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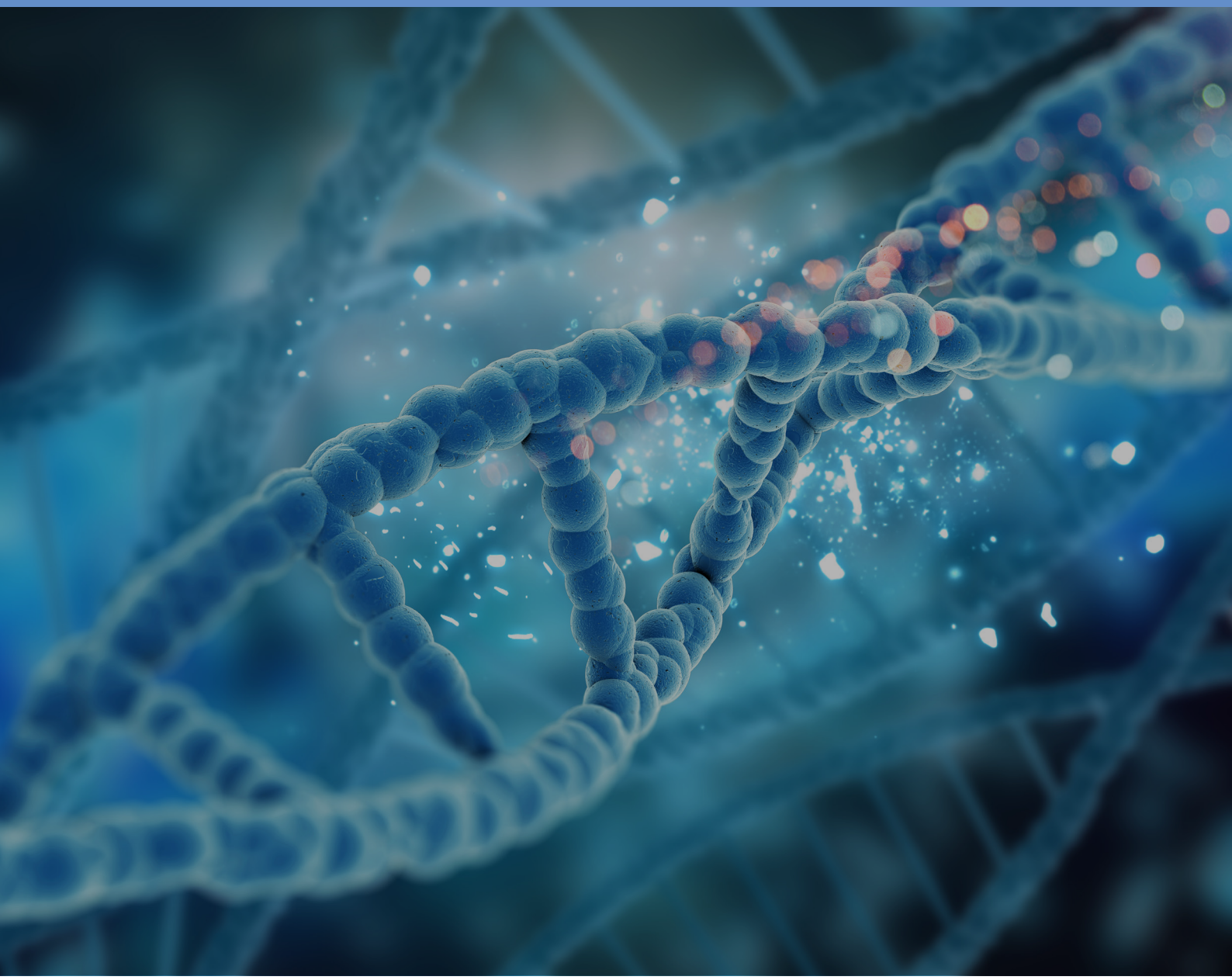

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MEDICINA BALEAR

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CONTENTS / ÍNDICE

ORIGINAL ARTICLES / ARTÍCULOS ORIGINALES

279 **Resultados funcionales y satisfacción del paciente tras la cirugía del hallux valgus**
Functional outcomes and patient satisfaction after hallux valgus surgery
Isabel Buendía-Ayala, Josefa Buendía-Ayala, Mateo Amando López-Cara, Belén-Almudena Tárraga-Marcos, Pedro Javier Tárraga-Marcos, Pedro Juan Tárraga-López

287 **Chronic hepatitis D virus infection among people living with HIV: a case series from southern bulgaria**
Infección crónica por el virus de la hepatitis D en personas que viven con VIH: una serie de casos del sur de bulgaria
Radka Komitova, Elitsa Golkocheva-Markova, Ani Kevorkyan, Ivan Baltadzhiev, Meri Hristamyan, Vanya Rangelova, Mariya Atanasova

297 **Gendered social patterning of cardiometabolic risk: an intersectional analysis using anthropometric and metabolic indices in a large working population**
Patrones sociales del riesgo cardiometabólico según el género: un análisis interseccional mediante índices antropométricos y metabólicos en una amplia población trabajadora
Ana Cecilia Romero-Aguirre, Astrid Lorelei Camero-Avalos, Neus Morell-Servera, Milton Lurquin-Lurquin, Daniel Guzmán-Capote, Claudia Tirado-Cabrera, Gabriela Villarroel-Soto

308 **Behavioral procrastination and metabolic syndrome in a large occupational cohort**
Procrastinación conductual y síndrome metabólico en una gran cohorte ocupacional
Manuel Sarmiento-Cruz, Pedro Juan Tárraga-López, Mónica Silu Piña-Dabreu, Lluis Rodas-Cañellas, Ángel Arturo López-González, José Ignacio Ramírez-Manent

324 **Long term visual results of optic nerve sheath fenestration surgery**
Resultados visuales a largo plazo de la cirugía de fenestración de la vaina del nervio óptico
Mediha Tok-Çevik, Bulent Yazici

REVIEW ARTICLES / ARTÍCULOS DE REVISIÓN

336 **Obesity in occupational health: The position of the occupational physician in preventive practice**
Obesidad en salud ocupacional: la posición del médico del trabajo en la práctica preventiva
Mª Teófila Vicente-Herrero, Miguel León-Sanz, Jordi-Carles Schlaghecke i Gras, Carmen Muñoz-Ruipérez

347 **Occupational exposure to chemical agents and hematological malignancies: a systematic review of epidemiological evidence**
Exposición ocupacional a agentes químicos y neoplasias hematológicas: una revisión sistemática de la evidencia epidemiológica
Marta Rodríguez-Suárez, D. Gutiérrez-Rodríguez, María Teófila Vicente-Herrero

361 **The evolutionary persistence of depressive and anxiety disorders: current hypotheses and clinical implications**
La persistencia evolutiva de los trastornos depresivos y de ansiedad: hipótesis actuales e implicaciones clínicas
Mauro García-Toro, Rocío Gómez-Juanes

CONTENTS / ÍNDICE

CLINICAL CASES / CASOS CLÍNICOS

372 **Infantile appendicitis presenting as acute scrotum: a case report and review of literature**
Apendicitis en un lactante con presentación como escroto agudo: reporte de un caso y revisión de la literatura
Esra Karakas, Mehmet Yazici, Fatma Saraç

377 **Maxilectomía total seguida de reconstrucción con implantes cigomáticos y un obturador quirúrgico inmediato**
A total maxillectomy followed by reconstruction with zygomatic implants and an immediate surgical obturator
Luis Amengual-Peñafiel, David Coronel-Fuentes, Jorge Arancibia-Arancibia, Sebastián Godoy-Ibáñez, Carlos Humeres-Sigala, Cristian Wulff-Zottele

ACADEMIC JOURNAL OF HEALTH SCIENCES
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Artículo original

Resultados funcionales y satisfacción del paciente tras la cirugía del hallux valgus

Functional outcomes and patient satisfaction after hallux valgus surgery

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Resumen

Objetivo: Conocer los resultados funcionales y la satisfacción de los pacientes tras la cirugía del hallux valgus.

Métodos: Estudio descriptivo retrospectivo sobre una población de 123 pacientes con hallux valgus sometidos a intervención quirúrgica. Variables a estudio: edad, género, grado de hallux valgus, presencia de comorbilidades, complicaciones, calidad asistencial, mejora funcional y satisfacción. Para valorar la calidad asistencial y mejora funcional se emplearon las escalas VAS y AOFAS-MI. La satisfacción percibida por los pacientes se evaluó con el cuestionario CSQ-8. El análisis estadístico de los datos se realizó con R y RStudio.

Resultados: En nuestra serie, el 82% de los pacientes intervenidos eran mujeres y la edad media en el momento de la cirugía fue de 57 años. El 14,6% presentaba diabetes mellitus, el 31% eran fumadores activos y el 13% seguía tratamiento antiagregante o anticoagulante, configurando una población con comorbilidad relevante. Casi el 60% de los casos correspondía a hallux valgus de grado moderado. La cirugía del hallux valgus se asoció con una clara mejoría clínica y funcional, pasando de valores medios preoperatorios de 7,4 puntos en la escala VAS y 56 puntos en la AOFAS-MI a 1,2 y 91 puntos, respectivamente, en el postoperatorio. La satisfacción fue elevada, con una puntuación media de 28,6 sobre 32 en la CSQ-8 y un 87% de los pacientes dispuestos a repetir el procedimiento. El AOFAS-MI preoperatorio fue el único predictor significativo de la magnitud de la mejoría funcional, mientras que la tasa global de complicaciones alcanzó el 20%, observándose una relación dosis-respuesta entre el número de comorbilidades y la frecuencia de complicaciones.

Conclusiones: La cirugía del hallux valgus ofrece resultados funcionales favorables y elevada satisfacción percibida por los pacientes.

Palabras clave: Cirugía de hallux valgus. Calidad. Satisfacción. VAS. AOFAS-MI. CSQ-8.

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Abstract

Objective: To evaluate functional outcomes and patient satisfaction after hallux valgus surgery.

Methods: We conducted a retrospective descriptive study of 123 patients with hallux valgus who underwent surgical correction. Variables included age, sex, hallux valgus severity, comorbidities, complications, quality of care, functional improvement, and satisfaction. Pain and functional outcomes were assessed using the VAS and AOFAS-MI scales, respectively. Patient satisfaction was evaluated with the CSQ-8 questionnaire. Statistical analyses were performed using R and RStudio.

Results: In our series, 82% of patients were women, and the mean age at surgery was 57 years. Diabetes mellitus was present in 14.6%, 31% were active smokers, and 13% were receiving antiplatelet or anticoagulant therapy, reflecting a cohort with relevant comorbidity. Nearly 60% of cases corresponded to moderate hallux valgus. Surgery was associated with clear clinical and functional improvement, with mean VAS scores decreasing from 7.4 preoperatively to 1.2 postoperatively and AOFAS-MI scores increasing from 56 to 91 points. Satisfaction was high, with a mean CSQ-8 score of 28.6 out of 32 and 87% of patients willing to undergo the procedure again. Preoperative AOFAS-MI was the only significant predictor of the magnitude of functional improvement. The overall complication rate was 20%, with a dose–response relationship between the number of comorbidities and the complication rate.

Conclusions: Hallux valgus surgery provides favorable functional outcomes and high patient-perceived satisfaction.

Keywords: Hallux valgus surgery. Quality of care. Satisfaction. VAS. AOFAS-MI. CSQ-8.

Introducción

El hallux valgus es una deformidad tridimensional, progresiva y multifactorial del primer radio del pie, caracterizada por la desviación lateral del hallux y la desviación medial del primer metatarsiano (M1), con alteración de la congruencia de la articulación metatarsofalángica y del complejo sesamoideo[1,2,3]. Es una patología muy frecuente en nuestra población, con una prevalencia estimada en torno al 26% - 46% de la población mayor de 40 años y supone una importante limitación funcional para las personas que lo presentan, por lo que es un frecuente motivo de consulta tanto en atención primaria como en traumatología[4,5].

La mayoría de los pacientes refieren dolor en el bunion, generalmente relacionado con el uso de un calzado estrecho junto con desviación del primer dedo del pie. Puede asociarse con metatarsalgia, acortamiento del tríceps sural o dedos en garra. En estadios avanzados suele aparecer pronación del hallux.

En la literatura se han descrito diversos factores de riesgo relacionados con la etiopatogenia del hallux valgus: el uso de calzado estrecho o zapato de tacón, ser del género femenino, edad adulta, historia familiar previa o aspectos biomecánicos como pie plano, hiperlaxitud, hipermovilidad cuneometatarsiana o la longitud del primer metatarsiano[2,3,6,7].

Diagnóstico del hallux valgus

El diagnóstico del hallux valgus se basa en una exhaustiva anamnesis y exploración física complementadas con unas radiografías en carga de los pies[1,2,5,8,9,10].

En la anamnesis, además de preguntar por los factores de riesgo descritos previamente, es importante reflejar las características del dolor, duración de los síntomas, presencia de comorbilidades asociadas y limitación funcional que el hallux valgus supone en su vida diaria.

La exploración física debe ser estática y dinámica. Es importante ser sistemático en la exploración para no olvidarnos de nada.

Finalmente, pasaremos a valorar las pruebas complementarias. La radiografía en carga anteroposterior (AP) y lateral de los pies es la prueba esencial para el estudio del hallux valgus.

Con la radiografía AP en carga mediremos diferentes ángulos:

- Ángulo metatarsofalángico o ángulo del hallux valgus (HVA):

Es el ángulo formado por la intersección de los ejes longitudinales de la primera falange y del primer metatarsiano; se considera normal un valor inferior a 15 grados.

- Ángulo intermetatarsiano (IMA):

Es el ángulo formado por la intersección entre las líneas que van desde el centro de la cabeza hasta el centro de la base de M1 y M2, respectivamente; se considera normal un valor inferior a 9 grados.

- Ángulo distal articular (DMAA, Distal Metatarsal Articular Angle o PASA, Proximal Articular Set Angle):

Es el ángulo formado entre el eje diafisario de M1 y la perpendicular a la línea formada tras la unión de los bordes más medial y lateral de la superficie articular. Nos indica la orientación de la superficie articular

distal de M1 respecto a su eje diafisario; se considera normal un valor inferior a 6-10 grados.

- Ángulo interfalángico del hallux (IFA):

Es el ángulo formado por la intersección de las líneas del eje longitudinal de las falanges proximal y distal del hallux; se considera normal un valor inferior a 10 grados.

Clasificación del hallux valgus

Existen diversas clasificaciones, siendo una de las más utilizadas la propuesta por Coughlin y Mann, que gradúa la deformidad del hallux valgus según el HVA e IMA en[1,5,11,12]:

- Normal (HVA <15°, IMA <9°)
- Leve (HVA 15-20°, IMA 9-11°)
- Moderado (HVA 20-40°, IMA 11-16°)
- Grave (HVA >40°, IMA >16°)

Clasificaciones más actuales incorporan la naturaleza triplanar de la deformidad del hallux valgus en los planos axial, sagital y coronal. Para ello evalúan la pronación del primer metatarsiano, la subluxación sesamoidea y la artrosis metatarsofalángica del hallux (MTF1) en radiografías AP y lateral de los pies en carga, radiografía axial de sesamoideos y TC en carga 3D cuando existe disponibilidad de esta.

La clasificación triplanar de hallux valgus (THAVC) utiliza el principio del centro de rotación de la angulación (CORA) para identificar el ápex de la deformidad en los tres planos[1,11,13]. Clasifica el hallux valgus en varios tipos:

- Tipo 1: aumento HVA/IMA sin pronación metatarsal ni artrosis MTF1
- Tipo 2: con pronación
  - Tipo 2a: sin subluxación sesamoidea
  - Tipo 2b: con subluxación sesamoidea
- Tipo 3: con metatarsus adductus >20°
- Tipo 4: con artrosis MTF1

Tratamiento del hallux valgus

El gold standard en el manejo del hallux valgus es el tratamiento conservador, siendo suficiente en la gran mayoría de casos leves, moderados y algunos graves paucisintomáticos o en aquellos pacientes con deformidades severas que presentan contraindicaciones o un riesgo alto de complicaciones con el tratamiento quirúrgico[6,15-21].

El tratamiento conservador del hallux valgus incluye el uso de fármacos y medidas físicas como calzado adecuado, ortesis, plantillas, crioterapia y fisioterapia mediante programas de movilizaciones y estiramientos.

Cuando fracasa el tratamiento conservador del hallux valgus, cobra especial relevancia su tratamiento quirúrgico. Este suele aplicarse a aquellos pacientes que, tras un periodo prudencial de 6-12 meses de tratamiento ortopédico, no consiguen mejorar y presentan dolor significativo con una limitación funcional relevante o progresión importante de la patología que interfiere en su calidad de vida[6].

El objetivo del tratamiento quirúrgico del hallux valgus consiste en corregir la deformidad para restaurar la alineación del primer radio, disminuyendo así el dolor del paciente y mejorando su calidad de vida. Para ello se han descrito múltiples técnicas quirúrgicas; por lo tanto, será fundamental individualizar el tratamiento para poder conseguir así mejores resultados[6,22-26].

Clásicamente, y a modo de síntesis, podríamos diferenciar:

- Realineación de partes blandas (McBride modificado): aislada, en las deformidades leves, o combinada con el resto de las técnicas en cualquiera de los grados de la deformidad.
- Osteotomías distales del primer metatarsiano (Chevron): deformidades leves.
- Osteotomías diafisarias o proximales del primer metatarsiano (Scarf): deformidades moderadas-severas.
- Artrodesis tarsometatarsiana del primer radio (Lapidus): deformidades severas con hipermovilidad importante.
- Artroplastia metatarsofalángica del hallux (Keller-Brandes): pacientes ancianos con baja demanda funcional.
- Osteotomías de la falange proximal (Akin): asociada a técnicas sobre el primer metatarsiano.
- Cirugía mínimamente invasiva (MIS): evolución de las técnicas clásicas, permite correcciones con pequeñas incisiones y recuperaciones más rápidas.

Complicaciones de la cirugía del hallux valgus

Las complicaciones de la cirugía del hallux valgus suponen un reto constante para el traumatólogo, ya que, a pesar de los avances en las técnicas quirúrgicas, siguen estando presentes con tasas globales en torno al 10-25% según las series[23,27-32].

Entre las complicaciones de la cirugía del hallux valgus encontramos: recurrencia (la más frecuente), intolerancia al material quirúrgico empleado, rigidez, infección, hallux varus, metatarsalgia de transferencia, neuropatías sensitivas, necrosis avascular de la cabeza del primer metatarsiano y retardos de consolidación o pseudoartrosis.

Material y métodos

Se realizó un estudio descriptivo retrospectivo para valorar la calidad asistencial, resultado funcional y satisfacción de los pacientes tras la cirugía del hallux valgus.

Se incluyó en el estudio a los pacientes con edad comprendida entre 18-85 años intervenidos de hallux valgus que no tenían antecedentes de cirugía previa en el mismo pie, clínica de metatarsalgia ni neuropatía periférica, cuyas historias clínicas estaban completas y aceptaron participar en el estudio. Se excluyó del mismo a los pacientes que no cumplieron los criterios de inclusión.

Se contactó telefónicamente con los pacientes y se les citó para una valoración presencial. Se les realizó una encuesta para registrar datos generales y específicos del estudio: género, edad, presencia de comorbilidades, hábito tabáquico, tratamiento antiagregante o anticoagulante, situación clínica, tiempo en lista de espera quirúrgica, presencia de complicaciones, dolor, calidad asistencial y satisfacción.

La evaluación de la calidad y mejora funcional se realizó con la Visual Analogue Scale (VAS) y la escala de la American Orthopaedic Foot and Ankle Society MTP-IP (AOFAS-MI). Se midió con ambas escalas su situación pre y postcirugía. La valoración de la satisfacción de los pacientes se realizó con el Client Satisfaction Questionnaire-8 (CSQ-8).

La escala VAS permite que el paciente indique el nivel de dolor que sufre sobre una línea horizontal de 10 centímetros, encontrándose en el extremo izquierdo la ausencia de dolor (0 puntos) y en el derecho el mayor dolor imaginable (10 puntos).

La escala AOFAS-MI evalúa varios aspectos: dolor (40 puntos), función (45 puntos) y alineación (15 puntos). La puntuación de esta escala oscila entre 0 y 100 puntos, siendo 0 el peor y 100 el mejor resultado esperable.

El cuestionario CSQ-8 consta de una escala Likert con 8 preguntas, pudiendo obtener en cada una de ellas entre 1 y 4 puntos. El resultado de CSQ-8 varía entre 8 y 32 puntos, siendo estas la peor y mejor puntuaciones alcanzables.

Análisis estadístico

El análisis estadístico se efectuó con R y RStudio, utilizando Microsoft Excel para la depuración inicial y la comprobación de resultados descriptivos. Se codificaron las variables clínicas y sociodemográficas, y se generaron indicadores derivados como la mejora absoluta en la escala AOFAS-MI y la diferencia pre-post en la escala VAS.

Las variables cuantitativas se resumieron mediante media, desviación estándar, mediana y rango intercuartílico; las cualitativas, mediante frecuencias absolutas y relativas. La normalidad de las distribuciones se evaluó con la prueba de Shapiro-Wilk, seleccionándose pruebas paramétricas (t) o no paramétricas (Wilcoxon, Kruskal-Wallis) según los resultados.

Se construyeron modelos de regresión lineal múltiple y logística. En los primeros, se incluyeron como variables dependientes la puntuación CSQ-8 y la mejora de AOFAS-MI; en el modelo logístico, la aparición de complicaciones. Se estimaron coeficientes β, R^2, odds ratio e intervalos de confianza del 95%.

La magnitud clínica de los cambios se valoró con el tamaño del efecto de Cohen (d). Este conjunto de procedimientos proporcionó un marco robusto y reproducible para la evaluación de la eficacia, función, satisfacción y eficiencia de la cirugía del hallux valgus.

Resultados

Características demográficas de la muestra

La muestra estuvo compuesta por un total de 123 pacientes intervenidos de hallux valgus. La edad de los pacientes osciló entre 18-85 años, con una media global de 57,4 años. Hubo un claro predominio del género femenino (82,1% mujeres). El 31,7% eran fumadores, el 14,6% diabéticos y el 13% recibían tratamiento antiagregante o anticoagulante.

Características clínicas preoperatorias

El 59,3% presentaba un hallux valgus moderado y un VAS medio preoperatorio de 7.4 puntos. La calidad funcional media previa a la cirugía fue de 56 puntos en la escala AOFAS-MI. (**Tabla 1**)

Tabla 1. Características clínicas.

Característica clínica	Total n=123
Grado hallux valgus (%)	
Leve	22,8
Moderado	59,3
Severo	17,9
VAS preoperatorio (0-10)	
Media (DE)	7,4 (1,1)
AOFAS-MI preoperatorio (0-100)	
Media (DE)	56,0 (7,5)

Tabla 2. Resultados funcionales y de satisfacción postoperatorios.

Variable (rango)	Preoperatorio Media (DE)	Postoperatorio Media (DE)	Mejora absoluta Media (DE)	d de Cohen (IC95%)
VAS dolor (0-10)	7,4 (1,1)	1,2 (0,7)	6,2 (1,3)	1,68 (1,42 – 1,94)
Reducción %	-	-	84,4%	
AOFAS-MI (0-100)	56,0 (7,5)	91,0 (4,7)	35,0 (8,7)	1,45 (1,21 – 1,69)
Mejora %	-	-	62,5%	

Resultados funcionales y de satisfacción postoperatorios

Se evidenció una mejora significativa en todos los parámetros funcionales postoperatorios. El dolor medido por VAS descendió a una media de 1,2 puntos y la escala AOFAS-MI alcanzó una media de 91 puntos.

La satisfacción global evaluada con el cuestionario CSQ-8 presentó una media de 28,6 puntos, lo que indica un nivel elevado de satisfacción en todos los modelos asistenciales.

Ante la pregunta sobre si aceptarían nuevamente la cirugía dentro del mismo modelo asistencial, el 87,0% de los pacientes expresó que lo haría en caso de ser necesario, mientras que el 13,0% no volvería a realizar el procedimiento. (**Tabla 2**)

Predictores de satisfacción

Se elaboró un modelo de regresión lineal múltiple que incluyó como variables predictoras la edad, el género, la presencia de complicaciones y la puntuación postoperatoria en el AOFAS-MI, con el objetivo de analizar su relación con la satisfacción (CSQ-8). El modelo no alcanzó significación estadística y ninguna de las variables mostró un efecto independiente relevante sobre la satisfacción postoperatoria. Este hallazgo sugiere que los niveles de satisfacción son altos y uniformes, sin depender de factores demográficos ni de la aparición de complicaciones.

Predictores de mejora funcional

El único predictor que alcanzó significación estadística fue la puntuación preoperatoria del AOFAS-MI (β = -0,966, $p < 0,001$), lo que refleja que, por cada punto adicional en la función basal, la ganancia funcional posterior se reduce en aproximadamente 0,97 puntos. Este patrón sugiere un efecto techo, ya que los pacientes con mejor estado funcional inicial presentan un margen de mejora menor. En cambio, variables como la edad, el sexo y el grado de severidad no mostraron una influencia independiente significativa sobre la evolución funcional.

Tabla 3. Factores asociados a complicaciones.

N.º de comorbilidades	n	% del total	Pacientes complicaciones (n)	Tasa de complicaciones (%)	OR crudo (IC95%)
0	63	51,2%	10	15,9%	1,00 (ref.)
1	46	37,4%	10	21,7%	1,47 (0,56-3,84)
2	12	9,8%	4	33,3%	2,65 (0,71-9,83)
3	2	1,6%	1	50,0%	5,30 (0,30-93,2)
TOTAL	**123**	**100%**	**25**	**20,3%**	

Factores asociados a complicaciones

Se desarrolló un modelo de regresión logística con el propósito de identificar los factores asociados a la aparición de complicaciones postoperatorias. En el análisis se incluyeron como variables predictoras la edad, el sexo, el hábito tabáquico, la presencia de diabetes, el uso de tratamiento antiagregante o anticoagulante y el grado de deformidad del hallux. (**Tabla 3**)

Fueron identificados dos factores independientes asociados significativamente con complicaciones:

- Género masculino: OR=5,39 (IC95%: 1,41-21,19, p=0,014), indicando que los hombres presentan 5,4 veces mayor riesgo de complicaciones que las mujeres.
- Diabetes mellitus: OR=8,37 (IC95%: 1,42-63,60, p=0,026), indicando que los pacientes diabéticos presentan 8,4 veces mayor riesgo de complicaciones.

Con el fin de analizar el impacto global de las comorbilidades en el riesgo de complicaciones postoperatorias, se elaboró un índice de comorbilidad acumulada calculado como la suma de tres factores: tabaquismo activo, diabetes mellitus y uso de tratamiento antiagregante o anticoagulante. El valor total del índice osciló entre 0 y 3 puntos.

Discusión

En nuestra serie de casos, la cirugía de hallux valgus proporcionó de forma global una mejora funcional marcada y altos niveles de satisfacción, sin que variables como edad o género condicionaran de manera relevante la ganancia funcional.

Características de la muestra

La cohorte analizada incluyó 123 pacientes, con un claro predominio femenino (82,1%; 101 mujeres y 22 hombres), en consonancia con la distribución descrita clásicamente para esta patología. La edad media fue de 57,4 años (rango 18–85), similar a la comunicada en la mayoría de los estudios sobre cirugía de hallux valgus[4,7,33].

Resultados funcionales

Se observaron resultados funcionales excelentes, con una reducción media del dolor de 6,2 puntos en la escala VAS (84,4%, p<0,001; d=1,68) y una ganancia de 35,0 puntos en la puntuación AOFAS-MI (62,5%, p<0,001; d=1,45), ambos con tamaños del efecto grandes. Estas mejoras son comparables a las comunicadas en la literatura internacional sobre cirugía de hallux valgus, donde AOFAS-MI y VAS siguen siendo las herramientas más utilizadas para evaluar resultados clínicos[34-36].

Satisfacción y experiencia del paciente

La satisfacción postoperatoria fue elevada, con una puntuación media de 28,6 sobre 32 en la escala CSQ-8 y un 87,0% de los pacientes que volverían a someterse al procedimiento. La CSQ-8, aunque menos frecuente en la literatura específica de hallux valgus, se ha empleado para evaluar la experiencia del paciente en otros contextos sanitarios dentro del sistema público español, respaldando su uso como medida de satisfacción global[37].

Factores pronósticos y complicaciones

En el análisis multivariante, el AOFAS-MI preoperatorio se identificó como único predictor significativo de la magnitud de la mejora funcional (β = -0,966; p<0,001), explicando el 72,0% de la varianza, mientras que edad, género, severidad de la deformidad u otras variables clínicas no mostraron efecto independiente relevante, en línea con trabajos que no encuentran un impacto claro de la edad sobre los resultados funcionales tras la cirugía de hallux valgus.

La tasa global de complicaciones fue del 20,3%, siendo la recidiva la más frecuente (12,2%), tal y como describen también múltiples series publicadas sobre esta cirugía[38].

El análisis de regresión logística mostró que el género masculino (OR=5,39; IC95%: 1,41–21,19; p=0,014) y la diabetes mellitus (OR=8,37; IC95%: 1,42–63,60; p=0,026) se asociaron de forma independiente con un mayor riesgo de complicaciones, en contraste con algunos estudios de cirugía mínimamente invasiva que no hallan diferencias significativas entre pacientes diabéticos y no diabéticos. Además, se observó una relación dosis-respuesta entre el número de comorbilidades y la tasa de complicaciones, pasando del 15,9% en pacientes sin comorbilidades al 50,0% en aquellos con tres comorbilidades, lo que refuerza la necesidad de optimizar el control del paciente con pluripatología antes de la intervención.

Conclusiones

La calidad asistencial y funcional tras la cirugía del hallux valgus es excelente, con una mejoría altamente significativa en AOFAS-MI y VAS.

Los pacientes perciben una satisfacción elevada tras la cirugía del hallux valgus evaluada con CSQ-8.

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Contribución de autoría

Isabel Buendia-Ayala: Conceptualización, Recopilación de datos, Análisis formal, Metodología, Validación, Investigación.

Josefa Buendia-Ayala: Conceptualización, Análisis formal, Metodología.

Mateo Amando López-Cara: Conceptualización, Metodología, Validación

Belén Almudena Tarraga-Marcos: Conceptualización.

Pedro Javier Tarraga-Marcos: Conceptualización.

Pedro Juan Tárraga-López: Conceptualización, Recopilación de datos, Análisis formal, Validación.

Conflictos de interés

Los autores declaran que no hay ningún conflicto de interés comercial o financiero para esta investigación.

Declaraciones éticas

Este trabajo cumple con la normativa de investigación y cuenta con la aprobación del Comité de Ética Área III Murcia.

Uso de herramientas de inteligencia artificial

Los autores declaran que no se ha utilizado ninguna herramienta de inteligencia artificial (como ChatGPT, Copilot, Gemini, u otras) en la redacción, análisis o revisión de este artículo.

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Original article

Chronic hepatitis D virus infection among people living with HIV: a case series from southern Bulgaria

Infección crónica por el virus de la hepatitis D en personas que viven con VIH: una serie de casos del sur de Bulgaria

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Abstract

Introduction: Chronic infection with hepatitis D virus (HDV) represents the most severe form of chronic viral hepatitis and is frequently associated with accelerated liver fibrosis and progression to liver cirrhosis. However, data on HDV prevalence and clinical outcomes among people living with human immunodeficiency virus (PLWH) in Bulgaria remain limited. This observational study aimed to characterize HDV infection and its clinical manifestations among PLWH in southern Bulgaria.

Materials and methods: The study was conducted at the Infectious Diseases Clinic of St. George University Hospital, Plovdiv, between April 2024 and December 2025. PLWH aged ≥18 years who tested positive for hepatitis B virus surface antigen (HBsAg) and/or HBV DNA were eligible for inclusion. Serological and molecular markers of hepatitis B virus (HBV), hepatitis C virus (HCV), and HDV were assessed using commercial assays. Clinical data, including liver fibrosis evaluation using the FIB-4 score, HIV viral load, and CD4+ T-cell count, were collected and analyzed.

Results: Among 167 PLWH who were screened, 18 (10.8%) met the inclusion criteria for HBV infection: 13 were HBsAg-positive, and 5 had occult HBV infection. Active HDV infection was identified in five patients (38.5% of HBV-infected individuals), including two cases with cirrhosis. No cases of isolated HDV exposure were detected. Viral co-infections were common: four patients presented with triple infection (HCV/HBV/HDV), while one had dual infection (HBV/HDV). Among the triple-infected individuals, three had low HBV DNA levels (<2,000 IU/mL), whereas one initially exhibited high HBV DNA (124,000,000 IU/mL), followed by spontaneous decline during follow-up. All patients were receiving tenofovir-containing antiretroviral therapy.

Conclusion: HDV infection among PLWH is associated with aggressive liver disease, including liver cirrhosis, and may influence the replication dynamics of co-infecting viruses. These findings highlight the importance of systematic screening for HDV in individuals infected with HBV, particularly among PLWH. Early detection and careful monitoring may help prevent progression to advanced liver disease, including liver cirrhosis, and improve long-term clinical outcomes.

Keywords: Hepatitis delta virus. Human immunodeficiency virus. Hepatitis B virus. Liver cirrhosis. Viral hepatitis co-infections.

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Resumen

Introducción: La infección crónica por el virus de la hepatitis D (VHD) representa la forma más grave de hepatitis vírica crónica y se asocia con frecuencia a una fibrosis hepática acelerada y a la progresión a cirrosis hepática. Sin embargo, los datos sobre la prevalencia del VHD y los desenlaces clínicos entre las personas que viven con VIH (PVVIH) en Bulgaria siguen siendo limitados. Este estudio observacional tuvo como objetivo caracterizar la infección por VHD y sus manifestaciones clínicas entre las PVVIH en el sur de Bulgaria.

Materiales y métodos: El estudio se llevó a cabo en la Clínica de Enfermedades Infecciosas del Hospital Universitario St. George, en Plovdiv, entre abril de 2024 y diciembre de 2025. Fueron elegibles para su inclusión las PVVIH de ≥18 años con resultado positivo para el antígeno de superficie del virus de la hepatitis B (HBsAg) y/o para ADN del VHB. Se evaluaron los marcadores serológicos y moleculares del virus de la hepatitis B (VHB), el virus de la hepatitis C (VHC) y el VHD mediante ensayos comerciales. Se recogieron y analizaron datos clínicos, incluida la evaluación de la fibrosis hepática mediante la puntuación FIB-4, la carga viral del VIH y el recuento de linfocitos T CD4+.

Resultados: Entre las 167 PVVIH evaluadas, 18 (10,8%) cumplieron los criterios de inclusión para infección por VHB: 13 eran positivas para HBsAg y 5 presentaban infección oculta por VHB. Se identificó infección activa por VHD en cinco pacientes (38,5% de los individuos con infección por VHB), incluidos dos casos con cirrosis. No se detectaron casos de exposición aislada al VHD. Las coinfecciones virales fueron frecuentes: cuatro pacientes presentaron infección triple (VHC/VHB/VHD), mientras que uno presentó infección dual (VHB/VHD). Entre los individuos con infección triple, tres tenían niveles bajos de ADN del VHB (<2.000 UI/mL), mientras que uno presentó inicialmente un nivel alto de ADN del VHB (124.000.000 UI/mL), seguido de un descenso espontáneo durante el seguimiento. Todos los pacientes estaban recibiendo terapia antirretroviral con tenofovir.

Conclusión: La infección por VHD entre las PVVIH se asocia con enfermedad hepática agresiva, incluida la cirrosis hepática, y puede influir en la dinámica de replicación de los virus coinfectantes. Estos hallazgos ponen de relieve la importancia del cribado sistemático del VHD en las personas infectadas por el VHB, en particular entre las PVVIH. La detección temprana y el seguimiento cuidadoso pueden ayudar a prevenir la progresión a enfermedad hepática avanzada, incluida la cirrosis hepática, y mejorar los desenlaces clínicos a largo plazo.

Palabras clave: Virus de la hepatitis delta. Virus de la inmunodeficiencia humana. Virus de la hepatitis B. Cirrosis hepática. Coinfecciones por hepatitis víricas.

Introduction

Hepatitis Delta Virus (HDV) is a defective RNA virus that requires the hepatitis B virus (HBV) to complete its life cycle. HDV can only be transmitted when HBV is present, either through co-infection (simultaneous infection with both HBV and HDV) or superinfection (HDV infection in an individual chronically infected with HBV). In most cases, co-infection leads to clearance of both viruses. In contrast, superinfection results in chronic HDV infection in 80–90% of individuals[1,2,3].

Chronic HDV infection is the most severe and rapidly progressing form of chronic viral hepatitis. It has been demonstrated that individuals infected with both HBV and HDV tend to experience a more rapid progression to liver-related complications compared to those with HBV alone. The average time from untreated HDV infection to cirrhosis is about ten years, and to hepatocellular carcinoma (HCC) is approximately five years[4]. Until the recent approval of bulevirtide, there were no specific treatments available for HDV. People living with HIV (PLWH) co-infected with HDV/HBV experience an even faster progression of liver disease, due in part to HIV-associated immunosuppression, even if their HIV is well controlled with antiretroviral therapy (ART)[5,6]. The mortality rate in this population exceeds 20%, and HDV co-infection is associated with a substantially increased risk of HCC[7].

The global prevalence of HDV (indicated by positive HDV antibody, HDVAb) among HBV-infected individuals is approximately 4.5%[8]. However, the prevalence of HDV varies geographically and is generally higher in specific populations, including men who have sex with men (MSM), intravenous drug users (IDU), and patients undergoing haemodialysis[9].

The epidemiological data regarding HDV infection in Bulgaria remain limited. A study, conducted in 1986, reported an 8.6% prevalence of HDV among HBsAg-positive patients with chronic liver disease[10]. Between 1986 and 1997, a clinical centre observed a 16% prevalence among HBV cases[11]. Data collected between 2008 and 2013 show that 3.6% of HBsAg-positive patients receiving antiviral therapy tested positive for HDV antibodies[11]. Recent unpublished findings (2015–2022) suggest a declining trend, with a seroprevalence of 3.2% [Prof. Y. Genov, personal communication]. However, the true prevalence of HDV may be underestimated, as most existing studies primarily involve clinically referred populations that do not reflect the general or high-risk populations.

To our knowledge, this study provides one of the first clinical characterisations of HDV infection among PLWH in southern Bulgaria. According to Bulgarian guidelines, PLWH are screened for HBV and hepatitis C virus (HCV) at the time of HIV diagnosis by testing

for the surface antigen of HBV (HBsAg) and HCV antibody (HCVAb), with follow-up testing conducted annually thereafter.

Materials and methods

Study design and settings

This observational single-centre study aimed to evaluate the prevalence and characteristics of HDV infection in PLWH receiving care at the Clinic of Infectious Diseases (HIV unit) at St. George's University Hospital, Plovdiv, Bulgaria, from April 2024 to December 2025.

Participants were consecutively recruited during their annual follow-up appointments. Eligibility criteria included being 18 years of age or older and testing positive for HBsAg and/or HBV DNA. Pregnant women were excluded from the study. The Ethics Committee of the Medical University of Plovdiv approved the research. Participants provided written informed consent in accordance with the Declaration of Helsinki.

Data collection

Data were extracted from the Bulgarian electronic HIV surveillance system. The information collected included:

- **Demographic data:** Information collected included sex, age at enrollment, ethnicity, and immigration status.
- **HIV-related information:** This included the mode of transmission (MSM, IDU, or heterosexual), the latest CD4 count, recent HIV RNA results, current HBV status, and details regarding HBV-active antiretroviral therapy (ART) such as tenofovir (in the form of disoproxil or alafenamide). Additionally, AIDS-defining conditions and treatment history were recorded.
- **Liver status:** Liver status was assessed using a liver panel test for alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, and platelet count (PLT). The non-invasive Fibrosis-4 (FIB-4) score was used to estimate fibrosis[12]. An FIB-4 score greater than 3.24 indicates advanced fibrosis, while a score below 1.45 suggests no significant fibrosis. The FIB-4 score is calculated using the formula: age (years) × AST (U/L) / platelets (10^9/L) × √ALT (U/L). Cirrhosis was diagnosed using a combination of clinical, laboratory, and imaging studies[13]. Other metrics, such as transient elastography, were not performed.

Laboratory investigations

The 167 PLWH included in the study were tested for HBV and HCV infection using HBsAg, HBV DNA, anti-HCV, and HCV RNA. At the time of enrollment, 13 patients were found to be positive for HBsAg, and 47 were positive for HCV Ab.

Active HBV infection was indicated by a positive HBsAg, HBeAg, or detectable HBV DNA. Occult HBV infection was defined by the presence of HBV DNA in serum at concentrations less than 200 IU/mL with a negative HBsAg test[14].

Individuals with evidence of HBV infection (13 patients with positive HBsAg and five with occult HBV) were subsequently screened for anti-HDV. Samples testing positive for anti-HDV underwent additional HDV RNA testing to confirm active infection. Molecular testing for HBV, HDV, and HCV was repeated as clinically indicated.

Quantitative measurements of HBV DNA and HCV RNA were performed using the ExiStation system (Bioneer, Republic of Korea), and HDV RNA was measured using the RoboGene HDV RNA Quantification Kit 3.0 (Roboscreen GmbH, Leipzig, Germany).

Serological testing for HCV and HBV markers was performed at the Virology Laboratory of St. George University Hospital in Plovdiv. Testing for HDV, including both antibody and HDV RNA assays, as well as nucleic acid amplification for HCV and HBV, was conducted at the National Reference Laboratory for Hepatitis Viruses, NCIPD, Sofia.

Statistical analysis

Descriptive statistics were used to summarize demographic and clinical characteristics. Categorical variables were expressed as absolute numbers and percentages. Continuous variables were reported as mean ± standard deviation (SD). Statistical analyses were performed using IBM® SPSS® Statistics for Windows, version 25.0 (SPSS Inc., Chicago, Ill., USA) with significance set at $p < 0.05$.

