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Original article

Metabolically healthy and unhealthy weight statuses, health issues and related costs: Findings from the 2013–2015 European Health Examination Survey in Luxembourg

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ABSTRACT

Aim. – To investigate the relationship between metabolically healthy and unhealthy weight statuses and a wide range of related health issues, and healthcare and loss-of-productivity costs.
Methods. – A total of 693 men and 729 women, aged 25–64 years, took part in the European Health Examination Survey conducted in Luxembourg between 2013 and 2015. Metabolically unhealthy normal-weight profiles were defined as having two or more cardiometabolic abnormalities (high blood pressure, high fasting glucose or triglycerides, low HDL cholesterol and/or previously diagnosed hypertension or diabetes) in people with normal weight. Metabolically healthy overweight/obesity was defined as having fewer than two of the above-mentioned abnormalities in people with overweight or obesity. For the present report, the participants' anthropometric, clinical, biological, sociodemographic, lifestyle and health-related data were analyzed.
Results. – Of the participants with normal weight, 20% had a metabolically unhealthy profile, whereas 60% with overweight and 30% with obesity had a metabolically healthy profile. Comparisons between metabolically healthy and unhealthy normal weight, overweight and/or obesity status revealed that participants presented with a metabolically unhealthy profile independently of weight status ($P < 0.0001$). People with a metabolically healthy profile were more likely to perceive their health as good (66%; $P < 0.0001$), and to report no physical pain (64%; $P = 0.03$), no limitations in daily activities (66%; $P = 0.0008$), no difficulties getting in or out of a bed or chair (63%; $P = 0.02$) or dressing and undressing (63%; $P = 0.003$), going shopping (63%; $P = 0.053$) or doing occasional heavy housework (64%; $P = 0.007$); they also displayed fewer gastrointestinal (63%; $P = 0.02$), arthrosis (64%; $P = 0.001$) and sleep apnoea issues (63%; $P = 0.002$) compared with those with a metabolically unhealthy profile. Healthcare- and loss-of-productivity-related costs were higher with a metabolically unhealthy profile, with differences of up to € 3000 ($P = 0.02$).
Conclusion. – The present work has highlighted that, independently of weight status, people may develop a metabolically unhealthy profile associated with several health issues as well as higher healthcare and loss-of-productivity costs.

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Introduction

Overweight and obesity have been widely associated with several medical conditions; especially cardiometabolic comorbidities, linked to increased healthcare expenditures and loss of productivity, and are frequently explained in the literature by poor nutritional status and lack of physical activity [1–4]. Yet, the latest research has highlighted the existence of metabolically healthy overweight (MHOV) and metabolically healthy obesity (MHO) profiles, characterized by high body mass index (BMI) scores ($\geq$ 25 kg/m^2) but, otherwise, no cardiometabolic issues in particular [5–8]. Metabolically unhealthy normal weight (MUNW) profiles have also been found with lower scores of BMI (18.5–25 kg/m^2) displaying poor cardiometabolic profiles [5–8]. Although no consensus has yet been established to define the cardiometabolic profile characteristics amongst those with metabolically healthy and unhealthy weight statuses, most definitions have included at least two of the following cardiometabolic risk factors: insulin resistance, inflammation, hyperglycaemia, dyslipidaemia, hypertension and/or abdominal obesity [5–11]. However, a clear definition is crucial in terms of public health, especially in order to better prevent and treat cardiometabolic complications independently of weight. Indeed, while the management of MUNW people is still often neglected, those with overweight or obesity but metabolically healthy profiles are not necessarily in need of intervention [9–12]. In fact, some interventions, such as energy-restricted diets, may even damage metabolic health in the MHOV and MHO, resulting in type 2 diabetes (T2D), even though this therapeutic approach is supposed to improve glucose and insulin abnormalities [6–9].

Beyond cardiometabolic considerations, the relationships between metabolically unhealthy normal-weight, overweight and obesity profiles, and other physical and mental health issues, are also being investigated, although such studies are still either only just beginning, or are scarce or controversial [10,13–16].

