Obesity Research & Clinical Practice 13 (2019) 548–554

Contents lists available at ScienceDirect

Obesity Research & Clinical Practice

journal homepage: www.elsevier.com/locate/orcp

Original Article

Metabolically healthy obesity (MHO) in the Malmö diet cancer study – Epidemiology and prospective risks

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ARTICLE INFO

Article history:
Received 21 August 2019
Received in revised form 15 October 2019
Accepted 18 October 2019

Keywords:
Cardiovascular
Epidemiology
Metabolic syndrome
Morbidity
Mortality
Obesity

ABSTRACT

Background/aims: Metabolically healthy obesity (MHO) remains controversial, since the underlying mechanisms behind this phenotype remain unclear. We aimed to investigate the characteristics of MHO, as well as prospective risks.
Method: A cross-sectional analysis was carried out in a subsample of 3812 obese subjects selected from the Malmo diet cancer study (n = 28,403). Subjects with MHO (n = 1182) were defined by having no records of hospitalization for somatic disorders prior to baseline examination. MHO subjects were further compared to subjects with metabolically unhealthy obesity, MUO (obese individuals with at least one recorded hospitalization: n = 2630), and all non-obese cohort controls (NOC; n = 24,591). Moreover, prospective risk analyses for incident cardiovascular (CV) morbidity and mortality were carried out.
Results: Compared to MUO individuals, MHO individuals reported a significantly lower proportion of sedentary life style (p = 0.009), but also significantly lower HbA_{1c} (p = 0.012), fasting glucose (p = 0.001) and triglyceride levels (p = 0.011) than MUO. Cox-regression analysis (follow-up 20 ± 6 years) showed both a significantly lower all-cause mortality risk for MHO individuals as compared to MUO (p = 0.001), as well as lower incident CV morbidity risk (p = 0.001). When comparing MHO individuals to NOC, there were no significant differences in neither mortality risk nor incident CV morbidity risk.
Conclusion: Compared to MUO individuals, MHO individuals presented with a higher level of physical activity, a more favorable lipid- and glucose profile and a lower prospective risk of total mortality and CV morbidity during 20-years follow-up. Notably, no significant differences could be seen in mortality and CV morbidity risks when comparing MHO subjects to non-obese controls.

Introduction

Obesity has become a growing global epidemic, contributing to the risk of developing numerous chronic diseases including cardiovascular disease (CVD) and diabetes type 2 (DM2) [1]. Furthermore, it has been well established that overweight and obesity are associated with a higher all-cause mortality risk compared to normal-weight subjects [2]. At least since the 1980s the prevalence of obesity and overweight individuals has been steadily increasing, today representing more than one third of the general population [3]. The definition of obesity is a Body Mass Index (BMI) ≥30 kg/m^2. Even if this measurement is not without critical remarks, it still is one of the most accurate assessment for predicting CVD mortality in overweight individuals [4].

In recent years, a controversial debate has arisen, discussing the heterogeneity of obesity and that some obese individuals might be less negatively influenced by their excess weight than others [5–7]. A phenomenon, known as the *obesity paradox*, suggests that

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; CV, cardiovascular; DM2, diabetes type 2; HF, heart failure; IR, Incidence rate; MDCS, Malmö diet cancer study; MDCS-CV, Malmö diet cancer study – cardio vascular arm; MHO, Metabolically healthy obesity; MHNW, Metabolically healthy normal weight; MUO, Metabolically unhealthy obesity; MUNW, Metabolically unhealthy normal weight; NOC, Non-obese cohort controls; SBP, Systolic blood pressure; SD, Standard deviation.

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https://doi.org/10.1016/j.orcp.2019.10.002
1871-403X/

many types of CVD, especially heart failure (HF), may have a better prognosis in the overweight or even obese patients compared to their leaner counterparts [8]. This could in part be explained by the fact that many of these disease conditions (e.g. HF) are associated with a chronic catabolic state, where lean body mass loss carries a negative prognosis, hence the term cardiac cachexia [9].

