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Role of physical activity and cardiorespiratory fitness in metabolically healthy obesity: a narrative review

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ABSTRACT

Obesity has been associated with a multitude of metabolic disorders, often clustering with risk factors of cardiovascular disease and type 2 diabetes mellitus, hypertension, dyslipidaemia. Overall, obesity is a worldwide, growing health concern. However, a subgroup of obese individuals with a low burden of metabolic abnormalities have been identified and described as metabolically healthy obese (MHO). Whether the MHO phenotype is protective against obesity-related metabolic disorders in the long-term is presently unclear, and current research examining the potential transition has yielded inconsistent results. In this current narrative review, we aim to provide insights on the role of physical activity (PA) and cardiorespiratory fitness (CRF) in MHO. Lifestyle factors such as PA and CRF may influence the MHO phenotype. Limited studies have characterised energy expenditure and CRF in MHO and metabolically unhealthy obese. However, higher levels of PA, less sedentary behaviour and higher CRF have been observed in MHO individuals. Considering the multiple benefits of PA, it is high time to advocate this lifestyle change beyond its influence on energy balance in a weight loss programme to improve cardiovascular and metabolic risk factors irrespective of body weight and fat mass changes. Improved CRF via increased PA, especially exercise participation, while avoiding weight gain is not only a realistic goal, but should be the primary intervention for MHO populations to prevent the transition to an abnormal metabolic state.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Although, metabolically healthy obese (MHO) may exhibit somewhat elevated risk compared with healthy lean individuals, they are protected against cardiometabolic disorders relative to their metabolically unhealthy obese (MUO) counterparts.
⇒ MHO individuals possess higher cardiorespiratory fitness (CRF) compared with their MUO counterparts, while decreased CRF is associated with greater visceral adiposity and worse metabolic profile irrespective of body mass index.

WHAT THIS STUDY ADDS

⇒ Studies using accelerometers have shown positive associations between physical activity (PA) and MHO.
⇒ Moderate-to-vigorous PA is necessary to elicit beneficial metabolic changes in obese individuals and prevent the transition to MUO status.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Increased PA in any form should replace and reduce sedentary time to decrease the chance of transitioning to unhealthy metabolic state.
⇒ Improved CRF via increased PA, while avoiding weight gain is not only a realistic goal, but should be the primary intervention for MHO populations to prevent the transition to an abnormal metabolic state.

INTRODUCTION

Epidemiological studies indicate the dramatic escalation of non-communicable diseases, namely type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD) and cancer all over the world in the past decades. Available evidence points to the current obesity epidemic as the principle cause of this health crisis. Actually, current data have suggested that obesity is responsible for almost one in five cases of overall mortality.[1] Moreover, significant correlations between diabetes and obesity have been reported, while obese individuals exhibit a greater risk of developing CVD.[2]

Obesity is a multifaceted disorder with a complex pathophysiology as the related metabolic abnormalities largely arise from excess fat accumulation, insulin resistance and low-grade systemic inflammation.[1 3] Interestingly, a subset of obese individuals with normal metabolic profile have been identified and described as metabolically healthy obese (MHO). The main problem in estimating the prevalence of MHO is the lack of consensus regarding its definition.[4] The need for harmonising MHO definitions has been addressed recently by the BioShare-European Union project, to characterise clinical and metabolic factors associated with MHO and

compare key characteristics defining MHO.[5] Although they have excess adipose tissue, they seem to be protected from obesity-related abnormalities, such as hyperinsulinaemia, dyslipidaemia, hypertension and diabetes.[6 7] The prevalence of MHO is approximately 20%–30% among the obese depending on the studied cohort and the exact definition of the metabolic disturbance.[6 8] It is also well established that MHO is more common in certain populations, such as women, younger adults and people with European descent.[9] A common definition in accordance with the guidelines of the American Heart Association (AHA) considers MHO (<3 risk factors) and metabolically unhealthy obese (MUO) (≥3 risk factors or physician diagnosed diabetes and/or use of medications) based on the following criteria: waist circumference, ≥88 cm female, ≥102 cm male; triglycerides ≥1.7 mmol/L; high-density lipoprotein (HDL) cholesterol<1.03 mmol/L male, 1.3 mmmol/L female; systolic BP ≥130 mm Hg and/or diastolic BP ≥85 mm Hg; fasting blood glucose ≥5.6 mmol/L.[10] Alternatively, recent recommendations call for stricter criteria, that is, 0 of the above listed metabolic criteria with the exclusion of waist circumference.[11] In fact, more than 30 distinct definitions have been applied in clinical and research studies in the field.[9] The majority of these investigations used the AHA or its alternative criteria mentioned above, but other components have also been included, such as C reactive protein (CRP), 2-hour blood glucose level during an oral glucose tolerance test and insulin sensitivity/resistance.[4]

