Cardiovascular and Metabolic Science www.ancam.org.mx

Editorial statement

Vol. 36 No. 3
July-September 2025

In search of an operational and science-based definition of obesity, a multifaceted and complex global health threat

En busca de una definición operativa y científica de la obesidad, una amenaza multifacética y compleja para la salud mundial

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Abbreviations:
AC = Alternating Current
ADP = Air Displacement Plethysmography
ASCVD = Atherosclerotic Cardiovascular Diseases
BFM = Body Fat Percentage
BIA = Bioelectrical Impedance Analysis
BMI = Body Mass Index
DM2 = type 2 Diabetes Mellitus
DXA = Dual-Energy X-ray Absorptiometry
HBP = High Blood Pressure

Obesity, one of the leading health problems worldwide, is not only a severe and disabling systemic disease itself, but also a significant risk factor for other threatening conditions, such as type 2 diabetes mellitus (DM2), high blood pressure (HBP), atherosclerotic cardiovascular diseases (ASCVD), and a cluster of many other health problems, including diverse mental and behavioral disorders. Due to its inherent complexity, multiple interconnections with various physiological and structural abnormalities, intertwining with psychological, socioeconomic, and environmental factors, and intricate origin, obesity is a poorly understood entity from genetic, social, nutritional, pathophysiological, anthropometric, psychological, and clinical perspectives. Science and scientific medicine require absolute precision and clarity in their terminology. Through its language, medical science unambiguously marks the nature and limits of the phenomena it scrutinizes, standardizes applicable terminology, and ensures the replicability of data obtained in research. This research, validating or rejecting conclusions drawn in independent studies. Obesity is apparently easily diagnosed to the point that a layperson can, in most cases, simply by looking at people, perceive whether they are obese. However, the matter is somewhat more complicated. Attempts to define and categorize obesity date back a long time. For example, Galen (129-216),[1] categorized corpulence into εὐσαρκία (*eusarkia*, literally «good fleshiness»), *παχύς* (*pachýs*, fat), εφσαρκος (*efsarko*, fleshy), and πολυσαρκο (*polisarko*, very fleshy),[2,3] simply by observation, without any objective measure of body mass. Together with him, several Greek and Roman physicians considered obesity an unhealthy condition and recommended a balanced diet and regular exercise to combat it,[1] as we still do today.

The Belgian scholar and statistician Lambert Adolphe Jacques Quetelet was not interested in medicine or physiology, but rather in social and demographic studies. In the distant year of

How to cite: López-Dionicio YI, Lara-Padilla E, Guevara G, Amador-Jara DI, García-Rodríguez J, Martínez-Quintero F et al. In search of an operational and science-based definition of obesity, a multifaceted and complex global health threat. Cardiovasc Metab Sci. 2025; 36 (3): 133-141. https://dx.doi.org/10.35366/121366

1835, he introduced the ratio of weight divided by height squared as part of his impossible search for the physical characteristics of the «average man». Following this erroneous search for average anthropometric measurements (in contradiction with natural diversity and ethnic differences), when body weight balances became available, weight was the only parameter used to define obesity, comparing an individual's body weight against the average value for their age and gender in the population. It must be said that in the last decades of the 19th century and in the first half of the previous century, life insurance companies had been interested in identifying health factors associated with premature death, such as blood pressure and body weight. Before physiologists and physicians, it was life insurance merchants and statistical actuaries who first identified the death risk associated with hypertension and obesity. The so-called «reference values» for weight and height in both genders and several age groups were derived from data collected during medical examinations as part of the life insurance acquisition process. In this way, the now-discredited concept of «ideal weight» was employed, with longevity as the primary definition trait. These tables of reference values, which were carried out in the United States population, were used worldwide, regardless of nutritional, anthropometric, ethnic, and national differences.[4]

Ancel Keys, the giant of physiology and epidemiology, analyzing the data from his seminal Seven Countries Study,[5] discredited the use of the ratio of weight to height to diagnose obesity and proposed Quetelet's relationship between weight/height squared (renaming it as the body mass index, BMI) to define obesity. Based on these observations, the World Health Organization (WHO) defined obesity as «a chronic, complex disease characterized *by excessive fat deposits that can impair health*».[6] Additionally, the diagnosis of overweight and obesity is determined by measuring a person's weight and height and calculating the BMI: weight (kg) ÷ height^2 (m^2). *Table 1*[6,7] shows the WHO classification of underweight, «normal» or desirable corpulence, overweight and obesity.

