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Marcus Y, Segev E, Shefer G, Eilam D, Shenkerman G, Buch A, Shenhar-Tsarfaty S, Zeltser D, Shapira I, Berliner S, Rogowski O. Metabolically Healthy Obesity Is a Misnomer: Components of the Metabolic Syndrome Linearly Increase with BMI as a Function of Age and Gender. Biology (Basel). 2023 May 15;12(5):719.

What We Know, Think We Know, or Are Starting to Know

We now know that all adiposity is not created equal, and that the specific site and distribution of body fat influences its metabolic activity and impacts on cardio-metabolic risk factors [1–3]. Additionally, anthropometric measures such as Body Mass Index [BMI] do not capture health-promoting characteristics such as cardiorespiratory fitness, the latter of which is associated with lower cardio-metabolic disease risk at categories of BMI classified as obese [e.g., BMI 30–35kg/m^2] [4].

It is therefore unsurprising that within obesity research, a phenotype known as "metabolically healthy obese" has been identified, defined as a subset of individuals with obesity [classified by BMI] but without cardio-metabolic risk factors such as high blood pressure or cholesterol [5,6]. Cohort studies have suggested that participants classified as metabolically healthy obese are not at higher risk of mortality, while those classified as metabolically unhealthy exhibit higher risk at any BMI category [7].

However, the definitions applied to characterise metabolically healthy overweight/obese have important implications, and the lack of standardised criteria to define the phenotype has plagued this area of research [8,9]. The phenotype has been derived from Metabolic Syndrome [MS] criteria, which requires ≥3 of 5 risk factors [based on waist circumference, triglycerides, HDL-cholesterol, fasting blood glucose, and systolic and diastolic blood pressure] to be present, with metabolically healthy overweight/obese characterised by ≤2 of 5 MS risk factors.

An obvious point of contention is that we cannot really consider an individual with even an isolated elevated risk factor to be considered "metabolically healthy", and more recent research has sought to apply more stringent criteria, which excludes individuals who exhibit a single criteria for MS [8,9].

This is an important step, because the estimates of prevalence of this phenotype vary relative to the criteria that has been applied, ranging from ~7% to 28% of persons with obesity [8]. Importantly, however, the phenotype appears to also exhibit significant sex differences in prevalence, with estimates of ~9% in men compared to ~28% in women [8]. This may relate to the well-established sex dimorphism in adipose tissue function [we covered this concept in a previous Research Lecture and Article].

The present study aimed to assess the prevalence of metabolically healthy overweight/obese using a strict criterion of zero MS risk factors across a full range of BMI categories from 18.5kg/m^2 to 46kg/m^2, and examine sex differences in prevalence of MS risk factors.

The Study

This was a retrospective analysis of data collected from participants between 2002 and 2013 for periodic routine health examinations. Participants were classified as "metabolically healthy obese" [MHO] if they had a BMI of ≥30kg/m^2 and no MS risk factors. In contrast, "metabolically healthy non-obese" [MHNO] was classified as a BMI of ≤30kg/m^2 and no MS risk factors. Other participants were classified according to the number of MS risk factors they exhibited, i.e., "MS1" to "MS5".

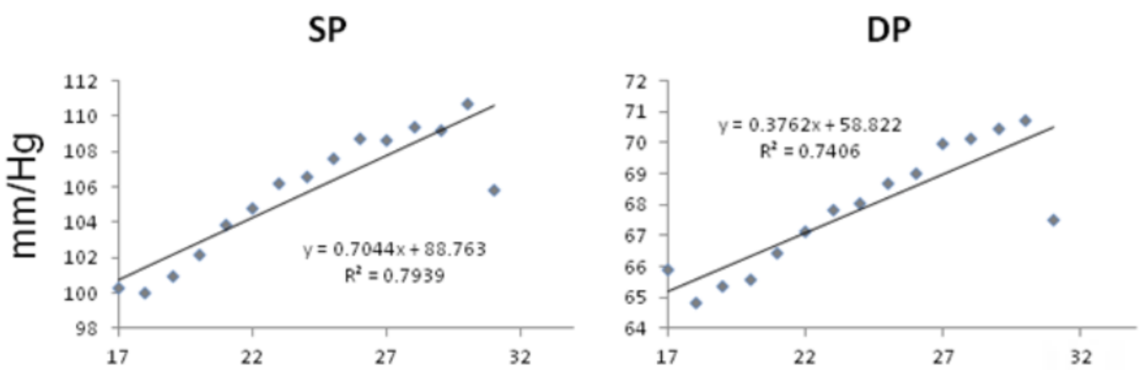
The study analysed the relationship between increasing BMI scores and number of MS risk factors, and the prevalence of MHO in the cohort. The analysis specifically compared men and women within each classification of metabolic health status and obesity.