Recently the concept of 'Metabolically Healthy Obesity' (MHO) has been described, based on the absence of risk factors of the Metabolic syndrome [5,10], reporting obese but metabolically healthy individuals with a more favorable inflammatory and metabolic profile [11]. Other studies that support this notion, further describe MHO individuals having a higher degree of physical activity (PA) and cardiorespiratory fitness (CRF) compared to their unhealthy counterparts – thus supporting a concept known as *fat but fit* [12]. Additionally, obesity has been linked to a state of chronic inflammation, leading to insulin resistance and disruption of other aspects of the energy homeostasis [13] – this may be downregulated in obese individuals considered metabolically healthy, but is yet to be proven. Nevertheless, a systematic review and meta-analysis showed that MHO individuals did run an increased risk of future CV events, compared to Metabolically Healthy Normal Weight (MHNW) individuals, but not increased risk of all-cause mortality [6]. However, other studies reported that relative risks for developing CVD was not significantly higher among individuals with MHO, compared to MHNW individuals [14]. Lastly, a recent systematic review and meta-analysis did show that MHO subjects had an increased risk for all-cause mortality as well as development of CV disease compared to MHNW subjects [15].

Thus, when considering the aforementioned contradicting studies, there is a need to better understand the underlying mechanisms behind obesity, as well as its heterogeneity, to be able to address the increasing prevalence and incidence of obesity in the world. By mapping MHO, we can gain a deeper understanding of risk determinants for obesity as well as biological mechanisms, life style and social factors, and in the extension how it could be treated causally and individualized.

The *aim* of this observational study is to describe determinants, characterizing patterns and prognosis for CVD and mortality among middle-aged individuals with MHO. We will compare individuals with MHO and metabolic unhealthy obese (MUO) individuals, when groups are defined by a history of long-term non-hospitalization for somatic disease versus hospitalization, respectively, but also with non-obese controls (NOC).

Subjects

The Malmö Diet Cancer Study (MDCS) started with baseline examination between 1991 and 1996 at the University Hospital in Malmö, Sweden, with the main goal to study the contribution of dietary patterns to cancer incidence and mortality. Men born 1923–1945 and women born 1923–1950, at the time residing in Malmö, were invited to participate. In all, 28,098 subjects participated (2/3 women, 41% attendance rate) [16] (see Fig. 1). At baseline, the participants were examined with anthropometric measurements, dietary assessment, a self-administered questionnaire and blood samples. A detailed description of the baseline investigations has been previously published [16,17].

Every second individual of MDCS was re-invited to participate in a cardiovascular sub-cohort of MDCS, between 1992 and 1994, (MDC-CV; n = 6103). The primary aim was to study the epidemiology of carotid artery disease, including ultrasound examination and laboratory analyses of additional fasting blood samples [18,19].

