro tests. However, no genotoxic effect was found at any desflurane exposure dose when sperm cells were evaluated[19]. Desflurane can increase genotoxicity in a dose-dependent manner, as Karpinski et al. demonstrated in their experimental investigation[20] Akin et al. demonstrated in a related investigation that desflurane exposure increases sister chromatid exchange in human cells. As a result, they stated that exposure to large doses of desflurane may result in genetic harm[21]. However, Branz et al investigations. 's examining the genotoxic effects of inhaler (isoflurane and sevoflurane) and intravenous (i.v.) anesthetic drugs (propofol) found no indication of DNA damage[22]. In order to assess the local genotoxicity of sevoflurane and desflurane in bronchoalveolar cells and to identify systemic DNA damage, Zafer et al. measured 8-OHdG levels in preoperative and postoperative bronchoalveolar lavage and serum samples from patients who were scheduled to undergo lumbar discectomy. They discovered no discernible change in 8-OHdG levels or comet properties between the two groups. But compared to the baseline levels, they discovered a significant rise in both the sevoflurane and desflurane groups[23]. Nogueira et al. examined desflurane-air and desflurane-60% $N_2O$ anesthesia maintenance techniques in their prospective randomized clinical investigations and discovered no significant differences in the biomarkers assessed for DNA damage[25]. There was no discernible change in the blood levels of 8-OHdG across the groups in Kantekin et al study's on rats (Group 1: control group; Group 2: patients treated desflurane at an 8 L/min flow rate; Group 3: patients administered desflurane at a 2 L/min flow rate). Both groups' levels of 8-OHDG in brain and liver tissue were greater than those in the control group[14]. Our study's findings are consistent with those of Kantekin et al. In our investigation, we were unable to find a significant difference between the two groups' serum 8-OHdG levels. Elmacolu et al. divided patients into three groups according to fresh gas flow rate as medium flow (2 L/min), low flow (1 L/flow), and minimum flow (0.5 L/flow) after taking into account studies in

the literature examining the effects of low and high flow inhaled agents on hemodynamic and respiratory parameters. In terms of hemodynamics, there was no statistically significant difference between the groups[25] In patients receiving one-lung ventilation, Geyik et al. compared the effects of 1L/min and 2L/min desflurane anesthesia on hemodynamic parameters, arterial blood gas values, and gas consumption. They discovered that $EtCO_2$ was statistically significantly lower in the 2L/flow group, particularly between 30 and 75 minutes of one-lung ventilation[26] This outcome is comparable to what we found in our investigation. In our investigation, there was no hemodynamic distinction between the two groups. Only at 90 minutes did the $ETCO_2$ levels between the two groups differ significantly. The low flow group was found to have considerably greater $ETCO_2$. Rebreathing during the use of low flow anesthetic was assumed to be the cause. In conclusion, in our study, there was no difference in terms of DNA damage in patients who were administered low flow desflurane anesthesia compared to the patients who were administered high flow desflurane, but the oxidative stress in the group administered high flow desflurane increased at the postoperative 3rd hour.

This study has some limitations. First, it was a single-center study. Secondly, the number of our patients was not high enough. This issue warrants multicenter and multidisciplinary studies with more patients.

Considering the use of safe anesthesia devices, its positive effects on the ecological system, the decrease in the amount of economically used volatile agent, the formation of a more suitable mucociliary clearance, and the reduction of heat-moisture loss, we recommend the use of low flow anesthesia with close monitoring of the patient.

### Conflicts of interest

The authors declare no conflicts of interest.

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ORIGINAL

# Impact of adherence to the Mediterranean diet on health-related quality of life in poorly controlled diabetics

*Impacto de la adherencia a la dieta mediterránea en la calidad de vida relacionada con la salud en diabéticos mal controlados*

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## Summary

***Introduction:*** When analyzing the current situation in Spain, derived from our current lifestyles far from following a Mediterranean lifestyle, there is an alarming prevalence of diabesity, which increases the global risk of suffering from cardiovascular disease (CVD) and decreases the quality of life related to health (QLRH). In order to guarantee, beyond glycemic control of patients with type 2 diabetes (DM2), adequate control of cardiovascular risk factors (CVRF) in DM2, it will be necessary to carry out a community intervention focused on the application of education programs focused on promoting the acquisition of healthy eating habits through the Mediterranean diet (DMED). This dietary pattern, together with physical exercise, has been shown to contribute to improving the QLRH of patients.

***Objective:*** To analyze the quality of life related to health, present in patients with poorly controlled type 2 diabetes, to determine the possible relationship between this and the degree of adherence to the Mediterranean diet and to examine whether there are differences between the sexes.

***Methods:*** Observational descriptive study in 93 patients diagnosed with DM2 with poor glycemic control (1Ac ≥ 7%), carried out in various health centers in Albacete and Cuenca, in which the baseline relationship between adherence to DMed and the HRQoL. They were administered a data collection sheet that included a survey of the degree of adherence to the DMed (MEDAS-14) and QLRH (SF-12v2) in the Primary Care (PC) medical and nursing consultations. The variables were analyzed: age groups, sex, years of evolution of DM2, body mass index (BMI), as well as basal glycemia (GB) and glycosylated hemoglobin (HbA1c). The "MEDAS-14" (adherence to DMED) was the main variable and the "SF-12v2" (QLRH) was the secondary variable.

***Results:*** Patients with poorly controlled DM2 and with low adherence to the MedDM show a non-significantly greater affectation in the physical sphere: fair general state of health, physical function I (limitation to make moderate efforts such as moving a table, vacuuming or walk more than an hour), physical function II (limitation to climb several flights of stairs), physical role (problems at work or daily activities doing less than loved ones), physical role II (they had to stop performing some tasks at work or activities of daily living) and regular body pain. Presenting less affectation in the mental field: emotional role I, emotional role II, mental health I, vitality and mental health II. Without affectation in the social function since they consider that rarely the emotional or physical problems have hindered their social activities.

***Conclusions:*** Diabetic patients with poor glycemic control have low adherence to the MedMD (<9 points) and have poor QLRH. Low adherence to the DMed and obesity are related to a greater affectation in the physical dimension and less affectation in the mental dimension without affectation in the "social function".

*Key words:* Quality of life, Mediterranean diet, MEDAS-14, type 2 diabetes, physical dimension, emotional dimension.

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## Resumen

***Introducción:*** El análisis de los hábitos de vida actuales en España, evidencian que lejos de seguir un estilo de vida mediterráneo, existe una prevalencia alarmante de diabesidad, que aumenta el riesgo global de padecer enfermedades cardiovasculares (ECV) y disminuye la calidad de vida relacionada a la salud (CVRS). Para garantizar, un adecuado control de los factores de riesgo cardiovascular (FRCV) en la DM2, más allá del control glucémico de los pacientes con esta patología, es necesario realizar una intervención comunitaria enfocada a aplicar programas educativos que promuevan la adquisición de hábitos alimentarios saludables a través de la dieta mediterránea (DMED). Se ha demostrado que este patrón dietético, junto con el ejercicio físico, contribuye a mejorar la CVRS de los pacientes.

***Objetivo:*** Analizar la calidad de vida relacionada con la salud, en pacientes con diabetes tipo 2 mal controlada, determinar la posible relación entre ésta y el grado de adherencia a la dieta mediterránea y examinar si existen diferencias entre sexos.

***Material y métodos:*** Estudio descriptivo observacional en 93 pacientes diagnosticados de DM2 con mal control glucémico (1Ac ≥ 7%), realizado en varios centros de salud de Albacete y Cuenca, en los que se analizó la relación basal entre la adherencia a la DMed y la CVRS. Se les administró una ficha de recogida de datos que incluía una encuesta del grado de adherencia al DMed (MEDAS-14) y QLRH (SF-12v2) en las consultas médicas y de enfermería de Atención Primaria (AP). Se evaluaron las variables: grupos de edad, sexo, años de evolución de la DM2, índice de masa corporal (IMC), glucemia basal (GB) y hemoglobina glicosilada (HbA1c). El "MEDAS-14" (adherencia a DMED) fue la variable principal y el "SF-12v2" (QLRH) fue la variable secundaria.

***Resultados:*** Los pacientes con DM2 mal controlados y con baja adherencia a la MedDM presentan una afectación no significativa mayor en el ámbito físico: estado general de salud regular, función física I (limitación para realizar esfuerzos moderados como mover una mesa, pasar la aspiradora o caminar más de una hora), función física II (limitación para subir varios tramos de escaleras), rol físico (problemas en el trabajo o actividades diarias haciendo menos que los seres queridos), rol físico II (tuvo que dejar de realizar algunas tareas en el trabajo o actividades de la vida diaria) y dolor corporal regular. Menor afectación en el campo mental: rol emocional I, rol emocional II, salud mental I, vitalidad y salud mental II. Sin afectación en la función social al considerar que rara vez los problemas emocionales o físicos han dificultado sus actividades sociales.

***Conclusiones:*** Los pacientes diabéticos con mal control glucémico tienen baja adherencia al MedMD (<9 puntos) y mala CVRS. La baja adherencia a la DMed y la obesidad se relacionan con mayor afectación en la dimensión física y menor afectación en la dimensión mental, sin que afecte a la "función social".


*Palabras clave:* Calidad de vida, dieta mediterránea, MEDAS-14, diabetes tipo 2, dimensión física, dimensión emocional.

## Introduction

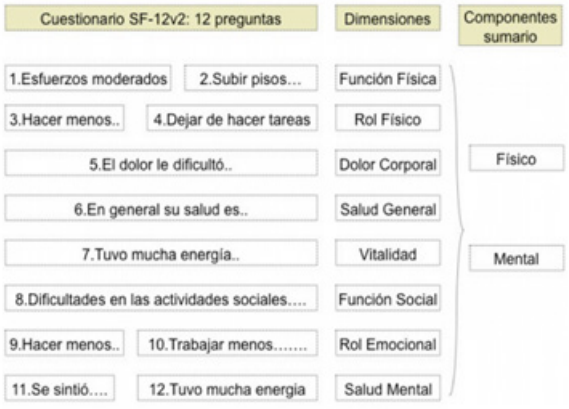
Changes in lifestyle have been modifying nutritional culture throughout history, transforming our traditional dietary habits since childhood[1,2]. Likewise, the state of confinement COVID-19 has implied changes in the life habits and dietary profiles of the population[3,4].

Health is the favorable result of the interaction between various determinants (biological, sociocultural, linked to lifestyle and health care system) according to the Lalonde[5] classification, whose harmony allows optimizing quality of life at the individual and collective level.

The term Quality of Life (QOL) arose in the mid-seventies, as a concept that refers to the perception of well-being by the individual, collecting objective and subjective aspects[6]. Health-related quality of life (QLRH), or perceived health, integrates those aspects of life directly related to physical, mental, emotional, social functioning and the state of well-being. It is used to assess the impact of chronic diseases and the effectiveness of individual medical treatments on health. Therefore, the conceptual model of HRQOL[6] is multidimensional and can be considered as one of the determinants of the level of health that adds the value of quantifying the perception (of the subject) of illness and health, as well as its consequences. Achieving a better quality of life in old age depends on aspects related to lifestyles[1].

The SF-12v2 is a reduced version of the SF-36 questionnaire, adapted for Spain by Alonso et al (2002)[7], unlike version 1, it is applicable to the general population and to patients with a minimum age of 14 years. This is a self-administered questionnaire, whose completion time is less than 2 minutes, unlike the SF-36 (between 5 and 10 min). It consists of 12 items from the 8 dimensions of the SF-36 that provide a profile of health status: Physical Function (2), Social Function (1), Physical Role (2), Emotional Role (2), Mental Health (2), Vitality (1), Body Pain (1) and General Health (1) (**Figure 1**)[7].

**Figure 1:** Content of the Spanish version SF-12 adapted by J. Alonso et al. et al.



The Mediterranean diet (DMed) is classically defined as the eating pattern typical of the early sixties in the countries of the Mediterranean area (Greece, southern Italy and Spain)[8], characterized by containing a high content of monounsaturated fats and low in fatty acids[9].

In Spain, derived from current lifestyles far from a Mediterranean lifestyle, there is a high prevalence of DM2 together with obesity (diabesity)[10,11], two of the great epidemics of the 21st century that increase CVD and decrease the (QLRH)[12,13]. Therefore, it was proposed to assess the effects of MedDM on the quality of life of diabetics.

**Figure 2:** MedD adherence test (MEDAS-14) in Spanish from the PREDIMED study..

| | | |
|---|---|---|
| **1. ¿Usa usted el aceite de oliva como principal grasa para cocinar?** | Sí = 1 punto | |
| **2. ¿Cuanto aceite de olliva consume en total al día (incluyendo el usado para freir, comidas fuera de casa, ensaladas, etc.)?** | 4 o más cucharadas = 1 punto | |
| **3. ¿Cuántas raciones de verdura u hortalizas consume al día?** (las guarniciones o acompañamientos = 1/2 ración) 1 ración = 200 g | 2 o más (al menos una de ellas en ensalada o crudas = 1 punto | |
| **4. ¿Cuantas piezas de fruta (incluyendo zumo natural) consume al día?** | 3 o más al día = 1 punto | |
| **5. ¿Cuantas raciones de carnes rojas , hamburguesas, salchichas o embutidos consume al día?** (ración: 100-150 g) | menos de 1 al día = 1 punto | |
| **6. ¿Cuantas raciones de mantequilla, margarina o nata consume al día?** (porción individual: 12 g) | menos de 1 al día = 1 punto | |
| **7. ¿Cuantas bebidas carbonatadas y/o azucaradas (refrescos, colas, tónicas, bitter) consume al día?** | menos de 1 al día = 1 punto | |
| **8. ¿Bebe usted vino? ¿Cuánto consume a la semana?** | 7 o más vasos a la semana = 1 punto | |
| **9. ¿Cuentas raciones de legumbres consume a la semana?** (1 plato o ración de 150 g) | 3 o más a la semana = 1 punto | |
| **10. ¿Cuantas raciones de pescado-mariscos consume a la semana?** (1 plato pieza o ración de 100-150 de pescado o 4-5 piezas o 200 g de marisco) | 3 o más a la semana = 1 punto | |
| **11. ¿Cuantas veces consume repostería comercial (no casera) como galletas, flanes, dulce o pasteles a la semana?** | menos de 2 a la semana = 1 punto | |
| **12. ¿Cuantas veces consume frutos secos a la semana?** (ración 30 g) | 3 o más a la semana = 1 punto | |
| **13. ¿Consume usted preferentemente carne de pollo, pavo o conejo en vez de ternera, cerdo, hamburguesas o salchichas?** (carne de pollo: 1 pieza o ración d e100 - 150 g) | Sí = 1 punto | |
| **14. ¿Cuantas veces a la semana consume los vegetales cocinados, la pasta, arroz u otros platos aderezados con salsa de tomate, ajo, cebolla o puerro elaborada a fuego lento con aceite de oliva (sofrito)?** | 2 o más a la semana = 1 punto | |

**Figure 3:** HRQoL test (SF-12V2). Own elaboration.

| | Ítems | Basal |
|---|---|---|
| 1 | In general, would you say that your health is | |
| 2 | Moderate efforts such as moving a table, vacuuming, bowling, or walking for more than 1 hour | |
| 3 | Climb several floors up the stairs | |
| 4 | Did you do less than you wanted to during the last 4 weeks? | |
| 5 | Did you have to stop doing some tasks at work or in your daily activities? | |
| 6 | Did you do less than you would have liked to do because of a family problem? | |
| 7 | Did you not do your work or your daily activities as carefully as usual, due to some emotional problem? | |
| 8 | During the past 4 weeks, to what extent has pain interfered with your usual work (including work outside the home and household chores)? | |
| 9 | During the past 4 weeks, how much time did you feel calm and peaceful? | |
| 10 | During the last 4 weeks, how much time did you have a lot of energy? | |
| 11 | During the past 4 weeks, how much time have you felt down and sad? | |
| 12 | During the past 4 weeks, how often have physical health or emotional problems made it difficult for you to do social activities (such as visiting friends or family)? | |
| | TOTAL SCORE SF-12V2 | |

## Method

This is a multicenter study in which adult type 2 diabetic patients with poor glycemic control (A1c greater than 7%) from various health centers in Albacete and Cuenca participated during the period between 2018 and 2019. A study is carried out Descriptive observational study to know the usual eating habit and the QLRH. To this end, it is proposed to use it due to its ease of use and after having demonstrated how effective it is to use tools such as the MEDAS-14[14] questionnaire to quantify adherence to the MedD and the SF-12v2[7] to determine the psychological effect that the disease has on their individual and social context.

The MEDAS-14[14] questionnaire (**Figure 2**), consisting of the assessment of adherence to the MedD based on the 14-point score also validated in the British population. A score greater than or equal to 9 points is a good level of adherence, values less than or equal to 8 are considered poor adherence.

The SF-12v2[7] questionnaire (**Figure 3**) is a qualitative variable to assess the initial HRQoL of DM2, using 12 items to provide a profile of the state of general health, well-being, and functional capacity. The version includes two dimensions (physical and mental) through eight health concepts such as general health (personal assessment of health), physical function (extent to which health limits physical activities), physical role (extent to which physical health interferes with work and daily activities), emotional role (extent to which emotional problems interfere with work or other activities), bodily pain (intensity of pain), mental health (general), vitality (feeling of energy and vitality) and social function (degree of physical and emotional health that affect normal social life).

According to the consulted bibliography, if the condition was not met, it is recorded with 0 points. If the condition was met, it is recorded with 1 point; If there are several options, it is recorded with 1,2,3,4 or 5 (from worst to best option) points for the category. However, there is no defined score range to classify HRQoL as good or bad.

### Statistic analysis

The statistical analysis was performed with the statistical package SPSS® (Statistical Package for Social Sciences) in its version 24.0. A descriptive analysis of the variables of interest was carried out, in which their distribution was observed in order to define cut-off points. To measure adherence to MedDM, the MEDAS-14 was assessed, classifying the participants into two categories: high adherence for a score ≥ 9, and low adherence if < 9. The qualitative variables were presented through the frequency distribution of the percentages of each category while in the quantitative variables it was explored whether or not they followed a normal distribution using the Kolmogorov-Smirnov test, and indicators of central tendency (mean or median) and dispersion (standard deviation or percentiles) were given. The association between these factors was investigated using hypothesis contrast tests, with comparison of proportions when both were qualitative (Chi square, Fisher's exact test); comparisons of means when one of them was quantitative (Student's t test, ANOVA), and if they did not follow a normal distribution, the Mann-Whitney U test, Kruskall-Wallis and Friedman in the case of repeated measures. Linear regression tests were performed when the dependent variable was quantitative. In the case of qualitative variables, the relative risk (RR) was calculated for the different proportions and their CIs. The analysis was complemented with graphic representations. The statistical significance level for this study was $p \leq 0.05$.

### Ethical aspects

The study was carried out following the recognized Ethics Standards and the Standards of Good Clinical Practice. The data was protected from uses not permitted by persons unrelated to the investigation and confidentiality was respected regarding the Protection of Personal Data and Law 41/2002, of November 14, the basic law regulating patient autonomy and rights. and obligations regarding information and clinical documentation. Therefore, the information generated in this study has been considered strictly confidential, between the participating parties.

## Results

Throughout the study, 93 adult diabetic patients participated, of which 60% were women with a mean age of 64 +/- 9 years. The BMI at the beginning was 32 kg/m$^2$ (grade I obesity), with a basal glycemia of 158mg/dl and a mean glycosylated hemoglobin of 7.88% (poor glycemic control). That is, the patients presented diabesity with poor metabolic control.

#### *1. Assessment of quality of life*

**Table I** shows the results of the 12 items of the SF-12v2 questionnaire on initial HRQoL, compared between women and men.

#### *2. Relationship between variables*

**Table I:** Items of the SF-12v2 questionnaire answered according to sex. Source: self made.

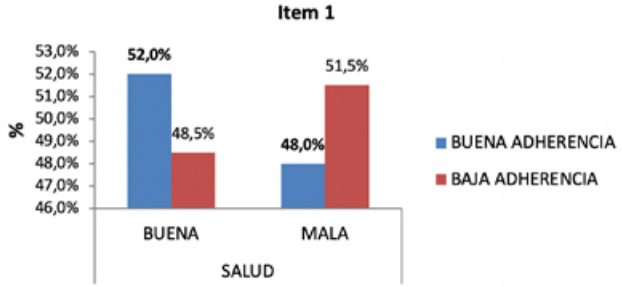
| | MEN | WOMAN | TOTAL | p |
|---|---|---|---|---|
| **ITEMS HRQoL SF-12v2** | | | | |
| **1st GENERAL HEALTH** | | | | |
| Excellent | 0 | 1,1%(n = 1) | 1,1% (n = 1) | NS |
| Very good | 0 | 4,3%(n = 4) | 4,3% (n = 4) | |
| Good | 15,1% ( n = 14) | 29% (n = 27) | 44,1% (n =41) | |
| Regular | 22,6% (n = 21) | 23,7% (n = 22) | 46,2% (n = 43) | |
| Bad | 2,2% (n = 2) | 2,2% (n = 2) | 4,3% (n = 4) | |
| **2nd PHYSICAL ROLE I** | | | | |
| it limits me a lot | | | | NS |
| limits me a bit | 7,5% (n = 7) | 3,2% (n = 3) | 10,8% (n = 10) | |
| nothing limits me | 23,7% (n = 22) | 36,6% (n = 34) | 60,2% (n = 56) | |
| **3rd PHYSICAL ROLE II** | | | | |
| it limits me a lot | 6,5% (n = 6) | 5,4% (n = 5) | 11,8% (n = 11) | |
| limits me a bit | 26,9% (n = 25) | 40,9% (n = 38) | 67,7% (n = 63) | |
| nothing limits me | 6,5% (n = 6) | 14% (n = 13) | 20,4% (n = 19) | |
| **4th PHYSICAL FUNCTION I** | | | | |
| Yeah | 24,7% (n = 23) | 26,9% (n = 25) | 51,6% (n = 48) | NS |
| No | 15,1% (n = 14) | 33,3% (n = 31) | 48,4% (n = 45) | |
| **5th PHYSICAL FUNCTION II** | | | | |
| Yeah | 23,7% (n =22) | 24,7% (n = 23) | 48,4 (n = 45) | NS |
| No | 16,1% (n = 15) | 35,5% (n = 33) | 51,6% (n = 48) | |
| **6th EMOTIONAL ROLE I** | | | | |
| Yeah | 15% (n = 14) | 23,7% (n = 22) | 38,7% (n = 36) | NS |
| No | 24,7% (n = 23) | 36,6% (n = 34) | 61,3% (n = 57) | |
| **7th EMOTIONAL ROLE II** | | | | |
| Yeah | 17,2% (n = 16) | 26,9% (n = 25) | 44,1% (n = 41) | NS |
| No | 22,6% (n = 21) | 33,3% (n =31) | 55,9% (n = 52) | |
| **8th BODY PAIN** | | | | |
| A lot | 1,1% (n = 1) | 0 | 1,1% (n = 1) | NS |
| Quite | 4,3% (n = 4) | 5,4% (n = 5) | 9,7% (n = 9) | |
| Regular | 18,3% (n = 17) | 19,4% (n = 18) | 37,6% (n = 35) | |
| A bit | 14% (n = 13) | 21,5% (n = 20) | 35,5% (n = 33) | |
| Nothing | 2,2% (n = 2) | 14% (n = 13) | 16,1% (n = 15) | |
| **9th MENTAL HEALTH I** | | | | |
| Always | 2,2%(n = 2) | 1,1% (n = 1) | 3,3% (n = 3) | < 0,048 |
| Almost always | 15,1% (n = 14) | 21,5% (n = 20) | 36,6% (n = 34) | |
| Many times | 5,4% (n = 5) | 23,7% (n = 22) | 29% (n = 27) | |
| Sometimes | 16,1% (n = 15) | 11,8% (n = 11) | 28% (n = 26) | |
| Just once | 1,1% (n = 1) | 2,2% (n = 2) | 3,3% (n = 2) | |
| Never | 0 | 0 | 0 | |
| **10th VITALITY** | | | | |
| Always | 2,2% (n = 2) | 0 | 2,2% (n = 2) | NS |
| Almost always | 3,2% (n = 3) | 9,7% (n = 9) | 12,9% (n = 12) | |
| Many times | 9,7% (n = 9) | 16,1% (n = 15) | 25,8% (n = 24) | |
| Sometimes | 18,3% (n = 17) | 29% (n = 27) | 47,3% (n = 44) | |
| Just once | 3,2% (n = 3) | 5,4% (n = 5) | 8,6% (n = 8) | |
| Never | 3,2% (n = 3) | 0 | 3,2% (n = 3) | |
| **11th MENTAL HEALTH II** | | | | |
| Always | 1,1% (n = 1) | 0 | 1,1% (n = 1) | NS |
| Almost always | 0 | 1,1% (n = 1) | 1,1% (n = 1) | |
| Many times | 8,6% (n = 8) | 9,7% (n = 9) | 18,3% (n = 17) | |
| Sometimes | 17,2% (n = 16) | 26,9% (n = 25) | 44,1% (n = 41) | |
| Just once | 7,5% (n = 7) | 10,8% (n = 10) | 18,3% (n = 17) | |
| Never | 5,4% (n = 5) | 11,8% (n = 11) | 17,2% (n = 16) | |
| **12th SOCIAL FUNCTION** | | | | |
| Always | 0 | 2,2% (n = 2) | 2,2% (n = 2) | NS |
| Almost always | 11,8% (n = 11) | 14% (n = 13) | 25,8% (n = 24) | |
| Rarely | 23,7% (n = 22) | 33,3% (n = 31) | 57% (n = 53) | |
| Never | 4,3% (n = 4) | 10,8% (n = 10) | 15,1% (n = 14) | |

## 1. Adherence to DMED (MEDAS-14):

No significant results are obtained, but it is worth noting:

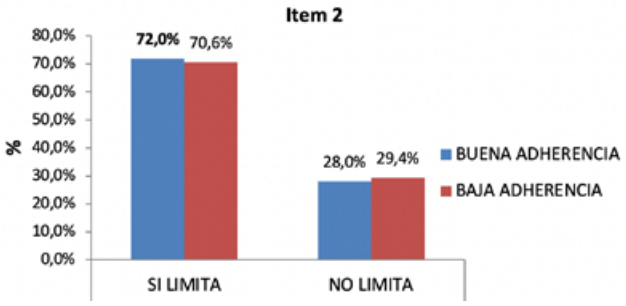
- **1st General health:** After delimiting "good health" and "bad health", in good adherence the response rates of good conception of their health is 52% compared to 48.5% in low adherence; Likewise, their conception of poor health is higher in low adherence with 51.5% compared to 48% in good adherence (**Figure 4**).

**Figure 4:** Relationship Item 1 SF12 with MEDAS-14 score. Source: self made.



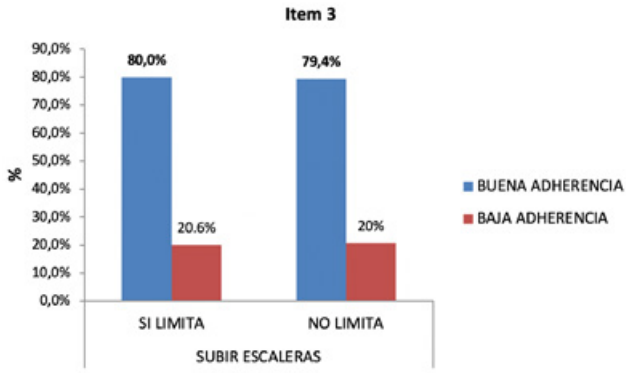
- **2nd Physical function I:** After delimiting "if it limits" and "does not limit", there are similar limitations in both groups both in "if it limits me" (72% vs. 71%), and in "it does not limit me" (28 % vs. 29%) (**Figure 5**).

**Figure 5:** Relationship Item 2 SF12 with MEDAS-14 score. Source: self made.



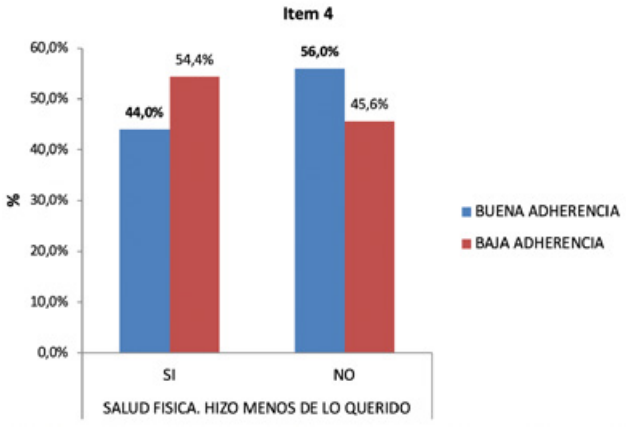

- **3rd Physical function II:** After delimiting "yes it limits" and "does not limit", the 47% with low adherence consider that they are somewhat limited to climb several floors up the stairs, it limits them a lot to the 10% of low adherence compared to the 1% good adherence (**Figure 6**).

**Figure 6:** Relationship Item 3 SF12 with MEDAS-14 score. Source: self made.



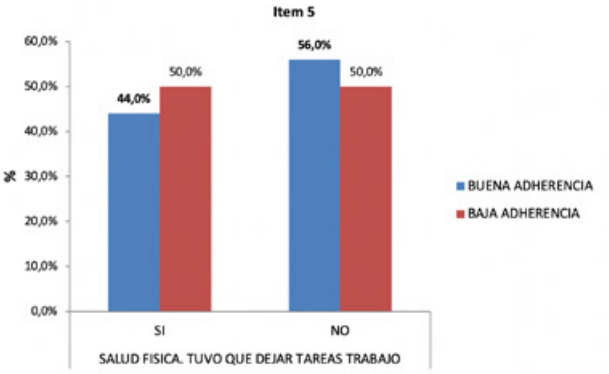

- **4th Physical Role I:** 54.4% of those with low adherence answered affirmatively (they did less than they would have wanted to do) and 56% of those with good adherence answered negatively (they did not do less than they wanted) (**Figure 7**).

**Figure 7:** Relationship Item 4 SF12 with MEDAS-14 score. Source: self made.



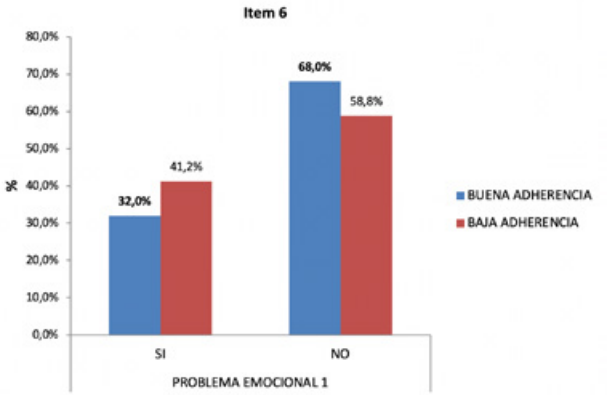

- **5th Physical role II:** 56% of the good adherence did not consider giving up any task at work because of their physique (**Figure 8**).

**Figure 8:** Relationship Item 5 SF12 with MEDAS-14 score. Source: self made.



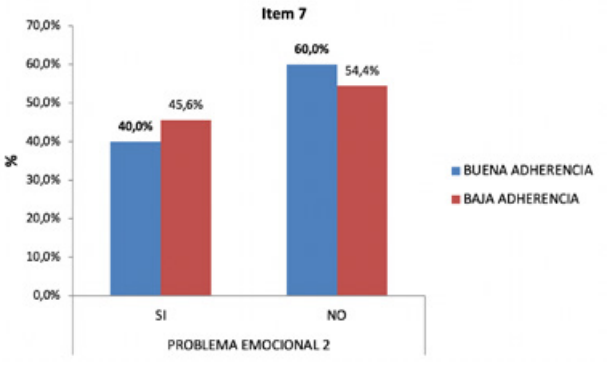

- **6th Emotional Role I:** During the last 4 weeks, 68% with good adherence and 58% with low adherence do not consider having problems at work due to any emotional problem (**Figure 9**).

**Figure 9:** Relationship Item 6 SF12 with MEDAS-14 score. Source: self made.



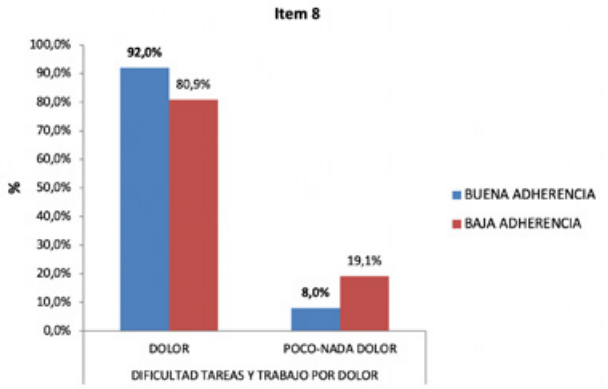

- **7th Emotional Role II:** 60% with good adherence and 55% of those with low adherence did not have to stop doing their daily activities so carefully due to emotional problems (**Figure 10**).

**Figure 10:** Relationship Item7 SF12 with MEDAS-14 score. Source: self made.



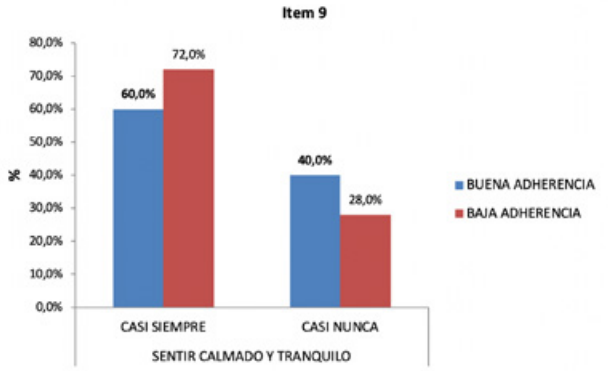
- **8th Body pain:** After delimiting the answers in "pain" and "little/no pain", during the last 4 weeks, both 92% with good adherence and 81% with low adherence considered that they had some degree of pain that made their usual work difficult (**Figure 11**).

