“OVIDIUS” UNIVERSITY OF CONSTANȚA
DOCTORAL SCHOOL OF MEDICINE
DOCTORAL FIELD: MEDICINE
UNIVERSITY YEAR 2025

SUMMARY OF THE DOCTORAL THESIS

SCIENTIFIC COORDINATOR:
PROFESSOR DOINA ECATERINA TOFOLEAN, MD, PHD

PHD CANDIDATE:
ANDREEA-BIANCA VRĂJITORU (MARRIED UZUN)

CONSTANȚA

"OVIDIUS" UNIVERSITY OF CONSTANȚA
DOCTORAL SCHOOL OF MEDICINE
DOCTORAL FIELD: MEDICINE
UNIVERSITY YEAR 2025

SUMMARY OF THE DOCTORAL THESIS

RESPIRATORY RECOVERY WITH INTERMITTENT HYPOXIA-HYPEROXIA IN PATIENTS WITH METABOLIC SYNDROME

SCIENTIFIC COORDINATOR:
PROFESSOR DOINA ECATERINA TOFOLEAN, MD, PHD

DOCTORAL ADVISORS:
PROFESSOR SIMONA CLAUDIA CAMBREA, MD, PHD
PROFESSOR ELENA DANTEȘ, MD, PHD
ASSOCIATE PROFESSOR LASZLO IRSAY, MD, PHD

PHD CANDIDATE:
ANDREEA-BIANCA VRĂJITORU (MARRIED UZUN)

The doctoral thesis includes:

- CURRENT STATE OF KNOWLEDGE – organized in 4 chapters
- PERSONAL CONTRIBUTION – organized into 2 chapters
- 350 bibliographic references
- 187 figures
- 63 tables

NOTE:

- The table of contents in the summary is the original one from the thesis.
- Bibliographic indices appear in ascending order but are not consecutively numbered, as the numbering from the full thesis was preserved.
- The complete bibliography used in the thesis is included at the end of the summary.

TABLE OF CONTENTS

INTRODUCTION

Metabolic syndrome (MS) is a major public health problem globally, with a continuously increasing prevalence and being closely associated with the development of important pathologies, such as pulmonary and cardiovascular pathologies, hypertension, and type 2 diabetes. WHO data indicate that MS affects about 25% of adults globally, with serious implications for public health. In addition to the direct risks to physical health, MS significantly contributes to increased healthcare costs and decreased economic productivity. In Romania, its prevalence is alarming, underscoring the urgent need for effective interventions to prevent and treat this condition.

MS is linked to alterations in lung function due to systemic inflammatory processes, impaired endothelial function, and the physical impact of obesity on the respiratory function.

Despite advances in conventional treatments for metabolic syndrome, such as lifestyle changes and medications, many patients do not achieve satisfactory results from these interventions. Thus, innovative therapies, such as intermittent hypoxia-hyperoxia therapy (IHHT), which stimulate the body physiologically to support adaptive benefits, appear to be a strategy with considerable potential.

In the realm of medical innovation, IHHT stands out as a highly relevant topic, integrating areas like medicine, biochemistry, physiology, and medical technology. Its investigation in the context of MS management is of notable significance. IHHT is a relatively recent but promising therapeutic approach that involves alternating periods of exposure to low oxygen (hypoxia) and high oxygen (hyperoxia), stimulating cell regeneration, erythropoiesis, angiogenesis, and improving insulin sensitivity. It may represent an important strategy in MS through its ability to stimulate beneficial adaptations at the pulmonary level, such as increasing ventilatory efficiency, improving oxygenation, and reducing obesity-associated pulmonary dysfunction.

The study of this therapy in the context of MS has the potential to address a significant medical need, providing an additional therapeutic approach with the possibility of improving current treatments and contributing to decreasing the prevalence and impact of MS globally. This theme aligns with global efforts to address chronic pathologies through preventive strategies and innovative therapies.

Personal motivation includes the desire to contribute to the development of personalized therapies for patients with MS. Investigation of IHHT offers the opportunity to tailor treatments to individual patient needs.

The specialized literature was systematized in a dedicated section (General Part), structured in 4 chapters, within which fundamental concepts and theories supporting the scientific approach of the thesis were analyzed in detail. Each chapter addressed essential aspects, explaining the theoretical foundations of the proposed therapy, the pathology addressed, the link between the pathology addressed and lung function, as well as relevant studies that contributed to the development of this research.

The special part of the work was structured in 2 chapters and followed the classic structure of an original study, including the sections of objectives, material and method, results, discussions, and conclusions, all based on the principles of evidence-based medicine.

During the study, we complied with the national legislation, in accordance with that of the European Union, in force, regarding research ethics, the identification and attribution of intellectual property rights over the results, and the informed consent of the patients.

This work will certainly contribute to the advancement of scientific research on the therapeutic potential of IHHT in managing MS and obesity. Advancing research in this field will enable the development of innovative treatment methods not only for obesity and MS but also for related conditions.

Chapter 1. Metabolic syndrome

MS is a complex of metabolic abnormalities that serve as a risk factor for type 2 diabetes mellitus (DM) and cardiovascular pathologies. The main characteristic components include hyperglycemia, increased blood pressure, elevated triglyceride levels, low high-density lipoprotein (HDL-cholesterol) levels, and obesity (especially central adiposity) [1].

The prevalence of MS varies worldwide and often corresponds with the prevalence of obesity. There is a wide variation in prevalence depending on age, sex, ethnicity, and the criteria used for diagnosis. MS affects one-fifth or more of the US population and about one-quarter of the European population. Southeast Asia has a lower prevalence, but is rapidly moving towards rates similar to the Western world [6]. In Romania, the prevalence of MS in adults aged 20 to 79 years was 38.5%, obesity affected 31.9% of individuals, while 34.7% were classified as overweight (Predatorr Study). Furthermore, 73.9% of Romanian adults exhibited abdominal obesity [12].

Treatment options for patients with MS include lifestyle modification and drug therapy. Lifestyle modification can be summarized as dietary changes, exercise, and smoking cessation. Drug therapy indicated for reducing cardiometabolic risk includes antihypertensives, insulin sensitizers, and cholesterol-lowering agents [69]. Drug therapy for lipid profile and hypertension is required in most cases. Hypertension should be carefully managed, with a target of 130/80 mmHg [19].

However, there are inconsistencies and gaps in the evidence, and further research is needed to define the most appropriate therapies for MS [74].

Chapter 2. Obesity

Obesity is a complex, multifactorial condition characterized by excess body fat, which has a negative impact on health, through its association with the risk of developing DM, cardiovascular pathologies, hypertension, and hyperlipidemia [75,76].

BMI is used according to WHO guidelines. In adults, the WHO defines overweight as a BMI of 25.0 to 29.9 and obese as a BMI ≥ 30.0. Obesity is classified into three levels of severity: class I (30.0–34.9 kilograms/square meters - kg/m2), class II (35.0–39.9 kg/m2), and class III (≥ 40 kg/m2) [75,82]. However, there are individual variations, and the BMI used [79].

Obesity is a global public health problem, and its increase is alarming. It is considered an epidemic, affecting one in three adults and one in six children in the United States. At the same time, many countries around the world have seen a doubling or even tripling of obesity prevalence over the last 30 years, a pattern commonly attributed to urban growth, lack of physical exercise, and greater intake of processed, calorie-packed foods [84,85].

Obesity rates have reached alarming levels in the European Union, including Romania, where the prevalence is estimated at 20–25% [87]. The reported prevalence of pediatric overweight and obesity in Romania is unclear: some studies estimate the overweight rate at 15–20% and the obesity rate at 8.7–10.7%, with a steadily increasing prevalence from 1980 to 2016 [88].

The implementation of weight management strategies aims to both prevent and treat obesity-related conditions, playing a key role in improving the overall health of the individual. These interventions are developed to address the complexity of obesity and to positively influence multiple aspects of lifestyle, health status, and optimal body functioning [99].

Evidence-based treatment of obesity includes 5 major categories:

- Behavioral interventions;
- Nutrition;
- Physical activity;
- Pharmacotherapy;
- Metabolic/bariatric procedures [171].

Chapter 3. Pulmonary function, obesity, and metabolic syndrome

Obesity has complex and incompletely understood effects on the respiratory system. There is increasing evidence that excess adiposity negatively impacts static and dynamic respiratory function, as measured by lung volumes and exercise capacity, to varying degrees. There is evidence to support the role of weight loss in achieving normalization of lung function parameters, but in the case of obesity, there are enormous challenges in achieving this goal for many subjects [179].

Obesity has long been recognized as having significant effects on respiratory function. Lung volumes tend to be reduced, especially expiratory reserve volume. Fat distribution, namely upper versus lower body, may be more important than BMI [180].

A systematic review by L.C. Melo et al. concluded that obese individuals demonstrated reduced lung volumes and capacities compared with normal-weight individuals. Although investigations have demonstrated the presence of changes in lung function in the obese population, the physiological mechanisms underlying this situation remain unclear [181].

Adiposity can alter lung function by affecting chest wall motion, airway size, respiratory muscle function, and the ventilation/perfusion ratio. Adipose tissue deposited in the upper respiratory tract, diaphragm, chest wall, and abdominal wall causes decreased thoracic compliance, which induces impaired lung ventilation function in a restrictive pattern. In particular, abdominal adiposity is associated with respiratory dysfunction [185].

Obesity is detrimental to lung function. Medical practitioners need to recognize its negative impact on lung function, and managing weight should be an integral part of treating airway diseases in obese patients [209]. Given the high prevalence of MS in the general population, it is necessary to understand how this metabolic disorder affects the lung and how its complications can be prevented [186].

Chapter 4. Intermittent hypoxia-hyperoxia therapy

A novel approach involving short-term adaptive periodic training, which alternates the oxygen levels between hypoxia to hyperoxia, has been validated both theoretically and through experiments. Adaptation to alternating hypoxia and normoxia showed protective effects on cell membranes in the heart and cerebral cortex, but also led to increased vulnerability to free radical damage and a reduction in antioxidant defense components in the liver. Training with hypoxia-hyperoxia cycles produced a stronger membrane-stabilizing effect in the heart, brain, and liver compared to hypoxia-normoxia. Unlike hypoxia-normoxia adaptation, the protective response in hypoxia-hyperoxia training emerged as early as 15 days after the training began [237].

In the past ten years, IHHT has started to be adopted in clinical and athletic settings, where intervals of breathing atmospheric air are substituted with inhalation of a hyperoxic mixture (30-40% O2). Some researchers suggest that delivering hypoxic and hyperoxic stimuli in sequence, rather than normoxic ones, during intermittent hypoxic training enhances the oxidative stress response (ORS) signal without increasing hypoxia [238].

The combination of hypoxia with periods of hyperoxia in a therapeutic protocol is based on the hypoxic-hyperoxic paradox, which is grounded in well-established physiological mechanisms. Exposure to hypoxia promotes mitogenesis and alters mitochondrial function through the activation of HIF-1 and the stimulation of vascular endothelial growth factor, other important molecular pathways, and stem cell proliferation. Hyperoxic stimuli, which involve increased oxygen availability, favor the generation of ROS and their capture, activating the same molecular cascades as hypoxia [239].

This therapy has proven to be both safe and effective in the patient groups evaluated in existing studies. IHHT and IHT protocols represent promising non-drug intervention methods that are generally well tolerated. As such, it is reasonable to consider their inclusion in the therapeutic management of various medical conditions [241].

Chapter 1. Study I – IHHT in obese patients

Working hypothesis/ Objectives

- **Primary objective:**

-To investigate how IHHT influences lung function in individuals with obesity – This goal focuses on evaluating the therapy`s effects on respiratory system performance in obese patients. Obesity can negatively influence pulmonary function by increasing the risk of sleep apnea, decreasing lung capacity, and changing in respiratory rhythm. This evaluation will help to understand the potential benefits of THHI in improving respiratory function.

- **The secondary objectives of the present research include:**

-Evaluation of the increase in exercise tolerance in the patients included in the study – Obesity can reduce exercise capacity due to early fatigue and difficult breathing. An important secondary objective of the study is to observe whether the application of IHHT contributes to improving exercise tolerance, an objective that may also refer to improving quality of life by increasing the level of physical activity.

-Determination of biological parameters potentially modifiable following the application of IHHT – This objective focuses on identifying biological parameters that may be influenced by IHHT. The study will analyze how IHHT can contribute to improving these parameters, which are essential in the management of obesity and associated comorbidities.

-Influence of IHHT on pre-existing pathologies – Obesity is often associated with pathologies such as hypertension, type 2 diabetes, dyslipidemia, or other cardiovascular pathologies. This objective aims to investigate how IHHT can influence these conditions. For example, it will be analyzed whether the therapy can contribute to improving glycemic control or reducing cholesterol levels, thus having a positive impact on overall health.

Materials and methods

Required materials

• The device that uses THHI (CellOxy);

• The device for performing spirometry;

• Medical equipment (pulse oximeter, blood pressure monitor, Tanita RD-953 scale);

• Facilities of the Balneal and Rehabilitation Sanatorium of Techirghiol (SBRT): medical offices, treatment spaces, technical equipment

• General clinical observation sheet of patients;

• Appendices: Patient information form (Appendix 1), patient informed consent (Appendix 2), obesity questionnaire (Appendix 3), questionnaire for the 6-minute walk test (Appendix 4);

Therapeutic intervention

The present work is based on the study of two groups of patients:

1. IHHT group (Intervention group) – Comprised of 40 obese individuals who received IHHT using the CellOxy device;

2. Control group - Included participants with similar characteristics who were not exposed to IHHT.

Patients in both groups benefited from complex medical rehabilitation treatment. In addition, those in the intervention group also benefited from THHI.

The study sample, composed of 80 patients, was selected according to the inclusion and exclusion criteria (Table I).

Table I – Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Patients with BMI ≥ 30 kg/m2	Patients with BMI < 30 kg/m2
Patients eligible for IHHT	Patients with IHHT contraindications (cardiovascular and/or pulmonary instability; acute systemic infections; hypoxia intolerance; decompensated pathologies; epilepsy; pacemaker; neoplasms; cardiac arrhythmias; vitamin C infusions or administration of high doses of vitamin C (oral over 1000 mg/day) or administration of beta-blockers)
Patient consent regarding study enrollment	Decline to provide informed consent

Patients under optimal drug therapy for associated thealth issues	Subjects without appropriate medication treatment for associated medical conditions
Age between 20-80 years old	Age under 20 or over 80
	General contraindications for balneal treatment
	General contraindications for performing physiotherapy procedures

IHHT was administered using the CellOxy device, manufactured by Physiomed [267]. The CellOxy device is a system that involves alternate breathing of hypoxic air (low oxygen level) with intervals of normoxic or hyperoxic air (high oxygen level). During the therapy, the patient lay in a comfortable position, slowly inhaling the air mixture provided through a mask [268].

Before starting the actual therapy, patients underwent two preliminary tests: Hypoxic Test 1 and Hypoxic Test 2, to assess the type of resistance and establish the optimal parameters for treatment.

After establishing the individual profile of each patient, which included determining the type of resistance and the target saturation, the actual therapy was initiated. The device automatically created personalized treatment plans for each patient based on the collected data.

After completing two hypoxic tests on the first day of hospitalization, patients in the intervention group began IHHT the next day. The treatment involved cycles of hypoxia with oxygen levels between 9% and 16%, 5 - 7 minutes, and hyperoxia at around 35% oxygen for 2 - 5 minutes, repeated 3 - 5 times [268].

During the 12-day SBRT hospitalization, patients in the intervention group received a total of nine sessions of IHHT. Alongside IHHT, the patients also received daily comprehensive medical rehabilitation care. In contrast, the control group only received the complex rehabilitation treatment, without any IHHT, neither real nor placebo.

Results and discussions

In the context of the continuous increase in the prevalence of obesity worldwide and its multidimensional impact on public health, medical studies have begun to pay increased attention to innovative and noninvasive methods. Among these, IHHT represents an approach that attracts increasing scientific interest, due to its potential to positively influence metabolic, inflammatory, and hormonal parameters associated with MS and obesity [241].