Although some evidence indicates that the risk of CVD and mortality of MHO individuals is similar to what is expected in lean healthy controls, others have concluded that obesity per se regulates the risk of morbidity and mortality.[7 12–14] First, an observational study reported that MHO did not increase CVD risk, while both lean and obese subject with two or more metabolic abnormalities experienced a greater hazard.[15] This evidence indicates that metabolic disruption is a more important determining factor of morbidity and mortality than body fatness. On the other hand, Bell *et al*[16] conducted a meta-analysis on the relationship between obesity and diabetes and concluded that regardless of metabolic health status, the risk of diabetes was elevated by fourfold in obese participants after adjustment for sociodemographic covariates compared with the normal weight cohort. However, it is increasingly evident that additional characteristics, such as cardiorespiratory fitness (CRF) should be considered to accurately describe the MHO phenotype and its health hazards.[2]

To summarise the current evidence, it appears that although they may exhibit somewhat elevated risk compared with healthy lean individuals, people with MHO are protected against cardiometabolic disorders relative to their MUO counterparts.[17] This review does not intend to discount the benefits of weight loss in health enhancement and certainly does not consider MHO a benign condition, but highlights the vital role of physical activity (PA) and CRF improvement in a multidisciplinary obesity treatment. Although, PA interventions result only in modest weight loss, the increased energy expenditure leads to the reduction of fat mass.[3 18] Most importantly, the majority of the studies that analysed the relationship between mortality and metabolic health in obesity have not adjusted for CRF. When CRF was accounted for, no difference in mortality rate has been evident between MHO and normal weight individuals,[11 19] thus as opposed to fatness the level of CRF is primarily responsible for the variances between these phenotypes.[7] The most significant conclusion in the fatness versus fitness debate supports the notion that CRF cannot be excluded as a significant predictor of cardiovascular and metabolic health, because compared with high body mass index (BMI), low CRF has a larger impact on mortality risk.[18] However, despite the increased attention and accumulating data in the past years, the underlying mechanisms of the MHO phenotype are not completely understood. There is an emerging consensus to shift the focus from body weight-centred approaches to lifestyle factors and more relevant metabolic/cardiovascular health parameters, such as CRF. Experts also recommend including CRF improvement as a primary end point of obesity treatment plans.[18–21] This review emphasises the central role of PA and CRF by summarising the most current data that emerged since a systematic review, meta-analysis and other experts' opinions on this topic.[17 19 20]

A narrative review of the literature was conducted with articles screened via PubMed, Embase and Scopus databases, using the following keywords and their combinations: "obesity", "metabolic health", "metabolically healthy obesity", "metabolically unhealthy obesity", "cardiorespiratory fitness", "physical activity" and "exercise". The reference lists of the relevant articles were also scanned for additional information.

CRF AND METABOLIC HEALTH

Seminal research reported that metabolic syndrome prevalence did not depend on CRF,[22] and indeed CRF was shown to be similar between metabolically healthy and unhealthy individuals (determined by insulin sensitivity).[23 24] However, more recent and larger inquiries disagree with these findings.[13 25 26] Specifically, mortality risk increased with lower CRF in every BMI category,[13] and decreased CRF was associated with greater visceral adiposity and worse metabolic profile irrespective of BMI.[26] Oral glucose tolerance test resulted in smaller glucose and insulin areas under the curve in participants with high CRF, who also demonstrated better plasma lipoprotein-lipid profiles, such as triglyceride, apolipoprotein B and total cholesterol/HDL ratio.[26] Subsequently, the current consensus is that high CRF is associated with decreased mortality risk, irrespective of BMI.[18 27 28] Indeed, a 13% and 15% reduction of all-cause and CVD mortality respectively, for every metabolic equivalent (MET) increase in CRF has been observed.[29]

With regard to MHO, research has shown that MHO individuals possess higher CRF compared with their MUO

counterparts, regardless of whether obesity was defined by BMI or body fat percentage.[7 30] MHO women also had a significantly (17%) higher VO_{2max} compared with the cohort with metabolic syndrome.[30] Most importantly, a logistic regression analysis indicated that CRF was the strongest predictor of the MHO phenotype in this investigation. Wedell-Neergaard *et al*[25] reported recently that while CRF showed a positive association with HDL, it was inversely related to overall metabolic score and other risk factors, such as triglycerides, blood pressure in middle-aged Danish men and women.