**Figure 11:** Relationship Item 8 SF12 with MEDAS-14 score. Source: self made.



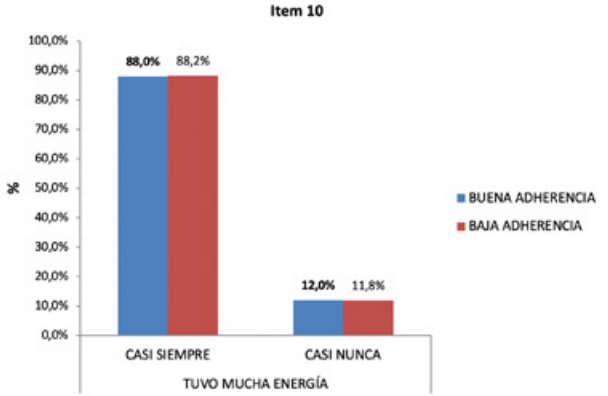

- **9th Mental health:** After narrowing down to "almost always" and "almost never", 72% with low adherence compared to 60% with good adherence, considered that in the last 4 weeks they almost always felt calm and calm (**Figure 12**).

**Figure 12:** Relationship Item 9 SF12 with MEDAS-14 score. Source: self made.



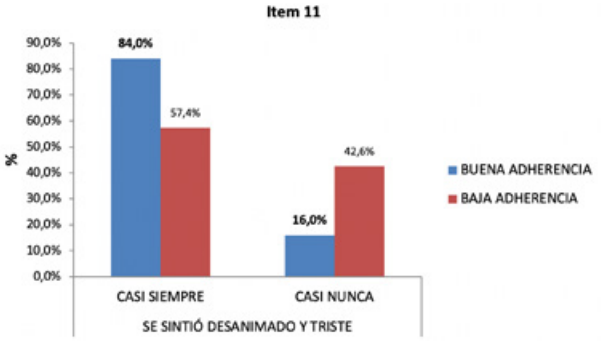

- **10th Vitality:** 88.2% with low adherence compared to 88% with good adherence almost always had a lot of energy (**Figure 13**).

**Figure 13:** Relationship Item10 SF12 with MEDAS-14 score. Source: self made.



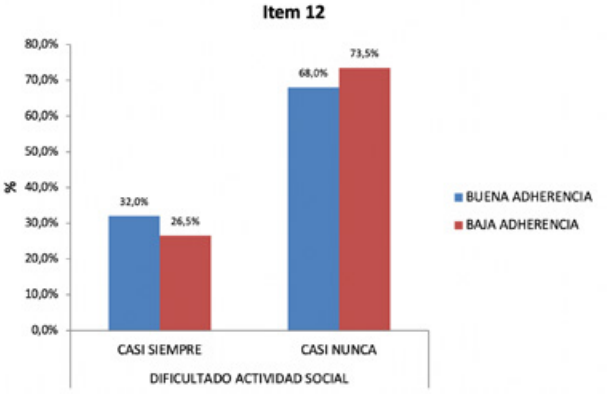

- **11th Mental Health I:** After delimiting "almost always" and "almost never", 84% of the patients with good adherence compared to 57% of those with low adherence, considered that in the last 4 weeks they felt discouraged and sad almost always (**Figure 14**).

**Figure 14:** Relationship Item 11 SF12 with MEDAS-14 score. Source: self made.




- **12th Social function:** After delimiting "almost always" and "almost never", in the last 4 weeks, only 26% of those with low adherence and 32% of those with good health had affected their social activity (**Figure 15**).

**Figure 15:** Relationship Item 12 SF12 with MEDAS-14 score. Source: self made.




## 2. Degrees of obesity:

No significant results are obtained, but it is worth noting:

- **1st General health:** Despite the fact that 42% of the obese consider themselves to be in good health, 40% consider that they are in regular health; as well as 4.5% of overweight patients and 2% of normal weight patients.
- **2nd Physical function I:** Half of the obese (53%) responded to a greater physical limitation than the overweight (5%) and or normal weight 2%.
- **3rd Physical function II:** In the same way, most of the obese (60%) consider that they are somewhat limited to climb several floors.
- **4th Physical Role I:** 52% of the patients, 47% being obese, did less than they would have wanted to do limited by their physical health.
- **5th Physical Role II:** The same percentage (52%, 47% of obese) did not consider having to stop doing any task at work.

- **6th Emotional Role I:** 61% of the total (56% of obese) do not consider having emotional problems to do less than expected.
- **7th Emotional Role II:** 56% of the total (50% of obese) did not have to stop doing tasks at work due to emotional problems.
- **8th Body pain:** 34% of the obese had regular pain that made their usual work difficult. However, the majority of overweight patients (3.2%) considered they had no pain.
- **9th Mental health:** 36% of the obese compared to 2% of overweight considered that they almost always felt calm and calm.
- **10th Vitality:** The 60% of overweight people often had a lot of energy, unlike the 45% of the obese who only sometimes.
- **11th Mental Health I:** 44% of the obese considered that in the last 4 weeks they felt discouraged and sad only sometimes.
- **12th Social function:** 55% of the obese considered that their health had rarely affected their social activity and 15% of the total (14% obese, 1% overweight) never.

## Discussion

QoL is a subject that is currently gaining much interest in health, especially in chronic pathologies[15]. There is currently little evidence available about the real impact of DM on HRQoL, since most of the research on HRQoL in DM has been directed more to the study of differences between subgroups according to possible determinants of health[16], than to the study of its impact.

The source of information for most of the studies that assess the impact of DM on HRQoL comes from health surveys conducted in the general population[17]. Despite the fact that there are 22 specific questionnaires to assess HRQoL in DM that report on the patient's perception of how diabetes affects their well-being and health in their physical and mental areas, only the 5 questionnaires in the Spanish version (ADDQoL-19, DAS -3sp, DQOL, DTSQ and MIAT-D) show great variability in measurements, standards and scales, which makes it difficult to compare results[16].

According to the different studies on DM, the dimensions that are most important are those that have to do with physical and psychosocial function and disease control[16,17,18].

Priority has been given to the use of a generic instrument, such as the SF-12v2, a subjective measure that is easy to apply individually, which has made it possible to obtain not only a physical profile, but also a mental and social one, in relation to HRQoL[15].

In this study, we found a non-significant association between good/low adherence to MedD and the dimensions of the SF-V12. Manifesting that patients with poorly controlled DM2 but with good adherence have a higher response rate of good conception of their health (52%), unlike those with low adherence who present a poor conception of health (51.5%). At the same time, most of the patients with low adherence present functional limitation, considering a large part (47%) that they are limited when climbing floors, for which 54% did less than they would have wanted to do but without having emotional problems that prevented them from doing so. limited (45%), considering themselves to have less bodily pain (19%) and more calm and calm (72%) compared to those with good adherence to MedDM (8% and 60%). Regarding the perception of vitality, it was very similar in both groups (88%), but the majority of the group with good adherence (84%) felt discouraged and sad compared to the group with low adherence (58%), without affectation. of the social function, being higher in the latter (74% and 68%). That is, the patients with low adherence to the MedD presented greater affectation in the physical sphere (limitation, bodily pain, vitality) and less in the mental sphere (they consider themselves calm and calm, without feeling discouraged or sad), affected equally to the social function (little limitation).

Few studies have examined the association of a comprehensive dietary pattern such as MedDM with HRQoL. Only one cross-sectional study (n = 8195) carried out in a Spanish population demonstrated that adherence to the MedD was associated with a higher score for self-perception of health (Muñoz et al., 2009)[19]. In the SUN[20] Project, a cohort of university graduates to establish the association between diet and chronic diseases that included 11,015 participants, a significant direct association was reported between greater baseline adherence to MedDM and better dimensions of physical and mental health measured with the SF-36, after 4 years[21]; showing the domains of physical role, bodily pain, general health and vitality significantly better with greater adherence to the MedD. On the other hand, Henríquez-Sánchez et al[22] observed a positive relationship between adherence to MedDM and four HRQoL physical health categories in younger subjects in their longitudinal evaluation of the SUN cohort, although there were no significant associations in the health dimensions. In addition, Pérez-Tasigchana et al[23] found better results in physical categories with the SF-12 questionnaire when high adherence to MedD was reported in the ENRICA[24] cohort. In the Moli-sani Project (2010)[25], a population-based cohort study in Italy has found that MedDM is associated with better baseline HRQoL. In the PREDIMED-Plus[26] study, greater adherence to MedDM was independently associated with significantly better scores in the 8 HRQoL dimensions (SF-36). Adjusted differences of ≥ 3 points were observed between the highest and lowest dietary adherence groups on the MedDM for vitality, emotional role, and mental health, and ≥ 2 points for the other dimensions.

When initially comparing the 12 items of the SF-v212 with the BMI degrees (normal weight, overweight, obesity), no significant results were obtained, but it should be noted that almost half of the obese (42%) consider themselves to be in good health, but however, they had physical limitations to make moderate efforts (53%), doing less than they would have wanted to do, but without emotional problems (56%) that limited them. 34% of the obese had regular pain that made it difficult for them to do their usual work. However, most of the overweight patients (3.2%) appreciated having no pain. Despite considering being almost always calm and only 44% of the obese judging themselves discouraged and sad, with little affectation of their social function; Less than half considered themselves to be vital, unlike those who were overweight, who did consider it mostly.

The results obtained are similar to those found in the systematic review carried out by Kolotkin et al[27], where the included articles verified that the HRQoL scores in the field of the physical component were lower when the BMI ≥ 25 kg/m$^2$, a relationship that it becomes even more apparent in higher BMI categories. The dimension with the lowest score within the physical component field was also the physical role. Regarding the mental field, there was a worsening of HRQoL in women with higher BMI, specifically in the dimensions of vitality and social function, but this did not occur in men. One reason could be the effect obesity stigma has on women compared to men.

## Conclusions

People with DM2 and poor metabolic control have a poor perception of health, especially in the physical sphere. Low adherence to the MedD is related to a greater affectation in the physical dimension ("general health", "physical function", "physical role" and "body pain"). Despite this, they have presented less affectation in the mental dimension ("emotional role" or "vitality"), without affectation in the "social function". In turn, patients with higher BMI (obesity) have a greater impact on the physical dimension and patients with lower BMI (overweight or normal weight) have better scores on mental dimensions, considering themselves to be better at a mental and physical level.

Due to the fact that the efficacy of a MedDM pattern on HRQoL has been demonstrated, more attention should be devoted to dietary interventions from a multidisciplinary approach from PC, to promote the Mediterranean lifestyle and improve unhealthy eating habits acquired in recent years. And that are having a negative impact not only on our physical and mental health but also on our perception of it.

### Conflict of Interest

The authors declared that there is no conflict of interest.

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ORIGINAL

# Determination of cardiometabolic risk scales in 7.962 hotel receptionists

*Determinación de escalas de riesgo cardiometabólico en 7.962 recepcionistas de hotel*

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## Summary

***Introduction:*** Cardiometabolic diseases are highly prevalent and have a multifactorial etiology, with socioeconomic factors playing a role in their appearance. The aim of this study was to assess the level of cardiometabolic risk in a large group of hotel reception workers, a group included among non-manual workers.
***Methods:*** Descriptive and cross-sectional study carried out in 7962 hotel reception workers from different Spanish regions in which different scales of cardiometabolic risk were assessed, including scales of insulin resistance, scales of nonalcoholic fatty liver disease, scales of atherogenic risk, scales of metabolic syndrome, and scales of cardiovascular risk.
***Results:*** The highest prevalences of high cardiometabolic risk parameters in this group were found for overweight-obesity scales, atherogenic indices and nonalcoholic fatty liver disease scales. Prevalences are higher in men.
***Conclusions:*** The prevalence of high values of the cardiometabolic risk scales in hotel reception workers can be considered moderate, but these data are especially relevant due to the low average age of this group. The variables that most increase cardiometabolic risk in these workers are age, male sex and, to a lesser extent, smoking.

*Key words:* Cardiometabolic risk, insulin resistance, nonalcoholic fatty liver disease, atherogenic risk, cardiovascular risk.

## *Resumen*

***Introducción.*** Las enfermedades cardiometabólicas son altamente prevalentes y presentan una etiología multifactorial, teniendo los factores socioeconómicos algún papel en su aparición. El objetivo de este estudio es valorar el nivel de riesgo cardiometabólico de un colectivo amplio de trabajadores de recepción de hoteles, colectivo englobado dentro de los trabajadores no manuales.
***Material y métodos.*** Estudio descriptivo y transversal realizado en 7.962 trabajadores de recepción de hoteles de distintas regiones españolas en los que se valoran diferentes escalas de riesgo cardiometabólico entre las que podemos incluir escalas de resistencia a la insulina, escalas de hígado graso no alcohólico, escalas de riesgo aterogénico, escalas de síndrome metabólico y escalas de riesgo cardiovascular.
***Resultados.*** Las prevalencias más elevadas de parámetros de riesgo cardiometabólico alto en este colectivo las encontramos para escalas de sobrepeso-obesidad, índices aterogénicos y escalas de hígado graso no alcohólico. Las prevalencias son superiores en los hombres.
***Conclusiones.*** Las prevalencias de valores altos de las escalas de riesgo cardiometabólico en trabajadores de recepción de hotel se pueden considerar moderadas, pero estos datos son especialmente relevantes debido a la baja edad media de este colectivo. Las variables que más incrementan el riesgo cardiometabólico en estos trabajadores son la edad, el sexo masculino y, en menor medida el consumo de tabaco.

*Palabras clave:* Riesgo cardiometabólico, resistencia a la insulina, hígado graso no alcohólico, riesgo aterogénico, riesgo cardiovascular.

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## Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide and is estimated to cause almost 18 million deaths annually[1]. Coronary heart disease, cerebrovascular disease and rheumatic heart disease are some of the disorders that affect both the heart and blood vessels[2]. Coronary heart disease and stroke account for more than four out of five CVD deaths, and one third of these deaths occur prematurely in people under the age of 70 years[3].

Unhealthy diet[4], physical inactivity[5], tobacco use[6] and harmful alcohol consumption[7] are the most important behavioral risk factors for heart disease and stroke. Hypertension[8], hyperglycemia[9] and hyperlipidemia[10], as well as overweight and obesity[11] are some of the effects of behavioral risk factors on individuals. In primary health care centers and occupational health units, these "intermediate risk factors" that indicate an increased likelihood of heart attack, stroke, heart failure and other conditions can be assessed[12].

It has been shown that the risk of CVD can be reduced by avoiding tobacco use[13], reducing the amount of salt in the diet, eating more fruits and vegetables, exercising regularly[14] and avoiding harmful alcohol consumption[15]. Health policies that focus on making healthy choices accessible and affordable are essential to motivate people to adopt and maintain healthy behaviors[16].

Identifying people at high risk of CVD and ensuring that they receive appropriate treatment is essential to prevent premature deaths.

There are other risk factors for CVD in addition to those described above and which form part of the so-called sociodemographic factors, among which we could highlight socioeconomic level[17].

There are not many studies that assess the relationship between socioeconomic level and the risk of CVD and even fewer that relate the type of work with these diseases, and for this reason the aim of this study is to assess the level of cardiometabolic risk in a group of non-manual workers (white-collar workers) such as hotel receptionists.

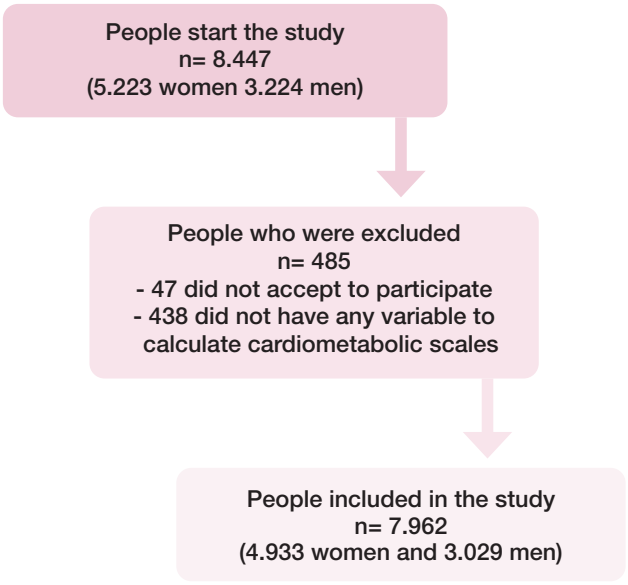
## Methods

During the period January to December 2019, a descriptive, cross-sectional study was conducted on a group of 7962 hotel receptionists from various autonomous communities in Spain. These communities included Balearic Islands, Andalusia, Canary Islands, Valencian Community, Catalonia, Madrid, Castilla La Mancha, Castilla Leon and Basque Country, and almost all Spanish regions were represented. This study selected hotel receptionists who underwent regular health examinations in all participating companies.

Inclusion requirements were:
- Be between 18 and 69 years of age.
- Maintain an employment contract with one of the participating companies.
- Agree to participate in the study and allow the use of the data for epidemiological purposes.

**Figure 1** shows a schematic of the study participant flowchart.

**Figure 1:** Flow chart of the study participants.




### *Determination of variables*

Medical professionals from the various participating companies determined the anthropometric, analytical and clinical variables necessary to calculate the various cardiometabolic risk scales. Measurement techniques were standardized to reduce potential biases in the process of obtaining variables.

Weight and height were obtained when the individual was in an upright position and with the abdomen relaxed, using a SECA model scale and a tape measure placed parallel to the floor at the level of the last rib to measure the abdominal waist circumference in the same position.

Blood pressure was measured with an OMROM-M3 sphygmomanometer. After ten minutes of rest, three measurements were taken with a one-minute interval between each one and the mean was obtained.

After a fast of at least twelve hours, different methods were used to measure blood glucose, triglycerides and total cholesterol, as well as precipitation methods for HDL cholesterol. The Friedewald formula was used to

calculate LDL-cholesterol, which is valid for triglyceride values up to 400.

Each of the analysis parameters was represented in milligrams per deciliter.

Altered values of cholesterol ≥ 200 mg/dl, LDL ≥ 130 mg/dl and triglycerides ≥ 150 mg/dl, or if they were being treated for any of these analytical alterations, were established as altered values.

The recommendations of the American Diabetes Association[18] were used to classify glycemia figures. Diabetics were those who had been previously diagnosed, had a blood glucose greater than 125 mg/dl, had an HbA1c of at least 6.5%, or were receiving blood glucose-lowering treatment.

Body mass index (BMI) was calculated by dividing weight (in kg) by height squared (in meters). A cut-off of 30 kg/m$^2$ was established to consider obesity.

***Scales to calculate body fat percentage:***

- CUN BAE (Body Adiposity Estimator of the University Clinic of Navarra)[19].
  Navarra)[15].
-44.988 + (0.503 × age) + (10.689 × sex) + (3.172 × BMI) - (0.026 × BMI2) + (0.181 × BMI × sex) - (0.02 × BMI × age) - (0.005 × BMI2 × sex) + (0.00021 × BMI2 × age). Male =0 Female =1.

- ECORE-BF (Equation Córdoba for Estimation of Body Fat)[20]
  Palafolls formula [21]
  Man =[ (BMI/waist) ×10] +BMI.
  Woman =[ (BMI/waist) ×10] +BMI+10.

- Deuremberg formula [22]
  1.2×(BMI) +0.23×(age) –10.8×(sex) –5.4 Man =0
  Woman =1.

- Relative fat mass (RFM)[23]
  Women: 76- (20 × (height/waist)) Men: 64- (20 × (height /waist)).

***Other indicators related to overweight and obesity:***

- Visceral adiposity index (VAI)[24]
  Men: (Waist/(39,68 + (1,88 x BMI)) x (Triglycerides/1,03) x (1,31/HDL)
  Women: (Waist/(36,58 + (1,89 x BMI)) x (Triglycerides/0,81) x (1,52/HDL)

- Body roundness index (BRI)[25]
  BRI=364.2–365.5 × √1-[(waist/ (2π) 2 )/(0.5 × height)$^2$].

- Body Surface Index (BSI)[26] is determined using the DuBois formula, where weight is expressed in kilograms and height in centimeters.
  BSA = weight0,425 x height 0,725 x 0,0007184
  BSI = weight/√BSA

- Conicity index[27]
  CI = (Waist/0,109) x 1/√ weight/height

- Body shape index (ABSI)[28]
  ABSI = Waist/BMI$^{2/3}$ x height$^{1/2}$

- Normalized weight-adjusted index (NWAI)[29]
  NWAI = (weight /10) - (10 x height) + 10
  Weight in kg and height in meters.

***Other indicators related to cardiovascular risk:***

- Triglyceride glucose index[30], Triglyceride glucose index-BMI[31], Triglyceride glucose index-waist[32].
  TyGindex = LN (triglycerides [mg⁄dl] × glycaemia [mg⁄dl]/2).
  TyGindex – BMI = TyGindex × BMI
  TyGindex – waist = TyGindex × waist

- Waist triglyceride index[33]
  waist (cm) × triglycerides (mmol)

- Cardiometabolic index[34].
  Waist to height ratio × triglycerides/HDL

***Nonalcoholic fatty liver disease risk scales:***

- Fatty liver index[35].

$$FLI = (e^{0.953*\log_e(\text{triglycerides}) + 0.139*\text{BMI} + 0.718*\log_e(\text{GGT}) + 0.053*\text{waist circumference} - 15.745}) / (1 + e^{0.953*\log_e(\text{triglycerides}) + 0.139*\text{BMI} + 0.718*\log_e(\text{GGT}) + 0.053*\text{waist circumference} - 15.745}) \times 100$$

- Hepatic steatosis index (HSI)[36]
  HSI = 8 × AST/ALT + BMI (+ 2 if 2 diabetes and+ 2 if female)
- Zhejiang University index (ZJU)[37]
  BMI + Blood glucose (mmol L) +Triglycerides(mmol L) +3 AST/ALT+2 if female

- Fatty liver disease index (FLD)[38]
  BMI+ triglycerides +3×( AST/ALT) +2 ×Hyperglycemia (presence=1; absence=0).
  If BMI ≥ 28 = 1 point, AST/ALT ≥ 0.8 = 2 points, type 2 diabetes mellitus = 1 point. Cut-off point for high risk 2 points.

- Lipid accumulation product (LAP)[39].
  Men= (waist (cm) - 65) × (triglycerides (mMol)).
  Women: (waist (cm) - 58) × (triglycerides (mMol))

***Atherogenic indices[40]***

- Total cholesterol/HDL (high values from 5 in men and 4.5 in women),
- LDL/HDL and Triglycerides/HDL (high values from 3 and above)
- logTriglycerides/HDL (high values from 3)
- Total cholesterol-HDL (high values from 130)

### *Metabolic syndrome*

- Metabolic syndrome was determined using three models[41]

a) When there are three or more of the following events: blood pressure higher than 130/85 mmHg; triglycerides higher than 150 mg/dl or specific treatment for this lipid disorder; low HDL and blood glucose lower than 100 mg/dl or specific treatment for this glycemic disorder, NCEP ATP III considers metabolic syndrome.

b) The International Diabetes Federation (IDF) requires, in addition to two of the other factors mentioned above for ATP III (triglycerides, HDL, blood pressure and blood glucose), a waist circumference greater than 80 centimeters in women and greater than 94 centimeters in men.

c) The JIS model establishes criteria that are similar to those of NCEP ATPIII but with abdominal waist cut-off points similar to IDF.

Atherogenic dyslipidemia[42] occurs when high triglyceride values (more than 150 mg/dL) coincide with low HDL values; if high LDL values are added in these individuals, we speak of a lipid triad[43].

### *Cardiovascular risk scales:*

The REGICOR[44] scale, adapted from the Framingham scale to the Spanish population, assesses the risk of suffering a cardiovascular event over a 10-year period. It can only be calculated in persons aged between 35 and 74 years. The risk is considered to be moderate from 5% and high from 10%.

We used the SCORE2[45] scale, a systematic coronary risk assessment, to evaluate the risk of suffering a fatal stroke within 10 years.

The Spanish cardiovascular risk equation, also known as ERICE, is based on seven investigations in population-based cohorts in Spain[46]. It estimates the risk of suffering a stroke in 10 years. The tables are used for people aged 30 to 80 years. The risk is measured on the basis of age, sex, smoking, diabetes, systolic blood pressure, antihypertensive treatment, and total cholesterol. The cut-off points suggested by the group responsible for the study were used: the risk was considered moderate if it exceeded 5%; moderate-high if it was between 15% and 19%; high if it was between 20% and very high if it exceeded 39%.

We used the Framingham model[47] to calculate vascular age. This requires information such as age, sex, HDL-c, total cholesterol, systolic blood pressure values, antihypertensive treatment, smoking and diabetes. It can be calculated from the age of thirty.

In addition, we calculated vascular age using the SCORE[48] model, which uses age, sex, systolic blood pressure, smoking and total cholesterol. The scale is valid for ages 40 to 65 years.

Avoidable years of life lost (ALLY)[49], which can be defined as the difference between vascular and chronological age, is a crucial concept that applies to both vascular ages.

We consider a person to be a smoker if he or she has consumed at least one cigarette in the last month or if he or she has quit smoking less than a year ago.

**Table I:** Characteristics of the population.

| | Men n=3.029 | Women n=4.933 | |
|---|---|---|---|
| | Mean (SD) | Mean (SD) | p-value |
| **Age (years)** | 38.5 (11.5) | 36.6 (10.8) | <0.0001 |
| **Height (cm)** | 176.6 (7.1) | 164.1 (6.5) | <0.0001 |
| **Weight (kg)** | 80.9 (14.8) | 64.1 (13.1) | <0.0001 |
| **Waist circumference (cm)** | 86.0 (11.0) | 73.6 (9.4) | <0.0001 |
| **Systolic blood pressure (mmHg)** | 126.8 (14.8) | 115.6 (14.7) | <0.0001 |
| **Diastolic blood pressure (mmHg)** | 77.5 (10.7) | 71.9 (10.1) | <0.0001 |
| **Total cholesterol (mg/dl)** | 188.6 (37.8) | 187.3 (34.0) | 0.101 |
| **HDL-cholesterol (mg/dl)** | 50.9 (7.9) | 56.9 (7.9) | <0.0001 |
| **LDL-cholesterol (mg/dl)** | 113.9 (35.9) | 113.0 (33.7) | 0.249 |
| **Triglycerides (mg/dl)** | 120.5 (76.7) | 87.2 (44.1) | <0.0001 |
| **Glycaemia (mg/dl)** | 89.7 (18.8) | 84.7 (11.4) | <0.0001 |
| **ALT (U/L)** | 28.7 (18.0) | 19.0 (10.5) | <0.0001 |
| **AST (U/L)** | 25.1 (11.8) | 17.7 (6.4) | <0.0001 |
| **GGT (U/L)** | 31.2 (29.3) | 19.3 (16.3) | <0.0001 |
| | % | % | p-value |
| **18-29 years** | 27.5 | 30.5 | <0.0001 |
| **30-39 years** | 27.7 | 32.5 | |
| **40-49 years** | 23.8 | 22.6 | |
| **50-59 years** | 17.5 | 11.6 | |
| **60-69 years** | 3.5 | 2.8 | |
| **Non-smokers** | 68.2 | 66.6 | 0.071 |
| **Smokers** | 31.8 | 33.4 | |

HDL-c High density lipoprotein cholesterol. LDL Low density lipoprotein cholesterol. AST Aspartate Aminotransferase. ALT Alanine Aminotransferase. GGT Gamma Glutamyl Transpeptidase.

### *Ethical considerations and aspects.*

The 2013 Declaration of Helsinki and the ethical standards of the institutional research committee guided all steps of this study. Data confidentiality and anonymity were guaranteed at all times. The study was approved by the Research Ethics Committee of the Balearic Islands (CEI-IB), which received the indicator IB 4383/20. Each participant had his or her data coded, so that only the study director could identify each participant. The research team committed to comply with Organic Law 3/2018, of December 5, which protects both digital rights and personal data. This implies that they have the right to access, correct, cancel, and oppose the data collected in this study.

### *Statistical analysis*

The mean and standard deviation of quantitative variables were calculated using Student's t test. The chi-square test was used for qualitative variables. Binary logistic regression was used to perform the multivariate analysis. SPSS 28.0 software was used to perform the statistical analysis, and a statistical significance level of $p<0.05$ was accepted.

## Results

**Table I** shows the characteristics of the sample. The mean age was approximately 37 years, with the majority group being between 18 and 39 years of age. Slightly less than one third of the receptionists were smokers (slightly higher in women). The variables show healthier values in women.

**Table II** shows the means of the different cardiometabolic risk scales studied, separated by sex. Except for the scales assessing body fat, the rest show significantly higher values in the men working at the hotel reception desk.

**Table III** shows the prevalence of elevated values for the different cardiometabolic risk scales considered in this study in both sexes. It can be seen that in all cases (except in relative fat mass), the prevalences are significantly higher in the group of male reception staff.

**Table IV** shows the results of the multivariate study using binary logistic regression. The variable that most

**Table II:** Differences in mean values of the scales related with cardiovascular risk by sex using the T-Student test.

| | Men n=3.029 | Women n=4.933 | |
|---|---|---|---|
| | Mean (SD) | Mean (SD) | p-value |
| Waist to height ratio (WtHR) | 0.49 (0.06) | 0.45 (0.06) | <0.0001 |
| Body mass index (BMI) | 25.9 (4.4) | 23.8 (4.6) | <0.0001 |
| CUN BAE | 24.1 (6.7) | 32.7 (6.9) | <0.0001 |
| ECORE-BF | 24.2 (6.3) | 32.6 (6.9) | <0.0001 |
| Relative fat mass | 22.3 (4.9) | 30.8 (5.1) | <0.0001 |
| Palafolls formula | 29.0 (4.6) | 37.0 (4.9) | <0.0001 |
| Deurenberg formula | 23.8 (6.6) | 31.6 (6.6) | <0.0001 |
| Body fat index | 21.9 (7.9) | 25.8 (7.0) | <0.0001 |
| Body surface index | 57.4 (7.8) | 49.0 (7.6) | <0.0001 |
| Normalized weight adjusted index | 0.44 (1.4) | 0.0 (1.3) | <0.0001 |
| Body roundness index | 3.2 (1.1) | 2.5 (1.0) | <0.0001 |
| Body shape index | 0.074 (0.006) | 0.070 (0.006) | <0.0001 |
| Visceral adiposity index | 7.1 (5.8) | 2.7 (1.6) | <0.0001 |
| Conicity index | 1.2 (0.1) | 1.1 (0.1) | <0.0001 |
| METS-VF | 6.1 (0.8) | 5.2 (0.8) | <0.0001 |
| Waist triglyceride index | 119.3 (82.6) | 73.5 (42.7) | <0.0001 |
| Waist weight index | 9.6 (0.7) | 9.2 (0.7) | <0.0001 |
| nº factors metabolic syndrome NCEP ATPIII | 1.1 (1.2) | 0.7 (0.9) | <0.0001 |
| nº factors metabolic syndrome JIS | 1.6 (1.3) | 0.7 (1.0) | <0.0001 |
| Total cholesterol/HDL-c | 3.8 (1.1) | 3.4 (0.9) | <0.0001 |
| Triglycerides/HDL-c | 2.5 (1.9) | 1.6 (0.9) | <0.0001 |
| LDL-c/HDL-c | 2.3 (0.9) | 2.1 (0.8) | <0.0001 |
| Total cholesterol-HDL-c | 137.7 (40.1) | 130.3 (36.1) | <0.0001 |
| Cardiometabolic index | 1.3 (1.0) | 0.7 (0.5) | <0.0001 |
| Triglyceride glucose index (TyG index) | 8.4 (0.6) | 8.1 (0.5) | <0.0001 |
| TyG index-BMI | 219.7 (45.7) | 193.6 (43.8) | <0.0001 |
| TyG index-waist circumference | 726.8 (118.3) | 598.0 (93.2) | <0.0001 |
| TyG index-WtHR | 4.1 (0.7) | 3.6 (0.6) | <0.0001 |
| METS-IR | 37.8 (8.3) | 32.8 (7.5) | <0.0001 |
| ALLY vascular age SCORE | 7.3 (6.7) | 3.9 (5.0) | <0.0001 |
| SCORE scale | 1.8 (2.1) | 0.5 (1.0) | <0.0001 |
| ALLY vascular age Framingham | 6.0 (10.4) | -0.5 (10.6) | <0.0001 |
| REGICOR scale | 3.2 (2.1) | 2.8 (2.3) | <0.0001 |
| ERICE scale | 4.5 (5.1) | 2.4 (3.1) | <0.0001 |
| Fatty liver index | 33.6 (26.8) | 13.5 (17.9) | <0.0001 |
| Hepatic steatosis index | 37.6 (7.2) | 35.1 (6.6) | <0.0001 |
| Zhejiang University index | 37.8 (6.0) | 35.6 (5.6) | <0.0001 |
| Fatty liver disease | 32.7 (5.8) | 28.9 (5.5) | <0.0001 |
| BARD scoring | 1.8 (1.1) | 1.8 (0.9) | 0.854 |
| Lipid accumulation product | 30.7 (30.4) | 16.4 (16.9) | <0.0001 |

CUN BAE Clinica Universitaria Navarra Body Adiposity Estimator; ECORE-BF Equation Córdoba for Estimation of Body Fat; METS-VF Metabolic score- visceral fat. ALLY Avoidable lost life years. SCORE Systematic COronary Risk Evaluation. REGICOR REgistre GIroni del COR. HDL-c High density lipoprotein cholesterol. LDL Low density lipoprotein cholesterol. METS-IR Metabolic score for Insulin Resistance. TyG Triglyceride glucose index

increased the risk of presenting high values for all the cardiometabolic scales was age, with statistically significant differences in all cases. Being male also influenced most of the cardiometabolic risk parameters analyzed (all except hypercholesterolemia, high LDL values, and high REGICOR values). Smoking increased risk in less than half of the scales.

The highest odds ratios were found for SCORE and Deuremberg in the case of age and for SCORE and hypertriglyceridemic waist in men.

## Discussion

Men working in hotel reception may be considered at moderate cardiometabolic risk while women could be classified as moderate-low. We should consider the prevalence of high values on the scales estimating body fat, dyslipidemia, atherogenic risk and cardiovascular risk to be of concern, since the average age of the workers is low.