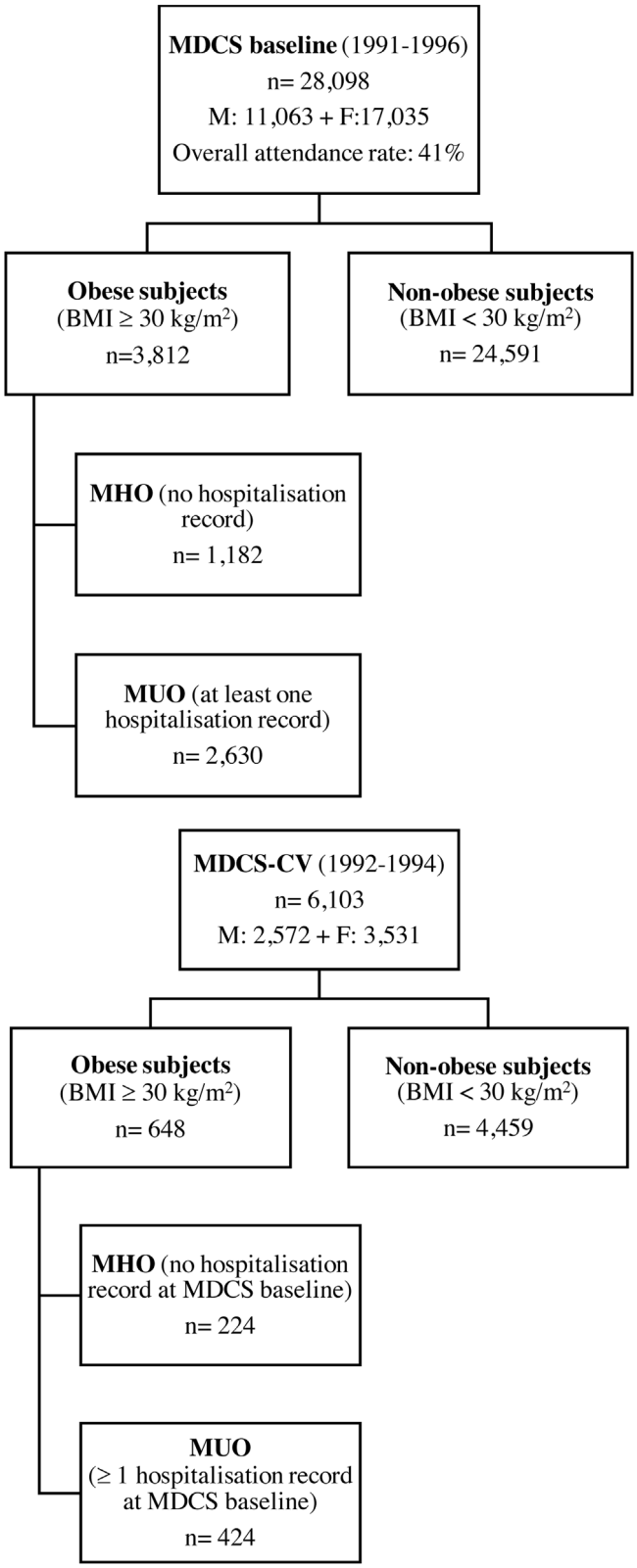

Fig. 1. Flow charts of (a) the MDCS baseline cohort and (b) the MDCS-CV sub-cohort stratified for obese and non-obese subjects respectively.

Metabolically healthy obesity (MHO)

All obese individuals (BMI ≥ 30 kg/m^2) from the MDCS baseline examination, were selected to be included in the study (n = 3812; 13.5%) (see Fig. 1). These individuals were sub-divided into two different groups, depending on absence or presence of hospitalization for somatic disease, as recorded in the Swedish National Hospital Inpatient Register, up until the baseline inclusion in MDCS. Hospitalization due to normal deliveries and external injuries/intoxications were considered non-hospitalization for our aim. Obese individuals with no recorded history of hospitalization before baseline were considered MHO (n = 1182; 4%), whereas obese individuals with at least one recorded history of hospitalization were considered MUO (n = 2630; 9.5%). These two groups were further compared with non-obese controls, NOC (n = 24,591), from the cohort. This novel approach of defining MHO individuals, has been previously applied in another local cohort from the same population [20].

Methods

Physical examination

At the MDCS baseline, all participants were examined for weight (kg) and height (cm) without shoes and in light indoor clothing and BMI was calculated (kg/m^2). Waist and hip circumference (cm), including waist-to-hip ratio, was measured in the standing position without clothing. Moreover, lean body mass and body fat was assessed by a bioelectrical impedance method. Furthermore, right arm blood pressure (mmHg) was measured twice in the recumbent position after a 5-minute rest, using the Korotkoff phase V [16,17,21].

Laboratory data

Fasting venous blood samples were drawn and stored at the biological bank −80 °C, but only in participants (n = 5540) from MDCS-CV. Laboratory blood tests for high sensitivity (hs) C-reactive protein (hsCRP) (mg/L), HbA_{1c} (%), fasting blood glucose (mmol/L), triglycerides, total cholesterol, LDL and HDL cholesterol (mmol/L), were analysed at the Department of Clinical Chemistry, Skåne University Hospital in Malmö, participating in a national standardisation and quality control system [19].

Questionnaire

The participants filled out a questionnaire including family history, demographic and socio-economic variables (including marital status and educational level), social network and support, previous and current occupation, recent stress exposure or mental problems, smoking status (yes, regularly/yes, occasionally/no, stopped smoking/no, never smoked), alcohol usage (g/day), medical history (previous and current diseases), and medications [21].

Leisure time physical activity

Method used, at the MDCS-baseline, was adapted from the Minnesota Leisure Time Physical Activity Questionnaire. The participants were asked, in the questionnaire, to report the amount of physical activity during their leisure time by being presented a list of eighteen different activities – they were then asked to fill in how many minutes per week they spent, on average, on each activity. The result was then multiplied using an activity-specific intensity coefficient, where the product was called a physical activity score. The variable for physical activity during leisure time provided the following answer alternatives: sedentary spare time (category 1), moderate exercise in spare time (category 2), regular exercise and training (category 3), and hard training or competition sport (category 4). This was further computed into binary (sedentary = 1/active = 2–4), creating a variable called sedentary spare time (%) [21].