Results

Study population

Among the 167 PLWH screened, 13 individuals tested positive for HBsAg (7.8%), and 11 of them had detectable HBV DNA. In addition, five cases of occult HBV infection were identified (3.0%). Among these cases, three tested positive for anti-HBc. Ultimately, 18 participants with evidence of HBV infection were included in the analysis (**Figure 1**). The mean age of the 13 HBsAg-positive participants was 41.5 ± 2.57 years, and the majority were male (n = 11). Reported transmission routes included injecting drug use (n = 6) and MSM (n = 3). In all cases, ART included tenofovir, which is active against both HIV and HBV (**Table 1**).

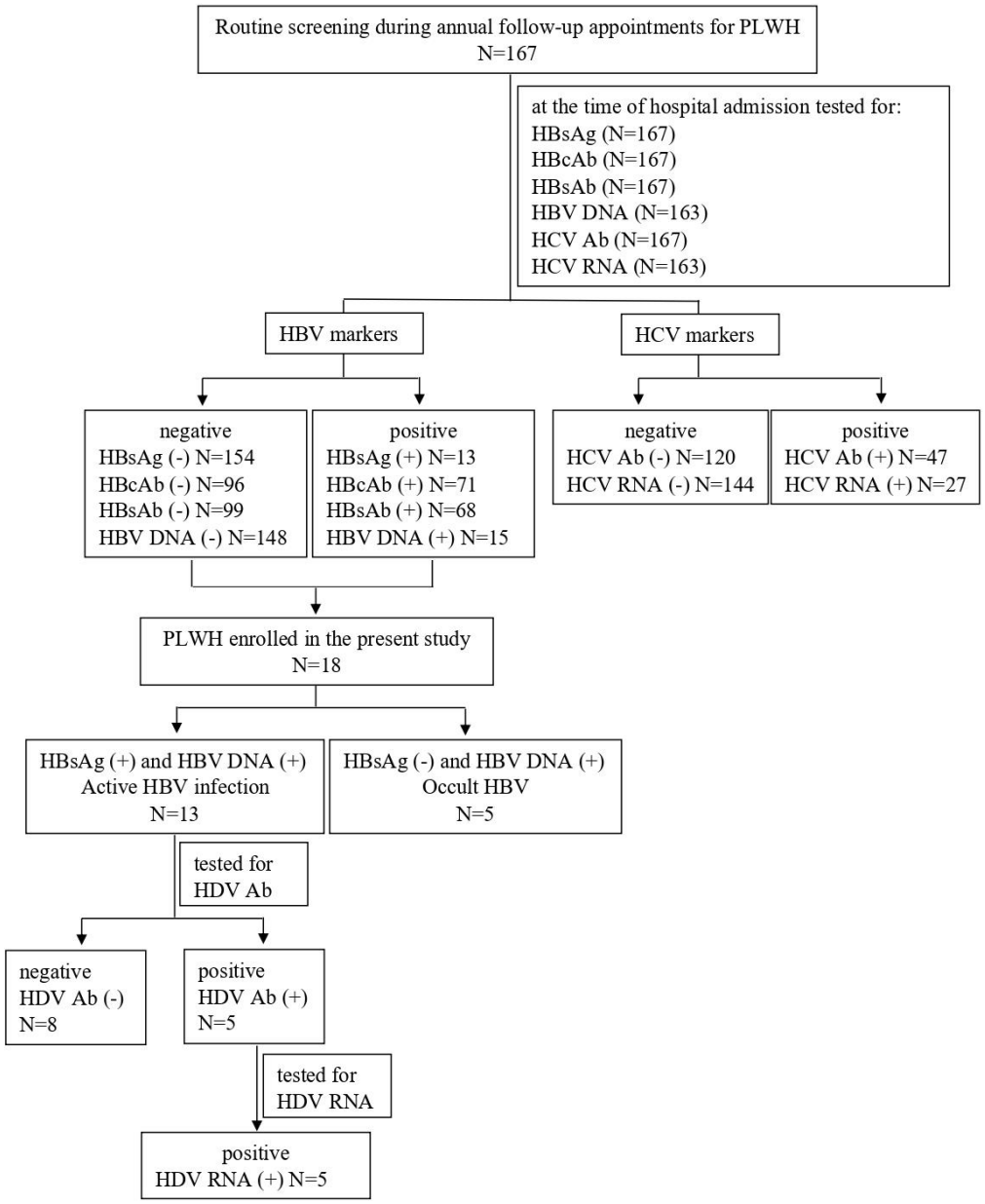

Figure 1. Flowchart of people living with HIV, included in the study[15].

Laboratory testing results

In most cases (n = 11), the recent CD4 count exceeded 200 cells/μL, and the most recent HIV RNA viral load was undetectable (n = 10) indicating effective virological control.

The majority of patients (n = 9) demonstrated low levels of HBV DNA (<2,000 IU/mL). However, two of the 11 patients exhibited elevated HBV DNA levels. One of these cases is described in detail (patient No. 2, **Table 2**).

Among the five cases with occult HBV, three tested positive for the anti-HBc, while two were negative. During the study, researchers did not identify isolated cases with HDV exposure among the five cases of occult HBV infection.

HDV among individuals with HBV and HCV infection

HDV antibody testing was performed in 18 PLWH with HBV markers, including 13 patients with overt chronic HBV infection and 5 patients with occult HBV infection. Among these 18 PLWH, five (27.8%) tested

Table 1. Baseline data for individuals living with HIV, infected with HBV and testing positive for HBsAg (n=13).

Variable	n, (%)
Age, years, mean (SD)	41.46 (2.57)
Male sex	11 (84.6)
Ethnicity Bulgarian Roma Turkish Immigrant	3 (23.1) 7 (53.8) 1 (7.7) 2 (15.4)
Mode of HIV transmission IDU MSM Heterosexual Unknown	 6 (46.2) 3 (23.0) 2 (15.4) 2 (15.4)
CD4 count > 200 cells/μl[a]	11 (84.6)
Undetectable HIV RNA[a, b]	10 (76.9)
Ever having an AIDS-defining condition	2 (15.4%)
HBV - active ART[c]	13 (100%)
Detectable HBV DNA[d]**, IU/mL** <2000 >2000	 9 (81.82) 2 (18.18)
HBeAg positive	3 (23.1%)
HCV Ab positive	4 (30.8%)
Undetectable HCV RNA	4 (30.8%)
ALT, IU/l, mean (SD)	44.75 (6.75)
AST, IU/l, mean (SD)	45.64 (2.33)
PLT x10, mean (SD)	170 (22.41)
FIB-4 score < 1.45 (no fibrosis) 1.45-3.25 (inconclusive) >3.25 (cirrhosis/advanced fibrosis)	 8 (6.1) 4 (3.1) 1 (0.8)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; PLT: platelets; IDU: intravenous drug users; MSM: men who have sex with men; ART: antiretroviral therapy; aspartate aminotransferase.

[a]Two participants were excluded from the calculation because they were enrolled in the study at the time of HIV diagnosis.
[b]Undetectable HIV RNA - HIV RNA < 40 IU/mL.
[c]HBV - active ART (i.e., tenofovir disoproxil, or tenofovir alafenamide).
[d]HBV DNA was detectable in 11 cases.

positive for anti-HDV, whereas all five patients with occult HBV tested negative for anti-HDV. Active HDV infection was confirmed in all five cases positive for anti-HDV, with HDV RNA levels ranging from 229 IU/mL to 4,541,000 IU/mL. (**Table 2**). Two patients were diagnosed with compensated cirrhosis, both of whom had acquired HBV infection perinatally (patients No. 3 and No. 5; **Table 2**). One patient had dual infection (HBV/HDV), whereas four patients had triple infection (HBV/HCV/HDV).

In three of the triple-infected cases, HBV DNA and HCV RNA levels were very low or undetectable. In contrast, the fourth patient demonstrated markedly elevated HBV DNA levels (124,000,000 IU/mL), whereas HDV RNA levels remained low. Testing for tenofovir resistance was not performed at that time. Follow-up evaluation one year later revealed a spontaneous decline in HBV DNA levels to low levels in this patient (patient No. 2, **Table 2**).

Table 2. Characteristics of patients with active HDV infection (n=5).

patient	Sex	age	Ethnicity	FIB-4 score	Presence of cirrhosis	HIV transmission	HBV DNA [IU/mL]	HDV		HCV	
								Ab	RNA [IU/mL]	Ab	RNA [IU/ml]
1.	M	23	Roma	1.13	No	IDU	50	Positive	5406	Positive	ND
2.	M	36	Roma	1.82	No	IDU	124,000,000 (in 2024) 94 (in 2025)	Positive	229	Positive	ND
3.	F	43	Bulgarian	5.31	Yes	Heterosexual	50	Positive	4,541,000 (in 2024) 1,438,000 (in 2025)	Negative	ND
4.	M	46	Roma	2.85	No	IDU	50	Positive	3,427	Negative	ND (in 2024) <50 (in 2025)
5.	M	39	Roma	2.71	Yes	IDU	ND	Positive	3,351,000	Negative	ND (in 2024) <50 (in 2025)

IDU:intravenous drug users; ND: not detected.

Discussion

The present study identified five patients with active HDV infection, two of whom had already progressed to cirrhosis. Both dual (HBV/HDV) and triple infections (HCV/HBV/HDV) were observed. In three patients with triple infection, HDV appeared to inhibit the replication of both HBV and HCV, whereas in the fourth patient, HBV was likely the predominant virus. The study further emphasizes that, despite the declining HBV prevalence due to vaccination, PLWH remain a vulnerable population for HDV, reinforcing the global call for integrated hepatitis and HIV care programs.

The implementation of nationwide neonatal HBV vaccination programs in developed countries, as well as Bulgaria, significantly decreased the prevalence of chronic HBV infection, including among PLWH[16]. Furthermore, the administration of tenofovir-based ART appears to provide an additional layer of protection against acquiring HBV[17]. Despite the recent advancements, HDV infection rates remain high among PLWH. Studies from the EuroSIDA and Swiss HIV cohorts report an overall HDV prevalence of about 15%, which increases to 50% among IDU[3,18]. Recent data from a European cohort with similar clinical settings show a decreased HDV prevalence of 4% among PLWH[19]. Therefore, the European AIDS Clinical Society (EACS) guidelines recommend screening for HDV in PLWH who are also co-infected with HBV[20]. Early detection of HDV improves patient outcomes by facilitating timely counselling, initiating antiviral therapy for HBV, conducting surveillance for HCC, and vaccinating family members against HBV.

Even in settings where HDV testing is available and reimbursed, its implementation in routine practice remains limited, despite its clinical importance. Multiple studies have shown that HDV screening rates in the PLWH population are suboptimal, with 15% to 60% of co-infected individuals not receiving HDV testing[21,22]. To improve HDV detection, the European Association for the Study of the Liver recommends reflex testing strategies. Under this approach, all individuals who test positive for HBsAg are automatically screened for anti-HDV, and if positive, HDV RNA testing is performed on the same blood sample[23]. This integrated strategy increases the efficiency and accessibility of HDV diagnostics, often providing same-day results.

Before this study, none of the patients had been tested for HDV infection. Subsequent screening identified five individuals with active HDV infection, two of whom had already developed cirrhosis. This finding suggests that HDV screening had been significantly delayed, allowing progression to advanced liver disease. Both patients exhibited high HDV RNA levels, a key driver of severe liver disease[24]. Chronic liver inflammation due to perinatally acquired HBV infection, combined with alcohol misuse in one patient, may have contributed to the observed disease severity. Given the increased risk of HCC, these patients should undergo regular ultrasonographic surveillance. Our findings underscore the need for routine HDV screening, consistent with European guidelines, as early detection allows timely antiviral intervention and surveillance for liver-related complications.

Current treatment strategies for HDV infection in PLWH aim to suppress both HBV and HDV replication. Bulevirtide, recently approved by the European Medicines Agency, is the first antiviral agent specifically targeting HDV by blocking viral entry into hepatocytes. Clinical studies have shown good tolerability in PLWH. However, its limited availability in several European countries, including Bulgaria, restricts patient access. Additionally, the optimal duration of bulevirtide therapy remains uncertain[23]. For HBV infection, tenofovir-based ART regimens continue to be the standard of care and were used in all patients included in this study.

Given the limited effectiveness of recent treatments for HDV infection, it is crucial to prioritise preventive strategies against HBV and associated HDV infections. It is essential to maintain a high rate of hepatitis B vaccination among PLWH. However, immunosuppression related to HIV makes it challenging for these individuals to develop immunity to HBV. EACS guidelines recommend administering four double doses of the HBV vaccine[20]. The CpG-adjuvanted vaccine HEPLISAV-B® (HepCpG) may induce faster and stronger immune responses, particularly in individuals who did not respond to older vaccines[25]. In our study, none of the participants showed serological evidence of HBV vaccination. This finding highlights the ongoing gaps between guideline recommendations and their implementation in clinical practice.

Multiple viral infections are common in PLWH due to overlapping transmission routes[26]. In this cohort, four patients had triple infection (HCV/HBV/HDV), and one had dual infection (HBV/HDV). In three of the triple-infected individuals, HDV appeared to be the dominant virus, as shown by higher HDV viral loads and suppressed HBV replication. Previous studies have demonstrated that HDV can suppress HBV replication, supporting the idea of HDV being the dominant virus in HBV–HDV co-infections[27]. Additionally, the absence of detectable HCV RNA may indicate successful viral clearance, a phenomenon previously reported in HBV/HDV co-infection[28].

The interaction between HBV and HDV is dynamic, with alternating phases of viral dominance[29]. Although HDV is usually the dominant pathogen, HBV may predominate in certain circumstances. This shifting dominance may explain the spontaneous decline in HBV DNA observed in one patient in our cohort. Alternatively, treatment adherence or delayed viral clearance might have also contributed to this finding[30]. Identifying the dominant virus is clinically important, as treatment strategies for HBV and HCV differ significantly[31]. Continuous monitoring of viral markers is therefore essential to guide optimal clinical management.

Recent studies suggest that HDV may persist even in the absence of detectable HBsAg and may remain viable for months following liver transplantation, independent of HBV replication[32]. Cases of HDV RNA detection in patients with occult HBV infection have also been reported. Detecting HDV in the absence of HBsAg remains challenging due to genetic variability in HDV antigens and limitations of current diagnostic assays[33]. In the present study, no HDV infection was detected among patients with occult HBV, likely reflecting the limited sample size or population-specific epidemiology, highlighting the need for larger multicentre studies.

This study has several limitations. First, the primary limitation is the small cohort size, which may limit the generalisability of the findings. Second, the assessment of liver fibrosis was limited by available methodologies, such as the FIB-4 score, which may be less reliable in the presence of active inflammation associated with chronic HDV infection. Transient elastography, a more accurate non-invasive method for assessing liver stiffness, was not performed. Additionally, other potential contributors to liver fibrosis, including alcohol consumption, metabolic disorders, and diabetes, were not systematically evaluated. Third, the inclusion of a control group would have allowed for direct comparison and stronger causal inference, but institutional practices limited access to a comparable HIV-negative, HBV-infected cohort. Finally, HDV genotyping was not performed, although genotype 1, which is associated with more severe disease, has recently been reported in Bulgaria[34]. Genotype analysis was not feasible due to the small number of positive samples.

Nonetheless, the current observational study provides unique insights into viral dominance and liver function in PLWH with HBV/HDV co-infection, offering valuable data that contribute to understanding disease dynamics in this population. These findings lay the groundwork for future studies, including matched controls or multicentre cohorts, to further validate and expand upon our observations.

Conclusion

The findings from the present study confirm the aggressive clinical course of HDV infection and emphasize the importance of systematic screening among PLWH who are infected with HBV. The delayed diagnosis of cirrhosis in two patients highlights the critical need for early HDV testing using both anti-HDV antibodies and HDV RNA, particularly in high-risk populations. Timely detection and continuous monitoring of HDV infection are essential for preventing progression to advanced liver disease and improving long-term clinical outcomes

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All authors have read and approved the final version of the manuscript.

Conflict of interest

No commercial, financial, or personal conflicts of interest were identified in relation to the research, authorship, and/or publication of this article.

AI statement

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Original article

Gendered social patterning of cardiometabolic risk: an intersectional analysis using anthropometric and metabolic indices in a large working population

Patrones sociales del riesgo cardiometabólico según el género: un análisis interseccional mediante índices antropométricos y metabólicos en una amplia población trabajadora

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Abstract

Background: Cardiometabolic risk is unevenly distributed across populations, following well-established socioeconomic gradients and sex-based differences. However, less is known about how gendered social structures and intersectional social positions shape these inequalities, particularly when different anthropometric and metabolic indices are used to define risk.

Objective: To examine the gendered social patterning of cardiometabolic risk within an intersectional framework in a large working population, and to assess whether different indices vary in their ability to capture underlying social inequalities.

Methods: A cross-sectional study was conducted among 154,327 working-age adults undergoing routine occupational health assessments. Cardiometabolic risk was defined using multiple anthropometric and metabolic indices, including body mass index (BMI), relative fat mass (RFM), body adiposity index (BAI), a body shape index (ABSI), and METS-VF. Intersectional categories combining sex, educational level, and occupational class were constructed. Multivariable logistic regression models were used to estimate adjusted odds ratios (ORs) and 95% confidence intervals (CIs), controlling for age and lifestyle factors.

Results: A clear socioeconomic gradient in cardiometabolic risk was observed, with prevalence increasing from 21.4% among individuals with higher education to 36.8% among those with primary or no education. Intersectional analyses revealed substantial heterogeneity, with the highest risk among women in manual occupations with low educational attainment (adjusted OR 2.41, 95% CI 2.28–2.55). Although men showed a higher overall prevalence, relative inequalities were more pronounced among women. The magnitude of associations varied across indices, with stronger gradients observed for measures reflecting visceral adiposity, particularly METS-VF (adjusted OR 1.97). A notable degree of misclassification was identified, as individuals classified as being at low risk by BMI were frequently reclassified as high risk by METS-VF, especially among women.

Conclusions: Cardiometabolic risk is strongly patterned by the intersection of gender and socioeconomic position. Inequalities are more pronounced when using indices that capture fat distribution and metabolic dysfunction, whereas reliance on BMI

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alone may underestimate risk in key population subgroups. Integrating intersectional approaches and more sensitive indices may improve the identification of high-risk individuals and inform more equitable prevention strategies.

Keywords: Cardiometabolic diseases. Socioeconomic factors. Gender identity. Obesity. Adiposity. Risk assessment.

Resumen

Introducción: El riesgo cardiometabólico se distribuye de forma desigual en la población, siguiendo gradientes socioeconómicos bien establecidos y diferencias relacionadas con el sexo. Sin embargo, se conoce menos sobre cómo las estructuras sociales de género y las posiciones sociales interseccionales configuran estas desigualdades, especialmente cuando se utilizan distintos índices antropométricos y metabólicos para definir el riesgo.

Objetivo: Examinar el patrón social del riesgo cardiometabólico según el género mediante un enfoque interseccional en una amplia población trabajadora, y evaluar si distintos índices difieren en su capacidad para captar las desigualdades sociales subyacentes.

Métodos: Se realizó un estudio transversal en 154.327 adultos en edad laboral sometidos a reconocimientos de salud laboral rutinarios. El riesgo cardiometabólico se definió mediante múltiples índices antropométricos y metabólicos, incluyendo el índice de masa corporal (IMC), la masa grasa relativa (RFM), el índice de adiposidad corporal (BAI), el índice de forma corporal (ABSI) y el METS-VF. Se construyeron categorías interseccionales combinando sexo, nivel educativo y clase ocupacional. Se utilizaron modelos de regresión logística multivariable para estimar odds ratios (OR) ajustados e intervalos de confianza del 95% (IC 95%), controlando por edad y los factores de estilo de vida.

Resultados: Se observó un claro gradiente socioeconómico en el riesgo cardiometabólico, con una prevalencia que aumentó del 21,4% en individuos con educación superior al 36,8% en aquellos con educación primaria o sin estudios. El análisis interseccional mostró una marcada heterogeneidad, con el mayor riesgo en mujeres en ocupaciones manuales y con bajo nivel educativo (OR ajustada 2,41; IC 95% 2,28–2,55). Aunque los hombres presentaron una mayor prevalencia global, las desigualdades relativas fueron más pronunciadas entre las mujeres. La magnitud de las asociaciones varió según el índice utilizado, siendo mayores para aquellos que reflejan adiposidad visceral, especialmente METS-VF (OR ajustada 1,97). Se observó una importante reclasificación, ya que las personas clasificadas como de bajo riesgo según IMC fueron frecuentemente reclasificadas como de alto riesgo según METS-VF, especialmente en mujeres.

Conclusiones: El riesgo cardiometabólico está fuertemente condicionado por la intersección entre género y posición socioeconómica. Las desigualdades son más pronunciadas cuando se utilizan índices que captan la distribución de la grasa y la disfunción metabólica, mientras que el uso exclusivo del IMC puede infraestimar el riesgo en subgrupos clave de la población. La integración de enfoques interseccionales y de índices más sensibles puede mejorar la identificación de personas con alto riesgo y contribuir al diseño de estrategias de prevención más equitativas.

Palabras clave: Enfermedades cardiometabólicas. Factores socioeconómicos. Identidad de género. Obesidad. Adiposidad. Evaluación del riesgo.

Introduction

Cardiometabolic diseases—including cardiovascular disease, type 2 diabetes, and related metabolic disorders—remain the leading causes of morbidity and mortality worldwide. Rather than arising from a single pathway, these conditions reflect the cumulative effects of multiple interrelated metabolic disturbances, such as excess adiposity, insulin resistance, dyslipidaemia, and low-grade inflammation, which frequently coexist within individuals and reinforce one another over time[1,2]. Despite sustained efforts in prevention and treatment, their global burden has not declined, pointing to the need for a broader understanding of the factors that shape cardiometabolic risk.

A consistent finding across populations is that cardiometabolic risk is unevenly distributed, following a clear socioeconomic gradient. Individuals in more disadvantaged socioeconomic positions—commonly defined by lower educational attainment, manual occupations, or limited access to resources—tend to exhibit a higher prevalence of obesity, metabolic syndrome, and cardiovascular disease[3,4]. These differences are not fully accounted for by lifestyle behaviours alone. Instead, they reflect a more complex interplay between material conditions, psychosocial stressors, environmental exposures, and access to health-promoting resources, all of which operate across the life course.

Alongside these socioeconomic patterns, differences between men and women in cardiometabolic health have long been recognised. Biological factors, including hormonal profiles and fat distribution, undoubtedly play a role[5]. However, focusing exclusively on biological sex provides only a partial explanation. Increasingly, attention has shifted towards

gender—that is, the set of socially constructed roles, expectations, and power relations that shape everyday experiences and opportunities. These gendered dimensions influence health in multiple ways, from occupational trajectories and income stability to caregiving responsibilities and exposure to chronic stress, all of which may ultimately affect cardiometabolic risk[6,7].

In this context, there has been growing interest in moving beyond single-axis analyses to more integrative approaches. The concept of intersectionality offers one such framework, emphasising that social categories such as gender, socioeconomic position, and occupation do not operate in isolation but intersect to produce distinct patterns of advantage and disadvantage[8]. From this perspective, the experience of a woman in a manual occupation may differ substantially from that of a man in a similar job, even when conventional socioeconomic indicators appear comparable. Emerging evidence suggests that these intersecting dimensions can shape cardiovascular risk profiles in ways that are not captured by analyses limited to sex or socioeconomic position alone[9,10].

A related but less explored issue concerns how cardiometabolic risk itself is measured. Body mass index (BMI) remains the most widely used indicator of adiposity, yet its limitations are well documented, particularly its inability to distinguish between fat and lean mass or to reflect fat distribution[11]. In response, alternative indices—such as relative fat mass (RFM), body adiposity index (BAI), and a body shape index (ABSI)—have been proposed, alongside composite metabolic scores that aim to capture underlying metabolic dysfunction more directly[12]. While these measures have shown promise, their performance may not be uniform across population subgroups. Differences by sex, age, and socioeconomic position may influence both their distribution and their ability to identify individuals at higher cardiometabolic risk[13].

Taken together, these considerations highlight several important gaps. First, although sex differences in cardiometabolic risk are well established, fewer studies have explicitly incorporated a gender perspective that accounts for social and structural dimensions. Second, intersectional analyses remain relatively scarce among large working populations, in which occupational and socioeconomic gradients are particularly relevant. Third, it is unclear whether different anthropometric and metabolic indices capture social inequalities in risk consistently or whether their performance varies across gendered social contexts.

Addressing these issues is not merely of theoretical interest. A more nuanced understanding of how gender and social position jointly shape cardiometabolic risk—and how this risk is captured by different measurement approaches—may help identify subgroups that are systematically under-recognised or misclassified. This, in turn, has direct implications for both risk stratification and the design of preventive strategies.

The aim of the present study was therefore to examine the gendered social patterning of cardiometabolic risk using an intersectional framework in a large working population. Specifically, we sought to explore how combinations of sex, socioeconomic position, and occupational characteristics are associated with a range of anthropometric and metabolic indices, and whether these indices differ in their ability to reflect underlying social inequalities in cardiometabolic risk.

Methods

Study design and population

A cross-sectional study was conducted using data from a large cohort of working-age adults who underwent routine occupational health examinations. These assessments are performed periodically as part of workplace health surveillance programmes and include standardized collection of sociodemographic, anthropometric, clinical, and laboratory data. These assessments are performed periodically as part of workplace health surveillance programmes and include the standardised collection of sociodemographic, anthropometric, clinical, and laboratory data. Similar occupational health settings have been used to examine work-related exposures together with anthropometric, blood pressure, and blood-based cardiometabolic biomarkers in large adult populations[14].

Participants aged 18 to 65 years with complete information on key sociodemographic variables and cardiometabolic indicators were eligible for inclusion. Individuals with missing data on the primary exposure or outcome variables were excluded from the analysis. The final analytical sample consisted of all participants who met these criteria.

The study was conducted in accordance with the principles of the Declaration of Helsinki and was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational research[15].

Exposure: intersectional social position

The main exposure was defined using an intersectional framework combining sex, socioeconomic position, and occupational characteristics.

Sex was recorded as male or female. Socioeconomic position was primarily assessed through educational attainment, classified into three categories (higher, intermediate, and primary or no formal education), a widely used and stable indicator of long-term social conditions[16]. Occupational characteristics were derived from job classification codes and grouped into categories reflecting manual and non-manual occupations.

To operationalise intersectionality, combined categories were constructed by crossing sex with educational level and occupational group. This approach allows the identification of distinct social positions that cannot be captured by single variables alone and is consistent with recommended quantitative approaches to intersectional analysis in population health research[17].

Cardiometabolic outcomes

Cardiometabolic risk was assessed using a set of anthropometric and metabolic indices capturing different dimensions of metabolic health.

Anthropometric indicators included body mass index (BMI), calculated as weight in kilograms divided by height in meters squared, and alternative indices such as relative fat mass (RFM), body adiposity index (BAI), and a body shape index (ABSI), which aim to better reflect body fat distribution and composition[12,13].

Metabolic risk was additionally assessed using validated surrogate indices of insulin resistance and cardiometabolic dysfunction, where available. These composite measures have been increasingly used in epidemiological research as they integrate multiple physiological parameters and may better capture underlying metabolic alterations than single markers alone[18].

For the primary analysis, a multidimensional cardiometabolic risk indicator was constructed by combining information across individual indices. Participants were classified as having elevated cardiometabolic risk based on predefined thresholds for each component, consistent with established approaches to risk clustering in epidemiological studies[19].

Covariates

All models were adjusted for age as a continuous variable. Additional covariates included lifestyle factors where available, such as smoking status and physical activity, given their established role in cardiometabolic health and their potential to confound associations between social position and metabolic risk[20].

Statistical analysis

Descriptive analyses were performed to characterise the study population across categories of sex, educational level, and occupational group. Continuous variables were summarised using means and standard deviations, while categorical variables were expressed as frequencies and percentages.

Associations between intersectional social position and cardiometabolic outcomes were examined using multivariable logistic regression models. Odds ratios (ORs) and 95% confidence intervals (95% CI) were estimated, using the most socially advantaged group (men with higher education and non-manual occupations) as the reference category.

To formally assess interaction, multiplicative interaction terms between sex and socioeconomic indicators were included in the models. This approach allows evaluation of whether the association between social position and cardiometabolic risk differs across sex groups[21]. In addition, analyses based on combined intersectional categories were conducted to capture joint effects, as recommended in intersectionality-informed epidemiological research[17].

Model fit and discrimination were assessed using standard diagnostic measures. Sensitivity analyses were performed using alternative definitions of cardiometabolic risk based on individual indices to evaluate the robustness of the findings.

All statistical analyses were conducted using standard statistical software, and a two-sided p-value <0.05 was considered statistically significant.

Results

Study population

A total of 154,327 participants were included in the final analysis after the exclusion of individuals with missing data on key variables. The mean age of the study population was 41.5 ± 10.2 years, and 46.2% were women.

Educational attainment showed a typical distribution for a working population, with 27.8% of participants having higher education, 42.6% having intermediate education, and 29.6% primary or no formal education. Manual occupations accounted for 45.3% of the sample, with a marked gradient across educational levels, being substantially more frequent among individuals with lower educational attainment.

Clear sex differences were observed in occupational distribution. Women were more frequently employed in non-manual occupations, whereas men were predominantly represented in manual jobs. The main

characteristics of the study population are presented in **Table 1**.

Distribution of cardiometabolic indicators

All anthropometric and metabolic indices showed substantial variability across the study population.

Women exhibited higher mean values of indices reflecting total adiposity, including relative fat mass and body adiposity index, whereas men showed higher values for indices associated with central adiposity and metabolic dysfunction.

Across socioeconomic groups, a consistent pattern emerged. Individuals with lower educational attainment and those in manual occupations presented higher levels of adiposity and less favourable metabolic profiles across most indices. This gradient was observed irrespective of the specific measure used, although its magnitude varied depending on the indicator.

Prevalence of elevated cardiometabolic risk

The overall prevalence of elevated cardiometabolic risk was 28.9%.

A clear socioeconomic gradient was observed. The prevalence increased progressively from 21.4% among individuals with higher education to 36.8% among those with primary or no education (p for trend <0.001). Similarly, participants in manual occupations showed a higher prevalence compared with those in non-manual roles.

When stratified by sex, the prevalence of elevated cardiometabolic risk was 31.2% in men and 26.3% in women. However, the relative increase in risk across educational categories was more pronounced among women. **Table 2** shows the association between educational level and cardiometabolic risk. A clear dose–response relationship was observed across educational categories.

Intersectional analysis

The intersectional analysis combining sex, education, and occupation revealed substantial heterogeneity in cardiometabolic risk across social groups.

Compared with the reference group (men with higher education in non-manual occupations), individuals in more disadvantaged positions showed markedly

Table 1. Baseline characteristics of the study population according to sex.

Variable	Total (N=154,327)	Men (n=83,054)	Women (n=71,273)	p-value
Age (years), mean ± SD	41.5 ± 10.2	42.3 ± 10.1	40.6 ± 10.3	<0.001
Educational level (%)				<0.001
◦ Higher education	27.8	25.1	30.9	
◦ Intermediate education	42.6	43.2	41.9	
◦ Primary/no education	29.6	31.7	27.2	
Occupational category (%)				<0.001
◦ Non-manual	54.7	42.2	68.6	
◦ Manual	45.3	57.8	31.4	
Cardiometabolic risk (%)	28.9	31.2	26.3	<0.001

Values are presented as mean ± standard deviation (SD) or percentages.

P-values were calculated using Student's t-test for continuous variables and chi-square test for categorical variables.

Table 2. Association between educational level and cardiometabolic risk.

Educational level	Prevalence (%)	Crude OR (95% CI)	Adjusted OR* (95% CI)
Higher education	21.4	1.00 (reference)	1.00 (reference)
Intermediate education	28.7	1.47 (1.42–1.52)	1.32 (1.27–1.37)
Primary/no education	36.8	2.13 (2.05–2.21)	1.84 (1.77–1.92)
p for trend	<0.001	<0.001	<0.001

OR: odds ratio; CI: confidence interval.

Adjusted for age, smoking status, and physical activity.

higher odds of elevated cardiometabolic risk. The highest risk was observed among women with primary education in manual occupations (adjusted OR 2.41, 95% CI 2.28–2.55), followed by men in the same socioeconomic position (adjusted OR 2.12, 95% CI 2.01–2.24).

Women with intermediate education in manual occupations also showed a significantly higher risk, whereas women with higher education in non-manual occupations had risk levels comparable to or slightly lower than those of the reference group.

Marked differences were observed across intersectional groups, with a clear gradient across the combined categories of sex, education, and occupation.

These findings indicate that the joint effects of gender and socioeconomic position are not merely additive but reflect more complex patterns of social stratification. The joint effects of sex, educational level, and occupational category on cardiometabolic risk are shown in **Table 3**.

Multivariable analysis

In multivariable logistic regression models adjusted for age and lifestyle factors, socioeconomic position remained independently associated with cardiometabolic risk.

Compared with individuals with higher education, those with intermediate education had increased odds of elevated risk (adjusted OR 1.32, 95% CI 1.27–1.37), while those with primary or no education showed substantially higher odds (adjusted OR 1.84, 95% CI 1.77–1.92). Manual occupation was also independently associated with increased risk (adjusted OR 1.41, 95% CI 1.36–1.46).

A statistically significant interaction between sex and educational level was observed (p for interaction <0.001), indicating that the association between lower socioeconomic position and cardiometabolic risk was stronger among women than men.

Comparison across cardiometabolic indices

The magnitude of socioeconomic inequalities varied depending on the index used to define cardiometabolic risk.

BMI-based definitions showed a clear gradient (adjusted OR for low vs high education 1.61, 95% CI 1.54–1.69). However, indices incorporating body fat distribution or metabolic parameters showed stronger associations. Relative fat mass and indices reflecting visceral adiposity such as METS-VF exhibited the largest gradients (adjusted ORs approaching 1.9–2.0), whereas ABSI showed a weaker but still significant association.

Sex-specific patterns were also evident. Indices reflecting total adiposity showed stronger gradients among women, whereas indices related to central adiposity showed more consistent patterns across both sexes. Comparative results across indices are presented in **Table 4** and illustrated in **Figure 1**.

Table 3. Association between intersectional social position and cardiometabolic risk.

Sex	Educational level	Occupation	Prevalence (%)	Adjusted OR (95% CI)
Men	Higher	Non-manual	20.8	1.00 (reference)
Men	Higher	Manual	24.7	1.21 (1.14–1.29)
Men	Intermediate	Non-manual	26.3	1.34 (1.26–1.42)
Men	Intermediate	Manual	31.8	1.68 (1.59–1.78)
Men	Primary	Non-manual	30.4	1.72 (1.63–1.82)
Men	Primary	Manual	35.9	2.12 (2.01–2.24)
Women	Higher	Non-manual	18.9	0.92 (0.87–0.98)
Women	Higher	Manual	22.6	1.14 (1.06–1.23)
Women	Intermediate	Non-manual	24.1	1.28 (1.20–1.36)
Women	Intermediate	Manual	30.7	1.78 (1.68–1.89)
Women	Primary	Non-manual	32.1	1.88 (1.78–1.99)
Women	Primary	Manual	38.7	2.41 (2.28–2.55)

OR: odds ratio; CI: confidence interval.

Adjusted for age, smoking status, and physical activity.

Table 4. Association between educational level and cardiometabolic risk according to different indices.

Index	Prevalence (%)	Adjusted OR (95% CI)*
BMI-defined risk	24.5	1.61 (1.54–1.69)
RFM-defined risk	27.8	1.88 (1.79–1.97)
BAI-defined risk	26.1	1.76 (1.68–1.85)
ABSI-defined risk	18.3	1.29 (1.23–1.35)
METS-VF-defined risk	30.2	1.97 (1.87–2.07)

OR: odds ratio; CI: confidence interval.

*Adjusted for age, smoking status, and physical activity.

Odds ratios correspond to the comparison between primary/no education and higher education.

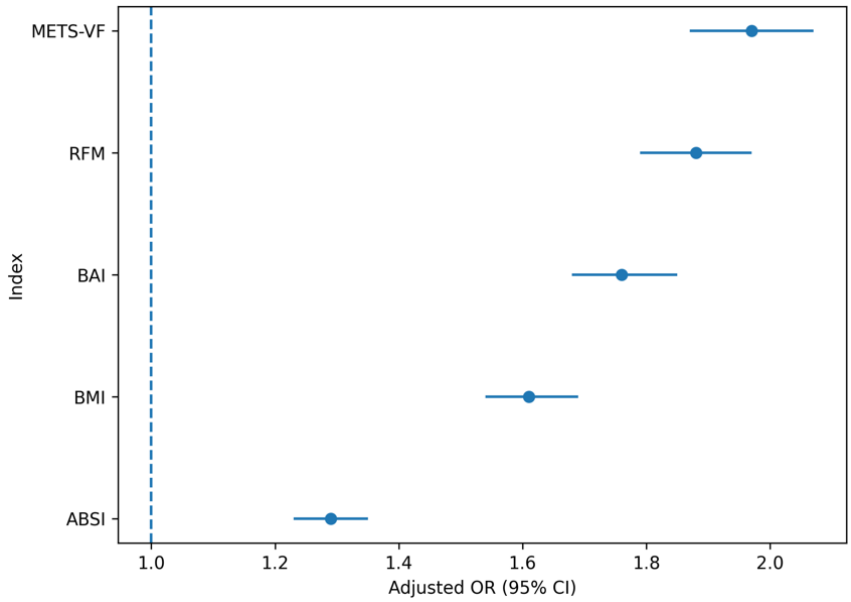

Figure 1. Association between educational level and cardiometabolic risk according to different indices.

Adjusted odds ratios (ORs) for cardiometabolic risk comparing individuals with primary/no education versus higher education according to different indices. Indices reflecting visceral adiposity and metabolic dysfunction showed stronger socioeconomic gradients compared with BMI.

Component-specific analyses

To better characterise the observed inequalities, additional analyses were conducted using individual cardiometabolic components.

A consistent socioeconomic gradient was observed across all indicators, although its magnitude varied. The strongest associations were observed for indices reflecting visceral and total adiposity, particularly METS-VF (adjusted OR 1.97) and relative fat mass (adjusted OR 1.88), whereas BMI showed more moderate gradients (adjusted OR 1.61). ABSI exhibited the weakest association (adjusted OR 1.29), although still statistically significant.

These findings indicate that different indicators capture distinct dimensions of cardiometabolic risk and vary in their sensitivity to underlying social inequalities.

Sex-stratified analyses

When analyses were stratified by sex, clear differences emerged in the magnitude of socioeconomic inequalities.

Among women, the association between lower educational attainment and cardiometabolic risk was stronger than among men. Women with primary education showed markedly higher odds of risk (adjusted OR approaching 2.0) compared with those with higher education, whereas the corresponding increase among men was more moderate (adjusted OR approximately 1.6–1.7 across indices).

Despite men presenting a higher overall prevalence of cardiometabolic risk, the relative socioeconomic gradient was consistently steeper among women across most indices. These patterns were observed for both adiposity-based and visceral fat indicators.

Misclassification across indices

To assess potential differences in risk classification across indices, we examined the agreement between BMI-defined risk and METS-VF-defined risk.

A substantial proportion of individuals classified as low risk according to BMI were identified as having elevated cardiometabolic risk when using METS-VF. This discordance suggests that BMI may underestimate cardiometabolic risk, particularly in individuals with higher levels of visceral adiposity.

Conversely, fewer individuals classified as high risk by BMI were reclassified as low risk when using METS-VF, suggesting that BMI-based definitions are less likely to overestimate risk.

This pattern of misclassification was more pronounced among women, consistent with the stronger gradients observed for indices reflecting visceral adiposity.

Overall, these findings highlight the limitations of BMI as a standalone measure and underscore the importance of incorporating alternative indices that better capture fat distribution and underlying metabolic risk.

This discordance is illustrated in **Figure 2**.

Sensitivity analyses

Sensitivity analyses using alternative definitions of cardiometabolic risk yielded consistent results. The direction and magnitude of associations remained stable when individual indices were analysed separately and when models were adjusted for additional covariates.

Stratified analyses by age group also showed similar patterns, with no evidence of substantial deviation from the main findings. These results support the robustness of the observed associations.

Discussion

Principal findings

In this large working population, cardiometabolic risk followed a clear and consistent social gradient, further shaped by gender and occupational context. Using an intersectional framework, we observed substantial heterogeneity across social groups, with the highest levels of cardiometabolic risk among women in manual occupations with low educational attainment. While men exhibited a higher overall prevalence of risk, the relative socioeconomic gradient was consistently steeper among women, indicating a differential impact of social disadvantage.