The relationship between cardiometabolic risk and the type of work, whether manual or non-manual, yields contradictory results and in some cases not very comparable due to the different classification of the type of work in the different countries.

After a thorough review of the existing literature, no study has been found that accurately determines the level of cardiometabolic risk in this group of workers. Therefore, we will have to make a comparison between our results and those obtained in research carried out in non-manual workers.

A study based on the Korean National Health and Nutrition Examination Survey (2010-2018) conducted in 4447 premenopausal married women50 showed that the prevalence of metabolic syndrome was higher among women with manual jobs (15.3%) than among women with non-manual jobs (10.5%), these data agree with those obtained by us, although our prevalence are lower, perhaps due to the lower mean age of the sample.

A Swedish study that included 72,855 workers (41% women) who attended occupational health examinations between the years 2014-2019 concluded that manual workers had a higher level of health risks (OR: 1.80; 95% CI 1.71-1.90) compared to non-manual workers who were taken as a reference51.

Another study[52] of this same group that included a total of 304,702 participants (mean age 42.5 years, 47% female) and conducted between 1982 and 2019 found that manual and low-skilled workers had a significantly

**Table III:** Differences in the prevalence of altered values of different scales related with cardiovascular risk by sex using the chi-square test.

| | Men n=3.029 | Women n=4.933 | |
|---|---|---|---|
| | % | % | p-value |
| **Waist to height ratio > 0.50** | 36.6 | 13.2 | <0.0001 |
| **Body mass index obesity** | 14.8 | 9.4 | <0.0001 |
| **CUN BAE obesity** | 42.1 | 32.5 | <0.0001 |
| **ECORE-BF obesity** | 41.9 | 31.7 | <0.0001 |
| **Relative fat mass obesity** | 29.7 | 39.1 | <0.0001 |
| **Palafolls formula obesity** | 82.5 | 60.2 | <0.0001 |
| **Deuremberg formula obesity** | 39.1 | 52.3 | <0.0001 |
| **METS-VF high** | 6.7 | 0.8 | <0.0001 |
| **Diabesity** | 2.0 | 0.6 | <0.0001 |
| **Hypertension** | 25.6 | 10.4 | <0.0001 |
| **Total cholesterol ≥ 200 mg/dl** | 36.7 | 32.9 | <0.0001 |
| **LDL-c ≥ 130 mg/dl** | 32.3 | 28.5 | <0.0001 |
| **Triglycerides ≥ 150 mg/dl** | 22.7 | 7.2 | <0.0001 |
| **Glycaemia 100-125 mg/dl** | 12.7 | 6.3 | <0.0001 |
| **Glycaemia ≥ 126 mg/dl** | 2.2 | 0.5 | <0.0001 |
| **Metabolic syndrome NCEP ATPIII** | 13.9 | 5.7 | <0.0001 |
| **Metabolic syndrome IDF** | 10.7 | 6.4 | <0.0001 |
| **Metabolic syndrome JIS** | 23.5 | 7.0 | <0.0001 |
| **Atherogenic dyslipidemia** | 7.7 | 3.1 | <0.0001 |
| **Lipid triad** | 2.2 | 0.7 | <0.0001 |
| **Hipertriglyceridemic waist** | 7.9 | 1.0 | <0.0001 |
| **Total cholesterol/HDL-c moderate-high** | 13.2 | 10.1 | <0.0001 |
| **Triglycerides/HDL-c high** | 24.1 | 5.9 | <0.0001 |
| **LDL-c/HDL-c high** | 21.6 | 11.6 | <0.0001 |
| **Total cholesterol-HDL-c high** | 55.5 | 48.0 | <0.0001 |
| **METS-IR high** | 8.1 | 3.8 | <0.0001 |
| **TyG index high** | 24.4 | 10.0 | <0.0001 |
| **LAP high** | 34.6 | 20.5 | <0.0001 |
| **Fatty liver index high risk** | 20.2 | 4.1 | <0.0001 |
| **SCORE scale moderate-high** | 26.9 | 4.5 | <0.0001 |
| **REGICOR scale moderate-high** | 20.0 | 17.5 | <0.0001 |
| **ERICE scale moderate-high** | 13.9 | 2.2 | <0.0001 |

CUN BAE Clinica Universitaria Navarra Body Adiposity Estimator; ECORE-BF Equation Córdoba for Estimation of Body Fat; METS-VF Metabolic score- visceral fat. ALLY Avoidable lost life years. SCORE Systematic COronary Risk Evaluation. REGICOR REgistre GIroni del COR. HDL-c High density lipoprotein cholesterol. LDL Low density lipoprotein cholesterol. METS-IR Metabolic score for Insulin Resistance. TyG Triglyceride glucose index

**Table IV:** Binary logistic regression.

| | ≥ 50 years | Male | Smokers |
|---|---|---|---|
| | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| Waist to height ratio (WtHR) < 0.50 | 1 | 1 | 1 |
| WtHR ≥0.50 | 1.78 (1.56-2.04) | 3.71 (3.32-4.15) | ns |
| Body mass index (BMI) non obesity | 1 | 1 | 1 |
| BMI obesity | 1.84 (1.59-2.19) | 1.61 (1.40-1.85) | ns |
| CUN BAE non obesity | 1 | 1 | 1 |
| CUN BAE obesity | 5.93 (5.20-6.75) | 1.39 (1.26-1.54) | ns |
| ECORE non obesity | 1 | 1 | 1 |
| ECORE obesity | 5.36 (4.72-6.09) | 1.45 (1.31-1.60) | ns |
| Relative fat mass non obesity | 1 | 1 | 1 |
| Relative fat mass obesity | 1.77 (1.57-2.00) | 0.63 (0.57-0.70) | ns |
| Palafolls formula non obesity | 1 | 1 | 1 |
| Palafolls formula obesity | 3.10 (2.63-3.66) | 3.02 (2.70-3.38) | ns |
| Deurenberg formula non obesity | 1 | 1 | 1 |
| Deurenberg formula obesity | 19.61 (16.09-23.90) | 0.43 (0.39-0.48) | ns |
| METS-VF normal | 1 | 1 | 1 |
| METS-VF high | 0.19 (0.15-0.25) | 0.12 (0.08-0.17) | ns |
| Non hypertension | 1 | 1 | 1 |
| Hypertension | 4.72 (4.12-5.41) | 2.83 (2.49-3.22) | ns |
| Total cholesterol < 200 mg/dl | 1 | 1 | 1 |
| Total cholesterol ≥ 200 mg/dl | 3.82 (3.38-4.32) | ns | ns |
| LDL-c < 130 mg/dl | 1 | 1 | 1 |
| LDL-c ≥ 130 mg/dl | 3.81 (3.37-4.30) | ns | ns |
| Triglycerides < 150 mg/dl | 1 | 1 | 1 |
| Triglycerides ≥ 150 mg/dl | 2.35 (2.02-2.73) | 3.65 (3.17-4.19) | 1.27 (1.10-1.46) |
| Glycaemia < 126 mg/dl | 1 | 1 | 1 |
| Glycaemia ≥ 126 mg/dl | 5.50 (3.62-8.35) | 4.05 (2.53-6.48) | ns |
| Non metabolic syndrome NCEP ATPIII | 1 | 1 | 1 |
| Metabolic syndrome NCEP ATPIII | 5.12 (4.35-6.04) | 2.44 (2.08-2.88) | ns |
| Non metabolic syndrome IDF | 1 | 1 | 1 |
| Metabolic syndrome IDF | 3.11 (2.61-3.70) | 1.61 (1.36-1.90) | ns |
| Non metabolic syndrome JIS | 1 | 1 | 1 |
| Metabolic syndrome JIS | 5.11 (4.41-5.92) | 3.92 (3.40-4.52) | ns |
| Non atherogenic dyslipidemia | 1 | 1 | 1 |
| Atherogenic dyslipidemia | 3.43 (2.77-4.25) | 2.37 (1.92-2.93) | 1.40 (1.13-1.73) |
| Non lipid triad | 1 | 1 | 1 |
| Lipid triad | 3.39 (2.28-5.04) | 2.87 (1.90-4.32) | 2.03 (1.37-3.00) |
| Non Hipertriglyceridemic waist | 1 | 1 | 1 |
| Hipertriglyceridemic waist | 1.97 (1.52-2.56) | 8.00 (5.87-10.90) | ns |
| Total cholesterol/HDL-c normal | 1 | 1 | 1 |
| Total cholesterol/HDL-c high | 4.65 (4.00-5.40) | 1.21 (1.05-1.40) | 1.27 (1.09-1.47) |
| Triglycerides/HDL-c normal | 1 | 1 | 1 |
| Triglycerides/HDL-c high | 3.06 (2.63-3.57) | 4.85 (4.19-5.61) | 1.22 (1.06-1.41) |
| LDL-c/HDL-c normal | 1 | 1 | 1 |
| LDL-c/HDL-c high | 4.04 (3.52-4.63) | 1.96 (1.73-2.23) | 1.17 (1.02-1.34) |
| SCORE scale low | 1 | 1 | 1 |
| SCORE scale moderate-high | 90.09 (54.35-149.33) | 15.80 (11.33-22.04) | 8.06 (5.84-11.13) |
| REGICOR scale low | 1 | 1 | 1 |
| REGICOR scale moderate-high | 1.73 (1.49-2.01) | ns | 1.30 (1.12-1.50) |
| Fatty liver index low-moderate risk | 1 | 1 | 1 |
| Fatty liver index high risk | 2.22 (1.83-2.68) | 5.65 (4.66-6.84) | ns |
| LAP low | 1 | 1 | 1 |
| LAP high | 2.11 (1.86-2.39) | 1.98 (1.79-2.20) | ns |
| BARD score low | 1 | 1 | 1 |
| BARD score high | 1.94 (1.20-3.14) | 0.57 (0.40-0.81) | ns |
| Non diabesity | 1 | 1 | 1 |
| Diabesity | 6.06 (3.99-9.21) | 2.82 (1.82-4.37) | ns |
| METS-IR bajo | 1 | 1 | 1 |
| METS-IR alto | 2.15 (1.74-2.67) | 2.09 (1.72-2.54) | ns |
| TyG index low | 1 | 1 | 1 |
| TyG index high | 2.94 (2.56-3.38) | 2.79 (2.46-3.16) | 1.24 (1.09-1.41) |

CUN BAE Clinica Universitaria Navarra Body Adiposity Estimator; ECORE-BF Equation Córdoba for Estimation of Body Fat; METS-VF Metabolic score- visceral fat. ALLY Avoidable lost life years. SCORE Systematic COronary Risk Evaluation. REGICOR REgistre GIroni del COR. HDL-c High density lipoprotein cholesterol. LDL Low density lipoprotein cholesterol. METS-IR Metabolic score for Insulin Resistance. TyG Triglyceride glucose index. LAP Lipid accumulation product.

higher risk of incident CVD compared to high-skilled white-collar workers, with the association mediated primarily by variation in lifestyle-associated variables.

Data from the 2011 South Asia Cardiometabolic Risk Reduction Center survey of 16,288 Indian adults saw that risks related to excess weight (BMI >25 kg/m$^2$ and waist-to-height ratio ≥0.5) were more common in non-manual workers. The same was true for metabolic risks, with a higher prevalence of diabetes, hypertension and dyslipidemias observed in these workers[53].

In two investigations carried out by the same group, one in more than 5000 farmers[54] and the other in almost 1100 Bolivian miners[55], it was found that these groups of manual workers had elevated values in cardiovascular risk scales such as REGICOR and SCORE, as well as in metabolic syndrome, nonalcoholic fatty liver disease and insulin resistance. These data are similar to those obtained by us in this study.

In Japan, more than 1.1 million people participated in a study[56] that found that manual workers had a higher risk of coronary heart disease but a lower risk of stroke.

Manual workers have more type 2 diabetes and higher levels of cardiometabolic risk, according to Australian research[57] that included half a million workers.

Our research group has carried out several investigations[58-61] in different work groups and has found a correlation between belonging to the most disadvantaged social classes and the high prevalence of various cardiometabolic risk scales, such as nonalcoholic fatty liver disease, excess weight, vascular age, and metabolic syndrome, among others.

### Strengths and limitations

Two of the advantages of the study are the large number of cardiometabolic risk scales analyzed and the sample size in both sexes. Surely, this study is the first to specifically evaluate cardiometabolic levels in waiters, which makes it a model for future research on this group of workers.

The main limitation is that most of the cardiometabolic risk parameters were calculated using risk scales rather than objective methods.

## Conclusions

The reception workers in this study, despite having a low mean age, have moderate prevalence of the different cardiometabolic risk scales, with higher values in men.

Age and sex (male) are the variables that most increase the risk of presenting high values in all the cardiometabolic risk scales, whereas smoking does not have an impact in most cases.

### Conflict of Interest

The authors declared that there is no conflict of interest.

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ORIGINAL

# The effectiveness of three-dimensional (3D) PCASL MR perfusion imaging in assessing cognitive status in patients with mild cognitive impairment and Alzheimer's disease

*Eficacia de la imagen de perfusión tridimensional (3D) PCASL MR para evaluar el estado cognitivo en pacientes con deterioro cognitivo leve y enfermedad de Alzheimer*

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## Abstract

***Objective:*** we aimed to evaluate the relationship between CBF values obtained through PCASL MRI imaging and scores from MMSE, CDR, and CDS tests in patients diagnosed with mild cognitive impairment and Alzheimer's disease.
***Materials and methods:*** The study encompassed four groups: Control (Group 1), Mild cognitive impairment (Group 2), Moderate cognitive impairment (Group 3), and Severe cognitive impairment (Group 4). we collected CBF values derived from Pseudo Continuous Arterial Spin Labeling Manyetik Rezonans (PCASL MRI) imaging. Additionally, for patients diagnosed with mild cognitive impairment and Alzheimer's disease, scores from MMSE, CDR, and CDS tests were meticulously documented.
***Results:*** Significant differences were observed across the groups based on measures like MMSE, CDR, and regions of the brain such as the Frontal, Temporal, Hippocampus, PCC, Precuneus, Occipital, and Cerebellum ($p<0.001$ for each comparison). MMSE was significantly correlated with CDR ($r= -0.736$, $p<0.001$), Frontal ($r= 0.464$, $p<0.001$), Temporal ($r= 0.325$, $p=0.017$), Hippocampus ($r= 0.509$, $p<0.001$), PCC ($r= 0.399$, $p=0.003$), and Precuneus ($r= 0.286$, $p=0.036$). However, there was no significant correlation between MMSE and Occipital ($p=0.113$) or Cerebellum ($p=0.535$).
***Conclusions:*** PCASL MR imaging detects neurodegenerative changes in Alzheimer's and its milder forms, supplementing neuropsychiatric evaluations like the mini-mental test. When contrasted with FDG-PET imaging, ASL MR perfusion stands out due to its non-invasive nature, absence of radiation exposure, and cost-effectiveness. Its easy applicability further underscores its prominence as a preferred diagnostic tool in assessing dementia.

*Key words:* Dementia, ASL MR perfusion, mini mental test score, clinic dementia rate, disability rate by mental state.

## *Resumen*

***Objetivo:*** Nuestro objetivo fue evaluar la relación entre los valores de CBF obtenidos mediante resonancia magnética PCASL y las puntuaciones de las pruebas MMSE, CDR y CDS en pacientes diagnosticados de deterioro cognitivo leve y enfermedad de Alzheimer.
***Materiales y métodos:*** El estudio abarcó cuatro grupos: Control (Grupo 1), Deterioro cognitivo leve (Grupo 2), Deterioro cognitivo moderado (Grupo 3) y Deterioro cognitivo grave (Grupo 4). Recogimos valores de CBF derivados de imágenes de Pseudo Continuous Arterial Spin Labeling Manyetik Rezonans (PCASL MRI). Además, en el caso de los pacientes diagnosticados de deterioro cognitivo leve y enfermedad de Alzheimer, se documentaron meticulosamente las puntuaciones de las pruebas MMSE, CDR y CDS.
***Resultados:*** Se observaron diferencias significativas entre los grupos en función de medidas como MMSE, CDR y regiones del cerebro como el Frontal, Temporal, Hipocampo, PCC, Precuneus, Occipital y Cerebelo ($p<0,001$ para cada comparación). El MMSE se correlacionó significativamente con CDR ($r= -0,736$, $p<0,001$), Frontal ($r= 0,464$, $p<0,001$), Temporal ($r= 0,325$, $p=0,017$), Hipocampo ($r= 0,509$, $p<0,001$), PCC ($r= 0,399$, $p=0,003$) y Precuneus ($r= 0,286$, $p=0,036$). Sin embargo, no hubo correlación significativa entre MMSE y Occipital ($p=0,113$) o Cerebelo ($p=0,535$).
***Conclusiones:*** La RM PCASL detecta cambios neurodegenerativos en Alzheimer y sus formas más leves, complementando evaluaciones neuropsiquiátricas como el mini-mental test. En comparación con las imágenes FDG-PET, la perfusión ASL MR destaca por su naturaleza no invasiva, la ausencia de exposición a la radiación y su rentabilidad. Su fácil aplicabilidad subraya aún más su prominencia como herramienta diagnóstica preferida en la evaluación de la demencia.

*Palabras clave:* Demencia, perfusión ASL MR, puntuación del mini test mental, tasa de demencia clínica, tasa de discapacidad por estado mental.

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## Introduction

Dementia is a disease characterized by a decline in cognitive functions, affecting primarily memory as well as visual perception, orientation, learning and reasoning abilities, character traits, language, and higher-level motor functions. Dementia has emerged as a significant concern across public health, economic, social, and political sectors, drawing substantial and growing research investments. According to the World Alzheimer Report 2015, approximately 46.8 million individuals globally have dementia. This number is estimated to rise to 74.7 million by 2030 and further soar to 131.5 million by 2050[1-4].

In the latest guidelines published in 2011, Alzheimer's disease is presented as a spectrum. This spectrum encompasses three distinct stages: first, an early preclinical stage marked by the accumulation of amyloid plaques and neuronal and synaptic losses, but which remains symptom-free. Second, the stage of mild cognitive impairment (MCI), where based on a patient's age and educational background, there are noticeable symptoms of enhanced forgetfulness and other cognitive impairments[5]. Yet, individuals in this stage can manage daily activities without being reliant on others. Lastly, there's the final stage of dementia. Here, symptoms such as forgetfulness, difficulty in word retrieval, and challenges with visual and spatial understanding progress to the extent that individuals can no longer independently manage their daily tasks. It's noteworthy that MCI can serve as the initial cognitive indicator of Alzheimer's disease, but it might also emerge due to other neurological, vascular, metabolic, systemic, or psychiatric conditions[6].

The Mini Mental State Examination (MMSE) is a 30-point questionnaire routinely used for dementia screening, assessing cognitive functions like orientation, memory, and speech. A score of 23/24 is considered the cut-off. While quick to administer and available in multiple languages, its major drawback is its insufficiency in early Alzheimer's diagnosis and distinguishing between dementia types[7,8]. The Clinical Dementia Rating (CDR) is another scale, categorizing cognitive and functional performance in Alzheimer's and other dementias. There's also the Cognitive Disability Score (CDS) that rates the impairment level. While these neuropsychiatric tests provide qualitative data, advanced diagnostic methods such as cerebrospinal fluid analysis, PET, and MRI are now recommended. Conventional MRI primarily detects volumetric loss in medial temporal and parietal lobes for Alzheimer's. With the advent of disease-modifying treatments, methods to diagnose Alzheimer's before atrophy onset are being explored. FDG-PET, a functional imaging technique, identifies decreased glucose metabolism, a characteristic of Alzheimer's. Furthermore, imaging methods using molecular markers, like amyloid-binding PET, can identify early changes. Arterial spin labeling (ASL) MRI is a non-invasive functional imaging technique measuring cerebral blood flow. Its advantages include being non-invasive, quick, and cost-effective. Studies have shown areas of hypo-metabolism in FDG-PET coincide with hypo-perfused areas in ASL MR perfusion in Alzheimer's patients, making ASL MR perfusion a promising diagnostic tool[8,9].

In this study, we aimed to evaluate the relationship between CBF values obtained through PCASL MRI imaging and scores from MMSE, CDR, and CDS tests in patients diagnosed with mild cognitive impairment and Alzheimer's disease.

## Materials and methods

### Patients and design

In this retrospective analysis, our focal group encompassed patients who consulted the dementia outpatient clinic of our hospital's neurology department, primarily due to complaints of dementia. Spanning June and July 2019, these patients were subjected to MRI screenings using a 1.5 Tesla instrument as a cornerstone of our established dementia diagnostic protocol. Our comprehensive dataset incorporated a diverse age range, spanning from 50 to 86 years, and consisted of 67 individuals. The study encompassed four groups: Control (Group 1), Mild cognitive impairment (Group 2), Moderate cognitive impairment (Group 3), and Severe cognitive impairment (Group 4).

### Eligibility

The inclusion parameters were meticulously defined to ensure the precision of our study. First and foremost, any patient presenting with forgetfulness at the dementia outpatient clinic was considered. They underwent a rigorous standard dementia screening process, which included not just a medical history assessment but also a holistic evaluation encompassing a physical and neurological examination. Furthermore, neuropsychiatric evaluations, laboratory tests, and MR imaging were imperative components of this screening. The subsequent diagnoses, pivotal for our study, relied heavily on established guidelines: the NINCDS-ADRDA criteria served as the backbone for diagnosing Alzheimer's disease, whereas the NIA-AA diagnostic criteria were foundational for identifying cases of mild cognitive impairment. Any patient diagnosed with either a distinct psychiatric ailment or another neurological disorder that wasn't dementia was immediately ruled out. Additionally, any cases evidencing cerebrovascular events were also omitted.

### Data collection

To ensure a thorough and complete assessment, we undertook a comprehensive review of the archived follow-up files for all 67 patients from the dementia outpatient clinic. During this review, we systematically extracted several key pieces of information. This included basic demographics like age and gender, as well as specific clinical data. The clinical data encompassed results from mini-mental tests, rates of clinically diagnosed dementia, metrics related to mental state disabilities, and familial

medical histories. Furthermore, we collected CBF values derived from Pseudo Continuous Arterial Spin Labeling Manyetik Rezonans (PCASL MRI) imaging. Additionally, for patients diagnosed with mild cognitive impairment and Alzheimer's disease, scores from MMSE, CDR, and CDS tests were meticulously documented.

## Ethical approval and informed consents

Approval was obtained from the Academic Council of the Department of Radiology at the University of Health Sciences with decision number 72 on 04/11/2019. Written informed consent was obtained from all individual participants and/or their gaurdians.

## PCASL MR data analysis and evaluation

Raw images obtained through PCASL MR with T1-weighted gray scale were processed using GE Ready View. After automatically coloring them based on different CBF values, colored perfusion maps are generated. Through ROIs (Regions of Interest) placed in any region of the brain parenchyma, blood flow values can be measured in mL/100 gr/min. The T1 map is provided by placing the multi-TI inversion-recovery fast spin echo (IR-FSE) images, where the standard model formula "S(t) = M0 (1–2Aexp(–tT1))" is used. In the standard model formula, the parameter denoted by A represents the 180° pulse inversion value.

To calculate blood flow, it's necessary to calibrate the sensitivities of the images to water for each voxel. To avoid areas with the partial volume of suppressed water, the maximum neighbor algorithm is used. The C sensitivity map is created with the following formula: C=PD/(CWM(1–exp(–TsatT1WM))). In this formula, PD stands for the flow-saturated proton density image intensity. CWM is the white matter tissue water concentration, which is accepted as 0.8 gm/ml. Tsat is the saturation time in the PD images and is 2 seconds. T1WM is the T1 value obtained from placing the IR-FSE images in the white matter. This calibration creates a sensitivity map named C. The value of C represents the MR signal intensity produced by one gram of water in every milliliter of brain tissue. With this C value, the brain's blood flow can be calculated using the formula: CBF=ρb(Sc–Sl) 2αCωaT1aexp(–wT1a)(1–exp(–tIT1a)). The abbreviations and values of the parameters in the formula are as follows:

- Pb represents the density of brain tissue, which is taken to be 1.05g/ml.
- α denotes the tagging efficiency, which is approximately considered to be 85%.
- W stands for Post labeling delay. For patients under 70 years of age, this is 152 ms; for those 70 and older, it is accepted as 2025 ms.
- T1a is the relaxation time of arterial blood. On the 1.5T MR device we used, this value is 1.4 seconds.
- ωa signifies the density of water in blood, which is 0.85 g/ml.
- Sl and Sc respectively represent the signal intensity in tagged images and control images.

Using the Harvard-Oxford Atlas, measurements were taken from the frontal, temporal, and occipital lobes, the hippocampus, the posterior cingulate gyrus, the precuneus, and the cerebellum through the ROIs (Regions of Interest) we placed in these areas (**Figure 1**, **2**, and **3**).

**Figure 1:** In the ASL MR perfusion map, ROIs placed in the hippocampus and axial T2-weighted PROPELLER sequence projections (indicated by arrows 3 and 4).

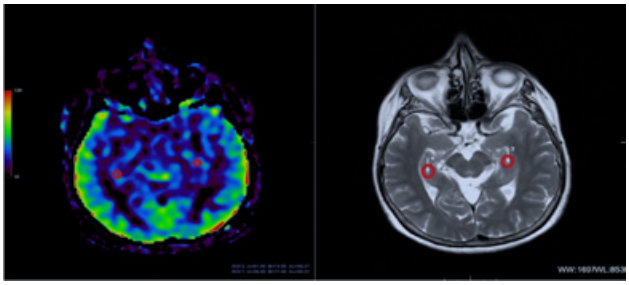


**Figure 2:** In the ASL MR perfusion map, ROI placed in the posterior cingulate gyrus and projection of the CUBE T1-weighted sequence (indicated by arrow 2).

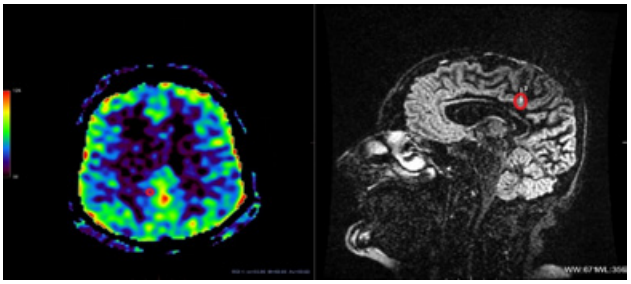
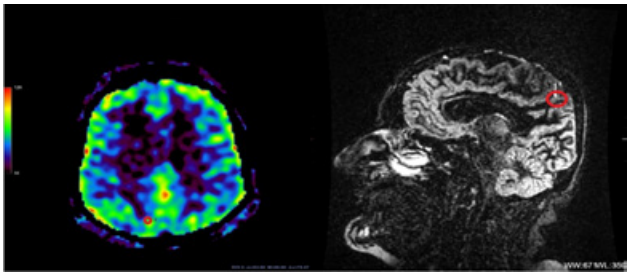


**Figure 3:** In the ASL MR perfusion map, ROI placed in the precuneus and projection of the CUBE T1-weighted sequence (indicated by arrow 3).



## Statistical analysis

The patient information was subjected to various statistical evaluations, which included generating descriptive statistics, pinpointing frequencies, and scrutinizing factors in each category. Quantitative information was displayed as the average ± standard variation. Tests like Shapiro-Wilk and Kolmogorov-Smirnov were used to check the consistency of continuous variables. For normally distributed data, we utilized the Student's T-test and ANOVA. The Tukey post-hoc test was used for subgroups comparisons. For data that didn't follow a normal distribution, we employed non-parametric tests. The Chi-Square test was used for categorical data. The corellation between variables was determined using the Pearson test. All analyses were executed with SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). A p-value of ≤ 0.05, in a two-tailed test, was considered to indicate statistical significance.

## Results

The demographic and clinical characteristics of the study participants are presented in **table I**. The mean age of the participants was 70.9 years with a standard deviation (SD) of 10.1 years. With regard to gender distribution, 59.70% (n=40) of the participants were female. The mean Mini-Mental State Examination (MMSE) score was 18.52 with a SD of 6.83, suggesting varying degrees of cognitive function among the participants. The Clinical Dementia Rating (CDR) averaged at 1.62 with an associated SD of 0.91, further emphasizing the diversity in the severity of cognitive impairment within the sample. Lastly, when inquiring about a family history of dementia or related conditions, 40.70% (n=22) of the participants reported a positive family history.

**Table I:** Demographic.

| | n or mean | % or SD |
|---|---|---|
| **Age (year)** | 70,9 | 10,1 |
| **Gender (F)** | 40 | 59,70% |
| **MMSE** | 18,52 | 6,83 |
| **CDR** | 1,62 | 0,91 |
| **Family history (yes)** | 22 | 40,70% |

*SD: standart deviation, MMSE: Mini-Mental State Examination, CDR: Clinical Dementia Rating.

Significant differences were observed across the groups based on measures like MMSE, CDR, and regions of the brain such as the Frontal, Temporal, Hippocampus, PCC, Precuneus, Occipital, and Cerebellum. For the MMSE, Control (Group 1) had a mean score of 27.69 (SD=1.32, N=13), which progressively decreased with severity: Group 2 had a mean of 22.33 (SD=1.91, N=18), Group 3 with 16.18 (SD=2.75, N=22), and Group 4 with 8.79 (SD=1.67, N=14) (p<0.001). Similarly, CDR scores increased with cognitive impairment severity, Group 2 at a mean of 0.81, Group 3 at 1.70, and Group 4 at 2.62 (p<0.001). When examining brain regions, starting with the frontal lobe, Group 1 had a mean value of 73.14, which decreased to 52.52 in Group 4. The hippocampus measurements for Group 1 averaged at 61.98, descending to 36.43 in Group 4. All analyzed regions presented significant differences among groups, as validated by ANOVA (p<0.001 for all parameters). The post-hoc Tukey test provided further insights into intergroup differences. Comparisons between Group 1 and Group 2 showed significant disparities for all parameters, with p-values mostly below 0.001. Group 2 and Group 3 had pronounced differences in the MMSE and CDR scores, with p-values of <0.001. A similar trend was observed when comparing Group 2 with Group 4. All paired group comparisons highlighted significant differences in many cognitive and brain regional measurements (**Table II**).

The study investigated cognitive and brain metrics differences between individuals with positive and negative family histories. For MMSE and CDR metrics, the positive history group averaged 17.22 (SD=4.92) and 1.59 (SD=0.98) respectively, compared to the negative history group's 15.68 (SD=6.12) and 1.64 (SD=0.88). Brain region comparisons, such as Frontal and Temporal, yielded similar results between groups, with no significant variations observed based on p-values. Overall, there were no major discernible differences between the two groups across the examined parameters (**Table III**).

MMSE was significantly correlated with CDR (r= -0.736, p<0.001), Frontal (r= 0.464, p<0.001), Temporal (r= 0.325, p=0.017), Hippocampus (r= 0.509, p<0.001), PCC (r= 0.399, p=0.003), and Precuneus (r= 0.286, p=0.036). However, there was no significant correlation between MMSE and Occipital (p=0.113) or Cerebellum (p=0.535) (**Table IV**).

**Table II:** Mean MMSE, CDR and cerebral blood flow values according to groups.

| Groups | | MMSE | CDR | Frontal | Temporal | Hippocampus | PCC | Precuneus | Occipital | Cerebellum |
|---|---|---|---|---|---|---|---|---|---|---|
| **Control (Group 1)** | Mean | 27.69 | | 73.14 | 69.11 | 61.98 | 75.88 | 79.87 | 68.37 | 66.09 |
| | n | 13 | | 13 | 13 | 13 | 13 | 13 | 13 | 13 |
| | SD | 1.32 | | 9.02 | 11.69 | 4.83 | 10.53 | 9.41 | 10.03 | 10.93 |
| **Mild cognitive impairment (Group 2)** | Mean | 22.33 | 0.81 | 62.96 | 57.30 | 46.48 | 57.37 | 51.08 | 55.14 | 53.61 |
| | n | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 |
| | SD | 1.91 | 0.39 | 8.84 | 7.47 | 6.76 | 13.22 | 11.04 | 9.34 | 7.55 |
| **Moderate cognitive impairment (Group 3)** | Mean | 16.18 | 1.70 | 64.99 | 60.50 | 47.10 | 57.61 | 55.17 | 62.78 | 61.62 |
| | n | 22 | 22 | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| | SD | 2.75 | 0.80 | 5.27 | 4.53 | 2.46 | 3.70 | 2.20 | 4.43 | 6.97 |
| **Severe cognitive impairment (Group 4)** | Mean | 8.79 | 2.62 | 52.52 | 50.80 | 36.43 | 46.15 | 45.13 | 48.77 | 50.94 |
| | n | 14 | 13 | 14 | 14 | 14 | 14 | 14 | 14 | 14 |
| | SD | 1.67 | 0.51 | 11.17 | 8.58 | 7.89 | 9.38 | 11.47 | 11.81 | 10.47 |
| **p-value (ANOVA)** | p | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| **Post-hoc Tukey test** | | | | | | | | | | |
| **Group 1 vs group 2** | p | <0.001 | --- | 0.009 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| **Group 1 vs group 3** | p | <0.001 | --- | 0.022 | 0.015 | <0.001 | <0.001 | <0.001 | NS | NS |
| **Group 1 vs group 4** | p | <0.001 | --- | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| **Group 2 vs group 3** | p | <0.001 | <0.001 | NS | NS | NS | NS | NS | 0.041 | 0.028 |
| **Group 2 vs group 4** | p | <0.001 | <0.001 | 0.006 | NS | <0.001 | 0.009 | NS | NS | NS |
| **Group 3 vs group 4** | p | <0.001 | 0.002 | <0.001 | 0.004 | <0.001 | 0.005 | 0.009 | <0.001 | 0.004 |

* SD: standart deviation, MMSE: Mini-Mental State Examination, CDR: Clinical Dementia Rating, PCC: Posterior Cingulate Cortex, NS: Not-significant.