Others have shown that CRF, along with insulin sensitivity, insulin secretion and subcutaneous fat distribution was among the most important components that correlated with metabolic health in normal weight, overweight and obese populations.[31] Therefore, it is unsurprising that overweight/obese individuals with high CRF demonstrate a lower incidence of metabolic abnormalities.[7 13 16 32] Increased CRF over a 6-year period was negatively associated with changes in blood pressure, total cholesterol, triglycerides and waist circumference with a 7%–22% lower incidence of these risk factors for every 1 MET increase.[12] Furthermore, the maintenance or improvement of CRF attenuated the negative consequence of increased amount of adipose tissue on CVD risk.[12] More specifically, in obese patients with diabetes, low CRF was related to both myocardial infarction and all-cause mortality, which was independent of the degree of abdominal obesity.[22] A recent cross-sectional analysis showed that participants with higher CRF also had lower liver fat content, which is a significant feature of MHO,[33] and further supports the importance of fitness level in metabolic health.[34] Despite that individuals with lower CRF demonstrate greater obesity and fat mass, one study showed no difference in the prevalence of hypertension or metabolic syndrome compared with those with higher CRF.[22] On the other hand, a large investigation evaluating 3800 Korean men concluded that although the risk of systemic hypertension was elevated in MHO compared with healthy non-obese participants, moderate-to-high CRF significantly reduced this risk.[35]

Disparity in the findings may be due to the limited clinical studies that have investigated the effects of CRF on metabolic abnormalities in obese individuals. Moreover, currently no standardised criteria exist for determining MHO,[9 36] which may confound this research, and cause problems when interpreting the results. For instance, a new study in Taiwan reported that the CRF of MHO and MUO in military recruits did not differ.[37] However, the authors arrived at this conclusion based on the results of a field test (3 km run time), without directly measuring or calculating CRF values or even reporting the participants' body weight. Moreover, the MHO and MUO participants in this investigation barely showed any clinically meaningful difference in the classification of metabolic status and were all below the obesity classification of 30 kg/m^2 BMI.

Despite this, a recent meta-analysis concluded that CRF, PA and sedentary behaviour all contribute to the MHO phenotype, with CRF showing the largest difference between healthy and unhealthy obese.[20] This analysis included data from 19 unique studies for CRF and unequivocally stated that these attributes/lifestyle factors should be expressly considered as principal characteristics of the MHO phenotype. Importantly, a longitudinal study with 6 years follow-up indicated that maintaining or improving CRF was associated with a substantial lower risk (26%–52%) of developing metabolic abnormalities compared with reduced fitness during the same period.[12] This evidence has a robust practical relevance due to the transient nature of MHO[8 38]; therefore focusing on CRF could provide a useful strategy to prevent the transition to serious metabolic abnormalities. Moreover, it is well established that by improving CRF, populations with the lowest fitness levels (obese individuals most likely belong to this category) would realise the greatest benefits regarding the reduction of mortality risk.[18]

PA and metabolic health

Current evidence comparing PA in MHO and MUO individuals is inconsistent.[20 23 32 34 39–45] Both differences[32 39 41–43 45] and no differences[23 34 40 44] in PA between MHO and MUO have been reported. Leisure time PA was associated with MHO in the NHANES 1999–2004 study.[39] In addition, data from The Maastrich Study reported that MHO participants had higher daily stepping time compared with their unhealthy counterparts, with low intensity stepping time accounting for the observed significant difference between the groups.[43] Accelerometer-based data also confirmed higher PA level in MHO when compared with the unhealthy obese, though MHO participants were still less likely to reach the recommended moderate-to-vigorous PA (MVPA) level than healthy, normal weight adults.[41] Data from the German Health Interview and Examination Survey also indicated that compared with the MUO group, a higher percentage (30% vs 18.9%) of MHO engaged in at least 2.5 hours of PA a week.[46] Moreover, Ortega *et al*[20] recently conducted a meta-analysis for PA, which showed significantly higher MVPA for MHO individuals.

