“Metabolic Healthy Obesity” –a more balanced view on overnutrition

An expedition starting from the “Weight Paradigm,” with a short stopover at the “Mediterranean Diet,” a meeting with “you are not fat, you are beautiful,” and a short rest at “Health at Every Size”, to “Metabolic Healthy Obesity.”

Overnutrition is a meaningful evolutionary mechanism

Our evolutionary past troubles us with a major risk factor for non-communicable diseases (NCDs): Overnutrition. Overnutrition easily turns into obesity, and the condition is difficult to get rid of again. For instance, metabolic mechanisms of total energy expenditure (TEE) limit the chance of losing extra kilograms by exercise (1, 2). Without the ability to store energy as fat, our forefathers would not have survived periods of severe starvation. Evolution shaped our organism, assisting us in surviving a very harsh environment as hunters and gatherers. The species “homo” appeared some 4.2 million years ago, with Australopithecus anamnesis evolving, until “Homo sapiens” arrived on the scene around 300.000 years back.

“Nothing in biology makes sense except in the light of evolution,” so the title of a review paper from Dobzhansky (1973), a recognized geneticist (3). So, how come discrediting a meaningful, evolutionary process as a major risk factor for non-communicable diseases (NCDs) and death, and even using rigorous measures to control overnutrition and obesity. To deal with health risks by drastic means or even force has a diverse effect on the society, initiating resistance and refusing to comply.

The “struggle” against obesity

Circumstances containing the control of overnutrition and obesity are less overbearing than what is utilized by direct and indirect force for vaccination during the spread of “Covid-19”. Admittingly, the burden on the health delivery system caused by NCDs is a global health problem. Among other reasons, overnutrition and obesity are major driving forces for the worldwide expansion of “lifestyle diseases” (4). Overnutrition is recognized as an epidemic of global magnitude (5). To reduce overnutrition and obesity, widespread behavioral changes are necessary but difficult to achieve. A range of dietary intervention methods is worked out and based on several behavioral models (6). Several population-based dietary intervention projects were conducted with controversial results and lacking sustainability (7). An even more drastic attempt is the suggestion to change health behavior through price policies (8).

Attempts were made to address the problem of NCDs on the level of the United Nations (UN) and the World Health Organization (WHO). NCDs are included in the Sustainable Development Goals (SDGs) under number 3 (9), and a High-Level Meeting of the UN at New York addressed the problem in 2011. The meeting results were disappointing, and similarly, the SDGs targets are labeled “vague, weak or meaningless” (10).

Despite all efforts on the policy level, obesity and overweight remained to increase over the years. Most recent population surveys, such as from the UK, underlined the problematic situation. By investigating the data from 2.9 million persons, the Body Mass Index (BMI) over

24.9 kg/m^2, correlated with “twelve obesity-related outcomes” (11). The diseases and health-related factors included type 2 diabetes (T2D), osteoarthritis, cardiovascular disease, and increased mortality. The hazard ratio of a BMI of 40 kg/m^2 and higher amounted to 12.4 for T2D, 3.46 for heart failure, and 3.21 for hypertension, with very narrow confidence intervals (11). Results like this request countermeasures. Propagation of a desirable weight and body shape continues but with limited effect (12). The commercial sector stepped in (13), and specific dietary schemes developed as dogma for those wanting to reduce their weight.

The uprising of the frustrated

To control the weight is easy to call for but difficult for many. It is not uncommon that after tormenting oneself, finally accomplishing losing some kilograms, being discouraged after a short while by gaining those kilograms again or even exceeding the former overweight. The frustration results in reduced self-esteem or even eating disorders (14). Increasing awareness about the burden of “obesity-related costs” on the health delivery system adds to the danger of discrimination and stigmatization for a growing proportion of the overweight population (15).

As one could have expected, the repercussion surfaced. A debate developed about the individual's responsibility about weight and size, propelled forward by social media but less so from the medical sector (16, 17). The slogan “you are not fat, you are beautiful” is well known but not always appreciated. Groups of people started to meet, such as a “body-positive outdoor group” mentioned in a recent publication in science (18). In the USA, civil rights groups are active such as the “National Association to Advance Fat Acceptance” and the “Council on Size and Weight Discrimination” (19).