Following the application of the Wilcoxon Signed Ranks Test, statistically significant results of the improvement of the HTi index were observed ($p<0.001$). The patient distribution within the intervention group demonstrated a positive result of this, given that 35 of the 40 participants recorded improvements in it, having a higher value at discharge of the HTI index than the value at admission. These data suggest a favorable response to the applied intervention, thus indicating the effectiveness of the treatment for the majority of participants.

The distribution of patients in the intervention group according to the existence of a higher HTi index value during hospitalization than the discharge value showed that 25 of the 40 patients recorded higher values during hospitalization, compared to the final discharge value. Although most patients presented a higher value at discharge than at admission, it is important to note that during hospitalization, they had even higher values of this index.

The outcome of the 6-minute walk test for the intervention group revealed statistically significant changes between the measured values at admission and those at discharge ($p<0.001$), according to the Wilcoxon Signed Ranks test. These data suggest an increase in the physical tolerance of the patients, given that most of them walked a greater distance at discharge than at admission. These results indicate that IHHT had a positive impact on the physical capacity of the patients, contributing to the improvement of exercise tolerance, an essential factor in the management of obesity and associated comorbidities. These data align with the conclusions of the systematic review conducted by T. Behrendt, who demonstrated that IHHT can lead to an improvement in maximal oxygen consumption and an increase in exercise tolerance [254].

In the intervention group, urea values showed only a slight variation, without reaching a statistically convincing level ($p = 0.057$). In contrast, a clear decrease in uric acid was noted ($p = 0.027$), suggesting a possible favorable therapeutic effect. Creatinine also showed a clear decrease ($p = 0.001$), which may reflect an improvement in renal function. These data are consistent with the conclusions of previous studies indicating that intermittent hypoxia therapy can have a positive impact on biochemical markers and the general health status of patients [241].

For the intervention group, changes in blood glucose levels over the study period did not reach statistical significance, as indicated by the analysis results. No notable difference was observed between the initial and final measurements ($p = 0.053$). Although the result did not exceed the threshold of statistical significance, the p-value is very close to 0.05, which could suggest a discrete effect of IHHT on glycemic control, which is worth exploring in future studies or on a larger sample. The specialized literature provides solid evidence regarding the beneficial effects of the therapy on glucose metabolism. Studies have shown that it can contribute to lowering blood glucose levels and improving glucose homeostasis, both in healthy subjects and in people with prediabetes [254, 283].

For the intervention group, the statistical analysis performed using the Wilcoxon Signed Ranks test revealed the presence of statistically significant differences between total cholesterol values at admission and at discharge ($p = 0.020$). These data suggest a beneficial impact of the intervention on the lipid profile of patients. This result is also supported by the literature, which indicates that IHHT can contribute to the reduction of total cholesterol levels, thus representing an effective complementary approach in the management of dyslipidemia in obese patients [239, 251, 284].

Compared to the control group, the results regarding liver function parameters in the intervention group showed a different effect of the intervention on liver enzymes. The Wilcoxon Signed Ranks test indicated the existence of statistically significant differences between AST values at admission and those at discharge ($p = 0.005$), suggesting a possible improvement of this liver marker following therapy. In contrast, ALT values did not show significant changes ($p = 0.640$), suggesting that the intervention did not significantly influence this liver parameter during the study. The specialized literature highlights the beneficial effects of IHHT on liver function, especially in the context of metabolic disorders. Available studies have demonstrated that IHHT can have a significant positive impact, contributing to the reduction of the degree of hepatic steatosis and the decrease in the level of liver fibrosis [284].

Analysis of Tiffeneau index values in the intervention group using the Wilcoxon Signed Ranks test revealed statistically significant differences between the time of admission and discharge ($p < 0.001$), indicating a notable improvement in pulmonary function. This result suggests that IHHT had a beneficial effect on respiratory function, an essential aspect in the context of obesity, where pulmonary function is frequently impaired. Given these observations, obese patients should be encouraged to lose weight to reduce the risk of developing respiratory pathologies or to improve pre-existing conditions [285].

Conclusions

Obesity is one of the most widespread public health problems worldwide, being associated with multiple metabolic, cardiovascular, and respiratory comorbidities. In this context, the identification of effective, safe, and accessible therapeutic interventions is of major importance. IHHT has increasingly emerged as a promising method in the therapeutic arsenal for obese patients, with the potential to induce a series of physiological benefits with significant clinical impact.

Regarding lung function, the Tiffeneau index has experienced a significant improvement, suggesting a respiratory benefit among obese patients undergoing therapy.

Improving the Tiffeneau index is a valuable result, especially in the context of obesity, where lung function is often compromised. Due to excess weight and mechanical limitations on the chest, breathing becomes more difficult, and ventilation capacity is reduced. Therefore, any sign of improvement in respiratory function is particularly important for these patients, contributing not only to respiratory comfort but also to better exercise tolerance and improved general health.

An increase in the distance covered in the 6-minute walk test indicates an improvement in overall functional capacity, cardiovascular and respiratory efficiency. In the case of obese patients, such a change reflects a positive response to therapy and better tolerance to daily physical exertion.

The increase in the HTi index value in the intervention group indicates a positive adaptation of the body to intermittent exposure to hypoxia-hyperoxia, which suggests an increased capacity to respond to hypoxic stress. A higher HTi implies that the patient becomes more efficient in using oxygen, which may have favorable implications on energy metabolism and exercise resistance.

The decrease in uric acid, creatinine, and total cholesterol values may indicate a general improvement in metabolic status and systemic health. Lower uric acid levels suggest an improvement in purine metabolism and a reduction in oxidative stress. At the same time, the decrease in creatinine may reflect an improvement in renal function, possibly by reducing systemic inflammation. The reduction in total cholesterol highlights an improvement in the lipid profile, contributing to a decrease in the risk of atherosclerosis and cardiovascular events.

Regarding liver function, an improvement in AST values was observed, suggesting a possible improvement in liver status. Although ALT did not show a statistically significant change, the decreasing trend close to the statistically significant threshold may indicate a beneficial effect, which could become more evident in a longer-term study.

Another important element of this study is that the therapy was well tolerated, with no adverse reactions reported during the study, which supports its favorable safety profile. This aspect is essential in the context of applying such an intervention on a large scale, including in patients with multiple comorbidities, where the tolerability of the therapy is a major criterion in the therapeutic decision.

In this study, not all variables measured in the intervention group presented statistically significant results. However, it is essential to emphasize that, despite the absence of statistical significance, favorable trends were observed in some patients, which may indicate an individual positive response to IHHT. Such trends may reflect the beginning of physiological adaptation processes, which could become more evident in interventions carried out over longer periods or in larger cohorts. These may represent a direction worth exploring in future research.

In conclusion, IHHT proves to be an innovative and effective strategy, with a favorable safety and efficacy profile, which deserves to be included in future therapeutic guidelines dedicated to obesity and its associated complications. Given the evidence of the beneficial effect of the therapy on pulmonary function, its inclusion in the therapeutic plan should be seriously considered in obese patients, in whom respiratory impairment represents a significant risk.

Chapter 2. Study II– IHHT in patients with metabolic syndrome

Working hypothesis/ Objectives

This paper aims to analyze how IHHT can influence the health status of patients diagnosed with MS by observing variations in the monitored parameters. This approach may provide a clearer perspective on the therapeutic potential of the method and on the factors that could condition the response to treatment.

- **Main objective of this study:**

-The effect of IHHT on lung function in patients with MS – Given that IHHT involves repeated exposure to controlled variations in oxygen concentration, it is important to evaluate to what extent this intervention can influence respiratory parameters. The study aims to observe possible changes in lung function and determine whether this method can bring additional benefits in the management of MS.

- **The secondary objectives of the present research include:**

-Determination of respiratory parameters of the PowerBreathe device potentially modifiable following the application of the therapy – This objective aims to evaluate the effect of IHHT on pulmonary function, using the PowerBreathe device, which measures different respiratory parameters. The aim is to identify the potential of this therapy based on alternating exposure to hypoxia and hyperoxia to improve the efficiency and resistance of the respiratory system.

-Increase in exercise tolerance in patients included in the study – This objective aims to evaluate the ability of patients to sustain a more intense physical effort following IHHT. The aim is to observe possible improvements in exercise tolerance, which could indicate a positive adaptation of the respiratory, cardiovascular, and muscular systems, thus contributing to an increased quality of life for patients with MS.

-Determination of the lipid profile potentially modifiable following the application of therapy --This objective involves the evaluation of IHHT on the levels of lipid components in the blood, such as total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides. By monitoring these parameters before and after the application of therapy, the aim is to identify changes that could indicate a favorable impact on the lipid metabolism of patients with MS.

-Determination of the glucose profile potentially modifiable following the application of therapy – This objective aims to monitor the glycemic values of patients undergoing IHHT, to highlight any changes that may occur following this intervention. This analysis can provide useful information on the potential of IHHT to contribute to maintaining glycemic balance in the patients studied.

-Determination of body composition using the Tanita scale, potentially modifiable following the application of therapy – The study will analyze changes in body composition using the Tanita scale, which allows the evaluation of parameters such as: body fat, body water, muscle mass, muscle quality, muscle score, bone mass, visceral fat, and metabolic age. The aim is to observe whether IHHT determines favorable changes in body structure, such as reduction of fat mass and improvement of muscle mass, indicators relevant in the context of MS.

Materials and methods

Required materials

- The device that uses THHI (CellOxy);
- The device for performing spirometry;
- The device for performing lung X-rays;
- Ultrasound for performing abdominal ultrasounds;
- The PowerBreathe device;
- Medical equipment (pulse oximeter, blood pressure monitor, Tanita RD-953 scale);
- Facilities of the Balneal and Rehabilitation Sanatorium of Techirghiol (SBRT): medical offices, treatment spaces, technical equipment;
- General clinical observation sheet of patients;
- Appendices: Patient information form (Appendix 1), patient informed consent (Appendix 2), Modified Medical Research Council Dyspnea Scale - mMRC (Appendix 3), questionnaire for the 6-minute walk test (Appendix 4).

Therapeutic intervention

This work is based on the comparative analysis of two groups of patients:

1. The intervention group (IHHT group) – It included 39 patients diagnosed with MS, who underwent IHHT generated by the CellOxy device;
2. The control group – It included 40 patients diagnosed with MS, who underwent simulated (placebo) IHHT.

During the hospitalization within SBRT, the patients underwent daily complex balneo-physical-kinetic treatment. This included IHHT (real in the case of the intervention group and simulated for the patients in the control group), hydrokinetotherapy in the water pool of Lake Techirghiol, peloidotherapy, electrotherapy, massage therapy, and kinetotherapy (performed by the patients of both groups).

The study was conducted for 12 days, during which the patients benefited from treatment for 10 days, distributed over 5 days each week, with a break on the weekend. The treatment was applied according to a pre-established therapeutic plan, adjusted according to the individual needs of each patient.

The selection of the study group consisting of 79 patients was carried out based on inclusion and exclusion criteria, respecting the methodological standards specific to scientific research (Table I).

Table I – Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Patients with a definite diagnosis of MS	Patients who do not have a definite diagnosis of MS
Patients eligible for IHHT	Patients with IHHT contraindications (cardiovascular and/or pulmonary instability; acute systemic infections; hypoxia intolerance; decompensated pathologies; epilepsy; pacemaker; neoplasms; cardiac arrhythmias; vitamin C infusions or administration of high doses of vitamin C (oral over 1000 mg/day) or administration of beta-blockers)
Patient consent regarding study enrollment	Refusal to sign the patient's informed consent
Patients undergoing optimal drug treatment for associated pathologies	Patients who are not receiving optimal drug treatment for associated pathologies
Age between 20-80 years old	Age under 20 or over 80
	General contraindications for balneal treatment
	General contraindications for performing physiotherapy procedures

Contraindications of the PowerBreathe device (recent stroke (hemorrhagic or ischemic); neoplasms; dementia; acute viral or somatic diseases; history of spontaneous pneumothorax; patients with bronchial asthma with frequent exacerbations; traumatic lung injuries that have not completely healed; pulmonary hypertension; large bubbles on chest X-ray; marked osteoporosis with a history of rib fractures; ruptured eardrum that has not completely healed or any other eardrum condition)

In this study, patients received IHHT generated by the CellOxy device, manufactured by Physiomed [267].

To establish optimal treatment parameters and assess the level of resistance, patients underwent two preliminary tests before therapy: hypoxic test 1 and hypoxic test 2. Based on the individual profile, established by the type of resistance and the target saturation, the actual therapy was started. The device automatically generated a personalized session plan for each patient, using the data obtained. After performing the two hypoxic tests on the first day of hospitalization, patients in the intervention group began IHHT on the following day. The procedure consisted of 3-5 cycles, each with a hypoxia phase (9-16% O2, 5-7 minutes) followed by hyperoxia (~ 35% O2, 2-5 minutes) [268].

Patients in the intervention group underwent nine IHHT sessions during the 12 days of hospitalization. Patients in the control group followed the therapy under the same conditions as the intervention group, but it was administered as a placebo; the patients received atmospheric air through a mask, without actually benefiting from IHHT, although hypoxic tests 1 and 2 were also performed for these patients. Simultaneously with IHHT (real or placebo), the patients also benefited from the complex medical rehabilitation treatment daily.

Results and discussions

In the face of increasingly evident challenges related to the efficacy and adherence to conventional treatments for MS, HHT is emerging as an alternative, non-invasive, and safe therapeutic option. Studies available in the literature confirm the safety profile and efficacy of IHHT, highlighting its practical applicability in the management of a varied spectrum of conditions [241].

The results of the Wilcoxon Signed Ranks test on the evolution of lung function, reflected by the Tiffeneau index, were different in the two groups. In the intervention group, the values of this index recorded a statistically significant increase from hospitalization to outpatient care ($p < 0.001$). This result suggests a favorable response to IHHT, through the improvement of respiratory function. In contrast, in the control group, the Tiffeneau index did not show a significant change, indicating that the placebo therapy did not cause any change in this parameter. The improvement in Tiffeneau index values in the intervention group is consistent with data from the literature, which supports the effectiveness of IHHT in improving respiratory parameters. Thus, it meets the idea that this information may be beneficial for patients with respiratory pathologies [330].

In the intervention group, where IHHT was applied, a statistically significant improvement in the results of the 6-minute walk test ($p < 0.001$) was observed, according to the Wilcoxon Signed Ranks test, which suggests a positive impact of the intervention on functional capacity. Considering that the 6-minute walk test is recommended by the guidelines as a tool for assessing exercise tolerance and estimating the prognosis in the underlying condition [331], the results obtained confirm the beneficial potential of IHHT, supporting the hypothesis that it can contribute to maintaining and improving functional capacity, but also exercise tolerance.

The results regarding the evolution of the mMRC dyspnea scale indicate a favorable trend in the intervention group, in which patients followed IHHT. In contrast, in the control group, where simulated therapy was applied, no improvement in this scale was observed. This difference suggests that IHHT may have a beneficial effect on the perception of dyspnea, although the proportion of patients with improvement remains relatively modest. The absence of any improvement in the control group supports the idea that the observed improvement is likely related to IHHT and not to other factors of medical rehabilitation. However, further studies, possibly over a longer period of time, would be needed to confirm this trend.

Following the application of the Wilcoxon Signed Ranks test, statistically significant results of the improvement of the HTi index were observed ($p<0.001$). The distribution of patients in the intervention group showed a positive result of this, since 32 of the 39 participants recorded improvements. These data suggest a favorable reaction to the applied intervention, thus indicating the effectiveness of the treatment for the majority of participants.

The results of the Wilcoxon Signed Ranks test for both groups show that there are no statistically significant differences between the leukocyte values at admission and at discharge ($p = 0.978$ in the intervention group, $p = 0.558$ in the control group, both > 0.05). This indicates that the leukocyte level remained stable during the treatment period, both in the group that benefited from real IHHT and in the group that benefited from placebo IHHT.

The analysis of hematological parameters revealed different developments depending on the analyzed group. For the intervention group, statistically significant increases were observed in both the number of erythrocytes ($p = 0.001$) and the concentration of hemoglobin ($p = 0.014$), between the time of admission and discharge. These results suggest a beneficial effect of THHI on the stimulation of erythropoiesis, an effect also supported by the specialized literature, which highlighted that intermittent exposure to hypoxia activates the production of EPO. A few minutes of exposure to hypoxia are sufficient to stabilize HIF-1 alpha, resulting in the transcription and production of the EPO gene [332]. In contrast, in the control group, no significant changes were recorded in the values of erythrocytes ($p = 0.245$), but the values of hemoglobin increased significantly ($p = 0.014$). This isolated change can be attributed to non-specific factors, considering that only hemoglobin was modified, while the value of erythrocytes did not show significant changes. In conclusion, only in the intervention group is a coherent and statistically significant hematological change in erythrocyte parameters observed, which supports the potential of IHHT to stimulate hematological components involved in oxygen transport.