**Table III:** Comparisons in terms of the family history.

| | Positive | | Negative | | |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | p-value |
| **MMSE** | 17.22 | 4,92 | 15,68 | 6,12 | 0.332 |
| **CDR** | 1,59 | 0,98 | 1,64 | 0,88 | 0,835 |
| **Frontal** | 63,53 | 8,09 | 59,38 | 10,4 | 0,123 |
| **Temporal** | 58,53 | 6,98 | 55,81 | 8,08 | 0,206 |
| **Hippocampus** | 45,81 | 5,75 | 42,96 | 8,1 | 0,162 |
| **PCC** | 54,83 | 9,25 | 54,37 | 11,27 | 0.876 |
| **Precuneus** | 52,07 | 6,75 | 50,6 | 11,01 | 0.580 |
| **Occipital** | 57,94 | 9,73 | 55,68 | 10,45 | 0.425 |
| **Cerebellum** | 58,61 | 6,36 | 54,5 | 10,62 | 0.111 |

* SD: standart deviation, MMSE: Mini-Mental State Examination, CDR: Clinical Dementia Rating, PCC: Posterior Cingulate Cortex.

**Table IV:** Correlations of MMTS, CDR, frontal CBF, hippocampal CBF, PCC CBF, precuneus CBF, occipital CBF and cerebellum CBF in all dementia patients.

| Correlations | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | MMSE | CDR | Frontal | Temporal | Hippocampus | PCC | Precuneus | Occipital | Cerebellum |
| **MMSE** | Pearson Correlation<br>Sig. (2-tailed)<br>N | 1 | -,736**<br>,000<br>57 | ,464**<br>,000<br>55 | ,325*<br>,017<br>54 | ,509**<br>,000<br>54 | ,399**<br>,003<br>54 | ,286*<br>,036<br>54 | ,218<br>,113<br>54 | ,086<br>,535<br>54 |
| **CDR** | Pearson Correlation<br>Sig. (2-tailed)<br>N | | 1 | -,292*<br>,032<br>54 | -,155<br>,269<br>53 | -,356**<br>,009<br>53 | -,336*<br>,014<br>53 | -,206<br>,139<br>53 | -,194<br>,165<br>53 | ,030<br>,829<br>53 |
| **Frontal** | Pearson Correlation<br>Sig. (2-tailed)<br>N | | | 1 | ,687**<br>,000<br>54 | ,569**<br>,000<br>54 | ,639**<br>,000<br>54 | ,570**<br>,000<br>54 | ,629**<br>,000<br>54 | ,453**<br>,001<br>54 |
| **Temporal** | Pearson Correlation<br>Sig. (2-tailed)<br>N | | | | 1 | ,532**<br>,000<br>54 | ,618**<br>,000<br>54 | ,581**<br>,000<br>54 | ,748**<br>,000<br>54 | ,589**<br>,000<br>54 |
| **Hippocampus** | Pearson Correlation<br>Sig. (2-tailed)<br>N | | | | | 1 | ,767**<br>,000<br>54 | ,726**<br>,000<br>54 | ,512**<br>,000<br>54 | ,556**<br>,000<br>54 |
| **PCC** | Pearson Correlation<br>Sig. (2-tailed)<br>N | | | | | | 1 | ,889**<br>,000<br>54 | ,670**<br>,000<br>54 | ,536**<br>,000<br>54 |
| **Precuneus** | Pearson Correlation<br>Sig. (2-tailed)<br>N | | | | | | | 1 | ,651**<br>,000<br>54 | ,608**<br>,000<br>54 |
| **Occipital** | Pearson Correlation<br>Sig. (2-tailed)<br>N | | | | | | | | 1 | ,713**<br>,000<br>54 |
| **Cerebellum** | Pearson Correlation<br>Sig. (2-tailed)<br>N | | | | | | | | | 1 |

* SD: standart deviation, MMSE: Mini-Mental State Examination, CDR: Clinical Dementia Rating, PCC: Posterior Cingulate Cortex.

## Discussion

In this study, we found that PCASL MR perfusion imaging is a highly successful method in determining the severity of dementia, especially in distinguishing severe dementia. Until today, previous studies have used various ASL techniques (pulsed and continuous) to examine CBF in MCI (Mild Cognitive Impairment) and Alzheimer's patients. All of them have demonstrated decreased CBF patterns, mainly located in the posterior cingulate cortex, precuneus, and bilateral parietal areas[10-16]. Only two of these studies directly compared the CBF of Alzheimer's patients, MCI patients, and control cases, and both used voxel analysis on 1.5-T non-whole brain data. Johnson and colleagues used relative CBF measurements to compare AH and MCI patients with a control group, identifying regions of relative hypoperfusion in patients diagnosed with AH in the bilateral posterior cingulate cortex, precuneus, and right inferior parietal lobe[12]. An overlapping but weaker pattern was found in MCI patients. Dai et al. found decreased CBF in the posterior cingulate cortex, precuneus, and inferior parietal cortex in AH and MCI patients, and the areas of hypoperfusion in AH were more extensive than those seen in MCI[15,17].

In our study, similarly, when patients with subjective complaints in the control group were compared with patients with mild cognitive impairment, moderate dementia, and severe dementia, CBF measurements from all brain regions were found to be higher in the control group. Again, the most significant decrease in

CBF values compared to the control group in all patient groups was observed in the precuneus, PCC, and hippocampus, consistent with the literature. However, when we compared the groups of severe dementia, moderate dementia, and mild cognitive impairment with each other, the lowest CBF values for all brain regions were present in the severe dementia group. Patients with moderate dementia and mild cognitive impairment had similar CBF values.

In the study by Binnewijzend and colleagues, we see that CBF values, adjusted for partial volume, are lower in all brain regions except the cerebellum in the patient group with Alzheimer's disease compared to the control group (1). Similar findings were obtained in our study, and the results were found to be consistent with this study. The positive correlation observed between hippocampal and PCC blood flow values, and between PCC and precuneus blood flow values in all patients except the control group, indicates the relationship between these neurofunctionally affected regions in dementia patients. This underscores that our study is in alignment with the literature.

When CDR was compared separately with CBF values from seven different regions in the brain for every patient group, including the control group, no significant correlation was found between the variables in any of the patient groups. However, when all dementia patients were combined into a single group for analysis, a negative correlation was identified between hippocampal and PCC CBF values and CDR. The significant emergence of the correlation in the study was attributed to the increased sample size resulting from the combination of patient groups. This correlation reflects the relationship between neurocognitive level and CBF. Additionaly, When the CBF values, clinical dementia rates and mini-mental test scores of those with a positive family history were compared with those with a negative family history, no significant difference was detected.

This study had several limitations. Firstly, our sample size was small. Secondly, the study was conducted using a 1.5T MRI machine. A higher magnetic field increases the signal-to-noise ratio. In comparison to 3T, 1.5T yields images with a lower signal-to-noise ratio. Thus, the fact that the study was performed using a 1.5T MRI machine is considered one of the limitations. Another limiting factor was that our workstation could not process raw images through various specialized programs to obtain partial volume corrections, remove tissues outside the brain, and perform tissue segmentation. The partial volume effect wasn't precisely and accurately calculated due to relatively low image resolution and limited tissue sampling. Another constraint was that the control group consisted of patients with subjective complaints rather than healthy individuals. We didn't conduct multiple scans at different delay times for each patient group to obtain the most appropriate labeling. Instead, images were acquired by adopting the optimal PLD parameter values recommended by Grade et al.'s study: 1525 ms for patients under 70 years old and 2025 ms for those over 70 [180]. We didn't adjust for potential factors that could affect brain perfusion, such as diabetes, smoking, and caffeine consumption shortly before the MRI scan.

## Conclusions

CBF values calculated in PCASL MR imaging reveal functional changes in the brain due to neurodegeneration in Alzheimer's disease and its milder clinical presentations, providing quantitative data that assist neuropsychiatric scores such as the mini-mental test, clinical dementia rating, and disability score according to mental state. In comparison to FDG-PET imaging, the absence of radiation exposure and non-invasive features, as well as its easy applicability and cost-effectiveness, place ASL MR perfusion in a more advantageous position, emphasizing its usefulness as a diagnostic tool in dementia evaluation.

### Conflict of interest

No

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ORIGINAL

# Sensitivity of bacteria from surgical wound Infection at Enugu State University Teaching Hospital

*Sensibilidad de las bacterias procedentes de la atención de heridas quirúrgicas en el Enugu State University Teaching Hospital*

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## Abstract

***Introduction:*** Surgical site infections are worldwide problems in the field of surgery contributing to increased mortality and morbidity. However, despite advances in the control of surgical site infections, the risk of acquiring these infections had not fully been eliminated due to the emergence and spread of resistant bacteria pathogens.
***Methods:*** This was a cross sectional study of patients with suspected surgical site infections in the hospital wards. Structured questionnaires were used to collect patient's data. Purposive sampling was employed and a total of 118 samples were collected from patients who gave their consent. The samples were processed through Gram stain, Culture, and an array of Biochemical tests. Subsequently, antibiotic susceptibility tests by Kirby Bauer disc diffusion technique were performed on the isolated bacteria. Data collection was analyzed using Statistical Package for the Social sciences (SPSS) version 25 and Microsoft Excel.
***Results:*** Based on the Sensitivity report, most of the SSI bacteria isolates were sensitive to Ciprofloxacin (67.3%) while most of the isolates were resistant to Chloramphenicol (55.1%). Staphylococcus aureus (16.1%) was the most prevalent organism while the highest bacteria isolates were seen among patients who had laparotomy (61.9%).
***Conclusions:*** Routine Culture should be performed whenever SSI is suspected and choice of Antibiotics for treatment of SSIs should be guided by routine antimicrobial sensitivity testing. Ciprofloxacin should replace first line antibiotics for empirical treatment of SSIs; and strict guidelines for antibiotics prescriptions in treatment of SSIs should be established.

*Key words:* Sensitivity, bacteria, surgical wound, infections.

## *Resumen*

***Introducción:*** Las infecciones quirúrgicas (ISQ) son un problema mundial en el campo de la cirugía que contribuye a aumentar la mortalidad y la morbilidad. Sin embargo, a pesar de los avances en el control de las ISQ el riesgo de adquirir estas infecciones no se ha eliminado por completo debido a la aparición y propagación de bacterias resistentes.
***Metodología:*** Se realiza un estudio transversal de pacientes con sospecha de infección quirúrgica en las salas del hospital. Se utilizaron cuestionarios estructurados para recoger los datos de los pacientes. Se empleó un muestreo intencional y se recogieron 118 muestras de pacientes que dieron su consentimiento. Las muestras se procesaron mediante tinción de Gram, cultivo y una serie de pruebas bioquímicas. Posteriormente, se realizaron pruebas de susceptibilidad antibiótica a las bacterias aisladas mediante la técnica de difusión en disco de Kirby Bauer. Los datos recogidos se analizaron con el paquete estadístico para las ciencias sociales (SPSS) versión 25 y Microsoft Excel.
***Resultados:*** Según el informe de sensibilidad, la mayoría de las bacterias de ISQ aisladas eran sensibles a la ciprofloxacina (67,3%), mientras que la mayoría eran resistentes al cloranfenicol (55,1%). Staphylococcus aureus (16,1%) fue el organismo más prevalente, mientras que el mayor número de bacterias aisladas se observó entre los pacientes sometidos a laparotomía (61,9%).
***Conclusiones:*** Deben realizarse cultivos sistemáticos siempre que se sospeche una ISQ y la elección de los antibióticos para el tratamiento de las ISQ debe guiarse por las pruebas sistemáticas de sensibilidad a los antimicrobianos. La ciprofloxacina debería sustituir a los antibióticos de primera línea en el tratamiento empírico de las ISQ, y deberían establecerse directrices estrictas para la prescripción de antibióticos en el tratamiento de las ISQ.

*Palabras clave:* Sensibilidad, bacterias, herida quirúrgica, infecciones.

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## Introduction

The incidence of surgical site infection is a major concern in many hospitals. It affects the patient's wellbeing as well as the healthcare personnel[1-3]. Therefore, surgical site infection (SSI) could be defined as an infection that occurs within 30 days of a surgical procedure or one year if an implant is left in place after the surgery and affects either the incision or the deep tissues at the surgical site. Infections involving organs or bodily space might be superficial or deep incisional infections[4].

Surgical site infections are a worldwide problem in the area of surgery; linked to longer hospital stays, higher treatment costs, and increased rates of morbidity and mortality[5]. SSIs are the second most common kind of nosocomial infection in hospitals in the United States, SSIs are linked to a 3.0% mortality rate, according to the Center for Disease Control and Prevention (CDC)[6]. Pre-existing medical disorders, the amount and type of resistant skin bacteria, and preoperative, intraoperative, and post-operative care are all factors that influence the risk of surgical site infection[7].

Deposition and multiplication of microorganisms create wound infections in surgical site of a susceptible host. Most infections of post-operative wounds are hospital acquired and vary from one hospital to another[8].

Lack of standardized criteria for diagnosis of SSIs present a challenge to monitor the global epidemiology of surgical site infection5. In addition to this, emergence of high antimicrobial resistance among bacterial pathogens has made the management and treatment of post-operative wound infection difficult[8].

Moreover, rapidly emerging nosocomial pathogens and the problem of multidrug resistance necessitates periodic review of isolation pattern and their sensitivity[9]. Many studies in different part of the world found that the most frequently isolated bacteria from surgical wound infections were Staphylococcus aureus, coagulase negative Staphylococcus (CoNS), Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Proteus species[10].

Infected wounds are wounds that are colonized with bacteria or other microorganisms that cause its deterioration and a delay in wound healing. In other words, infected wounds result when immune defenses of the body are stunned or cannot withstand common bacterial growth. Wound infection caused by surgery is a severe health challenge and surgical wounds are mostly contaminated by bacteria, previous studies have revealed that about 70 percent of the deaths of patients who have undertaken surgical operations are triggered by surgical site infections[11-13]. Surgical antimicrobial prophylaxis can help prevent SSIs. In the hospital setting, 30-50% of antibiotics are prescribed for surgical prophylaxis, and 30-90% of this prophylaxis is unnecessary. This incorrect use raises selection pressure, favoring the formation of pathogenic drug-resistant bacteria[14], complicating the selection of empirical antimicrobial drugs and thereby raising the risk of post-operative wound infections.

## Methodology

### Study Area

The study was conducted at ESUT teaching hospital G.R.A Enugu Urban, the capital city of Enugu state, Nigeria.

### Study design

A cross sectional research technique was used whereby the samples were collected from surgical wounds patients currently admitted at ESUTH.

### Study population

The population is a mix of both urban and rural dwellers. Enugu State University Teaching Hospital, Parklane Enugu.

### Sample size

Sample size was calculated using Cochran's formula

$n = Z^2pq / d^2$

Where:

n (minimum sample size/desired sample size) = ?

p (the percentage of target population estimated to have a particular characteristic) = 14.5%

(0.145) [14]

Z (standard normal deviation) = 1.96 (corresponding to 95% confidence interval)

d (margin of error) = 5% (0.05)

$q = 1 – p = 1 – 0.145 = 0.855$

Therefore, $n = (1.96^{2*} 0.145* 0.855) / 0.052 = 190$

### Sampling technique

The study adopted purposive sampling, The patients with suspected surgical site infection were identified by surgeons during the routine daily ward rounds. The surgeons would then document the clinical signs of infection in the patient file. The patients were briefed about the research and informed consents obtained prior to their inclusion as study participants. This included patients with SSI infection in the hospital wards.

### Inclusion and exclusion criteria

***Inclusion criteria:***

i. Patients of all age groups except neonates
ii. Presence of suspected post-operative SSIs
iii. Giving informed consent to participate.

***Exclusion criteria:***

i. Neonates
ii. Infection occurring 30 days after operation if no implant is in place
iii. Burn injuries and donor sites of split skin grafts
iv. Refusal to give consent for participating in the study

## Ethical issues

Approval for study was given by the Ethical Review committee of Enugu state university teaching hospital. Consent was obtained from the patients of the various post-surgical wards of Enugu state university teaching hospital. The study was carried out with the highest level of transparency and professionalism.

## Patient data collection

Structured questionnaires were used to extract data from the patients case notes; the information included were; demographic data, existing chronic disease (such as diabetes mellitus), past medical history, current drug use such as steroid, smoking, length of preoperative hospital stay, duration of operation and physical examination was done to determine location of the wounds.

## Specimen collection

The specimens were collected aseptically from patients presented with clinical evidence of infection (purulent drainage from incision or drain) before the wound was cleaned with antiseptic. Collection of pus and serous fluid from the deep viable tissues of the wound was done using moistened sterile swab sticks by Levine method (rotating the swab over 1 $cm^2$ area of viable tissues for 5 seconds).

## Laboratory procedure

Swab specimens were processed and tested in the microbiology laboratory. Specimens were immediately cultured upon arrival in the laboratory. Culturing for colony characteristics followed by Gram stain and biochemical tests were used to identify pathogenic bacteria. Culture media used were Blood agar, Nutrient agar and MacConkey agar. Culture media were made by reconstituting the commercial powder in distilled water and sterilizing at 121°C for 15 minutes in an autoclave as per manufacturer's instructions.

## Culture procedure

Culture of pus and surface swabs was carried out according to the set standards and procedures in bacteriology. A small amount of the specimen was applied on the agar surface of both MacConkey and Blood agar. Then using a sterile wire loop, the specimen was spread on the agar surface using the streaking method. Each swab was inoculated on a separate plate and after labeling them, the plates were incubated aerobically at 35-37°C for 18-24 hours. After incubation, Individual bacteria isolates were identified from their respective plates by observation of the growth pattern which included checking the form (circular), elevation (raised, flat or convex), margin (undulate or entire), opacity (translucent, opaque or transparent), hemolysis (beta, alpha or gamma), surface (smooth, dry or mucoid) and pigmentation (pink, golden yellow or white) of the colonies. Swarming characteristics of bacteria on blood agar surface was also used in the identification process. Plates with no growth after 18 hours of incubation were re-incubated while those with mixed growth were sub-cultured on separate plates until pure growth of discrete colonies was observed. Reporting of no growth was only done after the plates were incubated for 48 hours.

## Gram Stain

A colony was picked from pure culture smeared on a clean grease free slide and allowed to air dry. It was then heat fixed by passing the slide over blue flame of a Bunsen burner for about three times. The smear was flooded with crystal violet stain for 60 seconds and was washed off rapidly with clean water, it was then mordanted with Lugol's iodine for 60seconds and was washed off rapidly again with clean water. It was also decolorized with acetone or alcohol for 2 seconds and washed off immediately. Finally, the counter stain safranin was added for 60 seconds. It was then washed off with clean water and placed on a drinking rack to air dry. The smear was examined under high power oil immersion objective lens (x100) of light microscope. The gram-positive bacteria appeared purple while the gram-negative organism appeared pink color.

## Antimicrobial Susceptibility Testing

The antimicrobial susceptibility testing of all identified isolates from the surface swab samples was done according to the criteria of the Clinical and Laboratory Standards Institute method {CLSI). Briefly, from a pure culture a loopful of bacterial colony was taken and transferred to a tube containing 5 ml of normal saline and mixed gently until it formed a homogenous suspension. The turbidity of the suspension was then adjusted to the density of a McFarland 0.5 (Mary-l'Etoil, France) in order to standardize the inoculum size.

A sterile cotton swab was then dipped into the suspension and the excess was removed by gentle rotation of the swab against the surface of the tube. The swab was then used to distribute the bacteria evenly over the entire surface of Nutrient agar. The inoculated plates were left at room temperature to dry for 3-5 minutes.

With the aid of sterile forceps, the appropriate antibiotic sensitivity discs (gram positive or gram negative) were placed on the surface of the nutrient agar. For Gram negative the following antibiotics were used N-Nitrofurantion 100 mcg, GN-Gentamicin 10 mcg, CIP-Ciprofloxacin 10 mcg, C-Chloramphenicol 10 mcg, OF-Ofloxacin 10 mcg, MP-Meropenem 10 mcg, PF-Pefloxacin 10 mcg,CT-Cetriaxone 30 mcg, AX-Amoxicillin 30 mcg, ST-Streptomycin 30 mcg. For Gram positive organisms the following antibiotics were used AM-Ampicillin 30 mcg, CL-Cloxacillin 10 mcg, LV-Levofloxacin 10 mcg, CX-Cephalexin 30 mcg, CIP-Ciprofloxacin 5 mcg, GN-Gentamicin 10 mcg, OF-Ofloxacin 10 mcg, CD-Clindamycin 10 mcg, E-Erythromycin 10mcg, CT-Cetriaxone 30 mcg The plates were then incubated at 37ºC for 24 hours. Diameters of the zone of inhibition around the discs were measured using a digital caliper, and the isolates were classified as sensitive, intermediate and resistant according to the standardized table supplied by CLSI.

### Data analysis

Statistical analysis Package for Social Science (SPSS) version 25 and Microsoft excel were used for statistical analysis of the data generated. Chi square was used to compare between two or more variables. Statistical significance was considered at p-value <0.05 and confidence level of 95%.

## Results

**Table I** presents the background age and sex of the patients. Their age ranged from 18-87 years with mean and standard deviation, 44.70±16.69 and modal age group, 31-40 years (25.4%). Females (61.9%) were more than males (38.1%). Previous social history of alcohol consumption and smoking were 28.8% and 4.2% respectively. **Table II** shows sensitivity and resistance for *Pseudomonas aeruginosa*, **table III** shows sensitivity and resistance for *Proteus Mirabilis*, **table IV** shows sensitivity and resistance for Staphylococcus aureus and **table V** shows sensitivity and resistance for *Klebsiella pneumoniae*.

**Table I:** Sensitivity and Resistance for *E. Coli*.

| Antibiotics | Sensitive | Resistant |
|---|---|---|
| N | 3 | 15 |
| GN | 7 | 11 |
| CIP | 8 | 10 |
| C | 2 | 16 |
| OF | 6 | 12 |
| MP | 2 | 16 |
| PF | 5 | 13 |
| CT | 4 | 14 |
| AX | 7 | 11 |
| ST | 5 | 13 |

N-Nitrofurantion, GN-Gentamicin, CIP-Ciprofloxacin, C-Chloramphenicol, OF-Ofloxacin, MP-Meropenem, PF-Pefloxacin, CT-Cetriaxone, AX-Amoxicillin, ST-Streptomycin.

**Table II:** Sensitivity and Resistance for *Pseudomonas aeruginosa.*

| | Sensitive | Resistant |
|---|---|---|
| N | 0 | 4 |
| GN | 0 | 4 |
| CIP | 4 | 0 |
| C | 0 | 4 |
| OF | 1 | 3 |
| MP | 0 | 4 |
| PF | 0 | 4 |
| CT | 1 | 3 |
| AX | 1 | 3 |
| ST | 0 | 4 |

N-Nitrofurantion, GN-Gentamicin, CIP-Ciprofloxacin, C-Chloramphenicol, OF-Ofloxacin, MP-Meropenem, PF-Pefloxacin, CT-Cetriaxone, AX-Amoxicillin, ST-Streptomycin.

**Table III:** Sensitivity and Resistance for *Proteus Mirabilis.*

| | Sensitive | Resistant |
|---|---|---|
| N | 0 | 4 |
| GN | 0 | 4 |
| CIP | 2 | 2 |
| C | 0 | 4 |
| OF | 1 | 3 |
| MP | 0 | 4 |
| PF | 0 | 4 |
| CT | 1 | 3 |
| AX | 0 | 4 |
| ST | 0 | 4 |

N-Nitrofurantion, GN-Gentamicin, CIP-Ciprofloxacin, C-Chloramphenicol, OF-Ofloxacin, MP-Meropenem, PF-Pefloxacin, CT-Cetriaxone, AX-Amoxicillin, ST-Streptomycin.

## Discussion

The majority of the SSI bacteria isolates were Gram-negative rods 61.2% (30) with Gram-positive bacteria accounting for 38.8% (19) of the total isolates. These results were attributed to antibiotic resistance, because majority of the Gram-negative bacteria isolates were more resistant compared to Gram-positive isolates. These findings were in harmony with observations made by other research works which observed the predominance of Gram-negative bacteria over Gram-positive bacteria 56.5% versus 43.5% and 85 versus 27. However, the results were contrary to the work of two researchers who observed that Gram-positives were more compared to Gram-negatives[15].

Gram-negative isolates were mostly resistant to Chloramphenicol, Amoxicillin, Meropenem and Streptomycin. Nonetheless, relative success was observed with Ciprofloxacin, Ofloxacin and Nitrofurantion. While the gram-positive isolates were mostly sensitive to Ciprofloxacin, Cetriaxone, Levofloxacin and Ofloxacin and showed great resistance to Ampicillin, Cloxacillin and Cephalexin.

This study discovered that a majority of the SSI isolates were highly resistant to Chloramphenicol and Cloxacillin proving that the two drugs were no longer very effective in the treatment of surgical site infection at the hospital16. The sensitivity of SSI bacteria isolates to these drugs in this present study was actually low, this may be due to bacteria developing a very high resistance against the two drugs, it may also be attributed to the indiscriminate use of the drugs in the study area.

**Table IV:** Sensitivity and Resistance for *Staphylococcus aureus.*

| | Sensitive | Resistant |
|---|---|---|
| - AM | 3 | 16 |
| - CL | 1 | 18 |
| - LV | 9 | 10 |
| - CX | 2 | 17 |
| - CIP | 15 | 4 |
| - GN | 4 | 15 |
| - OF | 5 | 14 |
| - CD | 1 | 18 |
| - E | 2 | 17 |
| - CT | 14 | 5 |

AM-Ampicillin, CL-Cloxacillin, LV-Levofloxacin, CX-Cephalexin, CIP-Ciprofloxacin, GN-Gentamicin, OF-Ofloxacin, CD-Clindamycin, E-Erythromycin, CT-Cetriaxone.

**Table V:** Sensitivity and Resistance for *Klebsiella pneumoniae*

| | Sensitive | Resistance |
|---|---|---|
| N | 3 | 1 |
| GN | 2 | 2 |
| CIP | 4 | 0 |
| C | 1 | 3 |
| OF | 3 | 1 |
| MP | 0 | 4 |
| PF | 2 | 2 |
| CT | 2 | 2 |
| AX | 1 | 3 |
| ST | 3 | 1 |

N-Nitrofurantion, GN-Gentamicin, CIP-Ciprofloxacin, C-Chloramphenicol, OF-Ofloxacin, MP-Meropenem, PF-Pefloxacin, CT-Cetriaxone, AX-Amoxicillin, ST-Streptomycin.

## Conclusion

This study identified *Staphylococcus aureus* as the leading causative organism of SSIs among surgical patients at Enugu State University Teaching Hospital, Enugu with Ciprofloxacin as the most sensitive antibiotic and Chloramphenicol, Cloxacillin and Erythromycin respectively as least sensitive, pointing to the necessity of clinicians and microbiologists working hand in hand for the timely diagnosis and treatment of such infections.

### Conflict of interest

No

## References

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ORIGINAL

# Past themes and future trends in the economic dimension of COVID-19 research: a co-word analysis

*Temas pasados y tendencias futuras en la dimensión económica de la investigación sobre COVID-19: un análisis de co-palabras*

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## Abstract

***Background:*** This article aims to describe the development of research focusing on the economic dimension of COVID-19 from 2020 to 2023 (July), identifying the main themes and how they have evolved. It also aims to identify gaps in the literature to propose the future research agenda.
***Methods:*** A total of 2456 publications were analyzed using the Web of Science database. The analysis utilized the R program's bibliometrix package and the Scimat program in conjunction. The study data were examined in four periods: 2020, 2021, 2022, and 2023 (July) to observe the evolution of concepts.
***Results:*** The analysis revealed that the dominant themes in respective periods were motor themes, namely economics, lockdown, pandemic, and economics in that order. It was observed that the year 2022 had the highest number of studies conducted.
***Conclusion:*** While the years 2020 and 2021 might be considered the most impactful years of the COVID-19 pandemic, considering the publication timelines and the time it takes for the pandemic's economic effects to materialize, the higher number of studies in 2022 could be attributed to this delay. Additionally, although the pandemic started to be controlled in some countries with the commencement of vaccination campaigns in 2022, the persistence of variants and the course of the pandemic led to continued economic uncertainty. Authors interested in working in this field might primarily focus on mental health; those seeking more niche areas could explore economic policy uncertainty and economic themes. Furthermore, the decreasing or emerging themes appeared weakly structured and could be linked to specific research interest areas that could be significant for the entire research domain. Thus, studying the economic crisis theme related to COVID-19 is recommended.

*Key words:* COVID-19, economic, co-word analysis, bibliometric.

## *Resumen*

***Antecedentes:*** Este artículo tiene como objetivo describir el desarrollo de la investigación centrada en la dimensión económica de COVID-19 desde 2020 hasta 2023 (julio), identificando los principales temas y cómo han evolucionado. También tiene como objetivo identificar lagunas en la literatura para proponer la agenda de investigación futura.
***Métodos:*** Se analizaron un total de 2456 publicaciones utilizando la base de datos Web of Science. El análisis utilizó el paquete bibliométrico del programa R y el programa Scimat en conjunto. Los datos del estudio se examinaron en cuatro períodos: 2020, 2021, 2022 y 2023 (julio) para observar la evolución de los conceptos.
***Resultados:*** El análisis reveló que los temas dominantes en los respectivos períodos fueron temas motores, a saber, economía, confinamiento, pandemia y economía en ese orden. Se observó que el año 2022 tuvo el mayor número de estudios realizados.
***Conclusión:*** Si bien los años 2020 y 2021 podrían considerarse los años más impactantes de la pandemia de COVID-19, considerando los plazos de publicación y el tiempo que lleva que los efectos económicos de la pandemia se materialicen, el mayor número de estudios en 2022 podría atribuirse a este retraso. Además, aunque la pandemia comenzó a controlarse en algunos países con el inicio de las campañas de vacunación en 2022, la persistencia de variantes y el curso de la pandemia llevaron a una continua incertidumbre económica. Los autores interesados en trabajar en este campo podrían centrarse principalmente en la salud mental; aquellos que buscan áreas más especializadas podrían explorar la incertidumbre de la política económica y temas económicos. Además, los temas en disminución o emergentes parecían débilmente estructurados y podrían estar vinculados a áreas específicas de interés investigativo que podrían ser significativas para todo el dominio de investigación. Por lo tanto, se recomienda estudiar el tema de la crisis económica relacionada con COVID-19.

*Palabras clave:* COVID-19, económico, análisis de co-palabras, bibliométrico.

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## Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for the COVID-19 disease in 2019, is the seventh coronavirus known to transmit from other hosts like bats and rodents to humans1.In March 2020, following the assessment of the rapid global spread and severity of the deadly virus, the WHO Director-General declared COVID-19 a pandemic, alongside additional social distancing measures to curb its spread[1]. As countries imposed stringent restrictions to halt the virus's spread, the COVID-19 pandemic rapidly crippled economic activity, nearly grinding it to a halt. Alongside rising health and human losses, the already evident economic damage represents the most significant economic shock the world has faced in decades[2]. Since the peak of COVID-19, economic concerns have been on the rise worldwide. Research has shown that economic distress could lead to serious psychological and physical health issues that need to be considered by clinical professionals and policymakers[3]. Moreover, with technological advancements, information about the pandemic has been disseminated globally within a short span of time.

Initial estimations predicted that major economies might lose around 2.4% to 3.0% of their Gross Domestic Product (GDP) due to the COVID-19 pandemic in 2020[4]. Consequently, reduced incomes and high uncertainty have made it challenging for numerous businesses worldwide to sustain their financial operations[5].Governments responded to curb the spread of the virus by implementing various policies such as travel bans, quarantines, and closing internal and external borders. However, the impacts of the disease and the measures taken to combat it raised concerns about preparedness for pandemics[6].

The COVID-19 pandemic has led to the emergence of numerous new publications in the fields of medicine and science. Since the outbreak's onset, research on COVID-19 has rapidly escalated, resulting in the publication of numerous scientific articles. This rapid increase has directed scientists and researchers across the globe to engage in this subject due to the pandemic's severity and rapid spread. Consequently, the synthesis of the general literature on COVID-19 in an economic context has become imperative.

## Methodology

This study aims to explore research areas and thematic trends in publications focused on the economic dimension of COVID-19 using co-word analysis. The study sought to answer the following questions:

1. What are the thematic developments of COVID-19's economic dimension in research?
2. What are the future research directions for the economic dimension of COVID-19?

Co-word analysis was introduced to the literature by Callon et al. (1986). It's a method used in text mining and natural language processing fields[11]. This analysis unveils relationships and connections between words by examining the frequency of words appearing together in a specific text. It's considered an effective method for content analysis and text mining[7-9]. Co-word analysis is employed to comprehend conceptual structures in large datasets, detect textual similarities, and uncover new ideas or discoveries. It serves to exhibit connections between research themes and scientific disciplines[10].

The fundamental steps of co-word analysis are as follows:

***Data Collection:*** Collect text data related to the topic of interest. This data can include articles, books, blog posts, social media entries, or other text-based sources.

***Text Data Preprocessing:*** Preprocess the collected text data. This step involves cleaning processes like removing unnecessary characters, punctuation marks, stop words, and numbers. Additionally, transforming words to lowercase and applying stemming or lemmatization to words can be performed.

***Calculation of Word Frequencies:*** Calculate the frequency of words in the cleaned text data. This helps identify which words are more frequently used.

***Creation of Word Relationships:*** In co-word analysis, each word is associated with the co-occurrence of other words. This relationship is based on the frequency of two words appearing together in the same text.

***Formation of Co-Occurrence Matrix:*** Based on the word relationships, a co-occurrence matrix is formed. This matrix includes the co-occurrence frequencies of words in the text.

***Statistical Analysis:*** Conduct necessary statistical analyses based on the co-occurrence matrix. These analyses are used to understand relationships between words.

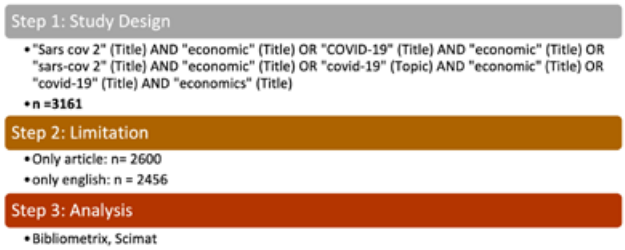
***Visualization:*** Typically, analysis results are presented using visualization methods. Visual tools like heatmaps, network graphs, etc., can be employed to clearly illustrate word relationships.

