Metabolically healthy obesity across the life course: epidemiology, determinants and implications

Short title: Metabolically healthy obesity: a life course perspective

Catherine M. Phillips [1,2]

[1] HRB Centre for Diet and Health Research, Dept. of Epidemiology and Public Health, University College Cork, Ireland and [2] HRB Centre for Diet and Health Research, School of Public Health, Physiotherapy and Population Science, University College Dublin, Ireland

Corresponding author: Dr. Catherine M. Phillips, HRB Centre for Diet and Health Research, Dept. of Epidemiology and Public Health, University College Cork, Ireland and School of Public Health, Physiotherapy and Population Science, University College Dublin, Ireland Email: c.phillips@ucc.ie catherine.phillips@ucd.ie Telephone: +353 (1) 716 3483

Key words: Metabolically healthy obesity; Definitions; Determinants; Stability; Life course; Personalised medicine;

Word count: 6779

Abstract

In recent years different sub-phenotypes of obesity have been described including metabolically healthy obesity (MHO), whereby a proportion of obese individuals despite excess body fat remain free of metabolic abnormalities and increased cardiometabolic risk. In the absence of a universally accepted set of criteria to classify MHO the reported prevalence estimates vary widely. Our understanding of the determinants and stability of MHO over time and associated cardiometabolic and mortality risk is improving, but many questions remain. For example, whether MHO is truly benign is debatable and whether risk stratification of obese individuals based on their metabolic health status may offer new opportunities for more personalised approaches in diagnosis, intervention and treatment of diabetes remains speculative. Furthermore, as most research to date has focussed on MHO in adults little is known about childhood MHO. In this review we focus on the epidemiology, determinants, stability and health implications of MHO across the life course.

Introduction

Obesity has become a worldwide epidemic and represents a major public health challenge. Over the last four decades, there has been a global shift from a time when underweight was twice as prevalent as obesity to one in which the numbers of obese individuals now surpass those who are underweight, both globally and in all regions, with the exceptions of areas of Asia and sub-Saharan Africa [1]. Examination of body mass index (BMI) trends from 1698 population-based data sources involving more than 19.2 million adults (9.9 million men and 9.3 million women) revealed that in 2014 the prevalence of obesity exceeded underweight in both men and women in 68% and 83% of the countries for whom estimates were available [1]. Recent estimates indicate that about 266 million men and 375 million women are obese in the world [1]. Future projections predict that over one billion people, or approximately 20% of the world's entire adult population, will be obese by 2030 [2]. Not only is the prevalence of adult obesity increasing so too is childhood obesity. Approximately one quarter of children worldwide are overweight or obese [3, 4]. Although there are indications that the prevalence of overweight and obesity in children is plateauing in some populations [4], current levels remain high. This is particularly concerning as it has been shown that childhood obesity tracks to adulthood and is associated with increased risk of cardiometabolic disease and premature mortality [5].

The current obesity epidemic is paralleled by escalating prevalence of type 2 diabetes mellitus (T2DM) and metabolic syndrome (MetS), a constellation of metabolic perturbations including obesity, insulin resistance, hypertension and dyslipidaemia. However over recent years it has become increasingly recognised that obesity is not a homogeneous condition and that a subset of obese individuals do not display disturbed metabolic profiles or increased risk of cardiometabolic disease. As such these individuals, who are characterised by preserved insulin sensitivity, normal blood pressure and lipid profiles despite their adiposity, may be described as being metabolically healthy obese (MHO). Similarly there exist normal weight individuals who display abnormal metabolic profiles and carry increased cardiometabolic risk. Thus a spectrum of metabolic health phenotypes according to BMI or body composition exist, ranging from metabolically healthy normal weight to metabolically unhealthy obese (MUO), along which MHO represents an intermediate stage. Research

on obesity phenotypes has mainly focussed on MHO among adults to date with a paucity of information available on childhood MHO. Therefore, in this review we focus on the epidemiology, determinants, stability and health implications of MHO over the life course from childhood into adulthood.

Metabolically healthy obesity in childhood and adolescence

The currently increasing prevalence of a range of adult chronic non-communicable diseases, including obesity, cannot be explained solely by genetic or adult lifestyle factors. Evidence from epidemiological studies suggest that the origins of many chronic diseases, including obesity, MetS, cardiovascular disease (CVD) and T2DM, actually begin in early life and that childhood insulin resistance and adiposity predispose to diabetes, MetS and CVD in adulthood [6-10]. Increasing evidence also suggests that early life exposure to a range of environmental factors, including nutrition for example, plays a critical role in defining offspring health, both in childhood and in later life. According to the Developmental Origins of Health and Disease hypothesis, transient environmental exposures during critical periods of development (such as the pre-conceptional, fetal and early infant phases of life) can alter normal physiology and have a persistent impact on metabolism and gene expression thereby influencing offspring phenotype and disease risk in later life [11, 12]. For example, growth velocity in utero and in early life, which are a read-out of early nutritional status, may affect cardiovascular and cancer risk. Stefan *et al.*, recently reviewed the literature on height (a genetically determined phenotype which is influenced by maternal and early life exposures) and cardiometabolic disease and cancer risk later in life [13]. Accumulating data suggest divergent associations, such that height is associated with lower cardiometabolic risk and higher cancer risk. The authors speculate that overnutrition, particularly of milk and dairy products, during child development may play a role. Thus avoiding such overnutrition during critical developmental periods may attenuate accelerated growth and development of obesity in children leading to lower cancer risk in later life. Therefore, investigating metabolic health and adiposity in childhood may have implications in terms of

preventative strategies for adverse metabolic health phenotypes in early life which may have long term impacts.