In addition, the magnitude of these inequalities varied depending on the cardiometabolic index used. Indices reflecting visceral adiposity, such as METS-VF, showed stronger gradients compared with BMI. A notable degree of misclassification was observed

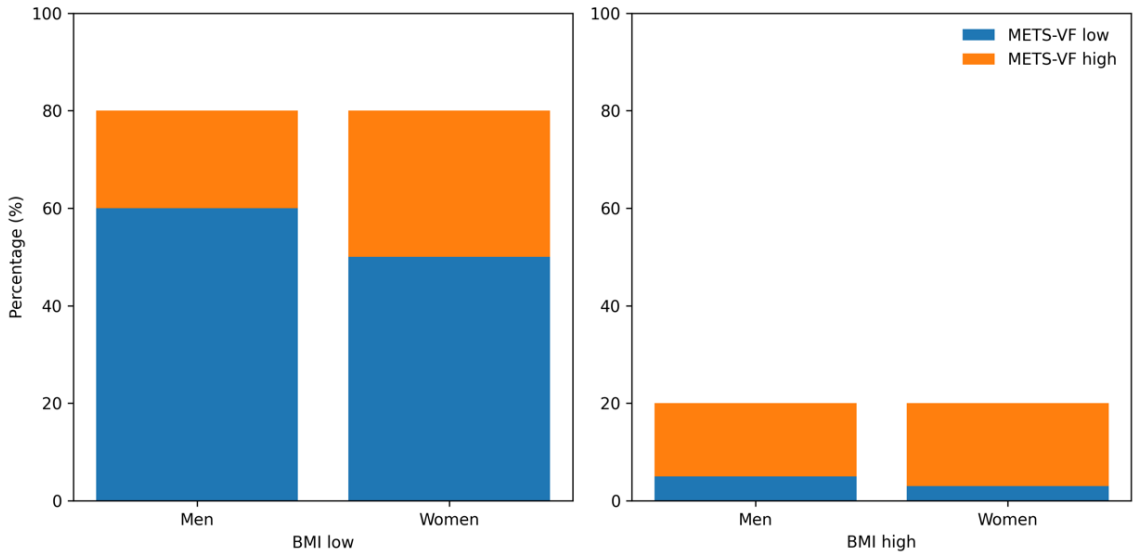

Figure 2. Discordance in cardiometabolic risk classification between BMI and METS-VF stratified by sex. Proportion of individuals classified as low or high cardiometabolic risk according to BMI and METS-VF. A higher proportion of women classified as low risk by BMI were reclassified as high risk when using METS-VF, indicating potential underestimation of risk when relying on BMI alone.

when comparing BMI with METS-VF, particularly among women, suggesting that conventional measures may underestimate risk in specific population subgroups.

Interpretation of findings

These findings reinforce the notion that cardiometabolic risk is not uniformly distributed but is structured by the interaction of social and biological dimensions. The stronger gradients observed among women may reflect the cumulative effects of gendered social roles, occupational segregation, and differential exposure to psychosocial stressors, which have been shown to influence cardiometabolic health through multiple pathways[22,23].

The observed differences across indices highlight the importance of measurement choice. While BMI remains widely used, it does not adequately capture fat distribution, particularly visceral adiposity, which is more strongly associated with metabolic dysfunction[24]. The stronger associations observed for METS-VF and RFM suggest that indices incorporating fat distribution may be more sensitive to underlying social inequalities.

The misclassification analysis further supports this interpretation. The identification of individuals classified as low risk by BMI but high risk by METS-VF indicates that reliance on BMI alone may lead to systematic underestimation of cardiometabolic risk. This is particularly relevant in women, among whom fat distribution patterns differ and may not be adequately reflected by BMI-based thresholds[25].

Socioeconomic inequalities and cardiometabolic risk

Our results are consistent with a large body of evidence demonstrating that socioeconomic position is a key determinant of cardiometabolic health. Lower educational attainment was associated with higher risk across all analyses, including both individual indices and intersectional categories. Importantly, these associations persisted after adjustment for lifestyle factors, suggesting that behavioural explanations alone are insufficient to account for observed inequalities.

These findings support the role of structural determinants—such as working conditions, income insecurity, and social environments—in shaping cardiometabolic risk[26,27]. Socioeconomic disadvantage is known to operate across the life course, contributing to the accumulation of metabolic risk through chronic stress, reduced access to health-promoting resources, and adverse environmental exposures[28].

Comparison with previous studies

Previous studies have identified socioeconomic gradients in cardiometabolic risk and have highlighted the role of social determinants in shaping disease distribution[22,29]. More recent research has also emphasised the importance of considering multidimensional and clustered representations of cardiometabolic risk, including latent phenotypes and multimorbidity patterns[30,31].

However, relatively few studies have combined an intersectional approach with the use of multiple cardiometabolic indices. By integrating these perspectives, the present study extends existing knowledge and provides a more nuanced understanding of how social inequalities are reflected in different dimensions of cardiometabolic risk.

Strengths and limitations

This study has several strengths. The large sample size and the use of a real-world working population enhance the robustness and generalisability of the findings within similar contexts. The simultaneous evaluation of multiple anthropometric and metabolic indices allowed for a comprehensive assessment of cardiometabolic risk. In addition, the use of an intersectional framework provides a more detailed understanding of how gender and socioeconomic position jointly shape health outcomes.

Nevertheless, some limitations should be acknowledged. The cross-sectional design precludes causal inference and limits the ability to assess temporal relationships. Residual confounding cannot be excluded, despite adjustment for key covariates. Furthermore, the use of surrogate indices rather than direct measures of body composition may introduce some degree of measurement error. Finally, the study population consists of employed individuals, which may limit generalisability to more disadvantaged populations.

Public health and clinical implications

The findings of this study have important implications for both public health and clinical practice. First, they highlight the need to incorporate social determinants and gender perspectives into cardiometabolic risk assessment. Second, they suggest that reliance on BMI alone may be insufficient to identify high-risk individuals, particularly in socially disadvantaged groups.

The use of indices that better capture visceral adiposity may improve risk stratification and help identify individuals who would otherwise remain undetected. From a public health perspective, interventions aimed

at reducing cardiometabolic risk should address not only individual behaviours but also the broader social and structural factors that shape health inequalities[26,32].

Conclusions

In conclusion, cardiometabolic risk is strongly patterned by the intersection of gender and socioeconomic position. Inequalities are more pronounced when using indices that capture visceral adiposity, and conventional measures such as BMI may underestimate risk in key population subgroups. These findings underscore the importance of integrating social context and measurement considerations in the assessment and prevention of cardiometabolic disease.

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Author contributions

Conceptualization: A.C.R.A; A.L.C-A and N.M.S.; Data collection and analysis: M.L.L; and D.G.C; Data curation: D.G.C; C.T.C. Methodology: A.C.R.A; A.L.C-A; C.T.C. Validation: G.V.S.; Formal analysis: A.C.R.A; A.L.C-A; Investigation G.V.S; Draft: A.C.R.A; A.L.C-A; M.L.L., G.V.S., and; Revision: N.M.S.; D.G.C; and G.V.S All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare that they have no conflicts of interest related to this work.

Ethics statement

The study was conducted in accordance with established ethical standards for biomedical research and adhered to the principles of the Declaration of Helsinki. All participants were informed about the study objectives and procedures and provided written informed consent prior to enrolment. The study protocol was reviewed and approved by the Ethics Committee of the Balearic Islands (Comité de Ética de la Investigación de las Islas Baleares, CEI-IB; reference IB 4383/20; approval date: 26 November 2020).

Data protection

All data were anonymised prior to analysis to ensure participant confidentiality. Data processing complied with the Spanish Organic Law 3/2018 on the Protection of Personal Data and Guarantee of Digital Rights, as well as with the European Union General Data Protection Regulation (EU 2016/679).

Data availability

The datasets supporting the findings of this study are held at ADEMA University School and are available from the corresponding author upon reasonable request, in accordance with applicable data protection and privacy regulations.

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Original article

Behavioral procrastination and metabolic syndrome in a large occupational cohort

Procrastinación conductual y síndrome metabólico en una gran cohorte ocupacional

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Abstract

Background: Behavioral procrastination has traditionally been considered a psychological construct related to self-regulatory failure and maladaptive coping behaviors. However, growing evidence suggests that procrastination may also influence physical health through unhealthy lifestyle patterns, chronic stress exposure, and impaired behavioral regulation. Nevertheless, the relationship between procrastination and objectively assessed cardiometabolic disease remains insufficiently explored.

Objective: To evaluate the association between behavioral procrastination and metabolic syndrome in a large occupational cohort of Spanish workers.

Methods: A cross-sectional study was conducted in 92,184 active workers undergoing routine occupational health assessments between 2021 and 2024. Behavioral procrastination was evaluated using the PPS-9 questionnaire and categorized into very low, moderate, high, and very high/chronic procrastination levels. Metabolic syndrome was defined according to harmonized international criteria. Anthropometric, clinical, biochemical, and lifestyle-related variables were analyzed. Logistic regression models were constructed to assess the independent association between procrastination and metabolic syndrome after adjustment for demographic, behavioral, and adiposity-related variables.

Results: Higher behavioral procrastination levels were consistently associated with a markedly less favorable cardiometabolic profile, including higher body mass index, waist circumference, blood pressure, fasting glucose, triglycerides, TyG index, and estimated heart age (all $p < 0.001$). The prevalence of metabolic syndrome increased progressively across procrastination categories, ranging from 0.1% in participants with very low procrastination to 34.6% in those with very high/chronic procrastination according to IDF criteria. In fully adjusted models including age, sex, smoking status, physical activity, dietary habits, educational level, and BMI, behavioral procrastination remained independently associated with metabolic syndrome. Compared with participants with very low procrastination, adjusted odds ratios were 5.87 (95% CI 3.99–8.63) for moderate procrastination, 12.35 (95% CI 8.34–18.29) for high procrastination, and 22.97 (95% CI 15.29–34.52) for very high/chronic procrastination (all $p < 0.001$). A significant dose-response relationship was observed across the full spectrum of procrastination scores.

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Conclusions: Behavioral procrastination was strongly and independently associated with metabolic syndrome and adverse cardiometabolic profiles in this large occupational cohort. The observed dose-response relationship and the persistence of the association after extensive adjustment suggest that procrastination may represent a relevant behavioral marker of cardiometabolic vulnerability. Future longitudinal studies are needed to clarify potential causal mechanisms and evaluate whether behavioral interventions targeting procrastination may contribute to cardiometabolic prevention strategies.

Keywords: Metabolic syndrome. Procrastination. Cardiovascular risk factors. Occupational health. Health behavior. Psychological stress.

Resumen

Introducción: La procrastinación conductual ha sido tradicionalmente considerada un constructo psicológico relacionado con el fracaso de la autorregulación y con estrategias desadaptativas de afrontamiento. Sin embargo, la evidencia reciente sugiere que la procrastinación podría influir también sobre la salud física mediante patrones de vida poco saludables, exposición crónica al estrés y alteraciones en la regulación conductual. No obstante, la relación entre procrastinación y las enfermedades cardiometabólicas objetivamente continúa siendo escasamente estudiada.

Objetivo: Evaluar la asociación entre la procrastinación conductual y el síndrome metabólico en una gran cohorte ocupacional de trabajadores españoles.

Métodos: Se realizó un estudio transversal en 92.184 trabajadores activos sometidos a reconocimientos médicos laborales rutinarios entre 2021 y 2024. La procrastinación conductual se evaluó mediante el cuestionario PPS-9 y se clasificó en niveles de procrastinación muy baja, moderada, alta y muy alta/crónica. El síndrome metabólico se definió según criterios internacionales armonizados. Se analizaron variables antropométricas, clínicas, bioquímicas y relacionadas con el estilo de vida. Se construyeron modelos de regresión logística para evaluar la asociación independiente entre procrastinación y síndrome metabólico tras ajustar por variables demográficas, conductuales y relacionadas con adiposidad.

Resultados: Los niveles más elevados de procrastinación conductual se asociaron de forma consistente con un perfil cardiometabólico significativamente más desfavorable, incluyendo mayores valores de índice de masa corporal, perímetro abdominal, presión arterial, glucosa basal, triglicéridos, índice TyG y edad cardíaca estimada (todos p < 0,001). La prevalencia de síndrome metabólico aumentó progresivamente a través de las categorías de procrastinación, desde el 0,1% en participantes con procrastinación muy baja hasta el 34,6% en aquellos con procrastinación muy alta/crónica según los criterios de IDF. En los modelos completamente ajustados por edad, sexo, tabaquismo, actividad física, hábitos dietéticos, nivel educativo e IMC, la procrastinación conductual permaneció independientemente asociada con síndrome metabólico. En comparación con los participantes con procrastinación muy baja, las odds ratios ajustadas fueron 5,87 (IC95%: 3,99–8,63) para procrastinación moderada, 12,35 (IC95%: 8,34–18,29) para la procrastinación alta y 22,97 (IC95%: 15,29–34,52) para procrastinación muy alta/crónica (todos p < 0,001). Se observó además una clara relación dosis-respuesta en todo el espectro de puntuaciones PPS-9.

Conclusiones: La procrastinación conductual se asoció de forma sólida e independiente con síndrome metabólico y con un perfil cardiometabólico adverso en esta gran cohorte ocupacional. La relación dosis-respuesta observada y la persistencia de la asociación tras amplios ajustes sugieren que la procrastinación podría representar un marcador conductual relevante de vulnerabilidad cardiometabólica. Son necesarios futuros estudios longitudinales que permitan aclarar los posibles mecanismos causales y evaluar si intervenciones dirigidas a reducir la procrastinación podrían contribuir a estrategias preventivas cardiometabólicas.

Palabras clave: Síndrome metabólico. Procrastinación. Factores de riesgo cardiovascular. Salud laboral. Conducta de salud. Estrés psicológico.

Introduction

Metabolic syndrome (MetS) represents one of the most important public health challenges worldwide because of its high prevalence and its close association with cardiovascular disease, type 2 diabetes mellitus, chronic kidney disease, and premature mortality[1,2]. The syndrome encompasses a cluster of interrelated cardiometabolic abnormalities, including central obesity, hypertension, dyslipidemia, and impaired glucose metabolism, which collectively increase vascular risk beyond the effect of each component individually[3]. Over recent decades, the global rise in sedentary lifestyles, unhealthy dietary patterns, psychosocial stress, and obesity has contributed to a substantial increase in the prevalence of MetS across both developed and developing countries[4,5]. In occupational populations, these trends are especially concerning because cardiometabolic disorders contribute significantly to absenteeism, reduced productivity, disability, and healthcare expenditures[6].

Traditionally, research on MetS has focused on biological and lifestyle determinants such as obesity, physical inactivity, smoking, alcohol consumption, and dietary habits[7,8]. However, growing evidence

suggests that psychological and behavioral factors may also play an important role in the development and maintenance of cardiometabolic dysfunction[9]. In this context, increasing attention has been directed toward the influence of self-regulation processes and health-related behaviors on long-term metabolic health[10].

Procrastination is commonly defined as the voluntary delay of an intended course of action despite expecting negative consequences resulting from the delay[11]. Although historically considered mainly an academic or personality-related phenomenon, procrastination is now increasingly recognized as a complex self-regulatory failure associated with maladaptive coping strategies, impaired emotional regulation, and unhealthy behavioral patterns[12,13]. Contemporary models conceptualize procrastination not simply as poor time management, but rather as a behavioral manifestation of difficulties in self-control and goal-directed behavior[14].

Recent studies have shown that procrastination is associated with several adverse health outcomes, including higher levels of stress, anxiety, depression, sleep disturbances, physical inactivity, and poorer general health perceptions[15-17]. Moreover, procrastination has been linked to delayed healthcare-seeking behaviors, lower adherence to preventive measures, and reduced engagement in healthy lifestyles[18]. These mechanisms are particularly relevant in the context of cardiometabolic disease because sustained unhealthy behaviors and chronic stress exposure are well-established contributors to metabolic dysfunction and vascular injury[19].

The "procrastination-health model" proposed by Sirois and colleagues suggests that procrastination may adversely affect health through two principal pathways: increased stress and poorer health behaviors[20]. Individuals with high levels of procrastination often report lower participation in physical activity, poorer sleep quality, unhealthy dietary patterns, and greater behavioral disengagement when facing demanding situations[16,20]. Such behavioral profiles may contribute over time to obesity, insulin resistance, hypertension, and systemic metabolic dysregulation. Supporting this hypothesis, previous evidence has demonstrated associations between trait procrastination and hypertension or cardiovascular disease, even after adjustment for demographic and personality-related variables[21].

Despite growing interest in the health consequences of procrastination, most available studies have focused predominantly on mental health outcomes or academic populations[15,16]. Research specifically examining the relationship between procrastination and objective cardiometabolic outcomes remains scarce. Furthermore, many previous investigations have been limited by relatively small sample sizes, restricted age ranges, and insufficient control of relevant confounding factors[15,21]. Consequently, the potential role of behavioral procrastination as a marker of cardiometabolic vulnerability in adult working populations remains insufficiently explored.

Occupational cohorts provide a particularly valuable framework for studying these associations because they include large populations of active adults exposed to heterogeneous socioeconomic, behavioral, and psychosocial conditions. In addition, workplace health assessments frequently incorporate standardized anthropometric, clinical, and biochemical measurements, enabling comprehensive characterization of cardiometabolic risk profiles[22]. Understanding whether behavioral procrastination is associated with MetS in occupational settings could contribute to identifying novel behavioral markers linked to cardiovascular prevention and health promotion strategies.

Accordingly, the aim of the present study was to evaluate the association between behavioral procrastination and metabolic syndrome in a large occupational cohort of adult workers. We hypothesized that higher levels of behavioral procrastination would be associated with a greater prevalence of MetS and unfavorable cardiometabolic profiles independently of major sociodemographic and lifestyle-related factors.

Methods

Study design and population

A cross-sectional study was conducted in a large occupational cohort composed of active workers undergoing routine occupational health evaluations between January 2021 and December 2024 in different regions of Spain. Occupational medical examinations were performed as part of standardized workplace health surveillance programs in accordance with Spanish occupational health regulations.

The study population initially included 94,327 workers from diverse economic sectors, including industry, construction, transportation, healthcare, administration, hospitality, and services. After exclusion of participants with incomplete anthropometric, biochemical, or behavioral information, the final analytical sample comprised 92,184 subjects aged between 18 and 69 years.

All participants provided informed consent prior to assessment. Data were anonymized before analysis to ensure confidentiality and compliance with

national and international ethical standards for biomedical research involving human subjects. The study protocol followed the principles established in the Declaration of Helsinki and complied with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations for observational research[23,24].

Clinical and anthropometric assessment

Anthropometric and clinical evaluations were performed by trained occupational health professionals following standardized procedures. Body weight and height were measured with participants wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m²). Waist circumference was measured midway between the lower rib margin and the iliac crest using a non-elastic measuring tape according to international recommendations[25].

Blood pressure was measured in the seated position after a minimum 5-minute rest period using validated automatic sphygmomanometers. Two measurements were obtained, and the average value was used for analysis. Hypertension was defined according to current European Society of Cardiology and European Society of Hypertension guidelines[26].

Venous blood samples were collected after overnight fasting. Biochemical analyses included fasting plasma glucose, triglycerides, total cholesterol, and high-density lipoprotein cholesterol (HDL-C). Laboratory determinations were performed in certified clinical laboratories using standardized automated methods.

Assessment of behavioral procrastination

Behavioral procrastination was assessed using the PPS-9 Procrastination Questionnaire, a brief self-administered instrument designed to evaluate habitual procrastination behaviors across different daily contexts. The questionnaire consists of nine items scored on a five-point Likert scale ranging from 1 ("strongly disagree") to 5 ("strongly agree"), with total scores ranging from 9 to 45 points. Higher scores indicate greater levels of behavioral procrastination. The PPS-9 has shown adequate psychometric properties in Spanish adult populations and constitutes a valid instrument for assessing generalized behavioral procrastination beyond student populations[27].

Based on the predefined questionnaire interpretation criteria, participants were categorized into four groups: very low/absent procrastination (9–17 points), moderate procrastination (18–26 points), high procrastination (27–35 points), and very high/chronic procrastination (36–45 points). In addition, procrastination scores were analyzed as a continuous variable in multivariate models.

Definition of metabolic syndrome

Metabolic syndrome was defined according to the harmonized criteria proposed by the International Diabetes Federation, the American Heart Association, and other international scientific societies[3]. Participants were considered to have MetS when at least three of the following criteria were present:

1. Increased waist circumference according to European population cut-off values;
2. Triglycerides ≥150 mg/dL or specific treatment for hypertriglyceridemia;
3. HDL-C <40 mg/dL in men or <50 mg/dL in women;
4. Blood pressure ≥130/85 mmHg or antihypertensive treatment;
5. Fasting plasma glucose ≥100 mg/dL or antidiabetic treatment.

Lifestyle and sociodemographic variables

Information regarding smoking habits, physical activity, dietary patterns, educational level, and occupational category was collected using standardized health questionnaires administered during occupational examinations.

Physical activity was assessed using the International Physical Activity Questionnaire (IPAQ), a validated instrument for measuring habitual physical activity levels[28]. Dietary habits were evaluated using the Mediterranean Diet Adherence Screener (MEDAS), a validated questionnaire developed within the PREDIMED study to assess adherence to the Mediterranean diet[29].

Smoking status was categorized as current smoker, former smoker, or never smoker. Physical activity was evaluated according to regular participation in moderate or vigorous exercise during leisure time. Adherence to healthy dietary patterns was assessed using routine nutritional screening questions incorporated into occupational health protocols.

Educational level was classified into primary, secondary, or university education.

Statistical analysis

Continuous variables are presented as mean ± standard deviation, whereas categorical variables are expressed as absolute frequencies and percentages.

Comparisons between procrastination categories were performed using analysis of variance (ANOVA) for continuous variables and chi-square tests for categorical variables.

The association between behavioral procrastination and metabolic syndrome was evaluated using logistic regression models. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated for the presence of MetS according to procrastination categories.

Three sequential models were constructed:

- Model 1: unadjusted analysis;
- Model 2: adjusted for age and sex;
- Model 3: additionally adjusted for smoking status, physical activity, dietary habits, educational level, and BMI where appropriate.

Trend analyses across procrastination categories were also performed. Potential multicollinearity among covariates was assessed before inclusion in regression models.

A two-tailed p-value <0.05 was considered statistically significant. Statistical analyses were conducted using IBM SPSS Statistics version 30.0 (IBM Corp., Armonk, NY, USA).

Results

Study population

The final study population included 92,184 active workers, of whom 55,444 were men (60.1%) and 36,740 were women (39.9%). The mean age of the cohort was 39.6 ± 10.3 years. According to PPS-9 categories, 18,829 participants (20.4%) had very low/absent procrastination, 41,122 (44.6%) had moderate procrastination, 26,818 (29.1%) had high procrastination, and 5,415 (5.9%) had very high/chronic procrastination.

Table 1 summarizes the baseline demographic, anthropometric, clinical, biochemical, and lifestyle characteristics of the study population according to behavioral procrastination category.

Higher levels of behavioral procrastination were consistently associated with a less favorable cardiometabolic profile, including older age, higher adiposity indices, elevated blood pressure, poorer glycemic and lipid parameters, lower levels of physical activity, and less healthy dietary habits. A clear dose-response relationship was observed across all procrastination categories (all p < 0.001).

Participants with higher procrastination levels showed a progressively older age profile and a more

Table 1. Baseline characteristics of the study population according to behavioral procrastination category.

Variable	Very low procrastination (9–17) n=18,829	Moderate procrastination (18–26) n=41,122	High procrastination (27–35) n=26,818	Very high procrastination (36–45) n=5,415	p-value
Age, years	33.0 ± 6.5	38.4 ± 8.2	44.8 ± 9.1	56.4 ± 5.7	<0.001
Male sex, n (%)	10,644 (56.5)	24,980 (60.7)	16,615 (61.9)	3,205 (59.2)	<0.001
BMI, kg/m²	22.3 ± 1.8	24.9 ± 3.2	27.6 ± 4.1	31.0 ± 4.6	<0.001
Waist circumference, cm	75.2 ± 7.6	82.6 ± 9.1	87.8 ± 10.2	91.5 ± 11.2	<0.001
Systolic BP, mmHg	113.0 ± 12.5	118.8 ± 13.6	125.7 ± 15.7	134.6 ± 18.2	<0.001
Diastolic BP, mmHg	71.5 ± 8.3	75.9 ± 9.1	80.6 ± 10.4	86.9 ± 11.7	<0.001
Fasting glucose, mg/dL	82.6 ± 10.5	86.9 ± 11.8	90.8 ± 13.9	95.6 ± 15.3	<0.001
Triglycerides, mg/dL	80.3 ± 42.5	103.8 ± 57.1	126.4 ± 71.5	154.5 ± 96.7	<0.001
HDL-cholesterol, mg/dL	55.6 ± 6.9	52.4 ± 7.1	49.7 ± 7.3	46.8 ± 7.5	<0.001
TyG index	8.00 ± 0.46	8.28 ± 0.49	8.49 ± 0.53	8.75 ± 0.57	<0.001
Estimated heart age, years	29.9 ± 8.9	39.4 ± 9.8	52.7 ± 10.4	70.4 ± 7.7	<0.001
Current smokers, n (%)	1,128 (6.0)	18,028 (43.9)	12,256 (45.7)	2,307 (42.6)	<0.001
Regular physical activity, n (%)	15,969 (84.8)	19,487 (47.4)	6,595 (24.6)	520 (9.6)	<0.001
Healthy dietary habits, n (%)	14,744 (78.3)	17,270 (42.0)	6,783 (25.3)	514 (9.5)	<0.001

BMI: body mass index; BP: blood pressure; HDL: high-density lipoprotein; TyG: triglyceride-glucose index.

Data are presented as mean ± standard deviation or number (%).

adverse cardiometabolic phenotype. Mean age increased from 33.0 ± 6.5 years in the very low procrastination group to 56.4 ± 5.7 years in the very high procrastination group. A similar graded pattern was observed for BMI, waist circumference, blood pressure, fasting glucose, triglycerides, and insulin-resistance-related indices.

Mean BMI increased from 22.3 ± 1.8 kg/m² in the very low procrastination group to 31.0 ± 4.6 kg/m² in the very high group. Waist circumference rose from 75.2 ± 7.6 cm to 91.5 ± 11.2 cm, systolic blood pressure from 113.0 ± 12.5 mmHg to 134.6 ± 18.2 mmHg, and fasting glucose from 82.6 ± 10.5 mg/dL to 95.6 ± 15.3 mg/dL across the same categories.

A clear worsening of lipid-related variables was also observed. Triglyceride concentrations increased from 80.3 ± 42.5 mg/dL to 154.5 ± 96.7 mg/dL, whereas HDL-cholesterol decreased from 55.6 ± 6.9 mg/dL to 46.8 ± 7.5 mg/dL. The TyG index increased progressively from 8.00 ± 0.46 to 8.75 ± 0.57, and estimated heart age rose from 29.9 ± 8.9 years to 70.4 ± 7.7 years.

Lifestyle characteristics

Health-related behaviors also differed markedly across procrastination categories. Regular physical exercise was reported by 84.8% of participants with very low procrastination, compared with only 9.6% of those with very high procrastination. A similar gradient was observed for healthy dietary habits, which decreased from 78.3% to 9.5% across the same categories.

Current smoking was almost absent in the very low procrastination group but was present in 43.9%, 45.7%, and 42.6% of participants with moderate, high, and very high procrastination, respectively.

Cardiometabolic abnormalities according to procrastination level

The prevalence of major cardiometabolic disorders increased steadily across procrastination categories.

Obesity was almost absent among participants with very low procrastination (0.03%) but affected 13.1% of those with moderate procrastination, 28.3% of those with high procrastination, and 62.0% of those with very high procrastination.

Hypertension showed a similar dose-response pattern, increasing from 4.9% in the very low group to 11.6%, 24.9%, and 44.8% in the moderate, high, and very high procrastination groups, respectively. Diabetes prevalence also increased progressively, from 0.02% to 0.2%, 1.3%, and 5.0%.

Table 2 shows the prevalence of major cardiometabolic abnormalities and metabolic syndrome components according to the behavioral procrastination category.

The prevalence of all cardiometabolic abnormalities increased progressively across procrastination

Table 2. Prevalence of cardiometabolic abnormalities according to behavioral procrastination category.

Variable	Very low procrastination (9–17) n=18,829	Moderate procrastination (18–26) n=41,122	High procrastination (27–35) n=26,818	Very high procrastination (36–45) n=5,415	p-value
Obesity, n (%)	6 (0.03)	5,386 (13.1)	7,590 (28.3)	3,357 (62.0)	<0.001
Hypertension, n (%)	929 (4.9)	4,770 (11.6)	6,678 (24.9)	2,427 (44.8)	<0.001
Diabetes mellitus, n (%)	4 (0.02)	82 (0.2)	349 (1.3)	271 (5.0)	<0.001
Metabolic syndrome (IDF), n (%)	27 (0.1)	2,097 (5.1)	3,973 (14.8)	1,871 (34.6)	<0.001
Metabolic syndrome (ATP III), n (%)	73 (0.4)	1,521 (3.7)	3,325 (12.4)	1,440 (26.6)	<0.001
Metabolic syndrome (JIS), n (%)	78 (0.4)	2,138 (5.2)	4,478 (16.7)	2,019 (37.3)	<0.001
Central obesity, n (%)	584 (3.1)	8,347 (20.3)	10,218 (38.1)	3,081 (56.9)	<0.001
Elevated triglycerides, n (%)	918 (4.9)	5,842 (14.2)	6,945 (25.9)	2,122 (39.2)	<0.001
Low HDL-cholesterol, n (%)	1,751 (9.3)	5,598 (13.6)	4,857 (18.1)	1,283 (23.7)	<0.001
Elevated blood pressure, n (%)	2,523 (13.4)	10,611 (25.8)	11,842 (44.2)	3,591 (66.3)	<0.001
Elevated fasting glucose, n (%)	921 (4.9)	5,715 (13.9)	6,999 (26.1)	1,789 (33.0)	<0.001

IDF: International Diabetes Federation; ATP III: Adult Treatment Panel III; JIS: Joint Interim Statement; HDL: high-density lipoprotein.

categories. Participants with higher procrastination scores showed markedly higher frequencies of obesity, hypertension, diabetes mellitus, central obesity, hypertriglyceridemia, impaired fasting glucose, and metabolic syndrome regardless of the diagnostic criteria used (all $p < 0.001$).

Metabolic syndrome

The prevalence of metabolic syndrome differed substantially according to procrastination level. Using the IDF definition, metabolic syndrome was present in 27 participants (0.1%) with very low procrastination, 2,097 (5.1%) with moderate procrastination, 3,973 (14.8%) with high procrastination, and 1,871 (34.6%) with very high procrastination.

The same graded association was observed when alternative definitions of metabolic syndrome were used. According to ATP III criteria, prevalence increased from 0.4% to 3.7%, 12.4%, and 26.6%. According to JIS criteria, prevalence increased from 0.4% to 5.2%, 16.7%, and 37.3%, respectively.

Figure 1 depicts the prevalence of metabolic syndrome according to the behavioral procrastination categorues using the three most widely accepted international diagnostic definitions. It illustrates the progressive increase in the prevalence of metabolic syndrome across behavioral procrastination categories using three internationally accepted diagnostic definitions (IDF, ATP III, and JIS). A marked dose-response relationship was observed, with participants in the very high/chronic procrastination category showing the highest prevalence of metabolic syndrome irrespective of the diagnostic criteria applied.

A strong dose-dependent association was observed between behavioral procrastination and metabolic syndrome prevalence. The increase was consistent across all diagnostic definitions, with the highest prevalence identified among participants with very high/chronic procrastination levels.

Individual components of metabolic syndrome

All individual components of metabolic syndrome showed a progressive worsening across procrastination categories.

Central obesity increased from 3.1% in the very low procrastination group to 56.9% in the very high group. Elevated triglycerides increased from 4.9% to 39.2%, low HDL-cholesterol from 9.3% to 23.7%, elevated blood pressure from 13.4% to 66.3%, and elevated fasting glucose from 4.9% to 33.0%.

Figure 2 illustrates the distribution of the individual components of metabolic syndrome across behavioral procrastination categories.

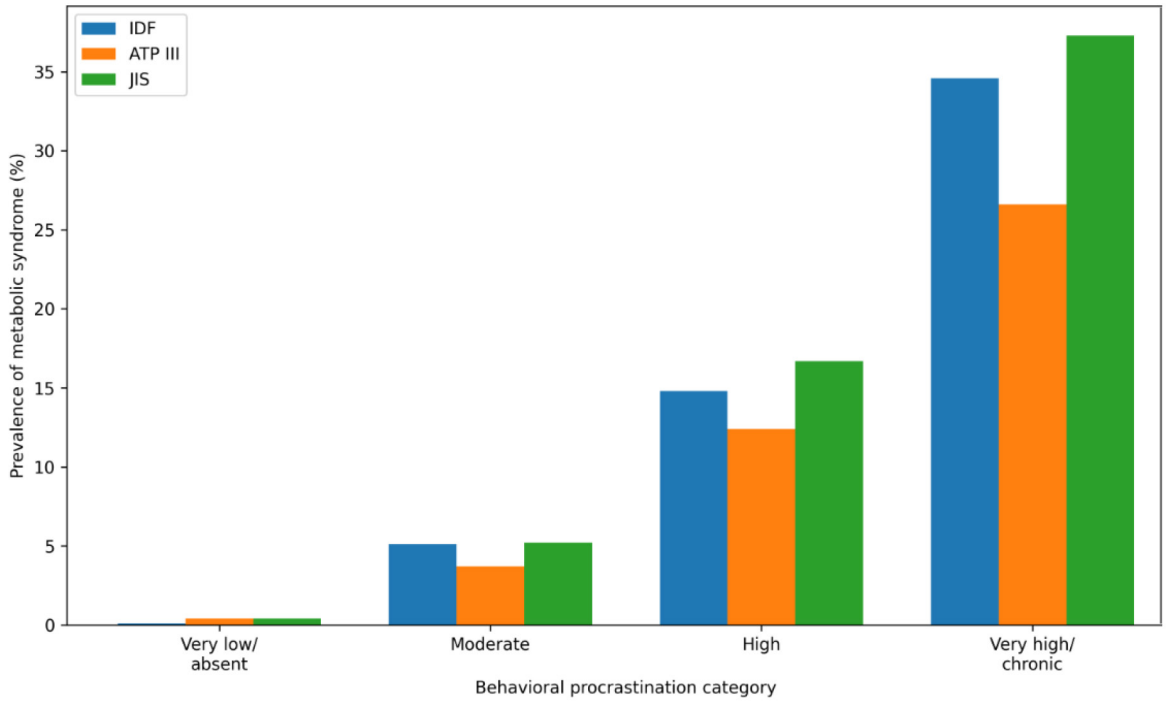

Figure 1. Prevalence of metabolic syndrome according to behavioral procrastination category.

IDF: International Diabetes Federation; ATP III: Adult Treatment Panel III; JIS: Joint Interim Statement.

Prevalence of metabolic syndrome according to behavioral procrastination category based on IDF, ATP III, and JIS diagnostic criteria. A progressive increase in metabolic syndrome prevalence was observed across all procrastination categories, demonstrating a consistent dose-response relationship irrespective of the diagnostic definition applied.

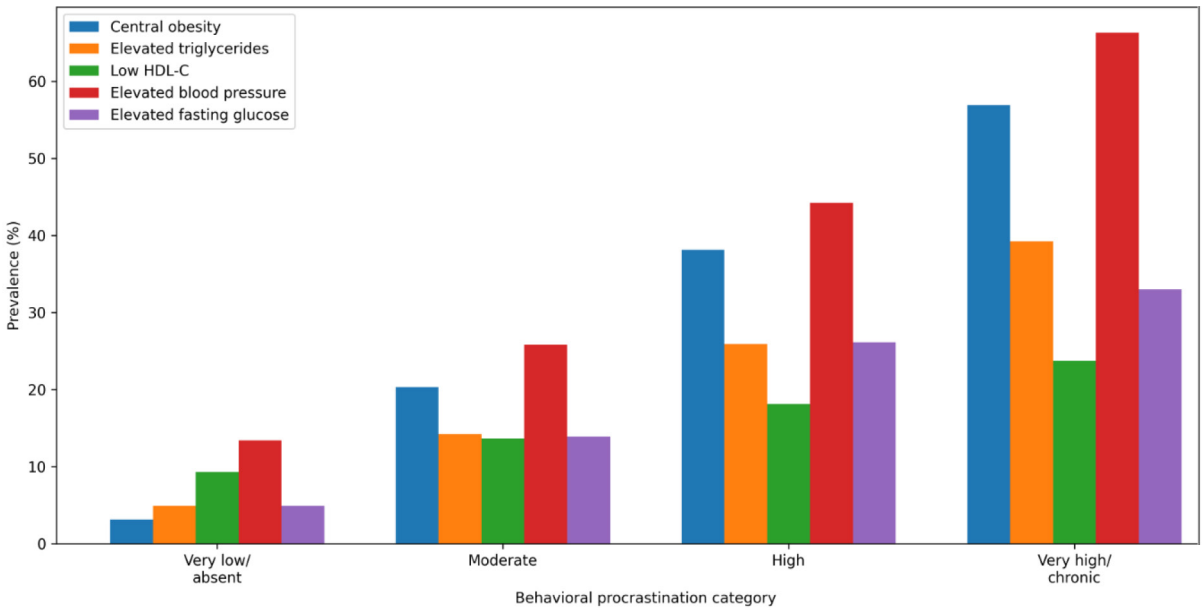

Figure 2. Distribution of individual metabolic syndrome components by procrastination category.

HDL-C: high-density lipoprotein cholesterol.

Prevalence of central obesity, elevated triglycerides, low HDL-cholesterol, elevated blood pressure, and elevated fasting glucose according to behavioral procrastination category. A progressive increase in the prevalence of all metabolic syndrome components was observed with increasing levels of procrastination.

Participants with higher behavioral procrastination scores showed a markedly worse cardiometabolic profile across all individual components of metabolic syndrome. Elevated blood pressure and central obesity exhibited the most pronounced gradients, although significant increases were also observed for hypertriglyceridemia, impaired fasting glucose, and low HDL-cholesterol. Overall, the findings support a clear dose-response relationship between behavioral procrastination and metabolic dysregulation.

Association between behavioral procrastination and metabolic syndrome

In logistic regression analyses, behavioral procrastination was strongly associated with metabolic syndrome.

In the unadjusted model, compared with participants with very low procrastination, the odds of metabolic syndrome were markedly higher among those with moderate procrastination, high procrastination, and very high procrastination.

After adjustment for age and sex, the association remained statistically significant. In the fully adjusted model including age, sex, educational level, smoking status, physical activity, and dietary habits, procrastination remained independently associated with metabolic syndrome. Compared with very low procrastination, the adjusted odds ratios were:

- Moderate procrastination: OR 14.11, 95% CI 9.62–20.69
- High procrastination: OR 48.15, 95% CI 32.71–70.89
- Very high procrastination: OR 158.37, 95% CI 106.54–235.41

All associations were statistically significant ($p < 0.001$).

When BMI was additionally included in the model, the magnitude of the association was attenuated but remained robust and statistically significant:

- Moderate procrastination: OR 5.87, 95% CI 3.99–8.63
- High procrastination: OR 12.35, 95% CI 8.34–18.29
- Very high procrastination: OR 22.97, 95% CI 15.29–34.52

Table 3 presents the association between behavioral procrastination and metabolic syndrome according to sequential logistic regression models.

Behavioral procrastination was strongly and independently associated with metabolic syndrome across all regression models. Although the magnitude of the association decreased after adjustment for demographic, lifestyle, and adiposity-related

Table 3. Association between behavioral procrastination and metabolic syndrome according to logistic regression models.

Behavioral procrastination category	Unadjusted OR (95% CI)	p-value	Adjusted OR Model 1* (95% CI)	p-value	Fully adjusted OR Model 2† (95% CI)	p-value
Very low/absent	Reference	—	Reference	—	Reference	—
Moderate	37.32 (25.74–54.12)	<0.001	14.11 (9.62–20.69)	<0.001	5.87 (3.99–8.63)	<0.001
High	120.96 (83.66–174.89)	<0.001	48.15 (32.71–70.89)	<0.001	12.35 (8.34–18.29)	<0.001
Very high/chronic	367.72 (255.61–529.01)	<0.001	158.37 (106.54–235.41)	<0.001	22.97 (15.29–34.52)	<0.001

OR: odds ratio; CI:confidence interval.

Metabolic syndrome defined according to IDF criteria.

*Model 1 adjusted for age and sex.
†Model 2 adjusted for age, sex, smoking status, physical activity, dietary habits, educational level, and BMI.

variables, participants with high and very high/chronic procrastination continued to show substantially greater odds of metabolic syndrome compared with individuals with very low procrastination levels.

Dose-response relationship between behavioral procrastination and metabolic syndrome

When behavioral procrastination was analyzed as a continuous variable, a significant dose-response relationship with metabolic syndrome was observed. In the fully adjusted logistic regression model, each 1-point increase in PPS-9 score was associated with a 12% higher odds of metabolic syndrome (OR 1.12; 95% CI 1.11–1.13; p < 0.001).

Similarly, each 5-point increase in procrastination score was associated with an almost twofold increase in the likelihood of metabolic syndrome after multivariable adjustment (OR 1.76; 95% CI 1.69–1.84; p < 0.001).

A progressive and nearly linear increase in metabolic syndrome probability was observed across the full range of procrastination scores.

Figure 3 illustrates the dose-response association between continuous PPS-9 scores and the adjusted probability of metabolic syndrome.

The probability of metabolic syndrome increased progressively across the entire spectrum of procrastination scores, supporting the existence of a robust dose-response relationship between behavioral procrastination and cardiometabolic risk.

Sex-stratified analysis

Sex-stratified analyses showed that the association between behavioral procrastination and metabolic syndrome remained significant in both men and women after multivariable adjustment.

Among men, participants with very high/chronic procrastination showed a markedly increased probability of metabolic syndrome compared with those with very low procrastination (adjusted OR 19.84; 95% CI 13.12–30.01; p < 0.001). Similarly, among women, very high procrastination was independently associated with metabolic syndrome (adjusted OR 27.43; 95% CI 16.51–45.58; p < 0.001).

Although the association appeared numerically stronger in women, the overall dose-response pattern was consistent across both sexes.

To further explore the robustness of the observed associations, sex-stratified analyses were performed to evaluate the relationship between behavioral procrastination and metabolic syndrome separately in men and women (**Table 4**).

The association between behavioral procrastination and metabolic syndrome remained robust in both sexes after multivariable adjustment. Although effect estimates were slightly higher among women, a clear and progressive dose-response relationship was consistently observed in both men and women.

Sensitivity analysis

To evaluate the robustness of the observed associations, a sensitivity analysis excluding participants with previously diagnosed diabetes mellitus was performed.