This method proves highly valuable in analyzing large datasets and identifying significant topics within text. Co-word analysis-based studies are used to explore connections between texts, and they find application in various fields such as content management, marketing strategies, and healthcare improvements.

In this study, a search was conducted in the Web of Science database for the period between January 1,

2020, and August 2, 2023. Keywords were searched using the "title" option, as depicted in **figure 1**, yielding an initial 3161 records. After filtering for English-language articles and excluding non-article types, 2456 studies were included for analysis. The analysis employed the bibliometrix package.

**Figure 1:** Search strategy.




## Results

**Figure 2** displays the publication counts of articles over the years. Accordingly, the highest number of publications, 918, occurred in the year 2022. In 2021, there were 726 publications, while 309 were produced in 2020. Although there seems to be a decline in publications in 2023, it's challenging to make a general assessment since data up to July have been considered. The publications notably experienced a significant leap from 2020 to 2021, showing a remarkable increase of 135%.

**Figure 2:** Number of publications by years.

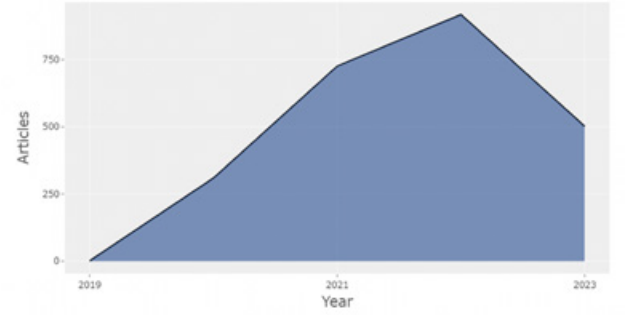



**Figure 3** presents the most frequently used keywords. According to this figure, the most commonly used keyword is "COVID-19" with a count of 1156. Following this are the keywords "Pandemic," "COVID-19 pandemic," and "Economic growth."

**Figure 3:** Most frequently used keywords.

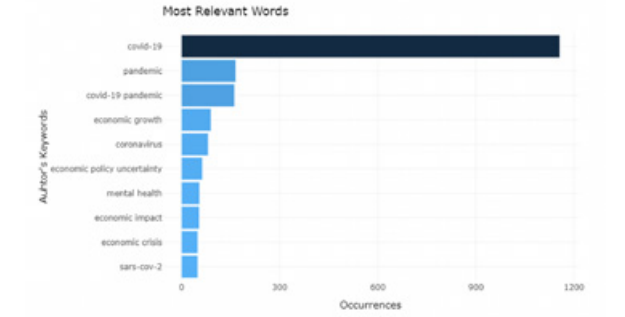



**Figure 4** depicts the network map of author keywords created by Bibliometrix. Keywords are divided into five clusters. The most frequently used cluster is represented by the color red, symbolizing the interplay between "COVID-19" and the economy. The blue cluster represents Economic Growth, the orange cluster signifies Sustainable Development, the green cluster represents Mental Health, and the purple cluster embodies Health Economics.

The formation of keywords was analyzed using the co-occurrence matrix in the SciMAT software. Similarities between clusters were calculated based on the "equivalence index."

**Figure 4:** Co Occurence network.

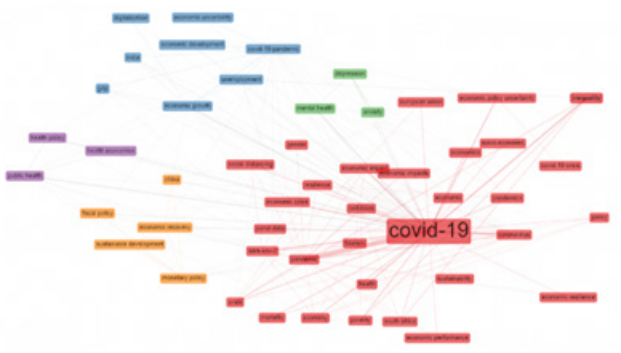
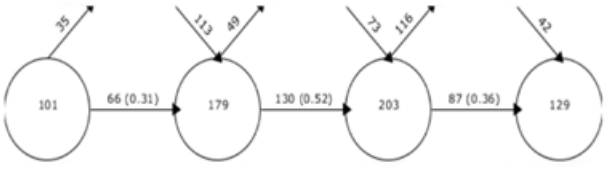



**Figure 5** illustrates the development of themes in studies related to the economic dimension of COVID-19. It shows the emergence of themes in a total of four time periods: 2020, 2021, 2022, and 2023 (July). The figure uses upward arrows to indicate disappearing terms, downward arrows to represent new terms, numbers within parentheses to denote the number of themes in the respective period, and horizontal arrows to show themes inherited from the previous period.

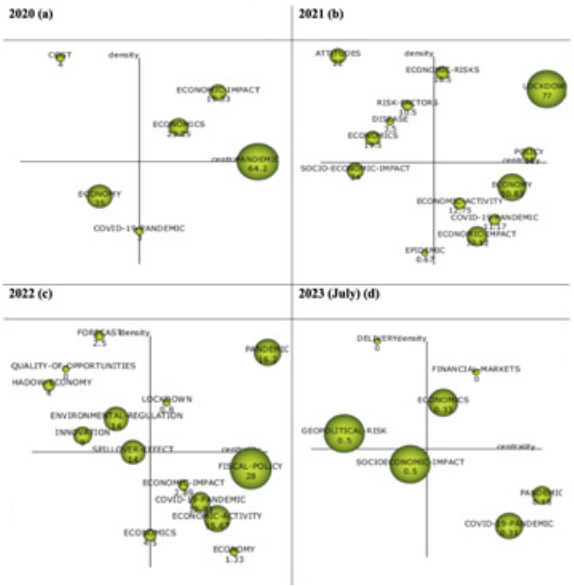
In 2021, out of the 179 themes, 73% (n=130) were carried over to the 2022 period, making it the period with the highest transfer of themes. The highest number of themes, 203, appeared in the year 2022. The year 2021 witnessed the introduction of the most new terms, with 113 themes. However, as the transition occurred from 2022 to 2023, 57% of the themes were lost, resulting in the highest loss of terms in this transition.

**Figure 5:** Thematic overlapping map of studies on the economic dimension of COVID19.



In **figure 6**, thematic maps with author keywords using SciMAT for research examining the economic dimension of COVID-19 are presented for four different years. **Table I** includes the themes of the periods. Clusters represent themes, and the numbers within them indicate the volume of the corresponding literature. As the number and cluster size increase, the usage of the theme also increases. The horizontal axis represents centrality, indicating the strength of the relationship with other themes. The larger the centrality, the more central it is in the research field and closely related to other themes. The vertical axis represents density, which indicates the degree of relationship among keywords within a theme. Higher density signifies closer internal connections and more mature theme development. The two-axis plane is divided into four quadrants[13].

**Figure 6:** The overall thematic map of studies related to the economic aspect of COVID-19.




The map is divided into four distinct themes: niche (top left), motor (top right), decreasing or emerging (bottom left), and foundational themes (bottom right). Motor themes and foundational themes are directly related to the research field, but while motor themes encompass well-developed research topics, foundational themes are less mature. Niche themes encompass well-developed research subjects but pertain to more marginal topics rather than the core domain. Decreasing or Emerging Theme: The terms "decreasing theme" and "emerging theme" are used to describe spatial patterns displayed on the map. Decreasing Theme: A decreasing theme depicts a model in which a specific feature or phenomenon diminishes in size or intensity from one area to another. Emerging Theme: An emerging theme illustrates a model in which a specific feature or phenomenon increases in size or intensity from one area to another[14].

**Figure 7** displays the overall thematic map of studies related to the economic dimension of COVID-19. This map was generated by Bibliometrix. According to the map, motor themes include mental health, thematic themes encompass COVID-19, niche themes address economic policy uncertainty, and emerging or declining themes involve economic crisis.

**Figure 7:** The overall thematic map of studies related to the economic aspect of COVID-19.

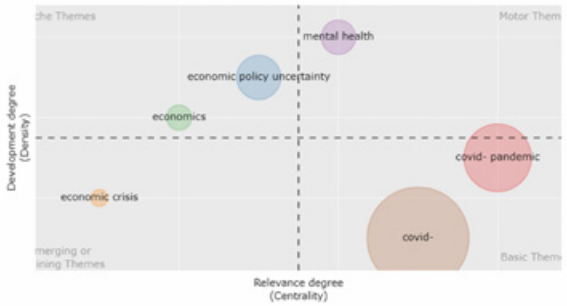



**Table I:** Themes by period.

| | 2020 | 2021 | 2022 | 2023 (temmuz) |
|---|---|---|---|---|
| **Motor Theme** | Economics | lockdown, | pandemic- | economics |
| **Basic Themes** | - | economy- | fiscal policy | COVID 19 pandemic |
| **Niche Themes** | Cost | Attidues | Environmental regulation | geopalitical risk |
| **Emerging Or Declining Themes** | Economy | Socio Economic Impact | - | Socio Economic Impact |

## Discussion

This study presents a co-word analysis of research conducted to comprehend the impact of the COVID-19 pandemic on the economy. The study analyzes data from four periods: 2020, 2021, 2022, and 2023 (July), with the aim of observing the development of concepts over these years. This article serves as a crucial source of information to assess current trends and research areas in studies related to the economic dimensions of the COVID-19 outbreak.

In the year 2020, it was observed that the central and most prominent concept was "economics." In the initial period of 2020, the number of terms was comparatively lower than in the subsequent periods. This was due to the new onset of the COVID-19 pandemic and the lower number of studies conducted during that time.

In the year 2021, the concept that saw the most significant growth as a central theme was "lockdown." The impact of

lockdown measures on the economy, stemming from the crucial step of combating the COVID-19 outbreak, led to it becoming a frequently used theme in studies. Studies on COVID-19 lockdown and the economy have been conducted by authors such as Atalan (2020), Gupta et al. (2021), Yaish et al. (2021)[18,19,20]. Research in this area showed a substantial increase of 135% compared to the first period. Additionally, this period witnessed the introduction of 113 new terms. It is believed that as the effects of the pandemic became more evident, the number of studies also increased. Particularly during this time, many countries initiated financial stimulus packages and rescue measures to prevent economic collapse and support businesses. Central banks lowered interest rates and provided liquidity, with the goal of supporting economic recovery.

In the third period, 2022, studies (n=918) examining the economic dimension of COVID-19 and related themes (n=203) reached the highest level, with the most significant theme identified as "pandemic." The pandemic started to come under control in certain countries with the initiation of vaccination campaigns. However, due to the emergence of variants and the unpredictable course of the pandemic, economic uncertainty persisted.

In the latest period, the most prominent theme resurfaced as "economics," similar to the first period. As the transition from 2022 to 2023 occurred, themes experienced a 57% decline, with the highest loss in the number of terms used and a decrease in publication numbers. Although the popularity of the topic seems to have diminished compared to the previous period, it should be noted that the data for 2023 only covers a seven-month span, making comparisons with previous periods challenging.

The overall thematic map of studies related to economic dimension of COVID 19 created by Bibliometrix revealed that prominent motor themes included "mental health," thematic themes encompassed "COVID," niche themes addressed "economic policy uncertainty," and emerging or declining themes involved "economic crisis." Studies by Gong et al. (2022), Zajacova ve diğerleri (2020), Alradhawi (2020) and Salameh (2020) have been conducted on mental health and economics of COVID 19[21,22,23,24]. Studies have been carried out on the COVID 19 economic policy uncertainty in the studies conducted by Iyke (2020), Al-Thaqeb (2022), Ahmed and Sarkodie (2021)[25,26,27]. In the studies conducted by Borio (2020), Ozli (2021), 30. Adams-Prassl (2020), studies were carried out on the COVID 19 economic crisis[28,29,30].

A study conducted by Zhong and Lin (2022) analyzed literature published since December 2019 to explore the economic impact of COVID-19. Bibliometric analysis and social network analysis methods were utilized. The study identified themes such as "financial market," "economic policy uncertainty," "coronavirus disease," "air quality," and "economic recovery scenario."Another study by Alshater et al. (2022) revealed that the most frequently used keywords included "COVID-19," "crisis," "economic impact," "crisis management," and "viral disease."Furthermore, a study by Mahi et al. (2021) examined pandemics starting from 1974 and included 1636 publications. The study found that the most impactful keywords were "impact," "health," "United States," "risk," "epidemic," and "mortality"[15,16,17].

In the conducted co-occurrence analysis, the themes have been categorized into 5 themes as follows: COVID-19 and the economy, economic growth, sustainable development, mental health, and health economy.

## Conclusions and limitations

In this study, research focusing on the economic dimension of COVID-19 has been examined through co-word analysis using complex software tools. This article has investigated shifts in themes during the course of the pandemic and its aftermath. Authors aspiring to work in this field can link the motor theme of mental health to the economic aspect of the COVID-19 pandemic.

The COVID-19 pandemic has been a significant event leading to global economic downturn and job losses. The economic aspect of the pandemic has been managed through government measures and economic support. However, the effects of the pandemic and the reshaping process continue to unfold. During this process, economic policymakers, businesses, and society need to work on long-term solutions that enhance resilience, promote economic justice, and facilitate recovery. This study strengthens academic research and highlights crucial gaps in the literature on the COVID-19 pandemic's intersection with economics. Furthermore, it provides insights into future research directions.

Nonetheless, this study has certain limitations. It covers articles published in the English-language Web of Science database in this field. The selection of articles was based on the guarantee of double-blind peer review. Additionally, if conferences were selected, the possibility of re-publication as articles could introduce duplication issues. The limitations should be considered, as the chosen database and software tools might have influenced the findings. The evaluation of 2023 is based only on data from a span of 7 months, thereby revealing a weakness in the study's ability to compare with other periods.

## Competing interests

All authors declare no competing interest.

## Funding

Not applicable

## Authors' contributions

The study has been conducted solely by the author.

## Ethical Approval

Ethics committee approval is not required because secondary data has been used in the study.

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# Relationship between heart age and cardiometabolic risk scales in 139634 Spanish workers

*Relación entre la edad del corazón y escalas de riesgo cardiometabólico en 139634 trabajadores españoles*

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## Abstract

***Introduction:*** Cardiometabolic diseases are highly prevalent worldwide and are responsible for high morbidity and mortality. Cardiovascular risk (CVR) is usually determined from scales that assess the probability of occurrence in a given period. Currently, other CVR scales have been developed that assess the aging of both the heart and blood vessels. The aim of this study is to assess the association between some cardiometabolic risk scales and heart age.
***Methods:*** Descriptive study in 139634 Spanish workers in which CVR was determined by applying the age of the heart and also different cardiometabolic risk scales such as atherogenic dyslipidemia, lipid triad, metabolic syndrome, diabesity, hypertriglyceridemic waist circumference, and risk of type 2 diabetes.
***Results:*** Heart age values are higher in people with high cardiometabolic risk applying all scales. The risk of presenting moderate or high values of heart age is higher among people with high cardiometabolic risk, especially in case of lipid triad and high values of the Findrisk test. The value of the Findrisk test for predicting moderate vascular age is low, whereas for high heart age the value of this test is high.
***Conclusions:*** There is a good association between heart age and the cardiometabolic risk scales analyzed. The predictive value of the Findrisk test is low for moderate heart age and high for high heart age.

*Key words:* Heart age, atherogenic dyslipidemia, metabolic syndrome, Findrisk test, diabesity, hypertriglyceridemic waist circumference.

## *Resumen*

***Introducción:*** Las enfermedades cardiometabólicas tienen una elevada prevalencia en el mundo y son responsables de una elevada morbimortalidad. El riesgo cardiovascular (RCV) se determina habitualmente a partir de escalas que valoran la probabilidad de aparición en un periodo determinado. Actualmente se han desarrollado otras escalas de RCV que valoran el envejecimiento tanto del corazón como de los vasos sanguíneos. El objetivo de este estudio es valorar la asociación entre algunas escalas de riesgo cardiometabólico y la edad del corazón.
***Material y métodos:*** Estudio descriptivo en 139634 trabajadores españoles en los que se determina el RCV aplicando la edad del corazón y también diferentes escalas de riesgo cardiometabólico como dislipemia aterogénica, triada lipídica, síndrome metabólico, diabesidad, cintura hipertrigliceridémica y riesgo de diabetes tipo 2.
***Resultados:*** Los valores de edad del corazón son más elevados en las personas con alto riesgo cardiometabólico aplicando todas las escalas. El riesgo de presentar valores moderados o altos de edad del corazón es mayor entre las personas con alto riesgo cardiometabólico, especialmente en caso de triada lipídica y valores altos del test de Findrisk. El valor del test de Findrisk para predecir edad vascular moderada es bajo, mientras que para edad del corazón alta el valor de este test es elevado.
***Conclusiones:*** Existe buena asociación entre edad del corazón y las escalas de riesgo cardiometabólico analizadas. El valor predictivo del test de Findrisk es bajo para edad del corazón moderada y alto para edad del corazón alta.

*Palabras clave:* Edad del corazón, dislipemia aterogénica, síndrome metabólico, test de Findrisk, diabesidad, cintura hipertrigliceridémica.

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## Introduction

Cardiometabolic pathologies are a group of diseases that affect the heart[1] and blood vessels[2] and are fundamentally caused by unhealthy lifestyles of individuals[3]. It is a process generally due to atherosclerosis[4], which is caused by the accumulation of cholesterol and other substances and results in hardening of the arterial wall.

According to data published by the World Health Organization (WHO), more people die each year worldwide from this cause than from any other cause[5]. The same organization states that 8 out of every 10 myocardial infarctions or cerebrovascular accidents could be prevented[6] if early detection[7] and healthy lifestyles[8] were established or if risk factors were effectively controlled[9].

Cardiometabolic diseases (CMD) include such prevalent pathologies as heart failure, arterial hypertension, dyslipidemia and diabetes mellitus.

The risk of presenting SCD has traditionally been defined as a percentage of risk in a given period of time, which is usually 10 years[10]. This percentage assessment can give a false sense of security, so other tools have been developed that establish, in absolute values, the estimated age of both the heart and the blood vessels, known as heart age[11] and vascular age[12]. These tools, according to some authors, facilitate understanding of the level of risk to which individuals are subjected[13].

The aim of this study is to assess the relationship between one of these tools, heart age, and different scales that assess cardiometabolic risk, such as atherogenic dyslipidemia, the lipid triad, metabolic syndrome, hypertriglyceridemic waist circumference, diabesity, and the risk of type 2 diabetes.

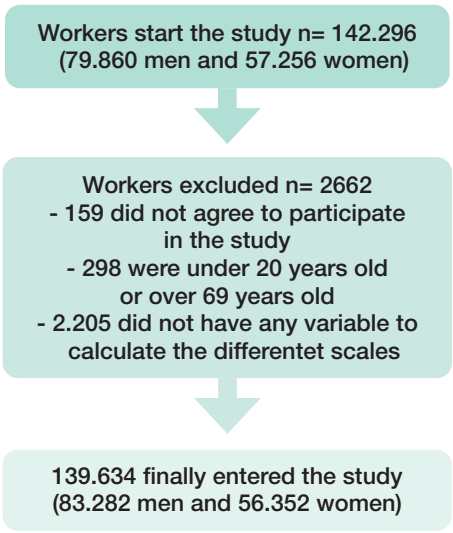
## Methods

An observational, descriptive and cross-sectional study was carried out in a group of 139634 workers from different Spanish regions between January 2019 and June 2020. The workers were selected among those who had attended the health examinations carried out in the different participating companies.

In order to be included in the study, a series of inclusion criteria were established, among which we highlight the following:
- To be between 18 and 69 years of age.
- To be part of the staff of one of the participating companies.
- Acceptance to participate in the study by consenting to the use of the data for epidemiological purposes.

The flow chart of the participants in the study is shown in **figure 1**.

**Figure 1:** Flow chart of the participants.




### *Determination of variables*

All the health professionals belonging to the different participating companies were responsible for obtaining the precise analytical, clinical and anthropometric parameters to determine the cardiometabolic risk scales and the age of the heart. In order to avoid possible biases in the measurements, all the measurement techniques were previously standardized.

Waist circumference was obtained with the person standing upright, with the abdomen as relaxed as possible and placing the tape measure parallel to the floor and at the level of the last floating rib.

Blood pressure was determined after a rest period of no less than 10 minutes. The person was placed in a seated position and three determinations were made at one-minute intervals, establishing the mean of the three as the final result.

The blood tests were performed after a fasting period of not less than twelve hours. Enzymatic techniques were used to determine triglycerides, cholesterol and glycemia. HDL values were obtained by precipitation techniques, LDL values were obtained from the Friedewald formula provided that triglycerides were not higher than 400 mg/dL, otherwise a direct determination was made.

Heart age (CE) is a novel scale that is determined on the basis of the classic Framingham Scale[14]. Unlike the traditional cardiovascular risk scales that estimate the probability of a cardiovascular event occurring in the next decade, the CE estimates how our heart has aged.

Its calculation requires a series of variables such as gender, age, height and weight, abdominal waist circumference, presence of family members with cardiovascular problems, smoking, diabetes, lipid profile,

systolic blood pressure, and antihypertensive treatment. All these data can be used to access a calculator (www.heartage.me.). The calculation of CE can be performed in the interval between 20-80 years.

A concept called ALLY[15] (avoidable years of life lost) has been developed, which is obtained by subtracting CAD from chronological age. In a previous article, our group[16] determined the cut-off points for moderate ALLY (11 years) and high ALLY (17 years).

Blood glucose levels were stratified according to the criteria of the American Diabetes Association[17], according to which a person is considered diabetic when blood glucose levels are above 125 mg/dL in two different measurements, or when HbA1c values ≥ 6.5% or if he or she is on hypoglycemic treatment.

As estimators of cardiometabolic risk, the following were calculated:

- Atherogenic dyslipidemia (AD) and lipid triad (LT).
Atherogenic dyslipidemia[18] was considered AD when high triglyceride values coexisted with low HDL values in the same person. If high LDL values were also associated, it was considered LT[19].

- Metabolic syndrome (MS).
MS was determined on the basis of two criteria[20]:

a) The presence of at least three of these parameters, blood pressure greater than 130/85 mmHg; triglycerides above 150 mg/dL or under treatment to lower it; low HDL, glycemia above 100 mg/dL or specific treatment for it and waist circumference above 88 cm in women and 102 cm in men corresponds to SM NCEP ATP III.

b) The International Diabetes Federation (IDF) establishes SM if: in addition to presenting at least two of the parameters mentioned above (triglycerides, HDL, blood pressure and glycemia), a waist circumference greater than 94 cm in men and 80 cm in women appears.

- Risk of type 2 diabetes with the Findrisk[21] test.
To determine the risk of presenting type 2 diabetes we will use the Findrisk test. This questionnaire includes 8 items: age, waist circumference, body mass index, physical activity, family history of diabetes, consumption of fruits and vegetables, consumption of antihypertensive drugs and personal history of hyperglycemia. Values above 14 will indicate a high risk[22].

- Diabesity.
Diabesity is considered to exist when the same person has obesity determined by a body mass index of 30 kg/m$^2$ or more and diabetes[23].

- Hypertriglyceridemic waist.
We speak of a hypertriglyceridemic waist when we find in the same person high triglyceride values (greater than 150 mg/dL) and high abdominal waist circumference values (greater than 102 cm in men and greater than 88 cm in women)[24].

A smoker is an individual who in the last month has consumed at least 1 cigarette per day (or a similar amount in other consumption modalities) or who has quit smoking less than 1 year ago.

When we applied the questionnaire on adherence to the Mediterranean diet (14 questions rated between 0 and 1 point), we considered adherence to be high at values of 925 or higher.

Physical activity was assessed with the International Physical Activity Questionnaire (IPAQ)[26].

Alcohol consumption was quantified using alcohol units (AU). Considering that 1 AU is equivalent to 10 grams of pure ethanol. We consider high consumption as from 14 AU in women and 21 in men per week[27].

Social class was determined based on the 2011 National Classification of Occupations (CNO-11)28 and applying the criteria of the Spanish Society of Epidemiology. We stratified it into: Social class I. Includes management personnel, university professionals, athletes and artists. Social class I. Includes intermediate occupations and skilled self-employed workers. Social class III. Includes low-skilled workers.

### *Ethical considerations and aspects*

The ethical standards of the Institutional Research Council and the 2013 Declaration of Helsinki are always followed, and anonymity and confidentiality are guaranteed. The study was approved by the Research Ethics Committee of the Balearic Islands (CEI-IB): IB 4383/20. The data of each employee included in the study were coded, and only those responsible for the study knew the identity of each individual.

The researchers undertook to strictly comply with the provisions of Organic Law 3/2018, of December 5, on the protection of personal data and guarantee of digital rights, which guarantees the right of participants to access, rectify, cancel, and oppose the data collected.

### *Statistical analysis*

For quantitative variables, Student's t test was used to calculate the mean and standard deviation. When the variables were qualitative, the chi-square test was used to calculate prevalence. For ROC curves, the areas under the curve were determined. Multivariate analysis was performed by applying multinomial logistic regression. SPSS 28.0 was used for statistical analysis. The accepted level of statistical significance was $p<0.05$.

## Results

**Table I** shows the values of the analytical, clinical, anthropometric, sociodemographic and healthy habits variables of the 139634 (83282 men 59.6% and 56352 women 40.4%) workers who participated in this study. The mean age of the sample was slightly over 40 years, with the largest group being 30-49 years. In all cases, the variables were less favorable in males. Most of the workers were of social class III and with primary education. The prevalence of sedentary lifestyle was higher in men, as was low adherence to the Mediterranean diet. Tobacco consumption, and especially alcohol consumption, was also higher in men.

**Table II** shows that the ALLY values for heart age were higher in both men and women when the cardiometabolic risk scales showed higher values. In all cases, these mean ALLY values were higher in men. The differences observed between both sexes were always statistically significant.

The prevalence of elevated ALLY heart age values also shows higher values when the cardiometabolic risk scales show higher values. As we have seen with the mean values, in the case of prevalences we also observed higher figures in men. The differences by sex are statistically significant in all cases. The complete data can be seen in **table III**.

**Table IV** shows the results of the multivariate analysis using multinomial logistic regression. In all cases, the risk of moderate or high ALLY increases as the values of the different cardiometabolic risk scales increase. The highest odss ratios appear for Findrisk and lipid triad.

**Figure 2** shows the areas under the Findrisk curve for predicting the occurrence of moderate and high ALLY. In women the areas are larger than in men. In both sexes the predictive value of Findrisk is higher for ALLY high heart age.

**Table I:** Characteristics of the population.

| | Men n=83,282<br>Mean (SD) | Women n=56,352<br>Mean (SD) | p-value |
|---|---|---|---|
| Age (years) | 41.4 (10.7) | 40.1 (10.4) | <0.0001 |
| Height (cm) | 173.8 (7.1) | 161.2 (6.5) | <0.0001 |
| Weight (kg) | 83.2 (14.6) | 66.3 (13.9) | <0.0001 |
| Body mass index (kg/m²) | 27.5 (4.5) | 25.5 (5.3) | <0.0001 |
| Waist circumference (cm) | 90.2 (10.3) | 76.3 (10.5) | <0.0001 |
| Waist to height ratio | 0.52 (0.06) | 0.47 (0.07) | <0.0001 |
| Systolic blood pressure (mmHg) | 126.2 (15.9) | 115.6 (15.7) | <0.0001 |
| Diastolic blood pressure (mmHg) | 76.6 (10.9) | 71.1 (10.7) | <0.0001 |
| Total cholesterol (mg/dl) | 199.6 (38.6) | 194.6 (36.9) | <0.0001 |
| HDL-cholesterol (mg/dl) | 50.0 (7.7) | 54.7 (9.2) | <0.0001 |
| LDL-cholesterol (mg/dl) | 122.6 (37.4) | 121.5 (37.1) | <0.0001 |
| Triglycerides (mg/dl) | 133.8 (95.6) | 90.8 (49.7) | <0.0001 |
| Glycaemia (mg/dl) | 93.0 (25.4) | 86.8 (18.1) | <0.0001 |
| n (%) | n (%) | p-value | |
| 18-29 years | 12558 (15.1) | 10110 (18.0) | <0.0001 |
| 30-39 years | 24648 (29.6) | 17460 (31.0) | |
| 40-49 years | 25178 (30.2) | 17094 (30.3) | |
| 50-59 years | 17370 (20.9) | 9984 (17.7) | |
| 60-70 years | 3528 (4.2) | 1704 (3.0) | |
| Social class I | 6234 (7.5) | 7632 (13.6) | <0.0001 |
| Social class II | 19856 (23.8) | 18112 (32.1) | |
| Social class III | 57192 (68.7) | 30608 (54.3) | |
| Primary school | 55306 (66.4) | 27086 (48.1) | |
| Secondary school | 22408 (26.9) | 22574 (40.0) | |
| University | 5568 (6.7) | 6692 (11.9) | |
| Non-smokers | 55618 (66.8) | 38252 (67.9) | <0.0001 |
| Smokers | 27664 (33.2) | 18100 (32.1) | |
| Non physical activity | 51984 (62.4) | 28962 (51.4) | <0.0001 |
| Yes physical activity | 31298 (37.6) | 27390 (48.6) | |
| Non healthy food | 54792 (65.8) | 29764 (52.8) | <0.0001 |
| Yes healthy food | 28490 (34.2) | 26588 (47.2) | |
| Non alcohol consumption | 56022 (67.3) | 47536 (84.4) | <0.0001 |
| Yes alcohol consumption | 27260 (32.7) | 8816 (15.6) | |

HDL High density lipoprotein LDL Low density lipoprotein

**Table II:** Mean values of ALLY heart age according different cardiometabolic risk scales by sex.

| ALLY heart age | n | Men Mean (SD) | p-value | n | Women Mean (SD) | p-value |
|---|---|---|---|---|---|---|
| No AD | 77846 | 6.1 (7,8) | <0.0001 | 53852 | 1.2 (9.5) | <0.0001 |
| Yes AD | 5436 | 16.1 (5.7) | | 2500 | 11.7 (8.4) | |
| No LT | 80918 | 6.4 (8.0) | <0.0001 | 55268 | 1.4 (9.6) | <0.0001 |
| Yes LT | 2364 | 17.1 (4.7) | | 1084 | 14.0 (7.3) | |
| No MS NCEP ATPIII | 69256 | 5.2 (7.5) | <0.0001 | 51860 | 0.6 (9.1) | <0.0001 |
| Yes MS NCEP ATPIII | 14026 | 14.2 (6.6) | | 4492 | 13.5 (7.9) | |
| NO MS IDF | 66966 | 5.3 (7.6) | <0.0001 | 53152 | 1.0 (9.3) | <0.0001 |
| Yes MS IDF | 16316 | 12.8 (7.0) | | 3200 | 12.7 (8.1) | |
| Finrisk low | 44928 | 4.2 (7.2) | <0.0001 | 38258 | -0.9 (8.4) | <0.0001 |
| Finrisk slightly elevated | 22418 | 7.1 (7.5) | | 9894 | 4.6 (9.6) | |
| Finrisk moderate | 6490 | 11.1 (7.6) | | 3724 | 7.1 (9.7) | |
| Finrisk high | 3780 | 13.0 (7.3) | | 2566 | 10.0 (9.3) | |
| Finrisk very high | 486 | 16.4 (5.8) | | 62 | 19.8 (0.4) | |
| No diabesity | 80826 | 6.4 (7.9) | <0.0001 | 55478 | 1.4 (9.5) | <0.0001 |
| Yes diabesity | 2456 | 17.4 (4.8) | | 874 | 17.2 (5.4) | |
| No HTGW | 71340 | 5.9 (7.9) | <0.0001 | 54806 | 1.4 (9.5) | <0.0001 |
| Yes HTGW | 11942 | 11.5 (7.6) | | 1546 | 12.2 (8.5) | |

ALLY HA Avoidable lost life life years

**Table III:** Prevalence of high values of ALLY heart age according different cardiometabolic risk scales by sex.

| ALLY heart age | Men | | | | | Women | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Normal % | Moderate % | High % | p-value | n | Normal % | Moderate % | High % | p-value |
| No AD | 77846 | 74.5 | 10.9 | 14.6 | <0.0001 | 53852 | 83.0 | 6.3 | 10.7 | <0.0001 |
| Yes AD | 5436 | 20.1 | 15.5 | 64.4 | | 2500 | 43.5 | 13.7 | 42.8 | |
| No LT | 80918 | 72.6 | 11.1 | 16.3 | <0.0001 | 55268 | 82.2 | 6.4 | 11.4 | <0.0001 |
| Yes LT | 2364 | 14.1 | 15.1 | 70.8 | | 1084 | 31.9 | 14.6 | 53.5 | |
| No MS NCEP ATPIII | 69256 | 78.9 | 10.0 | 11.1 | <0.0001 | 51860 | 85.4 | 5.9 | 8.7 | <0.0001 |
| Yes MS NCEP ATPIII | 14026 | 31.6 | 17.2 | 51.2 | | 4492 | 33.6 | 14.3 | 52.1 | |
| NO MS IDF | 66966 | 78.3 | 9.7 | 12.0 | <0.0001 | 53152 | 83.8 | 6.1 | 10.1 | <0.0001 |
| Yes MS IDF | 16316 | 40.7 | 17.5 | 41.8 | | 3200 | 38.2 | 15.3 | 46.6 | |
| Finrisk low | 44928 | 83.0 | 8.8 | 8.2 | <0.0001 | 38258 | 90.1 | 4.4 | 5.5 | <0.0001 |
| Finrisk slightly elevated | 22418 | 71.9 | 12.2 | 15.6 | | 9894 | 73.2 | 9.8 | 17.0 | |
| Finrisk moderate | 6490 | 49.5 | 17.7 | 32.8 | | 3724 | 62.5 | 12.5 | 25.0 | |
| Finrisk high | 3780 | 37.7 | 17.7 | 44.6 | | 2566 | 50.0 | 14.8 | 35.2 | |
| Finrisk very high | 486 | 17.7 | 17.3 | 65.0 | | 62 | 0.0 | 0.0 | 100.0 | |
| No diabesity | 80826 | 72.8 | 11.1 | 16.1 | <0.0001 | 55478 | 82.3 | 6.6 | 11.2 | <0.0001 |
| Yes diabesity | 2456 | 11.6 | 13.4 | 75.0 | | 874 | 15.6 | 8.5 | 75.9 | |
| No HTGW | 71340 | 74.9 | 10.4 | 14.7 | <0.0001 | 54806 | 82.4 | 6.4 | 11.2 | <0.0001 |
| Yes HTGW | 11942 | 47.4 | 15.7 | 36.9 | | 1546 | 40.4 | 13.2 | 46.4 | |

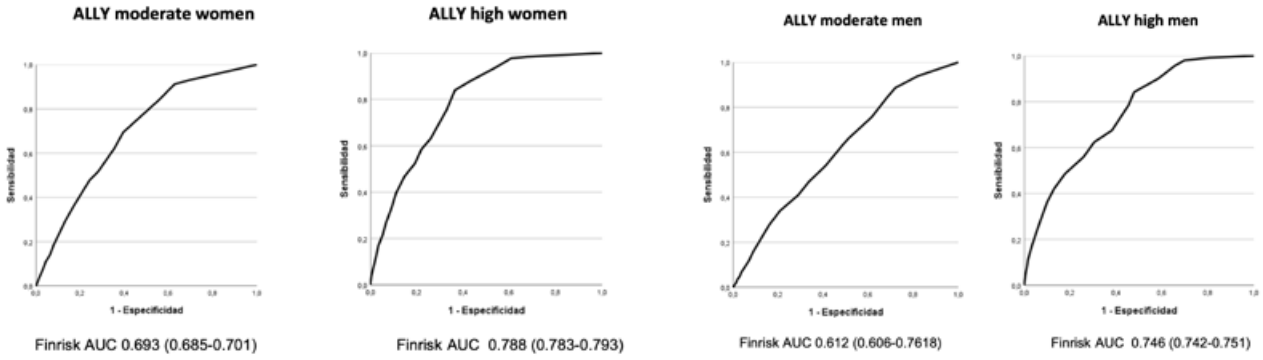
ALLY HA Avoidable lost life life years heart age. AD Atherogenic dyslipidemia. LT Lipid triad MS Metabolic syndrome NCEP ATPIII National Cholesterol Education Program Adult Treatment Panel III IDF International Diabetes Federation HTGW Hypertriglyceridemic waist phenotype

**Table IV:** Multinomial logistic regression.

| | ALLY HA moderate | ALLY HA high |
|---|---|---|
| | OR (95% CI) | OR (95% CI) |
| No AD | 1 | 1 |
| Yes AD | 2.15 (2.00-2.30) | 2.24 (2.09-2.40) |
| No LT | 1 | 1 |
| Yes LT | 4.37 (3.94-4.84) | 3.63 (3.31-3.98) |
| No MS NCEP ATPIII | 1 | 1 |
| Yes MS NCEP ATPIII | 2.59 (2.46-2.73) | 2.68 (2.53-2.83) |
| NO MS IDF | 1 | 1 |
| Yes MS IDF | 1.39 (1.32-1.47) | 1.13 (1.07-1.20) |
| Finrisk low | 1 | 1 |
| Finrisk slightly elevated | 2.40 (1.86-3.08) | 2.14 (1.74-2.63) |
| Finrisk moderate | 2.73 (2.13-3.51) | 2.57 (2.09-3.15) |
| Finrisk high | 4.75 (3.70-6.09) | 4.47 (3.65-5.47) |
| Finrisk very high | 8.94 (6.97-11.47) | 9.05 (7.38-11.10) |
| No diabesity | 1 | 1 |
| Yes diabesity | 2.17 (1.92-2.45) | 2.00 (1.81-2.21) |
| No HTGW | 1 | 1 |
| Yes HTGW | 1.33 (1.26-1.41) | 1.38 (1.30-46) |

ALLY HA Avoidable lost life life years heart age. AD Atherogenic dyslipidemia. LT Lipid triad
MS Metabolic syndrome NCEP ATPIII National Cholesterol Education Program Adult Treatment Panel III
IDF International Diabetes Federation HTGW Hypertriglyceridemic waist phenotype

**Figure 2:** ROC curves.




## Discussion

The mean values and the prevalence of high values of ALLY heart age increase in parallel with the increase in the values of the different cardiometabolic risk scales analyzed in this study.

