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Authors: Fingeret M, Marques-Vidal P, Vollenweider P

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Incidence of type 2 diabetes, hypertension, and dyslipidemia in metabolically healthy obese and non-obese

Running title: Metabolically Healthy Obesity

Fingeret M[1], Marques-Vidal P[2], Vollenweider P[2]

[1]NYU School of Medicine, New York, NY, USA; [2]Department of Internal Medicine, Lausanne University Hospital (CHUV), Lausanne, Switzerland

Authors' emails:

Margo Fingeret: Margo.Fingeret@nyumc.org

Pedro Marques-Vidal: Pedro-Manuel.Marques-Vidal@chuv.ch

Peter Vollenweider: Peter.Vollenweider@chuv.ch

Address for correspondence and reprints

Pedro Marques-Vidal

Office BH10-642, Department of Medicine, internal medicine

Lausanne University Hospital (CHUV)

Rue du Bugnon 46

1011 Lausanne

Switzerland

Phone: +41 21 314 72 65

Fax: +41 21 314 73 73

Email: Pedro-Manuel.Marques-Vidal@chuv.ch

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ABSTRACT

Background and Aims: Metabolically healthy obese (MHO) individuals are devoid of many metabolic abnormalities, but how this condition is maintained over time remains debated. We assessed the prevalence of MHO over time and the incidence of hypertension (HTN), dyslipidemia, and type 2 diabetes mellitus (T2DM) in MHO as compared with metabolically healthy non obese (MHNO).

Methods and Results: Prospective, population-based study including 3038 participants (49.9±9.9 years; 1753 women) free from metabolic syndrome and cardiovascular disease at baseline and examined after a follow-up of 5.6 years and 10.9 years on average. At each follow-up, prevalence of MHO, MHNO, metabolically unhealthy not obese (MUNO), and metabolically unhealthy obese (MUO), as well as of HTN, dyslipidemia, and T2DM, was calculated and stratified by sex, age group, and education.

At baseline, 179 (5.7%) MHO participants were identified, of which 62 (34.6%) and 79 (44.1%) remained MHO at 5.6 and 10.9 years follow-up, respectively. At 5.6 years follow-up, MHO participants were more likely to develop low HDL or be on hypolipidemic medication [multivariable-adjusted OR (95% CI): 1.56 (1.02-2.38)], to have dyslipidemia [1.94 (1.33-2.82)], and high triglycerides [2.07 (1.36-3.14)] than MHNO. At 10.9 years follow-up, MHO participants were significantly more likely to develop T2DM [3.44 (1.84-6.43)], dyslipidemia [1.64 (1.14-2.38)], and low HDL or be prescribed hypolipidemic medication [1.57 (1.08-2.27)] than MHNO. Conversely, no differences were found regarding hypertension.

Conclusion: A considerable fraction of MHO individuals lose their status over time, and in metabolically healthy adults, obesity confers a higher risk of developing cardiovascular risk factors.

Abstract word count: 249

Keywords: obesity; metabolically healthy obese; prospective; metabolic syndrome; dyslipidemia; hypertension; type 2 diabetes mellitus; epidemiology; Switzerland.

INTRODUCTION

Despite efforts to combat obesity, its prevalence, along with the prevalence of its associated cardiovascular risk factors (CVRFs), such as dyslipidemia, type II diabetes mellitus (T2DM), and hypertension (HTN), remains high [1]. In fact, such CVRFs continue to be responsible for an overwhelming number of deaths worldwide [2, 3]. Recent studies have identified various obesity phenotypes, notably metabolically healthy obese (MHO) individuals, who are devoid of multiple CVRFs, and metabolically unhealthy obese (MUHO), who present with many CVRFs. [4-6] However, the prevalence of MHO, as well as the comparative incidence of CVRFs and mortality, depends on the definition of metabolic syndrome applied, as there is little consensus on gold standard criteria for categorizing individuals as metabolically healthy or unhealthy obese [7, 8]. Indeed, in a previous study on a Caucasian cohort, we showed that the prevalence of the MHO phenotype ranged between 3.3 and 32.1% in men and between 11.4 and 43.3% in women [7]. Further work has also found a substantial prevalence of MHO in other ethnic groups [9, 10].

Several studies have suggested that MHO is an unstable condition, commonly leading to the development of metabolic abnormalities, but results have been inconsistent [4, 5, 11-13]. In fact, few prospective studies have focused on the natural course of MHO. The bulk of these studies focused primarily on endpoints of cardiovascular disease (CVD), T2DM, and all-cause mortality but reported contradictory results [12, 14-17]. Even fewer have examined the evolution of MHO as it concerns the incidence of dyslipidemia, T2DM, and HTN for MHO in comparison to that for metabolically healthy non-obese (MHNO) individuals. Clearly, the MHO state, along with its implications, remains poorly understood.

Thus, the aims of this study were to assess the prevalence of metabolically healthy obesity and the incidence of HTN, dyslipidemia, and T2DM in the MHO as compared with that in the MHNO after a 10-year follow-up in an adult Swiss population-based sample.