The analysis of biochemical parameters of renal function (urea, uric acid, and creatinine) revealed notable differences between the two groups. In the intervention group, statistically significant decreases in urea ($p = 0.023$) and uric acid ($p = 0.047$) were observed, indicating a beneficial effect of IHHT on renal function. In contrast, creatinine values remained stable ($p = 0.325$). In the control group, no significant changes were observed in urea ($p = 0.648$) and uric acid ($p = 0.830$), and a statistically significant negative change was observed in creatinine ($p = 0.038$, creatinine at discharge was higher than that at admission), indicating a lack of relevant changes in these renal parameters. The current scientific literature provides promising evidence regarding the beneficial effects of IHHT on renal function [330].

The Wilcoxon Signed Ranks test revealed significant differences between the blood glucose values at admission and those at discharge, both in the intervention and control groups. In the case of the intervention group, $p = 0.001$, indicating a clear decrease in blood glucose values at discharge, compared to the time of admission. In the control group, although the placebo intervention was applied, a decrease in blood glucose was still observed at discharge ($p = 0.014$). However, the level of statistical significance is lower compared to the intervention group, which may indicate a superior efficiency of IHHT compared to placebo treatment. These results can be interpreted in the context of the specialized literature, suggesting that, among the beneficial effects of IHHT, improvement in insulin sensitivity is also included [268].

Analysis of the evolution of the lipid profile by applying the Wilcoxon Signed Ranks test revealed significant differences between the two groups during the intervention period. In the intervention group, statistically significant improvements were observed in total cholesterol ($p = 0.017$), triglycerides ($p = 0.039$), as well as HDL cholesterol ($p < 0.001$). These changes indicate a favorable effect of the intervention on lipid metabolism. In contrast, LDL cholesterol values did not undergo statistically significant changes ($p = 0.238$), suggesting a possible limited influence of IHHT on this parameter. In the control group, only a significant improvement in HDL cholesterol was highlighted ($p = 0.040$), and the other lipid parameters did not show statistically significant changes ($p = 0.477$ for total cholesterol, $p = 0.554$ for LDL cholesterol, $p = 0.752$ for triglycerides). In the literature, IHHT is associated with a series of metabolic benefits, among which the reduction of lipid profile values is highlighted [268]. The results obtained in this study support this statement.

The evaluation of liver function parameters (AST and ALT) in this study by applying the Wilcoxon Signed Ranks test revealed a different evolution in the two groups. In the interventional group, a statistically significant decrease in AST values was found at discharge, compared to the time of hospitalization ($p = 0.025$), suggesting a possible improvement in liver status. Regarding ALT values, they did not show statistically significant changes in either of the two groups ($p = 0.102$ for the interventional group and $p = 0.856$ for the control group), indicating a stability of this liver marker throughout the analyzed period. In the control group, in addition to stable ALT values, AST also did not show statistically significant variations ($p = 0.856$), suggesting that placebo therapy could not influence liver function. IHHT has attracted increasing interest in the scientific literature due to its favorable effects, including on liver function. Research conducted in patients with metabolic disorders has revealed significant improvement in liver enzymes [239, 330].

Conclusions

The results obtained outline a complex action profile of IHHT, suggesting not only punctual benefits but also systemic effects.

One of the most significant results of the study was the improvement of pulmonary function, highlighted by the increase in the Tiffeneau index values. This parameter is essential in the assessment of pulmonary function and, implicitly, in the early detection of possible pathologies. In the context of MS, where chronic inflammation and oxidative stress can negatively influence pulmonary function, the improvement of this index represents an important gain.

The 6-minute walk test, as an indicator of exercise capacity, recorded significant improvements in the IHHT group, reflecting superior respiratory and cardiovascular capacity. This result is particularly important in the context of MS, where sedentarism and reduced exercise capacity contribute to the worsening of the general condition. The improvement in exercise tolerance is correlated not only with improved lung function but also with an efficiency of oxygen use at the muscular level.

IHHT generated significant changes at the hematological level, highlighted by the increase in erythrocyte and hemoglobin concentration. These results support the specialized literature that attributes to this therapy the ability to stimulate angiogenesis and erythropoiesis. Improving the oxygen transport capacity in the blood has direct implications on physical performance, energy metabolism, and general resistance of the body.

The effects observed in this study support the idea that IHHT is a therapy with multiple mechanisms of action, which could occupy an important place in personalized treatment strategies in patients with MS. Despite the limitations regarding the parameters that were not statistically significantly improved, the results are encouraging and justify the expansion of research in the direction of this treatment method.

The study confirms that IHHT represents a promising and safe therapeutic strategy in MS, with favorable effects on multiple levels: respiratory, metabolic, hematological, and functional. The focus on improving lung function, associated with increased exercise capacity and improvements in metabolic parameters, outlines a complex and effective therapeutic profile.

IHHT is distinguished not only by its favorable objective results but also by its non-invasive nature and adaptability for various categories of patients.

ORIGINALITY OF THE THESIS

The personal motivation in carrying out this thesis was guided by the desire to contribute to the development of more accessible, safer, and better-adapted therapeutic interventions for the needs of patients diagnosed with obesity and MS. A special emphasis was placed on optimizing pulmonary function, an often overlooked but essential component in the complex management of these conditions.

This thesis represents the first and, to date, the only research work in Romania that investigated and applied IHHT in a structured scientific study.

Although there are studies in the specialized literature investigating the effects of IHHT in patients with MS, the originality of the present study lies in the fact that the studied parameters were not analyzed simultaneously and in a similar experimental setting, which would include a strict intervention protocol and a dynamic follow-up of the therapeutic response.

To date, existing research does not provide studies investigating the association between obesity, MS, pulmonary function, and IHHT. This gap highlights the need to explore possible interactions between the respiratory component and metabolic markers in order to identify personalized therapeutic strategies.

The novelty is given not only by the experimental design, but also by how the results are correlated, offering a unique perspective on the body's response to this intervention.

The thesis brings an added originality by the complex evaluation of the parameters obtained by spirometry, by using the PowerBreathe device and the Tanita RD scale, as well as by performing a complete set of paraclinical investigations, performing a lung X-ray to identify possible radiological changes, performing an abdominal ultrasound to identify hepatic steatosis, performing tests and scales, correlated with other relevant parameters. This multidimensional approach is innovative because it integrates assessment tools and methods that have not previously been explored together in the specialized literature. By combining these data, the thesis provides a complex and detailed perspective on the impact on respiratory function, body composition, and other essential metabolic factors, thus significantly contributing to the enrichment of existing knowledge in the medical field.

I believe that IHHT can represent a valuable complementary solution, with the potential to improve the quality of life of patients and optimize various health parameters, such as pulmonary and metabolic function.

REFERENCES

1. Xu H, Li X, Adams H, Kubena K, Guo S. Etiology of Metabolic Syndrome and Dietary Intervention. Int J Mol Sci. 2018 Dec 31;20(1):128. doi: 10.3390/ijms20010128;
2. Saklayen MG. The Global Epidemic of the Metabolic Syndrome. Curr Hypertens Rep. 2018 Feb 26;20(2):12. doi: 10.1007/s11906-018-0812-z;
3. Swarup S, Goyal A, Grigorova Y, Zeltser R. Metabolic Syndrome. 2022 Oct 24. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–. PMID: 29083742;
4. Swarup S, Ahmed I, Grigorova Y, Zeltser R. Metabolic Syndrome. 2024 Mar 7. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 29083742;
5. https://jamestownspine.com/metabolic-syndrome/;
6. Rochlani Y, Pothineni NV, Kovelamudi S, Mehta JL. Metabolic syndrome: pathophysiology, management, and modulation by natural compounds. Ther Adv Cardiovasc Dis. 2017 Aug;11(8):215-225. doi: 10.1177/1753944717711379;
7. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA 2002; 287(3): 356–359;
8. Miller JM, Kaylor MB, Johannsson M, et al. Prevalence of metabolic syndrome and individual criterion in US adolescents: 2001–2010 National Health and Nutrition Examination Survey. Metab Syndr Relat Disord 2014; 12(10): 527–532;
9. Dev R, Behlouli H, Parry M, Raparelli V, Norris CM, Pilote L; GOING-FWD Consortium. Impact of Sex and Gender on Metabolic Syndrome in Adults: A Retrospective Cohort Study From the Canadian Primary Care Sentinel Surveillance Network. Can J Diabetes. 2024 Feb;48(1):36-43.e2. doi: 10.1016/j.jcjd.2023.08.008;
10. Hiramatsu Y, Ide H, Furui Y. Differences in the components of metabolic syndrome by age and sex: a cross-sectional and longitudinal analysis of a cohort of middle-aged and older Japanese adults. BMC Geriatr. 2023 Jul 17;23(1):438. doi: 10.1186/s12877-023-04145-0;
11. Slagter SN, van Waateringe RP, van Beek AP, van der Klauw MM, Wolffenbuttel BHR, van Vliet-Ostaptchouk JV. Sex, BMI and age differences in metabolic syndrome: the Dutch Lifelines Cohort Study. Endocr Connect. 2017 May;6(4):278-288. doi: 10.1530/EC-17-0011;
12. Ştefan AG, Clenciu D, Mitrea A, Vladu IM, Protasiewicz-Timofticiuc DC, Roşu MM, Maria DT, Dinu IR, Gheonea TC, Vladu BE, Efrem IC, Moţa E, Moţa M. Metabolic Syndrome and Insulin Resistance in Romania. Int J Mol Sci. 2025 Mar 7;26(6):2389. doi: 10.3390/ijms26062389;
13. Liang X, Or B, Tsoi MF, Cheung CL, Cheung BMY. Prevalence of metabolic syndrome in the United States National Health and Nutrition Examination Survey 2011-18. Postgrad Med J. 2023 Aug 22;99(1175):985-992. doi: 10.1093/postmj/qgad008;
14. Blanquet M, Legrand A, Pélissier A, Mourgues C. Socio-economics status and metabolic syndrome: A meta-analysis. Diabetes Metab Syndr. 2019 May-Jun;13(3):1805-1812. doi: 10.1016/j.dsx.2019.04.003;
15. Chong KS, Chang YH, Yang CT, Chou CK, Ou HT, Kuo S. Longitudinal economic burden of incident complications among metabolic syndrome populations. Cardiovasc Diabetol. 2024 Jul 10;23(1):246. doi: 10.1186/s12933-024-02335-7;
16. Scholze J, Alegria E, Ferri C, Langham S, Stevens W, Jeffries D, Uhl-Hochgraeber K. Epidemiological and economic burden of metabolic syndrome and its consequences in patients with hypertension in Germany, Spain and Italy; a prevalence-based model. BMC Public Health. 2010 Sep 2;10:529. doi: 10.1186/1471-2458-10-529;
17. Dhondge RH, Agrawal S, Patil R, Kadu A, Kothari M. A Comprehensive Review of Metabolic Syndrome and Its Role in Cardiovascular Disease and Type 2 Diabetes Mellitus: Mechanisms,

Risk Factors, and Management. Cureus. 2024 Aug 21;16(8):e67428. doi: 10.7759/cureus.67428;
18. Noce A, Di Lauro M, Di Daniele F, Pietroboni Zaitseva A, Marrone G, Borboni P, Di Daniele N. Natural Bioactive Compounds Useful in Clinical Management of Metabolic Syndrome. Nutrients. 2021 Feb 16;13(2):630. doi: 10.3390/nu13020630;
19. Zieve FJ. The metabolic syndrome: diagnosis and treatment. Clin Cornerstone. 2004;6 Suppl 3:S5-13. doi: 10.1016/s1098-3597(04)80093-0;
20. Petersen MC, Shulman GI. Mechanisms of Insulin Action and Insulin Resistance. Physiol Rev. 2018 Oct 1;98(4):2133-2223. doi: 10.1152/physrev.00063.2017;
21. Kawai T, Autieri MV, Scalia R. Adipose tissue inflammation and metabolic dysfunction in obesity. Am J Physiol Cell Physiol. 2021 Mar 1;320(3):C375-C391. doi: 10.1152/ajpcell.00379.2020;
22. Boden G, Shulman GI. Free fatty acids in obesity and type 2 diabetes: defining their role in the development of insulin resistance and beta-cell dysfunction. Eur J Clin Invest 2002; 32(Suppl. 3): 14–23;
23. Tooke JE, Hannemann MM. Adverse endothelial function and the insulin resistance syndrome. J Intern Med 2000; 247(4): 425–431;
24. Juhan-Vague I, Alessi MC, Mavri A, et al. Plasminogen activator inhibitor-1, inflammation, obesity, insulin resistance and vascular risk. J Thromb Haemost 2003; 1(7): 1575–1579;
25. Hirano T. Pathophysiology of Diabetic Dyslipidemia. J Atheroscler Thromb. 2018 Sep 1;25(9):771-782. doi: 10.5551/jat.RV17023;
26. Lewis GF, Steiner G. Acute effects of insulin in the control of VLDL production in humans. Implications for the insulin-resistant state. Diabetes Care 1996; 19(4): 390–393;
27. Wallace AM, McMahon AD, Packard CJ, et al.; on behalf of the WOSCOPS Executive Committee. Plasma leptin and the risk of cardiovascular disease in the west of Scotland coronary prevention study (WOSCOPS). Circulation 2001; 104(25): 3052–3056;
28. Lindsay RS, Funahashi T, Hanson RL, et al. Adiponectin and development of type 2 diabetes in the Pima Indian population. Lancet 2002; 360(9326): 57–58;
29. Zhou MS, Wang A, Yu H. Link between insulin resistance and hypertension: What is the evidence from evolutionary biology? Diabetol Metab Syndr. 2014 Jan 31;6(1):12. doi: 10.1186/1758-5996-6-12;
30. Vanecková I, Maletínská L, Behuliak M, et al. Obesity-related hypertension: possible pathophysiological mechanisms. J Endocrinol 2014; 223(3): R63–R78;
31. Mehta PK, Griendling KK. Angiotensin II cell signaling: physiological and pathological effects in the cardiovascular system. Am J Physiol Cell Physiol 2007; 292(1): C82–C97;
32. Dai Y, Mercanti F, Dai D, et al. LOX-1, a bridge between GLP-1R and mitochondrial ROS generation in human vascular smooth muscle cells. Biochem Biophys Res Commun 2013; 437(1): 62–66;
33. Sypniewska G. Pro-Inflammatory and Prothrombotic Factors and Metabolic Syndrome. EJIFCC. 2007 Feb 26;18(1):39-46;
34. Hotamisligil GS, Murray DL, Choy LN, et al. Tumor necrosis factor alpha inhibits signaling from the insulin receptor. Proc Natl Acad Sci U S A 1994; 91(11): 4854–4858;
35. Tsigos C, Kyrou I, Chala E, et al. Circulating tumor necrosis factor alpha concentrations are higher in abdominal *versus* peripheral obesity. Metabolism 1999; 48(10): 1332–1335;
36. Fried SK, Bunkin DA, Greenberg AS. Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. J Clin Endocrinol Metab 1998; 83(3): 847–850;
37. Bastard JP, Jardel C, Bruckert E, et al. Elevated levels of interleukin 6 are reduced in serum and subcutaneous adipose tissue of obese women after weight loss. J Clin Endocrinol Metab 2000; 85(9): 3338–3342;

