AIMS Public Health

AIMS Public Health, 13(4): 1104–1131.
DOI: 10.3934/publichealth.2026057
Received: 05 July 2026
Revised: 21 September 2026
Accepted: 09 October 2026
Published: 11 November 2026

https://www.aimspress.com/journal/aimsph

Research article

Lifestyle behaviors associated with the Gulliver syndrome: Smoking, physical activity, and Mediterranean diet in 395,660 Spanish workers

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Abstract: *Background:* The Gulliver syndrome is a recently proposed phenotype characterized by the simultaneous presence of multiple borderline cardiometabolic abnormalities that may represent an early stage of metabolic dysfunction. However, the contribution of modifiable lifestyle behaviors to this syndrome remains poorly understood. The aim of this study was to investigate the associations between smoking, physical activity, and adherence to the Mediterranean diet and the presence of Gulliver syndrome in a large cohort of Spanish workers. *Methods:* A cross-sectional study was conducted in 395,660 Spanish workers aged 18–69 years who underwent routine occupational health examinations between 2019 and 2020. Smoking status was categorized as never, former, or current smoking, while physical activity and adherence to the Mediterranean diet were assessed using standardized questionnaires, including the International Physical Activity Questionnaire (IPAQ) and the Mediterranean Diet Adherence Screener (MEDAS). Multivariable logistic regression and multinomial logistic regression analyses were performed to identify independent associations between lifestyle behaviors and Gulliver syndrome and across different cardiometabolic profiles. *Results:* The prevalence of Gulliver syndrome was 2.76%. Physically inactive participants exhibited a substantially higher prevalence of the syndrome than physically active individuals (4.43% *vs.* 0.92%; $p < 0.001$), while workers with low adherence to the Mediterranean diet had a markedly higher prevalence than

those with high adherence (4.28% *vs.* 0.86%; $p < 0.001$). In multivariable analyses, physical activity (*OR*: 0.40; 95% *CI*: 0.37–0.44) and high adherence to the Mediterranean diet (*OR*: 0.60; 95% *CI*: 0.55–0.66) were independently associated with lower odds of Gulliver syndrome. Smoking status was also significantly associated with Gulliver syndrome, with higher adjusted odds among former smokers (*OR*: 1.17; 95% *CI*: 1.11–1.23) and current smokers (*OR*: 1.12; 95% *CI*: 1.07–1.17) compared with never smokers. Similar inverse associations for physical activity and Mediterranean diet adherence were observed across progressively less favorable cardiometabolic profiles. *Conclusions:* Physical inactivity and low adherence to the Mediterranean diet were the modifiable lifestyle factors most strongly associated with Gulliver syndrome. These findings indicate that lifestyle behaviors are associated with the presence of this recently proposed cardiometabolic phenotype. Given the cross-sectional design, prospective studies are needed to determine the temporal and prognostic significance of these associations.

Keywords: cardiovascular diseases; lifestyle; motor activity; smoking; mediterranean diet; risk factors

1. Introduction

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide, accounting for nearly one-third of all deaths and representing a major challenge for healthcare systems and public health policies [1]. Although substantial advances have been achieved in the prevention and treatment of cardiovascular disease, its burden continues to increase, largely driven by the growing prevalence of modifiable lifestyle-related risk factors, including tobacco use, physical inactivity, unhealthy dietary patterns, and obesity [2,3].

The contemporary approach to cardiovascular prevention has progressively shifted from the treatment of established disease toward the promotion of cardiovascular health and the early identification of individuals at increased risk [4]. In this context, considerable attention has been paid to the role of lifestyle behaviors, which are estimated to account for a substantial proportion of premature cardiovascular events and deaths worldwide [5]. Several large prospective studies have shown that adherence to healthy lifestyle habits, including regular physical activity, avoidance of smoking, and consumption of high-quality dietary patterns, is associated with a markedly lower risk of cardiovascular disease, type 2 diabetes, and all-cause mortality [6–8].

The Mediterranean diet is one of the most extensively investigated dietary patterns in cardiovascular prevention. Characterized by a high consumption of fruits, vegetables, legumes, whole grains, olive oil, and fish, together with a low intake of processed foods and saturated fats, this dietary pattern has consistently been associated with reductions in cardiovascular events and cardiometabolic risk factors [9,10]. Likewise, regular physical activity exerts beneficial effects on body composition, blood pressure, insulin sensitivity, lipid metabolism, and systemic inflammation, thereby reducing the risk of developing cardiometabolic disorders [11,12]. Conversely, tobacco smoking remains one of the most important preventable causes of cardiovascular disease and has been linked to endothelial dysfunction, insulin resistance, chronic inflammation, and accelerated atherosclerosis [13,14].

Despite the overwhelming evidence supporting the importance of healthy lifestyle behaviors, cardiovascular risk assessment in routine clinical practice still relies predominantly on the presence or absence of individual risk factors according to predefined diagnostic thresholds. However, increasing evidence indicates that cardiovascular risk develops progressively along a continuum and that individuals may accumulate several modest abnormalities long before overt disease becomes apparent [15]. Consequently, there is growing interest in identifying intermediate phenotypes that may reflect early cardiometabolic dysregulation and provide opportunities for earlier preventive interventions.

To address this issue, López-Gil and colleagues recently proposed the concept of the Gulliver syndrome, a novel construct intended to identify individuals who simultaneously present multiple cardiovascular risk factors within borderline ranges [16]. The syndrome is named after Jonathan Swift's fictional character, who, despite his great strength, became immobilized by numerous small restraints. Analogously, individuals with Gulliver syndrome may carry a substantial cardiovascular burden due to the coexistence of several modest abnormalities that, when considered separately, appear clinically insignificant. The proposed diagnostic criteria include the simultaneous presence of borderline abdominal adiposity, prehypertensive blood pressure, impaired fasting glucose, and elevated non-high-density lipoprotein cholesterol concentrations [16].

Although the biological plausibility of this concept is considerable, the factors associated with Gulliver syndrome remain largely unknown. In particular, no previous studies have examined the association between modifiable lifestyle behaviors and this phenotype. This question is clinically relevant because unhealthy behaviors often precede the appearance of overt cardiometabolic disease and may contribute to the early clustering of borderline abnormalities through common pathophysiological pathways, such as visceral adiposity, insulin resistance, low-grade inflammation, and endothelial dysfunction [17,18].

Occupational cohorts provide an especially suitable setting in which to investigate these associations. Workers are frequently assessed before the onset of clinically overt disease and represent a broad spectrum of socioeconomic backgrounds and lifestyle behaviors. Identifying modifiable factors associated with Gulliver syndrome in this population could facilitate the implementation of early preventive strategies and contribute to reducing the future burden of cardiovascular disease.

Therefore, the aim of the present study was to investigate the association between smoking, physical activity, and adherence to the Mediterranean diet and the presence of Gulliver syndrome in a large cohort of Spanish workers. We hypothesized that unhealthy lifestyle behaviors would be independently associated with a higher prevalence of the syndrome and additionally explored sex-stratified associations and associations across different cardiometabolic profiles.

2. Materials and methods

2.1. Study design and population

A cross-sectional study was conducted using data obtained from routine occupational health examinations performed in Spanish workers between January 2019 and December 2020. Occupational health surveillance is mandatory in Spain and is carried out according to national legislation and

international recommendations, providing a valuable source of standardized clinical and lifestyle information in large working populations [19,20].