PARTICIPANTS AND METHODS

Participants

Participants were from the CoLaus study, a prospective study intended to evaluate the prevalence of CVRFs and to identify genetic determinants of these risk factors in a Swiss population aged between 35 and 75 years at baseline [18]. Sampling was performed as follows: the source population was defined as all subjects within the age range of interest registered in the population register of the city of Lausanne, Switzerland. The register includes all subjects living in this city for more than 90 days. A simple, non-stratified random sample of 19'830 subjects (corresponding to 35% of the source population) was drawn and the selected subjects were invited to participate by letter. If no answer was obtained, a second letter was sent, and if no answer was obtained, the subjects were contacted by phone.

Inclusion criteria were: (a) written informed consent; (b) willingness to take part in the examination and to provide blood samples; (c) Caucasian origin; (d) French language ability. For this study, we added the following inclusion criteria: (a) participants who completed the baseline, first, and second follow-up examinations and (b) availability of all variables analysed. For eligibility, we excluded (a) metabolically unhealthy participants (obese and non-obese) at baseline, as defined by Joint Interim Statement (JIS) criteria (see below for more details) and (b) type 1 diabetics at baseline. We further excluded (a) participants with cardiovascular disease at baseline; (b) participants with missing data at baseline; (c) participants without follow-up and (d) participants with missing data at follow-up.

Recruitment began in June 2003 and ended in May 2006, enrolling 6733 participants who underwent an interview, a physical exam, and a blood analysis. The first follow-up was performed between April 2009 and September 2012, 5.6 years on average after the collection of baseline data. The second follow-up was performed between May 2014 and July 2016, 10.9 years on average after the collection of baseline data. The information collected was similar to that collected in the baseline examination but contained questions regarding food consumption and detailed physical activity information.

Methods

All participants were examined in the morning after a fast of at least 8 hours. They were probed about their personal and family history of CVD, CVRFs, and cardiovascular treatment. CVD status at baseline was confirmed by further checking the available information provided by the participants (i.e. doctors, hospital registers, etc.). Smoking status was defined as never, former (no matter how long before the interview) and current. Educational level was categorized as low (primary), middle (apprenticeship), upper middle (high school), and high (university) for highest completed level of education. Physical activity was defined by answering positively to exercising 2 or more times per week for at least 20 minutes per session.

Body weight and height were measured while participants stood without shoes in light indoor attire. Body weight was measured in kilograms to the nearest 100 g using a Seca® scale (Hamburg, Germany) that was frequently calibrated. Height was measured to the nearest 5 mm using a Seca® (Hamburg, Germany) height gauge. Waist circumference was measured mid-way between the lowest rib and the iliac crest using a non-stretchable tape. The average of two measurements was taken and rounded to the nearest 0.5 cm. Blood pressure (BP) was measured thrice using an Omron® HEM-907 automated oscillometric sphygmomanometer after at least a 10 minute rest in a seated position, and the average of the last two measurements was used.

Venous blood samples (50 mL) were drawn in the fasting state. Most biological assays were performed at the clinical laboratory of the Lausanne university hospital (CHUV) within 2 hours of blood collection on fresh samples. Glucose was assessed by glucose dehydrogenase with a maximum inter- and intra-assay CV of 2.1% and 1.0%, respectively; total cholesterol by CHOD-PAP (1.6%–1.7%); HDL-cholesterol by CHOD-PAP + PEG + cyclodextrin (3.6%–0.9%); triglycerides by GPO-PAP (2.9%–1.5%).

Definition of variables and outcomes

Obesity was defined per World Health Organization (WHO) guidelines and convention as having a body mass index (BMI), calculated as weight in kilograms divided by height in

meters squared, as ≥30 kg/m^2 [19]. Non-obesity was defined as BMI <30 kg/m^2. To classify individuals as metabolically healthy or not healthy, we applied criteria outlined in the Joint Interim Statement (JIS) for Caucasian individuals in 2009. The criteria are as follows: (a) fasting plasma glucose ≥5.6 mmol/L or drug treatment; (b) fasting TG ≥1.7 mmol/L or drug treatment; (c) fasting HDL-C <1.30 mmol/L in women and <1.00 mmol/L in men or drug treatment; (d) Systolic blood pressure (SBP) ≥130 mm Hg, diastolic blood pressure (DBP) ≥85 mm Hg, or drug treatment; (e) waist circumference of ≥102 cm for men and ≥88 cm for women [20]. Per JIS recommendations, subjects with 2 or fewer of the JIS criteria were defined as metabolically healthy while subjects meeting 3 or more of the criteria were defined as metabolically unhealthy and thus suffering from metabolic syndrome [20]. Antihypertensive drug treatment was defined if the participant took any medication for high blood pressure. Lipid-lowering medication was defined if the participant took any medication listed under the Anatomical Therapeutic Chemical (ATC) classification as a C10 agent. Anti-diabetic drug treatment was defined if the participants took any medication to lower blood glucose.

