Metabolically Healthy Obesity and Ischemic Heart Disease: A 10-Year Follow-Up of the Inter99 Study

Louise Hansen,[1]* Marie K. Netterstrøm,[1]* Nanna B. Johansen,[1,2,3] Pernille F. Rønn,[1,4] Dorte Vistisen,[1] Lise L. N. Husemoen,[3] Marit E. Jørgensen,[1,5] Naja H. Rod,[6] and Kristine Færch[1]

[1]Steno Diabetes Center Copenhagen, 2820 Gentofte, Denmark; [2]Danish Diabetes Academy, 5000 Odense, Denmark; [3]Research Center for Prevention and Health, Center for Health, Capital Region of Denmark, 2600 Glostrup, Denmark; [4]Department of Public Health, Center for Arctic Health, Aarhus University, 8000 Aarhus, Denmark; [5]National Institute of Public Health, University of Southern Denmark, 1353 Copenhagen, Denmark; and [6]Section of Social Medicine, Department of Public Health, University of Copenhagen, 1014 Copenhagen, Denmark

Context: Recent studies have suggested that a subgroup of obese individuals is not at increased risk of obesity-related complications. This subgroup has been referred to as metabolically healthy obese.

Objective: To investigate whether obesity is a risk factor for development of ischemic heart disease (IHD) irrespective of metabolic health.

Design: In all, 6238 men and women from the Danish prospective Inter99 study were followed during 10.6 (standard deviation = 1.7) years.

Setting: General community.

Participants: Participants were classified according to body mass index and four metabolic risk factors (low high-density lipoprotein cholesterol, elevated blood pressure, triglycerides, and fasting plasma glucose). Metabolically healthy individuals were defined as having no metabolic risk factors, and metabolically unhealthy individuals were defined as having a minimum of one.

Main Outcome Measures: IHD.

Results: During follow-up, 323 participants developed IHD. Metabolically healthy obese men had increased risk of IHD compared with metabolically healthy normal-weight men [hazard ratio (HR), 3.1; 95% confidence interval (CI), 1.1 to 8.2)]. The corresponding results for women were less pronounced (HR, 1.8; 95% CI, 0.7 to 4.8). Being metabolically healthy but overweight was not associated with higher risk of IHD in men (HR, 1.1; 95% CI, 0.5 to 2.4), and in women the risk was only slightly increased and insignificant (HR, 1.5; 95% CI, 0.8 to 3.0). A substantial proportion of metabolically healthy individuals became metabolically unhealthy after 5 years of follow-up. When these changes in exposure status were taken into account, slightly higher risk estimates were found.

Conclusions: Being obese is associated with higher incidence of IHD irrespective of metabolic status, and we question the feasibility of denoting a subgroup of obese individuals as metabolically healthy.
(*J Clin Endocrinol Metab* 102: 1934–1942, 2017)

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received 1 October 2016. Accepted 1 March 2017.
First Published Online 7 March 2017

*These authors contributed equally to this study.

Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HDL, high-density lipoprotein; HR, hazard ratio; IHD, ischemic heart disease; MI, myocardial infarction; SD, standard deviation.

Overweight and obesity are major public health concerns with both individual and socioeconomic consequences (1). In 2014, >1.9 billion adults were overweight, including ~600 million obese (2). A subgroup of obese individuals has been identified with lower risk of developing obesity-related complications than expected according to their level of obesity (1). This subgroup has been referred to as metabolically healthy obese (1).

The concept of metabolically healthy obesity has been discussed during the past decade, and the conclusions are ambiguous. Some studies have reported that metabolically healthy obese individuals are not at increased risk of developing cardiovascular disease (CVD) compared with the metabolically healthy normal-weight or metabolically healthy nonobese individuals (3–10). Conversely, other studies indicate that metabolically healthy obese individuals are at increased risk of CVD compared with metabolically healthy normal-weight individuals (11–16).

Some studies found diverging results when using different definitions or outcomes or when stratifying by ethnicity and sex (17–21). Some of the discrepancy between the results relates to the use of different definitions of metabolic health and outcomes. In other words, there is lack of consensus in the way metabolically healthy obesity is defined (22, 23). In their main analyses, most previous studies allowed the metabolically healthy individuals to have at least one metabolic risk factor (3–8, 10–21, 24), limiting the interpretation of the findings, as risk factors differ within and between study populations, and they might affect the risk of CVD differently.

To better guide clinicians regarding CVD prevention, it is important to establish (1) whether obesity *per se* contributes to CVD in individuals with a metabolically healthy profile, and (2) whether metabolically healthy obesity is a permanent or a transient state. The aim of this study was therefore to investigate whether obesity is a risk factor for ischemic heart disease (IHD) irrespective of metabolic health using longitudinal data from a large Danish prospective cohort study. The current study uses a strict definition of metabolic health, defining metabolically healthy individuals as having none of the classical metabolic CVD risk factors.

Subjects and Methods

Study population

This study is embedded in the Inter99 study, which is a Danish randomized nonpharmacological intervention study with the primary purpose of preventing IHD in the Danish population through lifestyle changes (25). The Inter99 study has been described in detail elsewhere (25).

In brief, 12,934 individuals living in the southwestern part of Copenhagen County were invited for a clinical health examination in 1999 to 2001. Of these individuals, 6784 (52.5%) participated in a baseline examination. The participants were asked to complete a questionnaire, which included questions on lifestyle, education, chronic diseases, and psychosocial factors (25).

Before the baseline examination, the participants were prerandomized to high-intensity intervention (group A, 90%) or low-intensity intervention (group B, 10%) (25). Participants in group A, who were assessed as being at high risk of IHD, were offered participation in six group meetings on either smoking cessation, smoking reduction, or diet and physical activity. Participants at high risk in group B were referred to their general practitioner. Participants at low risk in groups A and B were not offered intervention (25).

After 5 years of follow-up the participants were invited for a re-examination, and after 10 years of follow-up information on IHD from Danish health care registries was collected on all participants.