Furthermore, while certain authors argue for reinforcement of healthy lifestyle interventions to treat MHO, and for bariatric surgery as a strategic treatment for metabolically unhealthy obesity (MUO), there is still no consensus regarding the potential implication of dietary habits and physical activity in the development of metabolically healthy or unhealthy weight status [9,17–21]. Cardiometabolic health management should also be cost-effective [9]. Yet, no health-related costs of MUNW, metabolically unhealthy overweight (MUOV) or MUO profiles have been investigated thus far.

Therefore, the present report aimed to investigate: (1) the relationships between MUNW, MUOV and MUO, and a wide range of physical and mental health issues; and (2) the costs related to healthcare and loss of productivity. The prevalence and associated correlates of these three profiles in the adult population residing in Luxembourg were also examined.

Methods

Participants

The European Health Examination Survey (EHES-LUX$_{2013–2015}$) was conducted between 2013 and 2015 in 1529 adult residents of Luxembourg, aged 25–64 years, who were randomly selected from the national population registry as previously described [22]. Of these 1529 randomly selected participants, data from 21 pregnant women, 24 participants with BMI scores $<$ 18.5 kg/m^2, and 62 who were missing values defining metabolically healthy/unhealthy weight status (one had no information on diabetes diagnosis, six had no information on blood pressure, and 55 had no data on triglycerides, high-density lipoprotein [HDL] and/or glycaemia concentrations) were excluded. For the present report, data from 693 men and 729 women (n = 1422) who had complete information on anthropometrics, clinical measurements, biomarkers, sociodemographic characteristics, lifestyle patterns and health status were ultimately analyzed. The study was authorized by our national committees for research ethics and data protection, and informed consent was obtained from each participant.

Anthropometric, clinical and biological assessments

Weight, height, BMI, blood pressure, fasting glucose, triglycerides and HDL cholesterol concentrations were assessed according to the EHES protocol [22,23].

Metabolically healthy and unhealthy weight statuses

Normal weight, overweight and obesity were defined as BMI scores of 18.5–25 kg/m^2, $>$ 25–30 kg/m^2 and $>$ 30 kg/m^2, respectively. According to the Ortega et al. [7] definition derived from the Alberti et al. [24] definition, metabolically unhealthy profiles are defined as the presence of two or more cardiometabolic abnormalities: high blood pressure ($\geq$ 130/85 mmHg); high fasting glucose ($\geq$ 100 mg/dL); high triglycerides ($\geq$ 150 mg/dL); low HDL cholesterol ($<$ 40 mg/dL in men, $<$ 50 mg/dL in women); and/or previously diagnosed hypertension or diabetes by a physician [7]. However, the Ortega et al. [7] definition did not include treatment for diabetes, lipids or hypertension, as did the Alberti et al. [24] definition, but instead used a wider definition based on physician-diagnosed diseases.

On this basis, six profiles were defined: metabolically healthy normal weight (MHNW); MUNW; MHOV; MUOV; MHO; and MUO [5,25]. Metabolically healthy profiles were also identified in people having none of the cardiometabolic components to test the sensitivity of Ortega et al. [7] definition.

Demographic and socioeconomic characteristics

The present study collected data on age, gender, administrative district of residence (Diekirch [north], Luxembourg [centre], Grevenmacher [south]), country of birth (Luxembourg, Portugal [whose nationals comprise the largest group in Luxembourg's overall migrant population], other European Union [EU] countries, non-EU countries), marital status (never married nor in civil partnership; married and/or in civil partnership; divorced and/or in dissolved civil partnership; widowed and/or surviving partner death), education (pre-primary, primary, lower secondary, upper secondary, post-secondary non-tertiary, tertiary), employment ('professionally active' in a job or profession, 'professionally inactive' including the unemployed, pupils, students, further traineeships or in unpaid work experience, in retirement, permanently disabled, in compulsory military or community service and/or fulfilling domestic tasks) and income (replaced by income-bracket medians in cases of missing data) [22,23].