The analysis considered two separate definitions of "metabolically healthy", the U.S. Adult Treatment Panel III [ATP-III] and the International Diabetes Federation [IDF], of which the latter is more stringent based on a lower threshold for waist circumference. Consequently, the results reported here reflect the IDF criteria.

Results: A total of 14,093 participants were included in the final analysis, of which 5,174 were classified as metabolically healthy according to the IDF criteria. The average age of participants was 38yrs. A total of 30 out of 5,174 participants were classified as MHO. The average BMI of participants in the MHO category was 31.2kg/m^2, while the average BMI in the MHNO category was 23kg/m^2.

***Risk Profile of Metabolically Healthy Non-Obese vs. Obese Participants*:** Although to be classified as metabolically healthy required participants to have MS risk factors in normal ranges, within this range participants classified as MHO had higher waist circumference, systolic/diastolic blood pressure [S/DBP], LDL-cholesterol, and high-sensitivity C-reactive protein [hsCRP, a marker of systemic inflammation].

***Associations Between Increasing BMI and MS Risk Factors in Metabolically Healthy Participants*:** Across a range of BMI from 19–32kg/m^2 in participants with no elevated MS risk factors, there was a linear association between increasing BMI and higher levels of S/DBP, LDL-C, triglycerides, and lower levels of HDL-C.



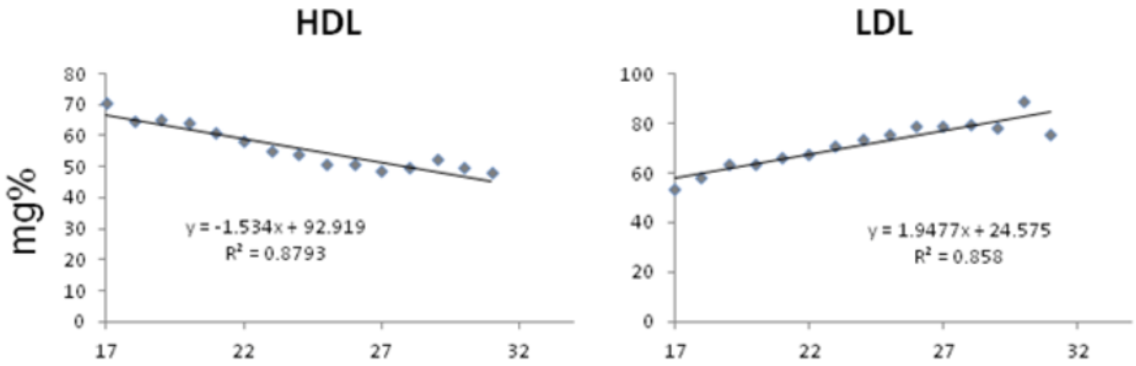


Figure from the paper illustrating the linear associations between increasing BMI and increasing risk factor levels. Bear in mind this analysis was in metabolically healthy participants, so these increases are all within the normal ranges for these risk factors. Nevertheless, they demonstrate that as weight increased among these participants, so the risk factors increased.