Male MHO participants as defined by Homeostatic Model Assessment were more regular exercisers compared with their MUO counterparts.[47 48] Conversely, intensity, daily total time and percentage of participants meeting the PA guidelines did not differ between MHO and MUO.[45] Another survey data reported similar amounts of leisure time PA between obese men and women with or without metabolic syndrome.[49] However, a more recent and very large cohort study supported the positive association between PA and MHO.[50] In that investigation of more than 200 000 Taiwanese adults, there was a large difference (0.94 MET hour/week) between the MHO and MUO groups in self-reported PA.[50]

Daily energy expenditure was not among the major determinants of transition to an abnormal metabolic

profile.[26 43] Indeed, at that time only two studies showed that PA energy expenditure was higher in MHO compared with MUO individuals.[39 51] However, new evidence confirms that when it is objectively quantified MHO adults expend more energy by PA.[52] Variations in the findings are likely due to differences in methods employed to quantify PA (ie, objective vs subjective measurements). Several studies that did not detect differences in PA levels used self-reported PA questionnaires instead of objective measures, such as accelerometers.[40 44 49] Studies employing accelerometers[30 41 43 52] have shown positive associations between PA and MHO. An exception is the study of MacLeod *et al*[53] which reported that total light PA and MVPA were not related to MHO. However, participants who met at least two of the four 24-hour Movement Guidelines Criteria (MVPA, light PA, sleep, screen time) were more likely to be metabolically healthy.[53]

Interestingly, according to comparative data, higher PA level was only apparent in MHO versus unhealthy obese when measured objectively by accelerometer as opposed to a subjective questionnaire.[41] Similarly, Numao *et al*[52] newly reported that in obese Japanese males the favourable metabolic profiles of the MHO participants was associated with higher MVPA and PA energy expenditure. PA must be of a sufficient intensity (moderate to vigorous) to reduce visceral fat even in the absence of caloric restriction.[54] This may explain why some PA interventions mentioned above did not show any positive effects of PA on MHO. Furthermore, males may demonstrate greater loss in visceral adiposity from PA compared with females, while there is no difference between various ethnic groups,[54] which may also explain disparity in the findings. When assessing the various PA domains, total and recreational PA described the MHO phenotype, with a 76% and 72% likelihood of belonging to this group for those who accumulated 500 MET min/week total and recreational PA, respectively.[55] Though, further adjustments disclosed that only total PA was associated with MHO and only in middle-aged (45–59 years) adults when stratified by age. Considering the high rate of transition from MHO to MUO state[8 56 57] and the fact that younger adults are more likely to exhibit a healthy metabolic state and resistance to unhealthy transition,[9 58] this age group may be the ideal target for preventive interventions, with PA in the forefront.

Slagter *et al*[59] described that MHO men and women had higher MVPA compared with their MUO counterparts, which was also reported in a Japanese study involving obese males.[52] Similarly, young MHO also engaged in more daily minutes of vigorous PA than MUO participants, while middle-aged and older adults in more moderate PA.[60] Thus, it appears that MVPA is necessary to elicit beneficial metabolic changes in obese individuals and potentially prevent the transition to MUO status. Increased PA likely has a positive effect on metabolic health, with several benefits including improved glucose and lipid metabolism, and decreased blood pressure, and inflammation even in the absence of adipose tissue loss.[3 61] These exercise-induced benefits were also confirmed by a new meta-analysis at least in healthy middle-aged and older adults.[62] More frequent PA participation was also inversely related to CRP expression; individuals who performed PA at least five times a week, displayed 37% lower CRP concentration compared with those who engaged in PA only once in the same period.[63] Recent data in MHO individuals also support these findings as both total PA and light PA duration were negatively correlated with inflammatory cytokine levels, while increased light PA was associated with lower insulin resistance and C-peptide levels.[64] In fact, according to a previous systematic review, higher level of PA counteracts the increased CVD risk in MHO, thus investigations of the MHO phenotype should include PA assessments.[65]