As is the case for adults no standard metabolic health definition exists for use in children. **Table 1** details some currently used criteria to define MHO among children and adolescents [14-20]. While metabolic health may be simply defined as the absence of insulin resistance [17], in the majority of studies MHO characterisation centres on the absence of MetS (or some of its cardiometabolic risk factors) [14-20] among those with excess body weight. It is important to note that how obesity is classified is also an issue, with different anthropometric measures and cut-offs being used. The Bogalusa Heart Study defined overweight/obesity as a BMI in the top quartile [16], the cross-sectional study by Prince *et al.,* defined obesity as a BMI ≥85th percentile [17], the studies by Vukovic *et al.,* [18, 19] and Camhi *et al.,* [14, 21] defined obesity as a BMI ≥95th percentile, whereas Zamrazilova *et al.,* [20] used a BMI ≥97th percentile to classify obesity. The Korean Children-Adolescent Study was based on abdominal obesity assessed by waist circumference [15]. Such variation in classification of both obesity and metabolic health undoubtedly hinders comparisons between studies and contributes to the observed disparity in MHO prevalence in these studies (ranging from 4.2% [16], 21.5% [17], 21.7% [18], 25% [19], 53% [15] to 68% [14]).

The determinants of and molecular mechanisms underlying MHO among children are under examined and as a result, poorly understood. Collectively the data indicate that MHO children are more likely to be younger (and in earlier stages of puberty) and female, of high birth weight with less visceral fat, preserved insulin sensitivity, high adiponectin concentrations, altered ghrelin levels, more favourable lipid profiles, reduced concentrations of transaminases and uric acid, and without hepatic steatosis [17-19, 22-28]. Although early weight gain was originally identified as a determinant of childhood MHO [23] a larger study of Danish men for whom childhood BMI was available failed to find robust evidence to support a role for either rapid BMI growth or early-onset obesity in the development of MHO [29]. Aside from laboratory and clinical based predictors limited data regards the role of environmental, lifestyle, behavioural or genetic factors in determining MHO status among children exist. Prince *et*

al., examined lifestyle predictors of MHO among 8-17 year olds attending a weight management clinic [17]. They identified dietary fat intake and moderate-to-physical activity as independent predictors. In contrast Camhi *et al.*, reported that physical activity, but not sitting or screen time differs between MHO and MUO in adults, but not in adolescents [14]. In further work these authors also demonstrated that MHO adolescents have better compliance with dietary guidelines compared to their MUO counterparts [21]. A study of 1213 Chinese children aged 6-18 years reported that walking to school and frequency of soft drink consumption, together with other demographic factors, contribute to the prediction of MHO status [30]. Interestingly this study also examined 22 genetic variants previously identified from genome wide association studies of obesity and diabetes. They found that both genetic predisposition and lifestyle factors and their interaction are independent predictors of MHO. More recently a study of teenage boys (13-17.9 years) investigated a range of potential determinants of MHO including duration of exposure to obesity, dietary intake and lifestyle factors. With the exception of carbohydrate intake, no other associations with MHO were identified with dietary or lifestyle factors. However a clear relationship between early onset of obesity and longer duration of its exposure with MUO was demonstrated [20]. Collectively these data suggest potential intervention windows and targets to improve cardiometabolic profiles in paediatric obesity with a view to achieving and maintaining better long term cardiometabolic health.

Metabolically healthy obesity in adulthood

The prevalence of MHO among adults varies greatly between studies. Although study specific differences such as age, ethnicity, sample size or environmental factors and genetics may be contributing factors, the lack of a universal definition of metabolic health and differences in obesity classification (BMI versus body fat percentage) account for a large proportion of the reported disparity [31]. **Table 2** details some currently used criteria to define MHO among adults [32-38]. At the very least metabolic health may be defined as the absence of insulin resistance [35], but as is the case in children for the most part current characterisation of MHO in adults is based on the absence of MetS

(or some of its components) among those with excess body weight, generally defined by BMI [34-38]. Some definitions additionally include favourable inflammatory status determined by C reactive protein levels [32, 33].

Although limited, comparative studies examining MHO prevalence across a range of currently used criteria have reported considerable variation in MHO prevalence and poor agreement between MHO definitions [39, 40]. In an Irish cross-sectional population representative sample of adults aged 50-69 years, among the obese (by BMI) participants MHO prevalence ranged from 6.8%-36.6% [39]. MHO prevalence was generally higher among females and conflicting associations were noted with age, depending on which definitions were used. In a Korean study of 186 obese (by BMI) male subjects Yoo *et al.,* [41] reported MHO prevalence ranging from 24.2% to 70.4%. This study did not observe any age related differences, which may be accounted for by the narrow and younger age range of the male only study participants (mean age 37 years). In a Swiss population-based sample of adults aged 35-75 years MHO prevalence ranged from 3.3-32.1% in men and 11.4-43.3% in women, with higher estimates reported when obesity was defined by body fat percentage (BF%) [40]. The latter finding highlights the importance of how obesity is classified. Direct measurement of body fat using dual-energy X-ray absorptiometry (DEXA) is the gold standard, however DEXA is generally not available or practical for most researchers. BMI is the most widely used method to classify excess adiposity, with values $\geq$ 30 kg/m^2 indicating obesity. However BMI does not discriminate between fat and lean body mass, thus individuals of short stature or muscular build may be misclassified. Indeed, accumulating evidence indicates that BMI may actually under estimate obesity prevalence [42]. Similarly, obesity classification influences MHO prevalence, with estimates ranging from a third to half of obese individuals by BMI and DEXA respectively [43]. Furthermore, recent data suggest that combined assessment of BMI and body fat percentage or other anthropometric measures to classify obesity may help identify individuals at greater cardiometabolic risk than BMI alone [44, 45]. Collectively these data underscore the importance of accurate obesity diagnosis in the context of more precise classification and risk stratification.