These cutoff points were established in populations of European origin. However, some studies have shown that the cutoff thresholds for the onset of type 2 diabetes mellitus (DM2) differ across distinct ethnicities.[9] This fact is often overlooked when applying the method to other ethnic groups, such as Asians, Blacks, and Latin Americans, among others.

Table 1: Body mass index categories (World Health Organization).

Category	Value of BMI (kg/m^2)
Underweight	< 18.5
Desirable	18.5-24.9
Overweight	25.0-29.9
Obesity (grade)	
I	30.0-34.9
II	35.0-39.9
III (morbid or extreme obesity)	≥ 40

Adapted from: Purnell JQ.[8]

The BMI was rapidly accepted as a credible and affordable diagnostic tool for assessing obesity or underweight in clinical settings, but not without criticisms. For obscure reasons, Ancel Keys (1904-2004) has been and continues to be the target of scientific and vicious personal attacks.[10] His comprehensive Seven Countries Study and the BMI he introduced to medical research have been criticized, sometimes legitimately, but sometimes driven by personal aversion.[10]

To begin with, BMI is a marker of corpulence, and not of the fat mass, as admitted by Keys himself (that is, it does not differentiate fat from muscle or water compartments). Additionally, it does not distinguish between fat distribution around the waist or in the femoral and gluteal regions (the so-called android and gynecoid types of obesity; the former is more associated with abnormal lipid and carbohydrate metabolism). Furthermore, the BMI does not provide insight into body composition, particularly fat percentage, which is expected to become the gold standard for diagnosing obesity in the near future.[11] Clearly, in addition to estimating BMI, clinical anthropometry routines should incorporate

abdominal circumference measurements,[12] which, in general (excluding cases of pregnancy, ascites, large abdominal hernias, and tumors from within and outside the abdominal cavity), reflects well the amount of subcutaneous and intrabdominal fat. BMI has many virtues and advantages, despite its limitations, making it suitable for epidemiological, anthropometric, and population research, as well as for individual clinical nutrition guidance and follow-up. It can be quickly and easily calculated using weight and height, which are part of a standard clinical assessment routine. It is also deeply ingrained in the minds of physicians, nutritionists, dietitians, and physical trainers, as well as the public. Furthermore, despite its shortcomings, it has been extensively tested in numerous research studies where its close relationship with all-cause death rates, the risk of DM2, and the incidence of ASCVD outcomes (mainly, myocardial infarction, stroke, heart failure, and cardiovascular mortality) has been found.[13-20] Furthermore, it has high correlation coefficients when compared with measurements of fat mass and Body Fat Percentage (BFM) estimated by electrical bioimpedance.[21] Furthermore, BMI has a moderate correlation with Air Displacement Plethysmography (ADP), a sophisticated and reliable technique for measuring body fat.[22]

Over the past few years, our group has developed a definition of obesity that meets clinical criteria and it is based on proven scientific facts. *Obesity is a chronic, heterogeneous, relapsing, and progressing structural disease characterized by an excessive accumulation and abnormal distribution of body fat due to the loss of balance between caloric intake and energy expenditure. Its basic anatomical and structural alterations include hypertrophy, hyperplasia (or both) of adipocytes, frequently associated with other functional and anatomical alterations, such as ischemia, macrophage invasion and activation, and necrosis, apoptosis, and autophagy of the fat tissue. At the same time, it is often accompanied by resistance to insulin and secondary hyperinsulinism, inflammation, oxidative stress, and endothelial dysfunction. The last tetrad leads to the development of morbid conditions that affect the arteries and the parenchyma of multiple organs and systems, causing various complications and comorbidities, shortening life span, and seriously affecting its quality*.[23] An important subclass of this condition is abdominal obesity (characterized by an abdominal circumference of ≥ 80 cm in women and ≥ 90 cm in men[24]), which is well-known to be related to insulin resistance, and the so-called «metabolic syndrome», more appropriately named, dysmetabolic obesity. Other names for this condition include «central obesity», «android obesity», and «visceral obesity», among others.