Register end-point data

All individuals were followed from baseline until the first CV-event, death (obtained from Swedish total population register Statistics Sweden [SCB]), migration or end of study December 31st 2016. Endpoints were retrieved through the Swedish Inpatient Registry and the Causes of Death register, administrated by the Swedish National Board of Health and Welfare. Furthermore, the definition of a stroke event was additionally supplemented by information through the local STROMA-register with its Relapse-register [22]. The definition of an incident CV-event (fatal or non-fatal) included *myocardial infarction* and *ischaemic heart disease* (ICD-9 codes 411–414; and ICD-10 codes I20, I24, I251–I259), *stroke* (ICD-9 430–434, 436 and ICD-10 I60–I64), *heart failure* (ICD-9 428 and ICD-10 I50, I11.0) and *atrial fibrillation/flutter* (ICD-9 427D, 4273 and ICD-10 I48).

Statistical methods

De-identified epidemiological data was analyzed using descriptive statistical methods, comparing MHO individuals to both MUO individuals and NOC. Analysis of the difference in continuous variables was made by one-way ANOVA, whereas dichotomous and category variables were analyzed through using Mann–Whitney U-test and Chi-squared test.

The values of the variables for smoking habits (1–4) were computed into binary (No: 1/ Yes: 2–4). Moreover, the variable for physical activity in free time (1–4) variable was computed into binary (sedentary: 1/ active: 2–4). In addition, a prospective risk analysis of mortality incidence and incident cardiovascular morbidity, from the time of start-up until the end of follow-up, was performed using Cox-regression analysis. All statistical analyses were made using IBM SPSS Statistics version 25 (SPSS, Chicago, IL, USA). Statistically significance level was set at p-value less than 0.05.

Results

MHO versus MUO subjects

Compared to MUO individuals (one-way ANOVA) MHO individuals were younger (58 ± 7 years vs. 60 ± 7 years; p = 0.001) and more likely to be male (41.2% vs. 37.1%; p = 0.016). Additionally, MHO individuals had a significantly lower BMI (MHO 32.6 kg/m^2 vs. MUO 33.1 kg/m^2; p = 0.001) as well as lower waist and hip circumference (p = 0.001), but no significant differences could be seen in the waist/hip ratio. No statistically significant difference in mean blood pressure was seen between the two groups. Moreover, MHO individuals reported a significantly lower proportion of sedentary life style than MUO (17.4% vs. 21.9%; p = 0.009), and were more likely to hold a university degree (13.4% vs. 9.4%; p = 0.003). MUO individuals were more likely to be ever smokers (MUO 61.8% vs. MHO 56.3%; p = 0.008) but no significant difference was seen in alcohol consumption (p = 0.3). Furthermore, MHO individuals had significantly lower HbA_{1c} (p = 0.012), fasting plasma glucose (p = 0.001) and triglyceride levels (p = 0.011), as compared to their MOU counterparts. No significant difference could be seen in cholesterol (total cholesterol, HLD-C and LDL-C) or hsCRP levels. See Table 1 for more detailed results.

Table 1
Descriptive comparison and significance testing for MHO (n = 1182) compared to MUO subjects (n = 2630); and MHO compared to NOC subjects (n = 24,591), with standard deviation (SD) or percentage (%) for metric and categorical variables, respectively.