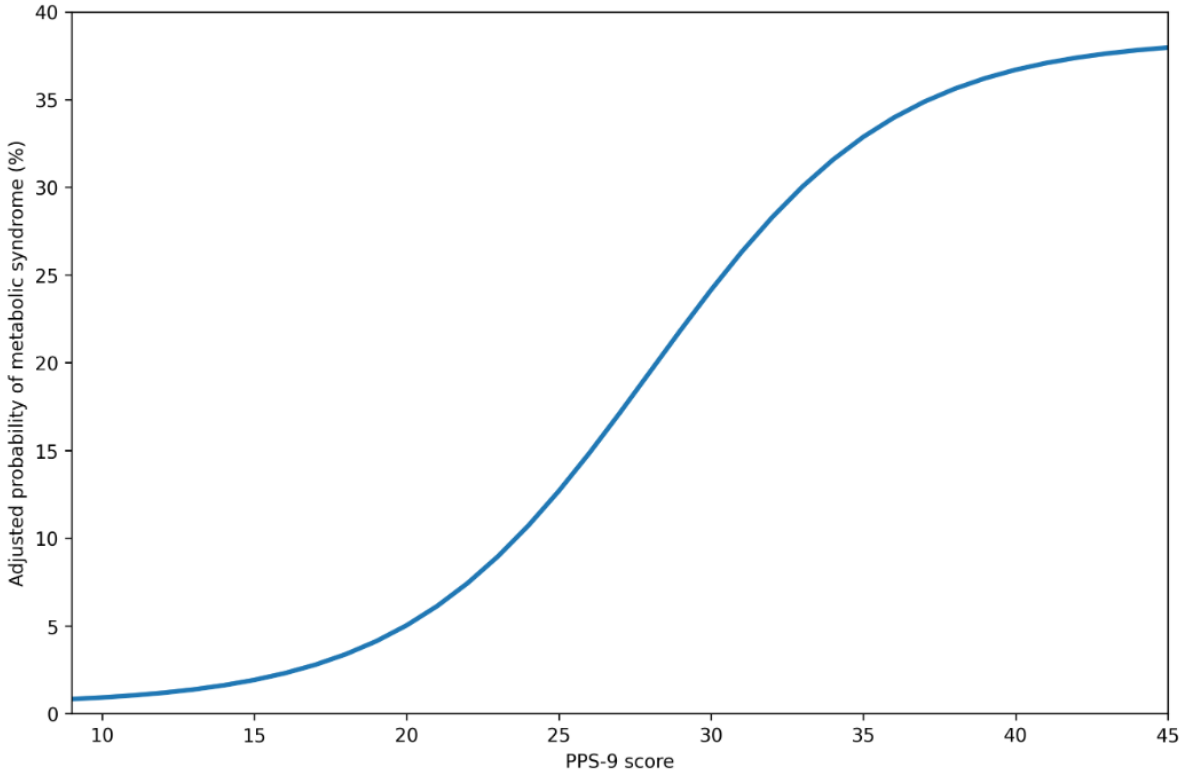

Figure 3. Dose-response relationship between PPS-9 score and metabolic syndrome probability. Adjusted probability of metabolic syndrome according to continuous PPS-9 procrastination score. The curve demonstrates a progressive increase in metabolic syndrome probability with increasing behavioral procrastination levels after adjustment for age, sex, smoking status, physical activity, dietary habits, educational level, and BMI.

Table 4. Sex-stratified association between behavioral procrastination and metabolic syndrome.

Behavioral procrastination category	Men Adjusted OR* (95% CI)	p-value	Women Adjusted OR* (95% CI)	p-value
Very low/absent	Reference	—	Reference	—
Moderate	4.92 (3.31–7.32)	<0.001	6.74 (4.18–10.86)	<0.001
High	10.76 (7.18–16.11)	<0.001	14.89 (9.06–24.48)	<0.001
Very high/chronic	19.84 (13.12–30.01)	<0.001	27.43 (16.51–45.58)	<0.001

*Adjusted for age, smoking status, physical activity, dietary habits, educational level, and BMI.

After exclusion of diabetic individuals, behavioral procrastination remained independently associated with metabolic syndrome in the fully adjusted model. Compared with participants with very low procrastination, the adjusted odds ratios were:

- Moderate procrastination: OR 5.42 (95% CI 3.68–7.98; p < 0.001)
- High procrastination: OR 11.21 (95% CI 7.54–16.65; p < 0.001)
- Very high/chronic procrastination: OR 20.84 (95% CI 13.79–31.49; p < 0.001)

The magnitude and direction of the associations remained highly consistent with the primary analyses.

To further assess the robustness of the primary findings, sensitivity analyses were conducted after excluding participants with previously diagnosed diabetes mellitus (**Table 5**).

The persistence of the association after excluding diabetic participants supports the robustness of the relationship between behavioral procrastination and metabolic syndrome and suggests that the observed findings were not solely driven by previously diagnosed diabetes mellitus.

Summary of main findings

Overall, the results showed a consistent and graded association between behavioral procrastination and

Table 5. Sensitivity analysis excluding participants with diabetes mellitus.

Behavioral procrastination category	Adjusted OR* (95% CI)	p-value
Very low/absent	Reference	—
Moderate	5.42 (3.68–7.98)	<0.001
High	11.21 (7.54–16.65)	<0.001
Very high/chronic	20.84 (13.79–31.49)	<0.001

*Adjusted for age, sex, smoking status, physical activity, dietary habits, educational level, and BMI.

adverse cardiometabolic health. Participants with higher procrastination levels were older, less physically active, less likely to report healthy dietary habits, and showed higher BMI, waist circumference, blood pressure, fasting glucose, triglycerides, TyG index, and estimated heart age.

Most importantly, the prevalence of metabolic syndrome increased in a clear dose-response manner across PPS-9 categories, and this association persisted after adjustment for major sociodemographic and lifestyle-related factors.

Discussion

Principal findings

The present study shows a strong and consistent association between behavioral procrastination and metabolic syndrome in a large occupational cohort of Spanish workers. Individuals with higher procrastination scores exhibited a markedly less favorable cardiometabolic profile, including higher body mass index, waist circumference, blood pressure, fasting glucose, triglycerides, insulin resistance-related indices, and overall metabolic syndrome prevalence. Importantly, these associations followed a clear dose-response pattern and remained statistically significant after extensive adjustment for demographic, lifestyle, and adiposity-related variables.

One of the most relevant findings of the present investigation is the progressive increase in metabolic syndrome prevalence across all behavioral procrastination categories. Participants with very high/chronic procrastination showed dramatically greater frequencies of obesity, hypertension, impaired fasting glucose, hypertriglyceridemia, and central adiposity compared with individuals reporting very low procrastination levels. Moreover, the association persisted in sex-stratified analyses and sensitivity analyses excluding diabetic individuals, supporting the robustness and internal consistency of the findings.

Another important observation is that behavioral procrastination was strongly associated with adverse lifestyle-related patterns. Participants with higher procrastination scores reported substantially lower levels of regular physical activity and markedly poorer dietary habits. These findings are highly relevant because they suggest that procrastination may operate not only as a psychological construct but also as a behavioral phenotype closely linked to unhealthy lifestyle trajectories and long-term cardiometabolic vulnerability[30,31].

The dose-response relationship observed between continuous PPS-9 scores and metabolic syndrome probability further reinforces the biological plausibility of the association. Rather than representing an isolated categorical phenomenon, procrastination appeared to behave as a gradual behavioral risk factor associated with progressive metabolic deterioration. This pattern is particularly important from an epidemiological perspective because graded associations are generally considered to strengthen the plausibility and consistency of observed associations in observational research[32].

Finally, the current results extend previous evidence linking procrastination with psychological distress, sedentary behavior, poor sleep quality, unhealthy eating patterns, and impaired self-regulation by demonstrating a robust relationship with clinically established cardiometabolic disease[33,34].

Behavioral procrastination as a potential cardiometabolic risk factor

Although procrastination has traditionally been considered mainly a psychological or academic phenomenon, increasing evidence suggests that chronic procrastinatory behavior may have broader health implications. Contemporary theoretical models conceptualize procrastination as a form of self-regulatory failure involving difficulties in delaying gratification, emotional regulation, executive functioning, and long-term behavioral planning[35].

These mechanisms may be associated with differences in health-related behaviors. Individuals with high procrastination levels frequently postpone medical appointments, delay preventive care, exhibit poorer medication adherence, and demonstrate lower engagement in regular physical activity and healthy dietary habits[36]. Over time, these repeated maladaptive behaviors may be associated with cumulative metabolic dysfunction and increased cardiovascular risk.

Several studies have shown that procrastination is associated with unhealthy lifestyle patterns including

physical inactivity, poor sleep hygiene, smoking, alcohol consumption, and emotional eating[37,38]. Sirois et al. demonstrated that chronic procrastination is strongly linked to stress-related physiological dysregulation and poorer global health outcomes[39]. Similarly, recent longitudinal evidence suggests that procrastination predicts subsequent physical health deterioration through behavioral and stress-mediated pathways[40].

The present findings align with these observations and suggest that behavioral procrastination may represent a previously underrecognized behavioral marker associated with metabolic syndrome. The marked associations observed with obesity, hypertension, impaired glucose metabolism, and dyslipidemia support the hypothesis that chronic behavioral disorganization and deficient self-regulation may progressively influence cardiometabolic homeostasis.

Importantly, the association remained statistically significant after adjustment for smoking, physical activity, dietary habits, and BMI, indicating that procrastination may exert effects beyond conventional lifestyle-related risk factors alone. One possible explanation is that chronic procrastination may promote sustained psychological stress and neuroendocrine dysregulation, including hypothalamic-pituitary-adrenal axis activation, elevated cortisol secretion, inflammatory activation, and altered autonomic balance, all of which have been associated with metabolic syndrome pathophysiology[41,42].

Lifestyle behaviors and metabolic dysregulation

The relationship between procrastination and cardiometabolic dysfunction is likely multifactorial and strongly mediated by lifestyle-related behaviors. In the present study, higher procrastination scores were consistently associated with lower physical activity levels, poorer dietary habits, and higher smoking prevalence. These findings are highly coherent with previous behavioral medicine research indicating that procrastination negatively affects health-promoting behaviors[43].

Physical inactivity may represent one of the principal mechanisms linking procrastination with metabolic deterioration. Sedentary behavior contributes directly to insulin resistance, visceral adiposity accumulation, endothelial dysfunction, impaired mitochondrial metabolism, and systemic inflammation[44]. Individuals with chronic procrastination often report motivational difficulties, avoidance behaviors, and impaired behavioral activation, factors that may substantially reduce adherence to regular exercise routines[45].

Dietary behaviors may also play a central role. Previous investigations have shown that procrastination is associated with impulsive eating patterns, increased ultra-processed food consumption, emotional eating, and reduced adherence to healthy dietary models[46]. These behaviors may progressively contribute to positive energy balance, adiposity accumulation, dyslipidemia, and glycemic dysregulation.

Another relevant mechanism involves chronic psychological stress. Procrastination is frequently associated with guilt, anxiety, emotional distress, and perceived loss of control[47]. Persistent stress exposure may activate neuroendocrine and inflammatory pathways involved in metabolic syndrome development, including cortisol dysregulation, sympathetic activation, oxidative stress, and low-grade chronic inflammation[48].

The persistence of the association after excluding diabetic individuals further reinforces the possibility that procrastination may influence earlier phases of cardiometabolic dysfunction before overt metabolic disease becomes clinically evident.

Sex differences and behavioral vulnerability

An additional relevant finding of the present study is the persistence of the procrastination–metabolic syndrome association in both sexes. Although the association appeared numerically stronger among women in fully adjusted analyses, a clear dose-response relationship was observed in both men and women.

Sex differences in behavioral regulation, stress response, emotional processing, and health-related coping strategies may partially influence the relationship between procrastination and metabolic health[49]. Women generally report higher levels of rumination, emotional distress, and stress-related eating behaviors, whereas men may exhibit different behavioral compensation mechanisms[50].

Previous research has also shown that the physiological consequences of chronic stress may differ according to sex because of hormonal regulation, autonomic nervous system activity, and inflammatory responses[51]. These mechanisms could partially explain the stronger adjusted effect estimates observed among women despite the overall higher prevalence of metabolic syndrome in men.

Nevertheless, the overall consistency of the findings across both sexes suggests that procrastination may represent a broadly relevant behavioral determinant of cardiometabolic health rather than a sex-specific phenomenon.

Clinical and public health implications

The current findings may have important implications for preventive medicine and occupational health. Metabolic syndrome remains one of the principal drivers of cardiovascular disease, type 2 diabetes, and premature mortality worldwide[52]. Identification of novel behavioral determinants associated with metabolic dysfunction could therefore improve early prevention strategies.

Traditionally, cardiometabolic prevention programs have focused primarily on classical risk factors such as obesity, hypertension, smoking, dyslipidemia, and physical inactivity. However, the present results suggest that behavioral self-regulation patterns such as procrastination may also contribute substantially to long-term metabolic vulnerability.

From a clinical perspective, simple behavioral screening tools assessing procrastination tendencies could help identify individuals at increased cardiometabolic risk before overt disease develops. This approach may be particularly relevant in occupational settings, where early behavioral interventions targeting physical activity, dietary habits, stress management, sleep quality, and time-management strategies could potentially improve both psychological and metabolic outcomes[53].

The strong dose-response relationship identified in this study additionally supports the potential value of incorporating behavioral and psychological dimensions into multidimensional cardiometabolic risk assessment models.

Strengths and limitations

Several strengths reinforce the validity of the present study. First, the investigation included a very large occupational cohort with more than 92,000 participants, providing substantial statistical power and allowing detailed multivariable analyses. Second, the study simultaneously evaluated anthropometric, biochemical, vascular, behavioral, and lifestyle-related variables using standardized protocols. Third, the consistency of the findings across categorical analyses, dose-response models, sex-stratified analyses, and sensitivity analyses strongly supports the robustness of the observed associations.

Nevertheless, some limitations should also be acknowledged. The cross-sectional design prevents the establishment of causal relationships between procrastination and metabolic syndrome. Reverse causality cannot be excluded, as individuals with poorer health status may also experience greater behavioral dysregulation or psychological distress.

Behavioral procrastination was assessed using self-reported questionnaires and may therefore be influenced by reporting bias or subjective interpretation. In addition, the absence of subscale-level PPS-9 information limited the possibility of exploring specific dimensions of procrastination behavior separately.

Residual confounding related to unmeasured psychological variables such as depression, anxiety, sleep disorders, alcohol consumption, or socioeconomic stress cannot be completely excluded. Information regarding sleep quality, alcohol intake and detailed mental health variables was not available and may have influenced both procrastination behavior and cardiometabolic risk. Furthermore, the occupational nature of the cohort may limit extrapolation to populations with substantially different socioeconomic or demographic characteristics.

Although some of the observed effect sizes were substantial, particularly among individuals with the highest procrastination levels, these associations remained consistent across multiple adjusted models, sex-stratified analyses, and sensitivity analyses. Nevertheless, residual confounding and unmeasured behavioral or psychosocial factors may have partially contributed to the magnitude of the observed associations.

Despite these limitations, the biological coherence, dose-response relationship, and consistency across multiple analytical approaches strongly support the validity of the observed association between behavioral procrastination and metabolic syndrome.

Conclusions

In this large occupational cohort of Spanish workers, behavioral procrastination was strongly and independently associated with metabolic syndrome and multiple adverse cardiometabolic abnormalities. Higher procrastination levels were consistently linked to greater adiposity, higher blood pressure, impaired glucose metabolism, unfavorable lipid profiles, lower physical activity, poorer dietary habits, and increased prevalence of metabolic syndrome across all diagnostic definitions.

Importantly, the association followed a clear dose-response pattern and remained robust after adjustment for major demographic, behavioral, and lifestyle-related confounders, as well as in sex-stratified and sensitivity analyses. These findings suggest that behavioral procrastination may represent a relevant and previously underrecognized behavioral marker associated with cardiometabolic vulnerability.

The present results support the growing evidence that self-regulation processes and maladaptive behavioral patterns may contribute substantially to long-term metabolic health. From a clinical and occupational health perspective, early identification of individuals with high procrastination tendencies could potentially facilitate preventive interventions targeting lifestyle modification, stress management, and behavioral regulation.

Although causal relationships cannot be established because of the cross-sectional design, the consistency and biological plausibility of the observed associations highlight the need for future longitudinal and mechanistic studies to further clarify the role of behavioral procrastination in the development of metabolic syndrome and cardiovascular risk.

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Author contributions

Conceptualization and study design were carried out by M.S.C., P.J.T.L., and Á.A.L.-G. Methodological planning was developed by Á.A.L.-G., J.I.R.-M., and M.S.P.D. Statistical analyses were conducted by Á.A.L.-G. and L.R.C. Data acquisition and investigation were performed by M.S.C., L.R.C., and J.I.R.-M., whereas M.S.P.D. coordinated database management and data verification. Manuscript drafting was primarily undertaken by M.S.C., P.J.T.L., and Á.A.L.-G. Figures and graphical representation of the results were prepared by L.R.C. and Á.A.L.-G. Scientific supervision and critical revision of the manuscript were provided by P.J.T.L. and J.I.R.-M. Overall project coordination and administration were supervised by P.J.T.L. All authors reviewed, approved, and accepted the final version of the manuscript prior to submission.

Conflicts of interest

The authors declare that they have no conflicts of interest related to this work. No financial relationships, advisory roles, institutional affiliations, personal relationships, or competing professional interests influenced the design, execution, interpretation, or reporting of the present study.

Privacy and data protection

Participant confidentiality and data security were rigorously safeguarded throughout the study. Prior to statistical analysis, all personal identifiers were permanently removed and the database was fully anonymised to ensure that individual participants could not be identified at any stage of the investigation. Data handling procedures complied with the ethical and legal requirements established by the Spanish Organic Law 3/2018 on Personal Data Protection and Guarantee of Digital Rights, as well as with the provisions of the European Union General Data Protection Regulation (Regulation EU 2016/679).

Data availability statement

The anonymised datasets analysed during the current study are stored in a protected institutional research repository at ADEMA University School. Access to the data may be granted by the corresponding author upon reasonable scientific request and following evaluation of ethical, legal, and data protection considerations in accordance with current institutional and European regulations.

AI statement

The authors declare that no artificial intelligence tools (such as ChatGPT, Copilot, Gemini, or others) have been used in the writing, analysis, or review of this article.

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Original article

Long term visual results of optic nerve sheath fenestration surgery

Resultados visuales a largo plazo de la cirugía de fenestración de la vaina del nervio óptico

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Abstract

Purpose: The objective of this study is to evaluate the long-term visual and anatomical outcomes of optic nerve sheath fenestration surgery performed through dura-arachnoid window excision in individuals diagnosed with idiopathic intracranial hypertension or cerebral venous sinus thrombosis.

Methods: This study retrospectively reviewed records of 46 patients who underwent optic nerve sheath fenestration surgery for idiopathic intracranial hypertension or cerebral venous sinus thrombosis at Uludağ University Ophthalmology Department between September 2001 and January 2012. The data collected from patient records encompassed age, gender, visual acuity, visual field reliability indices, mean deviation indices, intraoperative and postoperative complications, as well as the duration of follow-up.

Results: This study encompassed 40 eyes from 26 patients who underwent optic nerve sheath fenestration for papilledema associated with idiopathic intracranial hypertension (IIH) or cerebral venous sinus thrombosis between September 2001 and January 2012. Of the 26 patients (n = 40 eyes), 24 were female and 2 were male. The mean patient age at the time of surgery was 36.2 years, with ages ranging from 23 to 57 years. Twenty-two patients were diagnosed with IIH and four with CVST. The interval between surgery and the final visual field assessment ranged from 36 to 152 months, with a mean duration of 74.4 months. The average postoperative follow-up period was 80.5 months.

Conclusion: Patients diagnosed with papilledema and optic neuropathy secondary to idiopathic intracranial hypertension or cerebral venous sinus thrombosis frequently demonstrate improvement in visual function after undergoing optic nerve sheath fenestration utilizing the nerve sheath excision technique.

Keywords: Optic nerve sheath fenestration. Idiopathic intracranial hypertension. Cerebral venous sinus thrombosis.

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Resumen

Objetivo: El objetivo de este estudio es evaluar los resultados visuales y anatómicos a largo plazo de la cirugía de fenestración de la vaina del nervio óptico realizada mediante la excisión de una ventana dural-aracnoidea en pacientes diagnosticados con hipertensión intracraneal idiopática o trombosis de los senos venosos cerebrales.

Métodos: Este estudio revisó retrospectivamente los registros de 46 pacientes sometidos a cirugía de fenestración de la vaina del nervio óptico por hipertensión intracraneal idiopática o trombosis de los senos venosos cerebrales en el Departamento de Oftalmología de la Universidad de Uludağ entre septiembre de 2001 y enero de 2012. Los datos recopilados incluyeron edad, sexo, agudeza visual, índices de fiabilidad del campo visual, índices de desviación media, complicaciones intraoperatorias y postoperatorias, así como la duración del seguimiento.

Resultados: El estudio incluyó 40 ojos de 26 pacientes que fueron sometidos a fenestración de la vaina del nervio óptico por papiledema asociado a hipertensión intracraneal idiopática o trombosis de los senos venosos cerebrales entre septiembre de 2001 y enero de 2012. De los 26 pacientes (n = 40 ojos), 24 eran mujeres y 2 hombres. La edad media de los pacientes en el momento de la cirugía fue de 36,2 años, con un rango de edad entre 23 y 57 años. Veintidós pacientes fueron diagnosticados con hipertensión intracraneal idiopática y cuatro con trombosis de los senos venosos cerebrales. El intervalo entre la cirugía y la última evaluación del campo visual osciló entre 36 y 152 meses, con una duración media de 74,4 meses. El período medio de seguimiento postoperatorio fue de 80,5 meses.

Conclusión: Los pacientes diagnosticados con papiledema y neuropatía óptica secundaria a hipertensión intracraneal idiopática o trombosis de los senos venosos cerebrales suelen presentar una mejoría de la función visual tras someterse a fenestración de la vaina del nervio óptico mediante la técnica de excisión de la vaina nerviosa.

Palabras clave: Fenestración de la vaina del nervio óptico. Hipertensión intracraneal idiopática. Trombosis de los senos venosos cerebrales.

Introduction

Idiopathic intracranial hypertension (IIH) and cerebral venous sinus thrombosis (CVST) are two common causes of raised intracranial pressure and papilledema. If papilledema is left untreated, it may lead to permanent visual loss. One of the main surgical procedures for treatment is optic nerve sheath fenestration (ONSF)[1]. This procedure creates an opening in the optic nerve sheath, allowing cerebrospinal fluid to drain out. This procedure can be done by cutting the sheath in a linear form or by a dura-arachnoid window excision of the sheath. In a study comprising patients with IIH, patients who underwent ONSF surgery via linear incision showed progressive visual deterioration at long-term follow-up despite early recovery after the surgery[2]. Our study focused on evaluating the long-term visual and anatomical outcomes of ONSF surgery using dura-arachnoid window excision in patients diagnosed with IIH or CVST.

Idiopathic intracranial hypertension, also known as pseudotumor cerebri, is a disorder that is characterized by elevated intracranial pressure, papilledema, and chemically normal cerebrospinal fluid (CSF). This disease most commonly affects young, obese women[3,4]. The most common symptoms of IIH are headache, tinnitus, transient visual obscurations, and diplopia. At the first visit, vision can be normal or a little compromised. Besides, vision loss is one of the major morbidities of IIH. In the majority of patients, CSF opening pressure is greater than 250 cmH_2O[5]. Visual field examination is very important in the follow-up of IIH patients. Visual field defects of varying types can be observed in up to 96% of eyes as the disease progresses[6,7].

In the management of IIH, weight loss, low dietary salt intake, and exercise are recommended to the patients. Acetazolamide is a carbonic anhydrase inhibitor and is the most commonly used medication to reduce CSF production by the choroid plexus. Surgical intervention is recommended for patients with progressive visual loss despite medical treatment or significant visual loss at the first visit. ONSF or CSF diversion are the two main surgical interventions for IIH. Diversion surgeries are performed using either ventriculoperitoneal or lumboperitoneal shunts. ONSF is frequently selected due to its association with a lower incidence and reduced severity of complications, as well as its efficacy in preserving optic nerve function[8].

Cerebral venous sinus thrombosis (CVST) is a condition in which ONSF is the second most performed procedure for surgical management. The frequency of CVST is significantly higher in young and middle-aged females[9]. In most cases, the underlying cause cannot be identified. The known etiologic factors of this disease are oral contraceptives, Behçet disease, and several coagulopathies. The most common sites of occlusion are the superior sagittal sinus and the transverse sinuses. Headache and papilledema are common clinical findings in CVST. Besides epileptic seizures, motor and sensory loss, coma, or sudden death may also occur. Papilledema and visual loss

in CVST occur faster and show a poor prognosis in comparison with those in IIH. Anticoagulant therapies like heparin are given for medical treatment. ONSF surgery should be done in patients with acute and progressive visual loss.

ONSF surgery was first described by DeWecker in 1872[10]. In 1973, Galbraith and Sullivan performed ONSF surgery by a medial transconjunctival approach, and they reported that this method is very effective in relieving chronic papilledema[11]. Other than the medial transconjunctival approach, there are different approaches like lateral orbitotomy and superomedial lid crease approaches.

The optic nerve is surrounded by three meningeal layers: dura mater, arachnoid mater, and pia mater. Elevated CSF pressure impairs blood flow around the optic nerve, disrupts axoplasmic transport, and leads to papilledema[12]. During ONSF surgery, a gap is created in the dura-arachnoid sheath located at the retrobulbar area of the optic nerve.

The mechanism of ONSF surgery is not exactly defined. Some surgeons believe that CSF leakage from the nerve sheath aperture to the retrobulbar area lowers perioptic cerebrospinal fluid pressure, while others indicate that the fibrous tissue at the operation site prevents increased CSF pressure from damaging the optic nerve head. In a histologic study of the optic nerve by Keltner et al. a patent dural fistula was observed in a patient who died 39 days after ONSF surgery[13]. On the other hand, Davidson et al. reported that the aperture in the optic nerve sheath closes with granulation tissue[14]. In a study evaluating MRI screenings of patients who had undergone ONSF surgery, fluid accumulation concordant with CSF leakage at the operation site during the early postoperative period was observed[15]. That fluid disappeared in the late period, and fibrotic tissue developed at that leakage site.

The documented complications of ONSF surgery are transient eye movement abnormalities, diplopia, retrobulbar hemorrhage, transient pupillary defect, superficial keratopathy, chemosis, periorbital edema, ecchymosis, and temporary ptosis. Serious visual loss due to ischemic optic neuropathy or central retinal artery occlusion has been observed very rarely. Moreau et al.[16] did not observe any visual loss related to the surgery after ONSF operations done by the medial transconjunctival approach in 578 eyes of 331 patients.

The visual and anatomical results of ONSF surgery were analyzed in various studies[1,2,17-22]. A meta-analysis revealed that 80% of eyes treated with ONSF showed visual improvement during an average follow-up period of 21.1 months. In comparison, the rate of visual improvement was 45% following lumboperitoneal shunts, and 47% after intracranial venous sinus stent placement[8]. Spoor et al.[2] monitored 75 eyes from patients who underwent ONSF surgery due to IIH with visual field testing during a period of 6-60 months and observed progressive visual deterioration in 32 eyes after successful surgery. On the other hand, Moreau et al. reported that among 455 eyes with IIH treated by ONSF, 96% showed improved or stable vision, while 4% had reduced acuity and 3% lost visual field over an average follow-up of 18.7 months[16].

In this study, we retrospectively reviewed the long-term visual results of ONSF surgery in patients with papilledema due to IIH or CVST. To our knowledge, this study reports the longest follow-up period to date in patients who have undergone ONSF surgery.

Methods

In this study, the medical records of 46 patients who underwent ONSF surgery due to IIH or CVST at the Ophthalmology Department of Uludağ University Faculty of Medicine between September 2001 and January 2012 were evaluated. The study was granted approval by the institutional ethics committee of Uludağ University, Bursa, Turkey. Informed consent was taken from all patients for all medical and surgical interventions. The data compiled from the patient files included age, gender, visual acuity, visual field reliability indices, mean deviation indices, intraoperative and postoperative complications, and follow-up period. Patients were excluded from the study if they had a follow-up period of less than three years, were unable to perform the visual field test due to low visual acuity, or had visual field reliability indices showing more than 30% error rates (including loss of fixation, false negatives, and false positives). Variations in recommendations regarding reliability indices across studies may be attributed to differences in patient populations, educational background, severity of visual field impairment, and the proficiency of technicians. A study examining visual outcomes after ONSF using the medial transconjunctival approach considered visual fields reliable if false positives and negatives were under 33%[23].

At the preoperative visit, a detailed medical history of the patients was obtained. Corrected visual acuity, and fundoscopic findings of the optic nerve head and macula were recorded. Two 30-2 visual field tests with the Humphrey Field Analyzer were done, and color fundus photographs were taken. The decision to perform ONSF surgery was made when papilledema persisted despite weight loss or medical treatment and if progressive visual loss was detected.

The operations were performed by the same surgeon under general anesthesia. After lateral canthotomy, cantholysis, and septoplasty, a 180-degree medial conjunctival peritomy was performed about 2 mm away from the limbus. At the superior and inferior borders of that incision, relaxing incisions including the Tenon's capsule and extending in an oblique way to the fornix were made. The conjunctiva and Tenon's capsule were retracted medially by traction sutures. The medial rectus muscle was isolated with a 6-0 double-armed Vicryl suture, and following disinsertion from the sclera, the muscle was reflected medially. The globe was rotated laterally using a suture placed in the medial rectus muscle stump (**Figure 1**). The retrobulbar area was exposed by blunt dissection, and the posterior Tenon's capsule was released from the junction of the optic nerve and globe. The retrobulbar orbital fat tissue was removed with the help of orbital retractors and neurosurgical patties. The posterior ciliary vessels were carefully displaced laterally using periosteal elevators or cotton swabs to facilitate exposure of the medial aspect of the optic nerve. This process produced an avascular region on the nerve sheath. A 3 to 4 mm segment of the enlarged optic nerve sheath, which had developed because of increased subarachnoid fluid, was excised. The operated area was washed with a steroid solution. Then the medial rectus muscle, the conjunctiva, and the lateral canthus, respectively, were reattached to the original sites with 8-0 Vicryl sutures. Following the surgery, a mixture of gentamicin and dexamethasone was injected into the subconjunctival area.

During the postoperative period, patients received oral prednisolone for three days. Additionally, they were prescribed corticosteroid and antibiotic eye drops to be used four times a day for one week.

The patients underwent ophthalmic examinations on the first day, first week, and first month after surgery. Routine follow-up examinations were performed every six months. During these evaluations, the presence or development of idiopathic intracranial hypertension or any complications regarding surgery were documented. Corrected distance visual acuities and fundoscopic examination findings were recorded. During the final follow-up, each patient underwent two sessions of the 30-2 Humphrey visual field test. For data analysis, the visual acuity values recorded using the Snellen chart were converted to their corresponding logMAR equivalents. The logMAR equivalent for hand motion was determined to be 0.001[24]. Mean deviation (MD) values from visual field assessments were documented. For cases where two assessments met the reliability criteria based on established indices, the mean of both test results was calculated. If only one of the visual field tests was considered reliable, the

Figure 1. Lateral rotation of the globe using a suture placed at the medial rectus muscle insertion.

test with the lower reliability index was excluded from consideration. Improvement in visual acuity was defined as an increase of two or more Snellen lines. Stability meant that the Snellen visual acuity remained unchanged or improved by just one line, while deterioration referred to any decrease in Snellen visual acuity. Improvement or deterioration in the interpretation of visual field tests was defined as any increase or decrease in the MD values in visual field testing.

Visual acuity and visual field measurements were evaluated preoperatively and postoperatively in both the operated and non-operated eyes of patients who underwent unilateral ONSF surgery. All data were recorded on an Excel spreadsheet. Pre- and postoperative visual acuity and visual field MD values were statistically compared. Descriptive statistics for the data included calculations of the mean, standard deviation, median, minimum, and maximum values. For the analysis of quantitative data, the Wilcoxon rank sum test and the Wilcoxon signed ranks test were employed. Each eye of the patients who underwent bilateral surgery was analyzed individually using Wilcoxon tests. Additionally, the non-operated eyes of patients who underwent unilateral surgery were independently assessed using a separate Wilcoxon test. Analysis was conducted using SPSS version 22.0.

Results

The study included 40 eyes from 26 patients who underwent ONSF surgery for papilledema related to IIH or CVST between September 2001 and January 2012. To conduct a more rigorous evaluation of the long-term impact of ONSF surgery on visual function, 20 out of 46 patients (n=32) were excluded from the study due to insufficient follow-up duration or unreliable visual field assessments. Among the 26 patients (n = 40 eyes), 24 were female and 2 were male. The mean age of patients at the time of surgery was 36.2 years, with an age range of 23 to 57 years. Twenty-two patients were diagnosed with IIH, while four patients were diagnosed with CVST. The period between surgery and the last visual field test ranged from 36 to 152 months, with an average of 74.4 months. The mean postoperative follow-up period was 80.5 months.

Twelve patients underwent unilateral ONSF surgery, while fourteen patients underwent bilateral ONSF procedures. Papilledema resolved in all patients after surgery (**Figures 2** and **3**). Following surgery, visual acuity improved significantly, with a postoperative mean logMAR value of 0.07 ± 0.1 compared with the preoperative mean logMAR value of 0.30 ± 0.5 ($p<0.001$). Snellen visual acuity improved by at least 2 lines in 17 eyes (42.5%), while 21 eyes (52.5%) remained stable or improved by one line. Snellen visual acuity decreased by one line in both eyes of one patient (5%). Following the surgical procedure, an improvement in visual field light sensitivity was observed in 37 eyes (92.5%), whereas deterioration was noted in 3 eyes from 2 patients (7.5%). The mean visual field test MD value was -11.8 ± 9.7 dB preoperatively and improved to -6.95 ± 6.9 dB postoperatively ($p<0.001$) (**Table 1**).

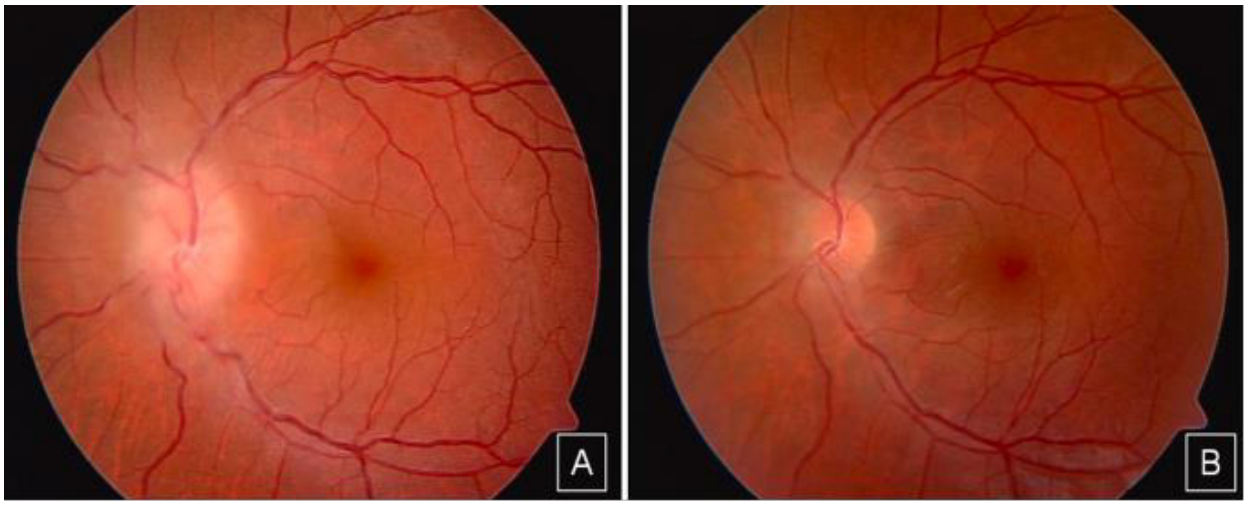

Figure 2. Optic nerve images of a patient with cerebral venous sinus thrombosis before (**A**) and after (**B**) optic nerve sheath fenestration.

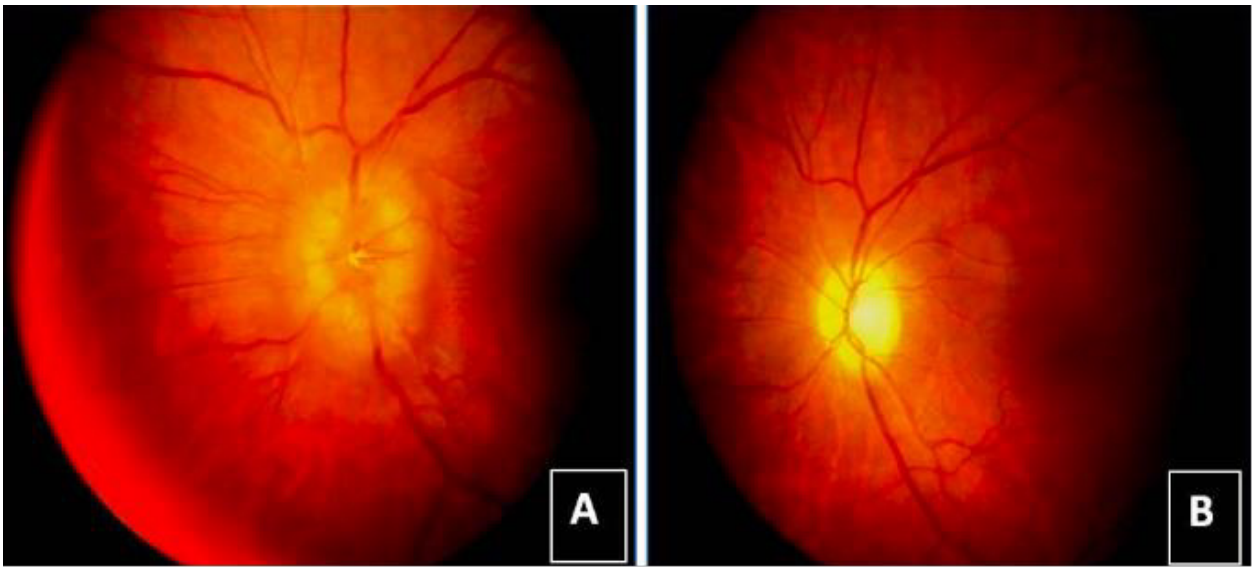

Figure 3. Papilledema (**A**) in a patient diagnosed with idiopathic intracranial hypertension. Resolution of the papilledema (**B**) after optic nerve sheath fenestration.

Table 1. Visual acuity and visual field mean deviation values before and after surgery in 40 eyes undergoing optic nerve sheath fenestration (Wilcoxon rank sum test, p<0.001).

	Visual Acuity (Log MAR)		Visual Field Mean Deviation (dB)	
	Preoperative	**Postoperative**	**Preoperative**	**Postoperative**
Mean (SD)	0.30 (0.5)	0.07 (0.1)	-11.8 (9.7)	-6.95 (6.9)
Data range	0.00 - 3.00	0.00 - 0.52	-1.08 - -34.11	-0.36 - -30.08

SD: Standard deviation.

During the postoperative follow-up period, the average number of visual field tests performed per eye was 7.1 (range 2-19). The average MD value from 21 reliable visual field tests conducted at the six-month follow-up visit was -7.0 ± 6.4 dB (p = 0.011) (**Table 2**). When examining changes in postoperative visual field MD values, initial noticeable improvement was seen at six months, with recovery continuing up to the fifth year (**Figure 4**). logMar visual acuity significantly improved (p=0.016) in 7 of 12 (58%) non-operated eyes in patients who underwent unilateral ONSF surgery. Before and after surgery, the last five patients maintained a visual acuity of 1.0. Of the 12 eyes that did not undergo surgery, 4 (33%) showed an improvement

Table 2. The change in the visual field "mean deviation" values of eyes undergoing optic nerve sheath fenestration after surgery (Wilcoxon signed ranks test, p<0.05).

	Preoperative	**3rd month**	**6th month**	**1st year**	**2nd year**	**3rd year**	**4th year**	**5th year**
Number of eyes	40	11	21	20	20	16	17	15
Mean Deviation "dB"(SD)	-11.8 (9.7)	-7.6 (5.8)	-7.0 (6.4)	-8.0 (7.4)	-6.6 (5.7)	-6.1 (7.3)	-6.4 (7.5)	-5.1 (4.6)
p-value		0.155	**0.011***	**0.021***	**0.023***	**0.001***	**0.000***	**0.027***

SD: Standard deviation.