According to the above, obesity is, essentially, an excess of fat mass. The challenges lie in defining «excess» and measuring it correctly, primarily in the daily clinical setting. It is known that body composition analysis, i.e., the percentage of corporeal mass of fat, is, so far, the better tool for that purpose.[25] An economical method for estimating body fat percentage was introduced in the 1970's and is based on measuring skinfold thickness at the chest, axilla, triceps, subscapular, and thigh sites with calipers.[26,27] Nevertheless, the procedure requires accredited training, is time-consuming, operator-dependent, and relies on comparing skinfold thickness results with body density and fat proportion obtained through the hydrostatic method of underwater weighing, which is based on Archimedes' principle.[28] The method has certain limitations, since the regression equations are specific to the population in which they were tested. In addition, while the slopes of the regression curves for different age and gender groups are similar, the intercepts differ.[28] For all the aforementioned reasons, this method is hardly suitable for use in an ordinary clinical setting. The other well-established method is Air Displacement Plethysmography. Unfortunately, although it is non-invasive and relatively easy to perform, it requires costly equipment that encloses the subject being studied immobile in an airtight chamber, which not everyone can tolerate or perform. Additionally, the results can be affected by the isothermal air close to or trapped in skin, hair, and loose clothing.[29]

Dual-Energy X-ray Absorptiometry (DXA) scan reveals well the fat content, its distribution, and bone density (in fact, it is the method used to analyze osteopenia or osteoporosis),

based on the different tissue absorption of two low-power X-ray beams.[30] The results are obtained by measuring the attenuation of the energy beam by the thickness and density of the body's various structures. This attenuation can differentiate between bone, fat, and lean (free-lipid soft tissue) masses. However, DXA does not directly measure body water. Another source of inaccuracy is the indirect analysis of soft tissue in pixels containing bone.[31] The exposure to ionizing radiation is not a problem because it is very low. However, the DXA machine's high price and bulky size make the method unusable in daily practice.

Bioelectrical Impedance Analysis (BIA) technology is another tool used in body composition analysis. The technique has gained popularity due to the portability and safety of BIA instruments. Unlike conventional scales that only measure weight, BIA scales utilize a low-intensity electric current to analyze the impedance of different body tissues, enabling the calculation of body composition. In basic physics, impedance is the combination of two phenomena: reactance and resistance.[32] The former is defined as the opposition of a capacitor to an alternating current (AC). A capacitor is a device that temporarily stores energy in an electric field by accumulating charges of opposite polarity on two conductors separated by an insulating material. The capacitor opposes a variable obstacle to the current flowing through it, especially at specific frequencies. Reactance increases when the frequency across the capacitor diminishes, and vice versa. In bioimpedance, the cell membrane, with a polar disposition of charges on either side, behaves as a capacitor. On the other hand, resistance is defined in physics as the opposition a material offers to the flow of electrons, according to its properties for electrical conduction (a conductor is a material that facilitates the transit of electrons, like copper or gold, while a resistor is a poor conductor, like glass or wood). Contrary to reactance, resistance remains constant despite the variations in the frequency of the AC signal. In bioimpedance, resistance is measured against the body's water and electrolytes, i.e., their capacity to conduct electricity,[33] while reactance refers to the opposition of the cell membranes to the flow of AC.

In conclusion, from a biophysical perspective, the term bioelectrical impedance refers to the behavior of tissues in response to an electric AC passing through them, encompassing the combined opposition to alternating electron flow across cell membranes and the intra- and extracellular fluid.

A low-voltage electric current through the trunk and the four extremities allows for analyzing the body compartments, including fat and free-fat masses, as well as bone, intracellular, and extracellular body water.[34] Although one of its first indications was measuring body water,[33] it subsequently extended its applications to analyze the composition of all the body compartments. Several BIA techniques are available, including those that utilize a single frequency and others that use multiple frequencies or an entire range of them (spectroscopy). Utilizing a broad-spectrum, multiple-frequency analysis differentiates the diverse body compartments more effectively.[35] In this way, BIA can discriminate between fat and free-fat masses based on the body compartments' different impedances.[36]

However, some shortcomings limit the certainty or applicability of this technique, starting with the considerable price of the most sophisticated BIA machines. Additionally, the equations used are based on assumptions derived from populations that differ in age, gender, clinical status, and ethnicity. Furthermore, hydration status can affect the accuracy of the assessment. Several studies comparing BIA and BMI for assessing obesity have found some differences between the two methods, but none are significant.[37] On the contrary, the correlation between BMI and fat content is around 0.8 or higher in both genders.[38] Also, BIA also has a good correlation with DXA (0.88 for both genders [0.78 in men, and 0.85 in women]).