A previous analysis evaluating the effect of the intervention in the Inter99 study found that the high-intensity intervention had no effect on IHD (26).

Definition of the outcome

Information on fatal and nonfatal IHD was obtained from both the National Hospital Registry and the Cause of Death Registry. The diagnosis at discharge and the date of the first hospitalization with IHD were used to define an event of IHD. In cases with no prior hospitalization with IHD, the date of death due to IHD was used as the date of diagnosis.

To define IHD, the International Classification of Diseases-10 codes I20 to I25 and International Classification of Diseases-8 codes 410 to 413 were used. Additionally, procedures relevant to IHD were included (Supplemental Table 1).

Definition and measure of body mass index and metabolic health

The exposure was defined as a combination of body mass index (BMI) and metabolic health.

According to the criteria of the World Health Organization, normal weight was defined as BMI of 18.5 to 24.9 kg/m^2, overweight as BMI of 25 to 29.9 kg/m^2, and obesity as BMI of ≥30 kg/m^2 (27). Weight was measured to the nearest 0.1 kg with participants wearing indoor clothes, no shoes, and having no items in their pockets. Height was measured to the nearest 0.5 cm with participants not wearing shoes.

We used a strict definition of being metabolically healthy. Metabolically healthy individuals were defined as having none of the following metabolic risk factors: high blood pressure (systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg), high plasma triglycerides (≥1.7 mmol/L), elevated fasting plasma glucose (≥ 6.1 mmol/L), and low plasma high-density lipoprotein (HDL) cholesterol (men, <1.0 mmol/L; women, <1.2 mmol/L). Individuals with one or more of the four metabolic risk factors were categorized as metabolically unhealthy. Participants had been fasting overnight before the health examination. The participants' blood pressure was measured twice after 5 minutes of rest with the participants in a supine position and the mean systolic and diastolic blood pressures were calculated. Plasma HDL cholesterol and triglycerides were measured in fasting blood samples by using enzymatic techniques (Boehringer Mannheim, Mannheim, Germany). Furthermore, the participants' plasma glucose

concentration was measured in the fasting blood samples using the hexokinase/glucose-6-phosphate dehydrogenase technique (Boehringer Mannheim).

Participants were divided into six exposure groups: (1) metabolically healthy normal weight (reference group), (2) metabolically healthy overweight, (3) metabolically healthy obese, (4) metabolically unhealthy normal weight, (5) metabolically unhealthy overweight, and (6) metabolically unhealthy obese.

Covariates

Based on standardized questionnaires, information on socioeconomic status, cohabitation, lifestyle factors, stress, and cardiovascular predisposition was obtained.

The participants were classified as follows: ethnicity—(1) Danish, Swedish, Norwegian, Icelandic, or Faroese origin, or (2) other origin; socioeconomic status—(1) no work and primary school only, (2) no work and ≥1 year of education/vocational training, (3) work and primary school only, (4) work and 1 to 3 years of education/vocational training, or (5) work and ≥4 years of education/vocational training; cohabitation—(1) yes or (2) no. The variable concerning physical activity takes physical activity at work and in leisure time into account (sedentary, light, moderate, high, and very high intensity) (28). Using a 48-item food frequency questionnaire, a dietary quality score was developed (29). Based on this score, the participants' dietary habits were considered as (1) healthy, (2) average, or (3) unhealthy (29). Other factors included: smoking—(1) daily smoker, (2) occasional smoker, (3) ex-smoker, or (4) never a smoker; alcohol—the average number of standard drinks per week.

For stress, information on psychological strain related to the job was used: (1) yes, (2) sometimes, (3) no, or (4) no job. To account for predisposition to IHD, a question asking whether the participants' parents had experienced an event of myocardial infarction (MI) was used and the participants were categorized as (1) yes (one or both parents had an MI), (2) no (neither parent had an MI), or (3) unknown (MI status unknown for one parent and no MI for the other parent or unknown for both parents). To account for the intervention of the Inter99 study, the participants were categorized as (1) group A, high risk; (2) group B, high risk; or (3) groups A and B, low risk.

Study sample

Of the 6784 participants, 65 participants with previous IHD were excluded. Furthermore, 37 participants were excluded due to (1) missing information on BMI, (2) missing information on all metabolic risk factors used to compute the exposure variable, or (3) missing information on one or more of the metabolic risk factors and favorable values on the rest of the metabolic variables. Hence, among these participants it was not possible to compute the exposure. The main analyses include information on sex, age, ethnicity, smoking, diet, physical activity, and cohabitation. Thus, participants with missing information on one or more of these covariates (n = 375) were excluded. Finally, 69 individuals with a BMI of <18.5 kg/m^2 were excluded, leaving a total of 6238 participants for the main analyses in this study.

Statistical analyses

Participants were followed in national registers from the date of the clinical health examination at baseline to the date of the first event of IHD, emigration, nontraceability in the registers, death from other causes than IHD, or the last day of follow-up without an event of IHD, whichever came first. The last day of follow-up was defined as 31 December 2010. The mean [standard deviation (SD)] follow-up time was 10.6 (1.7) years.

Cox proportional hazards regression analyses were used to estimate the risk of IHD in groups defined by BMI and metabolic health. The crude model was adjusted for age and intervention group (model 1). The main model was further adjusted for smoking, physical activity, diet, cohabitation, and ethnicity (model 2). Analyses were conducted for men and women separately.

To account for changes in exposure status during follow-up, an analysis was performed where each participant's time of follow-up was split in two parts (from baseline to 5 years of follow-up, and from 5 years of follow-up to 10 years of follow-up; model 3). When possible, the participants' exposure status at 5 years of follow-up was included; that is, if the participant had no missing values on any of the four metabolic risk factors or if at least one adverse value was registered. In the latter case, the participant was categorized as metabolically unhealthy. Participants with missing information on all metabolic risk factors at the 5-year follow-up examination maintained their baseline exposure status during the entire study period. Similarly, participants who had favorable values on the available metabolic risk factors but missing values on at least one metabolic risk factor were included with only their baseline exposure status. Confounders assessed at baseline and 5-year follow-up were included in the analyses. If confounders were missing at 5-year follow-up, the value from baseline was included. Models 1, 2, and 3 included 6238 participants (3049 men and 3189 women).