MHO prevalence has been recently examined in a number of large scale studies. Analysis of 10 cohort studies involving 163,517 individuals from 7 European countries revealed significant diversity in MHO prevalence across Europe (7-28% in women and 2-19% in men) [38]. Generally, MHO, which was defined as obesity (by BMI) without any MetS component and no previous CVD diagnosis, was more prevalent among women and decreased with age in both genders [38]. A worldwide meta-analysis of 31 studies reported overall prevalence of MHO of 7.27%, with highest prevalence among American populations, although wide ranges were reported between individual studies (MHO prevalence of 1.3-22.9% in Americans, 2.1-23.9% in Europeans and 2.8-25.8% in Asians) [46]. Despite study design and population differences, the observed variation in MHO prevalence reported both in the comparative studies and meta-analyses highlight the need for larger scale population representative studies, improved obesity classification and a global consensus on a standard MHO definition.

Characterisation and determinants of metabolically healthy obesity

Although the determinants of MHO and the molecular mechanisms underlying the MHO phenotype are not fully elucidated, accumulating evidence is improving our understanding of the biological factors which distinguish MHO on the one hand from obesity per say, and on the other hand, from metabolically unhealthy obesity [47, 48]. Here we summarise the recent literature regards determinants of metabolic health status, with a focus on potential biological, environmental and genetic factors involved in the pathogenesis of MHO.

Adiposity and body composition

It has been recognised that different body fat distribution patterns, most notably increased visceral adipose tissue (VAT) and ectopic fat deposition (intramuscular, hepatic and epicardial) are related to different metabolic phenotypes and obesity-related cardiometabolic risk [49-51]. Greater VAT is associated with impaired glucose tolerance, insulin resistance, increased secretion of very low density lipoprotein (VLDL) and increased intra-hepatic triglyceride content (IHTG) [52-56]. Hepatic fat has been

identified as a potential predictor of the MUO phenotype, type 2 diabetes and subclinical atherosclerosis [57-61]. It has been hypothesised that how the body channels surplus energy, arising from a combination of excessive caloric intake, reduced physical activity and increased time spent in sedentary behaviour, may determine an individual's predisposition to MHO or MUO. The pathway to MUO may be characterised by dysfunctional adipose tissue (larger fat cells), increased immune cell infiltration, raised pro-inflammatory status and reduced capacity of subcutaneous adipose tissue to expand leading to increased ectopic fat deposition resulting in lipotoxicity, insulin resistance in peripheral tissues and a range of metabolic derangements (**Figure 1**) [62]. Whereas in MHO individuals the excess calories are channelled into insulin-sensitive subcutaneous adipose tissue which is capable of expansion, thus visceral and ectopic adiposity are reduced, macrophage infiltration and raised pro-inflammatory state are attenuated, insulin sensitivity is preserved and the individual is protected from development of the MetS [47, 63-66].

It has been questioned whether increased VAT is just an innocent bystander acting as a marker of ectopic fat deposition or is indeed the culprit [67]. In a small study of 39 obesity-matched adolescents and adults Linder *at al.,* compared the impact of body fat distribution and ectopic fat, in particular liver fat, on insulin resistance with a view to establishing whether previously identified relationships in adults between liver fat and insulin resistance hold true among adolescents. Despite having lower VAT the overweight and obese adolescents were more insulin resistant than the gender and BMI-matched adults. Of note hepatic fat content, but not total body fat or VAT, was identified as an independent predictor of insulin resistance among both adolescents and adults [68]. An elegant study by Fabbrini *et al.,* examined the independent association of VAT and IHTG to metabolic function. They demonstrated increased VLDL-TG secretion and impaired insulin action in adipose tissue, skeletal muscle and liver of obese subjects with high IHTG, but not among those with high VAT matched for IHTG. Furthermore high IHTG was associated with altered expression and protein levels of CD36 (a protein involved in fatty acid metabolism) in adipose tissue and skeletal muscle, suggesting a role in ectopic fat accumulation. The authors concluded that IHTG, not VAT, is a better

indicator of metabolic functionality associated with obesity [69]. In later work this group examined the impact of weight gain among obese individuals defined by IHTG and insulin sensitivity as MHO and MUO [70]. Both groups were challenged with a high-fat diet to achieve ~6% weight gain. Despite similar fat mass increases there were distinct differences in the response to weight gain between the groups. Insulin sensitivity in adipose tissue, liver and skeletal muscle deteriorated and blood pressure, plasma TG, VLDL apoB100 concentrations and secretion rates increased among the MUO, but not the MHO individuals, suggesting that MHO subjects are protected against the adverse effects of weight gain. Such protection may be derived from the increased biological pathways and genes associated with adipose tissue lipogenesis observed among the MHO, but not the MUO, individuals [70]. From this evidence it seems that body composition and fat distribution, in particular VAT and hepatic fat, are both important players in determining cardiometabolic health status.