38. Abou Ziki MD, Mani A. Metabolic syndrome: genetic insights into disease pathogenesis. Curr Opin Lipidol. 2016 Apr;27(2):162-71. doi: 10.1097/MOL.0000000000000276;
39. Mohamed SM, Shalaby MA, El-Shiekh RA, El-Banna HA, Emam SR, Bakr AF. Metabolic syndrome: risk factors, diagnosis, pathogenesis, and management with natural approaches. Food Chem Adv. 2023;3:100335;
40. Hsu CN, Hou CY, Hsu WH, Tain YL. Early-Life Origins of Metabolic Syndrome: Mechanisms and Preventive Aspects. Int J Mol Sci. 2021 Nov 2;22(21):11872. doi: 10.3390/ijms222111872;
41. Rus M, Crisan S, Andronie-Cioara FL, Indries M, Marian P, Pobirci OL, Ardelean AI. Prevalence and Risk Factors of Metabolic Syndrome: A Prospective Study on Cardiovascular Health. Medicina (Kaunas). 2023 Sep 25;59(10):1711. doi: 10.3390/medicina59101711;
42. Yu E, Malik VS, Hu FB. Cardiovascular Disease Prevention by Diet Modification: JACC Health Promotion Series. J Am Coll Cardiol. 2018 Aug 21;72(8):914-926. doi: 10.1016/j.jacc.2018.02.085;
43. Marc J. Genetic Succeptibility to Metabolic Syndrome. EJIFCC. 2007 Feb 26;18(1):7-14;
44. Bermudez V, Olivar LC, Torres W, Navarro C, Gonzalez R, Espinoza C, Morocho A, Mindiola A, Chacin M, Arias V, Añez R, Salazar J, Riaño-Garzon M, Diaz-Camargo E, Bautista MJ, Rojas J. Cigarette smoking and metabolic syndrome components: a cross-sectional study from Maracaibo City, Venezuela. F1000Res. 2018 May 10;7:565. doi: 10.12688/f1000research.14571.3;
45. Godala M, Krzyżak M, Maślach D, Gaszyńska E. Relationship between Dietary Behaviors and Physical Activity and the Components of Metabolic Syndrome: A Case-Control Study. Int J Environ Res Public Health. 2022 May 27;19(11):6562. doi: 10.3390/ijerph19116562;
46. Bhalwar R. Metabolic syndrome: The Indian public health perspective. Med J Armed Forces India. 2020 Jan;76(1):8-16. doi: 10.1016/j.mjafi.2019.12.001;
47. Magkos F, Yannakoulia M, Chan JL, Mantzoros CS. Management of the metabolic syndrome and type 2 diabetes through lifestyle modification. Annu Rev Nutr. 2009;29:223-56. doi: 10.1146/annurev-nutr-080508-141200;
48. Jha BK, Sherpa ML, Imran M, Mohammed Y, Jha LA, Paudel KR, Jha SK. Progress in understanding metabolic syndrome and knowledge of its complex pathophysiology. Diabetology. 2023;4:134–159;
49. Das D, Shruthi NR, Banerjee A, Jothimani G, Duttaroy AK, Pathak S. Endothelial dysfunction, platelet hyperactivity, hypertension, and the metabolic syndrome: molecular insights and combating strategies. Front Nutr. 2023 Aug 8;10:1221438. doi: 10.3389/fnut.2023.1221438;
50. Moghadam-Ahmadi A, Soltani N, Ayoobi F, Jamali Z, Sadeghi T, Jalali N, Vakilian A, Lotfi MA, Khalili P. Association between metabolic syndrome and stroke: a population based cohort study. BMC Endocr Disord. 2023 Jun 6;23(1):131. doi: 10.1186/s12902-023-01383-6;
51. Senst B, Tadi P, Basit H, Jan A. Hypercoagulability. 2023 Aug 22. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan;
52. Oktay AA, Paul TK, Koch CA, et al. Diabetes, cardiomyopathy, and heart failure. In: Endotext. South Dartmouth, MA: MDText.com, Inc.; 2000;
53. Guembe MJ, Fernandez-Lazaro CI, Sayon-Orea C, Toledo E, Moreno-Iribas C; RIVANA Study Investigators. Risk for cardiovascular disease associated with metabolic syndrome and its components: a 13-year prospective study in the RIVANA cohort. Cardiovasc Diabetol. 2020 Nov 22;19(1):195. doi: 10.1186/s12933-020-01166-6;
54. Garvey WT, Ryan DH, Henry R, Bohannon NJ, Toplak H, Schwiers M, Troupin B, Day WW. Prevention of type 2 diabetes in subjects with prediabetes and metabolic syndrome treated with phentermine and topiramate extended release. Diabetes Care. 2014 Apr;37(4):912-21. doi: 10.2337/dc13-1518;

55. Shin JA, Lee JH, Lim SY, Ha HS, Kwon HS, Park YM, Lee WC, Kang MI, Yim HW, Yoon KH, Son HY. Metabolic syndrome as a predictor of type 2 diabetes, and its clinical interpretations and usefulness. J Diabetes Investig. 2013 Jul 8;4(4):334-43. doi: 10.1111/jdi.12075;
56. Chakraborty S, Verma A, Garg R, Singh J, Verma H. Cardiometabolic Risk Factors Associated With Type 2 Diabetes Mellitus: A Mechanistic Insight. Clin Med Insights Endocrinol Diabetes. 2023 Dec 25;16:11795514231220780. doi: 10.1177/11795514231220780;
57. Manna P, Jain SK. Obesity, Oxidative Stress, Adipose Tissue Dysfunction, and the Associated Health Risks: Causes and Therapeutic Strategies. Metab Syndr Relat Disord. 2015 Dec;13(10):423-44. doi: 10.1089/met.2015.0095;
58. Guebre-Egziabher F, Alix PM, Koppe L, Pelletier CC, Kalbacher E, Fouque D, Soulage CO. Ectopic lipid accumulation: A potential cause for metabolic disturbances and a contributor to the alteration of kidney function. Biochimie. 2013 Nov;95(11):1971-9. doi: 10.1016/j.biochi.2013.07.017;
59. Moghadam-Ahmadi A, Soltani N, Ayoobi F, Jamali Z, Sadeghi T, Jalali N, Vakilian A, Lotfi MA, Khalili P. Association between metabolic syndrome and stroke: a population based cohort study. BMC Endocr Disord. 2023 Jun 6;23(1):131. doi: 10.1186/s12902-023-01383-6;
60. Li X, Li X, Lin H, Fu X, Lin W, Li M, Zeng X, Gao Q. Metabolic syndrome and stroke: A meta-analysis of prospective cohort studies. J Clin Neurosci. 2017 Jun;40:34-38. doi: 10.1016/j.jocn.2017.01.018;
61. Kurl S, Laukkanen JA, Niskanen L, Laaksonen D, Sivenius J, Nyyssönen K, Salonen JT. Metabolic syndrome and the risk of stroke in middle-aged men. Stroke. 2006 Mar;37(3):806-11. doi: 10.1161/01.STR.0000204354.06965.44;
62. Zhang F, Liu L, Zhang C, Ji S, Mei Z, Li T. Association of Metabolic Syndrome and Its Components With Risk of Stroke Recurrence and Mortality: A Meta-analysis. Neurology. 2021 Aug 17;97(7):e695-e705. doi: 10.1212/WNL.0000000000012415;
63. Esposito K, Chiodini P, Colao A, Lenzi A, Giugliano D. Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. Diabetes Care. 2012 Nov;35(11):2402-11. doi: 10.2337/dc12-0336;
64. Braun S, Bitton-Worms K, LeRoith D. The link between the metabolic syndrome and cancer. Int J Biol Sci. 2011;7(7):1003-15. doi: 10.7150/ijbs.7.1003;
65. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med. 2003 Apr 24;348(17):1625-38. doi: 10.1056/NEJMoa021423;
66. Pothiwala P, Jain SK, Yaturu S. Metabolic syndrome and cancer. Metab Syndr Relat Disord. 2009 Aug;7(4):279-88. doi: 10.1089/met.2008.0065;
67. Coughlin SS, Calle EE, Teras LR, Petrelli J, Thun MJ. Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. Am J Epidemiol. 2004 Jun 15;159(12):1160-7. doi: 10.1093/aje/kwh161;
68. Leon BM, Maddox TM. Diabetes and cardiovascular disease: Epidemiology, biological mechanisms, treatment recommendations and future research. World J Diabetes. 2015 Oct 10;6(13):1246-58. doi: 10.4239/wjd.v6.i13.1246;
69. Fujioka K. Metabolic syndrome treatment strategies. Pharmacotherapy. 2006 Dec;26(12 Pt 2):222S-226S. doi: 10.1592/phco.26.12part2.222S;
70. Healthy diet [Internet]. World Health Organization; 2024 Aug [cited 2023]. Available from: https://www.who.int/news-room/fact-sheets/detail/healthy-diet;
71. Gorski MT, Roberto CA. Public health policies to encourage healthy eating habits: recent perspectives. J Healthc Leadersh. 2015 Sep 23;7:81-90. doi: 10.2147/JHL.S69188;
72. Alomar AO, Shaheen MF, Almaneea AS, Althaqeb EK, Alshahrani ZM, Jarman YA, Alhabdan S. The Effect of Bariatric Surgery on Metabolic Syndrome: A Three-center Experience in Saudi Arabia. Obes Surg. 2021 Aug;31(8):3630-3636. doi: 10.1007/s11695-021-05461-3;

73. Cordero P, Li J, Oben JA. Bariatric surgery as a treatment for metabolic syndrome. J R Coll Physicians Edinb. 2017 Dec;47(4):364-368. doi: 10.4997/JRCPE.2017.414;
74. Pérez-Martínez P, Mikhailidis DP, Athyros VG, Bullo M, Couture P, Covas MI, et al. Lifestyle recommendations for the prevention and management of metabolic syndrome: an international panel recommendation. Nutr Rev. 2017 May 1;75(5):307-326. doi: 10.1093/nutrit/nux014;
75. Lin X, Li H. Obesity: Epidemiology, Pathophysiology, and Therapeutics. Front Endocrinol (Lausanne). 2021 Sep 6;12:706978. doi: 10.3389/fendo.2021.706978;
76. Panuganti KK, Nguyen M, Kshirsagar RK. Obesity. 2023 Aug 8. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024 Jan;
77. Balke H, Nocito A. Vom Schönheitsideal zur Krankheit - eine Reise durch die Geschichte der Adipositas [A trip through the history of obesity]. Praxis (Bern 1994). 2013 Jan 16;102(2):77-83;
78. Ghesmaty Sangachin M, Cavuoto LA, Wang Y. Use of various obesity measurement and classification methods in occupational safety and health research: a systematic review of the literature. BMC Obes. 2018;5:28;
79. Lim Y, Boster J. Obesity and Comorbid Conditions. 2024 Jun 27. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024 Jan;
80. Weir CB, Jan A. BMI Classification Percentile And Cut Off Points. In: StatPearls. Treasure Island (FL): StatPearls Publishing; June 26, 2023;
81. Ballard RJ, Dewanti RA, Sayuti S, Umar N. Correlation between sum of 8 skinfolds to predicted % body fat range as a reliable measure of body composition assessment for well-trained athletes. Asian Soc Sci. 2014;10(5):12. doi:10.5539/ass.v10n5p12;
82. Nuttall FQ. Body Mass Index: Obesity, BMI, and Health: A Critical Review. Nutr Today. 2015 May;50(3):117-128. doi: 10.1097/NT.0000000000000092;
83. Zierle-Ghosh A, Jan A. Physiology, Body Mass Index. In: StatPearls. Treasure Island (FL): StatPearls Publishing; September 11, 2022;
84. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999-2008. JAMA. 2010 Jan 20;303(3):235-41;
85. Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, Singh GM, Gutierrez HR, Lu Y, Bahalim AN, Farzadfar F, Riley LM, Ezzati M; Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Body Mass Index). National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9·1 million participants. Lancet. 2011 Feb 12;377(9765):557-67. doi: 10.1016/S0140-6736(10)62037-5;
86. Misra A, Khurana L. Obesity-related non-communicable diseases: South Asians vs White Caucasians. Int J Obes (Lond). 2011 Feb;35(2):167-87;
87. Enache G, Rusu E, Ilinca A, Rusu F, Costache A, Jinga M, Pănuş C, Radulian G. Prevalence of overweight and obesity in a roma population from southern Romania - Calarasi county. Acta Endocrinol (Buchar). 2018 Jan-Mar;14(1):122-130. doi: 10.4183/aeb.2018.122;
88. Drăgănescu AC, Dinulescu A, Păcurar D, Jinga V, Pleşca DA. Prevalence and Determinants of Overweight and Obesity Among Romanian Children Aged 5-17: A Cross-Sectional Study. J Clin Med. 2025 May 10;14(10):3331. doi: 10.3390/jcm14103331;
89. Boutari C, Mantzoros CS. A 2022 update on the epidemiology of obesity and a call to action: as its twin COVID-19 pandemic appears to be receding, the obesity and dysmetabolism pandemic continues to rage on. Metabolism. 2022;133:155217. doi:10.1016/j.metabol.2022.155217;
90. Tremmel M, Gerdtham UG, Nilsson PM, Saha S. Economic Burden of Obesity: A Systematic Literature Review. Int J Environ Res Public Health. 2017 Apr 19;14(4):435. doi: 10.3390/ijerph14040435;

91. Lehnert T, Sonntag D, Konnopka A, Riedel-Heller S, König HH. Economic costs of overweight and obesity. Best Pract Res Clin Endocrinol Metab. 2013 Apr;27(2):105-15. doi: 10.1016/j.beem.2013.01.002;
92. Nagi MA, Ahmed H, Rezq MAA, Sangroongruangsri S, Chaikledkaew U, Almalki Z, Thavorncharoensap M. Economic costs of obesity: a systematic review. Int J Obes (Lond). 2024 Jan;48(1):33-43. doi: 10.1038/s41366-023-01398-y;
93. Tiwari A, Balasundaram P. Public Health Considerations Regarding Obesity. 2023 Jun 5. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024 Jan;
94. Vidra N, Trias-Llimós S, Janssen F. Impact of obesity on life expectancy among different European countries: secondary analysis of population-level data over the 1975-2012 period. BMJ Open. 2019 Jul 31;9(7):e028086. doi: 10.1136/bmjopen-2018-028086;
95. Cuevas AG, Chen R, Thurber KA, Slopen N, Williams DR. Psychosocial Stress and Overweight and Obesity: Findings From the Chicago Community Adult Health Study. Ann Behav Med. 2019 Oct 7;53(11):NP. doi: 10.1093/abm/kaz008;
96. Jin X, Qiu T, Li L, Yu R, Chen X, Li C, Proud CG, Jiang T. Pathophysiology of obesity and its associated diseases. Acta Pharm Sin B. 2023 Jun;13(6):2403-2424. doi: 10.1016/j.apsb.2023.01.012;
97. Shrestha N, Pedisic Z, Neil-Sztramko S, Kukkonen-Harjula KT, Hermans V. The Impact of Obesity in the Workplace: a Review of Contributing Factors, Consequences and Potential Solutions. Curr Obes Rep. 2016 Sep;5(3):344-60. doi: 10.1007/s13679-016-0227-6;
98. Okunogbe A, Nugent R, Spencer G, Powis J, Ralston J, Wilding J. Economic impacts of overweight and obesity: current and future estimates for 161 countries. BMJ Glob Health. 2022 Sep;7(9):e009773. doi: 10.1136/bmjgh-2022-009773;
99. Purnell JQ, Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, et al. Definitions, Classification, and Epidemiology of Obesity. South Dartmouth (MA): MDText.com, Inc. 2000;
100. An SM, Cho SH, Yoon JC. Adipose Tissue and Metabolic Health. Diabetes Metab J. 2023 Sep;47(5):595-611. doi: 10.4093/dmj.2023.0011;
101. Han J, Lee JE, Jin J, Lim JS, Oh N, Kim K, Chang SI, Shibuya M, Kim H, Koh GY. The spatiotemporal development of adipose tissue. Development. 2011 Nov;138(22):5027-37. doi: 10.1242/dev.067686;
102. Hafidi ME, Buelna-Chontal M, Sánchez-Muñoz F, Carbó R. Adipogenesis: A Necessary but Harmful Strategy. Int J Mol Sci. 2019 Jul 26;20(15):3657. doi: 10.3390/ijms20153657. PMID: 31357412; PMCID: PMC6696444.Desai M, Beall M, Ross MG. Developmental origins of obesity: programmed adipogenesis. Curr Diab Rep. 2013 Feb;13(1):27-33. doi: 10.1007/s11892-012-0344-x;
103. https://www.revistagalenus.ro/practica-medicala/tesutul-adipos-tipuri-si-functii/;
104. Hausman DB, DiGirolamo M, Bartness TJ, Hausman GJ, Martin RJ. The biology of white adipocyte proliferation. Obes Rev. 2001 Nov;2(4):239-54. doi: 10.1046/j.1467-789x.2001.00042.x;
105. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006 Dec 14;444(7121):860-7. doi: 10.1038/nature05485;
106. Giroud M, Jodeleit H, Prentice KJ, Bartelt A. Adipocyte function and the development of cardiometabolic disease. J Physiol. 2022 Mar;600(5):1189-1208. doi: 10.1113/JP281979;
107. Nedergaard J, Bengtsson T, Cannon B. Unexpected evidence for active brown adipose tissue in adult humans. Am J Physiol Endocrinol Metab. 2007 Aug;293(2):E444-52. doi: 10.1152/ajpendo.00691.2006;
108. Cypess AM, Lehman S, Williams G, Tal I, Rodman D, Goldfine AB, Kuo FC, Palmer EL, Tseng YH, Doria A, Kolodny GM, Kahn CR. Identification and importance of brown adipose tissue in adult humans. N Engl J Med. 2009 Apr 9;360(15):1509-17. doi: 10.1056/NEJMoa0810780;