For all analyses SAS 9.2 statistical package (SAS Institute, Cary, NC) was used, and $P < 0.05$ was considered significant.

Proportional hazards assumption

The assumption of proportional hazards was tested statistically and graphically. Both tests did not reveal any deviations from proportionality of particular shapes that warrant special modeling of the interaction. Hence, it is concluded that the estimates of the relative risk between the groups from the Cox model give an adequate description of the relative hazards between the groups.

Sensitivity analyses

Three sensitivity analyses were performed.

Adjustment for additional confounders. Alcohol consumption, socioeconomic status, family history of IHD, and stress were identified as potential confounders; however, these covariates were not included in the main Cox model due to a large number of missing values (alcohol consumption, n = 324; socioeconomic status, n = 557; family history of MI, n = 285; and work-related stress, n = 340). The multiple adjusted models were further adjusted for these covariates to examine whether the main results were biased due to lack of adjustment. This analysis included 2639 men and 2701 women.

Changing the definition of obesity. Waist circumference was used as an alternative measure of obesity. Waist circumference was defined as normal waist (men, ≤94 cm; women, ≤80 cm), medium waist (men, >94 and ≤102 cm; women, >80 and

≤88 cm), and large waist (men, >102 cm; women, >88 cm) (30). Participants with missing information on waist circumference were excluded, leaving 3049 men and 3179 women for the analysis.

Multiple imputation of missing variables. The analyses of models 1 and 2 were repeated on a dataset where missing data on the confounders in the models were imputed using the multivariate imputations by chained equations method (31) (mice package in R software) with missing-at-random assumptions. The data set included 6610 participants (3242 men and 3368 women) who had complete information on exposure variables, BMI ≥ 18.5 kg/m^2, and no previous IHD events. Fifty copies of the data, each with missing values suitably imputed, were independently assessed in the statistical analyses described previously. Estimates of parameters of interest were averaged across the copies according to Rubin's rules (32).

Results

Baseline characteristics

Baseline characteristics are shown in Table 1 for men and Table 2 for women.

A total of 58 men and 114 women were categorized as metabolically healthy obese, which corresponded to <3% of the study population. The mean (SD) age was 46.3 (7.8) years among men and 45.7 (8.0) years among women. Overall, the mean age increased with increasing BMI, and the mean age was higher among metabolically unhealthy participants compared with metabolically healthy participants.

By design, the mean values of the four metabolic risk factors were more adverse among metabolically unhealthy participants compared with metabolically healthy participants. Additionally, within the metabolically healthy and unhealthy groups the mean values of the metabolic risk factors worsened with increasing BMI. Within BMI groups, the mean BMI was higher among metabolically unhealthy participants compared with metabolically healthy participants.

Incidence of IHD

During follow-up, 206 men and 117 women experienced a first event of IHD. Ninety-nine men and 76 women died of other causes than IHD, and 26 men and 20 women emigrated. A total of 2711 men and 2965 women were followed to the last day of follow-up without an event of IHD.

Table 3 shows the risk of incident IHD among the exposure groups in 3049 men and 3189 women. The metabolically healthy normal-weight individuals were used as reference group. Among both men and women the risk of IHD was comparable in model 1 (adjusted for age and intervention) and model 2 (additionally adjusted for smoking, physical activity, dietary habits, cohabitation, and ethnicity). Metabolically healthy obese

Table 1. Baseline Characteristics of 3049 Men From the Danish Inter99 Study

	Exposure						
	Healthy			Unhealthy			
Covariates	Normal Weight (n = 507)	Overweight (n = 434	Obese (n = 58)	Normal Weight (n = 542)	Overweight (n = 1053)	Obese (n = 455)	All (n = 3049)
Age, y	44.4 (7.5)	44.2 (7.6)	45.2 (8.2)	46.1 (8.0)	47.4 (7.6)	48.1 (7.5)	46.3 (7.8)
Ethnicity, % DK, SE, NO, IS, FO	482 (95)	410 (95)	54 (93)	515 (95)	996 (95)	436 (96)	2893 (95)
SES, % no work, no education[a]	14 (3)	12 (3)	2 (4)	19 (4)	26 (3)	12 (3)	85 (3)
Cohabitation, % no	88 (17)	47 (11)	7 (12)	111 (21)	128 (12)	72 (16)	453 (15)
Physical activity, % sedentary	136 (27)	137 (32)	18 (31)	158 (29)	321 (31)	178 (39)	948 (31)
Dietary habits, % unhealthy	115 (23)	75 (17)	11 (19)	116 (21)	212 (20)	100 (22)	629 (21)
Smoking, % daily smoker	201 (40)	132 (30)	20 (35)	237 (44)	381 (36)	136 (30)	1107 (36)
Alcohol, standard drinks per week[a]	11.8 (12.5)	11.8 (11.7)	9.3 (8.5)	14.8 (15.9)	15.1 (16.1)	15.5 (23.1)	14.0 (16.2)
BMI, kg/m^2	22.8 (1.5)	26.8 (1.3)	31.9 (2.0)	23.2 (1.4)	27.4 (1.4)	33.4 (3.3)	26.8 (3.9)
HDL cholesterol, mmol/L[a]	1.5 (0.3)	1.3 (0.2)	1.2 (0.2)	1.3 (0.4)	1.2 (0.3)	1.1 (0.3)	1.3 (0.3)
Triglycerides, mmol/L[a]	0.9 (0.3)	1.0 (0.3)	1.1 (0.3)	1.6 (1.9)	1.8 (1.4)	2.2 (1.6)	1.5 (1.4)
Fasting plasma glucose, mmol/L[a]	5.3 (0.4)	5.4 (0.3)	5.6 (0.3)	5.8 (1.3)	5.9 (1.2)	6.4 (1.8)	5.8 (1.2)
Systolic BP, mm Hg)	121.8 (8.8)	124.1 (8.1)	125.9 (9.1)	135.8 (16.4)	138.6 (16.0)	144.1 (17.1)	133.8 (16.3)
Diastolic BP, mm Hg[a]	76.1 (6.7)	78.0 (6.5)	80.4 (5.3)	85.7 (10.2)	88.5 (10.3)	92.8 (10.7)	85.0 (10.9)
Family history of MI, % yes[a]	97 (20)	66 (16)	7 (12)	104 (20)	193 (19)	91 (21)	558 (19)
Work-related stress, % yes[a]	79 (16)	70 (17)	12 (21)	82 (16)	169 (17)	75 (17)	487 (17)

Continuous variables are presented as means (SD) and categorical variables are presented as n (%).

