Preventive Medicine 94 (2017) 7–11

Contents lists available at ScienceDirect

Preventive Medicine

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

Characterization of the metabolically healthy phenotype in overweight and obese British men

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ARTICLE INFO

Article history:
Received 20 June 2016
Received in revised form 31 October 2016
Accepted 6 November 2016
Available online 10 November 2016

Keywords:
Cardiorespiratory fitness
Physical activity
Metabolic healthy
Metabolic unhealthy
Obesity
Metabolic syndrome

ABSTRACT

We calculated the prevalence of the metabolically healthy but obese (MHO) phenotype in ($n = 9177$) British men (age 48.9 ± 7.4 years) attending preventive health screening between 2000 and 2009. We examined differences in cardiorespiratory fitness (Fitness) and self-reported physical activity levels, according to whether the men were metabolically healthy (<2 components of the metabolic syndrome), and by BMI category (normal-weight, overweight, obese). Fitness was estimated from treadmill exercise as VO_{2peak} and classified as: Low, Moderate, or High using age-specific cut-offs. We identified 21.6% of our sample as obese, of whom 83.1% were metabolically healthy. Compared with the metabolic unhealthy obese (MUO; 3.7% of sample), MHO phenotypes were fitter (effect size $d = 0.21$) and were more physically active ($d = 0.31$). Logistic regression showed high fitness (OR = 2.40, 95% CI 1.38–4.19), and being physically active (OR = 1.71, 95% CI 1.14–2.56) to be independently associated with the MHO phenotype. Our findings agree with US data suggesting that higher cardiorespiratory fitness is a characteristic of the MHO phenotype. Our finding that meeting physical activity guidelines was associated with the MHO phenotype independent of fitness is, however, novel. If confirmed, our findings indicate that public health messages that encourage active lifestyles to promote fitness should be encouraged regardless of weight status.

1. Introduction

Individuals with an adverse metabolic health profile have a three-fold greater risk of all-cause mortality than those who are metabolically healthy, regardless of their body mass index (BMI) (Kramer et al., 2013). This reduced mortality risk is greatest in obese individuals who remain metabolically healthy (Kramer et al., 2013; Roberson et al., 2014). Attempts to characterize the metabolically healthy obese (MHO) phenotype suggest they are younger and have a more favorable body fat distribution than metabolically unhealthy obese (MUO) individuals (Primeau et al., 2011). Visceral fat accumulation, birth weight, and adipose cell size have been implicated in the development of the MHO phenotype, but the authors did not explore the potential roles of physical activity or cardiorespiratory fitness (fitness).

A review of possible factors underlying the lower mortality risk associated with the MHO phenotype (Roberson et al., 2014) identified seven studies showing they were more active than MUO individuals. Roberson et al. (2014) identified one study (Katzmarzyk et al., 2005) which reported that differences in fitness accounted for the increased risk of cardiovascular mortality observed in MUO phenotypes, compared with normal-weight individuals of normal-weight (MHNw). Based on these findings, Roberson and colleagues suggested that all studies examining the MHO phenotype should assess physical activity or fitness due to their possible mediating effect on cardiovascular disease risk. Another recent review characterizing the role of fitness in the MHO phenotype identified ten studies reporting higher fitness in MHO compared with MUO phenotypes (Ortega et al., 2015). Findings were mostly limited to comparisons between small groups of post-menopausal women. However, a recent, larger study of >5000 US men and women (Ortega et al., 2013) also found significantly higher fitness in MHO versus MUO phenotypes. Ortega et al. (2015) suggested that such findings may help inform public health messages that emphasize the importance of tackling low fitness as well as weight loss per se. The cardio-protective effects of physical activity (Blair and Jackson, 2001) and fitness (Aspenes et al., 2011) independent of adiposity (Lee et al., 2012) are well documented, yet fitness remains an underused and underrated prognosticator (Mark and Lauer, 2003; Roger et al., 1998).

To evaluate this proposal, we aimed to undertake a detailed examination of differences in physical activity and fitness across groups defined by metabolic health and BMI status. Using criterion referenced standards for fitness and physical activity we also sought to clarify the

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http://dx.doi.org/10.1016/j.ypmed.2016.11.001
0091-7435/

relative contribution of physical activity and fitness to metabolic health within and across different BMI categories.

2. Methods

Ethical approval was granted by the Faculty of Society & Health ethics committee, Buckinghamshire New University. Men (aged 20–69 years) attended one of five Health & Wellbeing clinics around England for a three-hour preventative health assessment between 2000 and 2009. Participants attended general health examinations as an annual benefit provided by their corporate wellness schemes. Screening attendance was voluntary, as such the study participants represent a self-selected opportunity sample. Each participant was instructed in their pre-assessment information pack to avoid vigorous physical activity, alcohol and caffeinated beverages for 24 h prior to their assessment. Participants, in a supine position, underwent a resting electrocardiogram (ECG) for 5 min using the Marquette CASE Stress system (GE Healthcare, UK). Each participant signed and consented to the test battery which was countersigned by the duty medical officer.

2.1. Demographic and anthropometric measurements

Participants reported their date of birth, and home postcode. Date of birth was used to calculate age, and postcode was used to determine area-level deprivation using the English Indices of Deprivation (EID).