“Health at Every Size” (HAES)

The “weight-loss paradigm” advised everybody to be thin for good health and happiness. Those with overweight overeat and are too immobile. By dieting, everybody can be thin, happy, and healthy. Within the framework of medicine and public health, a paradigm shift was suggested, away from concentrating on weight toward “Health at Every Size” (HAES) (19-21). The HAES paradigm argued that neither thinness is necessarily healthy nor fat unhealthy and unappealing. People naturally have different body shapes and sizes, and dieting might even lead to weight gain and risk messing up eating habits. Mainly medical sociology was eager to support HAES, encouraging one to accept one own body as it is and rely on “internal regularly processes such as hunger and satiety.”

The concept was not outright rejected from the viewpoint of public health but requested “empirical evidence” that HEAS works on a population basis and voiced irritation about some sort of “ideological debate” (22). The critique to be too enthusiastic in promoting HEAS isn’t baseless. For instance, Bacon and Amphramor (2011) denigrated the result of an investigation showing that being overweight was associated with the increased risk of mortality by stating that this conclusion was only achieved by “restricting the analysis in excluding 78 percent of death” (19). It wasn’t mentioned that the investigation, published in the New England Journal of Medicine, investigated 1.46 million white adults, attempted to exclude the confounder of “smoking” from the result (23). To be strict in following one paradigm, rejecting an opposite

one, isn't very wise. It has been known for quite some time that overnutrition and obesity are severe risks for NCDs and mortality, but that doesn't hold for everyone being corpulent.

Where fat is stored matters – the Mediterranean Diet

It was recognized around 1960 that the dietary pattern of countries around the Mediterranean Sea caused fewer cardiovascular diseases than what was consumed in Northern Europe or the United States (24). The difference was the quality, not the quantity of food eaten. The calory intake was comparable. Ironically, it was Ancel Keys, together with his wife, who systematically started to study the health benefits of the Mediterranean diet (25). Keys, an outstanding scientist in physiology and nutrition, very much supported the weight and fat paradigm, exploring the connection of fat and cholesterol with cardiovascular diseases. He designed the diet for the American soldiers in World War II, and the Body Mass Index (BMI) can be tracked down to him. The Mediterranean diet is rich in vegetables, fruits, legumes, grains, and unsaturated fat such as olive oil (26). The latter, in the form of "extra virgin olive oil" (EVOO), is considered to be beneficial (27). The diet is associated with a "gynoid" body shape, the one observed more often in women and is negatively associated with risk factors for cardiovascular diseases (28, 29).

That body fat distribution relates to differences in health risks has been suspected for some time. The two main fat accumulation areas are over the stomach and the hips. Formerly called apple-, and pears shape, more professionally called gynoid and android fat distribution, and nowadays commonly addressed as visceral- and subcutaneous distribution. More recently, the difference in fat distribution in the body of males and females is of interest, and differences in dietary intake and the genetic influence on body fat distribution. Compared with Europeans, Asians have more, and Africans have less visceral fat. It could be that Asians might be more prone to type 2 diabetes mellitus (T2DM) compared to Africans and Europeans (30) since visceral fat stored in the abdomen is riskier for health compared to subcutaneous fat at thigs, arms, and the backside (31, 32).

Adipocytes come in different colors

The dissemination of fat at different positions and the kind of adipose tissue determines the nutritional status and health. Fat cells are called adipocytes. There are three types of fat tissue related to different functions, white, brown, and beige. White fatty tissue stores surplus energy. Clusters of small brown-like white adipocytes within the white fat tissue are described as beige adiposities. The brown adipose tissue (BAT), when activated, generates heat and mobilizes lipids and glucose, among other metabolizes (33).

Thinness is not necessarily healthy, and obesity is not always evil

The association of overnutrition and obesity with cardiovascular diseases and T2DM is more complex than previously thought. To gain weight might be even due to certain medications. A common drug to treat T2DM (thiazolidinediones) lets patients gain weight as subcutaneous fat but reduce insulin resistance (34, 35). Furthermore, thinness is not necessarily healthy. In an extensive metanalysis about all-cause mortality, grade 1 obesity (BMI 30 to <35) was not

associated with mortality, obesity 2 and 3 (BMI ≥35) significantly increased all-cause mortality, but overweight (25 to <30) reduced considerably all-cause mortality compared to normal weight (18.5 to <25) (36). However, a comment indicated that instead of categorizing weight by BMI groups, the use of continuous BMI variation and the effects of lifespan on mortality would be more valid (37). Nevertheless, lifestyle factors play a role as well. Not smoking, moderate alcohol intake, daily exercise for about half an hour, and a diet rich in vegetables and fruits could modify the risk pattern of overweight and obese individuals compared to normal weight persons (38). In clinical practice, patients turn up being overweight and even grossly obese without metabolic "disfunction" (18).