Abbreviations: DK, Danish; FO, Faroese; IS, Icelandic; NO, Norwegian; SE, Swedish; SES, socioeconomic status.

[a]For the 3049 men, data are complete for all variables except for HDL cholesterol (missing, n = 4), fasting plasma glucose (missing, n = 1), diastolic BP (missing, n = 1), triglycerides (missing, n = 5), alcohol (missing, n = 70), socioeconomic status (missing, n = 197), work-related stress (missing, n = 101), and family history of MI (missing, n = 127).

Table 2. Baseline Characteristics of 3189 Women From the Danish Inter99 Study

	Exposure						
	Healthy			Unhealthy			
Covariates	Normal Weight (n = 1096)	Overweight (n = 444)	Obese (n = 114)	Normal Weight (n = 555)	Overweight (n = 539)	Obese (n = 441)	All (n = 3189)
Age, y	43.8 (7.5)	45.0 (7.7)	45.1 (7.7)	46.8 (8.2)	47.7 (7.9)	47.3 (8.0)	45.7 (8.0)
Ethnicity, % DK, SE, NO, IS, FO	1048 (96)	417 (94)	106 (93)	536 (97)	516 (96)	423 (96)	3046 (96)
SES, % no work, no education[a]	25 (2)	10 (2)	5 (5)	31 (6)	40 (8)	29 (7)	140 (5)
Cohabitation, % no	208 (19)	84 (19)	24 (21)	118 (21)	90 (17)	94 (21)	618 (19)
Physical activity, % sedentary	382 (35)	173 (39)	52 (46)	204 (37)	225 (42)	204 (46)	1240 (39)
Dietary habits, % unhealthy	108 (10)	43 (10)	11 (10)	65 (12)	67 (12)	59 (13)	353 (11)
Smoking, % daily smoker	381 (35)	141 (32)	24 (21)	233 (42)	182 (34)	122 (28)	1083 (34)
Alcohol, standard drinks per week[a]	7.0 (7.7)	6.9 (7.7)	4.8 (5.2)	7.8 (8.6)	7.1 (9.6)	5.0 (7.0)	6.8 (8.1)
BMI, kg/m^2	22.2 (1.6)	26.9 (1.4)	32.8 (3.1)	22.8 (1.5)	27.3 (1.4)	35.0 (4.4)	25.9 (5.0)
HDL cholesterol, mmol/L[a]	1.7 (0.3)	1.6 (0.3)	1.5 (0.3)	1.5 (0.5)	1.4 (0.4)	1.3 (0.3)	1.6 (0.4)
Triglycerides, mmol/L[a]	0.8 (0.3)	0.9 (0.3)	1.1 (0.3)	1.3 (2.6)	1.5 (0.8)	1.7 (1.4)	1.2 (1.3)
Fasting plasma glucose, mmol/L[a]	5.1 (0.4)	5.2 (0.4)	5.4 (0.4)	5.5 (1.2)	5.7 (1.1)	6.1 (2.0)	5.4 (1.1)
Systolic BP, mm Hg[a]	116.7 (9.8)	120.1 (9.8)	124.4 (7.9)	133.2 (20.3)	136.1 (18.5)	140.2 (17.7)	126.9 (17.6)
Diastolic BP, mm Hg[a]	73.7 (7.0)	75.9 (6.9)	78.6 (5.9)	84.1 (12.5)	85.6 (10.9)	88.8 (11.9)	80.1 (11.2)
Family history of MI, % yes[a]	218 (20)	97 (22)	28 (25)	122 (23)	130 (25)	120 (28)	715 (23)
Work-related stress, % yes[a]	144 (14)	69 (16)	14 (13)	71 (13)	66 (13)	59 (14)	423 (14)

Continuous variables are presented as means (SD) and categorical variables are presented as n (%).

Abbreviations: DK, Danish; FO, Faroese; IS, Icelandic; NO, Norwegian; SE, Swedish; SES, socioeconomic status.

[a]For the 3189 women, data are complete for all variables except for HDL cholesterol (missing, n = 9), fasting plasma glucose (missing, n = 6), systolic BP (missing, n = 1), diastolic BP (missing, n = 2), triglycerides (missing, n = 8), alcohol (missing, n = 142), socioeconomic status (missing, n = 231), work-related stress (missing, n = 147) and family history of MI (missing, n = 88).

men had a threefold increased risk of developing IHD when compared with metabolically healthy normal-weight men [hazard ratio (HR), 3.1; 95% confidence interval (CI), 1.1 to 8.2)]. The increased risk of IHD in metabolically healthy women being obese (HR, 1.8; 95% CI, 0.7 to 4.8) or overweight (HR, 1.5; 95% CI, 0.8 to 3.0) was less pronounced and statistically insignificant, meaning that these groups might not be at increased risk. Metabolically healthy overweight men were not at increased risk of IHD (HR, 1.1; 95% CI, 0.5 to 2.4). Furthermore, among metabolically unhealthy individuals the risk of IHD was increased across all weight groups in men, whereas among women the increased risk was only borderline significant in subgroups of normal weight and obesity.