High values of all the cardiometabolic risk scales considered in this study increase the risk of moderate and high ALLY heart age, especially Findrisk and lipid triad.

The value of the Findrisk test for predicting the occurrence of ALLY moderate heart age is low, whereas for predicting ALLY high heart age it can be considered high. In both cases the values are higher in women.

Due to the absence of studies assessing the relationship between heart age and cardiometabolic risk scales, we cannot compare our results with those obtained by other authors. To try to compensate for this deficit, we will compare the cardiometabolic risk scales with other scales that assess cardiovascular risk.

The EVA study[29] carried out in 501 Spaniards with an average age of 55.9 years assessed the relationship between vascular and cardiac aging, lifestyle and the components of the metabolic syndrome. The results showed that those with metabolic syndrome had higher values for heart age and vascular age.

In the 18,490 participants of the global MARE[30] consortium assessing, among other things, healthy vascular aging, the prevalence of metabolic syndrome was found to be lower in those with healthy vascular aging.

A Spanish study using Bayesian networks[31] also found an association between cardiac age and metabolic syndrome.

A descriptive study of 59,041 Spanish workers[32] in the Mediterranean area found that those with prediabetes had higher values for the classic cardiovascular risk scales and also for heart age and vascular age.

Another Spanish study in a large sample assessed the relationship between the values of the Findrisk test and different cardiovascular risk scales[33], including heart age. It found, as we did, that the ALLY heart age values increased as the values of the Findrisk test increased.

An Iranian study[34] concluded that diabesity was a predictor of the incidence of cardiovascular disease and stroke.

Another Spanish study carried out in more than 418000 workers[35] assessed the relationship between atherogenic dyslipidemia and lipid triad with the values of different classic cardiovascular risk scales and with vascular age determined with the Framingham and SCORE criteria, observing that the ALLY values with both criteria were higher in persons with atherogenic dyslipidemia and lipid triad.

### Strengths and weaknesses

The main strengths of this study are the enormous sample size, the large number of cardiometabolic risk scales analyzed, and the fact that it is one of the first articles to assess the relationship between heart age and other cardiometabolic risk scales, so that it can become a reference for subsequent studies on this subject.

The main weakness is that some of the scales, such as Findrisk, assess risk and do not start from an objective value.

## Conclusions

There is a good relationship between the ALLY heart age values and the values of the different cardiometabolic risk scales analyzed (atherogenic dyslipidemia, lipid triad, metabolic syndrome with the NCEP ATPIII and IDF criteria, Findrisk test, diabesity and hypertriglyceridemic waist).

The risk scales that most increase the possibility of moderate or high ALLY heart age values are Findrisk and lipid triad.

The predictive value of the Findrisk test is low for moderate ALLY heart age in both sexes and high, also for both sexes in the case of high ALLY heart age.

## Conflict of Interest

The authors declare that there is no conflict of interest.

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ORIGINAL

# Progresión de la creatinina sérica neonatal como estudio de la función renal en un centro de tercer nivel (IIIb)

*Progression of neonatal serum creatinine as a study of renal function in a tertiary center (IIIb)*

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## Resumen

***Introducción:*** La población neonatal es vulnerable al daño renal, siendo necesario el estudio de la función renal en pacientes de riesgo. La concentración de creatinina sérica continúa siendo el marcador más usado, precisando contemplar variaciones relativas al proceso de maduración renal.
***Objetivo:*** Describir la evolución de la creatinina sérica como estudio de la función renal en pacientes neonatales desde el nacimiento hasta la realización de la analítica nutricional en un centro de tercer nivel.
***Población y método:*** Estudio descriptivo, retrospectivo, que incluye a pacientes ingresados en la Unidad de Cuidados Intensivos Neonatal (UCIN) de un hospital terciario entre enero de 2013 y diciembre de 2016. Se recogieron datos analíticos relacionados con la función renal de forma evolutiva desde el nacimiento hasta la primera analítica nutricional. Se identificaron cuatro grupos de pacientes según la edad gestacional. Para variables cualitativas, categóricas o binarias se emplearon frecuencias y porcentajes. Se realizó análisis Kruskal-Wallis/test de Wilcoxon para variables cuantitativas de medida repetida. El análisis estadístico se realizó empleando el programa SPSS (Versión 22.0,Inc.,Chicago,US). Los resultados se consideraron significativos con valor p<0.05.
***Resultados:*** En el tiempo de estudio se incluyeron un total de 158 pacientes, 111 (70.3%) prematuros. La creatinina sérica al nacimiento fue mayor a mayor edad gestacional (0.55±0.09mg/dL vs 0.87±0.24mg/dL, p<0.001). En los pacientes prematuros la creatinina continuó aumentando hasta las 24 horas de vida. Este incremento fue mayor a menor edad gestacional. Posteriormente se produjo un descenso progresivo del valor de creatinina sérica. En los pacientes a término se produjo un descenso progresivo desde el nacimiento, más llamativo a las 72 horas de vida (p<0.001). A partir de las 24 horas de vida, a excepción de la analítica nutricional, el valor de creatinina sérica fue mayor a menor edad gestacional (0.81±0.22mg/dL vs 0.55±0.29mg/dL, p<0.001). La velocidad de corrección parece ser más temprana a mayor edad gestacional (0.70±0.19mg/dL vs 0.48±0.29mg/dL, p<0.001).
***Conclusiones:*** Los valores de creatinina sérica en pacientes neonatales cambian independientemente de la presencia de daño renal. No sólo un aumento de la creatinina, sino también un descenso anormal, deberían ser tenidos en cuenta como afectación renal. Sería necesario realizar determinaciones seriadas en lugar de interpretar un único valor de creatinina sérica para estudiar la función renal neonatal.

*Palabras clave:* Creatinina, función renal, neonato.

## *Abstract*

***Introduction:*** The neonatal population is vulnerable to kidney damage, making it necessary to study kidney function in patients at risk. Serum creatinine concentration continues to be the most used marker, requiring consideration of variations related to the kidney maturation process.
***Aim:*** To describe the evolution of serum creatinine as a study of renal function in neonatal patients from birth to the performance of nutritional analysis in a tertiary center.
***Methods:*** Descriptive, retrospective study that includes patients admitted to the NICU of a tertiary hospital between January 2013 and December 2016. Analytical data related to renal function were collected in an evolutionary manner from birth to the first nutritional analysis. Four groups of patients were identified according to gestational age. For qualitative, categorical or binary variables, frequencies and percentages were used. Kruskal-Wallis analysis/Wilcoxon test was performed for repeated measurement quantitative variables. Statistical analysis was performed using the SPSS program (Version 22.0, Inc., Chicago, US). The results were considered significant with a p value <0.05.
***Results:*** During the study period, a total of 158 patients were included, 111 (70.3%) premature. Serum creatinine at birth was higher at higher gestational age (0.55±0.09mg/dL vs 0.87±0.24mg/dL,p<0.001). In premature patients, creatinine continued to increase until 24 hours of life. This increase was greater at lower gestational age. Subsequently, there was a progressive decrease in the serum creatinine value. In term patients there was a progressive decrease from birth, more striking at 72 hours of life (p<0.001). From 24 hours of life, with the exception of nutritional analysis, the serum creatinine value was higher at lower gestational age (0.81±0.22mg/dL vs 0.55±0.29mg/dL,p<0.001). The speed of correction seems to be earlier at higher gestational age (0.70±0.19mg/dL vs 0.48±0.29mg/dL,p<0.001).
***Conclusions:*** Serum creatinine values in neonatal patients change independently of the presence of kidney damage. Not only an increase in creatinine, but also an abnormal decrease, should be taken into account as kidney involvement. It would be necessary to perform serial determinations instead of interpreting a single serum creatinine value to study neonatal renal function.

*Key words:* Creatinine, renal function, neonate.

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## Introducción

El estudio de la función renal es necesario en la población neonatal. Se ha visto que el recién nacido es más vulnerable al daño renal debido fundamentalmente a la inmadurez funcional y a los múltiples cambios hemodinámicos que se producen durante los primeros días de vida[1,2]. La evaluación de la función renal en el recién nacido debe contemplar las diferencias que se producen según la edad gestacional y postmenstrual, añadido a las morbilidades asociadas que presentan estos pacientes, las medidas invasivas que reciben, o al propio manejo nutricional[3].

Para medir la función renal disponemos de varios marcadores. Aunque la medición del aclaramiento de inulina es el gold standard para determinar el filtrado glomerular, su uso es difícil en la población neonatal. La concentración de creatinina sérica, a pesar de sus limitaciones, es el marcador más ampliamente usado para valorar la función renal, pudiendo estimar con ello la tasa de filtración glomerular[3-5].

Los valores de creatinina sérica cambian tras el nacimiento independientemente de la presencia de daño renal[1]. Esta variabilidad es una característica clave en la población neonatal ya que los cambios fisiológicos son más pronunciados durante los primeros días de vida[3]. La interacción dinámica de la función renal materna, la masa muscular neonatal y el proceso de maduración de la función glomerular y tubular, hacen que la interpretación de un solo valor de creatinina sérica no sea adecuada al no tener en cuenta estos cambios fisiológicos que se producen en esta población[5-10].

Establecer la evolución de la creatinina sérica según la edad gestacional en la población neonatal durante los primeros días de vida podría ayudar a analizar la función renal, especialmente en recién nacidos prematuros.

Presentamos las característica clínica y epidemiológicas de pacientes neonatales de todas las edades gestacionales que precisaron ingreso en la unidad de cuidados intensivos neonatal (UCIN) de un centro de tercer nivel junto con la progresión de la creatinina sérica desde el nacimiento hasta la realización de la primera analítica nutricional permitiendo así establecer una tendencia en su evolución.

## Población y método

Identificamos retrospectivamente una cohorte de 158 pacientes neonatales ingresados en la Unidad de Cuidados Intensivos Neonatal (UCIN) del Hospital Clínico Universitario de Valladolid (HCUV) durante el período comprendido entre el 1 de enero del 2013 hasta el 31 de diciembre del 2016. Estos recién nacidos fueron seleccionados de un conjunto de datos que incluyó a 234 recién nacidos admitidos en la UCIN durante ese período.

Los criterios de inclusión del estudio comprenden haber nacido en el periodo de tiempo establecido de reclutamiento, precisar ingreso en la UCIN del HCUV y su supervivencia hasta el alta. Los pacientes reclutados han podido nacer en este centro o ser derivados de otros centros sanitarios al ser el HCUV de referencia de otras provincias de la Comunidad de Castilla y León. El nivel asistencial de la UCIN del HCUV corresponde a un nivel IIIb. El criterio de exclusión del estudio fue la necesidad de ingreso en la UCIN de nuestro centro pasadas las 24 horas de vida.

Un único neonatólogo revisó las historias clínicas e identificó a los neonatos que cumplieron los criterios de inclusión y exclusión. Se elabora una base de datos de Excel en la que se introducen los valores de las variables cuantitativas y cualitativas. La mayoría de las variables fueron recodificadas de forma numérica, siendo una minoría presentadas en forma de texto libre. Las variables en texto libre recogían información considerada relevante. Se incluyeron datos clínicos y demográficos, junto con características de la gestación. En los análisis se incluyeron todos los valores de creatinina sérica desde el nacimiento hasta la primera analítica nutricional, incluyendo las 24, 72 horas y semana de vida. Hubo múltiples mediciones de creatinina sérica en los primeros días de vida en cada recién nacido. Los valores referentes al nacimiento de creatinina sérica se refieren a muestras de sangre tomadas entre la hora y las dos horas de vida. Los parámetros posteriores fueron añadidos según la franja horaria correspondiente. La creatinina sérica se determinó mediante cuantificación enzimática.

La fluidoterapia intravenosa, nutrición parenteral y el aporte de electrolitos se administran de acuerdo a un protocolo preestablecido, en el que la cantidad diaria se establece de acuerdo con el cambio de peso diario y con los controles gasométricos. Los aportes durante las primeras 24 horas de vida estaban en torno a 60 a 80 ml/kg/día. Todos los iones, a excepción del calcio, se administraron a partir de las 48 horas de vida, ajustando los aportes según las concentraciones plasmáticas de cada ión. El inicio de la alimentación enteral utilizando leche materna extraída, leche donada o fórmula artificial se inició tan pronto como los lactantes alcanzaron la estabilidad cardiorrespiratoria. El volumen de aportes intravenosos se reajustó para compensar el aumento lento de la ingesta enteral, suspendiendo en la mayoría de los neonatos cuando alcanzaron 100 ml/kg/día de ingesta enteral. La nutrición enteral avanzó progresivamente hasta alcanzar un volumen en torno a 160-180 ml/kg/día.

La muestra se dividió en cuatro subgrupos según la edad gestacional para su estudio: por debajo de las 28 semanas, de las 28 semanas + 0 días hasta las

31 semanas + 6 días, de las 32 semanas + 0 días a las 36 semanas + 6 días y por encima o igual de las 37 semanas de edad gestacional. Los subgrupos se identifican como grupo 1, 2, 3, y 4 respectivamente.

En primer lugar, se realizó un análisis descriptivo de los datos. Se utilizaron las medidas de tendencia central para variables cuantitativas, como media y mediana; y las medidas de dispersión, desviación estándar (SD) y rango intercuartílico (RI). Para la descripción de variables cualitativas, categóricas o binarias se emplearon frecuencias y porcentajes.

El análisis estadístico se realizó empleando el programa SPSS (Versión 22.0,Inc.,Chicago,US). Se realizó análisis comparativo mediante pruebas no paramétricas. Primero se realizó un análisis de Kruskal-Wallis para muestras independientes, con un posterior análisis post hoc con el ajuste de Bonferroni para determinar la presencia de diferencias entre los cuatro grupos coincidiendo con las diferentes extracciones analítica realizadas. Posteriormente se analizó, mediante la prueba de rangos con signos de Wilcoxon, las diferencias en la evolución de la creatinina sérica entre las distintas franjas horarias analizadas en cada grupo de estudio. Se consideró significación estadística un valor de $p<0.05$.

## Resultados

La **tabla I** muestra las características de los recién nacidos seleccionados durante el período de estudio. 55 (34.8%) pacientes evaluados son niñas y 103 (65.2%) son niños. La mediana de días de realización de la analítica nutricional fue a los 15 días (RI 7 - 45).

La **figura 1** muestra la creatinina sérica media según grupos de edad gestacional desde el nacimiento hasta la realización de la primera analítica nutricional.

En las primeras 24 horas de vida el valor de creatinina sérica es más alto y variable, con un descenso posterior progresivo de su valor.

La creatinina sérica al nacimiento fue mayor conforme aumentó la edad gestacional. Sin embargo, a partir de las 24 horas de vida, la creatinina sérica fue mayor a menor edad gestacional durante toda la evolución, a excepción del valor extraído coincidiendo con la analítica nutricional.

**Figura 1:** Evolución de la creatinina sérica media durante toda la evolución según grupos de edad gestacional.

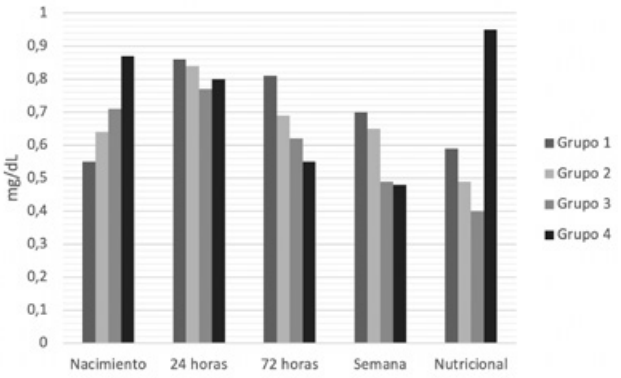


**Tabla I:** Características clínicas y epidemiológicas de la población estudiada de 2013 al 2016.

| | General | Grupo 1 | Grupo 2 | Grupo 3 | Grupo 4 |
|---|---|---|---|---|---|
| **RNPT[a]** | | **10 (6.3)** | **66 (41.8)** | **35 (22.2)** | |
| **RNT[a]** | | | | | **47 (29.7)** |
| **Edad gestacional[b]** | 33.1 (4.4) | 26.0 (1.1) | 29.8 (1.1) | 33.5 (1.3) | 38.9 (1.2) |
| **Peso (gramos)[b]** | 1974 (0.90) | 885 (0.18) | 1364 (0.32) | 1864 (0.42) | 3145 (0.51) |
| **Días de ingreso[b]** | 29 (25) | 50 (23) | 24 (13) | 28 (27) | 33 (33) |
| **Gestación gemelar[a]** | 54 (34.2) | 4 (40.0) | 32 (48.5) | 15 (57.1) | 3 (6.4) |
| **Parto vaginal[a]** | 54 (34.2) | 3 (30.0) | 20 (30.3) | 8 (22.9) | 23 (48.9) |
| **CIR[a]** | 26 (16.5) | 1 (10.0) | 10 (15.2) | 9 (25.7) | 6 (12.8) |
| **Esteroides prenatal[a]** | 100 (63.3) | 9 (90.0) | 60 (90.9) | 28 (80.0) | 3 (6.4) |
| **Vía central[a]** | 101 (63.9) | 10 (100.0) | 63 (95.5) | 19 (54.3) | 9 (19.1) |
| **ATB nefrotóxico[a]** | 130 (82.3) | 10 (100.0) | 60 (90.9) | 29 (82.9) | 31 (66.0) |
| **VMI[a]** | 52 (32.9) | 9 (90.0) | 23 (34.8) | 10 (28.6) | 10 (21.3) |
| **Transfusión[a]** | 52 (32.9) | 9 (90.0) | 34 (51.5) | 5 (14.3) | 4 (8.5) |
| **Tratamiento con surfactante[a]** | 42 (26.6) | 9 (90.0) | 25 (37.9) | 7 (20.0) | 1 (2.1) |
| **DBP[a]** | 26 (16.5) | 10 (100.0) | 16 (24.2) | 0 (0.0) | 0 (0.0) |
| **Tratamiento con diuréticos[a]** | 21 (13.3) | 7 (70.0) | 7 (10.6) | 4 (11.4) | 3 (6.4) |
| **Drogas vasoactivas[a]** | 13 (8.2) | 6 (60.0) | 2 (3.0) | 1 (2.9) | 4 (8.5) |
| **Tratamiento con ibuprofeno[a]** | 8 (5.1) | 7 (70.0) | 1 (1.5) | 1 (2.9) | 0 (0.0) |
| **NPT[a]** | 103 (65.2) | 10 (100.0) | 63 (95.5) | 21 (60.0) | 9 (19.1) |
| **Días de NPT[b]** | 8 (6) | 19 (11) | 7 (3) | 7 (6) | 4 (2) |
| **Analítica nutricional[a]** | 98 (62.0) | 10 (100.0) | 64 (97.0) | 22 (62.9) | 2 (4.3) |

a: número de casos (N) y porcentaje (%); b: media y desviación estándar; RNPT: recién nacido pretérmino; RNT: recién nacido a término; CIR: crecimiento intrauterino retardado; ATB: antibiótico; VMI: ventilación mecánica invasiva; DBP: displasia broncopulmonar; NPT: nutrición parenteral.

Se dividió la evolución de la creatinina sérica tras el nacimiento en dos fases, cuyas características variaron con la edad gestacional.

**Primera fase.** La creatinina sérica media aumentó durante las primeras 24 horas postnatales en todos los pacientes prematuros. Este incremento se situó entre el 22 y el 56%, mayor a menor edad gestacional. En los pacientes a término se produjo el descenso de la creatinina sérica desde el nacimiento.

**Segunda fase.** Se produjo un descenso de la creatinina sérica en todos los pacientes prematuros a partir de las 24 horas de vida. El descenso producido entre las 24 y las 72 horas de vida fue más llamativo a mayor edad gestacional. Posteriormente, los nacidos entre las 28 y 36 semanas presentaron una estabilización más rápida de la creatinina sérica media.

Por tanto, parece que la tendencia de la creatinina sérica es la disminución más precoz y a un ritmo más rápido a medida que aumenta la edad gestacional, con una estabilización posterior. Sin embargo, los pacientes a término presentaron coincidiendo con la analítica nutricional un incremento del valor medio de creatinina sérica.

La **tabla II** muestra los valores medios diarios y la desviación estándar por grupos de edad gestacional, junto con las diferencias estadísticas presentes entre los diferentes grupos. En la **tabla III** se muestran las diferencias en la evolución de la creatinina sérica entre las distintas franjas horarias durante toda la evolución.

**Tabla II:** Evolución de la creatinina (mg/dL). Expresado en media y desviación estándar. p = grado de significación estadística mediante prueba de Kruskall-Wallis. Post hoc = análisis Post hoc según ajuste de Bonferroni.

| | Grupo 1 | Grupo 2 | Grupo 3 | Grupo 4 | p | Post hoc |
|---|---|---|---|---|---|---|
| **Nacimiento** | 0.55 ± 0.09 | 0.64 ± 0.20 | 0.71 ± 0.22 | 0.87 ± 0.24 | <0.001 | G1 - G3 (0.024)<br>G1 - G4 (<0.001)<br>G2 - G4 (<0.001)<br>G3 - G4 (0.003) |
| **24 horas** | 0.86 ± 0.06 | 0.84 ± 0.19 | 0.77 ± 0.13 | 0.80 ± 0.33 | 0.025 | G2 - G4 (0.008) |
| **72 horas** | 0.81 ± 0.22 | 0.69 ± 0.17 | 0.62 ± 0.14 | 0.55 ± 0.29 | <0.001 | G1 - G3 (0.027)<br>G1 - G4 (<0.001)<br>G2 - G4 (<0.001)<br>G3 - G4 (0.026) |
| **Semana** | 0.70 ± 0.19 | 0.65 ± 0.15 | 0.49 ± 0.10 | 0.48 ± 0.29 | <0.001 | G1 - G3 (0.009)<br>G1 - G4 (<0.001)<br>G2 - G3 (0.003)<br>G2 - G4 (<0.001) |
| **Nutricional** | 0.59 ± 0.35 | 0.49 ± 0.16 | 0.40 ± 0.12 | 0.95 ± 0.64 | 0.058 | NO |

**Tabla III:** Grado de significación mediante prueba de rangos con signos de Wilcoxon.

| | Grupo 1 | Grupo 2 | Grupo 3 | Grupo 4 |
|---|---|---|---|---|
| **Nacimiento 24 horas** | 0.008 | <0.001 | 0.007 | 0.071 |
| **24 horas 72 horas** | 0.400 | <0.001 | 0.001 | <0.001 |
| **72 horas Semana** | 0.093 | 0.037 | 0.045 | 0.070 |
| **Semana Nutricional** | 0.074 | <0.001 | 0.013 | 0.180 |

## Discusión

Aunque los recién nacidos están sujetos a diferentes factores de riesgo asociados a su ingreso en la unidad de cuidados intensivos, se debe prestar especial atención a los factores inherentes al desarrollo y la fisiología renal neonatal.

Se proporcionan los valores medios de creatinina sérica posnatal en recién nacidos desde al nacimiento hasta la realización de la analítica nutricional.

Los valores de creatinina sérica neonatal cambian constantemente desde el nacimiento durante las primeras semanas de vida. Nuestros datos confirman los resultados descritos en otros estudios[3-6,9,11-13] demostrando que la creatinina sérica de los recién nacidos está elevada al nacimiento o en los primeros días de vida y que disminuye progresivamente.

Se ha afirmado que la creatinina sérica del recién nacido al nacimiento refleja la concentración plasmática materna[7,9,11,12,14-18]. Si las concentraciones de creatinina sérica entre el plasma de la madre y del feto están equilibradas a través de la placenta, los recién nacido a término deberían tener concentraciones de creatinina

sérica más elevadas al nacimiento comparado con los prematuros. Esta hipótesis concuerda con nuestros resultados, donde observamos concentraciones más bajas de creatinina sérica al nacimiento en los recién nacidos más prematuros, siendo los valores más elevados en pacientes a término. Go et al.[17] estudió los niveles de creatinina sérica materna y neonatal durante el período postnatal precoz en recién nacidos prematuros y a término, objetivando que las concentraciones de creatinina sérica materna fueron más bajas durante el segundo trimestre de gestación (0.59 mg/dL) en comparación con el tercer trimestre (0.61 mg/dL), reflejando la tendencia previamente descrita. En la misma línea, van Donge et al.[3] reportó referencias de los valores de creatinina sérica en pacientes prematuros desde el primer día de vida hasta las seis semanas de vida, concluyendo que la creatinina sérica neonatal en el primer día de vida aumentó gradualmente (un 6% por semana de edad gestacional) con la edad gestacional. Estos datos sugieren que la creatinina sérica materna se transfiere al feto hasta el momento del nacimiento.

Los pacientes prematuros presentaron en la cohorte estudiada un aumento de la creatinina sérica en las primeras 24 horas de vida, con un descenso posterior. Este incremento fue mayor a menor edad gestacional. Esto refleja la dificultad que tienen estos pacientes para eliminar el exceso de creatinina transferido de la madre debido a la inmadurez renal y al bajo aclaramiento renal en los primeros días postnatales[4,6], añadido a la reabsorción transitoria de creatinina sérica por el túbulo inmaduro[4,6,11,12,19,20] y a la depleción de volumen[18]. Esta evolución de la creatinina sérica inicial fue similar a otros estudios[3,5,9-11,20], donde los pacientes prematuros presentaron un aumento de la creatinina sérica, con un pico máximo en torno al tercer día de vida, mayor a menor edad gestacional, con descenso posterior. Por tanto, no es la disminución aguda de la función renal posnatal la responsable del aumento inicial de creatinina sérica después del nacimiento, sino simplemente la menor eliminación de la creatinina sérica en relación a la producción de la misma[3].

Las concentraciones séricas de creatinina fueron mayores a menor edad gestacional a partir de las 24 horas de vida, con un descenso progresivo. Varios estudios[3,5,6,9,12] corroboraron estos resultados. La creatinina sérica media del día 3 en los neonatos de 27 semanas en la cohorte de van Donge[3] fue de 0.87 mg/dl, similar a nuestro estudio, mientras que los neonatos menores de 27 semanas de la cohorte de Bateman[5] y Gallini[9] fueron algo mayores, de 0.95 mg/dL y en torno de 1.10 mg/dL, respectivamente. Los neonatos con mayor edad gestacional presentaron valores más bajos de creatinina en la misma franja horaria en todas las cohortes descritas[3,5,9]. A la semana de vida, la cohorte de van Donge[3] presentó valores de creatinina sérica de 0.70 mg/dL en los neonatos de 27 semanas y de 0.60 mg/dL en los neonatos de 32 semanas, similares a nuestra cohorte. Sin embargo, Bateman et al.[5] y Gallini et al.[9] presentaron valores algo más elevados. Una posible explicación de estos hallazgos incluye las diferencias en el balance de líquidos, la inclusión de diferentes factores de riesgo que comprometan la función renal, así como a las diferencias en la medición de la creatinina sérica. Se ha descrito que los patrones en la evolución de la creatinina sérica fueron similares entre los dos métodos de medida (cuantificación enzimática versus método cinético de Jaffé), aunque los valores de creatinina sérica siempre fueron más bajos para la cuantificación enzimática en comparación con la cuantificación mediante método de Jaffé[11], con una diferencia de 0.1-0.2 mg/dL[11]. Esto justifica las diferencias en los valores de creatinina sérica entre los estudios previos. En la cohorte de estudio, al igual que van Donge et al.[3], la creatinina sérica fue determinada mediante cuantificación enzimática, mientras que Bateman[5] y Gallini[9] determinaron el valor de creatinina sérica mediante método cinético de Jaffé.

En los recién nacidos prematuros la creatinina sérica puede permanecer elevada hasta el mes de vida, siendo su estabilización más temprana a mayor edad gestacional[3,5,6,12]. Al calcularse únicamente el valor de creatinina sérica hasta la realización de la analítica nutricional, no se pudo determinar el momento de la normalización de la creatinina sérica en estos pacientes, aunque parece mantenerse la tendencia de una estabilización más temprana a mayor edad gestacional: los prematuros tardíos (entre las 32 y 36 semanas) alcanzaron en la cohorte estudiada un valor cercano a la normalidad coincidiendo con la analítica nutricional.

En la cohorte estudiada, al igual que en el estudio de Boer et al.[4], quien estableció valores de referencia de la creatinina sérica de neonatos a término sanos hasta el año de vida, los recién nacido a término presentaron un descenso de la creatinina sérica desde el primer día de vida. La mediana de creatinina sérica presentada por Boer et al.[4] a las 24 horas de vida, tres días de vida y semana de vida fue de 0.62, 0.48 y 0.38 mg/dL, respectivamente. La cohorte de estudio presentó valores algo más elevados con respecto al estudio previo (de 0.80, 0.55, y 0.48 mg/dL, respectivamente).

Los pacientes a término normalizaron sus valores de creatinina sérica de forma más precoz, en torno a la semana de vida[4,6,12]. Sin embargo, los pacientes a término de la cohorte estudiada no alcanzaron esta normalidad a la semana de vida, produciéndose un nuevo aumento de la creatinina sérica coincidiendo con la analítica nutricional. Hay que tener en cuenta que la analítica nutricional no se extrae de manera reglada en pacientes por encima de las 32 semanas, y per se, en pacientes a término. Por ello, en los pacientes a término en los que se extrajo esta analítica debieron de presentar alguna malformación que justificaría el aumento de la creatinina sérica y no ser por ello la evolución normal.

Estos resultados confirman que la concentración de creatinina sérica debe interpretarse con precaución en los recién nacidos durante las primeras semanas posnatales debido a los eventos fisiológicos que se producen tras el nacimiento, haciendo que los parámetros cambien independientemente de la presencia de daño renal agudo. Así, un aumento de la creatinina sérica durante los primeros días de vida en un paciente prematuro con una disminución posterior puede reflejar una maduración postnatal normal. Sin embargo, la presencia de un aumento de creatinina sérica tras el nacimiento en un paciente a término o la falta de disminución de la creatinina podría reflejar una condición patológica. Por tanto, sería necesario realizar determinaciones seriadas en lugar de interpretar un único valor de creatinina sérica para identificar una alteración en la función renal.