Initially, 398,214 workers aged between 18 and 69 years underwent occupational health assessments during the study period. Participants with missing information on any of the variables required to define the Gulliver syndrome or on the lifestyle variables included in the present analyses were excluded. The final analytical sample comprised 395,660 workers. The participant selection process is summarized in Figure 1.

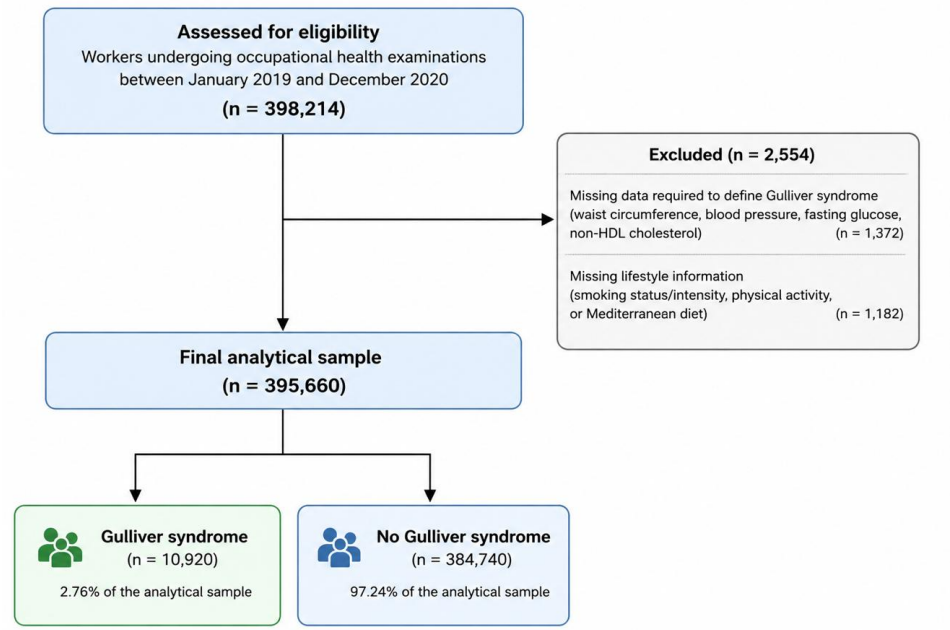


Figure 1. Flow chart of the study population.

All examinations were performed by trained occupational health professionals following standardized protocols. The study complied with the principles of the Declaration of Helsinki and was approved by the Research Ethics Committee of the Balearic Islands (CEI–IB 4383/20 PI, approved on November 26, 2020). Because the study was based on anonymized secondary data obtained during routine occupational examinations, the requirement for informed consent was waived.

2.2. Sociodemographic variables

Sex was classified as male or female. Age was analyzed both as a continuous variable and categorically into five groups: 18–29, 30–39, 40–49, 50–59, and 60–69 years.

Social class was classified into three categories (I, II, and III) according to the Spanish adaptation of the National Classification of Occupations, which is based on occupational position and socioeconomic characteristics [21].

Educational attainment was categorized into three levels: primary education, secondary education, and university education.

2.3. Lifestyle variables

2.3.1. Smoking status

Smoking status was systematically recorded for all participants and categorized into three mutually exclusive groups: never smokers, former smokers, and current smokers [22,23]. Never smokers were defined as participants who reported never having smoked. Former smokers were defined as participants who had previously smoked but had abstained from smoking for at least 12 months. Current smokers were defined as participants who reported active tobacco use at the time of the occupational health examination.

2.3.2. Physical activity

Physical activity was assessed using the short version of the International Physical Activity Questionnaire (IPAQ), a widely validated instrument for the evaluation of habitual physical activity in epidemiological studies [24]. The questionnaire collects information on the frequency and duration of vigorous-intensity activity, moderate-intensity activity, and walking performed during the previous seven days.

Based on the IPAQ scoring protocol, participants were classified as physically active or physically inactive according to current international recommendations for physical activity and health [24,25].

2.3.3. Mediterranean diet adherence

Adherence to the Mediterranean diet was assessed using the 14-item Mediterranean Diet Adherence Screener (MEDAS), originally developed within the PREDIMED study and subsequently validated in different populations [26–28]. The questionnaire evaluates the habitual consumption of key components of the Mediterranean dietary pattern, including olive oil, fruits, vegetables, legumes, nuts, fish, and red meat.

MEDAS scores range from 0 to 14 points. In the present study, participants with a score of 9 points or higher were considered to have high adherence to the Mediterranean diet, whereas those scoring below 9 points were classified as having low adherence.

2.4. Clinical and anthropometric measurements

Body weight and height were measured with participants wearing light clothing and no shoes using a SECA 700 mechanical scale and stadiometer (SECA Ltd., Hamburg, Germany). Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2) [29].

Waist circumference was measured midway between the lower rib margin and the iliac crest at the end of a normal expiration using a non-elastic measuring tape [30].

Blood pressure was measured in the seated position after at least five minutes of rest using a validated automated sphygmomanometer (OMRON M3, Omron Healthcare, Kyoto, Japan). Three

measurements were obtained at one-minute intervals and the mean of the last two measurements was used for analysis [31].

Venous blood samples were obtained after an overnight fast of at least 8 hours. Fasting plasma glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides were determined using standardized enzymatic methods in certified laboratories.

Non-HDL cholesterol was calculated as:

Non-HDL cholesterol = Total cholesterol − HDL cholesterol

2.5. Definition of Gulliver syndrome

Gulliver syndrome was defined according to the criteria proposed by López-Gil et al. [16]. Participants were classified as having Gulliver syndrome when all the following conditions were simultaneously present:

1. Waist circumference
   - 90–101 cm in men; 80–87 cm in women.
2. Blood pressure
   - Systolic blood pressure between 120 and 139 mmHg and/or diastolic blood pressure between 80 and 89 mmHg.
3. Fasting plasma glucose
   - 100–125 mg/dL.
4. Non-HDL cholesterol
   - 130–189 mg/dL.

For the present study, participants were classified into five mutually exclusive cardiometabolic profiles according to the number and severity of abnormalities in the four components used to define Gulliver syndrome: Group 1 (healthy), with none of the four components in the borderline or pathological range; Group 2 (partial borderline profile), with one to three components in the borderline range and no component in the pathological range; Group 3 (Gulliver syndrome), with all four components simultaneously in the borderline range; Group 4 (single pathological factor), with one component in the pathological range; and Group 5 (multiple pathological factors), with two or more components in the pathological range.

For the principal analyses, the dependent variable was dichotomized as:

- Gulliver syndrome: yes (Group 3); No Gulliver syndrome: no (Groups 1, 2, 4, and 5).

In addition, multinomial analyses were performed considering the five original cardiometabolic profiles in order to explore whether the associations between lifestyle behaviors and cardiometabolic health differed across the entire spectrum of metabolic risk.

2.6. Statistical analysis

Continuous variables are presented as mean ± standard deviation, whereas categorical variables are expressed as frequencies and percentages. The distribution of continuous variables was assessed using the Kolmogorov-Smirnov test.

Differences according to the presence of Gulliver syndrome were assessed using Student's *t*-test for continuous variables and the chi-square test for categorical variables.