Change of exposure status during follow-up

A substantial proportion of metabolically healthy individuals in all weight groups were categorized as metabolically unhealthy after 5 years of follow-up (Fig. 1). Additionally, some participants who were categorized as metabolically unhealthy at baseline were categorized as metabolically healthy at 5 years of follow-up. When changes in exposure status during 5 years of follow-up were taken into account (Table 3, model 3), the results showed slightly higher risk estimates for all groups except

Table 3. HRs (95% CI) of incident IHD in 3049 men and 3189 women from the Danish Inter99 study

	Men				Women			
Exposure	Events/N	Model 1	Model 2	Model 3	Events/N	Model 1	Model 2	Model 3
Healthy								
Normal weight	13/507	1 (ref.)	1 (ref.)	1 (ref.)	21/1096	1 (ref.)	1 (ref.)	1 (ref.)
Overweight	11/434	1.1 (0.5–2.4)	1.1 (0.5–2.4)	1.4 (0.7–3.1)	14/444	1.5 (0.8–3.0)	1.5 (0.8–3.0)	1.9 (0.9–3.7)
Obese	6/58	2.8 (1.1–7.4)	3.1 (1.1–8.2)	3.0 (1.2–7.7)	6/114	1.8 (0.7–4.6)	1.8 (0.7–4.8)	2.2 (0.9–5.6)
Unhealthy								
Normal weight	35/542	2.2 (1.2–4.2)	2.2 (1.2–4.3)	2.4 (1.2–4.6)	19/555	1.4 (0.7–2.6)	1.4 (0.7–2.5)	1.9 (1.0–3.8)
Overweight	94/1053	2.8 (1.6–5.0)	2.8 (1.6–5.1)	3.3 (1.8–6.0)	32/539	2.3 (1.3–4.0)	2.3 (1.3–4.0)	2.8 (1.5–5.1)
Obese	47/455	2.5 (1.3–4.6)	2.7 (1.4–5.2)	3.4 (1.8–6.7)	25/441	1.8 (1.0–3.4)	1.8 (0.9–3.4)	2.6 (1.3–5.0)

Model 1: adjusted for age and intervention group at baseline. Model 2: model 1 plus adjustment for smoking, physical activity, dietary habits, cohabitation, and ethnicity. Model 3: model 2 plus additionally taking into account change in exposure status at the 5-year follow-up examination.

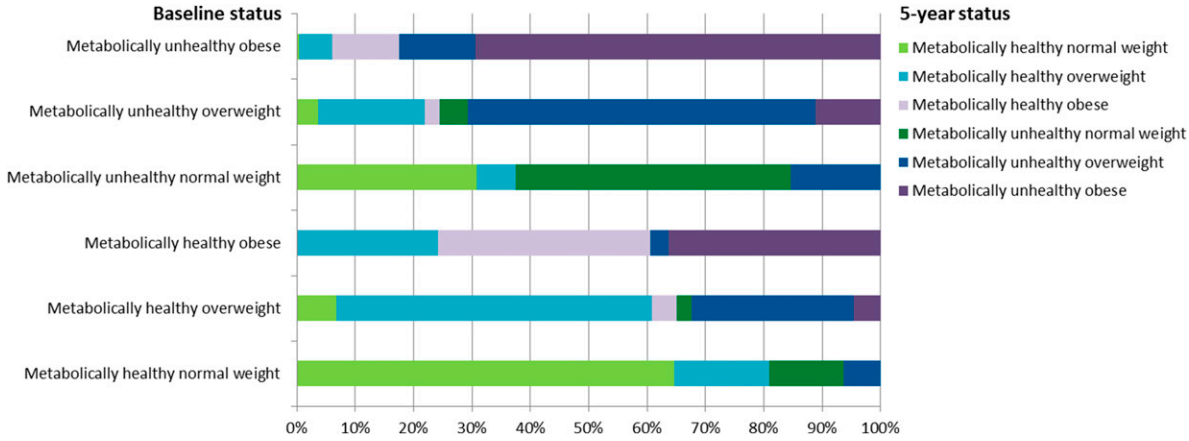

Figure 1. Exposure status after 5 years of follow-up given exposure status at baseline among 2061 men and 2045 women from the Danish Inter99 study. Participants with missing data on exposure status at year 5 were excluded. Participants with an event of IHD between baseline and year 5 were also excluded.

among metabolically healthy obese men. The increased risk among metabolically healthy overweight and obese women was only borderline significant.

Sensitivity analyses

In a sensitivity analysis the multiple adjusted HRs were further adjusted for alcohol consumption, socioeconomic status, family history of MI, and work-related stress in subgroups of 2639 men and 2701 women (Supplemental Table 2). The results from this analysis supported the original findings, and the additional covariates did not substantially alter the risk of IHD when the multiple-adjusted model was compared with the age-adjusted model.

When using waist circumference as a measure of obesity, fewer individuals were characterized as being overweight or obese. The risk of IHD was not markedly different from the main analysis (Supplemental Table 3). However, in this analysis, the risk of IHD was only borderline significant among metabolically healthy obese men compared with their leaner counterparts. Furthermore, the metabolically healthy women with a medium waist circumference were not at increased risk of IHD compared with metabolically healthy women with a normal waist circumference.

In the analyses with multiple imputation of missing data, the HRs were slightly attenuated as compared with the original analyses, especially among men (Supplemental Table 4). However, the same significant results were found in the original analyses and in the analyses with multiple imputation; thus, the main findings were not affected by missing data on confounders.

Discussion

In a large population-based study of >6000 middle-aged Danish men and women with 10 years of follow-up, we found that metabolically healthy obese individuals had a higher risk of IHD compared with their normal-weight counterparts. However, the increased risk among metabolically healthy obese women was only borderline significant. Hence, the findings in this study do not support the hypothesis that a subgroup of obese individuals is at low risk of IHD. In contrast, the results indicate that obesity is a risk factor for IHD irrespective of the presence of metabolic risk factors.