The "Metabolically Healthy Obesity"

Metabolic "disfunction" connects to factors itemized in the "metabolic syndrome" (39). Several studies related BMI categories to metabolic health (40), and the term "metabolic healthy obesity" (MHO) is now in use (41). However, there are various definitions of metabolic health (42). Even acknowledging that types of obesity are less harmful than others; still, the connection of obesity to diabetes, CVD, and many other diseases is evident. The results of the re-assessment of the "Nurses' Health Study" (NHS), a prospective cohort study, revealed that (43).

The "Nurses' Health Study" – characterization of MHO

The NHS recruited over 120 thousand female nurses aged 30 to 55. A self-administered questionnaire about lifestyle, health behavior, and medical history provided the information for the assessment. Follow-up questionnaires, exchanged by mail every two years, achieved a response rate of more than 90% (44). From 90.257 women, followed up from1980 to 2010, the incidence of cardiovascular diseases was recorded (43). BMI categories were related to metabolic health, as defined by an absence of diabetes, hypertension, and hypercholesterolemia. In addition, the change of the metabolic health status during follow-up was evaluated as well. Females with an MHO over the observation time still were at risk for cardiovascular diseases (CVD) compared with women with a healthy normal weight. However, the risk for the group with an MHO throughout 30 years was lower than those with MHO, who turned to develop "metabolic unhealthy obesity" (MUO) within the observation time. The initial MHO group converted to 84% to have MUO, while women initially being in a metabolic health status developed to 68% the risks of CVD. Particularly diabetes and hypertension increased the risk for CVD for the initially metabolic healthy women. For unhealthy metabolic women, the risk for CVD is high, regardless of their BMI.

Definition and prevalence of MHO

The results found by re-assessing the NHS point to two major aspects: MOH, even after being maintained for some time, still is a risk factor for CVD, and MHO tends to convert into MUO. Besides realizing the existence of MOH within the population, the extent of the condition is of interest as well. The spread out of MHO in the population depends on the definition of what it means to be metabolically healthy.

In proposing a new definition, two databases from major cohorts from the United States (US) (third National Health Examination Survey -NHAMES-III) and the United Kingdom (UK Biobank cohort) were utilized to quantify metabolically healthy and unhealthy people of different BMI categories (45). BMI categories comprised of normal weight (18.5-29.9), overweight (25.0-29.9), and obesity ($\geq$ 30.0). Besides BMI, waist circumference and waist-to-hip ratio, and blood pressure were included in the evaluation. Besides the biomarkers known from the "metabolic syndrome," Hemoglobin A_{1c} (HBA1c), Alanine aminotransferase, and gamma -Glutamyl transferase was also assessed. HBA1c was available only from the NHAMES-III study. A wide variety of baseline characteristics and behavioral determinants, such as medication, were considered too. Metabolic health was defined as a systolic blood pressure less than 130 mmHg, no blood pressure-lowering medication, no self-reported diabetes, and a waist-to-hip ratio less than 0.95 for women and less than 1.03 for men. The Cox proportional hazard regression was applied to associate total and CVD mortality with the independent variables.

The hazard ratio for blood pressure-lowering medication and CVD mortality was raised to be 2.41 (95% CI, 1.50-3.87) and for total mortality 2.05 (CI, 1.47-2.84). Also, diabetes and the combination of systolic blood pressure and the waist-for-hip ratio were significantly linked to CVD and total mortality. Compared with metabolically healthy normal weight, MHO was not associated with CVD and total mortality if BMI did not exceed 40 (45). The proportion of being metabolically healthy for the US cohort amounted to 80% for women and 75% for men in case of a normal weight, 56%, and 55% respectively for overnutrition, and 42% and 32% for obese people. For the UK cohort, the distribution of metabolically healthy people according to the different nutritional status was less favorable, probably because the UK cohort's average age was higher than the US one (18, 45).