109. Wu J, Boström P, Sparks LM, Ye L, Choi JH, Giang AH, Khandekar M, Virtanen KA, Nuutila P, Schaart G, Huang K, Tu H, van Marken Lichtenbelt WD, Hoeks J, Enerbäck S, Schrauwen P, Spiegelman BM. Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human. Cell. 2012 Jul 20;150(2):366-76. doi: 10.1016/j.cell.2012.05.016;
110. Giordano A, Smorlesi A, Frontini A, Barbatelli G, Cinti S. White, brown and pink adipocytes: the extraordinary plasticity of the adipose organ. Eur J Endocrinol. 2014 Apr 10;170(5):R159-71. doi: 10.1530/EJE-13-0945;
111. Corrêa LH, Heyn GS, Magalhaes KG. The Impact of the Adipose Organ Plasticity on Inflammation and Cancer Progression. Cells. 2019 Jun 30;8(7):662. doi: 10.3390/cells8070662;
112. Funahashi T, Shimomura I, Matsuzawa Y. Adipocytokines. Encyclopedia of Endocrine Diseases, Elsevier. 2004; 41-4. ISBN 9780124755703. https://doi.org/10.1016/B0-12-475570-4/01460-8;
113. Stanciu Liliana-Elena. Elemente de reabilitare medicală în patologia endocrino-metabolică – Note de curs. București: Editura Balneară; 2024;
114. Zorena K, Jachimowicz-Duda O, Ślęzak D, Robakowska M, Mrugacz M. Adipokines and Obesity. Potential Link to Metabolic Disorders and Chronic Complications. Int J Mol Sci. 2020 May 18;21(10):3570. doi: 10.3390/ijms21103570;
115. Taylor EB. The complex role of adipokines in obesity, inflammation, and autoimmunity. Clin Sci (Lond). 2021 Mar 26;135(6):731-752. doi: 10.1042/CS20200895;
116. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. J Clin Endocrinol Metab. 2004 Jun;89(6):2548-56. doi: 10.1210/jc.2004-0395;
117. Dubern B, Mosbah H, Pigeyre M, et al. Rare genetic causes of obesity: diagnosis and management in clinical care. Ann Endocrinol (Paris) 2022;83:63–72;
118. Gunay-Aygun M, Cassidy SB, Nicholls RD. Prader-Willi and other syndromes associated with obesity and mental retardation. Behav Genet 1997;27:307–24;
119. Masood B, Moorthy M. Causes of obesity: a review. Clin Med (Lond). 2023 Jul;23(4):284-291. doi: 10.7861/clinmed.2023-0168;
120. Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. Nature 1998;395:763–70;
121. Locke AE, Kahali B, Berndt SI, et al. Genetic studies of body mass index yield new insights for obesity biology. Nature 2015;518:197–206;
122. Herrera BM, Keildson S, Lindgren CM. Genetics and epigenetics of obesity. Maturitas 2011;69:41–9;
123. Jakicic JM, Davis KK. Obesity and physical activity. Psychiatr Clin North Am. 2011 Dec;34(4):829-40. doi: 10.1016/j.psc.2011.08.009;
124. Celik O, Yildiz BO. Obesity and physical exercise. Minerva Endocrinol (Torino). 2021 Jun;46(2):131-144. doi: 10.23736/S2724-6507.20.03361-1;
125. Spinelli S, Monteleone E. Food Preferences and Obesity. Endocrinol Metab (Seoul). 2021 Apr;36(2):209-219. doi: 10.3803/EnM.2021.105;
126. Ludwig DS, Ebbeling CB. The carbohydrate-insulin model of obesity: beyond "calories in, calories out". JAMA Intern Med 2018;178:1098–103;
127. Moon RJ, D'Angelo S, Holroyd CR. et al. Parent-offspring associations in body composition: findings from the Southampton Women's Survey Prospective Cohort Study. J Clin Endocrinol Metab. Published online 21 March 2023;
128. Oken E, Levitan EB, Gillman MW. Maternal smoking during pregnancy and child overweight: systematic review and meta-analysis. Int J Obes (Lond). 2008 Feb;32(2):201-10. doi: 10.1038/sj.ijo.0803760;
129. Rasmussen KM, Yaktine AL, eds. Institute of Medicine (US) and National Research Council (US) Committee to Reexamine IOM Pregnancy Weight Guidelines. Weight gain during pregnancy: reexamining the guidelines. Washington (DC): National Academies Press; 2009;

130. Parsons TJ, Power C, Logan S, et al. Childhood predictors of adult obesity: a systematic review. Int J Obes Relat Metab Disord 1999;23(Suppl 8):S1–107;
131. Miller MA, Kruisbrink M, Wallace J, Ji C, Cappuccio FP. Sleep duration and incidence of obesity in infants, children, and adolescents: a systematic review and meta-analysis of prospective studies. Sleep. 2018 Apr 1;41(4). doi: 10.1093/sleep/zsy018;
132. Harder T, Bergmann R, Kallischnigg G, Plagemann A. Duration of breastfeeding and risk of overweight: a meta-analysis. Am J Epidemiol. 2005 Sep 1;162(5):397-403. doi: 10.1093/aje/kwi222;
133. Baird J, Fisher D, Lucas P, Kleijnen J, Roberts H, Law C. Being big or growing fast: systematic review of size and growth in infancy and later obesity. BMJ. 2005 Oct 22;331(7522):929. doi: 10.1136/bmj.38586.411273.E0;
134. Chasens ER, Imes CC, Kariuki JK, Luyster FS, Morris JL, DiNardo MM, Godzik CM, Jeon B, Yang K. Sleep and Metabolic Syndrome. Nurs Clin North Am. 2021 Jun;56(2):203-217. doi: 10.1016/j.cnur.2020.10.012;
135. Koren D, Taveras EM. Association of sleep disturbances with obesity, insulin resistance and the metabolic syndrome. Metabolism. 2018 Jul; 84:67-75. doi: 10.1016/j.metabol.2018.04.001;
136. Che T, Yan C, Tian D, Zhang X, Liu X, Wu Z. The Association Between Sleep and Metabolic Syndrome: A Systematic Review and Meta-Analysis. Front Endocrinol (Lausanne). 2021 Nov 19;12:773646. doi: 10.3389/fendo.2021.773646;
137. Beccuti G, Pannain S. Sleep and obesity. Curr Opin Clin Nutr Metab Care 2011;14:402–12;
138. Young AI, Wauthier F, Donnelly P. Multiple novel gene-by-environment interactions modify the effect of FTO variants on body mass index. Nat Commun 2016;7:12724;
139. Verhaegen AA, Van Gaal LF. Drug-induced obesity and its metabolic consequences: a review with a focus on mechanisms and possible therapeutic options. J Endocrinol Invest. 2017 Nov;40(11):1165-1174. doi: 10.1007/s40618-017-0719-6;
140. Wharton S, Raiber L, Serodio KJ, Lee J, Christensen RA. Medications that cause weight gain and alternatives in Canada: a narrative review. Diabetes Metab Syndr Obes. 2018 Aug 21;11:427-438. doi: 10.2147/DMSO.S171365;
141. Domecq JP, Prutsky G, Leppin A, Sonbol MB, Altayar O, Undavalli C, Wang Z, Elraiyah T, Brito JP, Mauck KF, Lababidi MH, Prokop LJ, Asi N, Wei J, Fidahussein S, Montori VM, Murad MH. Clinical review: Drugs commonly associated with weight change: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2015 Feb;100(2):363-70. doi: 10.1210/jc.2014-3421;
142. What are insulinomas? Cancer Research UK. www.cancerresearchuk.org/about-cancer/neuroendocrine-tumours-nets/pancreatic-nets/insulinoma/what-are-insulinomas;
143. Kumar R, Rizvi MR, Saraswat S. Obesity and Stress: A Contingent Paralysis. Int J Prev Med. 2022 Jun 24;13:95. doi: 10.4103/ijpvm.IJPVM_427_20;
144. Tomiyama AJ. Stress and Obesity. Annu Rev Psychol. 2019 Jan 4;70:703-718. doi: 10.1146/annurev-psych-010418-102936;
145. Darbre PD. Endocrine Disruptors and Obesity. Curr Obes Rep. 2017 Mar;6(1):18-27. doi: 10.1007/s13679-017-0240-4;
146. Geng J, Ni Q, Sun W, Li L, Feng X. The links between gut microbiota and obesity and obesity related diseases. Biomed Pharmacother. 2022 Mar;147:112678. doi: 10.1016/j.biopha.2022.112678;
147. Ulker İ, Yildiran H. The effects of bariatric surgery on gut microbiota in patients with obesity: a review of the literature. Biosci Microbiota Food Health. 2019;38(1):3-9. doi: 10.12938/bmfh.18-018;

148. Lawrence VJ, Kopelman PG. Medical consequences of obesity. Clin Dermatol. 2004 Jul-Aug;22(4):296-302. doi: 10.1016/j.clindermatol.2004.01.012;
149. Bahmad HF, Daouk R, Azar J, Sapudom J, Teo JCM, Abou-Kheir W, et al. Modeling Adipogenesis: Current and Future Perspective. Cells. 2020 Oct 20;9(10):2326. doi: 10.3390/cells9102326;
150. Ma W, Zhu H, Yu X, Zhai X, Li S, Huang N, Liu K, Shirai K, Sheerah HA, Cao J. Association between android fat mass, gynoid fat mass and cardiovascular and all-cause mortality in adults: NHANES 2003-2007. Front Cardiovasc Med. 2023 May 18;10:1055223. doi: 10.3389/fcvm.2023.1055223;
151. Ahn J, Ban R, Simpkins C, Yang F. Android obesity could be associated with a higher fall risk than gynoid obesity following a standing-slip: A simulation-based biomechanical analysis. J Biomech. 2024 Feb;164:111962. doi: 10.1016/j.jbiomech.2024.111962;
152. Lätt E, Mäestu J, Jürimäe J. Longitudinal associations of android and gynoid fat mass on cardiovascular disease risk factors in normal weight and overweight boys during puberty. Am J Hum Biol. 2018 Sep;30(5):e23171. doi: 10.1002/ajhb.23171;
153. https://www.resilienthuman.co.uk/post/body-fat-and-what-it-really-means;
154. Klop B, Elte JW, Cabezas MC. Dyslipidemia in obesity: mechanisms and potential targets. Nutrients. 2013 Apr 12;5(4):1218-40. doi: 10.3390/nu5041218;
155. Powell-Wiley TM, Poirier P, Burke LE, Després JP, Gordon-Larsen P, Lavie CJ, Lear SA, Ndumele CE, Neeland IJ, Sanders P, St-Onge MP; American Heart Association Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Epidemiology and Prevention; and Stroke Council. Obesity and Cardiovascular Disease: A Scientific Statement From the American Heart Association. Circulation. 2021 May 25;143(21):e984-e1010. doi: 10.1161/CIR.0000000000000973;
156. https://www.medicalnewstoday.com/articles/effects-of-obesity#endocrine-system;
157. Klein S, Gastaldelli A, Yki-Järvinen H, Scherer PE. Why does obesity cause diabetes? Cell Metab. 2022 Jan 4;34(1):11-20. doi: 10.1016/j.cmet.2021.12.012;
158. Chandrasekaran P, Weiskirchen R. The Role of Obesity in Type 2 Diabetes Mellitus-An Overview. Int J Mol Sci. 2024 Feb 4;25(3):1882. doi: 10.3390/ijms25031882;
159. Al-Goblan AS, Al-Alfi MA, Khan MZ. Mechanism linking diabetes mellitus and obesity. Diabetes Metab Syndr Obes. 2014 Dec 4;7:587-91. doi: 10.2147/DMSO.S67400;
160. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. J Am Coll Cardiol. 2009 May 26;53(21):1925-32. doi: 10.1016/j.jacc.2008.12.068;
161. Lopez-Jimenez F, Almahmeed W, Bays H, Cuevas A, Di Angelantonio E, le Roux CW, Sattar N, Sun MC, Wittert G, Pinto FJ, Wilding JPH. Obesity and cardiovascular disease: mechanistic insights and management strategies. A joint position paper by the World Heart Federation and World Obesity Federation. Eur J Prev Cardiol. 2022 Dec 7;29(17):2218-2237. doi: 10.1093/eurjpc/zwac187;
162. Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, Eckel RH; American Heart Association; Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation. 2006 Feb 14;113(6):898-918;
163. Barber TM, Hanson P, Weickert MO, Franks S. Obesity and Polycystic Ovary Syndrome: Implications for Pathogenesis and Novel Management Strategies. Clin Med Insights Reprod Health. 2019 Sep 9;13:1179558119874042. doi: 10.1177/1179558119874042;
164. Dağ ZÖ, Dilbaz B. Impact of obesity on infertility in women. J Turk Ger Gynecol Assoc. 2015 Jun 1;16(2):111-7. doi: 10.5152/jtgga.2015.15232;

165. Fitzsimons KJ, Modder J, Greer IA. Obesity in pregnancy: risks and management. Obstet Med. 2009 Jun;2(2):52-62. doi: 10.1258/om.2009.090009;
166. Messinis IE, Messini CI, Anifandis G, Dafopoulos K. Polycystic ovaries and obesity. Best Pract Res Clin Obstet Gynaecol. 2015 May;29(4):479-88. doi: 10.1016/j.bpobgyn.2014.11.001;
167. Pati S, Irfan W, Jameel A, Ahmed S, Shahid RK. Obesity and Cancer: A Current Overview of Epidemiology, Pathogenesis, Outcomes, and Management. Cancers (Basel). 2023 Jan 12;15(2):485. doi: 10.3390/cancers15020485;
168. Lauby-Secretan B, Dossus L, Marant-Micallef C, His M. Obésité et cancer [Obesity and Cancer]. Bull Cancer. 2019 Jul-Aug;106(7-8):635-646. French. doi: 10.1016/j.bulcan.2019.04.008;
169. King LK, March L, Anandacoomarasamy A. Obesity & osteoarthritis. Indian J Med Res. 2013;138(2):185-93;
170. Stanciu LE, Iliescu MG. Oglinda obezității – fațete multiple – rezistența la insulină. Medical Market - Medicina fizică și de Reabilitare. 2023;
171. Elmaleh-Sachs A, Schwartz JL, Bramante CT, Nicklas JM, Gudzune KA, Jay M. Obesity Management in Adults: A Review. JAMA. 2023 Nov 28;330(20):2000-2015. doi: 10.1001/jama.2023.19897;
172. LeBlanc ES, Patnode CD, Webber EM, Redmond N, Rushkin M, O’Connor EA. Behavioral and pharmacotherapy weight loss interventions to prevent obesity-related morbidity and mortality in adults: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA. 2018;320(11):1172–1191. doi: 10.1001/jama.2018.7777;
173. Duan D, Kim LJ, Jun JC, Polotsky VY. Connecting insufficient sleep and insomnia with metabolic dysfunction. Ann N Y Acad Sci. 2023;1519(1):94–117. doi: 10.1111/nyas.14926;
174. Varkevisser RDM, van Stralen MM, Kroeze W, Ket JCF, Steenhuis IHM. Determinants of weight loss maintenance: a systematic review. Obes Rev. 2019;20(2):171–211. doi: 10.1111/obr.12772;
175. Oppert JM, Bellicha A, van Baak MA, et al. Exercise training in the management of overweight and obesity in adults: synthesis of the evidence and recommendations from the European Association for the Study of Obesity Physical Activity Working Group. Obes Rev. 2021;22(suppl 4):e13273. doi: 10.1111/obr.13273;
176. Grunvald E, Shah R, Hernaez R, et al. ; AGA Clinical Guidelines Committee. AGA clinical practice guideline on pharmacological interventions for adults with obesity. Gastroenterology. 2022;163(5):1198–1225. doi: 10.1053/j.gastro.2022.08.045;
177. Courcoulas AP, Daigle CR, Arterburn DE. Long term outcomes of metabolic/bariatric surgery in adults. BMJ. 2023 Dec 18;383:e071027. doi: 10.1136/bmj-2022-071027;
178. Eisenberg D, Shikora SA, Aarts E, et al. 2022 American Society for Metabolic and Bariatric Surgery (ASMBS) and International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO): indications for metabolic and bariatric surgery. Surg Obes Relat Dis. 2022;18(12):1345–1356. doi: 10.1016/j.soard.2022.08.013;
179. Robinson PD. Obesity and its impact on the respiratory system. Paediatr Respir Rev. 2014 Sep;15(3):219-26. doi: 10.1016/j.prrv.2014.06.003;
180. Molani Gol R, Rafraf M. Association between abdominal obesity and pulmonary function in apparently healthy adults: A systematic review. Obes Res Clin Pract. 2021 Sep-Oct;15(5):415-424. doi: 10.1016/j.orcp.2021.06.011;
181. Melo LC, Silva MA, Calles AC. Obesity and lung function: a systematic review. Einstein (Sao Paulo). 2014 Jan-Mar;12(1):120-5. doi: 10.1590/s1679-45082014rw2691;
182. Zewari S, Vos P, van den Elshout F, Dekhuijzen R, Heijdra Y. Obesity in COPD: Revealed and Unrevealed Issues. COPD. 2017 Dec;14(6):663-673. doi: 10.1080/15412555.2017.1383978;