When calculating the incidence of T2DM, dyslipidemia, and HTN, we did not take self-reported physician diagnoses into account given that many participants in our sample were diagnosed at the time of study. T2DM was defined as fasting plasma glucose ≥7.0 mmol/L and/or anti-diabetic drug treatment, per WHO guidelines [21]. HTN was defined two ways: (a) ≥140/90 mm Hg and (b) ≥130/85 mm Hg to consider both a less strict criterion for HTN and the JIS criterion. Dyslipidemia was broken down into: (a) fasting HDL-C <1.30 mmol/L in women and <1.00 mmol/L in men or drug treatment; (b) fasting TG ≥1.7 mmol/L; (c) any of the above criteria [20].

Ethical approval

The institutional Ethics Committee of the University of Lausanne, which afterwards became the Ethics Commission of Canton Vaud (www.cer-vd.ch) approved the baseline CoLaus study (reference 16/03). The approval was renewed for the first (reference 33/09) and the second (reference 26/14) follow-ups. The study was performed in agreement with the

Helsinki declaration and its former amendments, and all participants gave their signed informed consent before entering the study.

Statistical analysis

Statistical analyses were performed using Stata version 14.2 for windows (Stata Corp, College Station, Texas, USA). Bivariate analyses were performed using chi-square or Fisher's exact test for qualitative variables and Student's t-test. In the bivariate comparisons, results were expressed as number of participants (percentage) or as average±standard deviation. Changes in metabolic status during follow-up were expressed as percentage and (95% confidence interval). Multivariable analysis was performed using logistic regression and the results were expressed as Odds ratio (OR) and 95% confidence interval (CI). When computing the ORs for CVRFs (HTN, T2DM, and dyslipidemia), results were adjusted for baseline age, sex, smoking status, education, and physical activity. For each CVRF, analyses were performed on participants devoid of the condition at baseline.

As subjects who did not participate the follow-up differed from those who participated by a number of characteristics, a sensitivity analysis was performed. First, a propensity score was computed using nonparticipation in follow-up (coded as yes/no) as the dependent variable and gender, age, BMI, smoking, education, and physical activity as the independent variables. For each participant, the probability of nonparticipation was estimated and used in an inverse probability weighting model [22]. Statistical significance was assessed for a two-sided test with $p<0.05$.

RESULTS

Characteristics of participants

Of the initial 6733 participants, 1645 (24.43%) were excluded because of metabolic disease, and 8 (0.12%) because of type 1 diabetes at baseline, leaving 5080 participants (75.45%) eligible, of whom 203 (3.0% of the initial sample) presented with history of cardiovascular disease. After excluding participants devoid of follow-up data, the final

analytical sample consisted of 3038 participants (45.2% of the initial sample). The reasons for exclusion are summarized in **figure 1**. Excluded participants were more likely to be older, male, current smokers, less educated, and not physically active and had a higher average BMI (**Supplemental table 1**).

The characteristics of the participants according to obesity status at baseline are summarized in **table 1**. MHO participants were significantly less educated and less likely to complete physical activity and had a higher mean BMI and higher blood pressure levels than MNHO, while no differences were found for total cholesterol and fasting glucose.

Metabolic health

The results regarding metabolic health at 5.6 and 10.9 years are summarized in **table 2**. Of the initial 170 (5.6%) participants with MHO at baseline, 59 (34.7%) and 78 (45.9%) kept their status at 5.6 and 10.9 years follow-up, respectively. At 5.6 years follow-up, more than half of MHO participants became MUO, while at 10.9 years follow-up roughly 40% were classified as MUO. A small percentage of MHO participants at baseline became MHNO at first follow-up and second follow-up. A very small percentage of MHO participants at baseline became MUNO at either first or second follow-up.

Females and males tended to follow similar trends, but more females remained MHO or became MHNO and more males became MUO at both first and second follow-ups. Similar trends across age groups were also observed, with the highest proportion of participants becoming MUO at first follow-up for all age groups except for ages 45-54 in which the percentage of those remaining MHO was the same as those who became MUO. At second follow-up, ages 35-54 were most likely to retain their MHO status and second most likely to be MUO while ages 55-75 were most likely to be MUO and secondarily MHO.

At baseline, 2868 (94.4%) MHNO participants were identified, of which 2297 (80.1%) and 2340 (81.6%) remained MHNO at 5.6 and 10.9 years follow-up, respectively. At 5.6 years follow-up, 16.0% of MHNO participants at baseline became MUNO while at 10.9 years follow-

up only 11.4% were MUNO. A small percentage of MHNO participants at baseline became MHO or MUO at first and second follow-ups. Females and males tended to follow similar patterns, but more females remained MHNO and more males became MUNO at both first and second follow-ups. Similar trends across age groups were also observed as most MHNO retained their MHNO status, but as age increased, the percentage of those remaining MHNO decreased at both follow-ups. Correspondingly, as age increased, the likelihood of being MUNO increased at both follow-ups with the exception of age group 65-75.