Crude prevalence estimates and their corresponding 95% confidence intervals (95% *CI*s) were calculated according to smoking status (never smokers, former smokers, and current smokers), physical activity, and Mediterranean diet adherence.

Multivariable binary logistic regression analyses were performed to examine independent associations between lifestyle factors and Gulliver syndrome. Smoking, physical activity, and Mediterranean diet adherence were simultaneously entered into the models together with sex, age, social class, and educational attainment. Odds ratios (*OR*s) and their corresponding 95% confidence intervals (95% *CI*s) were estimated.

Additional multinomial logistic regression analyses were conducted using the five cardiometabolic profiles as the dependent variable, with the healthy group serving as the reference category.

Finally, sex-stratified analyses were performed to describe the associations between lifestyle behaviors and Gulliver syndrome separately among men and women.

All statistical analyses were performed using IBM SPSS Statistics version 31.0 (IBM Corp., Armonk, NY, USA). Statistical significance was established at a two-sided p value < 0.05.

3. Results

3.1. Characteristics of the study population

The final study population comprised 395,660 Spanish workers, including 240,174 men (60.7%) and 155,486 women (39.3%), with a mean age of 39.7 ± 11.2 years. Overall, 207,852 participants (52.5%) were classified as physically inactive according to the IPAQ questionnaire, and 175,848 (44.4%) showed high adherence to the Mediterranean diet (MEDAS score ≥ 9).

Compared with participants without Gulliver syndrome, those with the syndrome were significantly older (45.0 ± 10.0 *vs.* 39.5 ± 11.2 years; $p < 0.001$) and were more frequently men (84.2% *vs.* 60.0%; $p < 0.001$). They also exhibited a markedly less favorable lifestyle profile, characterized by substantially higher levels of physical inactivity (84.2% *vs.* 51.6%; $p < 0.001$) and lower adherence to the Mediterranean diet (13.9% *vs.* 45.3%; $p < 0.001$).

The general characteristics of the study population according to the presence of Gulliver syndrome are presented in Table 1.

Table 1. General characteristics of the study population according to the presence of Gulliver syndrome.

Variable	No Gulliver syndrome (*n* = 384,740)	Gulliver syndrome (*n* = 10,920)	*p* value
Age, years	39.5 ± 11.2	45.0 ± 10.0	<0.001
Sex, *n* (%)			<0.001
Men	230,974 (60.0)	9200 (84.2)	
Women	153,766 (40.0)	1720 (15.8)	
Age group, *n* (%)			<0.001
18–29 years	71,624 (18.6)	480 (4.4)	
30–39 years	127,832 (33.2)	2600 (23.8)	
40–49 years	113,524 (29.5)	4200 (38.5)	
50–59 years	60,920 (15.8)	3120 (28.6)	
60–69 years	10,840 (2.8)	520 (4.8)	
Educational attainment, *n* (%)			<0.001
Primary education	220,928 (57.4)	6880 (63.0)	
Secondary education	141,196 (36.7)	3600 (33.0)	
University education	22,616 (5.9)	440 (4.0)	
Social class, *n* (%)			<0.001
I	22,894 (5.9)	560 (5.1)	
II	91,400 (23.8)	2400 (22.0)	
III	270,446 (70.3)	7960 (72.9)	
Smoking status, *n* (%)			<0.001
Never smokers	177,118 (46.0)	4120 (37.7)	
Former smokers	71,254 (18.5)	2920 (26.7)	
Current smokers	136,368 (35.4)	3880 (35.5)	
Physical activity, *n* (%)			<0.001
Physically active	186,088 (48.4)	1720 (15.8)	
Physically inactive	198,652 (51.6)	9200 (84.2)	
Mediterranean diet adherence, *n* (%)			<0.001
High adherence (MEDAS ≥ 9)	174,328 (45.3)	1520 (13.9)	
Low adherence (MEDAS < 9)	210,412 (54.7)	9400 (86.1)	

Note: Values are presented as mean ± standard deviation or number (%). *p* values were obtained using Student's *t*-test for continuous variables and the chi-square test for categorical variables.

3.2. Prevalence of Gulliver syndrome according to lifestyle behaviors

The overall prevalence of Gulliver syndrome was 2.76% (95% *CI*: 2.71–2.81). Significant differences were observed according to smoking status ($p < 0.001$). The prevalence of Gulliver syndrome was 2.27% (95% *CI*: 2.20–2.34) among never smokers, 3.94% (95% *CI*: 3.80–4.08) among former smokers, and 2.77% (95% *CI*: 2.68–2.85) among current smokers.

Marked differences were observed according to physical activity and adherence to the Mediterranean diet. Physically inactive participants exhibited nearly a fivefold higher prevalence of

Gulliver syndrome than physically active individuals (4.43% *vs.* 0.92%; $p < 0.001$). Similarly, workers with low adherence to the Mediterranean diet showed a substantially greater prevalence of the syndrome compared with those with high adherence (4.28% *vs.* 0.86%; $p < 0.001$).

These results are summarized in Table 2 and illustrated in Figure 2.

Table 2. Prevalence of Gulliver syndrome according to smoking status, physical activity, and adherence to the Mediterranean diet.

Variable	Cases/Total	Prevalence % (95% *CI*)	*p* value
Smoking status			<0.001
Never smokers	4120/181,238	2.27 (2.20–2.34)	
Former smokers	2920/74,174	3.94 (3.80–4.08)	
Current smokers	3880/140,248	2.77 (2.68–2.85)	
Physical activity			<0.001
Physically active	1720/187,808	0.92 (0.87–0.96)	
Physically inactive	9200/207,852	4.43 (4.34–4.52)	
Mediterranean diet adherence			<0.001
High adherence (MEDAS ≥ 9)	1520/175,848	0.86 (0.82–0.91)	
Low adherence (MEDAS < 9)	9400/219,812	4.28 (4.19–4.36)	

Note: Data are presented as cases/total participants and prevalence estimates with corresponding 95% confidence intervals (95% *CI*s). *p* values were calculated using the chi-square test.

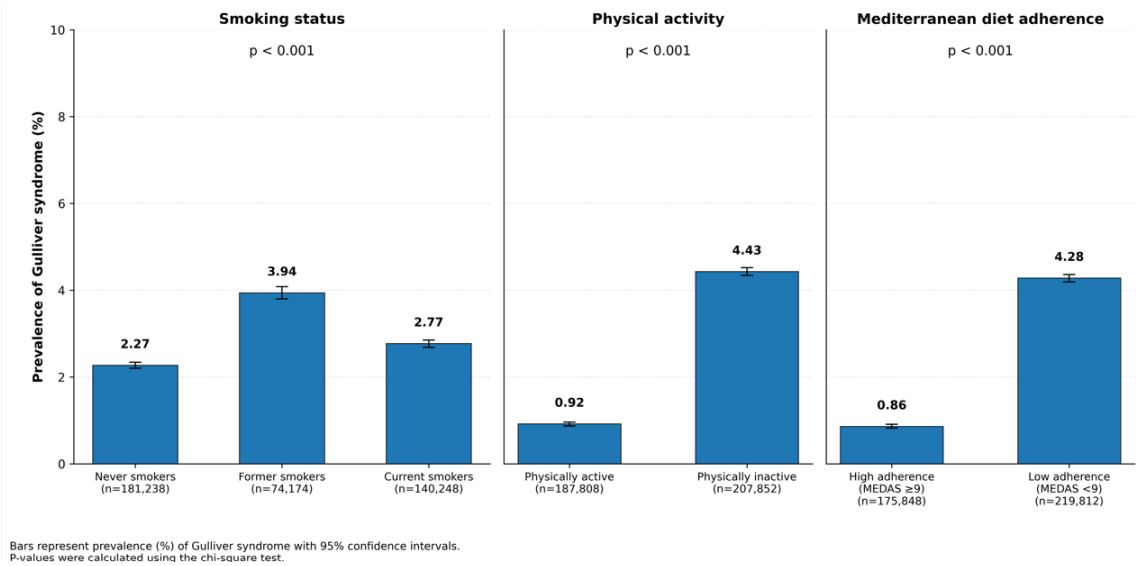


Figure 2. Prevalence of Gulliver syndrome according to lifestyle behaviors.