Variable	MHO	MUO	p-Value	NOC	p-Value
Anthropometric data (MDCS)					
N	1182	2630		24,591	
Gender (men, %)	487 (41.2)	975 (37.1)	0.016	9,754 (39.7)	0.306
Age (years, SD)	58 (7.2)	60 (7.4)	<0.001	58 (7.61)	0.026
BMI (kg/m^2, SD)	32.6 (2.6)	33.13 (3.06)	<0.001	24.64 (2.76)	<0.001
Waist (cm, SD)	99.7 (11.7)	101.22 (11.42)	0.002	81.66 (13.17)	<0.001
Hip (cm, SD)	111.2 (7.7)	112.47 (9.36)	<0.001	96.33 (6.7)	<0.001
Waist/hip ratio (n (25–75)) median (25–75)[a]	0.88 (0.82–0.98)	0.89 (0.83–0.98)	0.185	0.83 (0.77–0.92)	<0.001
SBP (mmHg, SD)	149 (18.6)	148 (19.13)	0.889	140 (19.9)	<0.001
DBP (mmHg, SD)	91 (9.4)	90 (9.59)	0.061	85 (9.84)	<0.001
Outcomes (MDCS)					
Mortality (n, %)	422 (36.3)	1201 (46.6)	<0.001	8,178 (33.6)	0.066
Incident CV-event (n, %)	260 (22.3)	749 (29)	<0.001	4,957 (20.4)	0.109
Incident rate for CV-event[b]	18.1	25.3	–	17.0	–
Prevalent diabetes (n, %)	82 (6.9)	296 (11.3)	<0.001	883 (3.6)	<0.001
Social and lifestyle data (MDCS)					
N	800	1612		17,837	
Smoking current or past, (n, %)[c]	450 (56.3)	997 (61.8)	0.008	10,896 (61.1)	0.006
Regular smoking (years, SD)	21.2 (13.5)	24.5 (13.8)	<0.001	23.2 (14.1)	0.006
Alcohol intake (g/day)	11.08 (14.8)	10.25 (15.44)	0.282	11.14 (12.25)	0.988
Sedentary leisure time, (n, %)[d]	139 (17.4)	353 (21.9)	0.009	1 899 (10.6)	<0.001
Physical Activity Score (SD)	7933 (5660)	7300 (5881)	0.079	8,417 (6759)	0.119
University degree, (n, %)[e]	107 (13.4)	152 (9.4)	0.003	2 825 (15.8)	0.065
Married, n (%)[f]	506 (63.2)	997 (61.8)	0.503	11,504 (64.5)	0.472
Laboratory data (MDCS-CV)					
N	224	424		4459	
Total cholesterol (mmol/L, SD)	6.25 (1.13)	6.30 (1.13)	0.845	6.14 (1.06)	0.293
hsCRP (mg/L, SD)	0.37 (0.44)	0.45 (0.58)	0.215	0.24 (0.42)	<0.001
HDL-C (mmol/L, SD)	1.24 (0.30)	1.20 (0.29)	0.287	1.41 (0.37)	<0.001
LDL-C (mmol/L, SD)	4.96 (0.88)	4.31 (1.04)	0.989	4.15 (0.98)	0.105
Triglycerides (mmol/L, SD)	1.59 (0.72)	1.76 (0.76)	0.011	1.26 (0.60)	<0.001
Fasting glucose (mmol/L, SD)	5.49 (1.36)	5.90 (1.92)	<0.001	5.06 (1.19)	<0.001
HbA_{1c} (%, SD)	5.09 (0.78)	5.77 (1.08)	0.012	4.85 (0.67)	<0.001
Drug treatment and diabetes (MDCS-CV)					
BP-lowering drugs (n, %)	53 (52 %)	178 (57 %)	0.108	676 (33 %)	0.003
Lipid-lowering drugs (n, %)	2 (2 %)	22 (7 %)	0.083	105 (5 %)	0.235

[a] Interquartile range (IQR) 25–75.
[b] Incident rate for any cardiovascular event per 1000 person-years.
[c] Dichotomized to 0 = no, never. 1 = yes, regularly; yes, occasionally; no, stopped smoking.
[d] Dichotomized to 0 = moderate exercise in leisure time; regular exercise and training; hard training or competition sport. 1 = sedentary leisure time.
[e] Dichotomized to 0 = no university degree. 1 = university degree.
[f] Dichotomized to 0 = unmarried. 1 = married.

MHO versus NOC subjects

When comparing MHO individuals to NOC subjects, differences could be seen in blood pressure, where NOC had a significantly lower systolic and diastolic blood pressure (140/85 ± 19.9/9.8 vs. 149/91 ± 18.6/9.4 mmHg; p = 0.001). Furthermore, NOC had a more favorable glycaemic profile with both significantly lower HbA_{1c} (NOC 4.85% ±0.67 vs. MHO 5.09% ±0.78; p = 0.001) and fasting blood glucose (p = 0.001). The inflammatory status, defined by measuring hsCRP, was lower in NOC (0.24 ± 0.42 vs. 0.37 ± 0.44 mg/L; p = 0.001). More MHO subjects had antihypertensive drugs and diabetes than NOC subjects. See Table 1 for more detailed results.