Incidence of cardiovascular risk factors

The results regarding the incidence of cardiovascular risk factors are summarized in **table 3**. In bivariate analysis, MHO participants had a higher incidence of T2DM, dyslipidemia and high triglycerides than MHNO participants at both follow-ups, while no association was found with HTN. MHO participants also had a higher incidence of low HDL or hypolipidemic drug treatment at 10.9 years follow-up.

The associations between MHO and incidence of T2DM or dyslipidemia were further confirmed by multivariable analysis at both follow-ups, while the association with high triglycerides was only found at 5.6 years follow-up. Sensitivity analyses using inverse probability weighting for non-participation due to lack of follow-up confirmed the results, the effect of MHO on low HDL becoming significant also at 5.6 years follow-up (**table 3**).

DISCUSSION

Our results show that a considerable fraction of MHO individuals lose their status over time and that obesity significantly increases the risk of developing CVRFs in individuals who are initially metabolically healthy, a finding in agreement with two large studies conducted in the USA [23, 24]. Our results confirm that MHO should not be considered as a benign status, at least in the US and in Europe.

Metabolic health

Almost half of participants who were MHO at baseline, versus approximately 20% of MHNO participants, lost their metabolically healthy status after 10.9 years follow-up. Despite using slightly modified criteria to define metabolic health and a follow-up period of 6 years, we nearly replicated Soriguer et al.'s results, which showed that roughly half of MHO participants at baseline remained MHO and roughly 20% of MHNO became metabolically unhealthy 6 years later [25]. Furthermore, despite creating their own criteria to define metabolic health, Achilike et al. also found that almost half of those with MHO at baseline transformed into MUHO over 7.8 years of follow-up [13]. This stark difference between MHO and MHNO in maintaining their metabolic health over time illustrates the negative effect of obesity. Similar findings were obtained when the analyses were stratified by age and sex with two notable exceptions: more women than men retained their good metabolic health and the percentage of participants within each age group who retained good metabolic health decreased with age. These results support previous findings that the prevalence of metabolic abnormalities has a positive association with age [10] and that men have a higher prevalence of metabolic abnormalities [18].

In this way, we showed that the MHO phenotype is relatively unstable over 10 years. Yet, due to the lack of consensus on a gold standard definition of metabolic syndrome, it is difficult to compare our results across the literature. We used the JIS criteria including abdominal obesity, as was applied in several other studies [10, 12, 15, 26]. Despite using different definitions for metabolic health, other studies similarly revealed that the MHO condition is unstable [4, 5, 25, 26]. In fact, MHO status may be akin to a "grace period" that will inevitably end after a given time. We saw that MHO participants who remained metabolically healthy after 10.9 years follow-up were significantly younger and had lower CVRF levels than MHO participants who became metabolically unhealthy (**Supplemental table 2**). As a result, it appears likely that MHO status is only transient before obese individuals develop additional metabolic abnormalities that put them at higher risk for CVD, death, and other comorbidities.

Incidence of cardiovascular risk factors

MHO participants had a higher likelihood of developing T2DM, low HDL or being on hypolipidemic medication, dyslipidemia, and high triglycerides depending on follow-up. When computing the relative incidence of CVRFs, we compared the MHO with individuals whose BMI was <30 kg/m^2. However, most other studies compared the incidences of CVRFs between MHO and metabolically healthy individuals of normal weight (BMI<25 kg/m^2). Thus, the differences between MHO and MHNO participants should be smaller in our study, as the effect of overweight status (25<BMI<30 kg/m^2) was not present in the other studies. Still, our findings were similar to previous work regarding incidence of T2DM [14, 15, 27-29] and dyslipidemia (both hypertriglyceridemia and low HDL-c) [30] even though these studies used metabolically healthy normal weight individuals as a reference and modified criteria to define metabolic health. In addition, one study that used slightly modified criteria to define metabolic health and HbA_{1c} levels to diagnose diabetes but compared the incidence of T2DM in MHO with BMI≥30 kg/m^2 with that in MHNO with BMI<30 kg/m^2 also found a higher incidence of T2DM in MHO individuals over 6 and 11 years of follow-up [25].

No difference was found between MHO and MHNO participants regarding the incidence of HTN, defined as either ≥130/85 or ≥140/90 mm Hg. A likely explanation resides in the small sample size, which led to a reduced statistical power. Indeed, the RR were compatible with an increased risk of developing HTN, although the association was not statistically significant. Interestingly, other studies also suggested that the impact of MHO on diabetes might be stronger (or occur sooner) than for other cardiovascular risk factors [24], the lowest RR being found for HTN. Chang et al., though using the same criteria to define metabolic syndrome, witnessed a significantly increased risk for pre-hypertension (defined as ≥130/85 mm Hg) in MHO individuals compared with metabolically healthy normal weight individuals [30]. Similarly, Lee et al., though using different criteria to define metabolic health, found a higher incidence of HTN (defined as ≥140/90 mm Hg) in healthy obese compared with healthy normal weight individuals [31]. Our results may not indicate this association by virtue

of our inclusion of overweight individuals into our reference group and/or our small number of MHO participants.