In conclusion, there is no perfect or universally applicable technique for assessing obesity in the clinical setting. Nevertheless, these methods can be used in daily caregiving with an acceptable degree of certainty. However, due to their ease and economy, clinicians would often choose BMI calculations,

waist perimeter assessments, and body composition calculations obtained from relatively inexpensive impedance devices, despite evidence that these estimations are only approximations. A similar phenomenon occurs with blood pressure measurement. There are relatively significant differences between the actual blood pressure measured through a catheter or needle placed into a systemic artery and the indirectly estimated blood pressure with a mercury sphygmomanometer. Also, the blood pressure values measured by mercury and digital manometers differ.[39] And yet, these latest devices have simplified measurement and «democratized» their use to the point that these electronic manometers are now part of domestic technology. Serious therapeutic decisions are made daily, some of which have vital relevance, based on these measurements that only approximately reflect reality.

To further obscure an already confusing situation, recently, the Lancet Diabetes & Endocrinology,[40] a renowned medical journal, gathered an international, multidisciplinary group of 58 experts on obesity and formed one of its self-appointed commissions whose aims were: «*to establish objective criteria for disease diagnosis, aiding clinical decision making and prioritization of therapeutic interventions and public health strategies*».[40] The Commission was established with the assistance of the Institute of Diabetes, Endocrinology, and Obesity at King's Health Partners, a group dedicated to education and research, comprising King's College London and three trusts of the National Health Service in the United Kingdom. No other governmental or international health agency has endorsed the conclusions of this group to date. Notwithstanding, one acceptable recommendation (that most obesity study groups worldwide have been following for some time now) is that although BMI is not a perfect instrument, it remains a useful diagnostic tool, especially when it is complemented with the measure of the abdominal perimeter, waist-to-hip ratio, waist-height ratio, or direct body fat measure.[40] However, although the first three anthropometric measures have a close relationship with the presence of visceral fat and the abnormal distribution of fat mass, they do not reflect the total amount of adipose tissue, which is the key anatomical abnormality of obesity. In this context, the Commission recommends DXA fat measurement,[40] despite its cost and impracticality for daily clinical use. Surprisingly, BIA scales are not mentioned among the Commission's recommendations, even though they are currently increasingly accessible and are becoming standard devices in clinical practice.

Nevertheless, the confusing problem arises when the Lancet Commission categorizes obesity into two categories: «preclinical» and «clinical obesity», based on the presence or absence of clinical manifestations of organ compromise or disability.[41] What is «preclinical» obesity in the Commission proposal? The excess of adiposity, but without organ dysfunction.[41] As it is known, clinical diagnosis involves identifying a health condition (disease, syndrome, toxicity, or trauma/injury) using the clinical history and physical examination, maybe with the help of simple instruments like stethoscopes, diagnosis lamps, magnifying lens, wires for assessing sensitivity, weight balances, metric tapes, and the like, that do not substitute our sense organs but only amplify their capacity and certainty. A preclinical condition refers to a stage of health that precedes the onset of clinical symptoms and signs. To reveal these structural or functional anomalies, the use of devices that go beyond the reach of our senses is necessary: radiological or magnetic resonance imaging, electrocardiogram, ultrasound registers, functional tests, etc. So, if a frankly obese person feels well and does not have any objective or subjective manifestation of cardiovascular, metabolic, liver, or bone-arthro-muscular dysfunction, is not clinically obese despite weighing 100 kg, and having a BMI of 35 kg/m^2. In other words, from the medical point of view, obesity is always a clinical entity, because with ordinary, basic anthropometry (the simple inspection, a weight scale, a stadiometer, and a measuring tape), it is possible to establish the excess of adiposity with a high degree of certainty, even in borderline cases.

The presence of symptoms or signs is not necessarily related to the amount of adiposity because there are numerous phenotypic variants and chance associations with several

risk factors. Whether it is a special phenotype or simply an early, transitory state of the disease, there are cases of «healthy or metabolically healthy obesity» without any evidence of cardiometabolic dysfunction.[42] On the other hand, biological tolerance to adiposity is modified phenotypically, or if obesity is associated, for example, with diabetes, genetically determined lipid abnormalities, high blood pressure, or behavioral factors such as binge eating, emotional hunger, smoking, excess alcohol consumption, or sedentary behavior. To this basic term, obesity, several distinctive features can be added, such as «central, android or abdominal», «femoro-gluteal or gynecoid», «normometabolic or dysmetabolic», «complicated or non-complicated», and if obesity is associated with diabetes («diabesity»), among others.