3.3. Lifestyle factors associated with Gulliver syndrome

In the multivariable logistic regression analysis, smoking status was significantly associated with Gulliver syndrome. Compared with never smokers, former smokers showed higher odds of presenting

the syndrome (*OR*: 1.17; 95% *CI*: 1.11–1.23; $p < 0.001$), as did current smokers (*OR*: 1.12; 95% *CI*: 1.07–1.17; $p < 0.001$).

Physically active participants had substantially lower odds of Gulliver syndrome than physically inactive individuals (*OR*: 0.40; 95% *CI*: 0.37–0.44; $p < 0.001$). Similarly, high adherence to the Mediterranean diet was independently associated with a lower probability of presenting the syndrome (*OR*: 0.60; 95% *CI*: 0.55–0.66; $p < 0.001$).

Among all modifiable lifestyle behaviors, regular physical activity showed the strongest inverse association with Gulliver syndrome. The results of the multivariable logistic regression analysis are presented in Table 3.

Table 3. Multivariable logistic regression analysis of lifestyle factors associated with Gulliver syndrome.

Variable	Adjusted *OR*	95% *CI*	*p* value
Smoking status			
Never smokers	1.00 (reference)	–	–
Former smokers	1.17	1.11–1.23	<0.001
Current smokers	1.12	1.07–1.17	<0.001
Physical activity			
Physically inactive	1.00 (reference)	–	–
Physically active	0.40	0.37–0.44	<0.001
Mediterranean diet adherence			
Low adherence (MEDAS < 9)	1.00 (reference)	–	–
High adherence (MEDAS ≥ 9)	0.60	0.55–0.66	<0.001
Sex			
Men	1.00 (reference)	–	–
Women	0.31	0.29–0.33	<0.001
Age group			
18–29 years	1.00 (reference)	–	–
30–39 years	2.40	2.19–2.64	<0.001
40–49 years	3.65	3.33–4.01	<0.001
50–59 years	4.46	4.08–4.88	<0.001
60–69 years	4.03	3.62–4.48	<0.001
Social class			
I	1.00 (reference)	–	–
II	0.57	0.49–0.68	<0.001
III	0.34	0.29–0.40	<0.001
Educational attainment			
Primary education	1.00 (reference)	–	–
Secondary education	0.67	0.63–0.71	<0.001
University education	0.28	0.24–0.33	<0.001

Note: Odds ratios were adjusted simultaneously for smoking status, physical activity, Mediterranean diet adherence, sex, age group, social class, and educational attainment.

Figure 3 illustrates the independent associations between lifestyle behaviors and Gulliver syndrome after adjustment for sex, age, social class, and educational attainment, showing particularly strong inverse associations for physical activity and adherence to the Mediterranean diet.

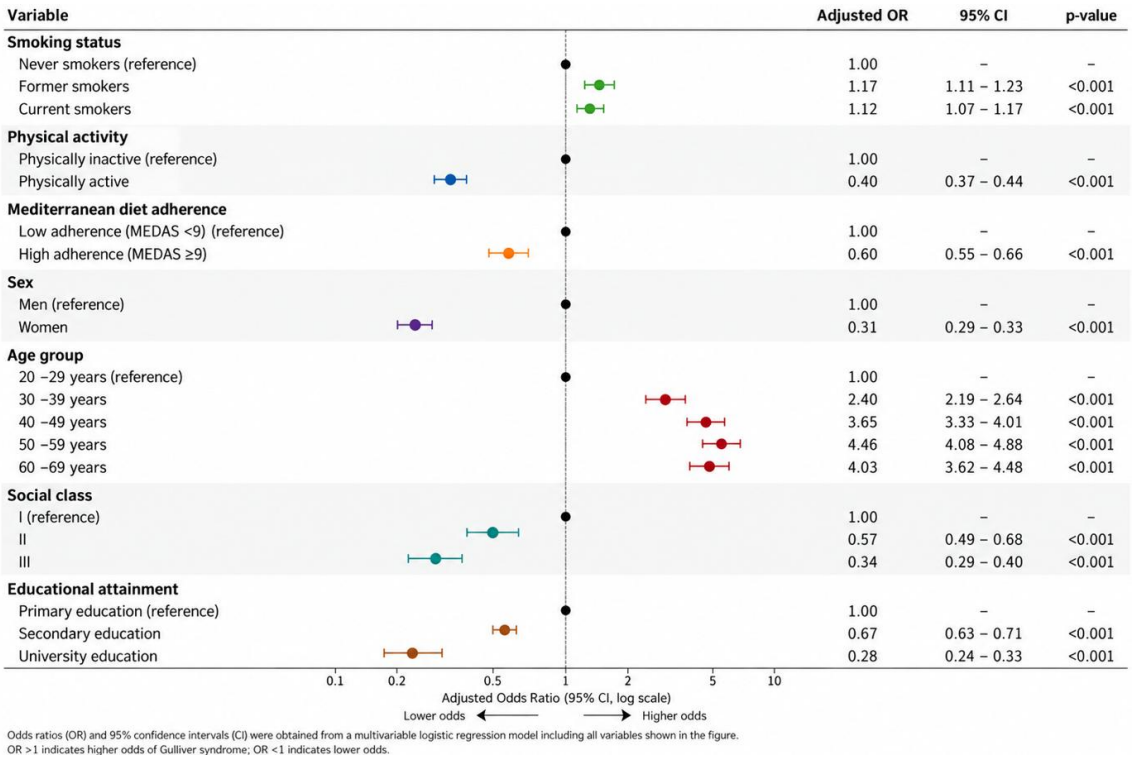


Figure 3. Forest plot of lifestyle factors associated with Gulliver syndrome.

3.4. Sex-stratified analyses

Among men, both former and current smoking were independently associated with higher odds of Gulliver syndrome compared with never smoking (former smokers: *OR*: 1.19; 95% *CI*: 1.13–1.26; $p < 0.001$; current smokers: *OR*: 1.15; 95% *CI*: 1.09–1.20; $p < 0.001$). In contrast, regular physical activity and high adherence to the Mediterranean diet were associated with significantly lower odds of the syndrome (*OR*: 0.42 and *OR*: 0.78, respectively; both $p < 0.001$). Age showed a strong positive association, with the highest odds observed among men aged 50–59 years (*OR*: 4.77; 95% *CI*: 4.28–5.32). The results of the multivariable logistic regression analysis in men are presented in Table 4.