Comparison with other studies

The existing evidence displays conflicting results regarding the risk of CVD among metabolically healthy obese individuals compared with metabolically healthy normal-weight individuals. Thus, the findings of the present study are in agreement with some studies (11–16) and partly in agreement with other studies (17–21). However, the results of this study are in conflict with studies showing that metabolically healthy obese individuals are not at increased CVD risk (3–10). It is, however, difficult to directly compare the results of the studies due to methodological differences in adjustment and different definitions of outcomes and metabolic health. This might explain the inconsistent results across studies. In line with a recent systematic review (22), we argue that the definition of metabolic health as having no metabolic risk factors is more appropriate to interpret the effect of obesity on IHD over and above the metabolic status. Furthermore, using a strict definition will make it easier for clinicians to identify and distinguish between individuals who are metabolically healthy and unhealthy.

Permanent or temporary condition

It has been discussed whether metabolically healthy obesity is a temporary condition (1, 33). The finding that many participants changed exposure status during follow-up supports this notion. Furthermore, in this study <3% of the study population was metabolically healthy obese.

Thus, the metabolically healthy obese phenotype may only apply to a small proportion of the population, and a significant number of this small proportion become metabolically unhealthy over time. Additionally, within the metabolically healthy groups the mean values of HDL cholesterol decreased and the mean values of blood pressure, triglycerides, and fasting plasma glucose concentrations increased with increasing BMI. This finding underscores that CVD risk is continuous and that arbitrary cut-off points do not optimally stratify individuals into low and high risk. Rather, the risk of IHD for participants below but close to the cut-off point is probably more similar to the risk of participants slightly above the cut-off point than the risk of participants with the lowest values of the particular variable. Furthermore, results have shown that metabolically healthy obese women had more subclinical atherosclerosis than metabolically healthy normal-weight women but less than metabolically unhealthy obese women (34). Taken together, these findings suggest that the metabolically healthy obese phenotype is perhaps not a benign condition, as it has previously been hypothesized. In combination, these aspects question the rationale of denoting a subgroup of obese individuals as metabolically healthy.

Strengths and limitations

This study was based on a large prospective cohort including more than 6000 participants who were followed for 10 years. A particular strength of the study was that we included changes in metabolic health status after 5 years of follow-up. In the definition of the exposure we used a set of *a priori* decided cut-off values for each of the five included continuous variables. These values were based on well-established cut-off points used by the World Health Organization, the Danish Society of Cardiology, and the World Heart Federation (27, 35–37). However, the categorization of a variable implies an assumption that individuals in the same group are at the same risk of a specific outcome. This is often not the case, as also shown in this study.

Owing to the low number of participants and consequently few cases, particularly in the metabolically healthy obese subgroups, the confidence intervals were relatively wide; thus, the estimates should be interpreted with caution. Particularly, we think that the lack of a statistically significant higher risk among healthy obese women as compared with men is due to lack of power rather than to a physiological difference in the role of obesity on IHD development in men vs women. Another challenge when studying metabolically healthy obesity is that individuals could potentially differ on metabolic risk factors not included in the definition. Plasma glucose levels measured during an oral glucose tolerance test are better predictors for future CVD than are fasting glucose levels (38). However, an oral glucose tolerance test is often not performed in clinical practice, as it is inconvenient and costly (39). Also, insulin resistance is considered a mediator in the association between obesity and IHD and could differ between the groups. However, measurement of insulin is costly and no uniform cut-off value for insulin resistance exists (40). Therefore, these factors were not included in our analysis. Furthermore, the use of medication may have improved the values of the metabolic risk factors and would thus have been relevant to include in the measure of exposure. However, medication information was only available for a limited number of participants and therefore was not included in the analysis. In addition to medication, residual confounding related to measurement errors and other variables not included in the analysis (*e.g.* genetic factors) is also likely to be present in this study.

BMI was used as a measure of obesity. However, BMI does not take fat distribution into account and does not distinguish between fat mass and muscle mass (22, 23). This lack of body fat distinction could explain why metabolically healthy overweight men were not at increased risk of IHD compared with metabolically healthy normal-weight men. It is likely that some men characterized as being overweight were muscular and well-trained, and that the use of BMI has misclassified them as being overweight. When using large waist circumference as a marker of obesity, neither the metabolically healthy men nor the metabolically healthy women had statistically significantly elevated risk of IHD. Because waist circumference is an equally strong predictor for CVD as BMI (41), we think that this finding is likely related to a relatively low number of individuals fulfilling the criteria for being obese by waist circumference, which underscores the mismatch between cut-off points for obesity defined by different measures.

The low participation rate at the baseline health examinations of the Inter99 study and the exclusion of participants for this analysis could be a source of concern regarding generalizability of our findings. Participants and nonparticipants in the Inter99 study differed at baseline, as nonparticipants had lower socioeconomic position, were of younger ages, and more frequently lived without a partner (42). In the present analysis, we found that excluded individuals were more likely to be smokers, have lower socioeconomic position, and were of non-Nordic origin. Because of these differences, the participants in this study are not fully representative of the Danish middle-aged population. However, we think that similar results would occur in another study population, as we expect the same mechanisms to underlie the association between obesity and IHD.

Conclusion

In a large prospective study of Danish middle-aged men and women we found that obesity was associated with IHD irrespective of metabolic status, especially among men. The combination of obesity and a metabolically healthy profile was only present in <3% of the study population, and a large majority of those with a metabolically healthy profile at baseline became metabolically unhealthy after 5 years of follow-up. This finding suggests that metabolically healthy obesity is not a permanent state. In conclusion, our results suggest that the metabolically healthy obese phenotype is not a benign condition, and we question the feasibility of denoting a subgroup of obese individuals as metabolically healthy.

Acknowledgments

We thank the Inter99 staff and all people participating in the study. The Inter99 study was initiated by Torben Jørgensen (principal investigator), Knut Borch-Johnsen (principal investigator on the diabetes part), Troels Thomsen, and Hans Ibsen. The current steering committee of the Inter99 study comprises Torben Jorgensen (principal investigator) and Charlotta Pisinger.