Diet and lifestyle factors

Environmental factors such as diet, physical activity, alcohol consumption and smoking play a role in the development of obesity. Simply put excessive caloric intake coupled with low levels of physical activity and/or increased sedentary time give rise to a positive energy balance leading to increased body fat accumulation. In the context of MHO diet, including dietary composition, dietary patterns and dietary quality, has been fairly widely studied. However the evidence supporting the role of diet in MHO has been surprisingly inconsistent to date. Interestingly similar total energy intake and dietary macronutrient intakes have been reported in MHO and MUO individuals [39, 71-73], leading researchers to examine dietary patterns, indices of dietary quality and compliance with dietary recommendations. A recent cross-sectional study involving 2415 middle-aged Australian adults reported that for every one standard deviation increase in the healthy dietary pattern, the likelihood of having a more metabolically healthy profile increased by 16% (OR 1.16, 95% CI 1.04-1.29) [74]. Using NHANES data (2007-2008 and 2009-2010) Camhi *et al.*, examined dietary quality assessed by the Healthy Eating Index 2005 (HEI-2005) scores among obese adolescents (n=133) and adults (n=1102) [21]. MHO was defined as obesity with two or less abnormal risk factors for fasting glucose,

hypertension, triglycerides and HDL-C [14]. HEI-2005 scores were higher among the MHO adolescents and women (aged 19-44 years) relative to their MUO counterparts, whereas no differences were noted among MHO and MUO men (aged 19-44 or 45-85 years). Examination of scores from specific food groups revealed that MHO adolescents had higher milk scores and scores from added sugars, solid fats and alcoholic beverages. Among the 19-44 year-old women, higher scores for whole fruits, whole grain, meat and beans were reported. These findings highlight the potential of dietary quality indices as intervention targets and the importance of such intervention starting earlier in life, as differences were only observed among adolescents and younger women. Park *et al.,* investigated Mediterranean Diet Scores (MDS) among 1739 adult participants of the National Health and Nutrition Examination Survey III (1988-1994) who were followed up for deaths until 2011 [75]. Metabolic health was defined using the Wildman definition [32]. Consumption of red meat and dairy products were lower among the MHO individuals, who also had a higher ratio of monounsaturated to saturated fatty acids, which contributed to their higher MDS. Furthermore, adherence to a Mediterranean style diet was associated with lower all-cause mortality among the MHO individuals (multivariable-adjusted hazard ratio of 0.44, 95% confidence interval (0.26-0.75) comparing the highest tertile to the first tertile of MDS), but not among the MUO subjects, perhaps suggesting that alternative strategies are required for MUO.

Given the range of MHO criteria available, we investigated in a cross-sectional cohort of 2047 middle-aged men and women to what extent differences between metabolically healthy and unhealthy obese and non-obese subjects, defined using a variety of metabolic health definitions may be explained by dietary composition, dietary quality and food pyramid compliance [39]. In keeping with previous findings total calorie intake, dietary macronutrient composition and also dietary quality were generally similar between the MHO and MUO individuals across MHO definitions. However better compliance with food pyramid recommendations was positively associated with MHO (defined by insulin resistance and Wildman). Furthermore, some differences in the number of daily servings of fruit and vegetables, dairy, meats, fats and high fat/sugar food and drinks were noted between the MHO and MUO subjects, depending on which MHO criteria used. Of note there was generally no effect of physical activity, smoking or alcohol intake observed between MHO and MUO individuals

across the range of MH definitions examined. Collectively these findings highlight the potential of dietary guidelines as intervention targets to improve cardiometabolic health status among obese individuals.

Diet and lifestyle interventions

Limited and inconsistent data regards the impact of dietary and exercise interventions in MHO exist [76-79]. Rondanelli *et al.,* reported significant improvements to a range of metabolic measures including HOMA, CRP, HDL-C, leptin, adiponectin, ghrelin, glucagon like peptide-1and fatty acid profiles among 103 MHO individuals following a 2 month prudent dietary intervention [80]. Unfortunately this study did not include MUO individuals. Kantartzis *et al.,* examined 262 MHO and MUO individuals, defined by HOMA and BMI, following a 9 month lifestyle intervention programme. Visceral fat was reduced in both groups post-intervention, however total body and liver fat was reduced among the MUO subjects only. These individuals also reported improvements in insulin sensitivity, although they remained insulin resistant [77]. In contrast Ruiz *et al.,* did not observe any differences in the magnitude of change in anthropometric measures between MHO (n=25) and MUO (n=53) women following a 12-week energy-restricted dietary intervention [81]. Janiszewski *et al*., reported reductions in body weight, total and visceral fat mass and enhanced insulin sensitivity in both MHO (n=63) and MUO (n=43) subjects following a 3-6 month exercise or diet-induced weight loss intervention, with greater improvements in insulin sensitivity among the MUO subjects [76]. A 5-10% reduction in body weight is considered to be clinically significant and as such can improve metabolic health among obese individuals. Lui *et al*., investigated the impact of a 5% lifestyle-based weight loss on the metabolic profiles of 392 MHO and MUO individuals [82]. Among those who achieved target weight loss, improvements to most risk factors were observed regardless of metabolic health status, suggesting that a clinically significant weight loss is beneficial to all obese individuals.