Table 4. Multivariable logistic regression analysis of lifestyle factors associated with Gulliver syndrome in men.

Variable	Adjusted *OR*	95% *CI*	*p* value
Smoking status			
Never smokers	1.00 (reference)	–	–
Former smokers	1.19	1.13–1.26	<0.001
Current smokers	1.15	1.09–1.20	<0.001
Physical activity			
Physically inactive	1.00 (reference)	–	–
Physically active	0.42	0.37–0.47	<0.001
Mediterranean diet adherence			
Low adherence (MEDAS < 9)	1.00 (reference)	–	–
High adherence (MEDAS ≥ 9)	0.78	0.69–0.87	<0.001
Age group			
18–29 years	1.00 (reference)	–	–
30–39 years	2.44	2.19–2.71	<0.001
40–49 years	3.99	3.59–4.43	<0.001
50–59 years	4.77	4.28–5.32	<0.001
60–69 years	3.09	2.66–3.59	<0.001
Social class			
I	1.00 (reference)	–	–
II	0.53	0.44–0.63	<0.001
III	0.35	0.29–0.42	<0.001
Educational attainment			
Primary education	1.00 (reference)	–	–
Secondary education	0.68	0.64–0.73	<0.001
University education	0.28	0.23–0.35	<0.001

Note: Odds ratios were obtained from a multivariable logistic regression model including smoking status, physical activity, Mediterranean diet adherence, age group, social class, and educational attainment.

Among women, former smokers showed significantly higher odds of Gulliver syndrome compared with never smokers (*OR*: 1.20; 95% *CI*: 1.05–1.36; $p = 0.005$), whereas current smoking was not significantly associated with the syndrome (*OR*: 1.07; 95% *CI*: 0.95–1.20; $p = 0.264$).

The strongest inverse associations were observed for physical activity and adherence to the Mediterranean diet. Physically active women showed an approximately 89% lower probability of presenting Gulliver syndrome (*OR*: 0.11; 95% *CI*: 0.08–0.16; $p < 0.001$), while high adherence to the Mediterranean diet was associated with an 87% reduction in the odds of the syndrome (*OR*: 0.13; 95% *CI*: 0.09–0.19; $p < 0.001$).

A pronounced age gradient was also observed, with women aged 60–69 years exhibiting more than eightfold higher odds of presenting Gulliver syndrome compared with those aged 18–29 years (*OR*: 8.32; 95% *CI*: 6.38–10.86; $p < 0.001$). The results of the multivariable logistic regression analysis in women are presented in Table 5.

Table 5. Multivariable logistic regression analysis of lifestyle factors associated with Gulliver syndrome in women.

Variable	Adjusted *OR*	95% *CI*	*p* value
Smoking status			
Never smokers	1.00 (reference)	–	–
Former smokers	1.20	1.05–1.36	0.005
Current smokers	1.07	0.95–1.20	0.264
Physical activity			
Physically inactive	1.00 (reference)	–	–
Physically active	0.11	0.08–0.16	<0.001
Mediterranean diet adherence			
Low adherence (MEDAS < 9)	1.00 (reference)	–	–
High adherence (MEDAS ≥ 9)	0.13	0.09–0.19	<0.001
Age group			
18–29 years	1.00 (reference)	–	–
30–39 years	2.57	2.02–3.27	<0.001
40–49 years	2.76	2.17–3.50	<0.001
50–59 years	3.74	2.94–4.75	<0.001
60–69 years	8.32	6.38–10.86	<0.001
Social class			
I	1.00 (reference)	–	–
II	1.03	0.49–2.17	0.929
III	0.33	0.16–0.69	0.003
Educational attainment			
Primary education	1.00 (reference)	–	–
Secondary education	0.56	0.45–0.68	<0.001
University education	0.37	0.18–0.78	0.009

Note: Odds ratios were obtained from a multivariable logistic regression model including smoking status, physical activity, Mediterranean diet adherence, age group, social class, and educational attainment.

3.5. Multinomial analysis across cardiometabolic profiles

Multinomial logistic regression analyses showed that lifestyle behaviors were associated with the different cardiometabolic profiles. Compared with healthy participants (Group 1), physically active individuals and those with high adherence to the Mediterranean diet exhibited substantially lower odds of belonging to all adverse cardiometabolic profiles, with the strongest inverse associations observed for Group 5. Smoking status also showed significant associations with several cardiometabolic profiles. Compared with never smokers, former smokers had higher odds of belonging to Groups 3, 4, and 5, while current smokers had higher odds of belonging to Groups 3 and 5 and lower odds of belonging to Group 2.

The detailed results of the multinomial regression analyses are presented in Table 6.

Table 6. Multinomial logistic regression analysis of lifestyle factors across the five cardiometabolic profiles.

Variable	Group 2 *OR* (95% *CI*)	Group 3 *OR* (95% *CI*)	Group 4 *OR* (95% *CI*)	Group 5 *OR* (95% *CI*)
Smoking status				
Never smokers	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Former smokers	1.02 (0.99–1.05)	1.27 (1.19–1.34)	1.09 (1.06–1.14)	1.22 (1.16–1.28)
Current smokers	0.87 (0.85–0.89)	1.08 (1.02–1.13)	0.99 (0.96–1.02)	1.24 (1.19–1.29)
Physically active	0.46 (0.45–0.48)	0.12 (0.11–0.13)	0.13 (0.12–0.14)	0.01 (0.009–0.012)
High adherence to the Mediterranean diet (MEDAS ≥ 9)	0.44 (0.43–0.46)	0.25 (0.23–0.28)	0.26 (0.25–0.28)	0.07 (0.06–0.08)

Note: Odds ratios were obtained from multinomial logistic regression models using the healthy profile (Group 1) as the reference category and adjusting for sex, age, social class, educational attainment, smoking status, physical activity, and adherence to the Mediterranean diet.

The pattern of associations across the different cardiometabolic profiles is illustrated in Figure 4. Overall, the magnitude of the protective associations observed for physical activity and Mediterranean diet adherence increased progressively as cardiometabolic status worsened.

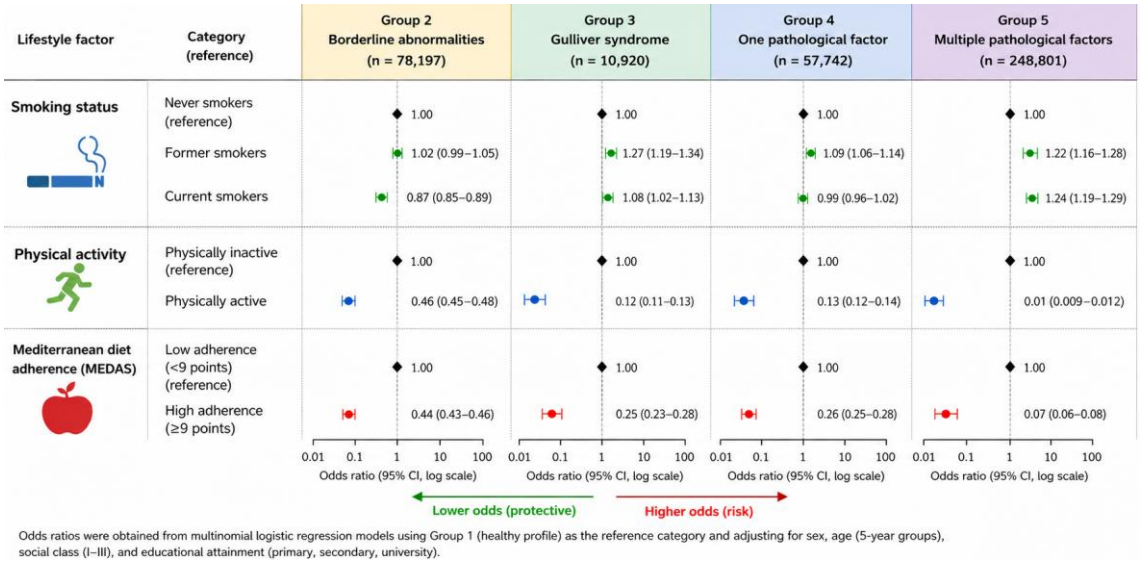


Figure 4. Forest plot of multinomial associations between lifestyle behaviors and cardiometabolic profiles.