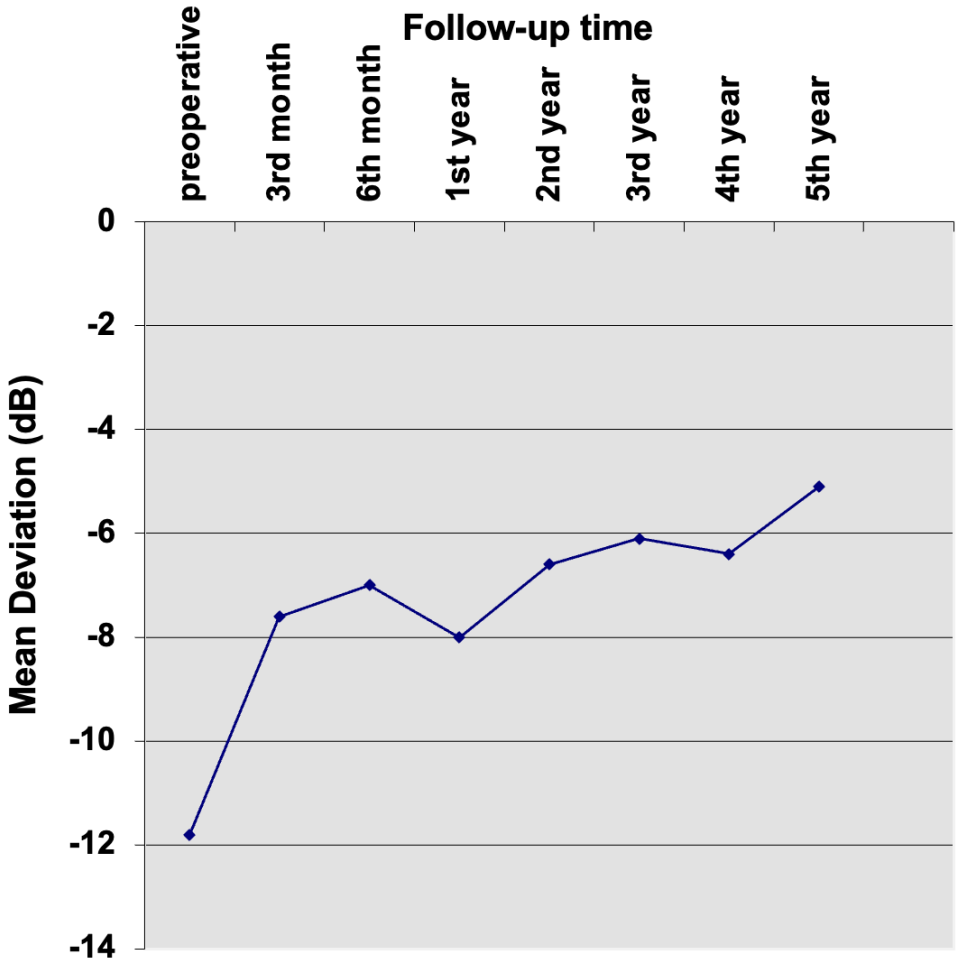

Figure 4. Changes in the visual field's mean deviation value over time in eyes treated with optic nerve sheath fenestration.

in visual acuity of at least two Snellen lines. Snellen visual acuity remained stable or improved by one line in eight eyes.

Among patients who received unilateral ONSF, visual field light sensitivities in the non-operated eyes demonstrated a statistically significant (p=0.003) improvement following surgery (preoperative mean MD: -11.4 ± 9.3 dB, range: -1.29 to -28.68 dB; postoperative mean MD: -4.3 ± 4.9 dB, range: -0.62 to -16.67 dB) (**Figure 5**). Of the 26 patients with headaches at their first visit, 19 (73%) had complete relief, 6 (23%) improved, and 1 (3.8%) still had headaches after surgery. The postoperative complications included esotropia and diplopia, perioptic pseudocyst formation, transient mydriasis, and anterior ischemic optic neuropathy. Each of these complications was observed in one eye.

Discussion

Patients with IIH and CVST may experience optic atrophy from papilledema, leading to permanent vision loss. Surgery is considered for patients who do not respond to medical treatment or have significant vision loss at initial examination. Due to its lower complication rate and superior efficacy in preserving optic nerve function, ONSF surgery is often the preferred surgical technique.

The visual outcomes of ONSF have been evaluated in several previous studies (**Table 4**). Numerous studies have found that patients with IIH and CVST often experience better visual function following ONSF. However, one study noted a relatively high incidence of postoperative decline in visual function[2]. Along with being mentioned in many studies about this observation, long-term results of ONSF surgery have been assessed in very few studies[20,25,26]. Our study provides the longest follow-up period to date for patients who have undergone ONSF surgery.

Acheson et al.[27] conducted ONSF surgery using a medial transconjunctival approach and nerve sheath excision on 20 eyes from 14 patients; of these, 11 had papilledema caused by IIH and 3 by CVST. Patients were followed for an average of 24 months (range: 12–84), with 5 of 11 eyes (45%) gaining at least two

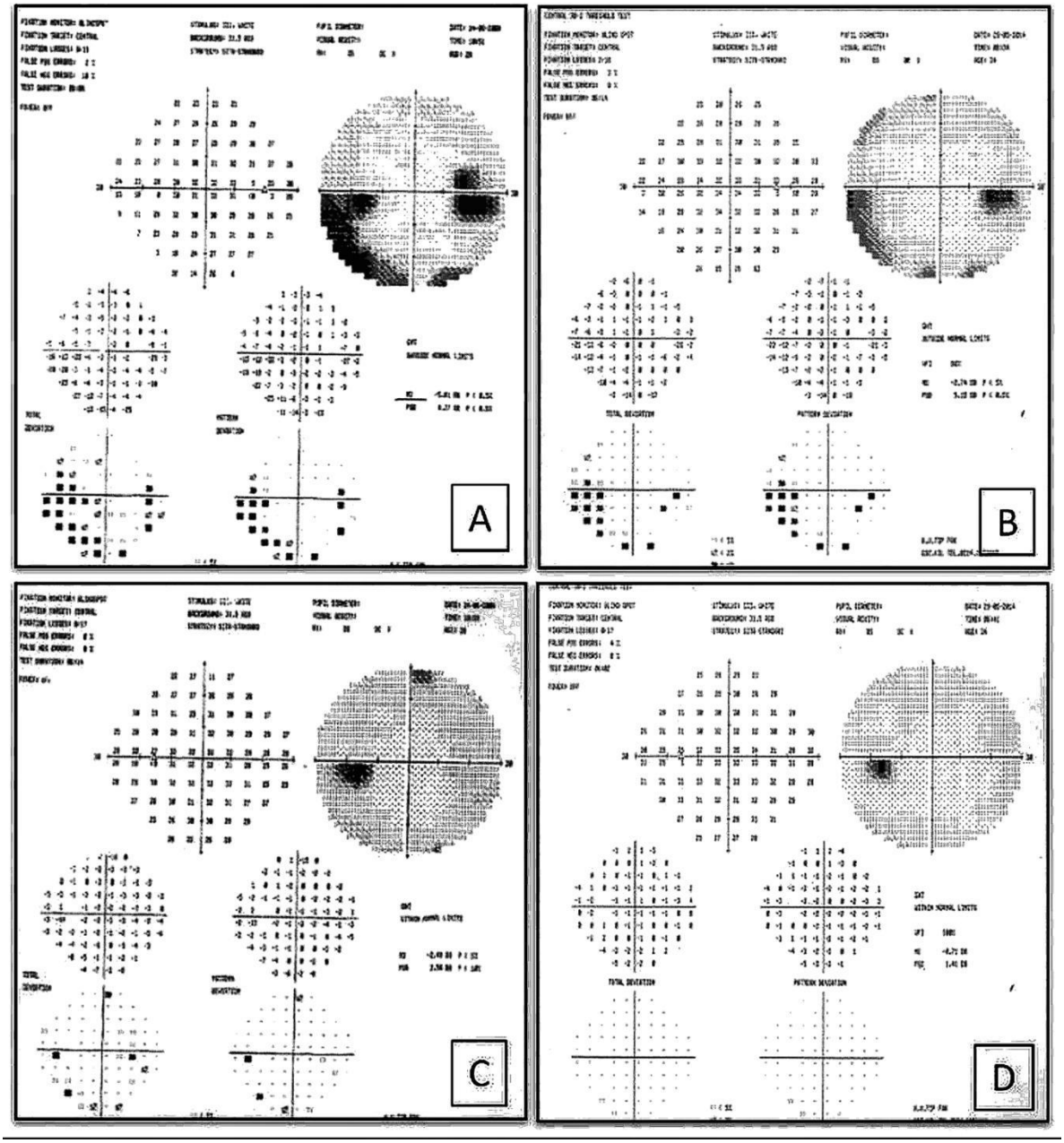

Figure 5. Visual field tests from a patient with idiopathic intracranial hypertension are shown before (**A**) and 70 months after (**B**) optic nerve sheath fenestration. (**C**) and (**D**) show natural improvement in the left eye's visual field for the same patient.

lines in Snellen visual acuity after surgery. Meanwhile, in 3 eyes (15%), visual acuity declined compared to preoperative values. No change was detected in the 9 eyes that had a preoperative visual acuity of 1.0. In that study, visual field assessments were conducted using Goldmann manual perimetry, and deterioration in the visual field was observed in 3 eyes (15%). Banta et al.[20] performed medial transconjunctival ONSF with nerve sheath excision on 158 eyes from 86 patients, with a mean follow-up of 20 months. In that study, visual field tests were conducted before and after surgery (although it was not specified whether manual or automated perimetry was used). Any decrease in visual field sensitivity was considered to indicate deterioration. In this study, following ONSF, 6 eyes experienced a decline only in visual acuity, another 6 showed deteriorations solely in the visual field, and 4 eyes exhibited declines in both visual acuity and visual field. Among the nine eyes that exhibited visual deterioration following the initial ONSF, subsequent improvement in visual function was observed after a second ONSF procedure.

Kelman et al.[1] conducted ONSF surgery using the nerve sheath incision technique on 21 eyes from 17 patients experiencing papilledema and worsening vision due to IIH. The patients were monitored for an average of 17 months, with follow-up periods ranging

from 11 to 26 months. Following surgery, papilledema resolved in every case, and visual acuity improved by at least two Snellen lines in 15 eyes. Of the five eyes that had a visual acuity of 1.0 prior to surgery, no changes were observed afterward.

A decrease in visual acuity was observed in one eye (5%). In that study, one eye developed an orbital hematoma and central retinal artery occlusion following surgery, resulting in loss of light perception in that eye. Spoor et al.[2] followed up on 75 eyes that underwent ONSF due to IIH over a period ranging from 6 to 60 months, and observed deterioration in visual function in 24 eyes (32%). In the study, the researchers used 30-2 Humphrey perimetry for visual field tests, considering changes of at least 2 dB in MD values to be significant. The authors noted that even after successful ONSF surgery in patients with IIH, long-term gradual worsening can still occur. This deterioration was noted after a mean duration of 10.4 months, with the observed data ranging from 1 to 39 months. Of the 24 eyes that underwent secondary ONSF, visual function improved in 5 eyes, remained unchanged in 13 eyes, and worsened in 6 eyes.

Chandrasekaran et al.[28] conducted ONSF on 51 eyes from 32 patients presenting with papilledema secondary to IIH. Among the 31 eyes with postoperative six-month follow-up data, 42% exhibited an improvement of at least 5 dB in visual field sensitivity. A deterioration of more than 5 dB was observed in one eye (3.2%), while in 17 eyes, the postoperative change was less than 5 dB. In that study, 13 out of 39 eyes (33%) showed an improvement of at least 2 Snellen lines in visual acuity. Fonseca et al.[29] used Humphrey automated perimetry for visual field testing and considered tests with less than 50% fixation losses to be reliable in their study comparing ONSF and shunt surgery in IIH. Of the 14 eyes that had undergone ONSF in the study, 7 improved by at least 5 ETDRS letters, 4 remained stable, and 3 showed a decrease of more than 5 letters in visual acuity. The mean MD value of the visual field before surgery was -23.59 dB, and after surgery it improved to -17.29 dB. Pineles et al.[22] performed ONSF on 50 eyes of 37 IIH patients, with follow-up ranging from 1 to 171 months (mean 52.5 months). Tests with less than 50% fixation loss on Humphrey automated perimetry were considered reliable. Reliable postoperative visual field tests were obtained in only 17 eyes. In those eyes following ONSF, mean visual field light sensitivity improved from -17 dB to -13 dB (p=0.2). In the postoperative period, deterioration in the visual field was observed in 3 eyes (18%). The study found that ONSF was most effective in patients who had better preoperative vision and received early treatment. Moreau et al.[16] conducted optic nerve sheath fenestration on 455 eyes in 236 patients diagnosed with IIH, with a mean follow-up period of 18.5 months. Of the 448 eyes with available preoperative and postoperative visual acuity data, 75 eyes (17%) showed an improvement of two or more Snellen lines. Additionally, visual acuity remained stable in 354 eyes (79%), while 19 eyes (4%) had a decrease of two or more Snellen lines. Nithyanandam et al.[30] performed ONSF on 41 eyes from 21 patients with papilledema due to IIH or CVST; in 10 eyes with IIH, Snellen visual acuity improved by at least two lines or remained stable. Based on the 30-2 Humphrey perimetry results, no deterioration in the visual field was detected in these 10 eyes. Postoperative visual recovery occurred in 4 out of 7 eyes that previously had no light perception and underwent ONSF due to cerebral venous sinus thrombosis.

Various studies have independently assessed patients who received unilateral and bilateral ONSF (**Table 3)**. Acheson et al.[27] reported that, after unilateral ONSF in 8 of 14 patients with IIH, 7 showed visual improvement in their non-operated eyes. Sergott et al.[18] reported that all 12 progressive IIH patients showed improvement in both eyes after unilateral ONSF. Alsuhaibani et al.[31] assessed papilledema in both operated and contralateral non-operated eyes of patients who underwent ONSF surgery for IIH. Papilledema grade significantly decreased in both operated and non-operated eyes. Our study also revealed improvement in visual function in non-operated eyes among patients who underwent unilateral ONSF. Preoperative and postoperative visual field mean MD values were -11.4 dB and -4.3 dB, respectively (p=0.003).

The mean follow-up period for patients in our study was 80.5 months, with a range from 36 to 152 months. This period is longer than that reported in the other studies (**Table 4**). We excluded patients with less than three years of follow-up to assess long-term outcomes of ONSF. One distinctive feature of our study compared to others is that we excluded visual field tests with reliability rates below 30% from the analysis. This approach facilitated the comparison of more reliable quantitative data.

Visual field light sensitivity improved in 37 out of 40 eyes (92.5%) following ONSF in our study, and none of these eyes exhibited any deterioration during the follow-up period. After ONSF, a reduction in visual field light sensitivity was observed in three eyes (7.5%, n=2 patients). For these eyes, the preoperative visual field MD values were -5.25 dB, -12.77 dB, and -6.56 dB. At the final postoperative visit, the values were -16.47 dB, -18.53 dB, and -8.91 dB, respectively. Visual field loss in one eye occurred immediately after surgery due to anterior ischemic optic neuropathy, resulting in optic nerve head swelling, soft exudates,

Table 3. Reported rates of bilateral ONSF across multiple studies in the literature.

Studies	Number of Patients	Number of Eyes	Bilateral ONSD (%)	Diagnosis
Kelman et al., 1992[1]	17	21	24	IIH
Acheson et al., 1994[27]	14	20	43	IIH and CVST
Sergott et al., 1988[18]	23	29	26	IIH
Banta et al., 2000[20]	86	158	84	IIH
Chandrasekaran et al., 2006[28]	32	51	59	IIH and CVST
Alsuhaibani et al., 2011[31]	78	88	62	IIH
Pineles et al., 2013[22]	37	50	35	IIH
Fonseca et al, 2014[29]	14	16	14	IIH
This study, 2015	26	40	54	IIH and CVST

ONSF: Optic nerve sheath fenestration; IIH: Idiopathic intracranial hypertension; CVST: Cerebral venous sinus thrombosis.

Table 4. Reported rates of visual acuity and/or visual field deterioration after optic nerve sheath decompression for idiopathic intracranial hypertension (IIH) in the English-language literature, according to follow-up duration.

Studies	Number of eyes	Visual acuity (%)	Visual Field (%)	Follow-up time (mean and data range, month)
Sergott et al.,1988[18]	29	2(%7)	2 (%7)	21,5 (3-45)
Kelman et al.,1992[1]	21	1 (%5)	1 (%5)	17(11-26)
Spoor et al.,1993[2]	75	-	24 (%32)	(6-60)
Acheson et al., 1994[27]	20	3 (15)	3 (%15)	24 (12-84)
Banta et al., 2000[20]	158	10 (%6)	10 (%12)	20 (1-108)
Knapp et al., 2005[21]	27	0	4 (%15)	9,6 (1-32 ay)
Chandrasekaran et al., 2006[28]	51	7 (%18)	1 (%3)	27,6 (0-121)
Pineles et al., 2013[22]	50	9 (%24)	3 (%18)	52,5 (1-171)
Moreau et al., 2014[16]	455	19 (%4)	7 (%3)	18,7 (0-120)
This study, 2015	40	2 (%5)	3 (%7,5)	80,5 (36-152)

hemorrhages, and an inferior altitudinal visual field defect. In our study, only 2 eyes from 1 patient (5%) showed long-term visual deterioration after ONSF. Visual field deterioration in this patient was identified during the 11-month follow-up following bilateral uncomplicated ONSF. Mitomycin-C was administered to both eyes of this patient during the surgical procedure. Although mitomycin-C is not typically part of the standard ONSF surgical protocol, it was administered to this patient to evaluate its potential for minimizing scar formation at the operation site. The potential toxic effect of mitomycin-C on the optic nerve in this patient may account for the gradual and delayed visual deterioration observed in both eyes[32].

In our study, following ONSF, Snellen visual acuity improved by two or more lines in 17 eyes (42.5%), while it remained stable or improved by one line in 21 eyes (52.5%). Snellen visual acuity decreased by one line in 2 eyes (5%) of 1 patient. Patients with stable vision demonstrated a visual acuity of 1.0 both preoperatively and postoperatively.

Two different theories regarding the mechanism of action of ONSF have been proposed. The first theory suggests that a gap in the optic nerve sheath leads to CSF leakage into the retrobulbar region, reducing CSF pressure in the perioptic space. The second proposes that fibrous tissue at the surgical site protects the optic nerve from elevated CSF pressure. Following unilateral ONSF, improvement of papilledema and visual function in the contralateral eye provides further support for the CSF leakage theory. A study analyzing secondary or tertiary ONSF in patients with IIH found

that short-term failure is most likely due to an insufficient gap in the optic nerve sheath, while long-term failure is probably caused by excessive fibrosis and scar formation[33]. We removed a 3x4 mm window from the dura-arachnoid sheath and washed the area with a steroid solution to reduce postoperative inflammation. We believe that this method may decrease the risk of recurrence and visual deterioration compared with the incisional technique.

Headache is another significant symptom of increased intracranial pressure, in addition to papilledema and visual loss, that can cause discomfort for patient. The effect of optic nerve sheath fenestration on headache varies across different studies. Banta et al.[20] reported that headache resolved in only 8 out of 61 patients (13%). Conversely, in a study conducted by Kelman et al.[1], 9 out of 10 patients (90%) who experienced headaches prior to surgery reported either complete relief or a reduction in their symptoms, while only one patient continued to experience headaches. In our study, headache resolved entirely in 19 of the 26 patients (73%) who presented with this symptom at their initial assessment. Six patients (23%) experienced a reduction in headaches, while one patient (4%) continued to have headaches following the operation.

Optic nerve sheath fenestration is typically associated with mild and transient complications, such as temporary ocular motility defects, diplopia, retrobulbar hemorrhage, transient pupillary irregularities, superficial keratopathy, chemosis, periorbital edema, ecchymosis, and ptosis. The most common complication is temporary ocular motility defects[16,34]. Only a small number of complications, such as traumatic optic neuropathy and central retinal artery occlusion, have been reported[1,21]. The largest study on this topic reported that 7.2% of 236 patients with IIH who underwent ONSF via the medial conjunctival approach experienced surgical complications[16]. The most common complication in that study was heterotropia-diplopia.

The complications observed in our study were esotropia and diplopia, perioptic pseudocyst, transient mydriasis, and anterior ischemic optic neuropathy. Anterior ischemic optic neuropathy developed in one eye immediately after surgery, resulting in decreased visual acuity. However, during follow-up, visual acuity returned to preoperative levels. Despite this improvement, an altitudinal visual field defect persisted. Esotropia resolved after strabismus surgery. Additionally, the perioptic pseudocyst was excised surgically.

This study demonstrates that, over the long term, ONSF surgery produces positive outcomes for patients with IIH and CVST. This procedure may be preferable for these individuals due to its lower complication rate and fewer reoperations compared with other treatments, such as lumboperitoneal or ventriculoperitoneal shunting.

Our study has certain limitations, notably its retrospective design and the fact that it reflects the experience of a single center. Additionally, the CVST subgroup is relatively small, and quantification of papilledema using optical coherence tomography as well as retinal nerve fiber layer thickness assessments was not performed. Furthermore, quality of life metrics were not applied to the patient cohort. Another limitation of our study is that it included only a single treatment option for IIH. Comparative groups involving alternative modalities such as shunting or medical management were not analyzed.

In conclusion, patients with papilledema and optic neuropathy caused by idiopathic intracranial hypertension or cerebral venous sinus thrombosis often experience improvement in visual function following optic nerve sheath fenestration surgery using the nerve sheath excision method. In this study, only 5% of eyes experienced long-term visual deterioration during the postoperative follow-up period.

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Author contributions

Bülent Yazıcı: Supervision

Mediha Tok Çevik: Data collection

All authors have read and approved the final version of the manuscript.

Conflict of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

AI statement

No artificial intelligence tools were used in the writing, analysis, interpretation, or review of this article.

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Review article

Obesity in occupational health: The position of the occupational physician in preventive practice

Obesidad en salud ocupacional: la posición del médico del trabajo en la práctica preventiva

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Abstract

Over recent decades, obesity has become firmly established as one of the leading public health problems worldwide, with a steadily increasing prevalence that substantially affects the working-age population. This excess adiposity is associated not only with a higher risk of morbidity and mortality from cardiovascular, metabolic, and musculoskeletal diseases but also with impaired functional capacity among workers, reduced productivity, and diminished long-term participation in the labor market.

In the field of occupational health, obesity interacts with organizational, ergonomic, and psychosocial factors, increasing the likelihood of occupational accidents, absenteeism, temporary disability, and early retirement, with a significant impact on both companies and social protection systems. Despite this evidence, obesity remains underrepresented in risk assessment, health surveillance, and preventive policies implemented in workplaces, which continue to focus predominantly on traditional physical, chemical, or biological hazards.

This article sets out the positioning of the occupational physician in preventive practice, considering obesity as a key determinant of occupational health. It proposes a comprehensive framework for addressing obesity in the workplace that integrates clinical, preventive, and organizational perspectives, with the aim of informing health policy decisions, guiding corporate strategies, and shaping priority research agendas.

Keywords: Obesity. Occupational health. Occupational medicine. Occupational risks. Workplace wellness programs. Health promotion.

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Resumen

En las últimas décadas, la obesidad se ha consolidado como uno de los principales problemas de salud pública a nivel mundial, con una prevalencia en constante aumento que afecta sustancialmente a la población en edad laboral. Este exceso de adiposidad se asocia no solo con un mayor riesgo de morbilidad y mortalidad por enfermedades cardiovasculares, metabólicas y musculoesqueléticas, sino también con una alteración de la capacidad funcional de los trabajadores, una reducción de la productividad y una menor participación a largo plazo en el mercado laboral.

En el ámbito de la salud laboral, la obesidad interactúa con factores organizacionales, ergonómicos y psicosociales, aumentando la probabilidad de accidentes de trabajo, absentismo, incapacidad temporal y jubilación anticipada, con un impacto significativo tanto en las empresas como en los sistemas de protección social. A pesar de esta evidencia, la obesidad sigue estando infrarrepresentada en la evaluación de riesgos, la vigilancia de la salud y las políticas preventivas implementadas en los lugares de trabajo, que continúan centrándose predominantemente en los riesgos físicos, químicos o biológicos tradicionales.

Este artículo establece el posicionamiento del médico del trabajo en la práctica preventiva, considerando la obesidad como un determinante clave de la salud laboral. Propone un marco integral para el abordaje de la obesidad en el lugar de trabajo que integra perspectivas clínicas, preventivas y organizacionales, con el objetivo de fundamentar las decisiones de política sanitaria, orientar las estrategias corporativas y configurar las agendas de investigación prioritarias.

Palabras clave: Obesidad. Salud laboral. Medicina del trabajo. Riesgos laborales. Programas de bienestar laboral. Promoción de la salud.

Introduction

Obesity is increasingly relevant in occupational health because it affects functional capacity, safety, chronic disease risk, and long-term work participation. In this context, occupational physicians need practical frameworks that go beyond body weight alone and help translate current obesity concepts into preventive action in the workplace.

The Lancet Commission article constructs a new definitional framework: it confers identity to "clinical obesity" as a disease in its own right, distinct from a mere risk factor; establishes dual diagnostic criteria (anthropometric plus clinical); and proposes a preclinical/clinical dichotomy as a tool to structure prevention and treatment[1].

The ES article acts as a critical appraisal: it endorses the conceptual advance and the critique of the Body Mass Index (BMI), but questions the operability of the binary model, the category of preclinical obesity, the exclusion of type 2 diabetes as a diagnostic manifestation, and the insistence on detailed causal attribution. In practice, it proposes harmonizing the Commission's framework with pre-existing staging systems such as the Edmonton Obesity Staging System (EOSS)[2], the European Association for the Study of Obesity (EASO)[3], and the American Association of Clinical Endocrinology (AACE)[4], as well as with more pragmatic, risk- and benefit-based access criteria[5].

The comparison between both approaches and their application in the daily practice of occupational physicians, from the perspective of prevention and health promotion within the healthy workplace framework, is presented in **Table 1**.

Beyond the occupational sphere, the conceptual evolution of obesity calls for progress towards models that integrate not only the characterization of adiposity and the presence of organ dysfunction but also a global functional assessment of the individual. In this regard, a clinical–functional approach makes it possible to move beyond both a purely anthropometric view and the strict dichotomy between preclinical and clinical obesity, by incorporating functional capacity, exercise tolerance, and impact on activities of daily living as key elements for decision-making. This model is applicable to diverse care contexts and populations and facilitates a more accurate, continuous, and person-centered assessment.

This paper argues that, in occupational health practice, obesity should be approached through a clinical–functional and preventive model that prioritizes work ability, early risk identification, and feasible workplace interventions.

Conceptual basis and scope of this position paper

This position paper is based on a narrative and practice-oriented analysis of recent conceptual frameworks on obesity, with particular emphasis on the Lancet Diabetes & Endocrinology Commission and the Endocrine Society critique, complemented by occupational health regulations, clinical staging systems, and evidence on workplace prevention strategies. Its aim is to define the role of the occupational physician in preventive practice and to translate current obesity frameworks into an operational model applicable to health surveillance, fitness-for-work assessment, and workplace health promotion.

Table 1. Comparison of the Lancet and ES publications and their practical application in occupational health.

Key axis	Lancet Commission framework (clinical / preclinical obesity)	ES / Endocrine Society approach	Operational message for workplace campaigns
Concept of health vs. disease	Distinguishes between "preclinical obesity" (excess adiposity without functional damage) and "clinical obesity" (organ dysfunction and/or limitations in activities of daily living due to adiposity).	It accepts the framework but questions the stability of this boundary; "preclinical" already entails high risk and may be interpreted as "not a disease," delaying action.	In the occupational setting, it is preferable to speak of a "risk continuum" rather than healthy/sick and to focus messages on preventing progression to functional damage and maintaining work ability.
Role of BMI	BMI is relegated to population screening; it insists on confirming excess fat with other indicators (waist circumference, waist-to-height ratio, body fat) before labeling obesity.	It agrees on moving beyond BMI alone, but stresses that implementing additional measures must be simple and realistic.	In occupational health surveillance, BMI can be used as an entry point, but protocols should include at least waist circumference and cardiometabolic risk, not just "weight".
Focus on function and work ability	Clinical obesity includes limitations in mobility and activities of daily living as a central criterion, aligned with impact on job performance and safety.	It emphasizes that classifications must be useful for treatment and prioritization decisions, and values staging systems that integrate functionality and mental health.	Key message: shift from "weight" to "function": ergonomics, fatigue, sleep, exercise tolerance, and safety in high-risk tasks as the core of preventive campaigns.
Management of "obesity without apparent comorbidity"	Preclinical obesity: recommends monitoring and health counseling, with more intensive intervention only in high-risk cases or specific contexts.	It points out that these individuals already have an increased risk of type 2 diabetes, CVD, and cancer; delaying intervention because they are in the "preclinical" category may be clinically questionable.	For companies, "obesity without disease" is an opportunity to implement preventive programs (physical activity, nutrition, sleep, stress) before the onset of limitations, safety and health risks, disability, or incapacity of any degree.
Stigma and communication	It insists on non-stigmatizing, person-centered language and on avoiding blaming the individual; it recognizes the importance of social determinants.	Shares concerns about equity and warns that complex diagnostic categories should not become filters for denying treatment.	Use a campaign narrative based on "work environments that promote health" and "shared employer–worker responsibility," avoiding blame-focused messages about weight and including specific training and information at all levels of the company, including middle management.
Practical classification tools	Proposes a solid conceptual framework but requires confirmation of adiposity and assessment of multiple organs, which is difficult to apply as a screening tool in companies.	Recommends relying on simpler staging systems (EOSS, EASO) that already integrate risk, comorbidity, and functionality and are more operational.	In occupational health, simple algorithms are advisable (BMI + waist circumference + comorbidities + functional capacity) as a basis for assessing fitness/capacity, referral, and prioritization, without replicating the full complexity of the clinical framework.

...continuation table 1

Key axis	Lancet Commission framework (clinical / preclinical obesity)	ES / Endocrine Society approach	Operational message for workplace campaigns
Intervention priority	The Lancet framework prioritizes resources for people with clinical obesity (functional damage), while maintaining preventive strategies for the preclinical category.	It stresses that the real constraint lies in the cost of treatments, not in the definition, and suggests prioritizing by risk/benefit rather than rigid labels.	Companies can justify the return on preventive investment and first target groups at higher functional risk (night shifts, physically demanding jobs, highly sedentary roles, obesity plus comorbidity) without abandoning universal interventions within a healthy-workplace framework.
Integration of mental health and quality of life	Mental health is mentioned but is not central to the criteria for clinical obesity.	It calls for explicit integration of depression, anxiety, and quality of life because of their prognostic importance.	Workplace campaigns should include modules on stress, sleep, nutrition, physical activity, psychosocial load, and organizational culture (shifts, overtime, demands), linking these factors to obesity, risk, absenteeism, and productivity.
Message to employers	"Clinical obesity" = chronic disease with functional damage that must receive treatment and support; "preclinical" = need for structured prevention.	It warns that redefining obesity must not be used to restrict access to effective interventions or to create additional bureaucratic barriers.	Positioning key: the company presents itself as a "preventive healthy environment" that reduces disability, absenteeism, and occupational contingencies and promotes the well-being of workers rather than acting merely as a "weight evaluator."

During the preparation of this position paper, a structured methodological process was followed, combining a narrative review of recent literature on conceptual frameworks for obesity with a practice-oriented analysis focused on prevention in the workplace. Drawing on the proposals of the Lancet Diabetes Endocrinology Commission and the critique by the Endocrine Society, the authors conducted a comparative reading of both texts and of the main clinical staging systems, as well as Spanish regulations on occupational health and international guidelines on health surveillance and workplace health promotion. This material was discussed in several successive rounds, with iterative exchange of drafts and internal peer review among the co-authors, until consensus was reached on the positioning of the occupational physician in preventive practice and on the clinical–functional model proposed as the central axis of the document.

Towards a clinical–functional model of obesity: implications for occupational health

From an occupational health perspective, the most useful approach is not a binary distinction between health and disease but a continuum-based model that links adiposity, functional capacity, cardiometabolic risk, and work ability.

The work of occupational physicians within occupational risk prevention services (ORPS) in Spain is highly regulated and constrained by a specific legal framework, and is primarily focused on health surveillance in relation to the risks arising from the work activity and the job. This framework includes: Law 31/1995 on the Prevention of Occupational Risks (LPRL)[6], which establishes the general duty of protection and the obligation of health surveillance; Royal Decree 39/1997[7] on Prevention Services, which defines the functions of ORPS and characterises them as multidisciplinary teams where occupational physicians interact with safety, hygiene, and ergonomics specialists; Royal Decree 843/2011[8], which regulates the basic criteria for organising resources to deliver the healthcare activities of ORPS, authorising them and maintaining their standards; and the Specific Health Surveillance Protocols issued by the Ministry of Health[9], which constitute the mandatory technical guidelines for conducting health examinations targeted at specific risks.

This regulatory context explains why occupational health approaches must be operational, proportionate, and prevention-oriented.

The core competencies of the specialty, as laid down in the formal training program, combine clinical, preventive, legal, and managerial functions with the overarching aims of protecting workers' health, preventing occupational diseases and accidents, and adapting work to the individual[10].

Within this clinical–functional framework, the concept of a "risk continuum" acknowledges that work ability exists along a dynamic spectrum, where the goal is to prevent progression from risk factors to functional impairment and work disability, rather than to classify workers dichotomously as healthy or ill. This biopsychosocial perspective emphasizes continuous functional assessment and the maintenance of work ability as central objectives of occupational medicine[11].

The 2025 guidelines of the American College of Occupational and Environmental Medicine (ACOEM) on the prevention of work disability state that clinicians should identify, at an early stage, individuals at risk of work disability and stratify that risk in order to provide stepped interventions. This paradigm, known as CLRRT (capacity, limitation, risk, restriction, and tolerance), facilitates this function-centered approach. The assessment should incorporate biological factors (tissue injury), psychological factors (fear-avoidance beliefs), and sociocultural factors (work environment) that influence the transition towards functional decline.

The Work Ability Index (WAI)[12] is a validated tool that operationalizes this continuum by evaluating the worker's current ability in relation to the job demands and their best-ever work ability. Factors such as age, self-reported diseases, and physically demanding work increase the likelihood of moderate or poor work ability. Although the supporting evidence is of limited quality, early intervention is generally associated with faster recovery and a lower risk of prolonged disability.

The 2026 ACC/AHA[13] guidelines recommend that combining waist circumference with BMI is the best approach to assess obesity-related risk. For the detection of metabolic syndrome in workers, multiple studies have shown that the waist-to-height ratio (WHtR) and waist circumference (WC) have greater predictive capacity than BMI[14]. To these parameters, one can add the Body Roundness Index (BRI), an anthropometric index developed in 2013[15] that integrates height, waist circumference, and body shape to better estimate total and visceral body fat compared with BMI. It is calculated using the following formula:

$$BRI = 364.2 - 365.5 \times \sqrt{1 - \left(\frac{WC/(2\pi)}{0.5 \times height}\right)^2}$$

where WC is the waist circumference.

Despite its robust theoretical underpinnings, there is disagreement regarding its ability to identify cardiovascular disease compared with WC and WHtR[16]. The main advantage of BRI is that it incorporates height into its calculation, making it independent of stature; however, this does not consistently translate into clinical superiority over WHtR, which is also height-independent and simpler to calculate.

In the world of work, the role of the occupational physician within prevention services is grounded in the evidence supporting the assertion that health surveillance protocols should incorporate at least waist circumference alongside BMI, as has been shown in studies conducted in working populations[17]. The approach should be holistic: assessing functional capacity, exercise tolerance, sleep quality, fatigue, and job-specific injury risk, rather than weight alone. This enables personalized interventions that enhance safety and productivity while respecting workers' dignity[18].

This pragmatic approach is consistent with simple decision-making strategies based on BMI, waist circumference, comorbidity, and functional capacity.

For practical purposes in occupational health, the most appropriate approach is to consider that obesity without metabolic disease should not be classified as benign or low risk but rather as an opportunity for primary prevention. Preventive programs focusing on physical activity, nutrition, sleep, and stress management are more effective when implemented before the onset of functional limitations, safety risks, disability, or incapacity. Even a 5–10% reduction in body weight produces clinically significant benefits without the need to achieve normal weight[19].

In occupational medicine, the narrative should shift from "individual responsibility for weight" to "work environments that promote health" and "shared responsibility between employer and worker." Successful programs require organizational commitment to environmental and policy changes, combined with voluntary opportunities for workers to engage in support programs. Multilevel training, particularly for middle management, is essential to implement this integrated model and to avoid blame-inducing messages that increase stigma and undermine health objectives[20].

The American Heart Association (AHA) defines seven traditional biometric measures for workplace screening: blood pressure, glucose, cholesterol, physical activity, diet, BMI, and tobacco use. Specifically, the AHA recommends adding waist circumference to BMI because the diagnostic accuracy of BMI for obesity is particularly limited in intermediate BMI ranges, in men, and in older adults; moreover, abdominal adiposity provides a more refined indicator of cardiovascular mortality risk than BMI alone[21]. The AHA also clearly states that "interventions targeting higher-risk employees appear to be particularly effective" and that screenings may be even more effective in identifying risk factors and yielding a better return on investment if they are directed towards higher-risk individuals[22].

Modules on stress, sleep, nutrition, physical activity, psychosocial load, and organizational culture should be integrated into workplace prevention campaigns because they are causally interconnected (stress affects sleep, diet, and physical activity; sleep affects appetite and metabolism), have synergistic effects on obesity and cardiometabolic risk, directly impact absenteeism, presenteeism, and productivity, and multicomponent interventions are more effective than isolated interventions (**Table 2**).

The company should position itself as a facilitator of an environment that makes it easier to be healthy, with the occupational physician responsible for assessing fitness for work and safeguarding workers' health. This approach entails a paradigm shift in obesity (**Table 3**): it reduces functional limitations or loss of function due to obesity and the associated stigma or discrimination; increases participation by avoiding worker blame; is more effective because it addresses environmental and organizational determinants; generates a higher return on investment by improving productivity, reducing absenteeism, and preventing disability; and complies with ethical principles of respect for body diversity and individual autonomy.

The evidence shows that investing in employee health should be a priority objective through comprehensive wellness programs that also improve performance and corporate profitability. Occupational physicians have sufficient tools to understand workers' health status and to propose that employers implement specific obesity programs. They also have supporting materials endorsed by scientific societies, such as the scientific–educational guide *Obesity and Work*, endorsed by the Spanish Association of Specialists in Occupational Medicine (AEEMT)[23], and the *Practical Handbook for Daily Clinical Practice*[24].

This approach not only redefines obesity but also contributes to evolving its management towards models centered on functionality, risk, and clinical benefit, moving beyond dichotomous views and facilitating more precise, person-centered decision-making.

In practical terms, this means that occupational health surveillance should combine simple anthropometric

Table 2. Multicomponent programs and their scientific evidence in obesity and work.

Module	Key content	Connection with obesity and productivity
1. Work-related stress	Demands–control–support, financial stress, coping techniques.	Chronic stress → overeating, inactivity, weight gain (OR 1.73 with cumulative exposure)[25,26].
2. Sleep	Sleep hygiene, optimal duration (7–8 h), detection of disorders.	Short sleep → increased energy intake, accumulation of visceral fat, higher risk of obesity[27].
3. Nutrition	Mediterranean diet, mindful eating, meal planning.	Unhealthy diet + long working hours = synergistic effect on obesity and cardiometabolic risk[28].
4. Physical activity	Reduction of sedentary time, active breaks, structured exercise.	Combined diet and physical activity interventions improve stress and sleep and reduce adiposity[29].
5. Working hours and shifts	Limits on working hours, shift rotation, recovery.	≥ 55 h/week are associated with higher risk of obesity and lower levels of exercise[30].
6. Organizational culture	Leadership, social support, participatory job redesign.	Low social support is associated with disturbed sleep and presenteeism; multilevel interventions are more effective[31, 32].

Table 3. Shift in the preventive approach to obesity in occupational health.

Traditional approach (to avoid)	"Healthy environment" approach (to adopt)
"Weight-control programme"	"Comprehensive wellness programme".
"Obesity assessment"	"Assessment of functional capacity and health".
"Weight loss as the goal"	"Improved energy, sleep, mobility, and well-being".
"Individual responsibility of the worker"	"Shared employer–worker responsibility".
"Incentives for weight loss"	"Incentives for participation in healthy activities".
"BMI screening"	"Screening of cardiometabolic risk and functional capacity".

measures, assessment of comorbidity and work ability, and early preventive interventions adapted to the specific occupational context.

Considerations of both approaches regarding their practical utility in occupational health

Although both frameworks are valuable, they serve different purposes in occupational health. The Lancet Commission offers greater conceptual precision for defining obesity as a disease, whereas the Endocrine Society approach is more applicable to everyday occupational practice because it is more compatible with multicausality, functionality-based assessment, and the operational constraints of prevention services (**Figure 1**).

In occupational medicine there is a need to make rapid decisions on fitness for work, to have tools that can be applied in health examinations/medical check-ups, and to rely on reproducible criteria in health surveillance.

- ES does not require strict proof of "caused by obesity," allows for multicausality (the rule among workers), and is compatible with systems such as EOSS or AACE, which are more usable in clinical practice.
- Lancet Commission requires fine causal attribution, which is difficult in real-world occupational practice and may entail additional testing, making it less feasible in collective surveillance.

Among workers, pathology is usually multifactorial (age, lifestyle, work, comorbidity), and it is rarely possible to demonstrate that a given condition is "caused solely by obesity".

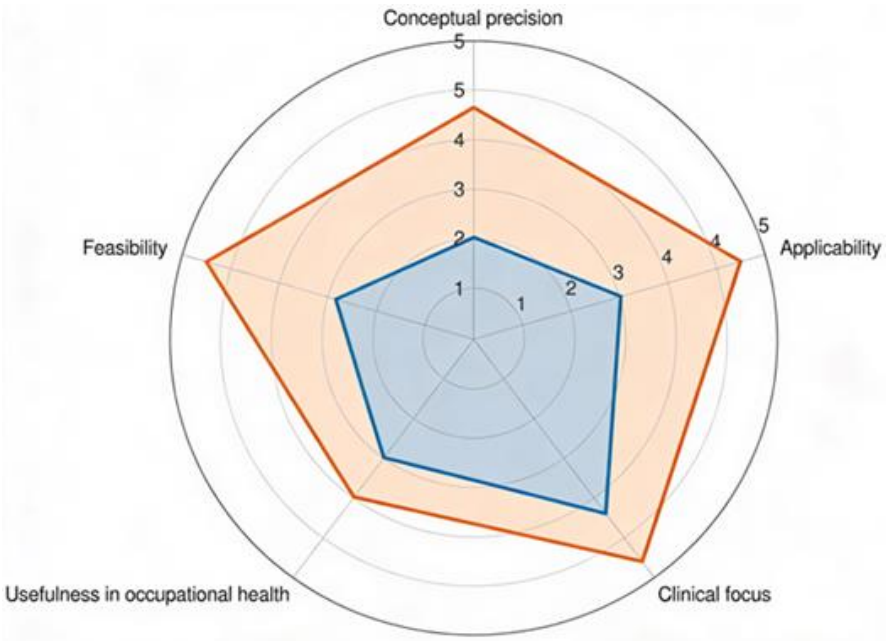

Figure 1. Comparison of The Lancet vs. JCEM in Occupational Health. Own elaboration

The model proposed by *The Lancet* shows greater conceptual strength, whereas *The Journal of Clinical Endocrinology & Metabolism* offers greater clinical applicability and usefulness in occupational health.