Exploring the genes didn't provide the answers expected

The genome wide association studies (GWAS) made it clear that searching for one gene to one particular function wasn't as successful and easy as expected. To understand the "genetic architecture" of common diseases, a stepwise approach from variants to the precise cause of a disease is necessary. For instance, there are more than 20 genes known to influence BMI (46, 47). Since the polymorphism with an illness or a trait is hidden in the noncoding region of the genome, it is difficult to "identify the causative gene …..and difficult to establish the direction of action and the precise mechanism of its effect on the phenotype" (48, 49). A recent short review about the genetic background of the human biology of adiposity expressed some "skepticism regarding the power of human genetics to illuminate biology." A picture in the publication showing various couples, and females with different profiles, is underlined with the conclusion that " there is considerable variation in human body weight, which is strongly influenced by genetic variants that often regulate appetite" (50).

Sixteen genes with rare "nonsynonymous" variants were associated with BMI and expressed in the brain, controlling appetite and energy balance (51). Variances in the genes might differ between population groups. The variance of the MC4R gene, for instance, contributes to obesity more often in Mexico compared to the UK. For the UK, it was found that an MC4R loss-of-function variant is linked to obesity at a younger age (52).

Meet the friendly “Adiponectin” from the fat tissue, shaking hands with “Leptin and Ghrelin.”

Not only the genetic setting according to age and population groups plays a role, but, as MHO suggests, there are “genetic loci that uncouple excess adiposity from its comorbidities” (53). There are sixty-two loci of “which the same allele is significantly associated with higher and lower cardiometabolic risk.” Genes of the loci were expressed in the adipose tissue, and “regulatory” variants influenced “nearby genes… affecting ...adipocyte differentiation”. Genes were identified to be related to important metabolic purposes, i.e., fat distribution, adipocyte function, insulin-glucose signaling, energy expenditure and fatty acid oxidation, browning of white adipose tissue, and inflammation.

It has been known for some time that fat tissue, here the white adipose tissue (WAT), is not only the storage place for excess calories in the form of fat. The fat tissue interacts with the autonomous nervous, endocrinological, and immunological systems (54). The central role of the adipocyte is to regulate nutrient and energy homeostasis, and mediators for this metabolic aspect are adiponectin, leptin, and fatty acids (55).

Leptin and its antagonist ghrelin are hormones to regulate food intake. Ghrelin is secreted by several organs, among others by the mucosa of the stomach. It is increased before meal intake and termed the hunger hormone. It decreases after food ingestions. As counteraction, leptin stimulates food intake and helps in mobilizing energy expenditure. The adipocytes dominate in secreting the hormone (56, 57).

Adiponectin enhances insulin sensitivity and sustains healthy adipose tissue. It appears to “encourage the ‘healthy’ expansion of adipose tissue.” The hormone acts on the fat cell and increases glucose uptake and adipogenesis, and adipocyte lipid storage. An increase in fat mass stimulates leptin excretion. Independently leptin increases adipose tissue lipolysis. Lipolysis triggered by leptin provides fatty acids, which influence glucose uptake through GLUT4. Under the influence of leptin, through the peripheral nervous system, lipolysis is initiated (55).

The mouse weighing the equivalent of 270 kg in man

For studying the complex metabolic regulations and interferences of adiponectin, genetically engineered mice are used, overproducing adiponectin but deficient in leptin (ob/ob). The mice tend to become grossly overweight with 130 g, which equals 270 kg for men. Yet, the mice remain metabolic healthy, even with improved insulin resistance and without developing diabetes (18). Unfortunately for the mice, their MHO doesn’t let them live as long as healthy mice should, but because of their weight, they can’t keep their balance and flip over or get stuck and die because of dehydration.

In mice an artificial overexpression of adiponectin can be stimulated to test the hormone's function up to its limits. The mice, even grossly overweight, remained “metabolically healthy.” However, an adiponectin “null mouse” developed aggravated glucose and lipid metabolism disturbances. The disorders increased with age and resulted in a shortened life span. When applying a transgenic mouse model with “elevated circulating adiponectin levels,” improved

insulin sensitivity was observed, fewer age-related metabolic ailments, along health span, and an improved median life span (58). Yet, due to a polymorphism at the adiponectin gene, people with altered adiponectin regulation increased the risk of developing diabetes and insulin resistance (59, 60).

Not the amount of fat nor the weight and BMI indicate whether the person's metabolism is healthy or not. Still, other factors such as adiponectin concentration play a more critical role.

Outlook

Scientists interested in expanding our knowledge about health and the metabolism, while admitting that obesity doesn't necessarily signify ill health, always are eager to add that they don't mean one shouldn't forget that obesity remains a serious health problem (18). Cautiously it is stated that fat doesn't cause lifestyle diseases for obese people independently, but other factors are involved as well. It is underlined by those working in genetics and those exploring the active role of the fat tissue in the metabolism that the mechanisms aren't fully understood.