Cardiorespiratory fitness

Higher levels of cardiorespiratory fitness (CRF) are independently associated with healthier metabolic profiles and reduced risk of incident CVD and CVD mortality [83-86]. However the roles of physical and cardiorespiratory fitness (CRF) have not been extensively investigated in the context of understanding the determinants of MHO status. Dalleck *et al.,* examined metabolic syndrome components in 332 adults before and after a supervised 14 week community-based exercise program designed to improve cardiometabolic risk factors [87]. This short-term intervention, which improved cardiorespiratory fitness (assessed by conventional submaximal exercise test protocols for walking or cycle ergometry) and eliminated MetS features, positively transitioned MUO individuals to MHO status. The greatest results were observed among those engaging in higher volumes of exercise, suggesting community based exercise as an effective model for primary prevention of cardiometabolic disease. Ortega *et al.,* examined fitness (assessed by a maximal exercise test on a treadmill), body fat composition and metabolic health status among 43, 265 adults participating in The Aerobics Center Longitudinal Study [88]. Their findings suggest that the MHO phenotype, defined using BMI or BF%, is associated with better CRF in both men and women, and that once CRF level is accounted for the MHO phenotype may be benign in terms of mortality and morbidity risk. These authors recently reviewed the current evidence regards CRF and MHO from cross-sectional and longitudinal studies [89]. They conclude that better CRF should be considered to be a characteristic of the MHO phenotype, signal that caution should be taken regards whether CRF plays a role in the prognosis of the MHO individuals, and recommend further investigation of the role of CRF in MHO.

Genetics

Limited data regards genetic predisposition to MHO exists. As mentioned already the Beijing Children and Adolescents Metabolic Syndrome study (BCAMS) explored the contribution of both genetic and environmental factors to the pathogenesis of MHO among 6-18 year olds [30]. Although a limited number of genetic variants (22 single nucleotide polymorphisms (SNPs)) were examined, both the *KCNQ1* rs227892 and rs227897 SNPs were identified as independent predictors of MHO. Each additional C allele of either SNP was associated with reduced risk of being metabolically healthy

based on both cardiometabolic risk markers (23% lower risk) and insulin resistance (24% lower risk), with stronger associations identified when a composite genetic predisposition score was examined.

Interestingly this study provided the first evidence of gene-nutrient (soft drink consumption) and gene-environment (with walking to school) interactions predisposing to MHO. Clearly much work remains to be done in this area to uncover the influence of genetics, nutrigenetics and epigenetics on MHO pathogenesis. Berezina *et al.*, examined potential relationships between genetic variants of the adipocytokine genes (leptin, leptin receptor and adiponectin) and metabolically healthy (without CVD) abdominal obesity among adults [90]. Although genetic associations and gene-nutrient interactions have been described previously between genetic variants of these genes and MetS [91, 92], this study identified for the first time a more than two fold greater likelihood of MUO among the T allele carriers of the adionectin T45T polymorphism relative to the G allele carriers. Genetic predisposition to weight and metabolic health related traits has been investigated longitudinally in almost 4000 adult and 1380 adolescent participants of the Norwegian HUNT2 (1995-1997) and HUNT3 (2006-2008) surveys [93]. Examination of 27 SNPs previously associated with obesity, eating disorders or metabolic risk revealed novel genetic associations between a number of genes involved in regulation of food intake and energy expenditure, eating behaviour, food reward and satiety with longitudinal changes in BMI/WC and development of adverse metabolic phenotypes. Such data highlight the importance of not only improving our current understanding of the genetics but also the neurobiology of body weight regulation in the context of developing future strategies to combat obesity, and especially MUO.

Stability of metabolically healthy obesity across the life course

MHO was initially regarded as a static condition and, although some individuals can maintain their metabolic health status over time, it is becoming increasingly evident that MHO status is transient in nature. It has been suggested that the MHO phenotype starts in childhood and persists into adulthood. The Bogalusa Heart Study is unique in the context of examining MHO stability over time, in that the 1098 individuals participated in the study both as children (aged 5-17 years) and also as young adults

(24-43 years), with an average follow-up of 24 years (range 14.1-28.6 years) [16]. Importantly this study provides the opportunity to examine what happens to MHO status as we age from childhood, through adolescence into adulthood. The results are intriguing. The MHO children display similar favourable cardiometabolic profiles when adults relative to their childhood MUO counterparts. On the other hand the MUO children had the worst cardiometabolic profiles as adults. Although adult MHO status was maintained in only 13% of the MHO children, the MHO children were 2.7-9.3 times more likely to be MHO adults compared to children from the other metabolic health categories. Even though the MHO children displayed intermediate levels of insulin, glucose and blood pressure as adults, suggesting intermediate risk of T2DM and hypertension, examination of carotid intima media thickness (CIMT), a marker of atherosclerosis, did not reveal increased CIMT in adulthood [16]. As the cardiometabolic profiles of MHO adults have been shown to be more favourable than that of metabolically unhealthy normal weight individuals and more comparable to those of their normal weight counterparts, a better understanding of what factors contribute to achieving and maintaining good metabolic health from childhood into adulthood is critical.