- ES acknowledges this explicitly.
- The Lancet Commission attempts to "isolate obesity as a cause," which is not very realistic in occupational risk prevention.

Health surveillance at work requires identifying risk—not only established disease—and acting at an early stage.

- Lancet Commission includes the category of preclinical obesity, which may be interpreted as "not a disease" and thus delay preventive interventions in workers.
- ES recognizes that there is already significant risk in early stages and promotes anticipatory intervention, which is key in occupational risk prevention.

Regarding the impact on fitness for work, occupational medicine is concerned not only with disease but also with functional capacity and safety conditions in the workplace.

- ES: better integrates functionality, quality of life, and mental health and is more closely aligned with decisions on fitness and job adaptation.
- Lancet Commission: focuses more on "objectifiable" organ dysfunction and may underestimate limitations that are relevant for work.

Under regulations such as Law 31/1995 on the Prevention of Occupational Risks and Royal Decree 39/1997, resources are limited and health surveillance must be efficient.

- Lancet Commission requires more tests and more extensive assessment, which makes it less viable in prevention services.
- ES is more flexible and therefore better adapted to real-world resource constraints.

Taking into account the biopsychosocial approach that underpins occupational health (and is crucial in the workplace):

- ES places greater emphasis on mental health and quality of life, which are highly relevant for absenteeism, performance, and temporary disability.
- Lancet Commission has a more limited capacity to integrate these dimensions into its diagnostic criteria.
- Se pueden destacar esos dos puntos con un breve apartado específico dentro del texto, por ejemplo al final de la comparación entre ambos modelos. Te propongo este desarrollo (en inglés, para mantener coherencia con el paper) que puedes ajustar en extensión:

Practical limitations of the Lancet Commission model

Despite its conceptual robustness, the Lancet Commission framework has important practical limitations in occupational health settings. It requires detailed causal attribution and confirmation of organ damage, which often demands additional tests and time that are not feasible in routine health surveillance or in large working populations. In real-world prevention services, where multimorbidity and multicausality are the rule, isolating obesity as the main cause of functional impairment is rarely possible and may delay early preventive action. In addition, the distinction between preclinical and clinical obesity may inadvertently reinforce a binary view of disease that does not fit the continuum-based approach needed to preserve work ability and prevent disability. From an operational perspective, its implementation would require complex screening protocols, a greater number of complementary tests, and advanced recording systems, which is in tension with the limited resources of many occupational health services and with the need for simple, reproducible tools that can be easily integrated into periodic medical examinations.

Potential biases and gaps in the Endocrine Society approach

The Endocrine Society's appraisal, although more pragmatic and aligned with everyday occupational practice, also presents potential biases and gaps. Its emphasis on clinical usability and flexibility may lead to heterogeneous implementation, with variability in how risk, functionality, and comorbidity are actually assessed across different companies or services. By prioritizing existing staging systems and operational criteria, there is a risk of underestimating the need for more precise definitions of obesity as a disease and for harmonized thresholds that facilitate comparisons across studies and health systems. Moreover, although the approach explicitly incorporates mental health and quality of life, it still provides limited operational guidance on how to systematically integrate psychosocial and organizational determinants of obesity into occupational risk assessment and preventive interventions. To translate its proposals into practice, it would be necessary to develop specific implementation tools for the workplace, such as screening algorithms that combine body mass index and waist circumference with work ability indices, stepped referral protocols according to functional risk, and multicomponent workplace programs (training modules on stress, sleep, nutrition, physical activity, and organizational culture) that can be applied consistently within the framework of health surveillance and workplace health promotion plans.

To mitigate the risk of limited international projection, this position paper deliberately situates its proposals within widely used global frameworks and guidelines and presents the Spanish regulatory context as a transferable example rather than an exceptional case. By grounding the recommendations in internationally recognized staging systems, cardiometabolic risk markers, and workplace health promotion evidence, the operational model described here can be adapted to different legal and organizational environments beyond Spain. Furthermore, the emphasis on simple, scalable tools for health surveillance and multicomponent workplace programs is intended to facilitate uptake in diverse occupational health systems, thereby enhancing the external validity and global relevance of the proposed approach.

Conclusion

In light of the strengths and weaknesses of both approaches in occupational health, it can be concluded that both models are of great interest; however, in line with The Lancet Commission recommendations, their applicability is greater for defining what constitutes disease (conceptual framework), for informing health policy, and for designing research projects in occupational medicine. The contribution of the *Journal of Clinical Endocrinology & Metabolism* is more useful for daily clinical practice, health surveillance, and decision-making regarding workers.

Although the framework proposed by The Lancet Commission provides a more precise conceptual definition of obesity as a disease, the ES approach is more useful in occupational health because of its greater clinical applicability, better adaptation to multicausality, integration of functionality, and feasibility in resource-limited settings, thereby facilitating decision-making in health surveillance and fitness-for-work assessment.

Based on the preceding analysis, this position paper explicitly advocates for a clinical–functional, continuum-based model of obesity that integrates adiposity, cardiometabolic risk, functional capacity, and work ability as the primary reference framework for occupational health practice. Within this model, the Endocrine Society–aligned approach, complemented by pragmatic staging systems such as EOSS, EASO, or AACE, is proposed as the preferred operational tool for decision-making in health surveillance, fitness-for-work assessment, and workplace health promotion.

The two conceptual frameworks are not presented as mutually exclusive but as complementary, with different areas of preferential use. The Lancet Commission model is particularly useful for defining what

constitutes disease, informing policy debates, and structuring research agendas in occupational medicine and public health, especially when precise nosological boundaries and comparative data across countries or systems are required. By contrast, the Endocrine Society approach is better suited to everyday occupational health settings, where multicausality is the norm, resources are limited, and clinicians must make timely, function-oriented decisions about fitness for work, job adaptation, and the prioritization of preventive interventions.

In occupational medicine, the key question is not whether excess weight is present in isolation, but whether obesity is already affecting function, safety, work ability, or future disability risk.

This perspective supports a shift towards early, function-oriented, and workplace-adapted preventive strategies.

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Miguel León-Sanz: Conceptualización, Análisis formal, Visualización y Supervisión.

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Use of artificial intelligence tools

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Review article

Occupational exposure to chemical agents and hematological malignancies: a systematic review of epidemiological evidence

Exposición ocupacional a agentes químicos y neoplasias hematológicas: una revisión sistemática de la evidencia epidemiológica

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Abstract

Objectives: Occupational exposure to chemical agents is a major preventable cause of cancer worldwide. This systematic review synthesized recent epidemiological evidence on the association between occupational chemical exposures and the risk of hematological malignancies, including leukemias, lymphomas, and multiple myeloma, in workers and, secondarily, in their offspring.

Methods: A systematic review was conducted in accordance with PRISMA 2020. MEDLINE (via PubMed), EMBASE, and Web of Science were searched for studies published between 2015 and 2025. Observational studies assessing occupational exposure to chemical agents and the incidence of hematological malignancies were included. Data extraction covered study design, population, exposure assessment, cancer subtype, and risk estimates. Methodological quality and risk of bias were assessed using standardized tools, and findings were synthesized qualitatively due to marked heterogeneity.

Results: Thirteen studies met the inclusion criteria (5 cohort, 6 case–control, and 2 population-based or ecological). Overall, the evidence indicates consistent associations between occupational exposure to selected chemical agents and increased risks of hematological malignancies, particularly lymphomas and leukemias. The most consistent associations were observed for pesticide exposures, especially organophosphate and carbamate insecticides, often with dose–response patterns. Associations with benzene, organic solvents, and radon were also reported, although with greater heterogeneity. Evidence on formaldehyde and parental occupational exposure was limited and inconclusive. Most studies showed moderate risk of bias, mainly due to exposure misclassification and residual confounding.

Conclusions: Occupational exposure to specific chemical agents, particularly certain pesticides, is associated with an increased risk of hematological malignancies. These findings support the prioritization of primary prevention, tighter exposure control, and strengthened occupational health surveillance in high-risk sectors and highlight the need for well-designed prospective studies with refined exposure assessment and detailed subtype analyses.

Keywords: Occupational exposure. Chemical agents. Hematological malignancies. Pesticides. Occupational cancer. Epidemiology.

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Resumen

Objetivos: La exposición ocupacional a agentes químicos es una de las principales causas prevenibles de cáncer a nivel mundial. Esta revisión sistemática sintetizó la evidencia epidemiológica reciente sobre la asociación entre las exposiciones químicas ocupacionales y el riesgo de neoplasias hematológicas, incluyendo leucemias, linfomas y mieloma múltiple, en los trabajadores y, de forma secundaria, en su descendencia.

Métodos: Se llevó a cabo una revisión sistemática de acuerdo con las directrices PRISMA 2020. Se realizó una búsqueda en MEDLINE (vía PubMed), EMBASE y Web of Science de estudios publicados entre 2015 y 2025. Se incluyeron estudios observacionales que evaluaban la exposición ocupacional a agentes químicos y la incidencia de neoplasias hematológicas. La extracción de datos abarcó el diseño del estudio, la población, la evaluación de la exposición, el subtipo de cáncer y las estimaciones de riesgo. La calidad metodológica y el riesgo de sesgo se evaluaron utilizando herramientas estandarizadas, y los hallazgos se sintetizaron cualitativamente debido a la marcada heterogeneidad.

Resultados: Trece estudios cumplieron los criterios de inclusión (5 de cohortes, 6 de casos y controles, y 2 poblacionales o ecológicos). En general, la evidencia indica asociaciones consistentes entre la exposición ocupacional a determinados agentes químicos y un mayor riesgo de padecer neoplasias hematológicas, particularmente linfomas y leucemias. Las asociaciones más consistentes se observaron en la exposición a plaguicidas, especialmente a insecticidas organofosforados y carbamatos, a menudo con patrones de dosis-respuesta. También se notificaron asociaciones con el benceno, los disolventes orgánicos y el radón, aunque con mayor heterogeneidad. La evidencia sobre el formaldehído y la exposición ocupacional de los padres fue limitada y no concluyente. La mayoría de los estudios mostraron un riesgo de sesgo moderado, debido principalmente a una clasificación errónea de la exposición y a factores de confusión residuales.

Conclusiones: La exposición ocupacional a agentes químicos específicos, particularmente a ciertos plaguicidas, se asocia con un mayor riesgo de neoplasias hematológicas. Estos hallazgos respaldan la priorización de la prevención primaria, un control más estricto de la exposición y el fortalecimiento de la vigilancia de la salud laboral en los sectores de alto riesgo, y resaltan la necesidad de realizar estudios prospectivos bien diseñados con una evaluación más precisa de la exposición y análisis detallados por subtipos.

Palabras clave: Exposición ocupacional. Agentes químicos. Neoplasias hematológicas. Plaguicidas. Cáncer ocupacional. Epidemiología.

Introduction

Occupational cancer represents a major public health problem and one of the most important preventable challenges in occupational health worldwide. Occupational exposure to carcinogenic agents continues to account for a substantial proportion of the global cancer burden, particularly in industrial sectors where exposure is chronic, multiple, and sustained over long periods. In this context, identifying and characterizing associations between occupational chemical exposures and the development of hematological malignancies is a priority to support effective primary prevention strategies, guide the regulation of hazardous substances, and reduce the health and economic burden associated with these diseases[1,2].

Hematological malignancies comprise a heterogeneous group of malignant tumors originating from hematopoietic progenitor cells and the lymphoid system, including leukemias, lymphomas, and multiple myeloma. These entities exhibit marked clinical, biological, and molecular diversity, which is reflected in their contemporary classification systems and in the variability of their clinical course and prognosis[3]. From a clinical perspective, initial symptoms are often non-specific, such as fatigue, fever, weight loss, recurrent infections, bleeding, or bruising, which may delay diagnosis and hinder the early identification of common risk factors.

At a global level, the burden of hematological malignancies is considerable. According to estimates from the Global Cancer Observatory (GLOBOCAN), more than 1.3 million new cases of leukemia, lymphoma, and multiple myeloma combined were diagnosed worldwide in 2020, representing a substantial proportion of all incident cancers[4]. Although age-standardized mortality rates have shown declining trends in some high-income countries, the absolute number of cases continues to rise, partly due to population aging and the persistence of relevant environmental and occupational exposures[4,5].

From an etiological perspective, hematological carcinogenesis can be understood as the result of interactions between individual biological susceptibility and external exposures capable of inducing genetic and epigenetic alterations in hematopoietic cells. In occupational settings, certain chemical agents have been consistently implicated in the risk of hematological malignancies. Benzene represents the paradigmatic example: its association with leukemia, particularly acute myeloid leukemia, is well established and has been recognized by the International Agency for Research on Cancer (IARC), which classifies benzene as a Group 1 human carcinogen[6]. In addition to benzene, epidemiological evidence has suggested possible associations with other common occupational exposures, such as polycyclic aromatic

hydrocarbons, diesel engine emissions, industrial solvents, and various pesticides, although with varying degrees of consistency and magnitude of risk[2,7,8].

Among compounds of current interest are substances whose carcinogenic potential remains the subject of scientific and regulatory debate, including certain pesticides and per- and polyfluoroalkyl substances (PFAS). A relevant example is glyphosate, classified by IARC as probably carcinogenic to humans (Group 2A), whereas subsequent regulatory evaluations within the European context have reached different conclusions regarding its carcinogenicity[9,10]. These discrepancies highlight the inherent challenges in integrating epidemiological, toxicological, and mechanistic evidence and underscore the need for updated systematic reviews that critically synthesize the available data, particularly with respect to hematological outcomes.

Beyond the direct risk to the working population, increasing attention has been paid to the potential association between parental occupational exposures and the development of hematological malignancies in offspring. This hypothesis is biologically plausible through several mechanisms, including genetic damage to germ cells, maternal exposure during pregnancy, or epigenetic effects induced by persistent chemical agents. However, the available epidemiological evidence is heterogeneous and subject to important methodological limitations, such as difficulties in reconstructing past exposures and the small number of cases in certain subgroups[11].

Despite the growing body of literature, recent epidemiological evidence remains fragmented, with substantial variability in exposure assessment methods, study designs, and classification of hematological malignancies. In addition, few studies have integrated biomarker-based evidence with epidemiological findings, and limited attention has been given to differences between specific malignancy subtypes. These gaps highlight the need for an updated and structured synthesis of the most recent evidence focusing on occupational chemical exposures and hematological outcomes.

Within this context, the present systematic review addresses two main research questions: (1) whether occupational exposure to chemical agents is associated with an excess risk of developing hematological malignancies among workers and (2) whether parental occupational exposure may be related to an increased risk of hematological cancer in their offspring. The overall objective is to critically synthesize and interpret recent epidemiological evidence on these associations. Specific objectives include analyzing risk by type of hematological malignancy (leukemias, lymphomas, and multiple myeloma) and assessing whether observed risks are linked to families of chemical agents or to specific compounds. This approach justifies the application of a systematic methodology in accordance with PRISMA, as described in the following section, to provide robust and relevant conclusions for occupational health prevention[12].

Methods

This study was designed as a systematic literature review of the scientific evidence, conducted in accordance with the PRISMA 2020 guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), with the aim of ensuring a transparent, reproducible, and methodologically rigorous process for evidence search, selection, and synthesis[12]. Although the review protocol was not prospectively registered in databases such as PROSPERO, the main methodological criteria were defined a priori before the literature search was initiated, including the research questions, eligibility criteria, information sources, search period, and general approach to evidence synthesis. No substantial modifications affecting the review question, eligibility criteria, or principal outcomes were introduced during the review process. The absence of prospective registration may represent a limitation in terms of transparency; however, predefined methodological criteria were consistently applied throughout the review process to ensure reproducibility and methodological rigour.

The research question was formulated using the PICO framework, which allowed a clear and operational definition of the key elements of the review:

- **P (Population):** Adult workers occupationally exposed to chemical agents and children born to workers at risk of occupational exposure.
- **I (Exposure):** Occupational exposure to chemical substances in the workplace.
- **C (Comparison):** Comparable populations not exposed to the chemical agents under study.
- **O (Outcomes):** Development of hematological malignancies, including leukemias, lymphomas, and multiple myeloma.

The literature search was conducted in three internationally recognized electronic databases selected for their relevance and coverage in the biomedical and occupational health fields: MEDLINE (via PubMed), EMBASE, and Web of Science (WoS). These sources were considered complementary and appropriate for identifying epidemiological and observational studies related to occupational exposure and hematological diseases.

The search strategy was adapted to the specific characteristics of each database, combining controlled vocabulary terms (e.g., MeSH terms in MEDLINE) with free-text terms in titles and abstracts. Equivalent strategies were developed for EMBASE and Web of Science, adjusting the syntax and database-specific filters accordingly. For reproducibility purposes, the complete search strategies for all databases, including syntax adaptations and additional keywords, should be provided as supplementary material. No explicit language restrictions were intentionally applied during the search; however, only studies accessible in the working languages of the review team were assessed in full text.

The search period was restricted to publications from 2015 to 2025, including all records available in the selected databases up to the time the search was conducted. The final literature search was conducted in January 2026. This time frame was chosen to focus the analysis on the most recent and methodologically up-to-date evidence.

Studies meeting all of the following criteria were included:

- Original studies evaluating the incidence of hematological malignancies (leukemias, lymphomas, and multiple myeloma).
- Studies analyzing the association between occupational exposure to chemical agents and the development of these malignancies.
- Observational study designs (cohort studies, case-control studies, or analytical cross-sectional studies).
- Publications within the predefined time period.
- Articles published in peer-reviewed scientific journals.

The following types of studies were excluded:

- Studies focusing exclusively on treatment, prognosis, or mortality of hematological malignancies.
- Narrative reviews, editorials, letters to the editor, or studies without original data.
- Studies lacking clear information on occupational exposure.
- Duplicate publications across databases.

The study selection process was conducted in accordance with the PRISMA 2020 recommendations and is summarized in **Figure 1**[12]. Study selection was performed independently by two reviewers, and any disagreements were resolved through discussion and consensus. When discrepancies persisted after the initial independent assessment, the reviewers re-examined the full text jointly and reached a final decision by consensus based on the predefined eligibility criteria. Inter-reviewer agreement was assessed using Cohen's kappa coefficient.

The initial search identified a total of 120 records. After removal of duplicates, 95 titles and abstracts were screened, of which 20 articles were selected for full-text assessment. Ultimately, 13 studies met all eligibility criteria and were included in the final qualitative synthesis, as shown in **Figure 1**.

From the included studies, the following relevant data were systematically extracted:

- Authors and year of publication.
- Country and study context.
- Study design.
- Type of chemical agent evaluated.
- Study population.
- Type of hematological malignancy analysed.
- Main findings and risk estimates.

The methodological quality of the included studies was assessed using standardized tools appropriate to each study design: AMSTAR-2 for systematic reviews and meta-analyses, PRISMA 2020 for systematic reviews, and STROBE for observational studies. Because STROBE is primarily a reporting guideline rather than a dedicated risk-of-bias tool, its use in this review was intended to assess the completeness and transparency of reporting in observational studies, not as a standalone instrument for formal bias assessment. Risk-of-bias judgments were therefore complemented by an appraisal of key methodological domains, including participant selection, comparability of study groups, exposure assessment, outcome ascertainment, and control of confounding. The criteria evaluated and the quality levels achieved are summarized in **Table 1**.

Given the heterogeneity of study designs, populations, and chemical agents analyzed, the results were synthesized using a qualitative, narrative approach, without performing a quantitative meta-analysis. A meta-analysis was not performed due to substantial heterogeneity in exposure definitions, outcome classification, and study design, which limited the comparability of effect estimates across studies. This heterogeneity was observed at several levels, including differences in the chemical agents evaluated, occupational settings, exposure assessment methods (self-report, job-exposure

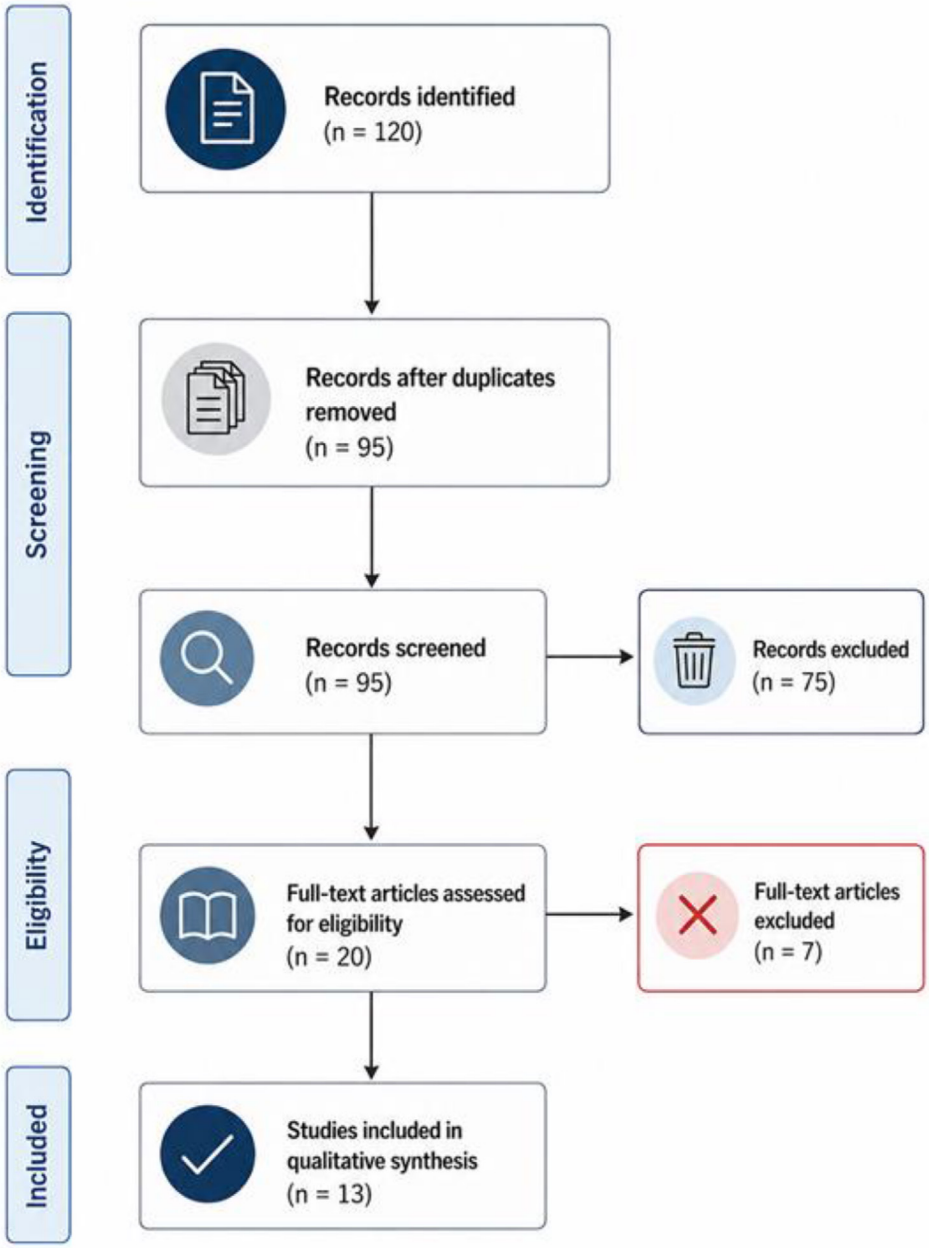

Figure 1. PRISMA flow diagram (simplified).

Note: n = number of records or studies.

Table 1. Methodological quality of the studies included in the review.

Study type	Assessment tool	Criteria evaluated	Quality level achieved
Systematic reviews and meta-analyses	AMSTAR-2	Search strategy, duplicate study selection, risk of bias assessment, publication bias	High (≥80% of critical domains fulfilled)
Systematic reviews	PRISMA 2020	PRISMA checklist, flow diagram, inclusion and exclusion criteria	Moderate–high (according to checklist adherence)
Observational studies (cohort, case–control)	STROBE	Definition of population, exposure, and outcomes; statistical methods	High in well-defined cohort studies; moderate in cross-sectional studies

Notes: AMSTAR-2: Shea et al., BMJ 2017; PRISMA 2020: Page et al., BMJ 2021; STROBE: Cuschieri, 2019.

matrices, biomarkers), study populations, and classification of hematological malignancy subtypes. In addition, the included studies differed in design (cohort, case--control, ecological, and population-based analyses), which further reduced the appropriateness of statistical pooling. Pooling such heterogeneous data could have led to misleading summary estimates. To improve interpretability, the synthesis was structured according to major exposure groups and the consistency of associations observed across different study designs.

Results

This section presents a structured synthesis of the empirical evidence identified in the systematic review, integrating both quantitative and qualitative findings on the association between occupational exposure to chemical agents and the risk of hematological malignancies. Across the included studies, three main exposure categories emerged: (1) pesticides, which showed the most consistent associations with hematological malignancies; (2) industrial chemical agents such as benzene and organic solvents, with moderate evidence of association; and (3) other agents, including formaldehyde and radon, for which the evidence was limited or heterogeneous. To facilitate comparison across studies, the results were synthesized according to exposure group, hematological outcome, study design, and direction of effect.

A total of 13 studies met the predefined eligibility criteria and were included in the review, encompassing cohort studies, case--control studies, and population-based or ecological analyses. Overall, the available evidence indicates consistent, although heterogeneous, associations between specific occupational chemical exposures and the development of leukemias, lymphomas, and, to a lesser extent, multiple myeloma. As shown in **Table 2**, multiple studies consistently report positive associations between occupational exposure to pesticides and the risk of hematological malignancies, particularly lymphomas and leukemias. In addition, **Table 5** presents a global summary of evidence for each major chemical agent or exposure group, including the number of studies identified, the predominant direction of effect, and the overall level of evidence. The tables were revised to improve comparability between studies and to ensure terminological consistency across lymphoma and leukemia subtypes.

Table 3 provides a structured overview of the main occupational settings and associated chemical agents, based on official occupational disease classifications, highlighting sectors with potentially higher exposure risk.

Table 4 summarizes the main quantitative risk estimates for selected chemical agents, integrating the most relevant associations identified across the included studies. These estimates should be interpreted cautiously because they derive from heterogeneous studies with important differences in exposure assessment, study design, and case definition.

Table 5 summarizes the results by exposure group, including the number of studies, direction of effect, and overall level of evidence.

Figure 2 illustrates the magnitude and direction of the associations between occupational exposure to selected chemical agents and the risk of hematological malignancies based on the available quantitative estimates.

The association between occupational exposure to pesticides and the development of hematological malignancies represents one of the most consistent findings in the reviewed literature. A recent study by Pandiyan et al. provided biological evidence by identifying a positive and statistically significant correlation between plasma levels of the organophosphate insecticide profenofos and the oxidative DNA damage marker 8-hydroxy-2-deoxyguanosine (8-OHdG) among exposed agricultural workers, supporting a potential underlying genotoxic mechanism[21]. The MCC-Spain case--control study by Benavente et al. identified a clear dose-response relationship between cumulative pesticide exposure and chronic lymphocytic leukemia (CLL)[18]. In the highest exposure tertile, odds ratios were significantly elevated for insecticides, herbicides, and fungicides, reinforcing the plausibility of a causal association. Similarly, analyses from the InterLymph Consortium by De Roos et al. on non-Hodgkin lymphoma revealed particularly relevant compound-specific associations: exposure to diazinon was associated with an increased risk of follicular lymphoma, whereas exposure to carbaryl was linked to T-cell lymphoma[19]. Taken together, these studies support pesticides as the exposure group with the most consistent epidemiological and mechanistic evidence in the review, as reflected in **Tables 2, 4, and 5** and in **Figure 2**.

To provide a balanced perspective, studies reporting non-significant results were also retained in the synthesis. The Swedish study by Rossides et al. on parental occupational exposure to pesticides did not observe a statistically significant increase in the risk of hematological cancer among offspring[22]. Likewise, the study by Moldenhauer et al. in Vietnam War veterans found no significant association between exposure to Agent Orange (TCDD) and concurrent

Table 2. Included studies evaluating occupational chemical exposures and hematological malignancies.

Study/Article	Authors (year)	Exposure group	Compounds	Main outcome(s)	Association measures	Main findings	Study-level certainty
Treatment and survival of Vietnam veterans with concurrent lymphoid malignancies	Moldenhauer MR et al. (2025)	Other agents	Agent Orange (TCDD)	Concurrent lymphoid malignancies	OR (95% CI includes 1)	No increased probability of concurrent lymphoid malignancies	Very low
Plasma pesticide residues and serum 8-OHdG levels	Pandiyan A et al. (2024)	Pesticides	Organophosphates (dimethoate, profenofos, diazinon), carbamates (carbaryl)	Lymphoma, leukemia; oxidative DNA damage biomarker	Pearson correlation (p=0.02; profenofos r=0.197, p=0.008)	Higher 8-OHdG levels in farmers vs. controls	Low
Comparative analysis of leukemia incidence in Ecuador	Espinosa-Ypez KR (2024)	Pesticides/ agricultural exposure	Not specified	Leukaemia	Adjusted morbidity and mortality rates	Higher rates in agricultural provinces	Very low
Parental occupational exposure to pesticides	Rossides M et al. (2022)	Parental occupational exposure/ pesticides	Herbicides, insecticides, fungicides	Lymphoma in offspring	OR (95% CI): Total lymphoma 1.42 (0.78–2.57); Hodgkin lymphoma 1.75 (0.79–3.85)	Non-significant risk in offspring	Low
Occupational exposure to insecticides and risk of non-Hodgkin lymphoma (InterLymph)	De Roos AJ et al. (2021)	Pesticides	Organochlorines, organophosphates (diazinon, carbaryl)	Non-Hodgkin lymphoma; subtype analyses	OR (95% CI): Organophosphates 1.22 (1.01–1.47); Diazinon 2.32 (1.16–4.64)	Association with follicular lymphoma (diazinon) and T-cell lymphoma (carbaryl)	Moderate
Occupational pesticide exposure and CLL (MCC-Spain)	Benavente Y et al. (2020)	Pesticides	Insecticides, herbicides, fungicides	CLL	OR (95% CI, highest tertile): Insecticides 2.13 (1.40–3.24); Total 1.64 (1.07–2.51)	Positive dose–response association	Moderate
Epigenome-wide study of pyrethroid exposure in California	Furlong MA et al. (2020)	Pesticides	Pyrethroids	Epigenetic alterations	Beta regression: 415 CpG sites with differential methylation	No changes in gene expression	Low
A task-based assessment of parental occupational exposure to organic solvents and other compounds and the risk of childhood leukemia in California	Metayer C et al. (2016)	Benzene / organic solvents; parental occupational exposure	Organic solvents, benzene, chlorinated hydrocarbons	Childhood ALL	OR for chlorinated hydrocarbons 2.5; benzene 2.0	Increased risk with paternal occupational exposure	Moderate

...continuation table 2.

Study/Article	Authors (year)	Exposure group	Compounds	Main outcome(s)	Association measures	Main findings	Study-level certainty
Comparison of hematological alterations and markers of B-cell activation in workers exposed to benzene, formaldehyde, and trichloroethylene	Bassig BA et al. (2016)	Benzene / organic solvents; formaldehyde	Benzene, formaldehyde, trichloroethylene	Hematological alterations / biomarkers	Hematological and biomarker comparisons	Reductions in myeloid cell counts support biological plausibility	Low
The carcinogenic effects of formaldehyde occupational exposure: a systematic review	Protano C et al. (2021)	Formaldehyde	Formaldehyde	NHL, myeloid leukaemia	Systematic review summary estimates	Weak associations	Limited
Assessment of associations between inhaled formaldehyde and lymphohematopoietic cancer through the integration of epidemiological and toxicological evidence with biological plausibility	Vincent MJ et al. (2024)	Formaldehyde	Formaldehyde	Leukaemia	Narrative review findings	Inconclusive evidence	Limited
Environmental/Occupational Exposure to Radon and Non-Pulmonary Neoplasm Risk: A Review of Epidemiologic Evidence	Mozzoni et al. (2021)	Radon	Radon	Leukaemia	SIR 1.51 (1.08–2.07)	Association in miners	Moderate
Cancer risks in a population-based study of 70,570 agricultural workers: results from the Canadian Census Health and Environment Cohort (CanCHEC)	Kachuri et al. (2017)	Pesticides / agricultural exposure	Agricultural occupational exposures	NHL, leukaemia	HR 1.1 men for NHL; HR 1.7 women for leukaemia	Sex-specific differences	Low–moderate

ALL: acute lymphoblastic leukemia; CLL: chronic lymphocytic leukemia; NHL: non-Hodgkin lymphoma; OR: odds ratio; HR: hazard ratio; SIR: standardized incidence ratio.

Notes: Study-level certainty reflects the appraisal of individual studies and should not be interpreted as equivalent to overall evidence certainty for each compound or exposure group.

Table 3. Occupational settings and chemical agents relevant to the reviewed evidence.

Occupations / Activities	Exposure group	Key compounds (RD 1299/2006 codes)	Related evidence in this review
Mechanics, cleaners, manual workers, healthcare staff	Benzene / organic solvents	Benzene (1K01, 6D01), PAHs (1K06), chlorinated hydrocarbons (1H02)	Benzene and solvents were associated with leukemia risk in specific studies and biomarker-based analyses
Agricultural workers (gardeners, livestock farmers)	Pesticides	Organophosphates (diazinon 1S01), carbamates (carbaryl 1S01), arsenic-based herbicides (1A01)	Most consistent associations, especially for NHL, CLL, and subtype-specific lymphoma risk
Miners	Radon	Radon (6M01)	Limited but positive evidence for leukemia in miners
Hairdressers, chemical and textile industry workers	Formaldehyde	Formaldehyde (1F01, 5A01)	Heterogeneous and limited evidence
Military personnel	Other agents	TCDD (Agent Orange)	No clear increase in concurrent lymphoid malignancies

Notes: This table contextualizes the occupational settings linked to the compounds assessed in Tables 2 and 4. **Ref:** Spain. Royal Decree 1299/2006, of 10 November, approving the schedule of occupational diseases in the Social Security system and establishing criteria for their notification and registration. Official State Gazette no. 302, 19-12-2006.

Table 4. Main quantitative oncohematological associations identified for selected compounds.

Compound	Exposure group	Associated malignancy	Association measure	95% CI	Compound-level interpretation
Diazinon	Pesticides	Non-Hodgkin lymphoma (follicular lymphoma subtype)	OR 2.32	1.16–4.64	Most consistent positive pesticide-specific association
Carbaryl	Pesticides	T-cell lymphoma	OR 1.97	1.12–3.45	Positive association in subtype-specific analysis
Glyphosate*	Pesticides	Non-Hodgkin lymphoma	OR 1.81	1.14–2.85	Results of variable consistency according to the studies
Radon	Radon	Leukaemia	SIR 1.51	1.08–2.07	Limited but positive evidence in miners
Formaldehyde	Formaldehyde	Myeloid leukaemia	OR 1.30	1.0–1.7	Weak and heterogeneous association
Benzene	Benzene / organic solvents	Childhood ALL / leukaemia	OR 2.0	As reported in the source study	Relevant association in specific occupational or parental exposure contexts

OR: odds ratio; SIR: standardized incidence ratio.

Notes: This table presents selected compound-level quantitative associations extracted from the studies summarized in Table 2.

Table 5. Global summary of evidence by exposure group.

Exposure group	Number of studies	Main outcomes	Direction of effect	Overall certainty of evidence
Pesticides	6	NHL, CLL, leukaemias	Predominantly positive	Moderate
Benzene / organic solvents	3	Leukemias, childhood ALL	Mostly positive but heterogeneous	Limited–moderate
Radon	1	Leukaemia	Positive in specific occupational settings	Limited
Formaldehyde	3	NHL, myeloid leukaemia	Inconsistent	Limited
Parental occupational exposure	2	Offspring hematological malignancies	Mostly null or inconclusive	Limited

Notes: Some studies contributed to more than one exposure group; therefore, row totals exceed the total number of included studies. This table provides group-level synthesis and should be interpreted together with the study-level information in Table 2 and the compound-level estimates in Table 4.

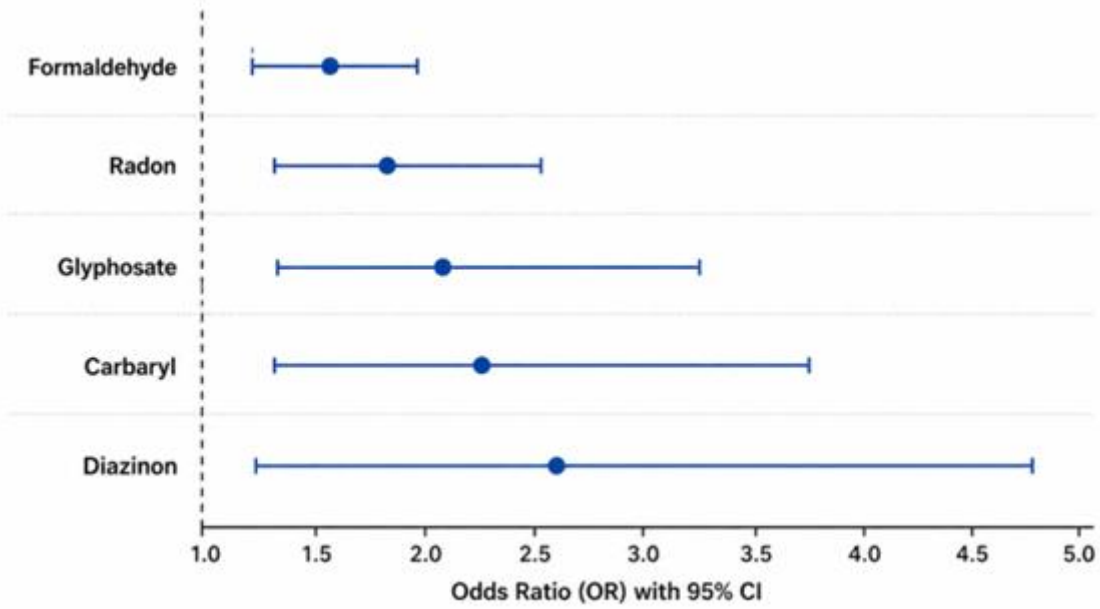

Figure 2. Forest plot of the risk of hematological malignancies associated with exposure to chemical compounds.

This figure was produced by the authors on the basis of the quantitative estimates reported in the included studies and is therefore an original figure rather than an adapted reproduction.

lymphoid malignancies. These findings were retained to reflect the heterogeneity of the evidence and to avoid overemphasizing only positive associations.

The review also identified relevant evidence for other chemical agents used across different industrial sectors. A study by Metayer et al. in California found that paternal exposure to organic solvents was associated with an increased risk of childhood acute lymphoblastic leukemia, particularly for chlorinated hydrocarbons and benzene[24]. Evidence on formaldehyde exposure was heterogeneous. While the systematic review by Protano et al. reported weak associations with non-Hodgkin lymphoma and myeloid leukemia[27], the review by Vincent MJ et al. concluded that the available evidence does not support a causal association between inhaled formaldehyde and lymphohematopoietic cancers, given the substantial systematic biases affecting the human studies and the lack of consistent significant associations in the meta-analyses[23]. Nevertheless, the study by Bassig et al. provided additional biological evidence by demonstrating that exposure to benzene and formaldehyde was associated with reductions in myeloid cell counts, supporting the biological plausibility of the observed epidemiological associations[25]. Compared with pesticides, the evidence for these agents was less consistent and more dependent on specific

occupational contexts and study designs, as summarized in **Tables 2, 4, and 5**.

The main sources of bias identified in the included studies, together with their potential impact and the mitigation strategies adopted, are summarized in **Table 1** and synthesized at the group level in **Table 5**. Exposure misclassification was the most frequent source of bias, with self-reported exposure predominating in a substantial proportion of studies, potentially leading to underestimation of true risk. Only a minority of studies employed biomarker-based exposure assessment, thereby reducing this bias[21,25]. Residual confounding related to multiple co-exposures and recall bias in case-control studies was also identified. This pattern supports an overall interpretation of moderate certainty for the most consistent associations and limited certainty for exposure groups supported by fewer or more heterogeneous studies.

Discussion

This systematic review synthesized recent epidemiological evidence on the association between occupational exposure to chemical agents and the risk of hematological malignancies. Overall, the findings indicate that selected occupational chemical exposures are associated with an increased risk of leukemias and lymphomas, although the strength and consistency of the evidence vary substantially across exposure groups. The most robust pattern was observed for pesticide-related exposures, whereas the evidence for other occupational agents was more limited and methodologically heterogeneous[12-14].

One of the main findings of this review is the relative consistency of the association between occupational pesticide exposure and hematological malignancies, particularly non-Hodgkin lymphoma and chronic lymphocytic leukemia. The included studies identified positive associations for organophosphate and carbamate insecticides, with compound-specific estimates and exposure-response relationships in the better-designed case-control investigations[18,19]. This convergence of findings across analytical studies, together with biomarker-based evidence of oxidative DNA damage, strengthens the plausibility of a causal interpretation and suggests that the observed associations are unlikely to be explained solely by chance or uncontrolled bias[21].

These findings are also broadly consistent with the wider occupational and toxicological literature, which has long suggested that certain pesticides may exert genotoxic, oxidative, epigenetic, and immunomodulatory effects relevant to hematological carcinogenesis[18,19]. In this context, the repeated implication of compounds such as diazinon and carbaryl is particularly important, as it reinforces concern regarding chemical groups that remain in occupational use or have structurally related substitutes. Although this review was not designed to establish causal certainty at the compound level, the overall pattern of evidence supports a precautionary interpretation for pesticide exposure in occupational settings.