Prospective risk of all-cause mortality and cardiovascular events

Incident rate (IR) for developing cardiovascular disease during 1000 person years was significantly lower for MHO individuals (18.1) compared to MUO subjects (25.3). Additionally, when comparing the IR between MHO and NOC (17.0), there were no significant differences. Cox-regression analysis adjusted for age, gender, smoking, blood pressure, sedentary behavior and waist/hip ratio (mean follow-up time 20 ± 6 years) showed a significantly lower all-cause mortality risk for MHO individuals as compared to MUO, HR 0.74 (95% CI: 0.66-0.82; p = 0.001), as well as lower total incident CV morbidity risk, HR 0.69 (95% CI: 0.60-0.80; p = 0.001). Interestingly, when comparing MHO individuals to NOC, there were no significant differences in neither mortality risk (p = 0.9), nor incident CV morbidity risk (p = 0.7), see Table 2 for additional data. Unadjusted Kaplan Meier curves presenting all-cause mortality risk and incident CV-event risk for MHO, MUO and NOC are shown in Figs. 2 and 3 respectively.

Discussion

The concept of MHO was approached by a newly adopted definition as previously described [20]: i.e. obese individuals with the absence of hospitalization for somatic disease up until approximately 60 years of age (the average age of MHO individuals being 58 ± 7 years). The key findings from our study include MHO individuals having a more metabolically favorable profile (lower levels of fasting blood glucose and HbA_{1c}, as well as lower triglyceride levels) than their MUO counterparts. There were no significant differences in the waist/hip ratio between MHO and MUO individuals, implying that the abdominal fat distribution did not significantly differ between the two groups. Furthermore, when examining social and lifestyle data, MHO subjects were characterized by less seden-

Table 2
Mortality risk in MHO (n = 1182) vs. MUO (n = 2630) and NOC (n = 24,591) subjects until end of follow-up. Cox regression analysis with 95% confidence intervals.

Variables	HR	95% CI for HR		p-Value
		Lower	Upper	
Total mortality risk				
MHO vs. MUO	0.80	0.70	0.92	0.001
Smoking status	1.20	1.05	1.37	<0.001
Gender (female)	0.71	0.62	0.81	<0.001
Age (years)	1.11	1.10	1.12	<0.001
SBP (mmHg)	1.01	1.00	1.01	0.003
Sedentary leisure time (%)	1.42	1.24	1.63	<0.001
Waist/hip ratio	3.00	2.03	4.34	<0.001
CV event risk[a]				
MHO vs. MUO	0.77	0.65	0.92	0.003
Smoking status	0.97	0.82	1.14	0.708
Gender (female)	0.58	0.48	0.69	<0.001
Age (years)	1.07	1.05	1.08	<0.001
SBP (mmHg)	1.01	1.01	1.02	<0.001
Sedentary leisure time (%)	1.31	1.10	1.57	0.003
Waist/hip ratio	2.27	1.31	3.92	0.003
Total mortality risk				
MHO vs. NOC	0.95	0.84	1.07	0.358
Smoking status	1.50	1.42	1.59	<0.001
Gender (female)	0.84	0.78	0.90	<0.001
Age (years)	1.12	1.12	1.13	<0.001
SBP (mmHg)	1.01	1.01	1.01	<0.001
Sedentary leisure time (%)	1.71	1.60	1.83	<0.001
Waist/hip ratio	4.29	3.12	5.91	<0.001
CV event risk[a]				
MHO vs. NOC	0.95	0.82	1.10	0.462
Smoking status	1.29	1.20	1.38	<0.001
Gender (female)	0.68	0.63	0.74	<0.001
Age (years)	1.08	1.07	1.08	<0.001
Systolic blood pressure (mmHg)	1.01	1.01	1.01	<0.001
Sedentary leisure time (%)	1.38	1.26	1.52	<0.001
Waist/hip ratio	4.38	3.23	5.94	<0.001

Values are presented as hazard ratios (HR) with 95% confidence interval (95% CI). SBP = systolic blood pressure.
[a] Incident CV-events, excluding individuals with prevalent CV-events.