Those worrying that obesity will be taken less and less seriously, it is pointed out, that MHO individuals may have a lower risk to suffer from CVD and diabetes. However, their risk is still higher compared to healthy lean persons. Those to classify as MHO are reminded that it is a good idea to still work on losing weight since the condition is proofed to be transient (61). It is concluded by Brüher (2020) that MHO should not be considered a safe condition, which doesn't require obesity treatment. The author somehow justifies the concept of MHO in that it may guide decision-making for a personalized and risk stratified obesity treatment (61).

How to compromise between the paradigm "decrease weight, while overweight and obese" and the "Health at Every Size (HAES)." Maybe the conclusion of a publication, twenty years ago, can help. The title read: "Health obesity: A heritable neurobehavioral disorder that is highly sensitive to environmental conditions" (62). The conclusion is cited word by word, to demonstrate how diplomatic even scientists, two decades ago, phrased a view opposed to a well-accepted paradigm by the majority: "We argue that a view of obesity that emphasizes the profound biological basis for inter-individual difference in responding to the challenge of achieving a healthy control of nutrient intake, should result in a more enlightened attitude toward people with obesity with a consequent reduction in their experience of social and economic discrimination."

Literature:

1. Pontzer H. Constrained Total Energy Expenditure and the Evolutionary Biology of Energy Balance. Exerc Sport Sci Rev. 2015;43(3):110-6.
2. Pontzer H, Durazo-Arvizu R, Dugas LR, Plange-Rhule J, Bovet P, Forrester TE, et al. Constrained Total Energy Expenditure and Metabolic Adaptation to Physical Activity in Adult Humans. Curr Biol. 2016;26(3):410-7.
3. Dobzhansky T. Nothing in biology makes sense except in the light of evolution. The American Biology Teacher 1973;35(3):5.

4. Ludwig DS, Friedman MI. Increasing adiposity: consequence or cause of overeating? JAMA. 2014;311(21):2167-8.
5. Chopra M, Galbraith S, Darnton-Hill I. A global response to a global problem: the epidemic of overnutrition. Bull World Health Organ. 2002;80(12):952-8.
6. Healey BJ, Zimmerman Jr., R.S. The new world of health promotion Sudbury, MA, USA: Jones and Bartlett Publishers, LLC; 2010.
7. Malhotra A, DiNicolantonio JJ, Capewell S. It is time to stop counting calories and time instead to promote dietary changes that substantially and rapidly reduce cardiovascular morbidity and mortality. Open Heart. 2015;2(1):e000273.
8. Sassi F, Belloni A, Mirelman AJ, Suhrcke M, Thomas A, Salti N, et al. Equity impacts of price policies to promote healthy behaviours. Lancet. 2018;391(10134):2059-70.
9. Singh Thakur J, Nangia R, Singh S. Progress and challenges in achieving non-communicable diseases targets for the sustainable development goals. FASEB Bioadv. 2021;3(8):563-8.
10. Stokstad E. United Nations. Sustainable goals from U.N. under fire. Science. 2015;347(6223):702-3.
11. Haase CL, Eriksen KT, Lopes S, Satylganova A, Schnecke V, McEwan P. Body mass index and risk of obesity-related conditions in a cohort of 2.9 million people: Evidence from a UK primary care database. Obes Sci Pract. 2021;7(2):137-47.
12. Lemstra M, Bird Y, Nwankwo C, Rogers M, Moraros J. Weight loss intervention adherence and factors promoting adherence: a meta-analysis. Patient Prefer Adherence. 2016;10:1547-59.
13. Gudzune KA, Doshi RS, Mehta AK, Chaudhry ZW, Jacobs DK, Vakil RM, et al. Efficacy of commercial weight-loss programs: an updated systematic review. Ann Intern Med. 2015;162(7):501-12.
14. Neumark-Sztainer D. Preventing obesity and eating disorders in adolescents: what can health care providers do? J Adolesc Health. 2009;44(3):206-13.
15. Finkelstein EA, Trogdon JG, Cohen JW, Dietz W. Annual medical spending attributable to obesity: payer-and service-specific estimates. Health Aff (Millwood). 2009;28(5):w822-31.
16. Murray S. Pathologizing “fatness”:Medical authority and popular culture. Sociology of Sport Journal 2008;25(1):14.
17. Saguy AC, Almeling, R. . Fat in the fire? Science, the news media, and the “obesity”. Sociological Forum. 2007;23(1):30.
18. Couzin-Frankel J. A lighter burden. Science. 2021;373(6554):480-3.
19. Bacon L, Aphramor L. Weight science: evaluating the evidence for a paradigm shift. Nutr J. 2011;10:9.
20. Bombak A. Obesity, health at every size, and public health policy. Am J Public Health. 2014;104(2):e60-7.
21. Robinson JI. Weight, health, and culture: Shifting the paradigm for alternative health care. Alternative Health Practitioner. 1999;5(1):24.
22. Penney TL, Kirk SF. The Health at Every Size paradigm and obesity: missing empirical evidence may help push the reframing obesity debate forward. Am J Public Health. 2015;105(5):e38-42.
23. Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, et al. Body-mass index and mortality among 1.46 million white adults. N Engl J Med. 2010;363(23):2211-9.