Body mass was measured using digital scales (Marsden Weighing, Rotherham, UK) and recorded to the nearest 0.1 kg. Clothing was worn but shoes and belts were removed, and participants evacuated their bladder before stepping onto the scales. Scales were calibrated daily with a known weight and bi-annually by the manufacturer. Stature was measured using a stadiometer (Seca, Hamburg, Germany) and recorded to the nearest 0.1 cm. Participants removed their shoes, stood on the platform with feet together, and head in the Frankfort plane. Buttocks and scapulae were in contact with the back of the stadiometer, shoulders relaxed with hands and arms loosely at the sides, the measurement was taken on full inhalation. Body mass index (BMI, $kg \cdot m^{-2}$) was calculated and categorized as normal-weight (18.5–24.9 $kg \cdot m^{-2}$), overweight (25–29.9 $kg \cdot m^{-2}$) or obese (≥30 $kg \cdot m^{-2}$). Waist circumference (WC) was measured to the nearest 0.1 cm using a flexible anthropometric tape measure, midway between the lowest rib and the iliac crest at minimal inspiration.

Participants reported the frequency of moderate weekly bouts of physical activity (e.g. at least 30 min of brisk walking) and vigorous sessions per week (e.g. at least 20 min of gym or sporting activity). Participants were categorized as physically active if they achieved ≥150 min of moderate activity or 75 $min \cdot week^{-1}$ vigorous activity per week. Participants also self-reported whether they smoked tobacco or drank alcohol and if so, how many units they consumed in a typical week.

2.2. Venous blood sampling

Participants presented in a fasted state (for the previous 12 h) but ate a snack (fruit or muesli bar) prior to the exercise test. At the start of each assessment, fasted venous blood samples were obtained using vacutainer tubes and heparinized whole blood was analyzed using the Piccolo blood chemistry analyzer (Abaxis, USA). The following analytes were measured: glucose, total cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein (HDL), tryglycerides, and TC/HDL ratio.

2.3. Exercise tolerance test

Participants positioned themselves on the T2100 treadmill (GE Healthcare, UK), and undertook an incremental exercise test using the Bruce protocol. Blood pressure was monitored at the second minute of each stage using the automatic Tango stress test BP monitor (Suntech Medical, Oxfordshire, UK). Ratings of Perceived Exertion were recorded at the end of each stage using the 6–20 Borg Scale. The ECG was monitored throughout the test. Participants exercised until they attained ≥85% of age-predicted maximum heart rate (220 − age) or met any of the test termination criteria outlined by the American College of Sports Medicine (ACSM, 2013). VO_{2peak} was estimated and reported in $ml \cdot kg^{-1} \cdot min^{-1}$.

2.4. Data treatment

We excluded participants with a BMI < 18.5 $kg \cdot m^{-2}$ and >40 $kg \cdot m^{-2}$, and those diagnosed with diabetes mellitus, coronary artery disease, or cancer.

We classified participants as metabolic healthy if they presented with <2 components of the metabolic syndrome (MetS) excluding waist circumference (Ortega et al., 2013, 2015; Primeau et al., 2011; Roberson et al., 2014). The four components assessed were: blood pressure > 130/85 mm Hg, HDL cholesterol < 1.036 $mmol \cdot l^{-1}$, triglycerides > 1.695 $mmol \cdot l^{-1}$ and fasting plasma glucose > 6.1 $mmol \cdot l^{-1}$ (Grundy et al., 2005). Data were divided into 10-year age strata and VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$) was categorized as low (≤20th percentile), moderate (>20–<80th percentile) or high (≥80th percentile) fitness based on age-specific reference values (Heyward, 2014).

2.5. Data analysis

We cross-tabulated metabolic health and BMI to create six phenotype groups: Metabolically Healthy Normal-weight (MHNw), Metabolically Unhealthy Normal-weight (MUNw), Metabolically Unhealthy Overweight (MUOw), Metabolically Healthy Overweight (MUOw), Metabolically Unhealthy Obese (MUO), and finally, Metabolically Healthy Obese (MHO). We examined between-phenotype differences in fitness and physical activity using two-way analysis of variance (ANOVA). If there was a significant main effect for metabolic health, between metabolically healthy and unhealthy groups we also calculated effect sizes (Cohen's d). Pearson's χ^2 tests were used to compare categorical variables across BMI categories and groups. Separate χ^2 tests were used to examine frequency differences within BMI categories.

Within each BMI category, multivariate logistic regression was used to calculate the age-adjusted odds of being metabolically healthy according to physical activity (active) and fitness (moderate, high). We first calculated age-adjusted OR of good metabolic health within Model 1. We then adjusted estimates of age, smoking status, alcohol consumption and BMI (continuous variable; Model 2). Finally, to account for the effects of central adiposity, we calculated a fully-adjusted model including waist circumference (Model 3). Collinearity diagnostics were performed to calculate tolerance and variance inflation factors (VIF); multicollinearity requiring was defined as a VIF > 4 and serious (requiring correction) if VIF > 10.

To assess whether associations between fitness, physical activity, and metabolic health were independent of BMI category, we calculated age-adjusted ORs of MH according to: Fitness (High, Moderate or Low), self-reported physical activity (Active or Inactive), and BMI category (Nw, Ow, O). We next adjusted this model for age, smoking status and alcohol consumption (Model 2) then additionally for WC (continuous; Model 3). All analyses were performed in SPSS version 22.0 (SPSS an IBM Company, IBM Ltd., NY, USA) used to analyze all data.

3. Results

We recruited $n = 9177$ men (age 48.9 ± 7.4 years) of whom 56.4% were overweight and 21.6% were obese (Table 1). Overall, 84.2% of participants were classified as metabolically healthy but this was less common in those who were obese (83.1%) compared with overweight or normal-weight. The MHO phenotype accounted for 17% of the total sample.