By contrast, the evidence for non-pesticide occupational agents was less cohesive. The studies included in the present synthesis suggested that benzene, organic solvents, radon, and formaldehyde may also be relevant in specific occupational contexts, but the corresponding literature was smaller and less consistent in exposure definition, study design, and magnitude of effect[20,23-25,27]. This heterogeneity limits direct comparison across compounds and reduces confidence in generalizations, particularly where exposure assessment relied on job titles, self-report, or ecological inference rather than objective biomarkers or task-based matrices.

The weaker consistency observed for formaldehyde and parental occupational exposure deserves particular attention[22-24,27]. In the included literature, formaldehyde-related findings were limited and inconclusive, while the evidence regarding parental occupational exposure and hematological malignancy risk in offspring remained insufficient to support firm inferences[22,24]. Although biologically plausible pathways have been proposed for transgenerational effects, including germ-cell damage and epigenetic mechanisms, the available epidemiological evidence remains constrained by retrospective exposure reconstruction, small subgroup sizes, and the difficulty of separating paternal, maternal, and shared environmental exposures[11].

Methodological limitations across the included studies should be considered when interpreting these findings. Exposure misclassification was likely the most important source of uncertainty, particularly in studies relying on self-reported occupational histories or broad occupational categories[21,22]. Residual confounding by co-exposures is another major concern in occupational epidemiology, especially in agriculture and industry, where workers are often exposed to complex mixtures rather than single agents[25]. In addition, heterogeneity in disease classification, particularly across lymphoma and leukemia subtypes, further complicates comparison between studies and may attenuate subtype-specific associations[27].

Despite these limitations, several aspects of the evidence support the credibility of the overall findings. First, the direction of association was relatively consistent for pesticides across different study designs. Second, some studies identified dose-response

gradients, which strengthen epidemiological inference. Third, the biomarker findings reported in exposed workers provide mechanistic support that is coherent with the observed epidemiological patterns. Taken together, these features argue against a purely spurious explanation for the associations observed with pesticide exposure.

From an occupational health perspective, the implications of these findings are substantial. The identification of recurrent associations between selected workplace chemical exposures and hematological malignancies supports the prioritization of primary prevention, stricter exposure control, and reinforced medical surveillance in high-risk sectors, particularly agriculture and selected industrial settings. These findings also support periodic re-evaluation of occupational exposure limits and the systematic implementation of collective and personal protective measures for workers exposed to potentially carcinogenic agents[12,25].

The review also highlights important priorities for future research. Prospective studies with long-term follow-up, refined classification of hematological malignancy subtypes, and robust exposure assessment strategies are needed to improve causal interpretation. The integration of epidemiological designs with biomonitoring, molecular epidemiology, and omics-based approaches may be particularly valuable in clarifying dose-response patterns, early biological effects, and mechanistic pathways linking occupational chemical exposures to hematological carcinogenesis.

Overall, the evidence synthesized in this review supports the conclusion that occupational exposure to certain chemical agents, most notably specific pesticides, is associated with increased oncohematological risk. At the same time, the variability in the evidence base across other exposure groups underscores the need for cautious interpretation and for better-designed studies capable of disentangling compound-specific effects within complex occupational exposure scenarios.

Conclusions

This systematic review synthesized recent epidemiological evidence on the association between occupational exposure to chemical agents and the risk of hematological malignancies. Overall, the evidence included in the final qualitative synthesis indicates that selected occupational chemical exposures are associated with an increased risk of leukemias and lymphomas, although the strength and consistency of the associations vary across exposure groups.

The most consistent evidence was observed for pesticide exposure, particularly for organophosphate and carbamate insecticides, which were repeatedly associated with non-Hodgkin lymphoma, specific lymphoma subtypes, and chronic lymphocytic leukemia. The convergence of positive associations across analytical studies, together with dose-response patterns and biomarker findings compatible with oxidative and genotoxic mechanisms, strengthens the plausibility of these associations.

By contrast, the evidence for other occupational chemical agents was more limited and heterogeneous. Although some included studies suggested potential relevance for non-pesticide exposures, the available evidence was less coherent in terms of study design, exposure definition, and effect magnitude. In particular, the evidence for formaldehyde and parental occupational exposure remained insufficient to support firm conclusions.

Taken together, these findings support the prioritization of primary prevention strategies for occupational exposure to potentially carcinogenic chemical agents, especially in sectors characterized by recurrent pesticide use. They also justify strengthening exposure control, occupational health surveillance, and periodic re-evaluation of preventive and regulatory standards in high-risk work environments.

Finally, this review highlights the need for future research based on prospective designs, refined exposure assessment, long-term follow-up, and detailed analyses by hematological malignancy subtype. Greater integration of epidemiological approaches with biomonitoring and molecular evidence will be essential to clarify compound-specific risks and to better inform occupational health policy and prevention.

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Author contributions

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María Teófila Vicente-Herrero: Conceptualization, Methodology, Writing – original draft, Formal analysis, Visualization, and Supervision.

All authors critically reviewed the manuscript, approved the final version, and take responsibility for its content.

Conflicts of interest

The authors declare that there are no commercial or financial conflicts of interest regarding this research.

Use of artificial intelligence tools

The authors declare that no artificial intelligence tools (such as ChatGPT, Copilot, Gemini, or others) were used in the drafting, analysis, or review of this article.

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Review article

The evolutionary persistence of depressive and anxiety disorders: current hypotheses and clinical implications

La persistencia evolutiva de los trastornos depresivos y de ansiedad: hipótesis actuales e implicaciones clínicas

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Abstract

Objectives: Depressive and anxiety disorders are highly prevalent conditions characterized by recurrent episodes and substantial heritability. From an evolutionary perspective, their persistence poses a longstanding question, given their association with functional impairment. Several explanatory models have been proposed in evolutionary psychiatry, yet no single account fully explains their clinical and epidemiological complexity. This non-systematic review aims to summarize the main evolutionary hypotheses proposed to explain the persistence of depressive and anxiety disorders and to explore the potential contribution of systems-oriented perspectives.

Methods: A narrative review of the literature published mainly between 2010 and 2026 was conducted, prioritizing integrative reviews, theoretical models, and representative empirical studies in evolutionary psychiatry, psychiatric genetics, and systems approaches to psychopathology.

Results: Proposed explanations include adaptive defense models, evolutionary mismatch, trade-offs and pleiotropy, mutation–selection balance in highly polygenic traits, and pathogen-defense hypotheses. In parallel, recent genetic and network approaches increasingly conceptualize depression and anxiety as emergent properties of complex regulatory systems. Within this context, the schismogenesis hypothesis is discussed as a possible integrative framework describing how reciprocal amplification processes triggered by stress may contribute to reversible biopsychosocial disconnection states.

Conclusions: The persistence of depressive and anxiety disorders is most plausibly explained by multicausal models involving evolutionary trade-offs, context dependence, and dynamic regulatory processes. Systems-level perspectives may help integrate existing theories and generate new hypotheses for research and clinical practice.

Keywords: Depressive disorders. Anxiety disorders. Evolutionary psychiatry. Complex systems. Psychopathology networks.

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Resumen

Objetivos: Los trastornos depresivos y de ansiedad son muy prevalentes y se caracterizan por una heredabilidad sustancial. Desde una perspectiva evolutiva, su persistencia plantea controversias, dada su asociación con un claro deterioro funcional. En psiquiatría evolutiva se han propuesto diversos modelos explicativos; sin embargo, ninguno de ellos explica plenamente su complejidad clínica y epidemiológica. Esta revisión no sistemática tiene como objetivo resumir las principales hipótesis evolutivas propuestas para explicar la persistencia de los trastornos depresivos y de ansiedad, así como explorar la posible contribución de algunos enfoques sistémicos.

Métodos: Se realizó una revisión narrativa de la literatura publicada principalmente entre 2010 y 2026, priorizando revisiones integradoras, modelos teóricos y estudios empíricos representativos en psiquiatría evolutiva, genética psiquiátrica y enfoques sistémicos de la psicopatología.

Resultados: Entre las explicaciones propuestas se incluyen los modelos de defensa adaptativa, el desajuste evolutivo, los *trade-offs* y la pleiotropía, el equilibrio mutación–selección en rasgos altamente poligénicos y las hipótesis de defensa frente a patógenos. Paralelamente, los enfoques recientes basados en genética y redes conceptualizan cada vez más la depresión y la ansiedad como propiedades emergentes de sistemas regulatorios complejos. En este contexto, la hipótesis de la cismogénesis se discute como un posible marco integrador que describe cómo procesos de amplificación recíproca desencadenados por el estrés pueden contribuir a estados reversibles de desconexión biopsicosocial.

Conclusiones: La persistencia de los trastornos depresivos y por ansiedad se explica con mayor plausibilidad mediante modelos multicausales que implican *trade-offs* evolutivos, dependencia del contexto y procesos regulatorios dinámicos. Las perspectivas sistémicas pueden ayudar a integrar las teorías existentes y generar nuevas hipótesis para la investigación y mejora de la práctica clínica.

Palabras clave: Depresión. Trastornos de ansiedad. Psiquiatría evolutiva. Sistemas complejos. Redes de psicopatología.

Introduction

Depressive and anxiety disorders are among the most prevalent mental health conditions worldwide and account for a substantial proportion of the global burden of disease[1]. Both conditions are highly recurrent, frequently comorbid, and associated with marked personal and societal costs[2,3]. Family and twin studies consistently indicate moderate to substantial heritability for depressive and anxiety phenotypes, suggesting that genetic factors contribute meaningfully to individual vulnerability[4]. From an evolutionary perspective, this combination of high prevalence, heritability, and clinical burden raises a long-standing question: why has natural selection not eliminated susceptibility to these conditions?

Evolutionary psychiatry addresses this issue by shifting attention from proximate mechanisms—such as neurotransmitter systems, cognitive biases, or specific environmental stressors—to more ultimate explanations concerning the design features and trade-offs of evolved emotional and regulatory systems[5,6]. In this framework, anxiety and low mood are often conceptualized as components of evolved defense systems, broadly analogous to pain or fever, which may be useful in appropriate contexts but become maladaptive when excessively intense, persistent, or poorly regulated[7,8]. This perspective does not deny the reality or severity of mental suffering, but it suggests that vulnerability to such states may be an inherent property of systems optimized for flexibility and sensitivity rather than for the complete avoidance of distress[6,9].

Over the past decades, several non-exclusive evolutionary accounts have been proposed to explain the persistence of depressive and anxiety disorders in human populations. These include adaptive defense and signal theories, which emphasize potential functional roles of negative affective states[6,9]; evolutionary mismatch models, which focus on the discrepancy between ancestral environments and modern conditions[10,11]; trade-off and pleiotropy models, which highlight the maintenance of genetic variation through context-dependent advantages and disadvantages[12]; mutation–selection balance in highly polygenic traits[13,14]; and pathogen–host defense hypotheses, which link depressive vulnerability to immune function[15]. None of these approaches alone appears sufficient to account for the full clinical and epidemiological complexity of depressive and anxiety disorders, but together they suggest that vulnerability is likely to reflect the properties of evolved regulatory systems operating under variable ecological and social conditions[6,16].

In parallel, advances in psychiatric genetics have shown that both depressive and anxiety disorders are characterized by highly polygenic architectures, with risk distributed across thousands of common variants of small effect and substantial genetic overlap with other internalizing and personality traits[17]. These findings further challenge simple "disease gene" models and are broadly consistent with evolutionary accounts based on trade-offs, pleiotropy, and context-dependent effects[18]. At the same time, systems-oriented approaches to psychopathology have increasingly emphasized the role of network dynamics, feedback loops, and state-dependent transitions in the emergence and maintenance of mental disorders[19,20]. From this perspective, depressive and anxious states may be viewed as relatively stable but

potentially reversible configurations of interacting symptoms and regulatory processes[21,22].

Within this broader conceptual landscape, the schismogenesis hypothesis has been proposed as a systems-level framework for understanding depressive and anxiety disorders as stress-related, potentially reversible states of functional disconnection across neural, cognitive, and social domains[23]. In its current formulation, this hypothesis suggests that when stress load exceeds individual vulnerability thresholds, self-reinforcing feedback processes may drive a reorganization of biopsychosocial systems toward a more disconnected configuration[21,24,25]. This state is interpreted, cautiously, as a possible protective regulatory response under conditions of overwhelming or inescapable stress, rather than as a primary deficit[26]. At present, this framework should be regarded as a heuristic and integrative proposal that requires further empirical evaluation, rather than as an established explanatory model[20,22].

The aim of this updated report is threefold. First, to review the main contemporary evolutionary explanations for the persistence of depressive and anxiety disorders, with a focus on models that are most relevant to internalizing disorders[5,13]. Second, to situate the schismogenesis hypothesis within this existing theoretical landscape and examine its points of convergence and compatibility with more established approaches[6,23]. Third, to discuss the potential conceptual and clinical implications of a multicausal, systems-oriented evolutionary perspective, while explicitly acknowledging the current limits of the evidence and the need for further empirical testing.

Methods

This article was conceived as an updated narrative review focused on evolutionary explanations for the persistence of depressive and anxiety disorders, with particular attention to models relevant to internalizing disorders and to systems-oriented perspectives. Given the conceptual and theoretical nature of the topic, the primary aim was not to perform a fully systematic meta-analysis, but to provide a structured and critical synthesis of influential and recent contributions.

The literature was surveyed with an emphasis on publications from approximately 2010 to early 2026, while also including earlier seminal works when necessary to provide conceptual continuity. Sources included peer-reviewed review articles, theoretical papers, meta-analyses, and selected empirical studies in the fields of evolutionary psychiatry, psychiatric genetics, affective neuroscience, psychoneuroimmunology, and systems psychopathology. Databases and publisher platforms commonly used in biomedical and psychological research were consulted, and reference lists of key articles were also screened to identify additional relevant sources.

The literature search was conducted using major biomedical and psychological databases, including PubMed/MEDLINE and PsycINFO, complemented by searches in publisher platforms and by manual screening of the reference lists of relevant articles. Formal exclusion criteria were not applied in a systematic manner. However, we prioritized publications from approximately 2010 onwards, peer-reviewed articles, integrative reviews, theoretical frameworks, and representative empirical studies directly relevant to evolutionary psychiatry and systems approaches to psychopathology. Studies not directly related to the conceptual scope of the review, or with limited relevance to depressive and anxiety disorders within an evolutionary or systems framework, were not included. The initial literature search and selection were conducted by the first author, and the conceptual organization and final selection of included studies were discussed and refined by both authors until consensus was reached.

The synthesis followed a thematic organization. First, major evolutionary approaches to depression and anxiety were outlined (see **Table 1**: adaptive defense models, mismatch, trade-offs and pleiotropy, mutation–selection balance, and pathogen–host defense hypotheses). Second, findings from psychiatric genetics and network approaches were briefly summarized to provide a contemporary empirical context. Third, the schismogenesis hypothesis was described and discussed in terms of its conceptual compatibility with these frameworks. Throughout, the emphasis was placed on points of convergence, complementarity, and theoretical plausibility, rather than on claims of definitive explanatory superiority.

Results and discussion

Evolutionary psychiatry and the problem of vulnerability

From an evolutionary perspective, the persistence of depressive and anxiety disorders is often framed not as a paradox to be solved by identifying a single "faulty" mechanism, but as a reflection of the design constraints and trade-offs inherent to complex regulatory systems[6,28,29]. Natural selection optimizes reproductive success under variable conditions rather than minimizing the risk of suffering or dysfunction[7,13]. Consequently, systems that regulate mood, motivation, and threat detection are expected to be sensitive, flexible, and context-dependent, even if this sensitivity increases the likelihood of dysregulation in some individuals or environments[5,16].

Table 1. Evolutionary models of depression and anxiety: core features, strengths, and limitations.

Model	Core idea	Main strengths	Main limitations
Adaptive defense/signal models	Anxiety and low mood reflect exaggerated or dysregulated defensive responses	Explains why basic affective systems are conserved; fits with clinical phenomenology	Does not fully explain chronicity or individual differences in vulnerability
Evolutionary mismatch	Modern environments chronically activate systems adapted to ancestral conditions	Accounts for links with lifestyle, chronic stress, and modern social contexts	Does not explain heritability or resilience in similar environments
Trade-offs and pleiotropy	Risk variants persist because they also confer advantages in other traits or contexts	Explains maintenance of genetic variation and overlap with personality/creativity	Largely indirect and context-dependent; difficult to test at the individual level
Mutation–selection balance	Polygenic risk persists because selection against small-effect variants is weak	Provides a population-genetic explanation for persistence of vulnerability	Does not explain phenomenology or stress dependence
PATHOS-D	Depression-related traits may enhance immune defense against pathogens	Integrates immune and behavioral aspects of depression	Unlikely to explain all forms of depression and anxiety

Within this framework, anxiety is commonly interpreted as a defensive system biased toward false positives, given the asymmetry between the costs of missing a real threat and those of responding unnecessarily[28,29]. Low mood and depressive states have similarly been interpreted as components of broader regulatory responses to loss, defeat, or intractable problems, which may be adaptive in certain contexts but maladaptive when excessive or prolonged[9,30]. These views suggest that vulnerability to internalizing disorders may be an intrinsic consequence of maintaining emotional systems that prioritize sensitivity and flexibility over stability[7,16].

At the same time, evolutionary accounts do not imply that depressive and anxiety disorders are "useful" in their clinical forms. Rather, they emphasize that the capacity for such states may arise from the same systems that, under more moderate or transient activation, support adaptive functioning. This distinction is important for avoiding overly simplistic functional interpretations and for maintaining a clear separation between explanatory hypotheses and clinical or ethical judgments[6].

Adaptive defense and functional response models

Adaptive defense and signal theories propose that many features of anxiety and depressive disorders can be understood as exaggerated or dysregulated versions of evolved responses that were shaped to deal with recurrent challenges such as danger, loss, or social conflict[5,6]. In the case of anxiety, heightened vigilance, avoidance, and physiological arousal may increase the probability of survival in genuinely threatening contexts, even at the cost of frequent false alarms[28,29,31]. In the case of depressive disorders, hypotheses such as the analytical rumination model suggest that low mood may promote sustained attention to complex social or personal problems by reducing engagement in other activities[32,33].

These accounts offer a plausible explanation for why the basic architecture of mood and anxiety systems has been conserved by selection[6,13]. However, they do not fully explain why these systems so often enter chronic or severely impairing states in modern populations[35,36]. Nor do they account for the marked interindividual differences in vulnerability and course, which appear to depend on a combination of genetic, developmental, and contextual factors[20].

Evolutionary mismatch

Evolutionary mismatch models emphasize the discrepancy between the environments in which human affective systems evolved and many features of contemporary societies, including chronic psychosocial stress, social isolation, sedentary lifestyles, disrupted circadian rhythms, and sustained exposure to abstract or inescapable stressors[10,28,31]. In ancestral contexts, stressors were often acute and time-limited, and recovery may have been facilitated by

social and ecological conditions that are less common today[26,36].

From this perspective, depressive and anxiety disorders may not be adaptations in themselves, but rather maladaptive outcomes of regulatory systems operating under conditions for which they were not designed[6,13]. This framework is consistent with epidemiological observations linking internalizing disorders to modern lifestyle factors and with experimental evidence showing that chronic stress can induce persistent changes in mood regulation and stress physiology[34,36]. Nevertheless, mismatch alone is unlikely to provide a complete explanation, as it does not fully address why some individuals remain resilient in the same environments or why vulnerability is partly heritable[10,13].

Trade-offs, pleiotropy, and balancing selection

Another influential line of explanation focuses on genetic trade-offs and pleiotropy. Many genetic variants influence multiple traits, and selection acts on their net effects rather than on single outcomes[12]. Variants that increase vulnerability to depressive or anxiety disorders may also contribute to advantageous traits such as heightened social sensitivity, creativity, persistence, or threat detection, depending on context[14].

In such scenarios, balancing selection or context-dependent selection could maintain variation in populations, as no single trait configuration is optimal across all environments or social niches[6,13]. This logic is consistent with findings from psychiatric genetics showing substantial genetic overlap between internalizing disorders, personality traits, and other behavioral phenotypes[17]. It also aligns with the broader evolutionary principle that vulnerability to dysfunction is often the cost of maintaining systems that are highly responsive and adaptable[5,16].

Mutation–selection balance and polygenic architecture

Large-scale genetic studies have demonstrated that both depressive and anxiety disorders are highly polygenic, with risk distributed across thousands of common variants of very small effect[17]. In such architectures, selection against individual variants is weak, and new mutations continually introduce additional variation[13,37]. Mutation–selection balance therefore provides a further, more formal population-genetic explanation for why vulnerability is not easily eliminated, even if severe forms of these disorders are associated with reduced fitness[14,38].

While this mechanism is likely to contribute to the persistence of risk, it does not, by itself, explain the characteristic phenomenology of depressive and anxiety disorders or their strong dependence on environmental stress[39]. Rather, it describes the background conditions under which vulnerability can be maintained, complementing rather than replacing functional and contextual explanations[40].

The pathogen–host defense (PATHOS-D) hypothesis

The PATHOS-D hypothesis proposes that alleles associated with depressive disorders risk have been retained because they enhance host defense against pathogens, particularly through pro-inflammatory immune responses[15,41]. In this view, behavioral features of depressive disorders, such as social withdrawal, reduced activity, and anhedonia, may be interpreted as components of a broader sickness-behavior repertoire that limits exposure to infection and reallocates energy toward immune function[42].

This model is supported by evidence linking inflammation and immune activation to a subset of depressive presentations and by evolutionary arguments regarding the historical burden of infectious disease[43-45]. However, it is unlikely to account for the full spectrum of depressive and anxiety disorders, especially those more closely tied to psychosocial stress, cognitive factors, and interpersonal dynamics[46]. As with other models, PATHOS-D is best viewed as one contributory explanation within a broader, multicausal framework[47,48].

Overall, the evolutionary models reviewed here show important areas of convergence as well as meaningful differences in explanatory scope. Adaptive defense and mismatch models primarily account for the functional design and environmental sensitivity of affective systems, whereas trade-off and pleiotropy frameworks better explain the maintenance of vulnerability at the genetic level. Mutation–selection balance provides a population-level account of persistent polygenic risk, while pathogen–host defense hypotheses highlight the role of immune-related mechanisms in specific depressive phenotypes. Although these models differ in their level of analysis and primary focus, they converge in suggesting that vulnerability to depressive and anxiety disorders arises from the properties of complex, context-sensitive regulatory systems rather than from single causal mechanisms. A more explicit comparative view indicates that no single model fully captures the clinical heterogeneity of these conditions, but that each contributes to explaining distinct aspects of their persistence, supporting a multicausal and integrative perspective.

Systems and network perspectives on psychopathology

In recent years, systems and network approaches have increasingly conceptualized mental disorders as emergent properties of interacting symptoms and regulatory processes rather than as the expression of a single latent disease entity[20,49]. In these models, feedback loops between symptoms, behaviors, and contextual factors can produce relatively stable pathological states that persist even in the absence of an ongoing external cause[21,50].

This perspective is particularly relevant to depressive and anxiety disorders, which often show nonlinear dynamics, threshold effects, and abrupt transitions between states of relative stability and marked dysfunction[21,25]. It also provides a conceptual bridge between evolutionary accounts of regulatory systems and more proximal models of symptom interaction and maintenance[22,24].

It is important to note that the level of empirical support varies across the frameworks discussed in this review. Findings from network analysis, longitudinal studies, and experimental research provide increasing empirical evidence for the role of feedback processes and dynamic interactions in the emergence and maintenance of psychopathology[19,20,49]. In contrast, broader integrative models—particularly those derived from evolutionary theory or systems-level conceptualizations—should be regarded as heuristic and theory-driven, aiming to organize existing evidence rather than to provide directly testable or fully validated accounts. Distinguishing between empirically grounded findings and more speculative or integrative proposals may help to clarify the current state of the field and to guide future research toward more precise and testable hypotheses.

The schismogenesis hypothesis as a systems-level framework

Within this broader context, the schismogenesis hypothesis has been proposed as a systems-level, stress-threshold model for understanding depressive and anxiety disorders[23,25]. In its current formulation, this hypothesis suggests that when stress load exceeds individual vulnerability thresholds, self-reinforcing feedback processes across neural, cognitive, and social domains may drive a reorganization of the system toward a more disconnected configuration[21,22]. This state is described as a reversible "biopsychosocial break-up" or disconnection, rather than as a fixed deficit[23,25,51,52](**Figure 1**).

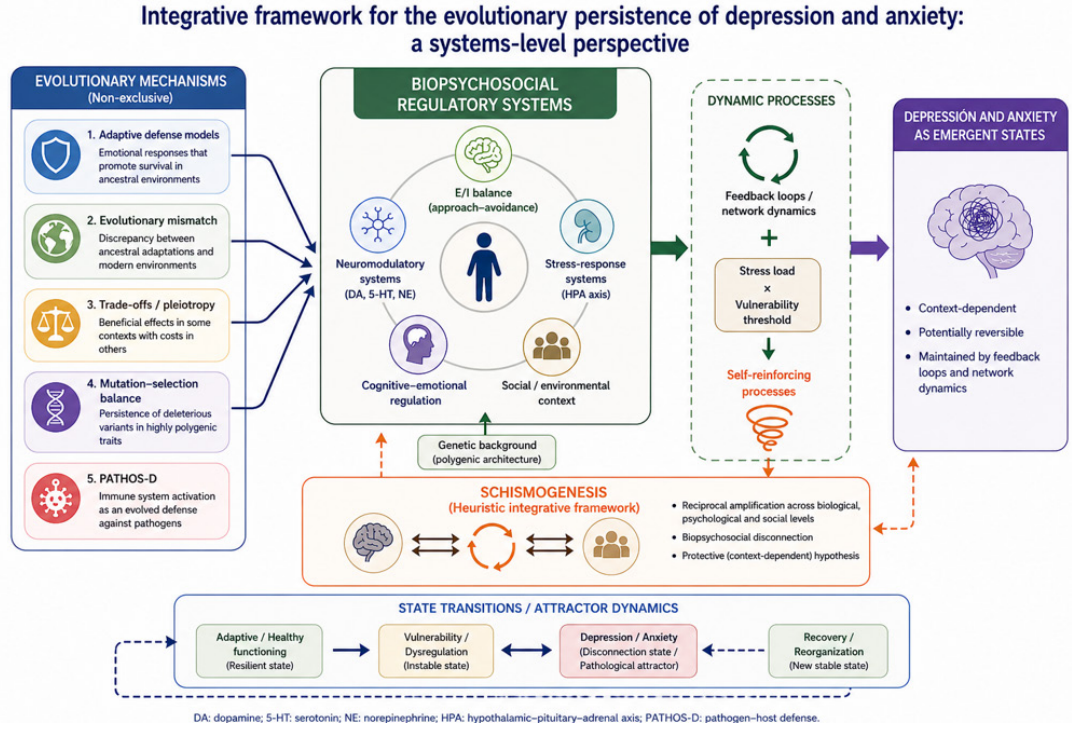

Figure 1. This schematic model illustrates how multiple non-exclusive evolutionary mechanisms (e.g., adaptive defense, mismatch, trade-offs, polygenic architecture, and immune-related processes) may converge on core biopsychosocial regulatory systems. Under conditions of elevated stress load and individual vulnerability, feedback loops and network dynamics may give rise to self-reinforcing processes, leading to depressive and anxiety disorders as emergent, context-dependent states. The schismogenesis framework is presented as a heuristic integrative model describing how reciprocal amplification across levels may contribute to potentially reversible biopsychosocial disconnection states.

Importantly, this framework does not claim that depressive or anxiety disorders are adaptations in their clinical forms. Rather, it cautiously proposes that such disconnection states may, under certain conditions, serve a protective regulatory function by limiting further exposure to overwhelming or inescapable stressors[25,53]. From an evolutionary standpoint, it is at least plausible that regulatory systems capable of temporarily reducing engagement with harmful environments could have conferred advantages in some contexts, even if they carry significant costs when prolonged or triggered inappropriately[23,54].

At present, the schismogenesis hypothesis should be regarded as a heuristic and integrative proposal rather than as an empirically established model. Nevertheless, it resonates with several lines of evidence, including stress-induced alterations in network dynamics[55,56], the presence of positive feedback loops in symptom networks[21,51], and the observed reversibility of many depressive and anxiety states under favorable conditions[25,53].

This perspective naturally invites integration with other models and supports a more comprehensive view of psychopathology as emerging from interacting processes across levels of analysis.

Integrating schismogenesis with other evolutionary models

Rather than competing with existing evolutionary explanations, the schismogenesis framework can be viewed as a dynamic regulatory layer that is broadly compatible with them[16,57]. Adaptive defense models describe the potential functions of emotional responses; mismatch models highlight the role of modern environments in maintaining chronic activation; trade-off and pleiotropy models explain why sensitivity and vulnerability may be conserved; and PATHOS-D emphasizes immune–behavior interactions[34,58]. Schismogenesis adds a systems-level account of how these factors might converge to produce stable yet potentially reversible states of dysregulation[7,27].

In this integrated view, depression and anxiety are best understood not as unitary diseases but as emergent states of evolved regulatory systems operating under particular combinations of genetic predisposition, developmental history, and environmental stress[3]. Such a multicausal framework does not resolve all outstanding questions, but it provides a coherent way of relating evolutionary theory, psychiatric genetics, and systems models of psychopathology while remaining open to empirical refinement and revision[39,59].

At present, the schismogenesis hypothesis should be regarded strictly as a heuristic and integrative proposal rather than as an empirically validated model. While it draws on a growing body of evidence supporting the role of stress-related network dynamics, feedback loops, and system-level dysregulation in psychopathology[19,20,25], the interpretation of these processes as coherent biopsychosocial "disconnection" states remains largely inferential. Accordingly, the hypothesis is best understood as a conceptual framework that aims to organize and link findings across levels of analysis, rather than to provide a definitive explanatory account. Explicitly distinguishing between empirically supported mechanisms and their broader theoretical interpretation may help to situate schismogenesis within the current evidence base and to guide future research toward more direct and testable predictions.

Clinical implications of evolutionary and schismogenesis-based models

An evolutionary perspective on depressive and anxiety disorders may inform clinical reasoning by framing these conditions as dysregulated states of evolved regulatory systems rather than as fixed disease entities[6,9]. Within this view, clinical goals could reasonably include not only symptom reduction but also the gradual restoration of systemic balance and flexibility, an approach that is broadly consistent with adaptive defense and mismatch models[7,35]. These perspectives suggest that many affective symptoms are context-sensitive responses that may become maladaptive when they are persistent, excessive, or triggered in inappropriate environments[5,60] (see **Table 2**).

Within this conceptual landscape, the schismogenesis hypothesis can be understood as a complementary and heuristic framework proposing that depressive and anxiety disorders may reflect reversible biopsychosocial disconnection states arising when stress load exceeds individual vulnerability thresholds, mediated by self-reinforcing feedback loops across neural, cognitive, and social levels[25,61]. Importantly, this disconnection is not necessarily a primary deficit, but may represent a context-dependent protective regulatory response under conditions of excessive or inescapable stress[23,62,63].

Clinically, this perspective highlights the relevance of stress reduction as an initial therapeutic target[25,64]. Interventions aimed at reducing ongoing stressors, enhancing safety, and stabilizing basic rhythms may be particularly important while overall stress load remains high[2,65,66]. It also supports a phased approach to treatment—initial containment

Table 2. Selected clinical and research implications derived from evolutionary and systems-oriented perspectives.

Perspective	Main clinical implication	Cautious interpretation	Testable prediction
Adaptive defense models	Symptoms may reflect exaggerated but context-sensitive responses	Symptom suppression alone may not address underlying regulatory functions	Examine whether context modification reduces symptom persistence
Mismatch models	Reducing chronic environmental stressors may be clinically relevant	Lifestyle and context changes are not sufficient for all patients	Test whether stress reduction moderates relapse risk or treatment response
Trade-offs / pleiotropy	Vulnerability may reflect heightened sensitivity rather than pure deficit	Individual differences should be interpreted in context	Study links between sensitivity traits, stress exposure, and outcomes
Network / systems models	Targeting feedback loops and maintaining factors may improve outcomes	Changes in one symptom may propagate through the system	Longitudinal modeling of symptom network dynamics during treatment
Integrated evolutionary view	Recovery may involve reorganization toward greater flexibility, not only symptom remission	Evolutionary models inform but do not replace evidence-based practice	Combine genetic, environmental, and network measures in longitudinal studies

and stress reduction, followed by stabilization of dysregulated feedback processes and gradual re-integration—although this should be regarded as a clinical hypothesis rather than a standardized protocol[23,67-70].

In addition, the framework offers a cautious reinterpretation of some cases of treatment resistance, suggesting that persistent symptoms may reflect unresolved stressors or contextual pressures rather than intrinsic refractoriness[23,25]. This view is consistent with network models emphasizing self-sustaining symptom interactions[19,20]. More broadly, schismogenesis aligns with evolutionary trade-off models, where heightened sensitivity may confer both advantages and vulnerability depending on context[14,27], and supports understanding recovery as a process of system reorganization toward greater flexibility rather than mere symptom disappearance[6,19] (**Figure 2**).

It should be noted that the clinical implications discussed here are largely derived from theoretical and integrative frameworks rather than from direct empirical validation. As such, they should not be interpreted as established clinical recommendations or treatment guidelines. Instead, these considerations are intended to offer a conceptual lens that may help inform clinical reasoning and generate hypotheses for future research. Further empirical studies, particularly longitudinal and interventional designs, are needed to determine the extent to which these system-oriented and evolutionary perspectives can meaningfully inform clinical practice and improve patient outcomes.

Conclusions and perspectives

Depressive and anxiety disorders remain challenging conditions to understand from both clinical and evolutionary perspectives, in part because they arise from complex interactions between genetic predisposition, developmental history, and environmental context. Contemporary evolutionary psychiatry suggests that vulnerability to these disorders is unlikely to reflect simple design flaws or single causal mechanisms, but rather the properties and trade-offs of evolved regulatory systems that prioritize flexibility and sensitivity over stability[6,27].

The evidence reviewed here indicates that several non-exclusive mechanisms may contribute to the persistence of depressive and anxiety disorders in human populations, including adaptive defense processes, evolutionary mismatch, trade-offs and pleiotropy, mutation–selection balance in highly polygenic traits, and immune-related selection pressures as described in the PATHOS-D hypothesis[15,41,71,72]. Systems and network approaches further suggest that these factors may converge to produce stable yet potentially reversible states of dysregulation maintained by self-reinforcing interactions[19,22].

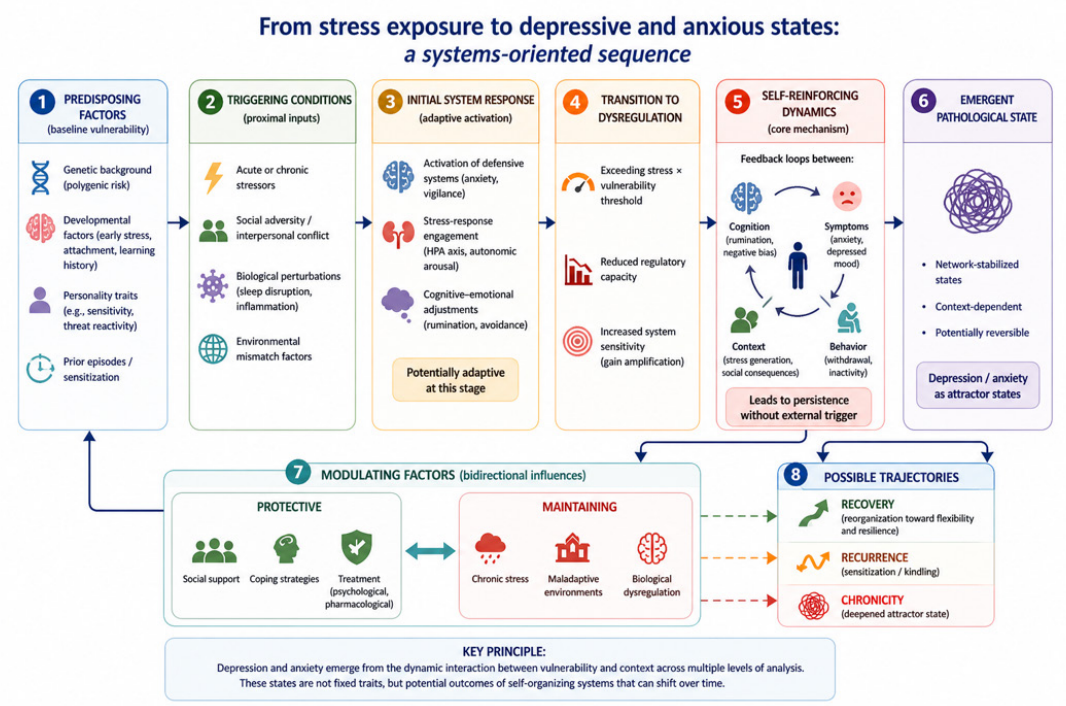

Figure 2. Systems-oriented sequence from stress exposure to depressive and anxiety disorders. The diagram illustrates how predisposing factors and triggering conditions interact with regulatory systems to generate dynamic processes, including feedback loops and stress-related thresholds. These interactions may lead to self-reinforcing dynamics and the emergence of depressive and anxious states, with potential trajectories toward recovery, recurrence, or chronicity depending on modulating factors.

Within this broader landscape, the schismogenesis hypothesis has been introduced as a systems-level, stress-threshold framework for conceptualizing depressive and anxiety disorders as potentially reversible biopsychosocial disconnection states[23,25]. At present, this proposal should be regarded as a heuristic model that may help to integrate evolutionary, genetic, and dynamic systems perspectives, rather than as a definitive explanatory account. Its main contribution may lie in emphasizing the role of stress load, feedback dynamics, and context in shaping transitions between states of relative integration and disconnection[73].

Future research could usefully focus on formalizing these ideas through computational and longitudinal models of stress-related state transitions, empirical studies of network dynamics in depressive and anxiety disorders, and investigations of how environmental modification and stress reduction influence recovery trajectories[74]. From a clinical standpoint, such work may help to refine interventions that aim not only at symptom reduction but also at restoring regulatory flexibility and contextual fit, while maintaining a cautious and evidence-based approach to the translation of evolutionary hypotheses into practice.

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Authors contributions

Mauro García-Toro: conceived the article, conducted the main literature review, and drafted the first version of the manuscript.

Rocío Gómez-Juanes: contributed to the conceptual development of the work and critically revised the manuscript.

Both authors approved the final version of the manuscript.

Declaration of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Use of artificial intelligence tools

During the preparation of this work, the authors used ChatGPT by OpenAI in order to search for relevant

information and to improve the language and readability of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the article.

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Clinical case

Infantile appendicitis presenting as acute scrotum: a case report and review of literature

Apendicitis en un lactante con presentación como escroto agudo: reporte de un caso y revisión de la literatura

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Abstract

Infantile appendicitis is a rare condition with atypical clinical manifestations. We present a case of appendicitis in a 43-day-old male infant presenting with acute scrotum and review the literature to identify and analyze similar cases presenting with acute scrotal findings.

Keywords: Infantile appendicitis. Acute scrotum. Pyocele.

Resumen

La apendicitis en lactantes es una enfermedad poco frecuente, con manifestaciones clínicas atípicas. Presentamos el caso de un lactante varón de 43 días de edad con apendicitis que se manifestó como escroto agudo, y revisamos la literatura con el objetivo de identificar y analizar casos similares con manifestaciones escrotales agudas.

Palabras clave: Apendicitis en lactantes. Escroto agudo. Piocele.

Introduction

Acute appendicitis represents one of the leading causes of surgical abdominal pain in the pediatric population and, if not treated, can result in severe complications, including perforation, peritonitis, and sepsis[1]. Acute appendicitis in infants is rare, accounting for approximately 0.1% to 0.34% of all cases[2].

Clinical manifestations are often nonspecific[3], and they tend to become more atypical with decreasing age. Consequently, the risk of misdiagnosis and subsequent perforated appendicitis increases. In particular, the misdiagnosis rate in patients aged ≤2 years has been reported to reach as high as 100%[4].

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Therefore, we present a rare case of infantile appendicitis manifesting as acute scrotum and review the previously reported cases in the literature.

Case report

A 43-day-old male infant, born at term with no known history of other illnesses, was referred to our center with a preliminary diagnosis of acute scrotum. One day prior to admission, he had developed irritability and vomiting. Concurrently, swelling and erythema of the right scrotum were noted. On admission, the patient was in good general condition and afebrile. Physical examination revealed a markedly edematous, hyperemic, and tender right hemiscrotum. Abdominal examination did not demonstrate findings suggestive of an acute abdomen. Initial laboratory investigations revealed a white blood cell count of 17.4 ×10^9/L (neutrophil count: 11.65 ×10^9/L), hemoglobin of 11.3 g/dL, hematocrit of 32.7%, and a C-reactive protein level of 20 mg/L (normal range: 0.5-5 mg/L).

Scrotal Doppler ultrasonography revealed septated free fluid up to 15 mm in the right scrotal sac and right inguinal canal and up to 8 mm of free fluid in the left scrotal cavity. Increased vascularity and soft tissue echogenicity were observed in the right inguinal canal, along with free fluid. Bilateral testicular and epididymal vascularity was increased, more prominently on the right side. The right spermatic cord appeared edematous with increased blood flow. Abdominal ultrasonography revealed no pathology other than a minimal amount of free fluid in the perihepatic region. A plain abdominal radiograph was also obtained due to a presumptive diagnosis of incarcerated inguinal hernia, which demonstrated bowel dilatation.

The patient was taken to surgery for acute scrotum with a differential diagnosis of incarcerated inguinal hernia or pyocele. Exploration was performed through a right inguinal incision, revealing a markedly fragile and edematous hernia sac. During dissection of the spermatic cord structures, the sac was opened and purulent fluid was drained. No significant pathology was identified in the testis. Due to the purulent nature of the fluid originating from the abdominal cavity, laparoscopic evaluation was planned to rule out intra-abdominal pathology. Following high ligation of the hernia sac, a 5-mm trocar was placed through the umbilicus. The bowel in the right lower quadrant appeared edematous and inflamed. Consequently, the umbilical incision was extended vertically by 1.5 cm, and a mini-laparotomy was performed. The cecum was exteriorized, and the appendix was found to be inflamed, edematous, and covered with fibrin. Appendectomy was performed without drain placement (**Figure 1**).