183. Ansari S, Haboubi H, Haboubi N. Adult obesity complications: challenges and clinical impact. Ther Adv Endocrinol Metab. 2020 Jun 22;11:2042018820934955. doi: 10.1177/2042018820934955;

184. Tashiro H, Kurihara Y, Kuwahara Y, Takahashi K. Impact of obesity in asthma: Possible future therapies. Allergol Int. 2024 Jan;73(1):48-57. doi: 10.1016/j.alit.2023.08.007;

185. Molina-Luque R, Molina-Recio G, de-Pedro-Jiménez D, Álvarez Fernández C, García-Rodríguez M, Romero-Saldaña M. The Impact of Metabolic Syndrome Risk Factors on Lung Function Impairment: Cross-Sectional Study. JMIR Public Health Surveill. 2023 Sep 5;9:e43737. doi: 10.2196/43737;

186. Baffi CW, Wood L, Winnica D, Strollo PJ Jr, Gladwin MT, Que LG, Holguin F. Metabolic Syndrome and the Lung. Chest. 2016 Jun;149(6):1525-34. doi: 10.1016/j.chest.2015.12.034;

187. Leone N, Courbon D, Thomas F, et al. Lung function impairment and metabolic syndrome: The critical role of abdominal obesity. Am J Respir Crit Care Med 2009;179(6):509–516; doi: 10.1164/rccm.200807-1195OC;

188. Forno E, Han YY, Muzumdar RH, et al. Insulin resistance, metabolic syndrome, and lung function in U.S. adolescents with and without asthma. J Allergy Clin Immunol 2015;136(2):304–311.e308; doi: 10.1016/j.jaci.2015.01.010;

189. Francisco CO, Catai AM, Moura-Tonello SCG, et al. Cardiorespiratory fitness, pulmonary function and C-reactive protein levels in nonsmoking individuals with diabetes. Braz J Med Biol Res 2014;47(5):426–431; doi: 10.1590/1414-431x20143370;

190. Huang H, Guo Q, Li L, et al. Effect of type 2 diabetes mellitus on pulmonary function. Exp Clin Endocrinol Diabetes 2014;122(6):322–326; doi: 10.1055/s-0034-1372579;

191. Sui DX, Zhou HM, Wang F, et al. Cell death-inducing DFF45-like effector C gene silencing alleviates pulmonary vascular remodeling in a type 2 diabetic rat model. J Diabetes Investig 2018;9(4):741–752; doi: 10.1111/jdi.12768;

192. Van Rooyen Y, Huisman HW, Schutte AE, et al. South African and international reference values for lung function and its relationship with blood pressure in Africans. Heart Lung Circ 2015;24(6):573–582; doi: 10.1016/j.hlc.2014.12.005;

193. Engstrom G, Wollmer P, Valind S, et al. Blood pressure increase between 55 and 68 years of age is inversely related to lung function: Longitudinal results from the cohort study "Men born in 1914." J Hypertens 2001;19(7):1203–1208; doi: 10.1097/00004872-200107000-00004;

194. Wu Y, Vollmer WM, Buist AS, et al. Relationship between lung function and blood pressure in Chinese men and women of Beijing and Guangzhou. PRC-USA Cardiovascular and Cardiopulmonary Epidemiology Research Group. Int J Epidemiol 1998;27(1):49–56; doi: 10.1093/ije/27.1.49;

195. Margretardottir OB, Thorleifsson SJ, Gudmundsson G, et al. Hypertension, systemic inflammation and body weight in relation to lung function impairment- an epidemiological study. COPD 2009;6(4):250–255; doi: 10.1080/15412550903049157;

196. Nishimura S, Manabe I, Nagasaki M, et al. CD8+ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. Nat Med 2009;15(8):914–920; doi: 10.1038/nm.1964;

197. Gowdy KM, Fessler MB. Emerging roles for cholesterol and lipoproteins in lung disease. Pulm Pharmacol Ther 2013;26(4):430–437; doi: 10.1016/j.pupt.2012.06.002;

198. Chen Y, Rennie D, Cormier YF, et al. Waist circumference is associated with pulmonary function in normal-weight, overweight, and obese subjects. Am J Clin Nutr 2007;85(1):35–39; doi: 10.1093/ajcn/85.1.35;

199. Vatrella A, Calabrese C, Mattiello A, et al. Abdominal adiposity is an early marker of pulmonary function impairment: Findings from a Mediterranean Italian female cohort. Nutr Metab Cardiovasc Dis 2016;26(7):643–648; doi: 10.1016/j.numecd.2015.12.013;
200. Goto Y, Yokokawa H, Fukuda H, et al. Body mass index and waist circumference are independent risk factors for low vital capacity among Japanese participants of a health checkup: A single-institution cross-sectional study. Environ Health Prev Med 2015;20(2):108–115; doi: 10.1007/s12199-014-0431-5;
201. Fang Ning Ning,Wang Zhi-Hao,Li Shao-Hua, Ge Yu-Yan, Liu Xin, Sui Dong-Xin. Pulmonary Function in Metabolic Syndrome: A Meta-Analysis. Metabolic Syndrome and Related Disorders. 2022/12/01; doi: 10.1089/met.2022.0045;
202. Bae MS, Han JH, Kim JH, Kim YJ, Lee KJ, Kwon KY. The Relationship between Metabolic Syndrome and Pulmonary Function. Korean J Fam Med. 2012 Mar;33(2):70-8. doi: 10.4082/kjfm.2012.33.2.70;
203. Lin WY, Yao CA, Wang HC, Huang KC. Impaired lung function is associated with obesity and metabolic syndrome in adults. Obesity (Silver Spring). 2006 Sep;14(9):1654-61. doi: 10.1038/oby.2006.190;
204. Rogliani P, Curradi G, Mura M, Lauro D, Federici M, Galli A, Saltini C, Cazzola M. Metabolic syndrome and risk of pulmonary involvement. Respir Med. 2010 Jan;104(1):47-51. doi: 10.1016/j.rmed.2009.08.009;
205. Molina-Luque R, Romero-Saldaña M, Álvarez-Fernández C, Rodríguez-Guerrero E, Hernández-Reyes A, Molina-Recio G. Waist to Height Ratio and Metabolic Syndrome as lung dysfunction predictors. Sci Rep. 2020 Apr 29;10(1):7212. doi: 10.1038/s41598-020-64130-0;
206. Willemien Thijs, Reza Alizadeh Dehnavi, Pieter S. Hiemstra, Albert de Roos, Christian F. Melissant, Kirsten Janssen, Jouke T. Tamsma, Klaus F. Rabe, Association of lung function measurements and visceral fat in men with metabolic syndrome, Respiratory Medicine, Volume 108, Issue 2, 2014, Pages 351-357, ISSN 0954-6111. https://doi.org/10.1016/j.rmed.2013.10.003;
207. Lee, YY., Tsao, YC., Yang, CK. et al. Association between risk factors of metabolic syndrome with lung function. Eur J Clin Nutr **74**, 811–817 (2020). https://doi.org/10.1038/s41430-018-0369-6;
208. Viviane Soares, Patrícia Espíndola Mota Venâncio, Ivan Silveira de Avelar, Neidiane Rosa Trindade, Grassyara Pinho Tolentino, Maria Sebastiana Silva, Metabolic syndrome impact on pulmonary function of women, Diabetes & Metabolic Syndrome: Clinical Research & Reviews, Volume 13, Issue 1, 2019, Pages 630-635, ISSN 1871-4021, https://doi.org/10.1016/j.dsx.2018.11.044;
209. Forno E, Han YY, Mullen J, Celedón JC. Overweight, Obesity, and Lung Function in Children and Adults-A Meta-analysis. J Allergy Clin Immunol Pract. 2018 Mar-Apr;6(2):570-581.e10. doi: 10.1016/j.jaip.2017.07.010;
210. Bickler PE, Buck LT. Hypoxia tolerance in reptiles, amphibians, and fishes: life with variable oxygen availability. Annu Rev Physiol. 2007;69:145-70. doi: 10.1146/annurev.physiol.69.031905.162529;
211. Meerson FZ. Adaptation, stress and prophylaxis. Berlin: Springer-Verlag; 1984. 329;
212. Hochachka PW. Mechanism and evolution of hypoxia-tolerance in humans. J Exp Biol. 1998 Apr;201(Pt 8):1243-54. doi: 10.1242/jeb.201.8.1243;
213. Meerson FZ, Pshennikova MG, Malyshev IYu. Adaptive defense of the organism. Architecture of the structural trace and cross protective effects of adaptation. Ann N Y Acad Sci. 1996 Sep 30;793:371-85. doi: 10.1111/j.1749-6632.1996.tb33529.x;
214. Rybnikova EA, Samoilov MO, Mironova VI, Tyul'kova EI, Pivina SG, Vataeva LA, Ordyan NE, Abritalin EY, Kolchev AI. The possible use of hypoxic preconditioning for the

prophylaxis of post-stress depressive episodes. Neurosci Behav Physiol. 2008 Sep;38(7):721-6. doi: 10.1007/s11055-008-9038-x;

215. Gonzalez-Rothi EJ, Lee KZ, Dale EA, Reier PJ, Mitchell GS, Fuller DD. Intermittent hypoxia and neurorehabilitation. J Appl Physiol (1985). 2015 Dec 15;119(12):1455-65. doi: 10.1152/japplphysiol.00235.2015;
216. Meerson FZ, Ustinova EE, Manukhina EB. Prevention of cardiac arrhythmias by adaptation to hypoxia: regulatory mechanisms and cardiotropic effect. Biomed Biochim Acta. 1989;48(2-3):S83-8;
217. Serebrovskaya TV, Karaban IN, Kolesnikova EE, Mishunina TM, Kuzminskaya LA, Serbrovsky AN, Swanson RJ. Human hypoxic ventilatory response with blood dopamine content under intermittent hypoxic training. Can J Physiol Pharmacol. 1999 Dec;77(12):967-73;
218. Serebrovskaya TV. Intermittent hypoxia research in the former soviet union and the commonwealth of independent States: history and review of the concept and selected applications. High Alt Med Biol. 2002 Summer;3(2):205-21. doi: 10.1089/15270290260131939;
219. Semenza GL. HIF-1: mediator of physiological and pathophysiological responses to hypoxia. J Appl Physiol (1985). 2000 Apr;88(4):1474-80. doi: 10.1152/jappl.2000.88.4.1474;
220. Corrado C, Fontana S. Hypoxia and HIF Signaling: One Axis with Divergent Effects. Int J Mol Sci. 2020 Aug 5;21(16):5611. doi: 10.3390/ijms21165611;
221. Rybnikova EA, Nalivaeva NN, Zenko MY, Baranova KA. Intermittent Hypoxic Training as an Effective Tool for Increasing the Adaptive Potential, Endurance and Working Capacity of the Brain. Front Neurosci. 2022 Jun 21;16:941740. doi: 10.3389/fnins.2022.941740;
222. Jenkins DR. Dressing for Altitude: US Aviation Pressure Suits, Wiley Post to Space Shuttle. Washington, DC: NASA SP; 2012;
223. Saxena K, Jolly MK. Acute vs. Chronic vs. Cyclic Hypoxia: Their Differential Dynamics, Molecular Mechanisms, and Effects on Tumor Progression. Biomolecules. 2019 Aug 3;9(8):339. doi: 10.3390/biom9080339;
224. Navarrete-Opazo A, Mitchell GS. Therapeutic potential of intermittent hypoxia: a matter of dose. Am J Physiol Regul Integr Comp Physiol. 2014 Nov 15;307(10):R1181-97. doi: 10.1152/ajpregu.00208.2014;
225. Serebrovskaya TV, Xi L. Intermittent hypoxia training as non-pharmacologic therapy for cardiovascular diseases: Practical analysis on methods and equipment. Exp Biol Med (Maywood). 2016 Sep;241(15):1708-23. doi: 10.1177/1535370216657614;
226. Sazontova TG, Stryapko NV, Arkhipenko YV. Addition of Hyperoxic Component to Adaptation to Hypoxia Prevents Impairments Induced by Low Doses of Toxicants (Free Radical Oxidation and Proteins of HSP Family). Bull Exp Biol Med. 2016 Jan;160(3):304-7. doi: 10.1007/s10517-016-3157-0;
227. Welch JF, Nair J, Argento PJ, Mitchell GS, Fox EJ. Acute intermittent hypercapnic-hypoxia elicits central neural respiratory motor plasticity in humans. J Physiol. 2022 May;600(10):2515-2533. doi: 10.1113/JP282822;
228. Ling Q, Sailan W, Ran J, Zhi S, Cen L, Yang X, Xiaoqun Q. The effect of intermittent hypoxia on bodyweight, serum glucose and cholesterol in obesity mice. Pak J Biol Sci. 2008 Mar 15;11(6):869-75. doi: 10.3923/pjbs.2008.869.875;
229. Steinback CD, Poulin MJ. Influence of Hypoxia on Cerebral Blood Flow Regulation in Humans. Adv Exp Med Biol. 2016;903:131-44. doi: 10.1007/978-1-4899-7678-9_9;
230. Li G, Zhang T, Chen X, Shang C, Wang Y. Effect of intermittent hypoxic training on hypoxia tolerance based on brain functional connectivity. Physiol Meas. 2016 Dec;37(12):2299-2316. doi: 10.1088/1361-6579/37/12/2299;