***Sex Differences in Prevalence of MS Risk Factors*:** Within the MHO category, women had significantly lower average levels of S/DBP, triglycerides, LDL-C, and higher HDL-C, compared to men. A significant interaction between sex and age was also observed, with men more likely to exhibit MS risk factors on average 2–5yrs younger than women [see **figure**, below].

The emergence of a first MS risk factor differed in prevalence; in men hypertension was the most prevalent first risk factor, while high waist circumference was the most prevalent in women.

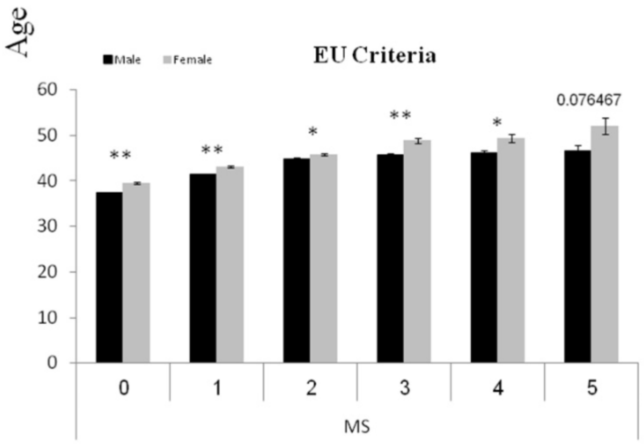


*Figure from the paper illustrating the respective average ages of men [**black bars**] and women [**grey bars**] according to number of MS risk factors exhibited, from 0 to 5. Overall, women maintained metabolic health status at older ages relative to men..*

Between the ages of 30 to 50yrs the proportion of participants with zero MS risk factors was 11% higher in women [see **figure**, above]. The proportion of participants with zero MS risk factors also declined as a function of age, however, sex differences in risk factor prevalence largely disappeared after ~55-60yrs.

The Critical Breakdown

Pros: The study aims were clearly stated, and included the specific aim to determine any sex and age-based differences in prevalence of MS risk factors. The overall sample size was large for the type of retrospective cross-sectional analysis of this particular study. The study analysed associations between MS risk factors across a very broad range of BMI categories from normal to overweight and obese, providing a sufficient contrast to examine potential linear relationships. The analysis also examined whether any differences in risk factor levels were present within the normal range of the MS criteria. Finally, using two different criteria for metabolic health provided a useful comparison and insight into the issue of definitions for this phenotype.

Cons: The study was retrospective and cross-sectional in design, and not an analysis of changing risk factors in the same participants over time [i.e., participants were classified as they were at the time of data collection]. The study sample is not a population-based sample and was recruited from a health screening programme, which may introduce some bias in representation. Although the overall sample size was large, the actual proportion of participants meeting the criteria for MHO was <1% of all participants. Thus, the study is limited in its power with regard to this phenotype specifically. In parts, the reporting of the findings is sloppy and does not always clearly identify which classifications of participants are being referred to.

Key Characteristic

To date, most studies on the MHO phenotype have classified metabolic health within a single class of BMI, i.e., overweight of BMI 25.5 to 30kg/m^2 or obese of BMI 30 to 35kg/m^2, comparing metabolic health both within an overall class [i.e., metabolically healthy vs. unhealthy] and to other BMI categories [i.e., metabolically healthy overweight to unhealthy normal weight].

However, the present study appears to be the first to analyse MS risk factors as a linear function of BMI across each BMI score, from the lower normal range to class I obese at BMI 32kg/m2. This approach is the real strength of the study [in addition to specific stratification by age and sex], because it allowed for analysis both relative to those participants with zero MS risk factors, and relative to the prevalence of risk factors.

We know from the Results section above that even within those participants with no elevated MS risk factors, the absolute levels of respective MS criteria increased linearly as BMI increased. And when including participants with risk factors, 16% of participants at a BMI of 19kg/m^2 exhibited one MS criteria, while at a BMI of 29kg/m^2 up to 75% of participants exhibited at least one MS criteria. Thus, examining the full range of BMI from 19 to 32kg/m^2 demonstrated that risk factor prevalence increased as a function of increasing BMI.