As already mentioned while some individuals can retain MHO status over time a substantial proportion of individuals with MHO cannot and may become metabolically unhealthy. Indeed, it is possible for any individual to transition between metabolically healthy and unhealthy states regardless of their BMI. Such transitions may also contribute to the observed disparity in MHO prevalence, inverse association with age and conflicting findings regards cardiometabolic and mortality outcomes. Longitudinal investigations suggest that MUO is a progressive phenotype along which MHO represents a dynamic intermediate stage. Data from some of the earlier studies indicate that MHO status is transient for about a third of individuals. Follow-up (5.5-10.3 years) of the North West Adelaide Health Study cohort of 4,056 adults revealed that 33% of the MHO subjects became MUO over time, whereas for the remaining individuals persistent MHO status was associated with favourable cardiometabolic outcomes [94]. In keeping with these findings data from the Pizarra study indicate that 37% of MHO subjects were no longer metabolically healthy after a 6-year follow-up [95]. More recent data suggest that the numbers of MHO individuals becoming unhealthy over time are

actually greater. Longitudinal follow-up of the Tehran Lipid and Glucose Study revealed that 43.3% of the metabolically healthy abdominally obese transitioned to MUO over a 10 year period [96]. Data from the English Longitudinal Study of Ageing indicate that 44.5% of the MHO individuals became MUO over the 8-year follow-up [97]. Consistent with these findings data from the San Antonio Heart Study suggest that almost half (47.6%) of MHO subjects at baseline transitioned to MUO over the follow-up period (median 7.8 years) [98].

Characterisation of the factors which distinguish those who progress to or maintain MHO from those who transition from MHO to MUO may uncover potential intervention targets. In the San Antonio Heart Study those who transitioned were older, had lower HDL cholesterol levels and increased adiposity compared to the individuals with persistent MHO [98]. Interestingly none of the adiposity measures (BMI, waist circumference and weight gain) were significant predictors of this change[98]. Moreover, lipid profiles emerged as the strongest determinants of metabolic health status likely to develop with weight gain. In addition to baseline lipid concentrations (triglycerides and HDL-cholesterol), findings from the Tehran Lipid and Glucose Study indicate that insulin resistance is a significant predictor of the change from MHO to MUO [96]. Additional predictors have been identified in the English Longitudinal Study of Ageing. Compared to those with persistent MHO, those who converted to MUO were more likely to have high blood pressure, display increased abdominal adiposity and have elevated levels of C-reactive protein, glycated haemoglobin and triglycerides [97]. Collectively these findings highlight the importance of healthy lipid and inflammatory profiles in achieving and maintaining optimal cardiometabolic health. Further characterisation of persistent metabolic health status and longitudinal investigation of the sustainability and predictors of the MHO phenotype over the life course is warranted.

MHO and long term health outcomes

The individual and joint contributions of metabolic health and BMI on long term cardiometabolic health outcomes and mortality are yet to be fully elucidated and further investigation is required. A large systematic review and meta-analysis of 2.88 million individuals confirmed significantly higher all-cause mortality with obesity when all grades are combined [99]. However, examination of individual obesity grades revealed that grade 1 obesity (BMI 30 to < 35 kg/m^2) was not associated with higher mortality. These conflicting findings may be partly explained by the existence of different obesity associated metabolic health phenotypes. Examination of trends in metabolic health in the Northern Sweden MONICA study from 1986 to 2009 demonstrated that more people are becoming overweight and obese, and that a larger proportion of those individuals are metabolically healthy [100], which has been suggested may reduce the impact of obesity as a CVD risk factor [101]. Supporting this idea, a 20 year follow-up of the Atherosclerosis Risk in Communities Study recently reported intermediate risk for stroke, coronary heart disease and survival probability in individuals with suboptimal health (≤ 2 cardiometabolic risk factors), between that of the healthy and unhealthy subgroups , with no effect of BMI [102], suggesting that metabolic health may be more important than BMI in the context of adverse cardiometabolic outcomes.

Findings from prospective studies tracking the development of CVD, T2DM and mortality in MHO have been inconsistent [101, 103-108]. Thus whether MHO represents true health among obese individuals is controversial and remains the subject of ongoing debate [109-112]. Examination of all-cause and CVD mortality after 17.7 years follow-up of the Whitehall II cohort of 5,269 adults aged 39-62 (prevalence of MHO 9-41% depending on definition used) revealed that both the MHO and MUO subjects had increased mortality risk (hazard ratio (HR) ranged from 1.81; 95% CI 1.16–2.84 to 2.30; 95% CI 1.13–4.70 for MHO and from 1.57; 95% CI 1.08–2.28 to 2.05; 95% CI 1.44–2.92 for the MAO) relative to the metabolically healthy normal weight subjects [106]. Furthermore, increased risk of both incident CVD and T2DM was reported among MHO individuals relative to their healthy normal weight counterparts [113]. However, the MHO individuals were at a lower risk of T2DM but not CVD, compared to the MUO subjects. Thus MHO may not be as benign as initially thought and results are largely dependent on what outcome is examined and what reference group is used. In the Uppsala

Longitudinal Study of Adult Men (30 years follow-up of 1,758 subjects) increased mortality risk was identified in obese subjects with and without the MetS (2.4 and 1.7 fold higher, respectively) relative to the normal weight participants without the MetS [103]. The Third National Health and Nutrition Examination Survey (NHANES III) (8.7 years follow-up of 6,011 subjects), reported similar increased mortality risk (approximately 2.8-fold) between obese participants with ≤1MetS feature and obese subjects with ≥2 MetS features relative to their metabolically normal non-obese counterparts [107]. Furthermore using waist circumference rather than BMI to classify obesity, follow-up (average time of 13.4 years) of the EPIC-MORGEN cohort of 22,654 individuals aged 20-59 years revealed higher mortality risk among metabolically healthy abdominally obese (MHAO) subjects relative to their metabolically healthy non-obese (MHNAO) counterparts (HR 1.43; 95% CI 95% 1.00-2.04) [108]. Similar HRs were obtained for the metabolically unhealthy not abdominally obese subjects (MUNAO) (HR 1.31; 95% CI: 1.08-1.59), whereas higher HRs were identified for the metabolically unhealthy abdominally obese (MUAO) subjects (HR 1.99; 95% CI: 1.62-2.43 NS) [108]. Moreover, the Study of Women's Health across the Nation (SWAN) of 475 middle-aged women reported greater subclinical CVD burden among the metabolically healthy overweight/obese subjects relative to the MHNO women [114]. Collectively these findings suggest that obese subjects, whether metabolically healthy or not, and regardless of how MHO is defined carry greater risk of CVD and mortality and thus MHO may not be as apparently healthy as originally considered.