Strengths and limitations

Strengths of our study include a 10-year follow-up period. Additionally, given our fairly homogenous study population, we were able to apply strict criteria to define metabolic health and thus metabolic syndrome, contrary to previous studies that did not take waist circumference into account [14, 25, 27, 28]. Moreover, our study outlined incidences for multiple specific CVRFs, as opposed to examining endpoints of all-cause mortality or CVD [6, 12, 29]. Our study also not only assessed the natural course of the MHO phenotype for CVRFs but additionally compared its natural course to that of the MHNO phenotype taken from the same source population, contrary to the many other studies that compared MHO individuals to metabolically healthy normal weight individuals [14, 15, 27-29]. Finally, to our knowledge, our study is one of few that looked specifically at the incidence of HTN in MHO individuals as compared with that in MHNO individuals.

Our study also has several limitations. First, our relatively small number of MHO (N=179) limited our statistical power. This is a common finding in most studies on MHO, as this condition is relatively infrequent: 2.9% in one study of subjects aged 45 to 64 [24] and 10% in a study of subjects aged 18 to 65 [23]). This small number was partly due to the large number of participants without follow-up data; further, participants without follow-up data presented more frequently with MHO than included participants (**supplemental table 3**). Also, participants devoid of follow-up were significantly older, more frequently men, current smokers and of lower educational level, were less physically active and had a higher BMI. Hence, it is likely that the incidence of cardiovascular risk factors (and thus the change in status from MHO to MUO) would have been higher had these participants been included in the analyses. Further, the retained sample can no longer be considered as representative of the original population, so generalizability to other populations is limited. Still, our results apply to participants with MHO who are within the age range studied, as other studies that focused on

this condition report similar findings [23, 24]. Overall, and despite the use of a propensity score to correct for selection bias, our results might underestimate the true impact of MHO on the incidence of cardiovascular and metabolic risk factors. We also did not collect information regarding bariatric surgery, which could explain why some MHO lost weight, becoming MHNO or MUNO. However, the relatively low number of MHO subjects becoming MHNO or MUNO at the second follow-up would likely not affect the significance of our results. Additionally, when calculating the incidence of T2DM, we did not use HbA_1c values due its lack of availability; instead, we defined those participants with a fasting plasma glucose ≥7.0 mmol/L to have T2DM. Yet, studies have shown that there exists a significant correlation between FPG and HbA_1c values so our conclusions would likely remain had we used HbA_1c values [32, 33]. Finally, this study enrolled only Caucasian participants, which might limit the generalization of our findings to other ethnic groups. However, studies across multiple other ethnic groups also revealed a higher incidence of CVRFs in the MHO group [23, 24, 29] and instability of the MHO phenotype [5].

Conclusion

Being obese yet metabolically healthy leads to a higher risk of developing CVRFs as compared with being metabolically healthy and not obese. Our study supports that the MHO state is transient and should be regarded by clinicians as a warning sign.

FUNDING

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ETHICS

The institutional Ethics Committee of the University of Lausanne, which afterwards became the Ethics Commission of Canton Vaud (www.cer-vd.ch) approved the baseline CoLaus study (reference 16/03, decisions of 13th January and 10th February 2003); the approval was renewed for the first (reference 33/09, decision of 23rd February 2009) and the second (reference 26/14, decision of 11th March 2014) follow-ups. The study was performed in agreement with the Helsinki declaration and its former amendments, and in accordance with the applicable Swiss legislation. All participants gave their signed informed consent before entering the study.