24. Simini B. Serge Renaud: from French paradox to Cretan miracle. Lancet. 2000;355(9197):48.
25. Montani JP. Ancel Keys: The legacy of a giant in physiology, nutrition, and public health. Obes Rev. 2021;22 Suppl 2:e13196.
26. Altomare R, Cacciabaudo F, Damiano G, Palumbo VD, Gioviale MC, Bellavia M, et al. The mediterranean diet: a history of health. Iran J Public Health. 2013;42(5):449-57.
27. Mazzocchi A, Leone L, Agostoni C, Pali-Scholl I. The Secrets of the Mediterranean Diet. Does [Only] Olive Oil Matter? Nutrients. 2019;11(12).
28. Flor-Alemany M, Marin-Jimenez N, Nestares T, Borges-Cosic M, Aranda P, Aparicio VA. Mediterranean diet, tobacco consumption and body composition during perimenopause. The FLAMENCO project. Maturitas. 2020;137:30-6.
29. Wiklund P, Toss F, Weinehall L, Hallmans G, Franks PW, Nordstrom A, et al. Abdominal and gynoid fat mass are associated with cardiovascular risk factors in men and women. J Clin Endocrinol Metab. 2008;93(11):4360-6.
30. Sun C, Kovacs, P., Guiu-Jurado, e. Genetics of body fat distribution: Comparative analyses in populations with European, Asian and African ancestries. Genes. 2021;12, 841.
31. Ronn PF, Andersen GS, Lauritzen T, Christensen DL, Aadahl M, Carstensen B, et al. Abdominal visceral and subcutaneous adipose tissue and associations with cardiometabolic risk in Inuit, Africans and Europeans: a cross-sectional study. BMJ Open. 2020;10(9):e038071.
32. Shuster A, Patlas M, Pinthus JH, Mourtzakis M. The clinical importance of visceral adiposity: a critical review of methods for visceral adipose tissue analysis. Br J Radiol. 2012;85(1009):1-10.
33. Symonds ME, Aldiss P, Pope M, Budge H. Recent advances in our understanding of brown and beige adipose tissue: the good fat that keeps you healthy. F1000Res. 2018;7.
34. Fonseca V. Effect of thiazolidinediones on body weight in patients with diabetes mellitus. Am J Med. 2003;115 Suppl 8A:42S-8S.
35. Ko KD, Kim KK, Lee KR. Does Weight Gain Associated with Thiazolidinedione Use Negatively Affect Cardiometabolic Health? J Obes Metab Syndr. 2017;26(2):102-6.
36. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. JAMA. 2013;309(1):71-82.
37. Keith SW, Fontaine KR, Allison DB. Mortality rate and overweight: Overblown or underestimated? A commentary on a recent meta-analysis of the associations of BMI and mortality. Mol Metab. 2013;2(2):65-8.
38. Matheson EM, King DE, Everett CJ. Healthy lifestyle habits and mortality in overweight and obese individuals. J Am Board Fam Med. 2012;25(1):9-15.
39. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet. 2005;365(9468):1415-28.
40. Kramer CK, Zinman B, Retnakaran R. Are metabolically healthy overweight and obesity benign conditions?: A systematic review and meta-analysis. Ann Intern Med. 2013;159(11):758-69.
41. Stefan N, Haring HU, Hu FB, Schulze MB. Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications. Lancet Diabetes Endocrinol. 2013;1(2):152-62.
42. Lotta LA, Abbasi A, Sharp SJ, Sahlqvist AS, Waterworth D, Brosnan JM, et al. Definitions of Metabolic Health and Risk of Future Type 2 Diabetes in BMI Categories: A Systematic Review and Network Meta-analysis. Diabetes Care. 2015;38(11):2177-87.