231. Manukhina EB, Downey HF, Shi X, Mallet RT. Intermittent hypoxia training protects cerebrovascular function in Alzheimer's disease. Exp Biol Med (Maywood). 2016 Jun;241(12):1351-63. doi: 10.1177/1535370216649060;
232. Ryou MG, Chen X, Cai M, Wang H, Jung ME, Metzger DB, Mallet RT, Shi X. Intermittent Hypoxia Training Prevents Deficient Learning-Memory Behavior in Mice Modeling Alzheimer's Disease: A Pilot Study. Front Aging Neurosci. 2021 Jul 1;13:674688. doi: 10.3389/fnagi.2021.674688;
233. Camacho-Cardenosa A, Camacho-Cardenosa M, Brooks D, Timón R, Olcina G, Brazo-Sayavera J. Effects training in hypoxia on cardiometabolic parameters in obese people: A systematic review of randomized controlled trial. Aten Primaria. 2019 Aug-Sep;51(7):397-405. doi: 10.1016/j.aprim.2018.03.011;
234. Serebrovska TV, Serebrovska ZO, Egorov E. Fitness and therapeutic potential of intermittent hypoxia training: a matter of dose. Fiziol Zh (1994). 2016;62(3):78-91. doi: 10.15407/fz62.03.078;
235. Serebrovskaya TV, Swanson RJ, Kolesnikova EE. Intermittent hypoxia: mechanisms of action and some applications to bronchial asthma treatment. J Physiol Pharmacol. 2003 Sep;54 Suppl 1:35-41;
236. Basovich SN. Trends in the use of preconditioning to hypoxia for early prevention of future life diseases. Biosci Trends. 2013 Feb;7(1):23-32;
237. Arkhipenko YV, Sazontova TG, Zhukova AG. Adaptation to periodic hypoxia and hyperoxia improves resistance of membrane structures in heart, liver, and brain. Bull Exp Biol Med. 2005 Sep;140(3):278-81. doi: 10.1007/s10517-005-0466-0;
238. Serebrovska TV, Grib ON, Portnichenko VI, Serebrovska ZO, Egorov E, Shatylo VB. Intermittent Hypoxia/Hyperoxia Versus Intermittent Hypoxia/Normoxia: Comparative Study in Prediabetes. High Alt Med Biol. 2019 Dec;20(4):383-391. doi: 10.1089/ham.2019.0053;
239. Bestavashvili AA, Glazachev OS, Bestavashvili AA, Ines D, Suvorov AY, Vorontsov NV, Tuter DS, Gognieva DG, Yong Z, Pavlov CS,Glushenkov DV, Sirkina EA, Kaloshina IV, Kopylov PY. The effects of intermittent hypoxic–hyperoxic exposures on lipid profile and infammation in patients with metabolic syndrome. Front Cardiovasc Med. 2021. https://doi.org/10.3389/fcvm.2021.700826;
240. Mallet RT, Burtscher J, Gatterer H, Glazachev O, Millet GP, Burtscher M. Hyperoxia-enhanced intermittent hypoxia conditioning: mechanisms and potential benefits. Med Gas Res. 2024 Mar 20;14(3):127–9. doi: 10.4103/mgr.MEDGASRES-D-23-00046;
241. Uzun AB, Iliescu MG, Stanciu LE, Ionescu EV, Ungur RA, Ciortea VM, Irsay L, Motoașcă I, Popescu MN, Popa FL, Pazara L, Tofolean DE. Effectiveness of Intermittent Hypoxia-Hyperoxia Therapy in Different Pathologies with Possible Metabolic Implications. Metabolites. 2023 Jan 25;13(2):181. doi: 10.3390/metabo13020181;
242. Susta D, Glazachev OS, Zapara MA, Dudnik EN, Samartseva VG. Redox Homeostasis in Humans Exposed to Intermittent Hypoxia-Normoxia and to Intermittent Hypoxia-Hyperoxia. High Alt Med Biol. 2020 Mar;21(1):45-51. doi: 10.1089/ham.2019.0059;
243. Gonchar O, Mankovska I. Moderate hypoxia/hyperoxia attenuates acute hypoxia-induced oxidative damage and improves antioxidant defense in lung mitochondria. Acta Physiol Hung. 2012 Dec;99(4):436-46. doi: 10.1556/APhysiol.99.2012.4.8;
244. Glazachev O, Kopylov P, Susta D, Dudnik E, Zagaynaya E. Adaptations following an intermittent hypoxia-hyperoxia training in coronary artery disease patients: a controlled study. Clin Cardiol. 2017; 40(6): 370-376;
245. Bayer U, Likar R, Pinter G, et al. Intermittent hypoxic-hyperoxic training on cognitive performance in geriatric patients. Alzheimers Dement (N Y). 2017 Feb 8; 3(1): 114-122.doi:10.1016/j.trci.2017.01.002;

246. Dudnik E, Zagaynaya E, Glazachev OS, Susta D. Intermittent Hypoxia-Hyperoxia Conditioning Improves Cardiorespiratory Fitness in Older Comorbid Cardiac Outpatients Without Hematological Changes: A Randomized Controlled Trial. High Alt Med Biol. 2018 Dec;19(4):339-343. doi: 10.1089/ham.2018.0014;
247. Tuter DS, Kopylov PY, Syrkin AL, Glazachev OS, Komarov RN, Katkov AI et al . Intermittent systemic hypoxic–hyperoxic training for myocardial protection in patients undergoing coronary artery bypass surgery: first results from a single-centre, randomised controlled trial. Open Heart 2018 Nov 10; 5;
248. Serebrovska ZO, Serebrovska TV, Kholin VA, Tumanovska LV, Shysh AM, Pashevin DA et al. Intermittent hypoxia–hyperoxia training improves cognitive function and decreases circulating biomarkers of Alzheimer's disease in patients with mild cognitive impairment: a pilot study. Int J Mol Sci. 2019 Oct 30; 20(21): 5405;
249. Chen PW, Hsu CC, Lai LF, Chi CP, Yu SH. Effects of Hypoxia-Hyperoxia Preconditioning on Indicators of Muscle Damage After Acute Resistance Exercise in Male Athletes. Front Physiol. 2022 Apr 19; 13:824210. doi:10.3389/fphys.2022.824210;
250. Behrendt T, Bielitzki R, Behrens M, Glazachev OS, Schega L. Effects of Intermittent Hypoxia-Hyperoxia Exposure Prior to Aerobic Cycling Exercise on Physical and Cognitive Performance in Geriatric Patients-A Randomized Controlled Trial. Front Physiol. 2022 May 26; 13:899096. doi: 10.3389/fphys.2022.899096;
251. Bestavashvili A, Glazachev O, Ibragimova S, Suvorov A, Bestavasvili A, Ibraimov S, Zhang X, Zhang Y, Pavlov C, Syrkina E, Syrkin A, Kopylov P. Impact of Hypoxia-Hyperoxia Exposures on Cardiometabolic Risk Factors and TMAO Levels in Patients with Metabolic Syndrome. Int J Mol Sci. 2023 Sep 24;24(19):14498. doi: 10.3390/ijms241914498;
252. Doehner W, Fischer A, Alimi B, Muhar J, Springer J, Altmann C, Schueller PO. Intermittent Hypoxic-Hyperoxic Training During Inpatient Rehabilitation Improves Exercise Capacity and Functional Outcome in Patients With Long Covid: Results of a Controlled Clinical Pilot Trial. J Cachexia Sarcopenia Muscle. 2024 Dec;15(6):2781-2791. doi: 10.1002/jcsm.13628;
253. Bischoff SC, Schweinlin A. Obesity therapy. Clin Nutr ESPEN. 2020 Aug;38:9-18. doi: 10.1016/j.clnesp.2020.04.013;
254. Behrendt T, Bielitzki R, Behrens M, Herold F, Schega L. Effects of Intermittent Hypoxia-Hyperoxia on Performance- and Health-Related Outcomes in Humans: A Systematic Review. Sports Med Open. 2022 May 31;8(1):70. doi: 10.1186/s40798-022-00450-x;
255. Ma LL, Wang YY, Yang ZH, Huang D, Weng H, Zeng XT. Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: what are they and which is better? Mil Med Res. 2020 Feb 29;7(1):7. doi: 10.1186/s40779-020-00238-8;
256. Parums DV. Editorial: The 2024 Revision of the Declaration of Helsinki and its Continued Role as a Code of Ethics to Guide Medical Research. Med Sci Monit. 2024 Dec 1;30:e947428. doi: 10.12659/MSM.947428;
257. Ma WY, Yang CY, Shih SR, Hsieh HJ, Hung CS, Chiu FC, Lin MS, Liu PH, Hua CH, Hsein YC, Chuang LM, Lin JW, Wei JN, Li HY. Measurement of Waist Circumference: midabdominal or iliac crest? Diabetes Care. 2013 Jun;36(6):1660-6. doi: 10.2337/dc12-1452;
258. Flegal KM. Waist circumference of healthy men and women in the United States. Int J Obes (Lond). 2007 Jul;31(7):1134-9. doi: 10.1038/sj.ijo.0803566;
259. Jaeschke L, Steinbrecher A, Pischon T. Measurement of waist and hip circumference with a body surface scanner: feasibility, validity, reliability, and correlations with markers of the metabolic syndrome. PLoS One. 2015 Mar 6;10(3):e0119430. doi: 10.1371/journal.pone.0119430;

260. Molarius A, Seidell JC, Sans S, Tuomilehto J, Kuulasmaa K. Waist and hip circumferences, and waist-hip ratio in 19 populations of the WHO MONICA Project. Int J Obes Relat Metab Disord. 1999 Feb;23(2):116-25. doi: 10.1038/sj.ijo.0800772;
261. Burton RF. The waist-hip ratio: a flawed index. Ann Hum Biol. 2020 Dec;47(7-8):629-631. doi: 10.1080/03014460.2020.1820079;
262. Bramhankar M, Pandey M, Rana GS, Rai B, Mishra NL, Shukla A. An assessment of anthropometric indices and its association with NCDs among the older adults of India: evidence from LASI Wave-1. BMC Public Health. 2021 Jul 9;21(1):1357. doi: 10.1186/s12889-021-11421-4;
263. Todea DA. Tratat de pneumologie. Cluj-Napoca: Școala Ardeleană; 2023;
264. https://www.beurer.ro/beurer-po-30-pulsoximetru-beurer_584.html?srsltid=AfmBOoqiFW_Ed8S5lKxA_TDU_Gd2dRtZyVZE8u2_-7IB_SqzZr6_6aql;
265. https://neomed.ro/tensiometre-manuale/226-tensiometru-mecanic-moretti-cu-manometru-la-para-cromat-dm345.html;
266. https://www.btl.ro/spirometry;
267. https://www.physiomed.ro/category/fizioterapie/hipoxie/;
268. CellOxy - Manual de utilizare;
269. Jaba E., Grama A., Analiza statistică cu SPSS sub Windows, Ed. Polirom, Iaşi, 2004;
270. Petcu, L.C., Statistică în SPSS-Note de Curs, Ed. Ovidius University Press, Constanţa, 2001;
271. Begu, L., Statistică şi software statistic, Ed. Clauet, Bucureşti, 1999;
272. https://ro.scribd.com/document/58561896/chestionar-obezitate;
273. Hinkle DE, Wiersma W, JUrs SG. Applied statistics for the behavioral sciences. Boston: Houghton Mifflin; 1988, p 118;
274. Jura M, Kozak LP. Obesity and related consequences to ageing. Age (Dordr). 2016 Feb;38(1):23. doi: 10.1007/s11357-016-9884-3;
275. Kapoor N, Arora S, Kalra S. Gender Disparities in People Living with Obesity - An Unchartered Territory. J Midlife Health. 2021 Apr-Jun;12(2):103-107. doi: 10.4103/jmh.jmh_48_21;
276. Cohen SA, Greaney ML, Sabik NJ. Assessment of dietary patterns, physical activity and obesity from a national survey: Rural-urban health disparities in older adults. PLoS One. 2018 Dec 5;13(12):e0208268. doi: 10.1371/journal.pone.0208268;
277. Yang HL, Tao YW, Cheng SM, Tang XQ, Cao JY, Shen DF. The effect of retirement on obesity in women: Evidence from China. SSM Popul Health. 2023 Mar 16;22:101379. doi: 10.1016/j.ssmph.2023.101379;
278. Ortiz GU, Lopes da Silva LS, da Silva Gonçalves L, Abud GF, Rossini Venturini AC, Ramos da Silva AS, Cristini de Freitas E. The association between body mass index, waist circumference and waist-to-hip-ratio with all-cause mortality in older adults: A systematic review. Clin Nutr ESPEN. 2025 Jun;67:493-509. doi: 10.1016/j.clnesp.2025.03.051;
279. Kim Y. The effects of smoking, alcohol consumption, obesity, and physical inactivity on healthcare costs: a longitudinal cohort study. BMC Public Health. 2025 Mar 5;25(1):873. doi: 10.1186/s12889-025-22133-4;
280. Dare S, Mackay DF, Pell JP. Relationship between smoking and obesity: a cross-sectional study of 499,504 middle-aged adults in the UK general population. PLoS One. 2015 Apr 17;10(4):e0123579. doi: 10.1371/journal.pone.0123579. Erratum in: PLoS One. 2017 Feb 8;12(2):e0172076. doi: 10.1371/journal.pone.0172076;
281. Golzarand M, Salari-Moghaddam A, Mirmiran P. Association between alcohol intake and overweight and obesity: a systematic review and dose-response meta-analysis of 127

observational studies. Crit Rev Food Sci Nutr. 2022;62(29):8078-8098. doi: 10.1080/10408398.2021.1925221;

282. Forero AY, Morales GE, Forero LC. Relationship between physical activity, sedentarism and obesity in adults, Colombia, 2015. Biomedica. 2023 Dec 29;43(Sp. 3):99-109. English, Spanish. doi: 10.7705/biomedica.7014;

283. Serebrovska TV, Portnychenko AG, Drevytska TI, Portnichenko VI, Xi L, Egorov E, Gavalko AV, Naskalova S, Chizhova V, Shatylo VB. Intermittent hypoxia training in prediabetes patients: Beneficial effects on glucose homeostasis, hypoxia tolerance and gene expression. Exp Biol Med (Maywood). 2017 Sep;242(15):1542-1552. doi: 10.1177/1535370217723578;

284. Bestavashvili A, Glazachev O, Bestavashvili A, Suvorov A, Zhang Y, Zhang X, Rozhkov A, Kuznetsova N, Pavlov C, Glushenkov D, Kopylov P. Intermittent Hypoxic-Hyperoxic Exposures Effects in Patients with Metabolic Syndrome: Correction of Cardiovascular and Metabolic Profile. Biomedicines. 2022 Feb 28;10(3):566. doi: 10.3390/biomedicines10030566;

285. Murugan AT, Sharma G: Obesity and respiratory diseases. Chron Respir Dis. 2008, 5:233-42. 10.1177/1479972308096978;

286. Vogtel M, Michels A. Role of intermittent hypoxia in the treatment of bronchial asthma and chronic obstructive pulmonary disease. Curr Opin Allergy Clin Immunol. 2010 Jun;10(3):206-13. doi: 10.1097/ACI.0b013e32833903a6;

287. Uzun AB, Nedelcu AD, Stanciu LE, Iliescu MG, Tofolean DE. Impact of intermittent hypoxia-hyperoxia therapy in COPD patients – pilot study. ARS Medica Tomitana. 2023; 29(1):18-24. doi:10.2478/arsm-2023-0004;

288. Masciocchi E, Maltais M, Rolland Y, Vellas B, de Souto Barreto P. Time Effects on Physical Performance in Older Adults in Nursing Home: A Narrative Review. J Nutr Health Aging. 2019;23(6):586-594. doi: 10.1007/s12603-019-1199-5;

289. Dutra MC, Uliano EJ, Machado DF, Martins T, Schuelter-Trevisol F, Trevisol DJ. Assessment of kidney function in the elderly: a population-based study. J Bras Nefrol. 2014 Jul-Sep;36(3):297-303. English, Portuguese. doi: 10.5935/0101-2800.20140043;

290. Scheen AJ. Diabetes mellitus in the elderly: insulin resistance and/or impaired insulin secretion? Diabetes Metab. 2005 Dec;31 Spec No 2:5S27-5S34. doi: 10.1016/s1262-3636(05)73649-1;

291. Silva Junior GB, Bentes AC, Daher EF, Matos SM. Obesity and kidney disease. J Bras Nefrol. 2017 Mar;39(1):65-69. Portuguese, English. doi: 10.5935/0101-2800.20170011;

292. Fabbrini E, Sullivan S, Klein S. Obesity and nonalcoholic fatty liver disease: biochemical, metabolic, and clinical implications. Hepatology. 2010 Feb;51(2):679-89. doi: 10.1002/hep.23280;

293. Nassir F, Rector RS, Hammoud GM, Ibdah JA. Pathogenesis and Prevention of Hepatic Steatosis. Gastroenterol Hepatol (N Y). 2015 Mar;11(3):167-75;