AUTHORS' CONTRIBUTIONS

MF completed the bibliographic search, performed part of the statistical analyses, and wrote the manuscript. PMV devised the study, conducted most of the statistical analyses, and revised the manuscript. PV devised the study and revised the manuscript for important intellectual content. All authors have read and approved this version of the manuscript.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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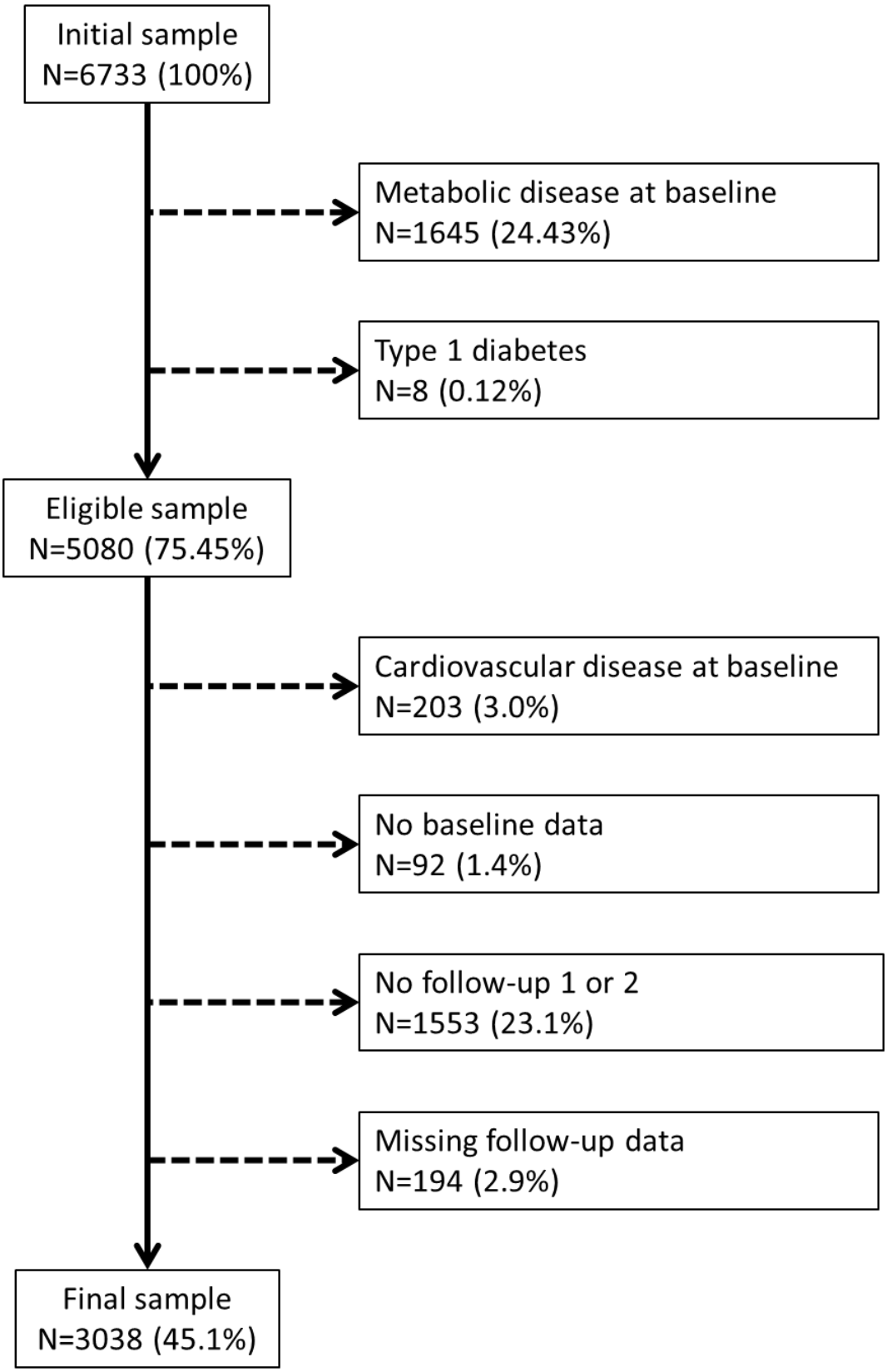
FIGURE LEGENDS

Figure 1: selection procedure, Colaus study, Lausanne, Switzerland.



TABLES

Table 1: Characteristics of metabolically healthy non-obese and metabolically healthy obese participants at baseline (2003-2006), Colaus study, Lausanne, Switzerland.

	MHNO (N=2868)	MHO (N=170)	p-value
Age (years)	49.9 ± 9.9	49.4 ± 9.7	0.486
Female sex	1658 (57.8)	95 (55.9)	0.621
Smoking status			0.158
Never	1241 (43.3)	73 (42.9)	
Former	895 (31.2)	63 (37.1)	
Current	732 (25.5)	34 (20.0)	
Education			<0.001
University	741 (25.8)	22 (12.9)	
High school	806 (28.1)	37 (21.8)	
Apprenticeship	945 (33.0)	64 (37.7)	
Mandatory	376 (13.1)	47 (27.7)	
Physically active	1732 (60.4)	76 (44.7)	<0.001
Body mass index (kg/m^2)	23.7 ± 2.8	32.8 ± 3.0	<0.001
SBP (mm Hg)	123 ± 16	127 ± 16	0.002
DBP (mm Hg)	77 ± 10	82 ± 10	<0.001
Total cholesterol (mmol/L)	5.5 ± 1.0	5.6 ± 1.1	0.455
Fasting glucose (mmol/L)	5.2 ± 0.6	5.3 ± 0.5	0.084

MHO, metabolically healthy obese; MHNO, metabolically healthy non-obese; SBP, systolic blood pressure; DBP, diastolic blood pressure. Results are expressed as number of participants (percentage) or as mean ± standard deviation. Between-group comparisons performed using student's t-test or chi square analysis.

Table 2: Prevalence of metabolically healthy obesity and metabolically healthy non-obesity, overall and stratified by sex or age group, 2006-2017, Colaus study, Lausanne, Switzerland.