4. Discussion

4.1. Principal findings

The present study, conducted in a large cohort of nearly 400,000 Spanish workers, demonstrates that modifiable lifestyle behaviors are strongly associated with the presence of Gulliver syndrome. Three principal findings emerge from our analyses. First, physically inactive individuals and those

with low adherence to the Mediterranean diet exhibited substantially higher odds of presenting the syndrome, with physical inactivity showing the strongest association among all modifiable behaviors examined. Second, smoking status was significantly associated with Gulliver syndrome, with former and current smokers showing higher adjusted odds of the syndrome than never smokers. Third, these associations persisted after adjustment for major sociodemographic factors and remained evident across the different cardiometabolic profiles evaluated in the multinomial analyses.

These findings support the conceptual framework proposed for Gulliver syndrome, namely that the simultaneous accumulation of several apparently mild abnormalities may reflect an early stage of cardiometabolic dysregulation rather than a benign intermediate state. Increasing evidence suggests that borderline elevations in waist circumference, blood pressure, glucose concentrations, and atherogenic lipoproteins are frequently accompanied by common underlying mechanisms, including insulin resistance, ectopic fat accumulation, endothelial dysfunction, and chronic low-grade inflammation, all of which may be profoundly influenced by lifestyle behaviors [32,33].

Another noteworthy observation is the progressive strengthening of the protective associations of physical activity and Mediterranean diet adherence across worsening cardiometabolic profiles. This gradient suggests that healthy lifestyle behaviors are associated with lower odds of adverse cardiometabolic profiles, including earlier stages of cardiometabolic deterioration represented by the Gulliver phenotype. Similar dose-response relationships between healthy lifestyle patterns and cardiometabolic risk have been described in prospective population-based cohorts and support the concept that prevention should begin long before traditional diagnostic thresholds are reached [34,35].

4.2. Smoking and Gulliver syndrome

An interesting finding of the present study is that smoking status was associated with Gulliver syndrome. The crude prevalence of the syndrome was 2.27% among never smokers, 3.94% among former smokers, and 2.77% among current smokers. After adjustment for sociodemographic characteristics, physical activity, and Mediterranean diet adherence, both former and current smokers showed higher odds of Gulliver syndrome compared with never smokers (*OR*: 1.17; 95% *CI*: 1.11–1.23 and *OR*: 1.12; 95% *CI*: 1.07–1.17, respectively).

The higher odds observed among former smokers should be interpreted cautiously. Given the cross-sectional design of the study, the temporal relationship between smoking cessation and the development of cardiometabolic abnormalities cannot be established. Former smokers may also differ from never smokers in previous cumulative tobacco exposure or other characteristics not fully captured in the present analysis. Consequently, these findings should not be interpreted as indicating an adverse effect of smoking cessation. Rather, they underline the importance of distinguishing former smokers from never smokers when evaluating the association between smoking status and cardiometabolic health.

Tobacco exposure has been associated with several mechanisms relevant to cardiometabolic dysfunction, including endothelial injury, oxidative stress, sympathetic nervous system activation, systemic inflammation, and impaired insulin sensitivity [36–40]. These mechanisms provide biological plausibility for an association between smoking and the clustering of cardiometabolic abnormalities. Nevertheless, the present cross-sectional findings do not establish causality, and longitudinal studies

incorporating detailed information on smoking duration, cumulative exposure, and time since cessation are needed to clarify the relationship between smoking history and Gulliver syndrome.

4.3. Physical activity and Gulliver syndrome

The strongest association observed in the present study was that between physical activity and Gulliver syndrome. Physically active individuals exhibited approximately 60% lower odds of presenting the syndrome than their inactive counterparts, with a descriptively lower *OR* observed among women in the sex-stratified analysis. Moreover, in the multinomial analyses, physical activity was associated with progressively lower odds of belonging to increasingly unfavorable cardiometabolic profiles, showing progressively stronger inverse associations across increasingly unfavorable cardiometabolic profiles. These findings indicate that regular physical activity is strongly associated with a lower likelihood of the early clustering of borderline cardiometabolic abnormalities that characterizes Gulliver syndrome.

The beneficial effects of physical activity on cardiometabolic health are supported by extensive epidemiological and experimental evidence. Regular exercise improves insulin sensitivity, reduces visceral adiposity, lowers blood pressure, enhances lipid metabolism, and attenuates systemic inflammation, all of which are key pathophysiological mechanisms implicated in the development of Gulliver syndrome [41,42]. Physical activity has also been associated with favorable changes in endothelial function and autonomic balance, potentially delaying the transition from subclinical metabolic abnormalities to overt cardiometabolic disease [43].

Our findings are consistent with previous studies demonstrating that physically active individuals have a lower prevalence of metabolic syndrome, prediabetes, and cardiovascular disease, regardless of age and body weight [44,45]. Notably, in the sex-stratified analysis, physically active women exhibited almost 90% lower odds of presenting Gulliver syndrome. Although the reasons underlying these descriptive differences in the sex-stratified estimates cannot be fully elucidated in a cross-sectional design, previous research suggests that women may derive greater metabolic benefits from moderate levels of physical activity, particularly regarding insulin sensitivity and central fat distribution [46].

The remarkably low odds of belonging to the most adverse cardiometabolic profile among physically active participants also deserve attention. Individuals who engage in regular physical activity tend to accumulate fewer metabolic abnormalities over time and exhibit lower levels of chronic inflammation and ectopic fat deposition [47]. Consequently, physical activity may be associated not only with a lower likelihood of established cardiometabolic disease but also with more favorable metabolic profiles, including a lower likelihood of intermediate phenotypes, such as Gulliver syndrome.

From a clinical perspective, these findings have important implications. The prevalence of physical inactivity remains unacceptably high worldwide and is particularly common among working populations due to increasingly sedentary occupational environments [48]. Identifying physically inactive individuals who already exhibit multiple borderline abnormalities may provide an opportunity to implement lifestyle interventions before irreversible cardiometabolic damage occurs. Indeed, exercise-based interventions have consistently demonstrated their ability to improve multiple cardiovascular risk factors simultaneously, supporting their potential role in the prevention and management of Gulliver syndrome [49].