Figure 1. Intraoperative appearance of the appendix.

On postoperative day 1, the patient's oral intake was initiated and well tolerated. Intravenous antibiotic (ampicillin and metronidazole) therapy was continued during hospitalization. On postoperative day 4, follow-up laboratory tests showed a white blood cell count of 12 ×10^9/L, hemoglobin of 11 g/dL, hematocrit of 33%, and a C-reactive protein of 5 mg/L, and the patient was discharged. The postoperative follow-up was uneventful.

Discussion

In neonates and infants, the diagnosis of acute appendicitis can be challenging due to atypical clinical presentations and nonspecific symptoms[5]. In infants under 3 years of age, the most frequently observed symptoms are vomiting, abdominal pain, fever, and diarrhea. Other common manifestations in this age group include irritability, cough, wheezing, limited movement of the right hip, pain, limping. Because the signs of acute appendicitis in this population are nonspecific, the average time from symptom onset to definitive diagnosis is typically 3 to 4 days. This delay may contribute to an increased risk of perforation and bowel obstruction. Other factors contributing to perforation include a thin-walled appendix and an immature omental barrier. The differential diagnosis in these children includes, but is not limited to, acute gastroenteritis, respiratory tract infections, urinary tract infections, cholecystitis, constipation, intestinal obstruction, nephrolithiasis, dehydration, sepsis, encephalopathy, and meningitis, blunt abdominal trauma, incarcerated inguinal hernia, testicular torsion, orchitis[6].

Acute scrotum is a surgical emergency that may require prompt intervention. Common causes include testicular torsion, torsion of the appendix testis, epididymo-orchitis, and incarcerated inguinal hernia[7]. Pyocele is an uncommon urological emergency and is not routinely included in the initial differential diagnosis[8]. In cases of suspected pyocele, prompt Doppler ultrasonography is recommended for differential diagnosis and to guide urgent management[9]. Pyocele has a variety of etiologies, including hematogenous spread, secondary infection from adjacent structures such as the testis or epididymis, and extension through a patent processus vaginalis[10]. In our case, infected intra-abdominal fluid accumulated in the scrotum via a patent processus vaginalis and was visualized as a septated collection on ultrasonography.

We performed a literature search from inception to March 2026 using the PubMed database. The search strategy included the following keywords: *infant*, *appendicitis*, *acute scrotum*, *pyocele*, *infected hydrocele*, and *incarcerated hernia*. A total of 19 relevant studies were identified. Of these, 10 studies did not meet the inclusion criteria: 2 articles were published in languages other than English, the full texts of 3 studies were unavailable, 1 case had been diagnosed preoperatively, 1 article evaluated Amyand hernias, 2 studies focused on acute scrotum cases in general, and 1 study described scrotal abscess as a postoperative complication. The remaining 9 studies were included in the analysis, as they involved patients similar to our case, in whom surgery was performed for acute scrotum and appendectomy was subsequently undertaken intraoperatively because of suspected acute appendicitis (**Table 1**). In one reported case[11], surgery was performed by a urologist for presumed left testicular torsion; however, no torsion was identified, and the procedure was terminated after a testicular biopsy was obtained. Because of persistent symptoms and clinical deterioration, the patient required multiple hospital admissions and subsequently underwent reoperation for appendicitis on postoperative day 12.

This case, together with the literature review, highlights that acute appendicitis in infants and children may present with atypical manifestations and that intra-abdominal pathologies should be considered when no underlying cause explaining the clinical

Table 1: Demographic and Clinical Features of the Cases.

Study	Year	Age	Symptoms	Initial Diagnosis	Diagnosis
Ahmann[12]	1976	2 y	Right scrotal redness, swelling, right abdominal pain	Acute scrotum	Acute Appendicitis
Graham[13]	1977	2 y	Nausea, vomiting, anorexia, left groin pain	Left testicular torsion	Perforated Appendicitis
Nagel[14]	1984	10 w	Hyper-pyrexia, irritable, tender scrotal swelling	Right testicular torsion	Perforated Appendicitis
Wilkins[11]	1985	12 y	Left testicular pain, nausea, vomiting, diarrhea, and low- grade fever	Left testicular torsion	Perforated Appendicitis
Friedman[15]	1995	7 y	Nausea, vomiting, anorexia, left scrotal swelling	Left testicular torsion	Perforated Appendicitis
Mendez[16]	1998	8 y	Right scrotal pain, swelling, diffuse abdominal pain, nausea, vomiting, anorexia, low-grade fever	Right testicular torsion	Gangrenous Appendicitis
Singh[17]	2002	2 y	Right scrotal pain and swelling, nausea, vomiting, anorexia, and low-grade fever	Right strangulated hernia	Gangrenous Appendicitis
Sharma[18]	2004	6 y	Abdominal pain, nausea, vomiting, scrotal pain	Acute Scrotum	Perforated Appendicitis
Kynes[19]	2011	23 m	Right inguinal mass, malaise, fever, vomiting	Strangulated inguinal hernia or testicular torsion	Perforated Appendicitis
Our case	2024	43 d	Right scrotal swelling, vomiting, irritability	Strangulated inguinal hernia or pyocele	Perforated Appendicitis

presentation is identified in patients presenting with acute scrotum. In this age group, abdominal ultrasonography is the first-line imaging modality for the diagnosis of acute appendicitis. Although it was performed in our patient, it did not provide diagnostic information regarding appendicitis. As appendicitis was not initially considered in the clinical differential diagnosis, the radiologist was not specifically directed to evaluate for this condition, and no findings suggestive of appendicitis were reported. In such cases, surgical intervention should be considered, taking into account potential underlying anatomical factors. The presence of a patent processus vaginalis may explain the atypical scrotal manifestation by allowing communication between the peritoneal cavity and the scrotum, thereby facilitating the spread of infected intra-abdominal fluid. This anatomical factor may contribute to misleading clinical and imaging findings, particularly in infants in whom this channel is more frequently patented. In such cases, if there is clinical suspicion, surgical intervention should be considered. Failure to recognize this may lead to delayed diagnosis and an increased risk of complications.

Conclusion

Appendicitis in infants is an uncommon condition that may present with atypical and misleading clinical features, posing a potentially life-threatening risk. This case emphasizes the need for thorough evaluation and a comprehensive differential diagnosis in infants presenting with scrotal pathology. Clinicians should maintain a high index of suspicion for underlying intra-abdominal disease, particularly in the presence of a patent processus vaginalis. Early recognition, timely diagnosis, and prompt surgical intervention are essential to minimize morbidity and prevent serious complications.

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Conflicts of interest

The authors declare that there is no commercial or financial conflict of interest for this research.

Author contributions

Conceptualisation: E.K.; Data collection: E.K.; Drafting, reviewing, and editing: M.Y., E.K., and F.S. All authors reviewed and approved the final version of the manuscript.

Ethics statement

Written informed consent for publication of the case details and any accompanying images was obtained from the patient's legal guardian. All identifying information was removed to protect patient confidentiality, in accordance with the Declaration of Helsinki and applicable data protection regulations.

AI statement

language translation and editorial refinement. The authors reviewed and verified all AI-assisted content and take full responsibility for the accuracy, integrity, and final content of the manuscript. No artificial intelligence tools were used for the study design, data collection, data analysis, interpretation of the findings, or generation of scientific content.

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Caso clínico

Maxilectomía total seguida de reconstrucción con implantes cigomáticos y un obturador quirúrgico inmediato

A total maxillectomy followed by reconstruction with zygomatic implants and an immediate surgical obturator

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Resumen

El objetivo de este trabajo es describir los pasos seguidos en el tratamiento quirúrgico-protésico inmediato de una paciente operada de un cáncer agresivo intraoral. El caso corresponde al de una mujer de 74 años diagnosticada con carcinoma de paladar, que fue sometida a una maxilectomía total y a un vaciamiento ganglionar cervical, seguida de una reconstrucción con la técnica Quad Zygoma y la adaptación de una prótesis obturadora quirúrgica inmediata. En el postoperatorio inicial se observó una recuperación progresiva de las funciones orales. Tras 12 meses de seguimiento, los resultados del tratamiento en la paciente permitieron concluir a nuestro equipo que este tipo de reconstrucción quirúrgico-protésica puede ser una alternativa viable en casos seleccionados para la rehabilitación de pacientes con maxilectomías totales.

Palabras clave: Maxilectomia. Implante. Obturador.

Abstract

The aim of this paper is to describe the steps followed in the immediate surgical-prosthetic treatment of a patient operated on for an aggressive intraoral cancer. The case concerns a 74-year-old woman diagnosed with palatal carcinoma, who underwent a total maxillectomy and cervical neck dissection, followed by reconstruction using the Quad Zygoma technique and the fitting of an immediate surgical obturator prosthesis. In the early postoperative period, a progressive recovery of oral functions was observed. After 12 months of follow-up, the treatment outcomes in this patient led our team to conclude that this type of surgical-prosthetic reconstruction may be a viable alternative in selected cases for the rehabilitation of patients undergoing total maxillectomy.

Keywords: Maxillectomy. Implant. Obturator.

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Introducción

La rehabilitación maxilofacial de pacientes con maxilectomía total como consecuencia de cáncer oral es un desafío interdisciplinario, que requiere de un minucioso diagnóstico, planificación y plan de tratamiento. Durante las últimas décadas, una variedad de métodos ha sido propuesta y perfeccionada utilizando implantes dentales, como son las técnicas de: a) reconstrucción del defecto mediante colgajo osteocutáneo libre vascularizado en conjunto con una prótesis dental implantosoportada, b) el uso de implantes cigomáticos e implantes subperiósticos en combinación con un injerto de tejido blando vascularizado, y c) el uso de implantes cigomáticos y prótesis obturadoras quirúrgicas inmediatas removibles. Técnicas que tienen el objetivo de restaurar y mantener las funciones orales dentro de lo posible[1].

En cuanto a la prótesis obturadora quirúrgica inmediata removible, se trata de un enfoque terapéutico indicado cuando no es posible la reconstrucción quirúrgica del defecto, y presenta una serie de ventajas, a saber: a) proporcionar una matriz para adaptar el colgajo al momento del cierre de la herida, b) proteger la herida de la contaminación bucal, c) permitir el habla y la mejora de la deglución en el postoperatorio inmediato, d) minimizar el impacto psicológico en el pacient, y e) reducir el tiempo de hospitalización[1].

Caso clínico

Esta investigación cumple con la Declaración de Helsinki, y la paciente firmó un formulario de consentimiento informado.

Una mujer de 74 años derivada en diciembre de 2024 al Hospital Leonardo Guzmán de la ciudad de Antofagasta, Chile, por un tumor de tipo exofítico en la zona derecha del paladar duro y blando. En el examen físico se observó que la paciente era normotípica, con adenopatías cervicales bilaterales (**Figura 1A**). En el examen clínico segmentario intraoral, se visualizó un extenso proceso tumoral verrugoso, de 25 x 35 mm, que abarcaba desde la zona mesial del canino superior izquierdo hasta la zona retromolar superior derecha, comprometiendo el paladar y el reborde dentoalveolar, con movilidad dentaria (**Figura 1B** y **1C**). Se solicitaron una biopsia incisional y tomografías axiales computarizadas (TAC) de cabeza, cuello y tórax.

El análisis histopatológico de la biopsia permitió establecer la presencia de un carcinoma verrugoso con focos de carcinoma escamoso de comportamiento agresivo (**Figura 1D** y **E**). Al examen de TAC, fue posible establecer un proceso expansivo de aspecto necrótico en el reborde alveolar maxilar parasagital derecho, con extensión nasosinusal ipsilateral, de dimensiones máximas aproximadas iguales de 29 x 26 x 19 mm en sus diámetros transversal, anteroposterior y cefalocaudal. Este hallazgo fue concordante con los antecedentes clínicos y estuvo asociado a

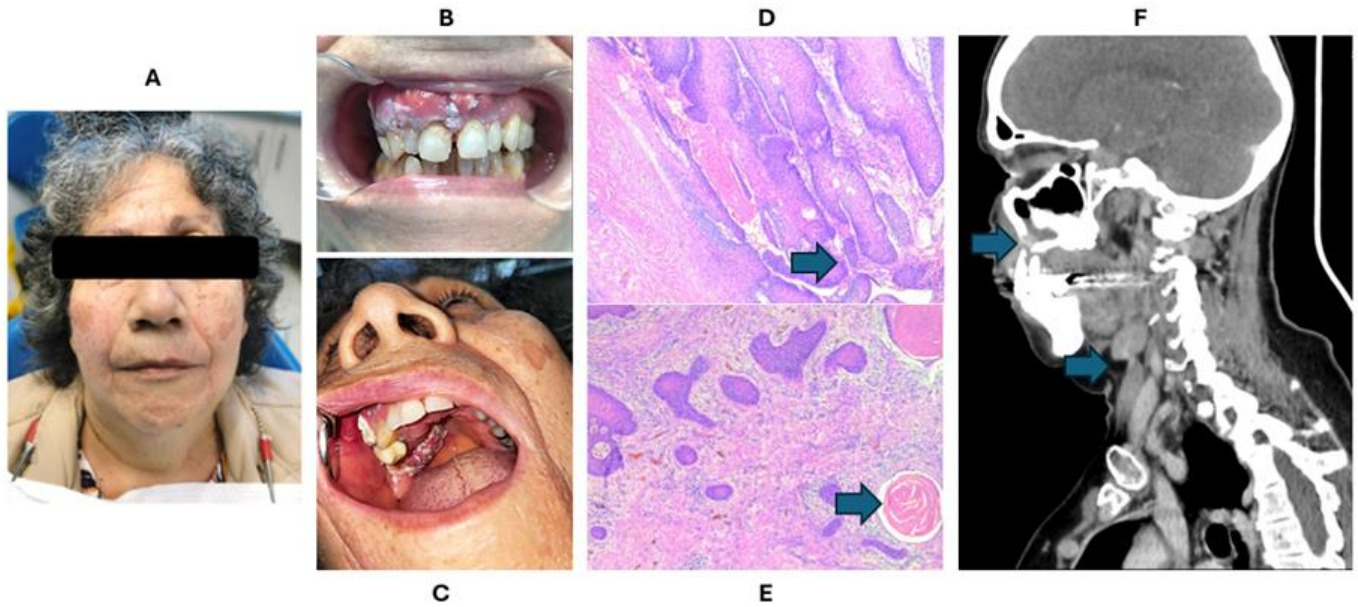

Figura 1. (**A**) Anamnesis de paciente mujer de 74 años, (**B**) tumor exofítico de 25 x 35 mm en zona derecha de paladar, (**C**) compromiso del reborde alveolar con movilidad dentaria. (**D**) Imagen histopatológica que muestra una hiperplasia pseudoepiteliomatosa asociada a hiperqueratosis; (**E**) se observa la presencia de nidos infiltrantes de células escamosas. (**C**) TAC, proceso expansivo de aspecto necrótico en reborde alveolar maxilar parasagital derecho, con extensión nasosinusal ipsilateral. Presencia de linfoadenopatías cervicales bilaterales supra/infrahioideas con aspecto de implantación secundaria.

múltiples linfoadenopatías cervicales bilaterales supra/infrahioideas con aspecto de implantación secundaria (**Figura 1F**).

En la reunión del Comité de Cabeza y Cuello del hospital, se planteó la posibilidad de una resección tumoral asociada a una reconstrucción microquirúrgica del defecto y, además, la opción de una quimioterapia adyuvante complementaria. Para ello, se propuso a la paciente la derivación a un centro especializado en Santiago de Chile, el Instituto Nacional del Cáncer (INC). Sin embargo, la paciente rechazó un eventual traslado de ciudad. El comité, considerando la decisión de la paciente, el crecimiento agresivo del tumor y el eventual tratamiento oncológico postquirúrgico, propuso a la paciente, en conjunto con el equipo del Servicio Dental del Hospital de Antofagasta, un tratamiento quirúrgico-protésico. Este consistió en una maxilectomía derecha extendida a izquierda con reconstrucción por medio de un colgajo mucoperióstico del paladar contralateral, más disección de cuello bilateral e implantes cigomáticos de titanio (técnica Quad Zygoma) en la misma cirugía oncológica, a fin de conectar un obturador protésico quirúrgico inmediato.

En los días siguientes, se citó a la paciente al servicio dental a fin de realizar la toma de impresiones anatómicas en alginato para la confección de tres juegos de modelos en yeso, con los cuales el laboratorio confeccionó obturadores quirúrgicos, uno inicial con frente estético y otro con dentadura completa para la etapa rehabilitadora posterior. Un tercer modelo se almacenó como referencia (**Figura 2A**). Además, se solicitó una tomografía computarizada de haz cónico (CBCT) maxilofacial. En paralelo, se enviaron los archivos DICOM (*Digital Imaging and Communications in Medicine*) del TAC a un centro especializado en impresión 3D (Valcor), para la confección de un modelo estereolitográfico en resina de la paciente por medio de una impresora Form 4BL™. A continuación, se realizó la planificación de la cirugía de implantes cigomáticos (2 implantes por lado), a través de la proyección de las trayectorias y longitudes en el CBCT (**Figura 2B**), y se definió su posición definitiva mediante la cirugía simulada en el modelo 3D (**Figura 2C**), determinándose la emergencia de las conexiones protésicas en la posición de los caninos y los primeros molares maxilares. Ya definidas las posiciones de los implantes, se realizaron guías quirúrgicas no restrictivas bilaterales sobre el modelo, en acrílico transparente (**Figura 2D**).

Debido a que no fue posible conseguir implantes cigomáticos específicamente diseñados para uso oncológico (ONC-55, Southerm Implants). Se utilizó el sistema de implantes cigomáticos de la compañía Straumann®, principalmente por sus características de diseño híbrido, es decir, una zona apical oseointegrable con tratamiento de superficie y el resto mecanizado pulido para facilitar la higiene. Específicamente, se emplearon dos implantes anteriores ZAGA™ Round de 4.3 x 50 mm y 2 posteriores ZAGA™

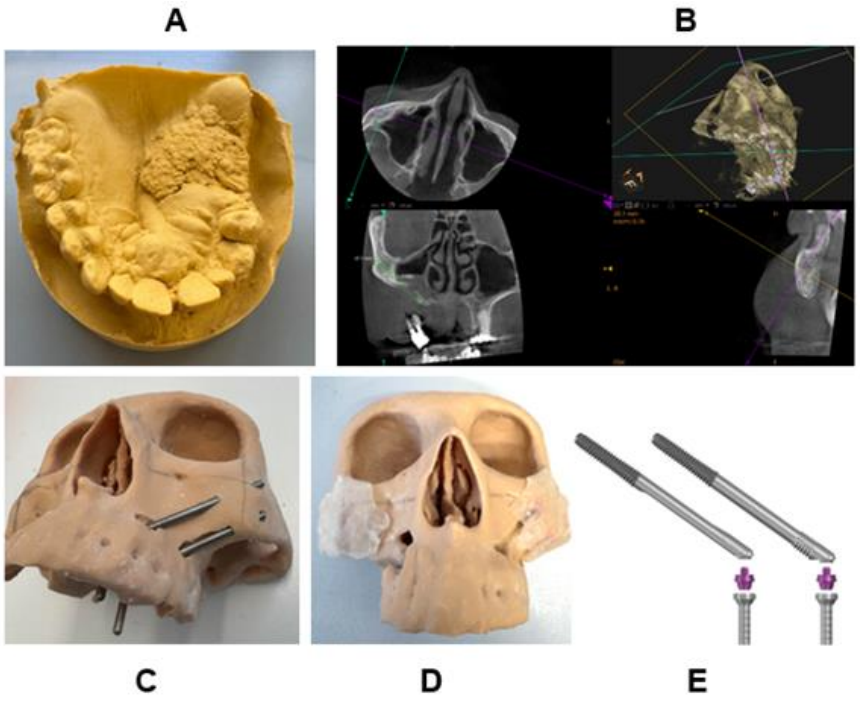

Figura 2. Secuencia de planificación: (**A**) modelo anatómico en yeso, (**B**) estudio en CBCT de la futura posición de los implantes cigomáticos, (**C**) cirugía de implantes en modelo 3D de la paciente, (**D**) confección de guías quirúrgicas.

Round 4.3 x 42 mm y 4.3 x 45 mm. La rehabilitación se planificó en base a pilares rectos, dada la ventaja de la plataforma protésica en 55° de estos implantes (**Figura 2E**).

La cirugía se realizó en un total de 16 horas, en 3 etapas: resección tumoral, cirugía de implantes cigomáticos con colocación de obturador quirúrgico inmediato y disección de cuello. Para la resección tumoral, se realizó un abordaje extraoral a través de un colgajo tipo Weber Ferguson bilateral (**Figura 3A**). Una vez expuesto el maxilar, este fue removido en bloque por medio de una osteotomía tipo Le Fort I modificada, con ayuda de una sierra quirúrgica reciprocante Stryker® (**Figura 3B**). Para la correcta posición de los implantes cigomáticos se utilizaron guías quirúrgicas no restrictivas bilaterales, las cuales fueron mantenidas en posición por medio de microtornillos (**Figura 3C**). De esta forma, y a través de las ranuras de las guías, se procedió al fresado para la colocación de los implantes, alcanzando los 40 N en la posición planificada (**Figura 3D** y **Figura 3E**). El cierre intraoral se realizó por medio de colgajos mucoperiósticos. A continuación, los implantes fueron ferulizados mediante una barra acrílica confeccionada previamente, adaptada de acuerdo con la emergencia de los pilares temporales de titanio, la cual contaba con 2 retenedores anteriores tipo LOCATOR® e imanes de 4 x 2 mm. Sobre esta estructura provisional se realizó el posicionamiento del obturador quirúrgico inmediato con frente estético (sin oclusión posterior), cuyos contornos fueron adaptados con material de rebase permanente de silicona blanda, Ufi Gel® P (**Figura 3F** y **G**). Ya con la prótesis en posición, se procedió al cierre de los tejidos faciales. Finalmente, se realizó una disección de cuello bilateral (**Figura 3H**), seguida de una traqueostomía y gastrostomía para el manejo postquirúrgico de la paciente. Una vez finalizada la cirugía, el análisis histopatológico de la pieza quirúrgica confirmó el diagnóstico, por lo que decidió planificar radioterapia coadyuvante (60 Gy en 30 fracciones).

Tras la cirugía, la paciente permaneció hospitalizada hemodinámicamente (HDM) estable, en la Unidad de Cuidados Intensivos (UCI) durante 5 días, 3 días en la Unidad de Tratamiento Intermedio (UTI) y 29 días entre la unidad de medicina y cirugía.

Es importante destacar que, a los 10 días de la postcirugía, el obturador fue removido para su limpieza y

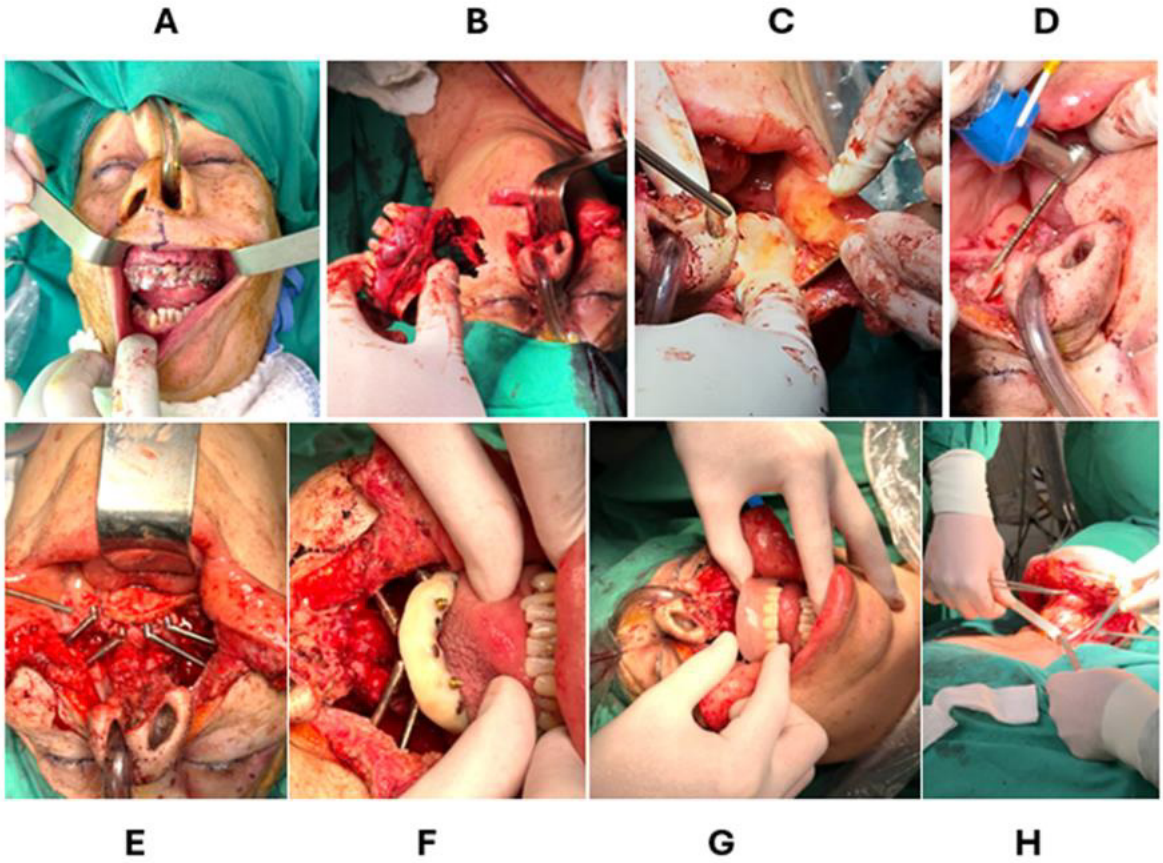

Figura 3. Secuencia quirúrgica: (**A**) demarcación de colgajo tipo Weber Ferguson bilateral, (**B**) extirpación de maxilar, (**C**) posicionamiento de guías quirúrgicas, (**D**) inserción de implantes cigomáticos, (**E**) conexión de férula con sistema de retención, (**G**) adaptación de obturador protésico, (**H**) disección de cuello bilateral.

ajustes. A los 20 días de la postcirugía, el obturador quirúrgico fue utilizado para confeccionar un nuevo obturador provisional con mejor adaptación a los tejidos. Además, durante esa semana se realizó la decanulación de la traqueostomía y la paciente comienza con la ingesta líquida en sorbos pequeños.

Al control quirúrgico-protésico de las 5 semanas, la paciente presentó una mecánica deglutoria funcional, sin signos de penetración/aspiración, por lo que se gestionó el alta de su hospitalización (**Figura 4A** y **B**). Específicamente, en el diagnóstico fonoaudiológico fue posible observar: Escala de la Severidad de la Disfagia (DOSS) nivel 4, es decir, disfagia orofaríngea de origen mecánico grado leve; Escala de Función Oral de Alimentación (FOIS) nivel 3, es decir, alimentación mixta por gastrostomía más vía oral en consistencia de papilla/líquido claro; Escala de Evaluación Oral de Beck (BOAS), disfunción oral leve; Trastorno de los Sonidos del Habla (TSH) de origen morfológico secundario a la maxilectomía; Comunicación verbal medianamente efectiva, con indicación de un plan de tratamiento ambulatorio para fortalecer la motricidad orofacial. Además, se refuerza la técnica de higiene bucal y de los elementos protésicos.

Al control clínico de las 8 semanas se constata que los implantes cigomáticos se encontraban oseointegrados, ya que presentaban estabilidad clínica, ausencia de movilidad y de dolor (**Figura 4C**). Sin embargo, se observa una recidiva de la lesión tumoral en los tejidos remanentes del piso nasal (**Figura 4D**), lo cual fue tratado mediante la radioterapia (**Figura 4E**), terapia que generó una mucositis oral grado 4, asociada a disgeusia, sialorrea, esfacelos mucosos y trismo, lo que se convirtió en un desafío para la mantención de la salud periimplantar y la función del obturador.

Satisfactoriamente, 2 meses después de la radioterapia, una vez que los tejidos se habían recuperado, se probó la superestructura metálica CAD-CAM en la paciente (**Figura 5A** y **B**), la cual proporcionó soporte y retención al obturador definitivo.

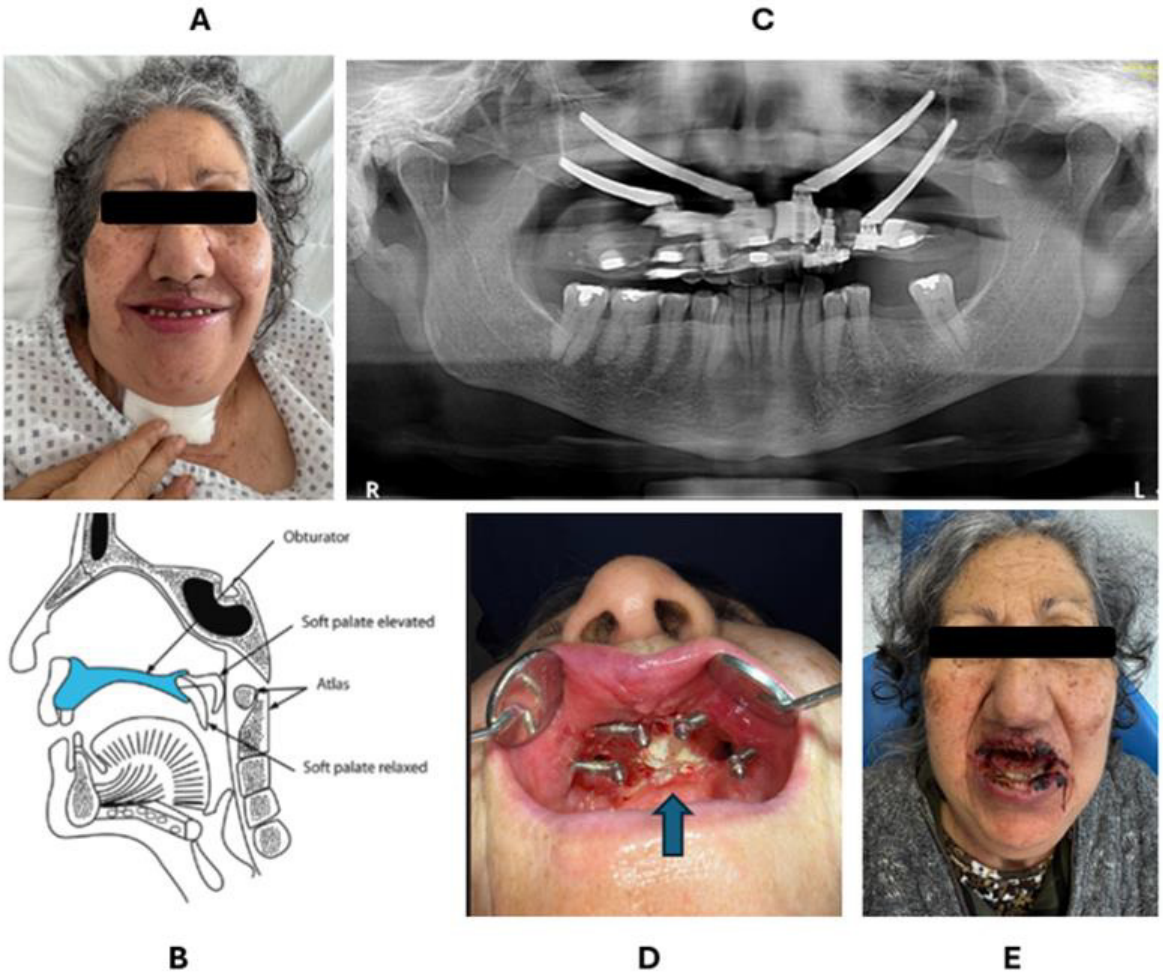

Figura 4. (**A**) control a las 4 semanas, (**B**) representación de un obturador funcional, (**C**) implantes oseointegrados, (**D**) recidiva tumoral en remanente de piso nasal, registro tomado tras la remoción de la férula acrílica, (**E**) imagen tomada tras 2 semanas de radioterapia, se puede observar una compleja mucositis.

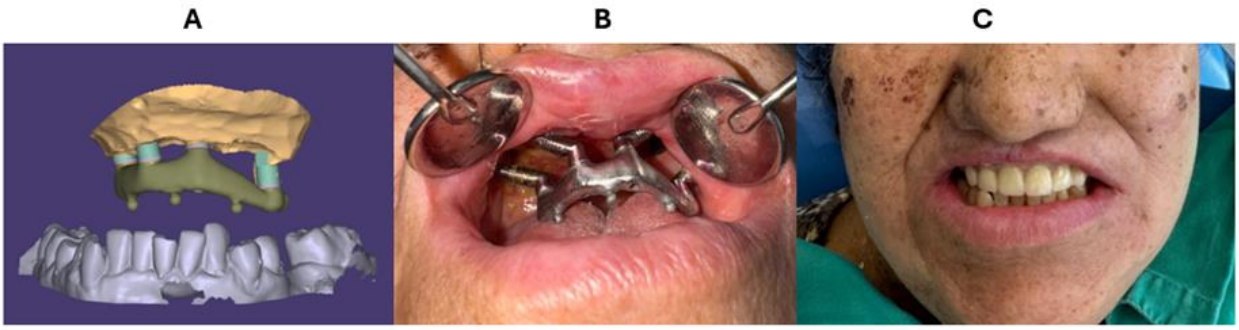

Figura 5. (**A**) Diseño de estructura metálica CAD/CAM para retención de obturador definitivo, (**B**) prueba de estructura con retenedores de bolita, (**C**) obturador definitivo a los 6 meses.

A los 6 meses después de la radioterapia, se observó una respuesta positiva al tratamiento, el examen PET-CT resultó negativo y no se evidenciaron signos locales de enfermedad. Los implantes se mantuvieron oseointegrados y sin signos de inflamación periimplantar.

Tras 12 meses de seguimiento postcirugía oncológica, la calidad de vida de la paciente ha mejorado sustancialmente. La paciente destacó que en todo momento estuvo con dientes, lo cual ayudó a reducir el impacto psicológico de perder su dentadura. En términos objetivos, en la evaluación mediante el cuestionario de la Organización Europea para la Investigación y el Tratamiento del Cáncer (EORTC) QLQ-H&N35, la paciente presentó ausencia de dolor y sensación de enfermedad, así como una mejora progresiva en las escalas de síntomas en áreas clave, como la capacidad de deglución, el habla, la alimentación y el contacto social. En cuanto a la masticación, la función se ha ido recuperando de forma paulatina; por tal motivo, se ha mantenido la indicación de alimentación mixta mediante una sonda de gastrostomía. La paciente está actualmente en controles periódicos interdisciplinarios y se espera una mejora en la función masticatoria a fin de alcanzar una alimentación exclusiva por vía oral.

Discusión

El objetivo de la rehabilitación maxilofacial es restaurar el habla, la deglución, la masticación y la estética. En esta línea, dos enfoques han evolucionado para la restauración de defectos maxilares extensos: el primero involucra cerrar el defecto, ya sea con un colgajo vascularizado osteomiocutáneo o faciocutáneo, y el uso de implantes dentales o implantes subperiósticos que perforan el colgajo[1]. El segundo enfoque consiste en dejar el defecto "abierto", que se restaura a través de un obturador protésico removible que va conectado a una barra metálica unida a implantes dentales[1]. La elección del enfoque terapéutico dependerá de varios factores: la etiología y el tamaño del defecto, el costo y la complejidad del tratamiento, la salud general del paciente, el tiempo de estadía hospitalaria, el tiempo de tratamiento, el número de procedimientos quirúrgicos, experiencia del equipo tratante y el acceso a tecnologías digitales[1].

Por ejemplo, por medio de la planificación digital, es posible el uso de guías quirúrgicas y de resección para el correcto posicionamiento de los implantes dentales en la porción ósea del colgajo libre vascularizado de peroné, el cual es osteotomizado tal como se planificó, adaptando una prótesis preparada o una barra de conexión a implantes. El colgajo es asegurado a la maxila residual y a la base de cráneo con microplacas para la creación de una nueva maxila. El defecto palatino remanente es cerrado con los tejidos blandos asociados al colgajo, y los vasos son anastomosados empleando un microscopio quirúrgico. Sin embargo, el principal desafío de este tipo de técnicas es la revascularización, lo que hace que este procedimiento sea, en algunos casos, impracticable en pacientes que serán sometidos a la resección de un neoplasma maligno[2]. En esta línea, también debemos considerar que, a pesar de la disponibilidad de herramientas como el PET Scan para el seguimiento de la recurrencia, muchos cirujanos oncológicos prefieren monitorizar el sitio quirúrgico directamente y no reconstruir tales defectos primariamente con colgajos vascularizados, justamente tras la remoción de tumores malignos[1].

Dejar el defecto "abierto" y colocar implantes cigomáticos oncológicos se ha transformado en el método de elección en muchos centros[1]. Incluso, el defecto puede ser manejado mediante la novedosa técnica ZIP, especialmente en tumores maxilares de bajo grado, en donde los implantes cigomáticos perforan un colgajo fasciocutáneo que cubre el defecto[3]. Los implantes cigomáticos oncológicos han generado un impacto apreciable en la forma en que se rehabilitan estos pacientes, proveyendo un soporte implantoasistido en el sitio del defecto, y pueden ser instalados

en el momento de la resección quirúrgica tumoral[1]. Cuando hay soporte bilateral del obturador, este se mantiene estable y virtualmente inmóvil durante la función; como resultado, el defecto puede ser sellado efectivamente, restaurando el habla y la deglución. Además, la masticación puede ser restaurada a niveles razonables. Sin embargo, la principal desventaja de este tipo de enfoque es que el paciente debe manejar una prótesis removible, lo cual puede llegar a ser un problema si es que el paciente no está familiarizado con estos dispositivos[4].

Uno de los principales desafíos de ambos enfoques terapéuticos para la supervivencia de los implantes a largo plazo es mantener una adecuada higiene por parte del paciente. En algunos casos, dada la naturaleza del defecto y la dificultad de acceso, se hace complejo sostener la salud periimplantaria, con el consiguiente riesgo de desarrollar periimplantitis. Más aún, en cirugías reconstructivas con colgajos osteomiocutáneos, los implantes están frecuentemente circunscritos por mucosa móvil y pobremente queratinizada. Con relación a este punto, las versiones modernas de los implantes cigomáticos para uso oncológico cuentan con una extensa área lisa, cuya finalidad es minimizar el acúmulo de placa bacteriana, la cual mejora la higiene de esta zona del implante. Esta sección del dispositivo, de acuerdo con la planificación, quedará expuesta desde la zona de anclaje hasta el área de la cavidad bucal. Por lo tanto, una ventaja del uso de obturadores quirúrgicos removibles en combinación con implantes cigomáticos, es que esta modalidad de tratamiento permite al paciente mantener la higiene del defecto maxilar y de los elementos protésicos. Asimismo, el equipo tratante puede tener acceso visual directo al defecto, lo que permite una mejor vigilancia de posibles recurrencias tumorales[1,5], tal como ocurrió en esta paciente a las 8 semanas del postquirúrgico (**Figura 4D**).

Una de las preocupaciones de la rehabilitación con implantes en pacientes maxilectomizados es el rol que juega la biomecánica en el riesgo de sobrecarga, dadas las configuraciones de implantes utilizadas[1]. En el caso presentado en este reporte, se utiliza una adaptación de la técnica conocida como Quad Zygoma, aquí los implantes están solo anclados al hueso residual, por lo que la función de grupo de los implantes a través de la ferulización mediante una barra de conexión (**Figura 5A** y **B**) es lo que hace resistente y viable al sistema. Esto, frente a la aplicación de fuerzas de flexión externas no axiales inducidas durante el funcionamiento[6]. Es importante destacar que el cuello del implante cigomático oncológico tiene un diseño de mayor grosor, área que alberga la conexión, estructura que soportará y retendrá el pilar conectado a la superestructura. Además, este tipo de implantes tiene una plataforma angulada en 55°, con el fin de que, al ingresar al espacio protésico, la rehabilitación sea con pilares lo más perpendiculares al plano oclusal, lo que contribuye a una adecuada biomecánica del sistema[7]. Si bien, este caso no fue planificado con implantes cigomáticos estrictamente oncológicos, de igual manera fueron empleados con éxito implantes cigomáticos Straumann ZAGA Round (**Figura 2E**), los cuales comparten un diseño muy similar[8].

En cuanto a la planificación quirúrgica en pacientes oncológicos, se recomienda la colocación de implantes simultáneamente a la resección quirúrgica tumoral, lo que se conoce como colocación primaria, inmediata o en la misma etapa. Esto debido a que una eventual radioterapia puede comprometer la vascularización y la capacidad de cicatrización de los tejidos circundantes, afectando la tasa de éxito de los implantes dentales. También aumenta el riesgo de osteorradionecrosis, especialmente en la porción ósea del colgajo en técnicas reconstructivas[5]. Los estudios muestran que la supervivencia de implantes en sitios irradiados puede llegar a ser del 76,36 %, frente al 93,1 % en implantes colocados previo a la radiación y el 57,69 % cuando los implantes son colocados en zonas previamente irradiadas[1]. Por lo tanto, se recomienda comenzar la radioterapia al menos 6 semanas tras la colocación de los implantes, a fin de alcanzar la osteointegración de los dispositivos, tal como se planificó en este caso[5].

Limitaciones del estudio

Entendemos las limitaciones metodológicas propias del diseño, ya que se trata de un reporte de caso único, sin comparación ni análisis estadístico.

Conclusión

La reconstrucción inmediata con implantes cigomáticos y obturador quirúrgico puede constituir una alternativa terapéutica viable en pacientes seleccionados con maxilectomías extensas, especialmente cuando la reconstrucción microvascular no es factible.

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Uso de inteligencia artificial

No se utilizaron herramientas de inteligencia artificial en la redacción, análisis, interpretación o revisión de este artículo.

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