Baseline Status		**First follow-up**				**Second follow-up**			
	N	**MHNO**	**MHO**	**MUNO**	**MUO**	**MHNO**	**MHO**	**MUNO**	**MUO**
MHO									
Total	170	9.4 (5.5 - 14.8)	34.7 (27.6 - 42.4)	2.4 (0.6 - 5.9)	53.5 (45.7 - 61.2)	13.5 (8.8 - 19.6)	45.9 (38.2 - 53.7)	1.8 (0.4 - 5.1)	38.8 (31.5 - 46.6)
By sex									
Female	95	12.6 (6.7 - 21.0)	38.9 (29.1 - 49.5)	3.2 (0.7 – 9.0)	45.3 (35.0 - 55.8)	15.8 (9.1 - 24.7)	49.5 (39.1 - 59.9)	2.1 (0.3 - 7.4)	32.6 (23.4 – 43.0)
Male	75	5.3 (1.5 - 13.1)	29.3 (19.4 - 41.0)	1.3 (0 - 7.2)	64.0 (52.1 - 74.8)	10.7 (4.7 - 19.9)	41.3 (30.1 - 53.3)	1.3 (0 - 7.2)	46.7 (35.1 - 58.6)
Age group (years)									
35-44	67	9.0 (3.4 - 18.5)	41.8 (29.8 - 54.5)	1.5 (0 – 8.0)	47.8 (35.4 - 60.3)	11.9 (5.3 - 22.2)	50.7 (38.2 - 63.2)	3.0 (0.4 - 10.4)	34.3 (23.2 - 46.9)
45-54	57	12.3 (5.1 - 23.7)	42.1 (29.1 - 55.9)	0 (0 – 6.3)	45.6 (32.4 - 59.3)	7.0 (1.9 - 17)	52.6 (39.0 – 66.0)	1.8 (0 - 9.4)	38.6 (26 - 52.4)
55-64	31	6.5 (0.8 - 21.4)	16.1 (5.5 - 33.7)	6.5 (0.8 - 21.4)	71.0 (52.0 - 85.8)	25.8 (11.9 - 44.6)	29.0 (14.2 - 48)	0 (0 – 11.2)	45.2 (27.3 - 64)
65-75	15	6.7 (0.2 - 31.9)	13.3 (1.7 - 40.5)	6.7 (0.2 - 31.9)	73.3 (44.9 - 92.2)	20.0 (4.3 - 48.1)	33.3 (11.8 - 61.6)	0 (0 – 21.8)	46.7 (21.3 - 73.4)
MHNO									
Total	2868	80.1 (78.6 - 81.5)	1.8 (1.4 - 2.4)	16.0 (14.6 - 17.4)	2.1 (1.6 - 2.7)	81.6 (80.1 – 83.0)	3.9 (3.3 - 4.7)	11.4 (10.2 - 12.6)	3.1 (2.5 - 3.8)
By sex									
Female	1658	83.1 (81.2 - 84.9)	1.9 (1.3 - 2.6)	13.3 (11.7 – 15.0)	1.7 (1.2 - 2.5)	84.7 (82.9 - 86.4)	4.7 (3.7 - 5.8)	8.4 (7.1 - 9.8)	2.2 (1.6 - 3.1)
Male	1210	76.0	1.8	19.7	2.6	77.4	2.9	15.5	4.3

		(73.4 - 78.3)	(1.1 - 2.7)	(17.5 – 22.0)	(1.7 - 3.6)	(74.9 - 79.7)	(2.0 – 4.0)	(13.5 - 17.6)	(3.2 - 5.6)
Age group (years)									
35-44	1063	87.2	2.5	8.7	1.5	84.4	5.2	7.3	3.1
		(85.0 - 89.2)	(1.7 - 3.7)	(7.1 - 10.6)	(0.9 - 2.4)	(82.1 - 86.5)	(3.9 - 6.7)	(5.8 - 9.1)	(2.1 - 4.3)
45-54	922	82.4	1.6	14.1	1.8	80.8	3.0	12.8	3.4
		(79.8 - 84.8)	(0.9 - 2.7)	(11.9 - 16.5)	(1.1 - 2.9)	(78.1 - 83.3)	(2.0 - 4.4)	(10.7 - 15.1)	(2.3 - 4.7)
55-64	642	70.7	1.4	24.8	3.1	80.4	3.3	12.9	3.4
		(67.0 - 74.2)	(0.6 - 2.6)	(21.5 - 28.3)	(1.9 - 4.8)	(77.1 - 83.4)	(2.0 – 5.0)	(10.4 - 15.8)	(2.2 - 5.1)
65-75	241	64.7	0.8	31.5	2.9	75.5	3.7	19.5	1.2
		(58.3 - 70.8)	(0.1 - 3.0)	(25.7 - 37.8)	(1.2 - 5.9)	(69.6 - 80.8)	(1.7 – 7.0)	(14.7 - 25.1)	(0.3 - 3.6)

MHO, metabolically healthy obese; MHNO, metabolically healthy non-obese; MUO, metabolically unhealthy obese; MUNO, metabolically unhealthy non-obese. Results are expressed as percentage and (95% confidence interval).