Conversely several studies have not reported higher risk of CVD and all-cause mortality among their MHO participants. Seven year follow-up of 22,303 men and women (mean age 54.1 years) from the Health Survey for England and Scottish Health Survey failed to demonstrate increased risk of CVD (HR 1.26; 95% CI 0.74-2.13) or all-cause mortality (HR 0.91; 95% CI 0.64-1.29) among MHO subjects (defined by NCEP ATP III, the Wildman definition and BMI) relative to their metabolically healthy non-obese counterparts [101]. Of note increased risk of all-cause mortality was observed among the MUO individuals (HR 1.72 95%CI 1.23-2.41) compared to the MHO subjects. Similar results were obtained when WC was used to define obesity. Calori *et al*., in a follow-up of 2,011 middle-aged adults over 15 years, reported increased CVD, cancer and all-cause mortality risk (HR 1.40; 95% CI

1.08-1.81) among the obese insulin resistant individuals, but not in the obese insulin sensitive (MHO) subjects relative to their non-obese insulin sensitive counterparts [104]. In addition to higher prevalence of CVD, greater severity of angiographic CAD has also been reported in a study of 856 Korean subjects among the metabolically unhealthy (defined by NCEP ATPIII) obese or normal weight subjects compared to the MHO or MHNO groups [115]. Examination of mortality risk in NHANES III (12-18 years follow-up of 4,373 men and women) demonstrated that MHO individuals (defined according to HOMA, NCEP ATP III, Karelis definition) were not at increased risk of all-cause mortality compared to the MHNO individuals [105]. More recently Guo *et al.,* investigated the relative impact of body weight and metabolic health on health outcomes using data from 2 large cohorts (Coronary Artery Risk Development in Young Adults Study and the Atherosclerosis Risk in Communities Study, with 18.7 and 20 years follow-up, respectively) [102]. They reported lower risk for T2DM, CVD, stroke and mortality among the MHO individuals relative to the MUO subjects, but increased diabetes risk compared to the MHNO subjects. Clearly the data on long term impact of MHO on cardiometabolic health and mortality risk is conflicting, which may be at least partly due to differences in study design, obesity classification, MHO definitions and reference groups. Whether obesity or metabolic health is a more important predictor of future health and/or disease remains unclear and further investigation of obesity associated metabolic health phenotypes is warranted.

MHO: role in risk stratification and personalised treatment?

Obesity is a multifaceted public health problem; the sheer complexity of the interacting biological, environmental and social determinants has been nicely illustrated by the UK Foresight obesity systems map [116]. However, it is becoming apparent that the situation is further complicated at a personal level by the existence of subtypes of obesity based on an individuals' metabolic health status. Despite an ever increasing evidence base which has highlighted potential intervention points including food production and consumption, physiology, individual physical activity, the physical activity environment, and both individual and social psychology, obesity prevalence continues to rise.

This begs the question of whether more personalised strategies to combat obesity, based on an individual's metabolic health background, may offer new opportunities in obesity diagnosis, intervention and treatment.

The existence, clinical utility and limitations of the MHO phenotype have been widely questioned and debated [109-112, 117-119]. While the lack of a universally accepted MHO definition and usefulness of BMI to accurately classify obesity are clearly pertinent issues, the concept that any form of obesity could be described as healthy is controversial. In a recent commentary Rey-Lopez argued that "more efforts must be allocated to reducing the distal and actual causal agents that lead to weight gain, instead of the current disproportionate scientific interest in the biological processes that explain the heterogeneity of obesity" [112]. However perhaps the heterogeneity of obesity, in terms of an individuals' phenotype and inter-individual differences in responsiveness to dietary or lifestyle interventions, should not be ignored. Recent evidence indicates that despite similar overall dietary intake between metabolic health subtypes that favourable lifestyle factors including higher dietary quality, healthy diet pattern, greater compliance with food pyramid recommendations, being less sedentary and more (moderately) physically active may all be positively associated with MHO [21, 39, 74, 120]. Interestingly examination of stable and unstable MHO suggests that a healthy lifestyle index may determine transition to MUO [121]. Furthermore a recent proteomics study identified dysregulated inflammatory and lipid processes as molecular hallmarks of MHO [122], confirming earlier findings that MHO individuals display more favorable lipoprotein [123] and inflammatory profiles [65]. Collectively such investigations may identify new behavioural and biological targets which may aid the development of more effective evidence based risk stratification, intervention and treatment strategies to reduce both obesity and its metabolic complications.