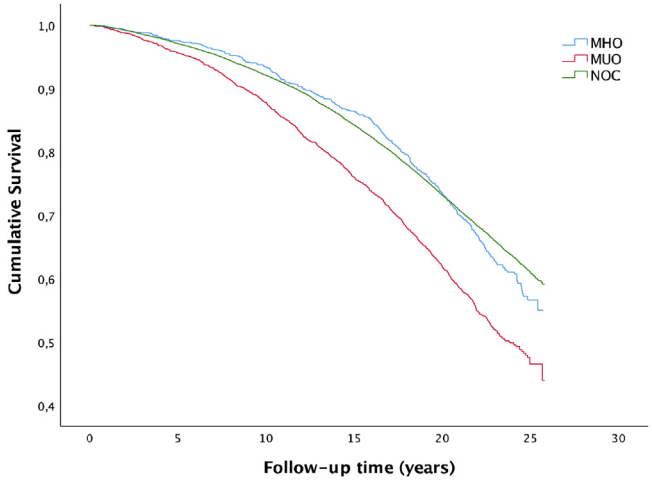

Fig. 2. All-cause mortality risk for MHO (n = 1182), MUO (n = 2630) and NOC (n = 24,591) respectively.

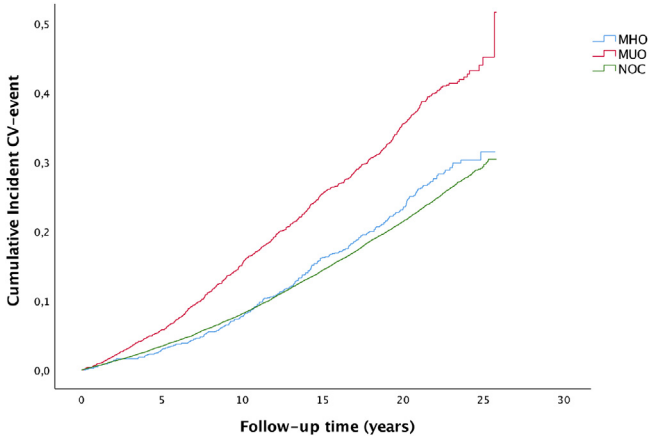

Fig. 3. Incident CV-event risk for MHO (n = 1182), MUO (n = 2630) and NOC (n = 24,591) respectively.

tary behavior, a lower proportion of smokers and additionally a higher educational level than MUO subjects. These traits could play an important role when analyzing the prospective risks, which revealed a significantly lower mortality risk for MHO individuals along with a lower risk of incident, non-fatal CV events, compared to MUO.

On the other hand, when comparing MHO with NOC individuals the latter displayed a more benign metabolic status, with lower levels of glucose, inflammatory protein and lipids in their blood and additionally lower blood pressure, apart from having a lower BMI. Despite these differences, prospective risk analyses (mean follow up-time 20 ± 6 years) for both all-cause mortality and incident CV events could not detect any significant differences between these two groups.

The concept of MHO has been eagerly debated during recent years, casting doubt on its mere existence. Even the media has tried to illustrate this phenomenon, citing findings from the *Nurses' Health Study*, supporting the notion that there is still a significantly higher risk of developing CV disease in obese individuals regardless

of metabolic health status [23]. Furthermore, accumulating evidence is clarifying the MHO phenotype, based on the absence of risk factors, to be a transient state [23–25], where MHO with time will transform into MUO. We hypothesize, however, that in some individuals this phenotype (MHO) is perhaps more stable than in others based on a more strict definition of MHO. Thus, an evident pitfall is how MHO is defined. In general, the definition of MHO focuses on the presence or absence of the metabolic syndrome (MetS) or whether the individual has developed a certain number of risk factors for MetS or not [26]. Furthermore, another common way of defining MHO is based upon insulin resistance levels by using the insulin sensitivity Index (HOMA-IR), with a certain cut-off point [27,28]. The dilemma of these definitions is that many of the risk factors involved and used to define MetS (i.e. triglyceride- and HDL-C levels, fasting glucose), shift intra-individually during repeated measurements at different time points. Moreover, accumulating evidence points out that the absence of MetS in obese subjects is not an entirely harmless condition [5].

By using this definition of MHO as being non-hospitalized for somatic disease up until midlife in spite of obesity, i.e. the MDCS baseline examination, we were able get an objectively defined phenotype which could serve as an alternative to the conventional way of defining MHO. Not to be overlooked, some individuals might be treated for chronical illnesses in a primary care unit and thus avoiding inpatient care; however, the outpatient care in Sweden up until the 1990's was limited [29] and not as developed as presently.