43. Eckel N, Li Y, Kuxhaus O, Stefan N, Hu FB, Schulze MB. Transition from metabolic healthy to unhealthy phenotypes and association with cardiovascular disease risk across BMI categories in 90 257 women (the Nurses' Health Study): 30 year follow-up from a prospective cohort study. Lancet Diabetes Endocrinol. 2018;6(9):714-24.
44. Colditz GA, Manson JE, Hankinson SE. The Nurses' Health Study: 20-year contribution to the understanding of health among women. J Womens Health. 1997;6(1):49-62.
45. Zembic A, Eckel N, Stefan N, Baudry J, Schulze MB. An Empirically Derived Definition of Metabolically Healthy Obesity Based on Risk of Cardiovascular and Total Mortality. JAMA Netw Open. 2021;4(5):e218505.
46. Choquet H, Meyre D. Genomic insights into early-onset obesity. Genome Med. 2010;2(6):36.
47. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, et al. Genetic studies of body mass index yield new insights for obesity biology. Nature. 2015;518(7538):197-206.
48. Cannon ME, Mohlke KL. Deciphering the Emerging Complexities of Molecular Mechanisms at GWAS Loci. Am J Hum Genet. 2018;103(5):637-53.
49. Wellcome Trust Case Control C. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature. 2007;447(7145):661-78.
50. Yeo GSH, O'Rahilly S. Finding genes that control body weight. Science. 2021;373(6550):30-1.
51. Akbari P, Gilani A, Sosina O, Kosmicki JA, Khrimian L, Fang YY, et al. Sequencing of 640,000 exomes identifies GPR75 variants associated with protection from obesity. Science. 2021;373(6550).
52. Wade KH, Lam BYH, Melvin A, Pan W, Corbin LJ, Hughes DA, et al. Loss-of-function mutations in the melanocortin 4 receptor in a UK birth cohort. Nat Med. 2021;27(6):1088-96.
53. Huang LO, Rauch A, Mazzaferro E, Preuss M, Carobbio S, Bayrak CS, et al. Genome-wide discovery of genetic loci that uncouple excess adiposity from its comorbidities. Nat Metab. 2021;3(2):228-43.
54. Trayhurn P, Beattie JH. Physiological role of adipose tissue: white adipose tissue as an endocrine and secretory organ. Proc Nutr Soc. 2001;60(3):329-39.
55. Stern JH, Rutkowski JM, Scherer PE. Adiponectin, Leptin, and Fatty Acids in the Maintenance of Metabolic Homeostasis through Adipose Tissue Crosstalk. Cell Metab. 2016;23(5):770-84.
56. Klok MD, Jakobsdottir S, Drent ML. The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review. Obes Rev. 2007;8(1):21-34.
57. Verdes G, DuTa CC, Popescu R, MituleTu M, Ursoniu S, Lazar OF. Correlation between leptin and ghrelin expression in adipose visceral tissue and clinical-biological features in malignant obesity. Rom J Morphol Embryol. 2017;58(3):923-9.
58. Li N, Zhao S, Zhang Z, Zhu Y, Gliniak CM, Vishvanath L, et al. Adiponectin preserves metabolic fitness during aging. Elife. 2021;10.
59. Hara K, Boutin P, Mori Y, Tobe K, Dina C, Yasuda K, et al. Genetic variation in the gene encoding adiponectin is associated with an increased risk of type 2 diabetes in the Japanese population. Diabetes. 2002;51(2):536-40.
60. Stumvoll M, Tschritter O, Fritsche A, Staiger H, Renn W, Weisser M, et al. Association of the T-G polymorphism in adiponectin (exon 2) with obesity and insulin sensitivity: interaction with family history of type 2 diabetes. Diabetes. 2002;51(1):37-41.
61. Bluher M. Metabolically Healthy Obesity. Endocr Rev. 2020;41(3).

62. O'Rahilly S, Farooqi IS. Human obesity: a heritable neurobehavioral disorder that is highly sensitive to environmental conditions. Diabetes. 2008;57(11):2905-10.

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