Supporting this concept, the American Association of Clinical Endocrinologists (AACE) in 2014 suggested a complication-centric approach to the management of weight loss, whereby more aggressive therapeutic approaches for those patients with obesity-related complications were advocated [124]. More recently the AACE and the American College of Endocrinology (ACE),

motivated according to the Chair of the AACE Obesity Scientific Committee by "the lack of comprehensive and evidence-based guidelines to real-world clinical care of patients with obesity", have developed new clinical practice guidelines (CGP) which acknowledge the need for a more individualised treatment approach to obesity [125]. These evidence-based CPGs address a range of aspects of obesity care including screening, diagnosis, clinical evaluation, treatment options, selection and goals. A notable shift here is the additional target of improving metabolic health rather than just weight loss per say. This development is timely, as it is evident that up to now approaches focussed on preventing and/or attenuating obesity and body weight have not achieved much success in halting the rising tide of obesity. While data on the impact of the new guidelines on the obesity epidemic will take some time to filter through it seems likely that high risk groups, such as the MUO who carry the greatest risk of both adverse cardiometabolic and mental health outcomes [101, 102, 104, 105, 115, 126], could really benefit from such risk stratification. However, if metabolic health is a more important driver of future health than obesity it could be argued that improving metabolic health and attenuating development of cardiometabolic disease in intermediate risk subgroups (with or without obesity), such as MHO and metabolically unhealthy non-obese individuals, may also be worthwhile.

Conclusions

It is clear that a great body of research on obesity-associated metabolic health phenotypes has been performed to date. However much remains to be done. Despite the knowledge that different obesity subtypes exist the research community has been slow to refine obesity and metabolic health definitions. While advances in the development of new obesity treatment guidelines are encouraging whether these will have the desired impact on reducing obesity and its complications remains to be seen. Better understanding of both the lifestyle determinants of MHO and the molecular mechanisms that mediate the MHO phenotype is warranted. To advance the state-of-the-art future research will need to focus on these issues from a life course perspective, as well as conducting larger evidence-

based lifestyle intervention studies and longitudinal follow-up, with a view to opening up new avenues of personalised obesity medicine.

Acknowledgements

This work was supported by a research grant from the Irish Health Research Board (reference HRC/2014/13).

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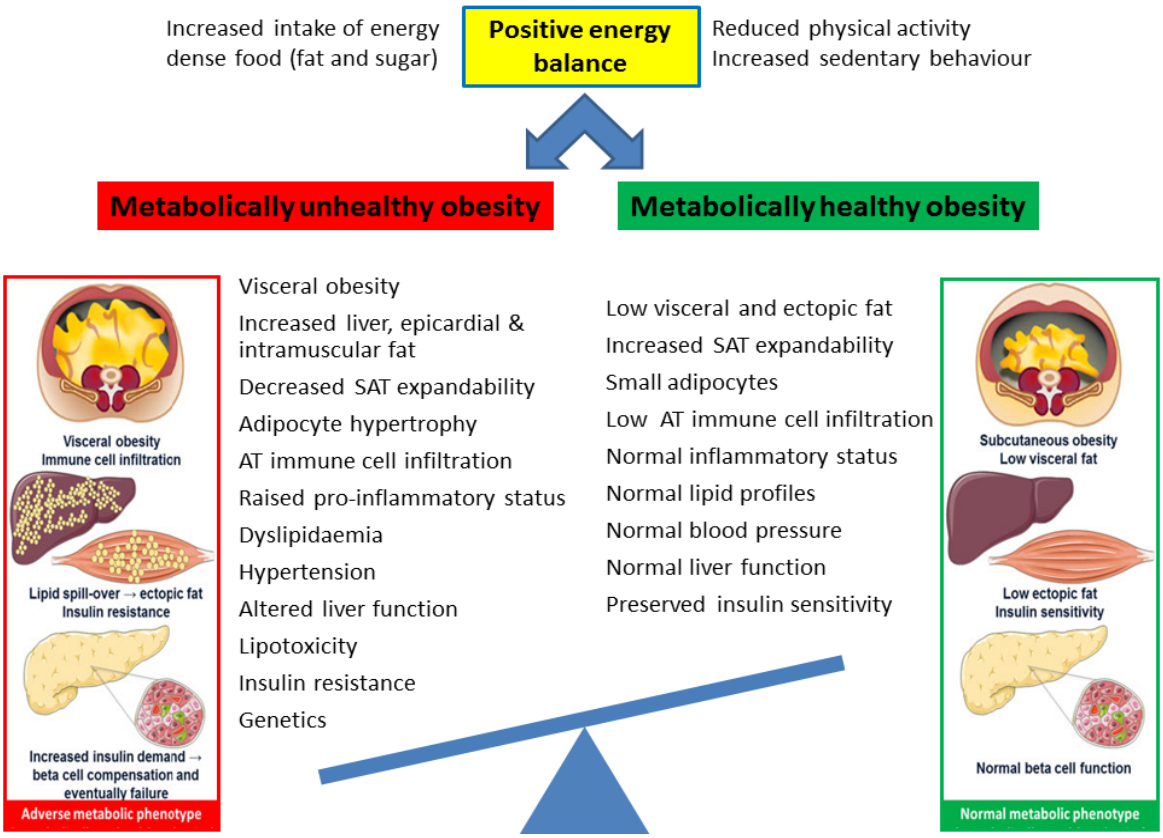
Figure 1



In this model it is hypothesized that the body's coping mechanism to a positive energy balance, arising from a combination of excessive caloric intake, increased levels of sedentary behaviour and reduced physical activity, may determine an individual's predisposition to MHO or MUO. The pathway to MUO may be characterised by dysfunctional adipose tissue, increased immune cell infiltration and reduced capacity of subcutaneous adipose tissue to expand leading to increased ectopic fat deposition resulting in lipotoxicity, insulin resistance in peripheral tissues and a range of metabolic derangements. Adapted from McMorrow *et al.*, [62].