4.4. Mediterranean diet and Gulliver syndrome

Another important finding of the present study is the strong inverse association between adherence to the Mediterranean diet and the probability of presenting Gulliver syndrome. Participants with high adherence to this dietary pattern exhibited approximately 40% lower odds of the syndrome in the overall analysis, with a descriptively lower *OR* observed among women in the sex-stratified analysis. Furthermore, the multinomial analyses demonstrated a progressive reduction in the odds of belonging to increasingly unfavorable cardiometabolic profiles among individuals with higher Mediterranean diet adherence. These findings suggest that dietary habits are associated not only with overt cardiometabolic disease but also with earlier stages of metabolic deterioration represented by the Gulliver phenotype.

The Mediterranean diet is widely recognized as one of the most effective dietary strategies for cardiovascular prevention. Its benefits appear to result from the synergistic combination of multiple components, including olive oil, fruits, vegetables, legumes, whole grains, nuts, and fish, all of which contribute to reducing oxidative stress, improving endothelial function, attenuating systemic inflammation, and enhancing insulin sensitivity [50,51]. Several of these mechanisms closely mirror the pathophysiological pathways proposed to underlie Gulliver syndrome, particularly low-grade inflammation, visceral adiposity, and metabolic dysfunction.

A growing body of evidence indicates that adherence to the Mediterranean diet is associated with a lower incidence of type 2 diabetes, metabolic syndrome, and cardiovascular events. In the PREDIMED trial, a Mediterranean dietary intervention substantially reduced the incidence of major cardiovascular events in high-risk individuals, highlighting the capacity of dietary modification to alter cardiometabolic trajectories [52]. Likewise, prospective cohort studies have consistently shown inverse associations between Mediterranean diet adherence and markers of metabolic dysfunction, including central obesity, insulin resistance, hypertension, and dyslipidemia [53,54].

The descriptively low OR observed among women in the sex-stratified analysis deserves special consideration. Although the reasons for this descriptive difference in the sex-stratified estimates remain uncertain, previous studies suggest that women may exhibit greater improvements in inflammatory markers, insulin sensitivity, and body fat distribution in response to Mediterranean dietary interventions [55]. Hormonal factors, differences in dietary patterns, and greater adherence to healthy behaviors among women may also contribute to these findings. However, given the cross-sectional nature of our study, these hypotheses should be interpreted cautiously and warrant further investigation.

An additional aspect worth emphasizing is that the inverse association of the Mediterranean diet became progressively stronger across worsening cardiometabolic profiles. This observation is consistent with the concept that dietary habits are associated with cardiometabolic health across the entire continuum rather than with specific diseases in isolation. The simultaneous improvement of several interrelated metabolic pathways may explain why individuals adhering to the Mediterranean diet are less likely to accumulate the multiple borderline abnormalities that define Gulliver syndrome.

From a public health perspective, these findings are particularly relevant because dietary habits are potentially modifiable through relatively simple interventions. Workplace-based nutritional programs, dietary counseling, and initiatives aimed at increasing adherence to Mediterranean dietary patterns could represent effective strategies for identifying and managing individuals at risk of

developing early cardiometabolic dysfunction. Since the prevalence of unhealthy dietary habits remains high even in Mediterranean countries, promoting adherence to this dietary pattern may constitute an important component of future prevention strategies targeting Gulliver syndrome and related cardiometabolic conditions.

4.5. Sex-stratified findings and potential mechanisms

One of the most intriguing findings of the present study is the presence of descriptive differences by sex in the associations between lifestyle behaviors and Gulliver syndrome. Although men exhibited a considerably higher prevalence of the syndrome, the inverse associations of physical activity and adherence to the Mediterranean diet showed descriptively lower *OR*s among women than among men. In particular, physically active women and those with high adherence to the Mediterranean diet had nearly 90% lower odds of presenting the syndrome, whereas the corresponding *OR*s were descriptively higher in men. These sex-stratified analyses showed descriptive differences in the magnitude of the associations between lifestyle behaviors and Gulliver syndrome.

Several biological mechanisms could potentially contribute to these descriptive patterns. Women generally exhibit a more favorable cardiometabolic profile during early and middle adulthood, characterized by greater insulin sensitivity, lower visceral fat accumulation, and a more anti-inflammatory adipokine profile than men [56,57]. Estrogen appears to play a central role in these differences through its effects on adipose tissue distribution, endothelial function, glucose metabolism, and mitochondrial activity. These biological differences could potentially contribute to the descriptive patterns observed in the sex-stratified analyses, although this possibility cannot be established from the present analyses.

Differences in body fat distribution may also contribute to the descriptive differences observed in the sex-stratified estimates. Men tend to accumulate fat preferentially in visceral depots, whereas women generally exhibit a predominance of subcutaneous adipose tissue before menopause [58]. Since visceral adiposity is strongly associated with insulin resistance, chronic inflammation, and endothelial dysfunction, the transition from a healthy phenotype to a state characterized by multiple borderline abnormalities may occur through different biological pathways in men and women. This could partly explain the descriptive differences in the magnitude of the associations observed in the sex-stratified analyses.

Behavioral and sociocultural factors should also be considered. Women generally report healthier dietary habits, greater adherence to preventive recommendations, and a higher likelihood of participating in healthcare activities than men [59]. Moreover, several studies have suggested that women may derive greater metabolic improvements from lifestyle interventions, including dietary modification and regular physical activity, particularly with regard to insulin sensitivity and central adiposity [60]. These observations are broadly consistent with the descriptive differences observed in our sex-stratified analyses and highlight the need for further investigation of potential sex-related differences.

Another noteworthy finding was the descriptive difference in the age-related estimates between men and women. Among women, the odds of presenting Gulliver syndrome were more than eightfold higher at ages 60–69 years than at ages 18–29 years, whereas a smaller OR was observed for the

corresponding age comparison among men. Although information on menopausal status was unavailable in our study, this pattern may reflect the loss of hormonal protection that occurs after menopause. The menopausal transition is accompanied by unfavorable changes in body composition, increased visceral adiposity, deterioration of insulin sensitivity, and worsening of cardiovascular risk factors, all of which could facilitate the accumulation of borderline metabolic abnormalities [61,62].

These descriptive findings warrant further investigation. Current preventive strategies often adopt a uniform approach to lifestyle recommendations despite growing evidence that men and women differ substantially in their cardiometabolic responses to behavioral exposures and interventions. The descriptive differences observed in the sex-stratified analyses support the need for future studies specifically designed to evaluate potential sex-related differences in these associations and their underlying biological and behavioral mechanisms.

4.6. Clinical and public health implications

The findings of the present study have several potentially important clinical and public health implications. Current approaches to cardiovascular prevention are largely based on the identification and treatment of isolated risk factors once predefined diagnostic thresholds have been reached. However, an increasing body of evidence indicates that cardiometabolic risk develops gradually and that vascular and metabolic damage may already be present during earlier stages of risk factor accumulation [63,64]. In this context, Gulliver syndrome may represent a clinically relevant intermediate phenotype that identifies individuals who do not yet meet the criteria for overt cardiometabolic disease but who may already be following an unfavorable metabolic trajectory.

Our findings suggest that individuals with Gulliver syndrome constitute an attractive target population for preventive interventions. The strong associations observed with physical inactivity and low adherence to the Mediterranean diet indicate that the syndrome is closely associated with modifiable lifestyle behaviors. Importantly, lifestyle interventions have repeatedly demonstrated their ability to improve multiple cardiometabolic risk factors simultaneously, including body composition, blood pressure, insulin sensitivity, lipid metabolism, and systemic inflammation [65,66]. Consequently, identifying individuals with Gulliver syndrome could facilitate the implementation of early interventions before the development of irreversible cardiometabolic damage.