Address all correspondence and requests for reprints to: Kristine Færch, PhD, Steno Diabetes Center, Niels Steensens Vej 6, DK-2820 Gentofte, Denmark. E-mail: kristine.faerch@regionh.dk.

The Inter99 study was funded by the Danish Research Councils, Health Foundation, the Danish Center for Evaluation and Health Technology Assessment, Copenhagen County, the Danish Heart Foundation, the Ministry of Health and Prevention, the Association of Danish Pharmacies, the Augustinus Foundation, Novo Nordisk, the Velux Foundation, the Becket Foundation, and the Ib Henriksens Foundation. K.F. is supported by the Novo Nordisk Foundation. The funders had no influence on study design or conduct, analyses, or interpretation of results.

Author contributions: L.H., M.K.N., N.B.J., N.H.R., and K.F. contributed to the conception and design of the study. L.H. and M.K.N. analyzed data and wrote the first draft of the manuscript. D.V. performed the sensitivity analysis with multiple imputation of missing data. All authors discussed data analyses and interpretation and contributed to subsequent versions of the manuscript, and all critically revised the manuscript and approved the final version of the manuscript. K.F. is the guarantor.

Clinical trial registry: ClinicalTrials.gov no. NCT00289237 (registered 19 September 2005).

Disclosure Summary: The authors have nothing to disclose.

References

1. Stefan N, Häring H-U, Hu FB, Schulze MB. Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications. *Lancet Diabetes Endocrinol*. 2013;**1**(2):152–162.
2. World Health Organization. Obesity and overweight. Available at: http://www.who.int/mediacentre/factsheets/fs311/en/. Accessed 12 December 2015.
3. Appleton SL, Seaborn CJ, Visvanathan R, Hill CL, Gill TK, Taylor AW, Adams RJ; North West Adelaide Health Study Team. Diabetes and cardiovascular disease outcomes in the metabolically healthy obese phenotype: a cohort study. *Diabetes Care*. 2013;**36**(8):2388–2394.
4. Calori G, Lattuada G, Piemonti L, Garancini MP, Ragogna F, Villa M, Mannino S, Crosignani P, Bosi E, Luzi L, Ruotolo G, Perseghin G. Prevalence, metabolic features, and prognosis of metabolically healthy obese Italian individuals: the Cremona Study. *Diabetes Care*. 2011;**34**(1):210–215.
5. Geetha L, Deepa M, Anjana RM, Mohan V. Prevalence and clinical profile of metabolic obesity and phenotypic obesity in Asian Indians. *J Diabetes Sci Technol*. 2011;**5**(2):439–446.
6. Hamer M, Stamatakis E. Metabolically healthy obesity and risk of all-cause and cardiovascular disease mortality. *J Clin Endocrinol Metab*. 2012;**97**(7):2482–2488.
7. Ortega FB, Lee DC, Katzmarzyk PT, Ruiz JR, Sui X, Church TS, Blair SN. The intriguing metabolically healthy but obese phenotype: cardiovascular prognosis and role of fitness. *Eur Heart J*. 2013;**34**(5):389–397.
8. Song Y, Manson JE, Meigs JB, Ridker PM, Buring JE, Liu S. Comparison of usefulness of body mass index versus metabolic risk factors in predicting 10-year risk of cardiovascular events in women. *Am J Cardiol*. 2007;**100**(11):1654–1658.
9. Sung K-C, Ryu S, Cheong ES, Kim BS, Kim BJ, Kim YB, Chung PW, Wild SH, Byrne CD. All-cause and cardiovascular mortality among Koreans: effects of obesity and metabolic health. *Am J Prev Med*. 2015;**49**(1):62–71.
10. Mørkedal B, Vatten LJ, Romundstad PR, Laugsand LE, Janszky I. Risk of myocardial infarction and heart failure among metabolically healthy but obese individuals: HUNT (Nord-Trøndelag Health Study), Norway. *J Am Coll Cardiol*. 2014;**63**(11):1071–1078.
11. Aung K, Lorenzo C, Hinojosa MA, Haffner SM. Risk of developing diabetes and cardiovascular disease in metabolically unhealthy normal-weight and metabolically healthy obese individuals. *J Clin Endocrinol Metab*. 2014;**99**(2):462–468.
12. Hinnouho G-M, Czernichow S, Dugravot A, Nabi H, Brunner EJ, Kivimaki M, Singh-Manoux A. Metabolically healthy obesity and the risk of cardiovascular disease and type 2 diabetes: the Whitehall II cohort study. *Eur Heart J*. 2015;**36**(9):551–559.
13. Katzmarzyk PT, Church TS, Janssen I, Ross R, Blair SN. Metabolic syndrome, obesity, and mortality: impact of cardiorespiratory fitness. *Diabetes Care*. 2005;**28**(2):391–397.
14. St-Pierre AC, Cantin B, Mauriège P, Bergeron J, Dagenais GR, Després JP, Lamarche B. Insulin resistance syndrome, body mass index and the risk of ischemic heart disease. *CMAJ*. 2005;**172**(10):1301–1305.
15. Keihani S, Hosseinpanah F, Barzin M, Serahati S, Doustmohamadian S, Azizi F. Abdominal obesity phenotypes and risk of cardiovascular disease in a decade of follow-up: the Tehran Lipid and Glucose Study. *Atherosclerosis*. 2015;**238**(2):256–263.
16. Meigs JB, Wilson PW, Fox CS, Vasan RS, Nathan DM, Sullivan LM, D'Agostino RB. Body mass index, metabolic syndrome, and risk of type 2 diabetes or cardiovascular disease. *J Clin Endocrinol Metab*. 2006;**91**(8):2906–2912.
17. Arnlöv J, Ingelsson E, Sundström J, Lind L. Impact of body mass index and the metabolic syndrome on the risk of cardiovascular disease and death in middle-aged men. *Circulation*. 2010;**121**(2):230–236.
18. Hinnouho G-M, Czernichow S, Dugravot A, Batty GD, Kivimaki M, Singh-Manoux A. Metabolically healthy obesity and risk of mortality: does the definition of metabolic health matter? *Diabetes Care*. 2013;**36**(8):2294–2300.
19. Ogorodnikova AD, Kim M, McGinn AP, Muntner P, Khan U, Wildman RP. Incident cardiovascular disease events in