Lifestyle variables

Data on lifestyle included the following variables: daily consumption of fruit and vegetables (daily number of fruit and vegetable portions consumed, daily frequency of consumption: once or more a day or less than once a day); work-related physical activity (WRPA; rates of people physically active at work: usually walking at work and/or having moderate to physically demanding work); transport-related physical activity [TRPA; quintiles of metabolic equivalents of task (METs) per min of weekly walking/

Table 1
Metabolically healthy (MH) and unhealthy (MU) weight statuses from the European Health Examination Survey in Luxembourg in 2013–2015 (EHES-LUX$_{2013-2015}$): general characteristics.

	EHES-LUX$_{2013-2015}$ (n = 1422)			Normal weight (n = 594)			Overweight (n = 536)			Obesity (n = 292)		
Phenotypes (%)	MU n = 534 (37%)	MH n = 888 (63%)	P[a]	MUNW n = 109 (18%)	MHNW n = 485 (82%)	P[a]	MUOV n = 222 (41%)	MHOV n = 314 (59%)	P[a]	MUO n = 203 (70%)	MHO n = 89 (30%)	P[a]
Demographic and anthropometric characteristics												
Age (years, mean ± SD)	48 ± 10	43 ± 10	< 0.0001	47 ± 10	42 ± 10	< 0.0001	47 ± 10	45 ± 10	0.02	50 ± 9	43 ± 9	< 0.0001
Gender (%)												
Male	51%	49%	< 0.0001	33%	67%	< 0.0001	51%	49%	< 0.0001	79%	21%	0.0005
Female	24%	76%		10%	90%		26%	74%		60%	40%	
BMI (kg/m^2, mean ± SD)	29 ± 5	25 ± 4	< 0.0001	23 ± 1	22 ± 2	< 0.0001	27 ± 1	27 ± 1	0.01	35 ± 4	33 ± 3	0.001
+Waist circumference (cm, mean ± SD)	100 ± 13	87 ± 11	< 0.0001	85 ± 7	80 ± 7	< 0.0001	96 ± 7	92 ± 7	< 0.0001	112 ± 11	105 ± 10	< 0.0001
Socioeconomic characteristics												
District of residence (%)												
Diekirch	36%	64%	0.90	15%	85%	0.64	42%	58%	0.56	62%	38%	0.57
Grevenmacher	38%	62%		21%	79%		36%	64%		70%	30%	
Luxembourg	38%	62%		18%	82%		42%	58%		71%	29%	
Country of birth (%)									0.53			0.45
Luxembourg	37%	63%	0.03	80%	20%	0.07	62%	38%		31%	69%	
Portugal	46%	54%		74%	26%		56%	44%		30%	70%	
Other European Union	35%	65%		86%	14%		57%	43%		25%	75%	
Non-European Union	33%	64%		88%	12%		53%	47%		44%	56%	
Marital status (%)												
Single	33%	67%	0.29	20%	80%	0.93	69%	60%	0.21	60%	40%	0.42
Married/in registered partnership	39%	61%		18%	82%		70%	56%		71%	29%	
Widowed/surviving partner death	28%	72%		20%	80%		75%	80%		60%	40%	
Divorced/dissolved partnership	39%	61%		18%	82%		56%	68%		74%	26%	
Immigration (%)												
Not immigrants	37%	63%	0.93	23%	77%	0.03	35%	65%	0.07	69%	31%	0.96
First-generation	38%	62%		16%	84%		44%	56%		70%	30%	
Second-generation	37%	63%		13%	87%		46%	54%		70%	30%	
Education level (%)												
Pre-primary, primary, lower secondary	48%	52%	< 0.0001	26%	74%	0.018	47%	53%	0.16	73%	27%	0.37
Upper secondary, post-secondary,	40%	60%		20%	80%		42%	58%		71%	29%	
no tertiary	28%	72%		14%	86%		36%	64%		63%	37%	
Tertiary												
Employment (%)												
Professionally active	43%	57%	0.01	21%	79%	0.33	44%	56%	0.51	77%	23%	0.10
Professionally inactive	36%	64%		18%	82%		41%	59%		67%	33%	
Income	(n = 481)	(n = 796)	0.42	(n = 92)	(n = 431)	0.60	(n = 205)	(n = 284)	0.70	(n = 184)	(n = 81)	0.92
Median[b] (euros)	4970	5000		5500	5500		4750	5000		4525	4500	
(Q1, Q3)	(3500, 7000)	(3500, 7500)		(4000, 7500)	(3750, 7500)		(3500, 7000)	(3330, 7500)		(3500, 6800)	(3250, 7000)	
Lifestyle characteristics												
Work-related physical activity												
1: Yes	37%	63%	0.006	18%	82%	0.43	39%	61%	0.70	67%	33%	0.08
2: No	35%	65%		18%	82%		41%	59%		65%	35%	
3: Not working	46%	54%		23%	77%		45%	55%		80%	20%	
Transport-related physical activity	(n = 533)	(n = 886)	0.88	(n = 109)	(n = 483)	0.74	(n = 221)	(n = 314)	0.41	(n = 203)	(n = 89)	0.56
(metabolic equivalents/min)	396	396		445.5	396		445.5	390		330	396	
Median[b] (Q1, Q3)	(66, 1002)	(132, 1040)		(132, 1040)	(132, 1040)		(66, 1040)	(66, 834)		(0, 864)	(132, 1040)	
Aerobic physical activity (%)												
1: Yes	29%	71%	< 0.0001	17%	83%	0.34	34%	66%	0.009	58%	42%	0.02
2: No	43%	57%		20%	80%		46%	54%		73%	27%	
Muscle-strengthening physical activity (%)												
1: Yes	28%	72%	0.0002	15%	85%	0.29	34%	66%	0.06	61%	39%	0.24
2: No	40%	60%		19%	81%		44%	56%		71%	29%	