### Conflicto de intereses

No existen conflictos de intereses.

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ORIGINAL

# Bone Marrow Aspirate Injection Technique in the Treatment of Scaphoid Fracture Utilizing Percutaneous Screw Fixation

*Técnica de inyección de aspirado de médula ósea en el tratamiento de la fractura de escafoides mediante fijación percutánea con tornillos*

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## Abstract

***Background and Objective:*** Scaphoid fractures are common and can lead to serious complications. Percutaneous screw fixation is a common treatment, and Bone Marrow Aspirate (BMA) injection is an emerging adjunct treatment that may enhance healing. The aim of this study was to investigate the effectiveness of BMA injection in the treatment of scaphoid bone fractures with percutaneous screw fixation.

***Methods:*** Between April 2022 and July 2023, the prospective interventional study was conducted in three hospitals involving 60 patients with scaphoid fractures. The patients were divided into two groups: one group received percutaneous volar screw fixation alone (control group), and the other group received the same fixation along with a intraoperative injection of Bone Marrow Aspirate Concentrate (BMAC) into the fracture site (cases group).

***Results:*** The disparity observed in the reduction of disability scores between the fixation BMAC group and the Fixation alone group highlights the substantial impact of the surgical technique on alleviating disability in the arm, shoulder, and hand of the patients who underwent the procedure. These results suggest that the use of fixation BMAC may lead to a greater reduction in wrist and hand disability compared to fixation alone, indicating the positive impact of the surgical method on reducing disability in the intervened patients.

***Conclusions:*** The results of this study showed that using bone marrow aspirate injection in conjunction with fixation through the skin can lead to a reduction in wrist disability compared to fixation alone in the treatment of scaphoid fractures.

*Key words:* Bone marrow, fracture fixation, fractures, stem cell.

## *Resumen*

***Antecedentes y objetivo:*** Las fracturas de escafoides son frecuentes y pueden dar lugar a complicaciones graves. La fijación percutánea con tornillos es un tratamiento habitual, y la inyección de aspirado de médula ósea (AMB) es un tratamiento complementario emergente que puede mejorar la curación. El objetivo de este estudio era investigar la eficacia de la inyección de AMB en el tratamiento de las fracturas óseas del escafoides con fijación percutánea con tornillos.

***Metodología:*** Entre abril de 2022 y julio de 2023, se llevó a cabo el estudio prospectivo de intervención en tres hospitales con 60 pacientes con fracturas de escafoides. Los pacientes se dividieron en dos grupos: un grupo recibió fijación percutánea con tornillo volar solo (grupo de control), y el otro grupo recibió la misma fijación junto con una inyección intraoperatoria de concentrado de aspirado de médula ósea (BMAC) en el foco de fractura (grupo de casos).

***Resultados:*** La disparidad observada en la reducción de las puntuaciones de discapacidad entre el grupo de fijación BMAC y el grupo de fijación sola pone de relieve el impacto sustancial de la técnica quirúrgica en el alivio de la discapacidad en el brazo, el hombro y la mano de los pacientes sometidos a la intervención. Estos resultados sugieren que el uso de la fijación BMAC puede conducir a una mayor reducción de la discapacidad en muñeca y mano en comparación con la fijación sola, lo que indica el impacto positivo del método quirúrgico en la reducción de la discapacidad en los pacientes intervenidos.

***Conclusiones:*** Los resultados de este estudio mostraron que el uso de la inyección de aspirado de médula ósea junto con la fijación a través de la piel puede conducir a una reducción de la discapacidad de la muñeca en comparación con la fijación sola en el tratamiento de las fracturas de escafoides.

*Palabras clave:* Médula ósea, fijación de fracturas, fracturas, células madre.

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## Introduction

The scaphoid plays a crucial role in wrist kinematics by articulating with the radius and trapezium and connecting the distal and proximal carpal rows, thereby stabilizing the wrist[1,2]. The scaphoid bone has a complex blood supply with varying perfusion levels, and the proximal portion has the poorest blood flow. This constrained blood supply makes the scaphoid susceptible to nonunion and osteonecrosis when fractured[3,4].

Scaphoid fractures are a prevalent type of wrist injury, comprising 60-70% of all carpal bone fractures, 11% of hand fractures, and 2% of all fractures. These kinds of fractures frequently originate from falls onto an outstretched hand, sports-related mishaps, or direct damage to the wrist [5, 6]. Most cases of scaphoid fractures occur in physically active young adult men. The estimated annual incidence is 5 fractures per 10,000 people[7].

Scaphoid fractures can be divided into three groups according to their position (proximal, middle, and distal), displacement, and angulation[8,9]. Among scaphoid fractures, proximal pole fractures make up around 10% and tend to have a higher risk of complications due to the tenuous blood supply in that area[10,11].

Symptoms of a scaphoid fracture include pain, swelling, tenderness, limited range of motion, and possible bruising. Pain in the wrist, specifically in the anatomical snuffbox, is a common indication. Swelling and tenderness around the scaphoid bone may also be observed, and the fracture may impede the normal range of motion of the wrist[5,12].

To diagnose a scaphoid fracture, a physical examination is done to assess wrist symptoms. Although X-ray imaging is a common diagnostic procedure, specialized views or MRI may be necessary to detect subtle fractures and assess complications. CT scans can provide three-dimensional images for accurate assessment. A combination of these diagnostic methods is used to ensure precise identification and determine the appropriate treatment plan in complex cases[6,13,14].

The treatment of scaphoid fractures is based on factors such as the type of fracture, extent of displacement, and presence of complications. Nonoperative treatment with immobilization is typically preferred for non-displaced or minimally displaced fractures without complications [6, 15]. Surgical options include open reduction and internal fixation (ORIF) and percutaneous screw fixation (PSF). PSF is a minimally invasive surgical method that employs a fluoroscopically guided cannulated screw to stabilize and align broken bone pieces. This method has gained popularity due to reduced surgical complications and improved functional outcomes compared to traditional open treatments[16,17].

Despite advances in fixation methods, nonunion rates for scaphoid fractures treated with screw fixation alone range from 5% to 15% due to a lack of blood supply and difficulties in achieving total stability[18,19]. Adjuvant biologic therapy, such as Bone Marrow Aspirate (BMA), is used to increase scaphoid fracture healing and union rates after screw implantation. BMA provides necessary progenitor cells, growth factors, and osteogenic proteins to accelerate bone repair at the fracture site[20,21]. Several trials of BMA for nonunion fractures have shown high union rates and favorable clinical outcomes with low risk of complications[22,23].

Combining BMA injections with percutaneous screw fixation for scaphoid fractures is a new concept, and more research is necessary to evaluate its safety and efficacy. Since there have been limited studies in this field in the Middle East, the aim of this study is to investigate the effectiveness of bone marrow aspirate injection in the treatment of scaphoid fractures using percutaneous fixation.

## Methods and Material

### Study design and setting

This prospective interventional study was conducted between April 2022 and July 2023 in three hospitals: Shar Teaching Hospital, Sulaimani Surgical Teaching Hospital, and Anwar Shiekha Medical City.

The target population of this study was patients who had a scaphoid bone fracture in the first six weeks of injury. A total of 60 patients with scaphoid fractures were selected and included in the study using the available sampling method. These patients were divided into two groups:

- 30 patients treated with percutaneous volar screw fixation alone (control group).
- In the case group, a total of 30 patients underwent percutaneous volar screw fixation along with a single intraoperative injection of 1.5 cc of Bone Marrow Aspirate Concentrate (BMAC) directly into the fracture site.

### Inclusion and Exclusion Criteria

Inclusion criteria included individuals 18 years or older with non-displaced or minimally displaced unilateral scaphoid fractures located in the middle-third and distal pole, occurring within the first six weeks of the injury and classified as type 3 and 4 according to the MAYO classification. Exclusion criteria consisted of patient refusal to participate in the study, comminuted or displaced scaphoid fractures, fractures associated with other carpal bone fractures or carpal dislocation, and presentation after six weeks.

### Study Procedure

The study consisted of three main phases: the preoperative phase, the operative phase, and the postoperative phase.

Preoperative planning: In the preoperative phase, screening, recruitment, and baseline data collection were conducted. This involved reviewing patient medical records, conducting imaging studies (anteroposterior, lateral, and scaphoid views), MAYO classification, and administering questionnaires (DASH and PRWE scores). Baseline demographic and clinical information, as well as surgical procedure specifics, were carefully documented in a secure electronic database.

Operative technique: The Operative technique involved bone marrow aspiration and scaphoid fracture fixation. For bone marrow aspiration, the patient was positioned in a prone position after receiving general anesthesia. Adequate padding was applied to all bony pressure points and areas of potential nerve compression. After palpating the bony landmarks, the procedural site was sterilely prepared and widely draped to ensure a suitable surgical field. BMAC was harvested from the posterior superior iliac crest region using a trochar and needle inserted percutaneously. 1 mL of Heparin (1000 U/mL) was used to prevent clot formation, and approximately 30 mL of bone marrow was aspirated. A sterile dressing was applied, and the patient was repositioned supine. The harvested BMA was processed using a specialized centrifuge to discard the buffy coat layer and the platelet-poor plasma layer.

In the supine position, the patient's shoulder was abducted, forearm supinated, and wrist gently extended while the ulnar deviated. A longitudinal incision of approximately 5-10 mm was made at the apex, exposing the scaphoid tuberosity. Blunt dissection techniques were used to reveal the scaphotrapezial articulation while preserving the anterior capsule of the wrist joint. A 1.1 mm guidewire was carefully inserted through the scaphoid tubercle, aiming to center it in the proximal pole. The wire was advanced until it reached a suitable position in both views by directing it toward the center of the proximal pole of the fractured scaphoid.

To compensate for the incomplete visibility of the scaphoid on the lateral radiograph, the wire was carefully guided toward the central region of the proximal pole. The goal was to place it precisely at the midpoint between the end surface of the Radius or the Lister tubercle. The required screw length was determined either by using a depth gauge or by comparing the lengths of two parallel pins that were placed at the proximal and distal poles. During the surgical procedure, a specialized cannulated drill bit with a protective sleeve was used to create a hole in the scaphoid bone within 2 mm of the proximal cortex. To guide the screw insertion, a K-wire was utilized. Self-tapping headless compression titanium acutrak screws with a diameter of 3.5 mm and a length range of 16-20 mm were employed in all cases. During screw insertion, around 1.5 ml of concentrated bone marrow was injected through the screw, and drill bit holes were in the proximal fragment to facilitate bone healing. The screw was fully inserted over the K-wire under fluoroscopy control until the fracture was compressed appropriately. Afterward, the end of the screw was buried beneath the distal surface of the scaphoid. Before closing the skin, an additional milliliter of bone marrow concentrate was injected into the fracture site using a syringe under fluoroscopy guidance. The skin was closed using sutures and a sterile dressing.

Postoperative care: Patients were immobilized with a thumb slab for two week, followed by active finger exercises and regular follow-up appointments until a radiological union was established. Sutures were removed after two weeks, and patients underwent physiotherapy for wrist mobilization. Complete loading of the wrist was allowed only after the clinical and radiological union was achieved, and patients were discharged within 24 hours of admission.

### Statistical Analysis

Descriptive and inferential statistical analyses were employed to examine the data. Mean and standard deviation were used to summarize continuous variables, whereas frequencies and percentages were utilized for categorical variables. Group comparisons involved t-tests for continuous variables and chi-square tests for categorical variables. Statistical significance was determined with a threshold of $p<0.05$.

### Ethical Considerations

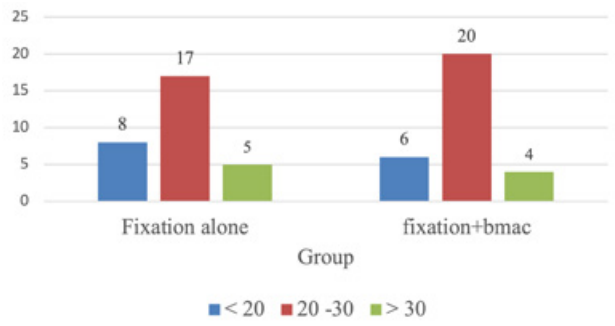
The study adhered to the principles of the Declaration of Helsinki and complied with all relevant ethical guidelines and regulations for clinical research. Informed consent was obtained from all participants, and the study protocol was approved by the Institutional Review Board of the hospital.

## Results

The study included a total of 60 patients with scaphoid fractures, divided into two groups of 30 patients each. The mean age of patients in the Fixation alone group was 24.933±5.476 years, while in the fixation BMAC group, it was 25±4.683 years. In the Fixation alone group, 8(26.7%) patients were younger than 20 years old, whereas, in the fixation BMAC group, 6 (20%) patients fell under this age group. Among the patients aged between 20 to 30 years, 17 (56.7%) patients were in the fixation bone group, and 20 (66.7%) patients were in the fixation BMAC group. Furthermore, 5 patients (16.7%) in the fixation bone group and 4 patients (13.3%) in the fixation BMAC group were older than 30 years old. These age groups were illustrated in **Figure 1**.

The study revealed a notable distinction in the employment status of patients between the two groups. In the Fixation alone group, 14 patients (46.7%) were engaged in manual work occupations, whereas 16 patients (53.3%) held office-based employment. Conversely, in the fixation BMAC group, 11 patients (36.7%) were involved in manual work occupations, while 19 patients (63.3%) were employed in office-based roles. The demographic information of the patients is presented in **Table I**.

**Figure 1:** Age group in patients of two treatment groups.




The clinical characteristics of the patients are shown in **Table II**. Variable analysis of clinical characteristics showed that most patients in both fixation alone and BMAC fixation groups had involvement in their right hand. Specifically, 23 patients (76.7%) in the Fixation alone group and 27 patients (90%) in the fixation BMAC group had involvement in their right hand. The study found a significant difference between the two groups of patients in terms of the dominant hand ($P \leq 0.05$). In the Fixation alone group, 25 patients (83.3%) were right-handed, while in the fixation BMAC group, all patients (100%) were right-handed. The remaining patients in both groups were right-handed (**Figure 2**).

The most common location of fractures in both groups was the waist region, with 28 patients (93.3%) in each group having fractures in this area. Fractures in the distal pole region were observed in only 2 patients (6.7%) in both groups, indicating that this location is less commonly affected in scaphoid fractures.

The study analyzed the mechanism of scaphoid injury in both the Fixation alone group and the fixation BMAC group. The results showed that the most common mechanism of injury in both groups was "Falling down." Specifically, 26 patients (86.7%) in the Fixation alone group and 21 patients (70%) in the fixation BMAC group experienced injuries due to falling down. In the Fixation alone group, 3 patients (10%) had injuries as a result of direct trauma, while in the fixation BMAC group, 8 patients (26.7%) had injuries due to direct trauma. Only 1 patient (3.3%) in both groups had injuries due to traffic accidents.

The results of examining the Union time in weeks as checked by using plain radiograph variable revealed significant differences between the two groups. In the Fixation alone group, none of the patients achieved a Union time of 8 weeks. Instead, 9 patients (30%) attained a Union time of 10 weeks, 18 patients (60%) reached 12 weeks, and 3 patients (10%) required 16 weeks for Union. In contrast, in the fixation BMAC group, 9 patients (30%) had a Union time of 8 weeks, 17 patients (56.7%) had a Union time of 10 weeks, and 4 patients (13.3%) had a Union time of 16 weeks. These findings suggest that the use of fixation BMAC may lead to a shorter Union time compared to fixation alone. Significantly, the statistical analysis indicated a substantial difference in Union time in weeks between the two treatment groups ($P \leq 0.001$). A visual representation of the Union time in weeks for both groups can be observed in **Figure 3**, which vividly illustrates the contrasting Union time durations observed in the two groups.

The analysis of the mean duration of fracture in the two groups of patients showed that the mean duration of fracture in the Fixation alone group was 3±1.661 weeks, while the mean duration of fracture in the fixation BMAC group was 2.8±1.424 weeks. There was no significant difference in the duration of fracture between the two groups.

The initial assessment before surgery was performed using QDASH-KU and PRWHE-KU to determine the degree of initial disability and then repeated in the eighth and sixteenth weeks using the same tools. The mean disability score based on QDASH-KU before intervention was 54.316±5.596 in the Fixation alone group and 56.81±4.719 in the fixation BMAC group, with no significant difference between the two treatment groups. The mean disability score in the eighth week after intervention based on QDASH-KU was 29.54±3.036

**Table I:** Demographics characteristics of fractured patients in two treatment groups.

| Characteristic | | Group | | P-value |
|---|---|---|---|---|
| | | Fixation alone | Fixation+BMAC | |
| **Age** | | 24.933±5.476# | 25±4.683 | 0.96** |
| **Age group** | < 20<br>20 - 30<br>> 30 | 8 (26.7%) &<br>17 (56.7%)<br>5 (16.7%) | 6 (20%)<br>20 (66.7%)<br>4 (13.3%) | 0.5* |
| **Sex** | Male<br>Female | 28 (93.3%)<br>2 (6.7%) | 29 (96.7%)<br>1 (3.3%) | 0.5* |
| **Residency** | Inside City<br>Outside city | 22 (73.3%)<br>8 (26.7%) | 23 (76.67%)<br>7 (23.3%) | 1 |
| **Education** | Yes<br>No | 29 (96.7%)<br>1 (3.3%) | 28 (93.3%)<br>2 (6.7%) | 1 |
| **Job** | Manual work<br>Office employ | 14 (46.7%)<br>16 (53.3%) | 11 (36.7%)<br>19 (63.3%) | 0.6* |

*P-value Chi-Square, **t-test, & Frequency (%), #Mean ± SD

in the Fixation alone group and 18.866±3.55 in the fixation BMAC group, showing a significant difference in the mean disability score between the two groups (P ≤ 0.001). The mean disability score in the sixteenth week after intervention based on QDASH-KU was 8.93±4.348 in the Fixation alone group and 5.36±2.02 in the fixation BMAC group, indicating a significant difference in the mean disability score between the two groups (P ≤ 0.001). The disparity observed in the reduction of disability scores between the fixation BMAC group and the Fixation alone group highlights the substantial impact of the surgical technique on alleviating disability in the arm, shoulder, and hand of the patients who underwent the procedure.

**Figure 2:** Involved limb in patients of two treatment groups.

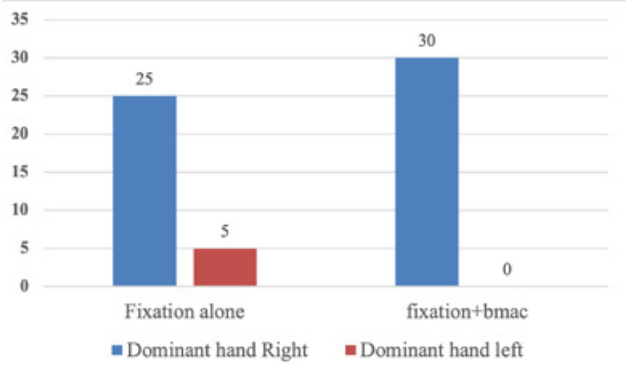



**Figure 3:** Union time in weeks in patients of two treatment groups.

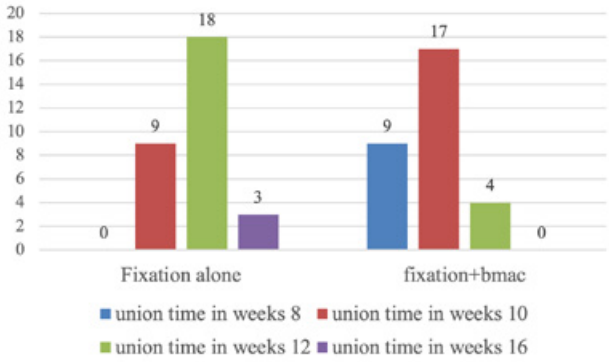



**Table II:** Clinical characteristics of fractured patients in two treatment groups.

| Characteristic | | Group | | P-value |
|---|---|---|---|---|
| | | Fixation alone | Fixation+BMAC | |
| **Involved limb** | Right<br>Left | 23 (76.7%)&<br>7 (23.3%) | 27 (90%)<br>3 (10%) | 0.299* |
| **Dominant hand** | Right<br>Left | 25 (83.3%)<br>5 (16.7%) | 30 (100%)<br>0 | **0.05*** |
| **Concomitant illness** | Yes<br>No | 1 (3.3%)<br>29 (96.7%) | 1 (3.3%)<br>29 (96.7%) | 1 |
| **Mechanism of injury** | Falling down<br>Direct trauma<br>Road traffic | 26 (86.7%)<br>3 (10%)<br>1 (3.3%) | 21 (70%)<br>8 (26.7%)<br>1 (3.3%) | 0.313* |
| **Union time in weeks** | 8<br>10<br>12<br>16 | 0<br>9 (30%)<br>18 (60%)<br>3 (10%) | 9 (30%)<br>17 (56.7%)<br>4 (13.3%)<br>0 | **0.001*** |
| **Duration (weeks)** | | 3±1.661# | 2.8±1.424 | 0.619** |

*P-value Chi-Square, **t-test, & Frequency (%), #Mean ± SD

**Table III:** Assessment of disability using DASH-KU and PRWHE-KU tools in two treatment groups.

| Characteristic | | Group | | P-value |
|---|---|---|---|---|
| | | Fixation alone | Fixation+BMAC | |
| **QDASH** | QDASH 1<br>Before intervention | 54.316±5.596** | 56.81±4.719 | 0.06 |
| | QDASH 2<br>8th<br>After intervention | 29.54±3.036 | 18.866±3.55 | 0.001 |
| | QDASH 2<br>16th<br>After intervention | 8.93±4.348 | 5.36±2.02 | 0.001 |
| **PRWHE** | PRWHE 1<br>Before intervention | 62.05±4.43 | 53.833±7.786 | 0.001 |
| | PRWHE 2<br>8th<br>After intervention | 35.116±1.501 | 20.85±3.744 | 0.001 |
| | PRWHE 3<br>16th<br>After intervention | 10.983±2.283 | 7.566±1.275 | 0.001 |

*P-value t-test** Mean ± SD

The results of the investigation of the disability score variable based on PRWHE-KU showed that the mean disability score before intervention was significantly higher in the Fixation alone group (62.05±4.43) than in the fixation BMAC group (53.833±7.786) (P ≤ 0.001). In the eighth week after intervention, the mean disability score in the Fixation alone group was 35.116±1.501, while in the fixation BMAC group, it was 20.85±3.744, indicating a significant difference between the two groups (P ≤ 0.001). Similarly, in the sixteenth week after intervention, the mean disability score in the Fixation alone group was 10.983±2.283, and in the fixation BMAC group, it was 7.566±1.275, showing a significant difference between the two groups (P ≤ 0.001). These results suggest that the use of fixation BMAC may lead to a greater reduction in wrist and hand disability compared to fixation alone, indicating the positive impact of the surgical method on reducing disability in the intervened patients. (**Table III**).

## Discussion

In this study, the effectiveness of bone marrow aspirate injection was examined in the treatment of scaphoid fracture using percutaneous fixation compared to alone fixation. Disability assessment and the impact of injection on reducing disability were evaluated using DASH-KU and PRWHE-KU tools in two treatment groups. Based on these results; it was shown that bone marrow aspirate injection in the treatment of scaphoid fracture using percutaneous fixation led to a reduction in wrist disability compared to fixation alone, indicating the positive impact of the surgical method on reducing disability in the intervention group of patients.

Scaphoid bone fractures are among the most common wrist fractures, often due to a fall on an outstretched hand[24]. Since this fracture is often not diagnosed and improper treatment can lead to complications such as non-union, avascular necrosis, and the development of osteoarthritis, its diagnosis, and treatment are of particular importance[25].

The evaluation of treatment outcomes for improving and enhancing the patient's quality of life is vital. A study conducted in the Netherlands by Cohen et al. (2021) aimed to examine the changes after surgery in scaphoid bone fractures. The PRWHE questionnaire was used to evaluate the treatment interventions in this study. The study demonstrated that the mean PRWHE score decreased from 47 before the surgery to 11 after the surgery, which is consistent with the findings of the current study, indicating that patients can expect improved functional outcomes after scaphoid surgery[26].

In China, Tang et al. (2020) carried out a study to assess the efficacy of percutaneous injection of bone marrow aspirate combined with platelet-rich plasma (PRP) in treating delayed fractures. This prospective study involved 66 patients with fractures, and its outcomes aligned closely with the findings of the present investigation. The results indicated that the percutaneous injection of bone marrow aspirates had a substantial positive effect on the treatment of the condition, facilitating accelerated fracture healing and reducing the overall recovery time[27].

In a recent study conducted by Chanthana et al. (2023) in Thailand, the primary objective was to explore the patterns and preferences of patients with wrist injuries or diseases. In this retrospective study, 183 patients with wrist injuries or diseases who visited the clinic or were hospitalized for surgery between 2017 and 2020 were included in the study. The researchers collected data through the administration of four questionnaires: DASH, MHQ, PRWHE, and EQ-5D. The findings of the study indicated that these questionnaires exhibited satisfactory accuracy and capability in assessing treatment interventions. Notably, the PRWHE questionnaire was deemed more significant to patients compared to the other questionnaires [28]. Based on the similar findings of the current study, it is crucial to employ appropriate tools in evaluating treatment interventions. The use of suitable questionnaires, such as DASH and PRWHE, for assessing surgical interventions is highly important. These questionnaires are effective and reliable and can be extensively utilized[29-31].

Paying attention to changes in functionality and movement of individuals who experience hand fractures is necessary. In a study conducted in the United States by Weinstock-Zlotnick et al. (2015), patient reports and preferences were examined. A total of 60 participants with 74 cases of hand fractures were included in this study. They completed the Disabilities of the Arm, Shoulder, and Hand Questionnaire (DASH), the Michigan Hand Outcomes Questionnaire (MHQ), and the Patient-Rated Wrist/Hand Evaluation (PRWHE) in three trials. The results of these three questionnaires, which align with and validate the findings of the current study, demonstrated that patients showed improved functionality and reduced disability after undergoing treatment interventions. By utilizing these tools, the evaluation of changes in patients' functionality after treatment interventions were effectively conducted[32].

It is important to acknowledge that the open reduction and internal fixation method for scaphoid bone fractures has certain disadvantages and potential risks. These risks include the possibility of damaging the radiocarpal ligament, causing destruction of the scaphotrapezial joint, compromising blood flow to the bone, and the potential development of hypertrophic scars[33]. However, these issues can be mitigated by utilizing the bone marrow aspiration injection technique[21,34].

Overall, the injection treatment method administered through the skin for scaphoid bone fractures was found to be an appropriate and effective approach. It

not only accelerates fracture healing but also improves wrist functionality while reducing the incidence of complications. Given the availability of resources, the injection treatment method can be preferred over other treatment methods for scaphoid bone fractures.

## Conclusions

The results of this study demonstrate that bone marrow aspirate injection in conjunction with percutaneous fixation can lead to a reduction in wrist disability compared to fixation alone in the treatment of scaphoid fractures. Furthermore, using DASH-KU and PRWHE-KU questionnaires, it was shown that bone marrow aspirate injection improved patient performance and significantly reduced patient limitations.

### Acknowledgments
We would like to express our gratitude to all the participants who took part in this study and made it possible.

### Availability of data and materials
The data and materials used in this study are available upon request.

### Competing interests
The authors declare no competing interests that could potentially bias the findings or interpretation of this study.

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SPECIAL ARTICLE

# Tipo y prevención de complicaciones orales en pacientes oncológicos

*Type and prevention of oral complications in oncology patients*

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## Resumen

Se describen las complicaciones orales que pueden presentar los pacientes oncológicos en función del tratamiento que reciben, mucositis, estomatitis, hemorragia gingival, xerostomía, candidiasis oral, caries y enfermedad periodontal, con atención detallada final a su prevención.

*Palabras clave:* Complicación, oral, oncología.

## *Abstract*

The oral complications that oncologic patients may present depending on the treatment they receive, mucositis, stomatitis, gingival hemorrhage, xerostomia, oral candidiasis, caries and periodontal disease are described, with final detailed attention to their prevention.

*Key words:* Complication, oral, oncology.

## Introducción

Actualmente son numerosas las posibilidades de tratamiento en pacientes oncológicos, las cuales nos han permitido en los últimos años aumentar la supervivencia ante esta enfermedad; pero no debemos olvidar los efectos secundarios que producen y que pueden comprometer su calidad de vida a la hora de afrontar la patología.

Las complicaciones orales son uno de los principales problemas de la terapia de los pacientes con cáncer, tal como se denunció en un par trabajos que han devenido en clásicos[1,2]. Un 40% de los pacientes que reciben quimioterapia y hasta un 76% de los pacientes trasplantados de médula ósea desarrollan problemas bucales, siendo los más frecuentes: mucositis, infección local, dolor y hemorragia[3]. Además, en los pacientes con cáncer de cabeza y cuello, la radioterapia puede dañar irreversiblemente las glándulas salivares, la mucosa oral, la musculatura y el hueso alveolar ocasionando xerostomía, enfermedades dentales y osteoradionecrosis[4]. Los agentes quimioterápicos y/o las radiaciones ionizantes, que actúan sobre las células en la fase multiplicativa, afectan de manera importante a la mucosa del tracto digestivo, tejido de rápida proliferación celular, produciendo lesiones como la estomatitis o mucositis.

### 1. MUCOSITIS

Inflamación de las mucosas acompañada de una disminución en la tasa de renovación del epitelio basal, que se adelgaza y presenta úlceras en tejidos blandos, principalmente en los no queratinizados, como la mucosa bucal y labial y las superficies ventrales y laterales de la lengua. Un 40% de los pacientes que reciben quimioterapia la desarrollan[5].

### 2. ESTOMATITIS

La estomatitis está muy relacionada con la administración del metotrexato que como antagonista del ácido fólico que es, genera su deficiencia, lo que interfiere en la

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La estomatitis está muy relacionada con la administración del metotrexato que como antagonista del ácido fólico que es, genera su deficiencia, lo que interfiere en la producción y maduración de las células epiteliales y lleva a una atrofia o extinción de las papilas linguales y formación de úlceras, que a su vez causan una deficiencia nutricional al paciente por el dolor que provocan. Una revisión amplia de esta patología ha sido publicada, con información actualizada[6].

### 3. HEMORRAGIA GINGIVAL

Se genera por una trombocitopenia (disminución del número de plaquetas) inducida por la droga y por coagulación intravascular diseminada, sobre todo en pacientes con niveles plaquetarios de 20,000 a 50,000 por $mm^3$ [7]. Estos medicamentos alteran la síntesis y la maduración de las células sanguíneas provocando leucopenia, trombocitopenia y anemia, privando al sistema inmune de protección. La mielosupresión puede precipitar el sangrado espontáneo del periodonto y agudizar la enfermedad periodontal crónica, así como los problemas pulpares.

### 4. XEROSTOMÍA

Una revisión muy reciente 8 confirma que la xerostomía se presenta como efecto secundario o agregado a la mucositis, ya que hay una reducción en cantidad y calidad del flujo salival a partir del segundo día de tratamiento; además, existe atrofia hacinar, necrosis celular, degeneración y fibrosis de la glándula salival, lo que provoca disminución del flujo salival y su pH, así como de la capacidad buffer de la saliva. Todo esto acelera el deterioro periodontal y favorece la aparición de caries dental.

### 5. CANDIDIASIS ORAL

Es una de las enfermedades más frecuentes de la mucosa bucal y, sin duda, la afección micótica más común en esta localización, como muy bien se describe en este editorial[9]. La magnitud de la infección micótica depende fundamentalmente de las condiciones del paciente, pues esta sobreinfección ocurre cuando se perturban los parámetros de equilibrio fisiológico que mantienen la homeostasia del medio bucal.

Los factores de riesgo para la aparición de esta infección micótica son los tratamientos prolongados con antibióticos, la diabetes, la anemia, la radioterapia y la quimioterapia antineoplásicas, las drogas inmunosupresoras y, en general, todo medicamento o procedimiento que debilite los mecanismos de defensa del complejo bucal.

### 6. CARIES DENTAL

Es una enfermedad multifactorial que se caracteriza por la destrucción de los tejidos del diente como consecuencia de la desmineralización provocada por los ácidos que genera la placa bacteriana, y que constituye un problema de salud en incremento[10]. Las bacterias fabrican ese ácido a partir de los restos de alimentos de la dieta que se les quedan expuestos. La destrucción química dental se asocia a la ingesta de azúcares y ácidos contenidos en bebidas y alimentos, así como también se asocia a errores en las técnicas de higiene, falta de cepillado dental, o no saber usar bien los movimientos del lavado bucal, ausencia de hilo dental; y, en menor medida, con una etiología genética.

Se ha comprobado así mismo la influencia del pH de la saliva en relación a la caries, el cual suele ser muy ácido en estos pacientes. Si al medio ácido se le suma una disminución de la calidad y cantidad de saliva producida, el riesgo de desarrollar caries dental se incrementa notablemente.

### 7. ENFERMEDAD PERIODONTAL

La periodontitis ocurre cuando se presenta inflamación o infección de las encías (gingivitis) y no es tratada. La infección e inflamación se diseminan desde las encías hasta los ligamentos y el hueso que sirven de soporte a los dientes. La pérdida de soporte hace que los dientes se aflojen y finalmente se caigan[11].

La placa y el sarro se acumulan en la base de los dientes. La inflamación a raíz de esta acumulación hace que entre la encía y los dientes se formen "bolsas" o huecos. La falta de higiene junto con la susceptibilidad a la aparición de infecciones debido al compromiso inmunológico de estos pacientes, hacen que la aparición y progresión de la periodontitis sea muy prevalente.

La incidencia de complicaciones orales puede reducirse llevando a cabo evaluaciones de la cavidad oral antes de iniciar la terapia, eliminando las fuentes potenciales de infección o irritación y usando medidas preventivas durante todo el tratamiento onco-hematológico, detalladas a continuación desde la amplia experiencia de una de las firmantes de este trabajo, CV, absolutamente en línea con lo publicado como revisión muy recientemente en Estados Unidos[12].

Los factores de mayor riesgo descritos para la aparición de complicaciones orales son:

- Respiración oral: favorece la boca seca y el desequilibrio bacteriano.
- Cavidad oral mal cuidada, principalmente por una higiene oral deficiente.
- Patología dental: caries, obturaciones fracturadas.
- Enfermedad periodontal: infección de los tejidos que sostienen los dientes.
- Prótesis dentales defectuosas o mal ajustadas.