Fortunately, entities that can only superficially cast doubt on the aforementioned concepts are rare. One such entity is lipodystrophy syndrome,[43] a heterogeneous set of congenital or acquired conditions characterized by partial or complete loss of fat tissue. This condition is accompanied by ectopic fat deposits in the liver, heart, pancreas, skeletal muscle, and other areas. In general, lipodystrophy is associated with severe insulin resistance and significant metabolic and cardiovascular complications. Paradoxically, in some varieties of partial lipodystrophy, the lack of fatty tissue in most body regions is associated with an abnormal accumulation of abdominal visceral fat. In those cases, the anthropometric diagnostic clue is the discrepancy between a low BMI and an expanded waist circumference. In any case, since lipodystrophy is a disorder of fat tissue, it is not a state of obesity, but rather the opposite.[44]

This definition of «entanglement» stems from the fact that the commissioners become embroiled in the outdated and, in our opinion, irrelevant debate about whether obesity is or is not a disease.[45,46] The classical definition of disease is any structural or functional alteration of an organ or part of a body system, resulting from genetic or developmental errors, metabolic disorders, infectious, parasitic, or toxic/poisonous factors, nutritional deficiencies or excesses, and traumatic or environmental causes.[45] A structural disease has specific macro- or microanatomic hallmark lesions, contrasting with a functional disease, which has only an abnormal function without specific anatomic alterations. Liver cirrhosis, myocardial infarction, and hypertrophic myocardial disease are examples of structural diseases, while fibromyalgia and anxiety are functional conditions. Symptoms and signs frequently accompany structural abnormalities, but sometimes, even during a considerable lapse, do not cause clinical manifestations. The increase in the size (thickness, length, or both) of left ventricular cardiac myocytes (hypertrophy), frequently accompanied by an increase in dense collagen in the extracellular matrix (dystrophy), defines myocardial hypertrophy. The disease is known as hypertrophic cardiomyopathy, leading to functional disorders like systolic or diastolic left ventricular dysfunction, which can remain asymptomatic for an extended period. To reveal its existence and assess its severity, paraclinical studies are required, including electrocardiograms, chest X-ray films, transthoracic echocardiograms, computed tomography scans, magnetic resonance images, and other diagnostic tests. Once the carrier of this condition experiences dyspnea or other clinical manifestations of cardiac dysfunction, they are in the clinical phase of the disease, suffering overt heart failure. Similarly, obesity is characterized by an expansion of fatty tissue, resulting from the hyperplasia or hypertrophy (or both) of adipocytes, a structural phenomenon. While the nutrient vessels of the fatty tissue (an angiogenesis phenomenon) increase proportionally to the fat expansion, there is no adipocyte dysfunction. Genetic and epigenetic influences partly determine the extension of the angiogenic phenomenon.[47] But, when growth exceeds the angiogenic capacity, ischemia of the fatty tissue develops, which in turn triggers the series of events that characterize anatomically and functionally the dysmetabolic obesity: local inflammation, recruitment and activation of macrophages, necrosis, apoptosis, autophagy of the fatty tissue, and a fibrous scar reaction. All these structural alterations are accompanied by systemic low-grade inflammation, insulin resistance/hyperinsulinemia, nitroxidative stress, and endothelial dysfunction, among

other functional disorders. Other structural abnormalities that occur when the balance between fatty tissue expansion and angiogenesis is disrupted include the deposition of fat in non-adipose tissues, such as striated muscle, heart, kidney, pancreas, brain, and others. Our group has coined the term extra-adipocyte lipothesaurosis (literally, fat storage), which is part of the physiologic and anatomical pathology of obesity. This abnormal structural fact is responsible for the production of toxic lipid metabolic byproducts, which damage the cell and lead to apoptosis (lipotoxicity).[48] All these abnormalities can be expressed in an abundant conjunction of symptoms and clinical signs, which are added to those that are due to the effect of obesity on the osteo-arthro-muscular complex, the nervous system and behavior, the skin, and the rest of the organs and systems of the body.

The Lancet Commission proposal offers no benefits in clarifying the basic conceptualization of this complex disease. Not only does it not help in the management of the entity, but it can also contribute to the obese patient not becoming aware of his illness and not actively collaborating with the interdisciplinary team (physicians, nutritionists, physical trainers, and psychologists) to control it. Telling obese persons that they are not obese (only «preclinical obese») and that they do not suffer from a disease, but only a risk factor, because there are no symptoms or disability, can lead to abandonment of diet, psychotherapy, or drug therapy.

To avoid blindly and uncritically following what is said or dictated in other latitudes, all those interested in obesity in our country should convene a meeting where we develop our concept of this disease and formulate clinical, preventive, and therapeutic recommendations for our community and health authorities.

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