Vegetable & fruit consumption												
$<$ 1 portion a day	43%	57%	0.018	24%	76%	0.036	47%	53%	0.11	67%	33%	0.60
1–4 portions a day	35%	65%		15%	85%		39%	61%		69%	31%	
$\geq$ 5 portions a day	36%	64%		20%	80%		35%	66%		76%	24%	
Fruit consumption (%)												
Once or more a day	35%	65%	0.016	16%	84%	0.067	39%	61%	0.16	69%	31%	0.97
Less than once a day	41%	59%		22%	78%		44%	56%		69%	31%	
Vegetable consumption (%)												
Once or more a day	34%	66%	0.002	14%	86%	0.002	39%	61%	0.25	68%	32%	0.67
Less than once a day	42%	58%		24%	76%		44%	56%		71%	29%	
Alcohol (%)												
Non-drinker	33%	67%	$<$ 0.0001	14%	86%	0.001	36%	64%	0.11	62%	58%	0.0026
1–6 drinks/week	34%	66%		16%	84%		42%	58%		68%	33%	
$>$ 6 drinks/week	48%	52%		28%	72%		47%	53%		83%	17%	
Sleep duration (%)												
Workers with $\leq$ 6 h	41%	59%	$<$ 0.0001	20%	80%	0.02	46%	54%	0.02	64%	36%	0.31
Workers with $>$ 6 h	33%	67%		17%	83%		38%	62%		69%	31%	
Non-workers with $\leq$ 6 h	56%	44%		39%	61%		62%	38%		71%	29%	
Non-workers with $>$ 6 h	38%	62%		16%	84%		35%	65%		78%	22%	