Bearing in mind the importance of body fat distribution and low-grade systemic inflammation in metabolic health, it is evident that increased engagement in PA and exercise training can provide a pragmatic solution for the prevention of metabolic abnormalities.[66–70]

TRANSITION BETWEEN METABOLIC STATES

Many studies, especially those with long-term follow-up periods, implied that MHO is a transient condition.[8 38 44 56 57] Early data indicated that after 6 years of follow-up 30.1%–47.8% of previously MHO participants became metabolically unhealthy depending on the criteria used to define the healthy phenotype.[8] Schröder *et al*[38] reported data of similar magnitude, that is, 49.2% of the healthy obese shifted to an abnormal metabolic profile during a 10-year period in their study with equal prevalence in male and female participants. Increased BMI and waist circumference were predictors of this transition, pointing to the crucial role of central obesity in metabolic health. A more recent investigation in Japanese Americans also indicated that the majority (64.7%) of MHO participants converted to an unhealthy profile over the 10-year follow-up period.[44] Baseline visceral fat was found to be the most significant predictor of this transition in this study, confirming previous data. Given the aforementioned importance of body fat distribution (ie, visceral fat) and MHO phenotype, reducing waist circumference appears prudent in preventing the transition from MHO to MUO.

Lifestyle was identified as an important component of the transition between metabolic states with healthy diet and absence of smoking contributing the most to the favourable metabolic profile.[44] Individuals who preserved their metabolic health over 12 years exhibited the same CVD risk as their healthy lean counterparts.[71] However, studies disagree on the role of PA in metabolic health and its long-term maintenance. While some investigators reported different PA levels in healthy and unhealthy obese,[20 41] others indicated no differences between these phenotypes or specified that daily energy expenditure was not among the major determinants of transition to an abnormal metabolic profile.[23 44] Alternatively, another study has recently shown that after a successful, 16-week lifestyle programme, participants quickly transitioned back to MUO without the

supervised exercise and diet intervention.[72] New data also support the importance of PA in the transition between metabolic states. Even though the proportion of MUO increased from 22% to 32% in African obese adults after 10 years of follow-up, PA was inversely related to the escalation of metabolic syndrome.[56] Moreover, while overall PA decreased among all participants, those who remained the most active 10 years later were able to sustain better metabolic health along with unchanged BMI. Most importantly, a very large recent investigation demonstrated that higher level of PA increased the probability of transition from MHU to MHO.[50]

CONCLUSIONS

Without effective lifestyle interventions MHO appears to be an intermediate stage towards completely unhealthy metabolic and disease states. On the contrary, maintaining a stable MHO profile, especially without weigh gain and increased abdominal fat can prevent the shift to metabolic syndrome and to the development of diabetes. First stabilising then reversing the early metabolic disturbances of obesity can result in attenuated progression and declining rate of T2DM. Although, even a small body fat loss, especially visceral fat, can result in substantial mortality and morbidity risk reduction, new evidence also indicates that targeting weight loss alone may not be the most effective approach of health improvement as many obesity-related hazards (eg, lipid profile, glucose metabolism/insulin action, endothelial function, inflammation) can be mitigated independently of body weight.[73–76] Increased CRF and the change in diet composition and quality even in the absence of weight loss can bring about significant health benefits and better quality of life. Moreover, clinical trials indicated that significantly more participants achieved the recommended PA target to improve CRF than the weight loss goal of 5%–7% bodyweight.[3] Another significant downside of weight loss interventions is the poor long-term success rate, which often manifests in weight cycling and is associated with high BMI.[18] Therefore, future studies should elucidate the underlying mechanisms of the MHO phenotype along with the transition between healthy and unhealthy metabolic states, focusing on the role of CRF and PA.

Considering the multiple benefits of PA, it is high time to advocate this lifestyle change beyond its influence on energy balance in a weight loss programme to improve cardiovascular and metabolic risk factors irrespective of body weight and fat mass changes.[18–21 77] Improved CRF via increased PA, especially exercise participation,[78] while avoiding weight gain is not only a realistic goal, but should be the primary intervention for MHO populations to prevent the transition to an abnormal metabolic state. In addition, new important data has been presented in a large study, demonstrating that increased PA can also promote the transition from MUO to MHO state.[50] Increased PA (occupational, transportation, household) should also replace and reduce sedentary time, which is the hallmark of unhealthy obesity and a major risk factor for early mortality and morbidity.

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