The occupational setting may offer a particularly valuable opportunity for the early detection and management of this phenotype. Most individuals included in the present study were apparently healthy workers undergoing routine occupational examinations, a context in which early cardiometabolic abnormalities can be identified before the appearance of clinically overt disease. Occupational health programs have proven effective in promoting physical activity, improving dietary habits, and reducing cardiovascular risk factors, particularly when interventions are individualized and integrated into the workplace environment [67,68]. Therefore, incorporating the concept of Gulliver syndrome into occupational health surveillance could help identify workers who may benefit from targeted preventive strategies.

Another important implication relates to therapeutic inertia. Borderline abnormalities are frequently underestimated in routine clinical practice because each individual component is often considered insufficiently severe to justify intervention. However, the coexistence of several modest

abnormalities may indicate a substantially greater degree of underlying metabolic dysfunction than each component considered in isolation. The concept of Gulliver syndrome may therefore provide clinicians with a practical framework for recognizing the cumulative impact of multiple borderline alterations and for encouraging earlier and more intensive lifestyle counseling [69].

From a public health perspective, the high prevalence of unhealthy lifestyle behaviors observed in this large cohort of Spanish workers is concerning. More than half of the participants were physically inactive, over one-third were current smokers, and fewer than half exhibited high adherence to the Mediterranean diet. These findings highlight the considerable potential for primary prevention strategies aimed at improving lifestyle behaviors in working populations. Even modest improvements in physical activity levels and dietary quality could translate into substantial reductions in future cardiometabolic disease burden if implemented before the onset of established disease [70].

Finally, our results support a broader shift in preventive cardiology from a dichotomous approach based exclusively on diagnostic thresholds toward a more dynamic model that recognizes cardiometabolic risk as a continuum. The identification of intermediate phenotypes, such as Gulliver syndrome, may contribute to the development of more personalized and proactive prevention strategies and help close the gap between the appearance of early metabolic dysfunction and the initiation of preventive interventions.

5. Conclusions

In this large cohort of 395,660 Spanish workers, unhealthy lifestyle behaviors were strongly associated with the presence of Gulliver syndrome, a novel phenotype characterized by the clustering of multiple borderline cardiometabolic abnormalities. Physical inactivity and low adherence to the Mediterranean diet were the modifiable lifestyle factors most strongly associated with the syndrome and showed consistent associations across the entire spectrum of cardiometabolic profiles. Smoking status was also significantly associated with Gulliver syndrome, with former and current smokers showing higher adjusted odds of the syndrome than never smokers.

The marked inverse associations observed for regular physical activity and adherence to the Mediterranean diet suggest that these lifestyle behaviors are associated with more favorable cardiometabolic profiles, including at earlier stages of cardiometabolic deterioration. These findings support the concept that Gulliver syndrome may represent an intermediate stage of metabolic dysfunction and a potential window of opportunity for preventive interventions. From a clinical and public health perspective, the identification of individuals with Gulliver syndrome could facilitate earlier implementation of lifestyle-based strategies aimed at improving cardiometabolic risk profiles. Future longitudinal studies are needed to determine the prognostic significance of this phenotype and to evaluate whether targeted interventions can modify its natural history and reduce the subsequent burden of cardiovascular disease.

Strengths and limitations

The present study has several strengths that should be acknowledged. First, to our knowledge, this is the first investigation specifically designed to examine the association between lifestyle

behaviors and Gulliver syndrome, a recently proposed phenotype intended to identify individuals with early cardiometabolic dysregulation. The novelty of the concept and the absence of previous studies in this field make the present findings particularly relevant and provide an initial framework for future research.

Second, the study included an exceptionally large sample of 395,660 Spanish workers, providing substantial statistical power to detect associations and allowing robust subgroup analyses according to sex and cardiometabolic profile. The large sample size also increases the precision of the estimated associations and reduces the likelihood that the findings are attributable to random variation. Moreover, the inclusion of workers from a wide range of occupational and socioeconomic backgrounds enhances the internal validity of the study and provides a comprehensive overview of lifestyle behaviors in an apparently healthy working population.

Third, all anthropometric and clinical measurements were obtained by trained occupational health professionals using standardized protocols and validated instruments. Physical activity was assessed using the IPAQ questionnaire and adherence to the Mediterranean diet was evaluated using the MEDAS questionnaire, both of which have been extensively validated in epidemiological research. The use of standardized measurements and questionnaires reduces information bias and strengthens the reliability of the findings.

Another important strength is the simultaneous evaluation of several complementary analytical approaches, including prevalence estimates, multivariable logistic regression analyses, sex-stratified models, and multinomial analyses across the entire spectrum of cardiometabolic profiles. This comprehensive strategy allowed us not only to identify factors associated with Gulliver syndrome but also to explore whether these associations varied according to the degree of cardiometabolic deterioration.

Several limitations should also be considered. First, the cross-sectional design precludes establishing causal relationships or determining the temporal sequence between lifestyle behaviors and the development of Gulliver syndrome. It cannot be excluded that some individuals may have modified their behaviors after becoming aware of their cardiovascular risk factors, leading to potential reverse causation. Longitudinal studies are therefore needed to determine whether unhealthy lifestyle behaviors truly precede the appearance of the syndrome.

Second, some lifestyle variables were based on self-reported questionnaires and may therefore be subject to recall bias and social desirability bias. In particular, smoking habits, physical activity, and dietary intake may have been misclassified to some extent. However, any potential misclassification is likely to be non-differential and would therefore tend to attenuate rather than exaggerate the observed associations.

Third, several potentially relevant confounders were unavailable in the present database. Information regarding alcohol consumption, sleep quality, psychological stress, family history of cardiovascular disease, medication use, menopausal status, and objectively measured cardiorespiratory fitness was not available. Consequently, residual confounding cannot be completely excluded.

Fourth, the study population consisted exclusively of actively employed individuals. Therefore, our findings may not be directly generalizable to unemployed individuals, institutionalized populations, or patients with severe chronic diseases. The possibility of a healthy worker effect

should also be considered, as employed populations generally exhibit better health indicators than the general population.

Finally, Gulliver syndrome is a recently proposed construct and its long-term prognostic significance remains to be fully established. Although the biological plausibility of the syndrome is considerable and our findings support its association with unfavorable lifestyle behaviors, prospective studies are needed to determine whether individuals with this phenotype experience a higher incidence of future cardiovascular events, type 2 diabetes, or premature mortality.

Despite these limitations, the consistency of the associations observed across multiple analytical approaches, their biological plausibility, and the exceptionally large sample size support the robustness of our findings and suggest that Gulliver syndrome may represent a useful framework for identifying individuals at an early stage of cardiometabolic risk accumulation.

Data protection

Personal data were anonymized before analysis to safeguard participant confidentiality. All data handling procedures complied with the Spanish Organic Law 3/2018 on Personal Data Protection and Digital Rights, as well as with the European Union General Data Protection Regulation (EU 2016/679).

Data availability

The data supporting the findings of this study are stored at ADEMA University School and can be made available by the corresponding author upon reasonable request, subject to applicable legal and data protection requirements.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Authors' contributions

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

Conflicts of interest

The authors declare that there are no competing interests related to this study.

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