## RESPIRACIÓN ORAL

La respiración oral introduce aire frio y seco cargado de polvo a la boca y faringe. El aire que no pasa por la nariz, pierde el calentamiento, la humidificación y la filtración que evita la irritación de las mucosas bucal y faríngea.

Esta irritación, sumada a los cambios estructurales que sufren las encías durante los tratamientos oncológicos, induce un deterioro importante de los tejidos de sostén de los dientes.
Además, la respiración oral induce la sequedad de la misma, favoreciendo un medio ácido que promueve el crecimiento de bacterias virulentas alterando el equilibrio bacteriano tan necesario para nuestra salud bucal.

La saliva es un fluido fisiológico crucial en nuestra salud y nuestra vida, ya que posee todos los componentes necesarios para la curación de nuestros dientes y encías. Por este motivo, es especialmente importante trabajar la estimulación salival con los pacientes para mejorar no sólo la salud bucal sino la digestiva, ya que la boca y la saliva componen las bases de la primera fase de la digestión.

## CEPILLADO MECÁNICO

El paciente debe mantener una correcta higiene bucal con cepillado diario de los dientes, lengua y encías, después de las comidas y al acostarse utilizando un dentífrico no irritante libre de tóxicos, un cepillo suave y seda dental o cepillos inter-proximales para la limpieza interdental.

Ante signos de sangrado o en pacientes con plaquetopenia, se utilizará una torunda de gasa o bastoncillos de algodón para el cuidado de la boca.

## USO DE ENJUAGUES

Los enjuagues son un complemento a la limpieza mecánica diaria con cepillo dental. Se utilizarán preferentemente de solución salina, bicarbonato sódico o una mezcla de ambos y se deberán evitar aquellos que contienen alcohol, ya que resecan la mucosa.

En pacientes con dificultades para el cepillado, se puede usar aceite vegetal de coco, sésamo y/o oliva junto con aceites esenciales de orégano, clavo, árbol de té o menta que contienen propiedades antiinflamatorios, antibacterianas y antifúngicas. De ese modo, evitamos componentes químicos o alcoholes que pueden empeorar la cavidad oral de estos pacientes.

## PRÓTESIS DENTALES

Las prótesis dentales deben ser limpiadas y cepilladas igual que la boca, y sumergidas cada noche en solución de hipoclorito sódico al 1% (si no hay metal) o en solución con aceites esenciales para su desinfección. Es importante su higiene, ya que pueden estar colonizadas por hongos y bacterias que posteriormente colonizan la cavidad oral de los pacientes.

## OTRAS MUCOSAS

Los labios deben ser lavados y conservarse perfectamente hidratados con manteca de karité, aceite de oliva o coco. Se debe evitar la utilización de vaselina o glicerina, por los efectos deshidratantes que producen sobre el tejido labial.

## ESTADO EMOCIONAL

El estrés fisiológico o mental de estos pacientes puede alterar su sistema nervioso central y del mismo modo su sistema inmune interfiriendo en la capacidad de recuperación y regeneración celular. Por ello, es muy importante el acompañamiento emocional durante todo el proceso de tratamiento, de modo que el paciente entienda qué está experimentando su cuerpo y de qué modo se puede minimizar los efectos secundarios de los tratamientos recibidos.

**Conflicto de intereses**
Ninguno para ambos autores

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SPECIAL ARTICLE

# Apnea obstructiva del sueño: un problema de salud pública de primer orden

*Obstructive sleep apnea: a major public health concern*

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## Resumen

La apnea obstructiva del sueño (AOS) es actualmente un problema de salud pública de primer orden por diferentes razones. Por un lado es, en la mayoría de centros, la derivación desde atención primaria a especializada (especialmente a neumología) más frecuente y la que más listas de espera provoca. Por otro lado la padecen más de un billón de personas en todo el mundo y se asocia a un incremento de la morbimortalidad tanto a corto como a largo plazo. Su diagnóstico en la mayoría de las ocasiones puede realizarse de forma domiciliaria y presenta un tratamiento muy efectivo para las formas graves y sintomáticas como es la presión positiva nocturna sobre la vía aérea (CPAP). A pesar de todo ello, y de que su falta de detección cuesta a la sanidad pública entre dos y tres veces más que aquellos pacientes en los que ha sido detectada y tratada correctamente, es una enfermedad enormemente infradiagnosticada.

*Palabras clave:* Apnea del sueño, salud pública, CPAP.

## *Abstract*

Obstructive sleep apnea (OSA) is currently a major public health problem for different reasons. On the one hand, in most centers is the most frequent referral from primary care to specialized care (especially pulmonology) and the cause of the longest waiting lists. On the other hand, more than a billion people suffer from OSA worldwide and it is associated with an increase in morbidity and mortality in both the short and long term. In most cases, its diagnosis can be made easily at home and it presents a very effective treatment for severe and symptomatic forms such as nocturnal positive airway pressure (CPAP). Despite all this, and the fact that its lack of detection costs to the public health between two and three times more than those patients in whom it has been detected and treated correctly, it is a greatly underdiagnosed disease.

*Key words:* Sleep apnea, public health, CPAP.

Según el último consenso internacional sobre apnea obstructiva del sueño (AOS), esta enfermedad se define como la presencia de un índice de apneas e hipopneas (IAH) superior a 15 eventos por hora de sueño, o bien superior de 5 eventos por hora si además se acompaña de síntomas secundarios como excesiva somnolencia diurna, sueño no reparador, cansancio excesivo y/o de deterioro de la calidad de vida, no justificables por otras causas. En este contexto una apnea se define como un cese completo del flujo respiratorio durante al menos 10 segundos, mientras que la hipopnea se define como un cese parcial del flujo aéreo de similar longitud pero que además se acompañe de una desaturación de oxígeno significativa o bien de un despertar[1]. La suma de eventos apneicos e hipopneicos por hora de sueño define el anteriormente citado IAH. En casos graves (IAH superior a 30 eventos/hora) podrían existir cientos de estos eventos durante la noche (para una duración media del sueño de 7-8 horas). La desaturación intermitente (o carga hipóxica)[2] así como la fragmentación del sueño producidos por estos eventos respiratorios durante el sueño se han relacionado con múltiples síntomas (cansancio diurno, sueño no reparador, roncopatía crónica, hipersomnia diurna, etc)[1], a un incremento en la incidencia de factores

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de riesgo cardiovascular como hipertensión arterial[3-5], arteriosclerosis[6,7], estados procoagulantes[8], resistencia a la insulina[9,10] así como a un exceso de eventos cardiovasculares, cerebrovasculares, metabólicos, neuropsiquiátricos, tumorales e incluso a una mayor mortalidad[4,10]. La prevalencia del AOS aumenta con la edad, y sobre todo con el sobrepeso y la obesidad[11-13]. El tratamiento de elección, además de las medidas higiénico-dietéticas en todos los pacientes, es la presión positiva continua de la vía aérea (CPAP) para las formas graves (AHI>30 eventos/hora) o sintomáticas (aunque no sean graves según este parámetro)[1] salvo en algunos casos que se pueden beneficiar de tratamiento farmacológico[14].

El AOS, desde un punto de vista epidemiológico y de salud pública, es una de las enfermedades que más ha avanzado en cuanto a su número de diagnósticos, a pesar de que se estima que hasta un 80% de los casos sigue sin diagnóstico entre otras circunstancias por su gran heterogeneidad[15]. Posiblemente este hecho responda a que es una enfermedad relativamente joven en cuanto a su estudio científico (la primera CPAP en el mundo se prescribió en la década de los 80 del siglo pasado), y que con el advenimiento de la pandemia de obesidad y los cada vez más sencillos y portátiles dispositivos de diagnóstico y concienciación de la comunidad médica sobre su importancia, su número de diagnósticos se ha multiplicado de una forma exponencial en los últimos años[16]. Hoy por hoy, y ya desde hace unos años, la sospecha de AOS es la derivación más frecuente que se realiza a los servicios de neumología y a los centros de especialidades desde atención primaria. En neumología hospitalaria es la enfermedad que supone el mayor número de primeras consultas (habitualmente por encima del 30%) incluso en grandes hospitales [1]. Es además la enfermedad en el ámbito de la neumología que mayores listas de espera supone a pesar de que se han desarrollado sistemas portátiles de diagnóstico domiciliario[17], y finalmente la CPAP es la terapia respiratoria domiciliaria más frecuentemente prescrita (supone entre el 65-70% de todas las terapias respiratorias domiciliarias en España y es, con mucho, la que más gasto sanitario supone)[18]. Finalmente, además, no diagnosticar y tratar a estos individuos, sobre todo en sus formas graves, supone un gasto sanitario entre 2-3 veces mayor que hacerlo, dadas las consecuencias importantes para la salud que se derivan de esta enfermedad si no es tratada[19].

Esta circunstancia epidemiológica no es casual y responde, a la enorme prevalencia del AOS. Un estudio de estimación publicado recientemente en una revista de gran prestigio internacional concluye que el AOS es padecido por más de un billón (1.000 millones) de personas en el mundo, la gran mayoría no diagnosticados[20]. Por lo tanto, ya nadie duda de que el AOS es un problema de salud pública de primer orden, dada su enorme prevalencia, la presión asistencial que supone, su gran infradiagnóstico, sus elevados costes y las negativas consecuencias para la salud que supone.

Actualmente la esperanza de vida está aumentando, de forma que el incremento de la población mundial existente (más de 8,000 millones de individuos en este momento) es producida más por un incremento en el número de ancianos que por un aumento en la tasa de natalidad[21]. Un estudio publicado en Lancet augura que aquellos individuos que han nacido en el siglo XXI, probablemente alcancen en un porcentaje elevado de casos el centenar de años, y además lo hagan sin grandes dependencias[22]. En España, por ejemplo, la prevalencia de personas de más de 65 años ya ha superado el 20% de la población[23]. Trasladando estos números al mundo del AOS, aparece el gran problema al que se enfrenta la sociedad con esta enfermedad (como con otras enfermedades crónicas) ya que el AOS lo padece más del 20% de la población mayor de 65-70 años y algunos estudios han demostrado que aun en estas edades las formas sintomáticas se benefician de un tratamiento con CPAP[24]. De hecho, un estudio realizado en España en más de 51.000 estudios de sueño realizados en 7 Unidades de Sueño repartidas por todo el territorio nacional ya observó que el 25% de las pruebas se realizaban en mayores de 65 años, y que de ellos, casi el 70% eran tratados con CPAP[25]. Este estudio fue realizado con datos derivados de los años 2002 a 2008, por lo que, aunque no hay datos posteriores, dos décadas después probablemente estos porcentajes sean incluso superiores.

Por lo tanto el panorama sanitario presente, pero sobre todo futuro, que se plantea no parece muy halagüeño. Es realmente difícil conciliar un gran número de diagnósticos y el enorme coste que ello puede suponer, también para el paciente[26], así como las ingentes listas de espera. En este sentido, los autores del presente editorial, todos nosotros trabajadores con años de experiencia en AOS, queríamos expresar algunas ideas que pensamos pueden ser interesantes: 1. Es indispensable la educación e información sobre esta enfermedad tanto a la ciudadanía como a los profesionales médicos, en especial para detectar las formas clínicamente más graves (no tratarlas, como ya ha sido comentado, supone un gasto público extra), o qué derivaciones deben de ser urgentes o preferentes, pero también para no se derivan aquellas formas con baja probabilidad de padecer la enfermedad y evitar con ello el colapso de las Unidades de sueño; 2. Es muy importante la actividad multidisciplinar y multidimensional en esta disciplina dado que el colectivo de enfermería y técnicos de sueño pueden hacer una labor fundamental en el control de miles de pacientes estables que pueden evitar pasar por consultas médicas especializadas aliviando las mismas. De la misma forma otras especialidades como la medicina de familia (detección de casos), medicina interna y sus especialidades (consecuencias del AOS), neurofisiólogos, otrorrinolaringólogos, cirugía máxilo-facial, endocrinología y nutrición (manejo de la obesidad), entre otras, son absolutamente indispensables; 3. La utilización de dispositivos simplificados para el screening rápido es fundamental dado que evita procedimientos mucho más costosos y acortan en gran medida el

proceso diagnóstico-terapéutico; 4. El AOS es una enfermedad que puede protocolizarse con bastante facilidad, por lo que la recogida de datos no solo médicos, sino económicos, logísticos o de gestión son indispensables para conocer la evolución de la misma e implementar por parte de la administración las medidas necesarias; y finalmente el AOS es probablemente una de las enfermedades que por sus características, más se beneficien de las consultas telemáticas[27]. La mayoría de consultas médicas, realización de pruebas diagnósticas y manejo de dispositivos terapéuticos pueden manejarse bajo el paraguas de la telemedicina, de una forma eficaz y coste-efectiva evitando traslados innecesarios.

Sirva esta editorial para concienciar a los diferentes estamentos sociales, administrativos y sanitarios sobre la gran (y creciente) importancia en términos epidemiológicos de esta enfermedad, y sobre la necesidad de actuaciones urgentes, coordinadas y coste efectivas a tal respecto, porque lejos de tener controlada esta enfermedad, su incidencia sigue aumentado a pasos agigantados, y las consecuencias sobre la salud de los individuos que la padecen (si la enfermedad no es detectada y tratada) son enormemente costosas en términos socio-sanitarios.

### Conflictos de interés

Los autores no declaran ningún conflicto de interés

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CASE REPORT

# A rare case of a giant phyllodes tumor with degeneration and bleeding: diagnosis and treatment difficulties

*Un caso raro de tumor filoides gigante con degeneración y hemorragia: dificultades de diagnóstico y tratamiento*

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## Abstract

One of the leading problems worldwide in oncology and surgery is breast cancer. There were 2,261,419 newly diagnosed cases of breast cancer in 2020, which is 11.7% of the total number of diagnosed cases of malignant tumors of various localizations and is one of the leading causes of mortality in women. The diagnosis of breast cancer is often a difficult case when there is no histological verification of the tumor or the results are inconclusive. In these setting proper exclusion of benign masses is essential. Among the benign neoplasms, a special place is occupied by an extremely rare type of tumor – a phyllodes tumor, which makes up 0.3-0.5% of all breast tumors. A phyllodes tumor is a fibroepithelial neoplasm characterized by an extreme rate of development and the ability to transform into a malignant tumor (sarcoma). The current case report describes a giant phyllodes tumor with degeneration and bleeding the required emergency treatment.

*Key words:* phyllodes tumor, mastectomy, breast cancer.

## *Resumen*

Uno de los principales problemas a nivel mundial en oncología y cirugía es el cáncer de mama. En 2020 se diagnosticaron 2.261.419 nuevos casos de cáncer de mama, lo que supone el 11,7% del total de casos diagnosticados de tumores malignos de diversas localizaciones y es una de las principales causas de mortalidad en la mujer. El diagnóstico del cáncer de mama es a menudo un caso difícil cuando no hay verificación histológica del tumor o los resultados no son concluyentes. En estos casos es esencial excluir adecuadamente las masas benignas. Entre las neoplasias benignas, ocupa un lugar especial un tipo de tumor extremadamente raro: el tumor filodes, que constituye el 0,3-0,5% de todos los tumores de mama. Un tumor filodes es una neoplasia fibroepitelial caracterizada por una tasa de desarrollo extrema y la capacidad de transformarse en un tumor maligno (sarcoma). El presente caso describe un tumor filodes gigante con degeneración y hemorragia que requirió tratamiento de urgencia.

*Palabras clave:* Tumor filodes; mastectomía; cáncer de mama.

## Introduction

One of the leading problems worldwide in oncology and surgery is breast cancer. Early diagnosis, prevention and treatment should be aimed at organ-preserving methods. Breast cancer is one of the most common malignancies among women[1]. According to GLOBOCAN[2], in 2020, 2,261,419 new cases of breast cancer were registered in the world, which is 11.7% of the total number of newly diagnosed cases of malignant tumors of various localizations. Mortality was 6.9% of the total number of deaths from malignant neoplasms, which corresponds to 684,996 cases. Therefore oncological screening and alertness among physicians in the diagnosis of neoplasms of various localization is essential.

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However, some of the mass lesions of the mammary gland are also benign neoplasms, which can be initially diagnosed as cancer. Among the benign neoplasms, a special place is occupied by an extremely rare type of tumor - a phyllodes tumor, which makes up 0.3-0.5% of all breast mass lesions[3]. A phyllodes tumor is a fibroepithelial neoplasm characterized by an extreme rate of development and the ability to transform into a malignant tumor (sarcoma). The etiology and pathogenesis of phyllodes tumors has not yet been clarified. There are many hypotheses of their origin, including the influence of genetic factors. Phylloid (leaf-shaped) tumor has a favorable prognosis and a 10-year survival rate of 87%[4,5].

This article presents a clinical case of management of a patient with a phyllodes tumor. Initially, after a comprehensive examination, she was suspected to have breast cancer. The patient was urgently hospitalized to the clinic due to the degeneration of the tumor that resulted in bleeding.

## Case report

A 52-year-old woman, has been under observation for two years due to a mass of the left mammary gland, which she accidentally identified during palpation. The patient also had uterine myoma and iron deficiency anemia. Regarding the latter, she was consulted by a hematologist and underwent corrective treatment. Planned hospitalization and surgical treatment for breast formation were postponed several times due to difficult-to-correct anemia, with a decrease in hemoglobin level to 60 g/l and she was lost to follow-up on multiple occasions. In the period from 2020 to 2021, she noted an increase in size of the mass, and in May 2021, the patient was consulted by an oncologist. During examination there was a mass in the upper outer quadrant, that deformed the contour of the mammary gland. The skin was pale pink, the nipple and areola were without particularities but there was a positive symptom of "lemon peel" on the border of the outer quadrants of the left breast. She had a nodular mass in the upper outer quadrant of the left breast, on palpation with clear uneven contours, stiff, about 6 cm in size (negative progression compared to the data from 2020). The skin over the mass was hyperemic, not mobile; there were no discharge from the nipple. According to the ultrasound examination of the mammary glands from May 2021: at the border of the outer quadrants of the left mammary gland, there was a hypoechoic mass with a clear uneven contour of 4.5 * 5.5 * 4.1 cm. Mammography from May 2021 demonstrated a clustered microcalcifications and numerous areas of increased density, covered by surrounding tissues (**Figures 1A, 2A**).

**Figure 1:** Lateromedial mammography. **A** - 2021; **B** - 2022.

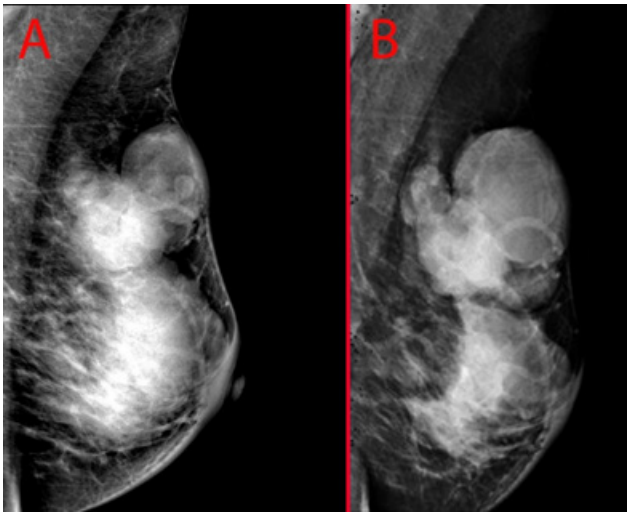



**Figure 2:** Craniocaudal mammography. **A** - 2021; **B** - 2022.

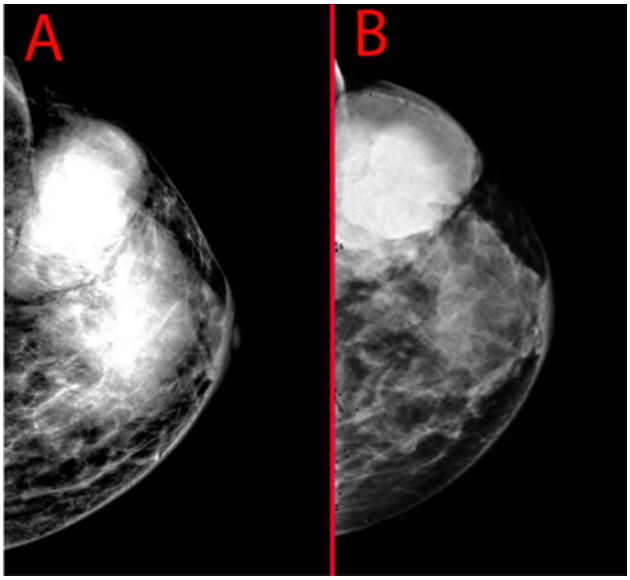
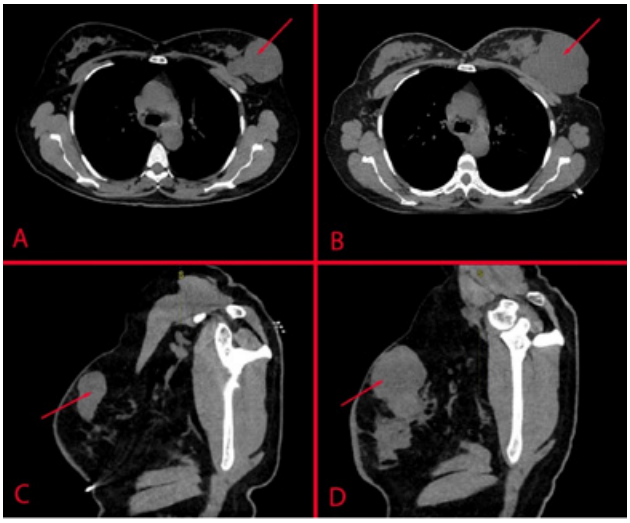



**Figure 3:** Mass of the mammary gland with a difference of one year (CT scan of the chest,). A - CT image from 2021 (axial section, the mass is indicated by an arrow); C - CT image from 2022 (axial section, the mass is indicated by an arrow); C - CT image from 2021 (sagittal section, the mass is indicated by an arrow); D - CT image from 2022 (sagittal section, the mass is indicated by an arrow).



The patient undergone a core-needle biopsy of the mass. According to the results of a histological study from May 2021 the specimen was presented by columns of breast tissue with fibrous and hyalinized stroma and proliferation foci with mild nuclear polymorphism. Mitoses were not reliably detected. The stroma showed compressed and dilated ducts with focal hyperplasia without atypia. The conclusion of the histological examination was that the mass was a fibroepithelial tumor of the mammary gland with an uncertain potential of malignancy. On CT scan of the chest from September 2021, the mass of the left mammary gland was determined as a group of nodes up to 72 mm, with a density of 13 HU. There were single subpleural foci up to 8 mm in size in both lungs (C8 segments), which did not allow to exclude secondary genesis (**Figures 3A, C**).

The patient was consulted by an oncologist due to suspected metastatic lung disease. However, the patient was lost to follow-up and came to the appointment only in October 2022. Repeated mammography showed an increase in the size of the mass (**Figures 1B, 2B**). During this period the patient was observed in the clinic, carried out the correction of anemia. A CT scan of the chest was performed in October 2022, which demonstrated that the lungs were without infiltrative changes only single dense small nodules of a post-inflammatory nature. There was an increase in the mass of the left breast (**Figures 3B, 3D**). An oncological consilium was held in October 2022. The consilium recommended PET-CT scan of the whole body in order to exclude secondary metastatic lesions. Due to the deterioration of the patients' condition, the degeneration of the tumor, its breakthrough to the surface of the skin and bleeding, she was hospitalized at the end of October 2022 on an emergency basis to our hospital.

During preoperative examination of the patient she had severe anemia (hemoglobin - 63 g/l). Objective examination the surface of the skin revealed an ulcerated protruding brown mass up to 10 cm in diameter that teared the skin, without involvement of the nipple (**Figures 4 A, B**). In the conditions of the oncological surgical department, as part of the preoperative preparation for surgery, anemia was corrected by transfusion of blood components (2 doses of erythrocyte suspension equal to 600 ml) and intravenous administration of iron (Likferr 20 mg/ml - 5 ml for 3 days). The bleeding was stopped by hemostatic sponges.

Ultrasound of the breast revealed fibrocystic mastopathy, multiple anechoic cysts, a mass with a lobulated contour, richly vascularized in the Doppler mapping mode (**Figure 5**).

Breast-sparing procedure was no possible due to the size of the mass, that occupied the majority of the breast. We performed a left mastectomy after preoperative stabilization and correction of anemia (hemoglobin 80 g/l). The postoperative period was uneventful, without complications and she received antibacterial treatment (1 g of cefotaxime 2 times a day), iron infusion (Likferr 20 mg/ml - 5 ml), symptomatic therapy (diclofenac 50 mg/ml - 3 ml and ketorol 20 mg/day). She was discharged on the 3rd day after surgery in a satisfactory condition.

**Figure 4:** Preoperative image of the mammary gland. A - anterior projection; B - lateral projection.

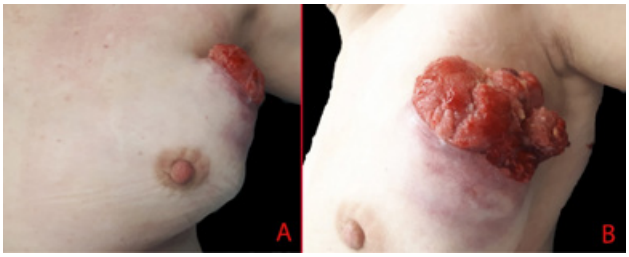
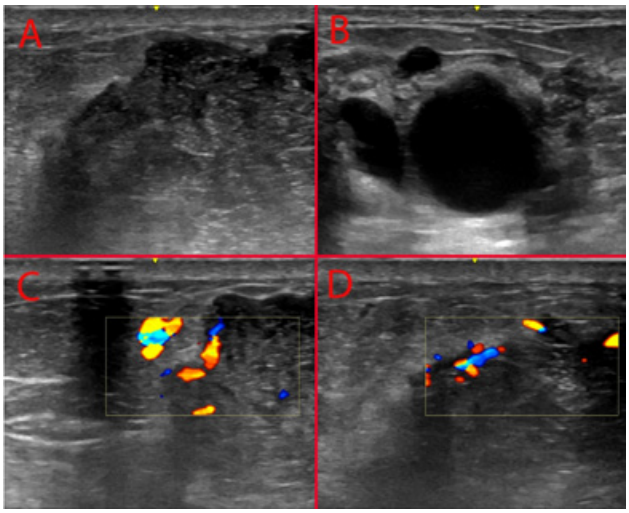



**Figure 5:** Ultrasound image of a mass of the mammary gland. A - The border of healthy and affected tissue; B - Multiple anechoic cysts of the mammary gland; C, D - the tumor is penetrated by large vessels.




According to histological examination the areas of breast tissue had growth of a leaf-shaped tumor with a typical epithelial lining of the ductal type, slightly increased cellularity of the stroma and numerous focal degenerative changes. The foci had multiple sites of degeneration and necrosis, lymphohistiocytic infiltrates, mycosidosis, hyalinosis, leukocyte infiltrates and ulceration of the skin over the tumor. There were no tumor emboli in blood and lymphatic vessels and intact resection margins (R0). According to the results of immunohistochemical studies an insignificant part of the tumor cells was positive for CD117 and p53, and Ki67 was 5%. Based on these results the tumor was classified as a benign phyllodes tumor of the mammary gland with degenerative and inflammatory changes. During the observation of the patient over a 6-month period there were no data for relapse after surgery and her hemoglobin level stabilized at the level of 90-100 g/l.

## Discussion

Phylloid (leaf-shaped) tumor is a rare fibroepithelial tumor that can be benign, malignant or borderline. There is no definite algorithm for the management and treatment of patients with this type of tumor. There are mostly separate clinical observations and literature reviews on phyllodes tumors, but they are descriptive in nature and reveal the management of the patient only in a certain situation.

The standard for diagnosing both benign and malignant neoplasms of the breast are mammography and ultrasound of the mammary glands, but the sensitivity and accuracy of these methods for diagnosing a phyllodes tumor are minimal[6]. MRI of the mammary glands provides a more accurate result. According to a number of authors, there are features that may be more characteristic for phyllodes tumors when comparing patients with various tumors. The presence of a cystic component, strong lobulation (presence of septa) suggests a phyllodes tumor in 63%-74% of cases. Delayed phase contrast enhancement of T1WI demonstrates a heterogeneity of the structure of the mas that is more common in phyllodes tumors than in fibroadenomas and other benign neoplasms, while the homogeneity of the structure of the mass in 67% of cases was characteristic of fibroadenomas[7].

In most cases, these methods do not provide high accuracy in the diagnosis of phyllodes tumors, therefore histological verification is necessary. Fine-needle aspiration of a mass is uninformative taking into account that the sensitivity of the method is 22.7%. A core-needle biopsy followed by an immunohistochemical study is required for a morphological diagnosis. The sensitivity of the method is 66.2% and according to the available data, the diagnosis of a phyllodes tumor is established using a core biopsy in about half of the cases[5]. There are several grading systems, but the most common is classification as benign, borderline and malignant. This is based on the assessment of nuclear pleomorphism of stromal cells, stromal overgrowth, increased mitoses, increased stromal cellularity, which is usually diffuse, and infiltrative borders[3]. One study showed a correlation between the histological characteristics of a phyllodes tumor obtained by core-needle biopsy and the results of postoperative histological and immunohistochemical studies. Cases in which a phyllodes tumor was not ruled out were evaluated for cellular component, stromal distribution and outgrowth, nuclear atypia, and mitotic activity. The use of Ki67, topoisomerase IIa, CD34, CD117 and Bcl-2 may be helpful to properly classify the tumor. The obtained results correlated with the results of subsequent postoperative studies. In 58% of cases, the results of core-needle biopsy were identical with the results of postoperative histological studies. Hypercellularity and pseudoangiomatous hyperplasia of the stroma, moderate nuclear atypia, mitotic activity, and indistinct boundaries of the lesion, in 73-87% of cases, correlated with the postoperative pathomorphological diagnosis of a phylloid tumor[8,9]. Other immunohistochemical markers may include p53, EGFR, p16, and VEGF. Therefore, the abovementioned histological and immunohistochemical parameters can make it possible to predict the diagnosis of a phyllodes tumor based on core-needle biopsy data, but the accuracy of the method is far from ideal. The differential diagnosis should include: fibroadenoma, sarcomas, periductal stromal tumor, metaplastic carcinoma[4].

In the presented clinical case, the patient was not diagnosed based on core-needle biopsy. The patient did not undergo surgery for a long time due to a concomitant pathological condition (difficult to correct anemia), as well as suspicions of a malignant process and metastasis. During the year of observation, an intensive growth of the mas was noted (its increase by 2 times), as well as skin rupture, degeneration and bleeding, uncharacteristic for a benign mass. However, cancer tend to invade the surrounding tissue and grow through the skin, which was not noted in this case. In the literature, there are clinical cases of a giant phyllodes tumor, where the formation reached 45 cm, was accompanied by its decay, anemia, axillary lymphadenopathy, but without bleeding. The patient in the reported case underwent surgery in the amount of mastectomy and regional lymphadenectomy[10].

There is no data indicating bleeding from phyllodes tumors and skin rupture. In the reported clinical observations, the mass usually increased in size, the skin over them becomes thinner, acquires a bluish tint, but does not tear the skin under pressure.

The criteria (rapid growth of the lesion, skin rupture, degeneration of the lesion, bleeding), described in our clinical case, gave reason to differentiate this lesion from a malignant process. However, the management of such patient is difficult due to uncertain initial diagnosis. In an emergency situation that arose in the patient, it was important to quickly and efficiently provide medical care and, to the extent possible, to choose a radical method of surgical treatment.

Taking into account the large size of the tumor, we decided to perform a mastectomy after preoperative preparation. According to the literature, the treatment of benign phyllodes tumors is limited to surgery. For small tumors, a sectoral resection of the mammary gland is performed. Tumor enucleation is unacceptable due to almost 100% risk of tumor recurrence. The standard of care for phyllodes tumors is complete surgical excision with intact resection margins. In case of large bulky phyllodes tumors, mastectomy without lymphadenectomy is often the only possible

surgical procedure. Jae Hyuck Jang and coworkers in their retrospective study conducted from January 1995 to July 2009 reviewed 164 cases of surgical treatment of phyllodes tumors. A total of 148 (90.2%) patients underwent surgical excision of the tumor in the amount of sectoral resection. Mastectomy was performed in 16 patients (9.8%)[9]. The ultimate goal of such procedures should be breast preservation. Unfortunately, this is not always possible in case of large tumors with degeneration and bleeding. However, due to the rare incidence of such tumors diagnosis can be difficult. Based on SEER data registry (2000-2004) only 500 cases of phyllodes tumor are diagnosed in the US annually[11]. Breast reconstruction can be performed in these patients with other myocutaneous flaps or implant. However, they require a higher expertise level involving microsurgery and plastic surgery, a longer operative time and hospital stay[12-14]. In our case this was not possible due to emergency procedure, unstable condition and possible infectious complications after surgery.

Taking into account the size of the mass at admission, it was not possible to carry out an organ-preserving operation, because the tumor occupied most of the gland. The presented clinical case of a phyllodes tumor shows the complexity of diagnosis and the importance of a thorough history, examination of the patient and interpretation of the acquired data.

## Conclusion

Phyllodes tumor is a rare benign tumor that can undergo transformation into sarcoma. In rare instances these tumors can grow to large size and can even breakthrough the skin requiring emergency treatment. In case of giant tumors, the optimal treatment option is excision with clear surgical margin when possible. This group of patients are rarely admitted in emergency settings with signs of tumor degeneration and bleeding that requires emergency mastectomy. However, the presented clinical case of a phyllodes tumor shows the complexity of diagnosis and the importance of a thorough history, examination of the patient and interpretation of the acquired data. Proper preoperative evaluation may lead to high index of suspicion that the tumor may actually be benign in its nature.

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### Informed Consent Statement

Written informed consent has been obtained from the patient to publish this paper.

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### Conflicts of Interest

The authors declare no conflict of interest.

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