There are several limitations of this study. First, the poor overall attendance rate at the MDCS baseline examination (41%) could imply a health selection bias. Furthermore, there is an imbalance of gender, with a majority of women (61%) adding to the selection bias and thus not being fully representative of the local population. When gathering social and lifestyle information at baseline, reporting biases cannot be excluded. We also acknowledge that BMI was only measured at the baseline examination and that this variable indeed could shift intra-individually over time, but mostly as an increase in mid-life. Additionally, BMI does neither measure body composition nor fat distribution [30]. Lastly, another limitation of the study was that subjects with non-hospitalisation prior to baseline could still have prevalent hypertension or diabetes, two risk factors for clinical events and not really compatible with the concept of MHO. On the other hand, these conditions could have been milder or counterbalanced by protective mechanisms in the affected subjects leading to a status of "non-hospitalisation" in our analyses. Furthermore, we do not include data on risk factors during follow-up as the analyses were focused on clinical events only.

On the other hand, the MDCS is a large (n = 28,098), well-characterized prospective cohort, and not to forget, population-based, with a follow-up time of 20 years. Moreover, the MDCS-baseline and MDCS-CV sub-cohort have been linked to excellent national and well validated register data on hospitalization, why it was possible to apply our new approach to define MHO. Hospitalization as a marker of poor health could serve as a better indicator to describe an individual's health status than changing risk factor levels.

In this observational study we have shown obesity to be a heterogenous phenomenon, where certain obese individuals that escape hospitalization for somatic disease up until mid-life have a more benign prognosis than other obese subjects. At the same time, individuals characterized as MHO do not seem to have an increased risk of developing CV-disease, during a follow up time period of approximately 20 years, compared to non-obese individuals. This suggests an alternative interpretation as compared to several other studies [6,12,23,25,31], where subjects with MHO had an increased risk of developing CV-disease, when compared to MHNW individuals. What characterizes MHO, when compared to MUO (apart from a more favorable metabolic profile) is a less sedentary lifestyle. This supports the notion of MHO individuals being *fat but fit*, which is in line with a recent systematic review [12].

It would indeed be interesting to define MHO with a higher cut-off BMI value (i.e. BMI $\geq 35\ kg/m^2$), like in our previous study in another cohort [20], but too few individuals could be included when studying the MDCS-CV population. Likewise, it would be compelling to analyze MHO individuals with more precise body measurements, such as CT- and MRI-scanning for fat and muscle distribution. Furthermore, a meta-analysis describing MHO individuals' prospective risks would likewise be interesting; however, this requires additional studies adopting the same concept of a non-hospitalization status. Another interesting research aim would be to examine differences regarding socioeconomic factors, biomarkers and genetic variants between MHO and MUO subjects.

Conclusion

By applying a novel approach to define MHO as non-hospitalization for somatic disease individuals up until approximately 60 years of age, we observed a more favorable metabolic profile, a less sedentary lifestyle and a higher educational level compared to their MUO counterparts. Prospective risk analyses for all-cause mortality and incident CV morbidity confirmed this phenotype as more benign, as MHO individuals had, for both outcomes, a decreased risk compared to MUO. Interestingly, when comparing MHO to non-obese individuals, there were no significant differences in neither total mortality nor incident CV risk. Our results are in line with previous research in this field, based on other definitions, but differ regarding a more favorable incident CV risk for MHO individuals.

Conflicts of interest

The following authors report no conflict of interest: JK, AJ, MM, and PMN. One author is an employee of AstraZeneca: EB.

Funding

The study was funded by the Research Council of Sweden, Research Funds of Region Skåne and the Ska°ne University Hospital Funds and Foundations (Sweden). Author MM was supported by grants from the Medical Faculty of Lund University, Skane University Hospital, the Crafoord Foundation, the Ernhold Lundstroms Research Foundation, the Region Skane, the Hulda and Conrad Mossfelt Foundation, the Southwest Skanes Diabetes Foundation, the Kockska Foundation, the Research Funds of Region Skåne, the Swedish Heart and Lung Foundation and the Wallenberg Center for Molecular Medicine, Lund University.

Ethical statement

We have read and have abided by the statement of ethical standards for manuscripts submitted to the Obesity Research & Clinical Practice.

Acknowledgements

We thank Anders Dahlin, data manager. The Knut and Alice Wallenberg foundation is acknowledged for generous support.

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