metabolically benign obese individuals. *Obesity (Silver Spring)*. 2012;**20**(3):651–659.
20. Thomsen M, Nordestgaard BG. Myocardial infarction and ischemic heart disease in overweight and obesity with and without metabolic syndrome. *JAMA Intern Med*. 2014;**174**(1):15–22.
21. Schmiegelow MD, Hedlin H, Mackey RH, Martin LW, Vitolins MZ, Stefanick ML, Perez MV, Allison M, Hlatky MA. Race and ethnicity, obesity, metabolic health, and risk of cardiovascular disease in postmenopausal women. *J Am Heart Assoc*. 2015;**4**(5):e001695.
22. Roberson LL, Aneni EC, Maziak W, Agatston A, Feldman T, Rouseff M, Tran T, Blaha MJ, Santos RD, Sposito A, Al-Mallah MH, Blankstein R, Budoff MJ, Nasir K. Beyond BMI: the "metabolically healthy obese" phenotype & its association with clinical/subclinical cardiovascular disease and all-cause mortality—a systematic review. *BMC Public Health*. 2014;**14**:14.
23. Phillips CM. Metabolically healthy obesity: definitions, determinants and clinical implications. *Rev Endocr Metab Disord*. 2013;**14**(3):219–227.
24. Choi KM, Cho HJ, Choi HY, Yang SJ, Yoo HJ, Seo JA, Kim SG, Baik SH, Choi DS, Kim NH. Higher mortality in metabolically obese normal-weight people than in metabolically healthy obese subjects in elderly Koreans. *Clin Endocrinol (Oxf)*. 2013;**79**(3):364–370.
25. Jørgensen T, Borch-Johnsen K, Thomsen TF, Ibsen H, Glümer C, Pisinger C. A randomized non-pharmacological intervention study for prevention of ischaemic heart disease: baseline results Inter99. *Eur J Cardiovasc Prev Rehabil*. 2003;**10**(5):377–386.
26. Jørgensen T, Jacobsen RK, Toft U, Aadahl M, Glümer C, Pisinger C. Effect of screening and lifestyle counselling on incidence of ischaemic heart disease in general population: Inter99 randomised trial. *BMJ*. 2014;**348**:g3617.
27. World Health Organization. Obesity and overweight. Available at: http://who.int/mediacentre/factsheets/fs311/en/. Accessed 27 March 2017.
28. Aadahl M, Kjaer M, Jørgensen T. Associations between overall physical activity level and cardiovascular risk factors in an adult population. *Eur J Epidemiol*. 2007;**22**(6):369–378.
29. Toft U, Kristoffersen LH, Lau C, Borch-Johnsen K, Jørgensen T. The dietary quality score: validation and association with cardiovascular risk factors: the Inter99 study. *Eur J Clin Nutr*. 2007;**61**(2):270–278.
30. World Health Organization. Waist circumference and waist-hip ratio. Available at: http://apps.who.int/iris/bitstream/10665/44583/1/9789241501491_eng.pdf. Accessed 12 December 2015.
31. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. *Stat Methods Med Res*. 2007;**16**(3):219–242.
32. Marshall A, Altman DG, Holder RL, Royston P. Combining estimates of interest in prognostic modelling studies after multiple imputation: current practice and guidelines. *BMC Med Res Methodol*. 2009;**9**:57.
33. Blüher M. Are metabolically healthy obese individuals really healthy? *Eur J Endocrinol*. 2014;**171**(6):R209–R219.
34. Khan UI, Wang D, Thurston RC, Sowers M, Sutton-Tyrrell K, Matthews KA, Barinas-Mitchell E, Wildman RP. Burden of subclinical cardiovascular disease in "metabolically benign" and "at-risk" overweight and obese women: the Study of Women's Health Across the Nation (SWAN). *Atherosclerosis*. 2011;**217**(1):179–186.
35. World Health Organization. About diabetes. Available at: http://www.who.int/diabetes/action_online/basics/en/index2.html. Accessed 12 December 2015.
36. World Heart Federation. Cholesterol. Available at: http://www.world-heart-federation.org/cardiovascular-health/cardiovascular-disease-risk-factors/cholesterol/. Accessed 12 December 2015.
37. Danish Society of Cardiology. Dyslipedæmi. Available at: http://nbv.cardio.dk/dyslipidaemi. Accessed 12 December 2015.
38. Færch K, Vistisen D, Johansen NB, Jørgensen ME. Cardiovascular risk stratification and management in pre-diabetes. *Curr Diab Rep*. 2014;**14**(6):493.
39. World Health Orginization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia. Available at: http://www.who.int/diabetes/publications/Definition%20and%20diagnosis%20of%20diabetes_new.pdf. Accessed 15 March 2016.
40. Gayoso-Diz P, Otero-González A, Rodriguez-Alvarez MX, Gude F, García F, De Francisco A, Quintela AG. Insulin resistance (HOMA-IR) cut-off values and the metabolic syndrome in a general adult population: effect of gender and age: EPIRCE cross-sectional study. *BMC Endocr Disord*. 2013;**13**:47.
41. Flint AJ, Rexrode KM, Hu FB, Glynn RJ, Caspard H, Manson JE, Willett WC, Rimm EB. Body mass index, waist circumference, and risk of coronary heart disease: a prospective study among men and women. *Obes Res Clin Pract*. 2010;**4**(3):e171–e181.
42. Bender AM, Jørgensen T, Helbech B, Linneberg A, Pisinger C. Socioeconomic position and participation in baseline and follow-up visits: the Inter99 study. *Eur J Prev Cardiol*. 2014;**21**(7):899–905.