Interesting Finding

As noted in the ***What We Know…*** section above, a major headache in this area has been the definitions applied to metabolically healthy overweight/obese, which often allowed for mission creep in designating individuals with an elevated risk factor as "metabolically healthy".

Recently, more stringent criteria have been applied, not only lowering the thresholds considered "metabolically healthy" [e.g., SBP from <140mmHg to <130mmHg], but now requiring that an individual exhibit zero MS criteria at a BMI of ≥30kg/m^2 (8,9).

And what is particularly interesting in the present study is just how little participants met a more strict, but true, definition of MHO. In total, 3,074 men and 2,130 women were classified as metabolically healthy, of which those with a BMI of ≥30kg/m^2 constituted just 0.8% of men and 0.3% of women.

When the analysis included only participants with a BMI of ≥30kg/m^2 [*n* = 2,087], just 10% exhibited zero MS risk factors at a BMI of 30kg/m^2, which declined to <1% at a BMI of ≥36kg/m^2. Overall, this study suggests that a true phenotype of MHO may be much more limited in prevalence when stricter definitions of metabolic health are applied.

Relevance

This study adds to the evidence that, even with stricter definitions of metabolic health applied, the phenotype of MHO differs as a function of age and sex. In relation to sex, this is not necessarily a surprising finding and likely reflects that women, due to greater storage of subcutaneous fat in the gluteal-femoral region, exhibit lower circulating blood lipids and maintain insulin sensitivity [see previous Research Lecture and Article].

In relation to age, it is important to recall that the differences across age in the present study are *not* prospective data of the same participants over time, but a snapshot of the age of participants as they were at the time of data collection. Nevertheless, the findings from the present study add to wider research indicating that metabolic health is a transient state, and that higher risk of cardio-metabolic disease over time may reflect the continued accumulation of MS risk factors (10–12).

Moreover, this study does concur with wider research that suggests an effect of bodyweight itself even within classifications of metabolically healthy. Recall that participants classified as MHO in the present study still exhibited higher absolute levels of multiple risk factors compared to MHNO participants. In an analysis of the U.S. Nurses' Health Study, participants with obesity that were classified as "stable metabolic health", defined as absence of diabetes, hypertension, or elevated cholesterol over the ~30yr follow-up, had a 34% higher risk of cardiovascular disease [CVD] (11).

The present study also indicates a transition from a true definition of metabolically healthy to metabolically unhealthy, i.e., ≥1 MS risk factors, as a function of increasing BMI and age. The transition over time from metabolically healthy to unhealthy is associated with higher CVD risk in individuals with BMI in both obesity and normal categories (11). Another prospective study showed that, of 643 participants classified as MHO at baseline, 46.8% transitioned to metabolically unhealthy and had 2-fold higher odds of developing subclinical atherosclerosis during ~4yrs follow-up (12).

In the largest study to date including 3.5-million participants, compared to normal BMI participants with no diabetes, hypertension, or elevated cholesterol, participants with the same metabolic status but BMI ≥30kg/m^2 had a 49% higher coronary heart disease risk [(10)]. Overall, the MHO phenotype does not find much support as a classification of low cardio-metabolic risk over time.

Application to Practice

Lines of evidence such as this can be difficult to translate in a sensitive and effective way that has regard both for the challenges of losing weight, and of the adverse effects of weight stigma and weight bias [(13,14)]. Nevertheless, it is equally disempowering and deagentifying to pretend, as some circles in the nutrition world do, that weight is uncorrelated with risk [(15)].

It should be noted that elevated risk factors confer cardio-metabolic risk at any BMI. And it should be noted that these are population studies where BMI is suitable for use, however, it is not suitable for considering individual-level risk, where factors like body composition, sex, physical activity, etc., may better be assessed.

However, the evidence does appear to indicate that at higher BMI in the obese category range, maintaining true metabolic health becomes a significant challenge over time. Ultimately, the aim is to control risk factors whether through weight loss, lifestyle and diet, drugs, or any combination thereof.

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