294. Park S, Lee S, Kim Y, Lee Y, Kang MW, Kim K, Kim YC, Han SS, Lee H, Lee JP, Joo KW, Lim CS, Kim YS, Kim DK. Causal linkage between adult height and kidney function: An integrated population-scale observational analysis and Mendelian randomization study. PLoS One. 2021 Jul 29;16(7):e0254649. doi: 10.1371/journal.pone.0254649;

295. Mao T, He Q, Yang J, Jia L, Xu G. Relationship between gout, hyperuricemia, and obesity-does central obesity play a significant role?-a study based on the NHANES database. Diabetol Metab Syndr. 2024 Jan 22;16(1):24. doi: 10.1186/s13098-024-01268-1;

296. Shen W, Punyanitya M, Chen J, Gallagher D, Albu J, Pi-Sunyer X, Lewis CE, Grunfeld C, Heshka S, Heymsfield SB. Waist circumference correlates with metabolic syndrome indicators better than percentage fat. Obesity (Silver Spring). 2006 Apr;14(4):727-36. doi: 10.1038/oby.2006.83;

297. Ali N, Sumon AH, Fariha KA, Asaduzzaman M, Kathak RR, Molla NH, Mou AD, Barman Z, Hasan M, Miah R, Islam F. Assessment of the relationship of serum liver enzymes activity with general and abdominal obesity in an urban Bangladeshi population. Sci Rep. 2021 Mar 23;11(1):6640. doi: 10.1038/s41598-021-86216-z;
298. Blaha MJ, Gebretsadik T, Shintani A, Elasy TA. Waist circumference, not the metabolic syndrome, predicts glucose deterioration in type 2 diabetes. Obesity (Silver Spring). 2008 Apr;16(4):869-74. doi: 10.1038/oby.2008.12;
299. Oh H, Quan SA, Jeong JY, Jang SN, Lee JE, Kim DH. Waist circumference, not body mass index, is associated with renal function decline in korean population: hallym aging study. PLoS One. 2013;8(3):e59071. doi: 10.1371/journal.pone.0059071;
300. Ma W, Zhu H, Yu X, Zhai X, Li S, Huang N, Liu K, Shirai K, Sheerah HA, Cao J. Association between android fat mass, gynoid fat mass and cardiovascular and all-cause mortality in adults: NHANES 2003-2007. Front Cardiovasc Med. 2023 May 18;10:1055223. doi: 10.3389/fcvm.2023.1055223;
301. Munnangi S, Sundjaja JH, Singh K, et al. Placebo Effect. [Updated 2023 Nov 13]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan;
302. https://www2.esaote.com/ultrasound/ultrasound-system/mylab-x6/PowerBreathe - Manual de utilizare;
303. Fernández-Lázaro D, Gallego-Gallego D, Corchete LA, Fernández Zoppino D, González-Bernal JJ, García Gómez B, Mielgo-Ayuso J. Inspiratory Muscle Training Program Using the PowerBreath®: Does It Have Ergogenic Potential for Respiratory and/or Athletic Performance? A Systematic Review with Meta-Analysis. Int J Environ Res Public Health. 2021 Jun 22;18(13):6703. doi: 10.3390/ijerph18136703;
304. Yorke J, Khan N, Garrow A, Tyson S, Singh D, Vestbo J, Jones PW. Evaluation of the Individual Activity Descriptors of the mMRC Breathlessness Scale: A Mixed Method Study. Int J Chron Obstruct Pulmon Dis. 2022 Sep 15;17:2289-2299. doi: 10.2147/COPD.S372318;
305. https://tanita.com/products/rd-953pro?Color=White;
306. Kumar NV, Ismail MH, P M, M G, Tripathy M. Neck circumference and cardio-metabolic syndrome. J Clin Diagn Res. 2014 Jul;8(7):MC23-5. doi: 10.7860/JCDR/2014/8455.4641;
307. Blanco-Grau A, Gabriel-Medina P, Rodriguez-Algarra F, Villena Y, Lopez-Martínez R, Augustín S, Pons M, Cruz LM, Rando-Segura A, Enfedaque B, Riveiro M, Casis E, Ferrer-Costa R, Buti M, Rodriguez-Frias F. Assessing Liver Fibrosis Using the FIB4 Index in the Community Setting. Diagnostics (Basel). 2021 Nov 29;11(12):2236. doi: 10.3390/diagnostics11122236;
308. Agarwal AK, Raja A, Brown BD. Chronic Obstructive Pulmonary Disease [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan– [updated 2023 Aug 7; cited 2025 May 3];
309. Sarah Mathew M, M V, Saravanan K, Grace A, P A. Exploration of the Reasons for Poor Adherence Among Metabolic Syndrome Patients Attending a Tertiary Care Hospital in Tamil Nadu, India: A Mixed Method Study. Cureus. 2024 Nov 29;16(11):e74753. doi: 10.7759/cureus.74753;
310. Bartman CM, Awari DW, Pabelick CM, Prakash YS. Intermittent Hypoxia-Hyperoxia and Oxidative Stress in Developing Human Airway Smooth Muscle. Antioxidants (Basel). 2021 Aug 31;10(9):1400. doi: 10.3390/antiox10091400;
311. Smit C, De Hoogd S, Brüggemann RJM, Knibbe CAJ. Obesity and drug pharmacology: a review of the influence of obesity on pharmacokinetic and pharmacodynamic parameters. Expert Opin Drug Metab Toxicol. 2018 Mar;14(3):275-285. doi: 10.1080/17425255.2018.1440287;

312. Chen X, Orom H, Hay JL, Waters EA, Schofield E, Li Y, Kiviniemi MT. Differences in Rural and Urban Health Information Access and Use. J Rural Health. 2019 Jun;35(3):405-417. doi: 10.1111/jrh.12335;

313. Suiter SV, Meadows ML. Educational Attainment and Educational Contexts as Social Determinants of Health. Prim Care. 2023 Dec;50(4):579-589. doi: 10.1016/j.pop.2023.04.007;

314. Robards J, Evandrou M, Falkingham J, Vlachantoni A. Marital status, health and mortality. Maturitas. 2012 Dec;73(4):295-9. doi: 10.1016/j.maturitas.2012.08.007;

315. Genetic Alliance; The New York-Mid-Atlantic Consortium for Genetic and Newborn Screening Services. Understanding Genetics: A New York, Mid-Atlantic Guide for Patients and Health Professionals. Washington (DC): Genetic Alliance; 2009 Jul 8. APPENDIX B, FAMILY HISTORY IS IMPORTANT FOR YOUR HEALTH. Available from: https://www.ncbi.nlm.nih.gov/books/NBK115560/;

316. Semple S. Assessing occupational and environmental exposure. Occup Med (Lond). 2005 Sep;55(6):419-24. doi: 10.1093/occmed/kqi135;

317. Li B, Tang X, Le G. Dietary Habits and Metabolic Health. Nutrients. 2023 Sep 14;15(18):3975. doi: 10.3390/nu15183975;

318. Hernández-Rubio A, Sanvisens A, Bolao F, Cachón-Suárez I, Garcia-Martín C, Short A, Bataller R, Muga R. Prevalence and associations of metabolic syndrome in patients with alcohol use disorder. Sci Rep. 2022 Feb 16;12(1):2625. doi: 10.1038/s41598-022-06010-3;

319. Balhara YP. Tobacco and metabolic syndrome. Indian J Endocrinol Metab. 2012 Jan;16(1):81-7. doi: 10.4103/2230-8210.91197;

320. Li C, Tao T, Tang Y, Lu H, Zhang H, Li H, Liu X, Guan W, Niu Y. The association of psychological stress with metabolic syndrome and its components: cross-sectional and bidirectional two-sample Mendelian randomization analyses. Front Endocrinol (Lausanne). 2023 Dec 8;14:1212647. doi: 10.3389/fendo.2023.1212647;

321. Chomiuk T, Niezgoda N, Mamcarz A, Śliż D. Physical activity in metabolic syndrome. Front Physiol. 2024 Feb 19;15:1365761. doi: 10.3389/fphys.2024.1365761;

322. Nair GR, Jadhav SL, Palal D, Rathod H, Verma P, Bhawalkar J, Rathi MA, Ray S, Madamanchi D. The Role of Neck Circumference as a Screening Tool for Obesity in Female Adults: A Cross-Sectional Study in Western Maharashtra. Cureus. 2024 Jul 31;16(7):e65814. doi: 10.7759/cureus.65814;

323. Cui T, Yan BH, Liu Z, Yang H, Gyan M, Ma YX. Neck circumference: A valuable anthropometric measurement to detect metabolic syndrome among different age groups in China. Diabetes Metab Res Rev. 2018 Mar;34(3). doi: 10.1002/dmrr.2966;

324. Cameron AJ, Magliano DJ, Shaw JE, Zimmet PZ, Carstensen B, Alberti KG, Tuomilehto J, Barr EL, Pauvaday VK, Kowlessur S, Söderberg S. The influence of hip circumference on the relationship between abdominal obesity and mortality. Int J Epidemiol. 2012 Apr;41(2):484-94. doi: 10.1093/ije/dyr198;

325. Widjaja NA, Arifani R, Irawan R. Value of waist-to-hip ratio as a predictor of metabolic syndrome in adolescents with obesity. Acta Biomed. 2023 Jun 14;94(3):e2023076. doi: 10.23750/abm.v94i3.13755;

326. Janjic D. Obésité de type androïde et obésité de type gynoïde [Android-type obesity and gynecoid-type obesity]. Praxis (Bern 1994). 1996 Dec 3;85(49):1578-83. French. Erratum in: Schweiz Rundsch Med Prax 1997 Jan 28;86(5):149;

327. Almeda-Valdés P, Cuevas-Ramos D, Aguilar-Salinas CA. Metabolic syndrome and non-alcoholic fatty liver disease. Ann Hepatol. 2009;8 Suppl 1:S18-24;

328. Dixon AE, Peters U. The effect of obesity on lung function. Expert Rev Respir Med. 2018 Sep;12(9):755-767. doi: 10.1080/17476348.2018.1506331;

329. Amihăesei IC, Chelaru L. Metabolic syndrome a widespread threatening condition; risk factors, diagnostic criteria, therapeutic options, prevention and controversies: an overview. Rev Med Chir Soc Med Nat Iasi. 2014 Oct-Dec;118(4):896-900;
330. Uzun AB, Iliescu M, Stanciu LE, Nedelcu AD, Petcu A, Popescu MN, Beiu C, Petcu LC, Tofolean DE. The Impact of Intermittent Hypoxia-Hyperoxia Therapy on Metabolism and Respiratory System in Obese Patients as Part of Comprehensive Medical Rehabilitation. Cureus. 2024 Oct 14;16(10):e71501. doi: 10.7759/cureus.71501;
331. Matos Casano HA, Anjum F. Six-Minute Walk Test. [Updated 2023 Aug 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK576420/;
332. Wojan F, Stray-Gundersen S, Nagel MJ, Lalande S. Short exposure to intermittent hypoxia increases erythropoietin levels in healthy individuals. J Appl Physiol (1985). 2021 Jun 1;130(6):1955-1960. doi: 10.1152/japplphysiol.00941.2020;
333. Thomas ET, Guppy M, Straus SE, Bell KJL, Glasziou P. Rate of normal lung function decline in ageing adults: a systematic review of prospective cohort studies. BMJ Open. 2019 Jun 27;9(6):e028150. doi: 10.1136/bmjopen-2018-028150;
334. Ortiz A, Mattace-Raso F, Soler MJ, Fouque D. Ageing meets kidney disease. Nephrol Dial Transplant. 2023 Feb 28;38(3):523-526. doi: 10.1093/ndt/gfac199;
335. Kim IH, Kisseleva T, Brenner DA. Aging and liver disease. Curr Opin Gastroenterol. 2015 May;31(3):184-91. doi: 10.1097/MOG.0000000000000176;
336. Vespasiani-Gentilucci U, De Vincentis A, Ferrucci L, Bandinelli S, Antonelli Incalzi R, Picardi A. Low Alanine Aminotransferase Levels in the Elderly Population: Frailty, Disability, Sarcopenia, and Reduced Survival. J Gerontol A Biol Sci Med Sci. 2018 Jun 14;73(7):925-930. doi: 10.1093/gerona/glx126;
337. Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Rev Cardiol. 2018 Sep;15(9):505-522. doi: 10.1038/s41569-018-0064-2;
338. Aune D, Norat T, Vatten LJ. Body mass index and the risk of gout: a systematic review and dose-response meta-analysis of prospective studies. Eur J Nutr. 2014 Dec;53(8):1591-601. doi: 10.1007/s00394-014-0766-0;
339. El-Eshmawy MM. Impact of obesity on liver function tests: is nonalcoholic fatty liver disease the only player? A review article. Porto Biomed J. 2023 Oct 16;8(5):e228. doi: 10.1097/j.pbj.0000000000000228;
340. Oeser A, Chung CP, Asanuma Y, Avalos I, Stein CM. Obesity is an independent contributor to functional capacity and inflammation in systemic lupus erythematosus. Arthritis Rheum. 2005 Nov;52(11):3651-9. doi: 10.1002/art.21400;
341. Perswani P, Ismail SM, Mumtaz H, Uddin N, Asfand M, Khalil ABB, Ijlal A, Khan SE, Usman M, Younas H, Rai A. Rethinking HDL-C: An In-Depth Narrative Review of Its Role in Cardiovascular Health. Curr Probl Cardiol. 2024 Feb;49(2):102152. doi: 10.1016/j.cpcardiol.2023.102152;
342. Zhou Y, Xuan YJ, Yang LS, Rutayisire E, Zhang LJ, Xuan P, Tao XY, Sheng J, Tao FB, Wang SF. Weight changes since age 20 and cardiovascular risk factors in a middle-aged Chinese population. J Public Health (Oxf). 2018 Jun 1;40(2):253-261. doi: 10.1093/pubmed/fdx057;
343. Gordon T. Factors associated with serum alkaline phosphatase level. Arch Pathol Lab Med. 1993 Feb;117(2):187-90;
344. Rachubińska K, Mińko A, Rotter I, Sołek-Pastuszka J, Ustianowski P, Skonieczna-Żydecka K, Grochans E. The Association Between Obesity, Chronic Inflammation, Metabolic Disorders and Mood Disorders Among Patients up to 12 Months After Hospitalization for SARS-CoV-2. Diagnostics (Basel). 2024 Oct 23;14(21):2357. doi: 10.3390/diagnostics14212357;

345. Li Y, Yi S, Jiang W, Gong M. Exploring the Relationship Between Different Obesity Metabolism Indices and Hyperuricemia in Patients with Hypertension and Coronary Heart Disease. Diabetes Metab Syndr Obes. 2024 Oct 18;17:3817-3832. doi: 10.2147/DMSO.S491255;

346. Fahed G, Aoun L, Bou Zerdan M, Allam S, Bou Zerdan M, Bouferraa Y, Assi HI. Metabolic Syndrome: Updates on Pathophysiology and Management in 2021. Int J Mol Sci. 2022 Jan 12;23(2):786. doi: 10.3390/ijms23020786;

347. Chirapongsathorn S, Jinatongthai P, Sirichana S, Boonyavarakul A, Treeprasertsuk S, Sansanayudh N. Correlation between neck circumference and hepatic steatosis determined by controlled attenuation parameter. Clin Obes. 2024 Jun;14(3):e12647. doi: 10.1111/cob.12647;

348. Zhao X, Song B, Yao T, Fan H, Liu T, Gao G, Wang K, Lu W, Liu C. Waist circumference glucose, a novel and effective predictor of type 2 diabetes: a prospective cohort study. Front Endocrinol (Lausanne). 2024 Jul 29;15:1427785. doi: 10.3389/fendo.2024.1427785;

349. Ferhatbegović L, Mršić D, Kušljugić S, Pojskić B. LDL-C: The Only Causal Risk Factor for ASCVD. Why Is It Still Overlooked and Underestimated? Curr Atheroscler Rep. 2022 Aug;24(8):635-642. doi: 10.1007/s11883-022-01037-3;

350. Heitmann BL, Frederiksen P, Lissner L. Hip circumference and cardiovascular morbidity and mortality in men and women. Obes Res. 2004 Mar;12(3):482-7. doi: 10.1038/oby.2004.54.