Table 3: Incidence of hypertension, type 2 diabetes mellitus, dyslipidemia, high triglycerides and low HDL-cholesterol or hypolipidemic drug treatment at the first and the second follow-up, in metabolically healthy obese and metabolically healthy non-obese participants, Colaus study, Lausanne, Switzerland.

		First follow-up			Second follow-up		
	N	**Bivariate**	**Multivariable**	**Multivariable §**	**Bivariate**	**Multivariable**	**Multivariable §**
HTN (≥140/90 mm Hg)							
MHNO	2310	347 (15.0)	1.0 (ref.)	1.0 (ref.)	519 (22.5)	1.0 (ref.)	1.0 (ref.)
MHO	111	22 (19.8)	1.39 (0.84 - 2.31)	1.34 (0.79 - 2.26)	31 (27.7)	1.19 (0.76 - 1.85)	1.11 (0.70 - 1.74)
p-value		0.169	0.201	0.280	0.200	0.445	0.665
HTN (≥130/85 mm Hg)							
MHNO	1928	394 (20.4)	1.0 (ref.)	1.0 (ref.)	510 (26.5)	1.0 (ref.)	1.0 (ref.)
MHO	94	26 (27.7)	1.43 (0.88 - 2.33)	1.44 (0.87 - 2.38)	32 (34.0)	1.29 (0.82 - 2.05)	1.30 (0.80 - 2.09)
p-value		0.092	0.154	0.161	0.105	0.272	0.286
Type 2 diabetes							
MHNO	2834	62 (2.2)	1.0 (ref.)	1.0 (ref.)	62 (2.2)	1.0 (ref.)	1.0 (ref.)
MHO	164	8 (4.9)	2.31 (1.05 - 5.08)	2.42 (1.06 - 5.50)	14 (8.5)	4.01 (2.12 - 7.58)	4.45 (2.23 - 8.88)
p-value		0.027	0.037	0.036	<0.001	<0.001	<0.001
Dyslipidemia							
MHNO	2339	445 (19.0)	1.0 (ref.)	1.0 (ref.)	508 (21.7)	1.0 (ref.)	1.0 (ref.)
MHO	134	42 (31.3)	1.83 (1.24 - 2.70)	1.90 (1.27 - 2.85)	43 (32.1)	1.61 (1.10 - 2.37)	1.65 (1.10 - 2.47)
p-value		<0.001	0.002	0.002	0.005	0.015	0.015
Low HDL or Rx							

MHNO	2639	334 (12.7)	1.0 (ref.)	1.0 (ref.)	482 (18.3)	1.0 (ref.)	1.0 (ref.)
MHO	150	27 (18.0)	1.52 (0.98 - 2.38)	1.66 (1.04 - 2.66)	40 (26.7)	1.59 (1.08 - 2.33)	1.66 (1.11 - 2.50)
p-value		0.058	0.063	0.034	0.010	0.018	0.014
High triglycerides							
MHNO	2532	258 (10.2)	1.0 (ref.)	1.0 (ref.)	201 (7.9)	1.0 (ref.)	1.0 (ref.)
MHO	151	31 (20.5)	2.05 (1.33 - 3.15)	1.94 (1.27 - 2.97)	19 (12.6)	1.52 (0.91 - 2.54)	1.40 (0.82 - 2.39)
p-value		<0.001	0.001	0.002	0.043	0.110	0.212

MHO, metabolically healthy obese; MHNO, metabolically healthy non-obese; HTN, hypertension; Rx, hypolipidemic drug treatment. Type 2 diabetes was defined as fasting plasma glucose of ≥7.0 mmol/L and/or anti-diabetic drug treatment. Dyslipidemia was defined as fasting HDL-C <1.30 mmol/L in women and <1.00 mmol/L in men and/or high triglycerides (defined as fasting TG ≥1.7 mmol/L) and/or hypolipidemic drug treatment. Results are expressed as number of participants (%) or as odds-ratio [95% confidence interval]. For each risk factor, analyses were performed on participants devoid of the condition at baseline. Bivariate analysis was done using chi-square; multivariable analysis was done using logistic regression adjusting for baseline age, sex, smoking status, education, and physical activity. § Sensitivity analyses were conducted using inverse probability weighting for non-participation due to lack of follow-up. P-values relate to the chi-square for bivariate analyses and to the odds-ratio for multivariable analyses.

Highlights

- Over half of metabolically health obese individuals lose their status over time
- In metabolically healthy adults, obesity increases risk of dyslipidemia by 64%
- In metabolically healthy adults, obesity increases risk of diabetes by 240%
- In metabolically healthy adults, obesity did not increase risk of hypertension