MUNW/MHNW: metabolically unhealthy/healthy normal weight; MUOV/MHOV: metabolically unhealthy/healthy overweight; MUO/MHO: metabolically unhealthy/healthy obesity; BMI: body mass index
[a] $P < 0.025$ threshold significance value for individual analyses based on Bonferroni correction (two comparisons) with $P < 0.05$ significance threshold.
[b] Ranked data divided into two groups: 25% of data are below first quartile (Q1), 25% of data are above third quartile (Q3).

cycling to reach workplace]; frequency of people performing at least 150 min of aerobic physical activity (APA) per week; frequency of people doing, on at least 2 days a week, muscle-strengthening physical activity (MSPA) such as stretching, gymnastics, yoga, resistance training; weekly consumption of standard alcoholic drinks; and sleep duration during the week (threshold of 6 h/night, the minimum of sleep duration recently recommended by the US National Sleep Foundation [22,23,26–28].

Self-reported health status

Participants were asked how they perceived their health, physical pain intensity during the past month, potential long-standing limitations in their daily activities because of physical or mental health problems during the last 6 months, particularly functional physical limitations (walking half a kilometre without aid, walking up or down 12 stairs), limitations in personal-care activities (getting in and out of a bed or chair, dressing and undressing, using the toilet, bathing or showering) and/or limitations in household activities (shopping, preparing meals, doing light housework or occasional heavy housework).

Participants were also asked to self-report on the presence of several chronic diseases, if any, over the past 12 months, such as cardiometabolic (arterial hypertension, hypercholesterolaemia, diabetes, coronary heart disease, myocardial infarction, stroke), gastrointestinal (stomach or duodenal ulcer), liver (cirrhosis or other disease), renal (urinary incontinence), osteoarticular (osteoporosis, arthrosis, rheumatoid arthritis, lower-back disorders), respiratory (asthma, sleep apnoea) and mental (chronic anxiety) disorders [23]. For more accurate evaluation of hypertension, hypercholesterolaemia and/or diabetes in participants with metabolically healthy and/or unhealthy weight statuses, participants were asked if they were taking any medications related to these three comorbidities. Their self-reported responses were then matched with their clinical and biological assessments, as well as their self-declared medications.

The Berlin Questionnaire (BQ) was used to calculate sleep apnoea risk (BQ score ≥ 1: presence of snoring; feeling drowsy or tired during the day; having hypertension and obesity) [29]. Also assessed was the presence of depressive symptoms, according to the depression module of the Patient Health Questionnaire (PHQ-9): scores < 4, no depression; ≥ 5 but ≤ 14, mild-to-moderate depression; and ≥ 15 but ≤ 27, moderately severe-to-severe depression [30].

Direct and indirect costs of disease

Healthcare use was reported in the EHES following the guidelines of Drummond et al. [31]. Both healthcare-related costs (visits to the general practitioner [GP], dentist, specialist, physiotherapist, psychologist, and inpatient and day-patient days) and indirect costs (cost of loss of productivity associated with days absent from work) were included. Healthcare-related costs were calculated by multiplying unit use by unit costs, while the cost of loss of productivity was estimated using the human capital approach, multiplying reported days of absence with the average per capita gross domestic product (GDP), including employer insurance premiums, for Luxembourg. Where Luxembourger unit costs [32] were not available (of the eight unit costs investigated, four Luxembourger unit costs were missing; Appendix B; see supplementary materials associated with this article online), Dutch unit costs [33] were used instead, and adjusted for inflation and purchasing power parity (PPP). Dutch average unit costs are available from their national costing guidelines [33]. When Luxembourger data were available, the figures were comparable to the Dutch ones. For dentists, psychologists and physiotherapists,

data for healthcare resource use only indicated whether a service was used in the last 12 months. When a service was used, it was assumed to have been used only once. Where data were available for 4 weeks, they were linearly extrapolated to 52 weeks. Detailed unit costs are presented in Appendix D (see supplementary materials associated with this article online). Statistical significance was calculated by bootstrapping the *t* test with 10,000 samples, as cost data are generally heavily skewed [34].

Statistical analyses

Descriptive statistics of the participants and the prevalence of metabolically healthy and unhealthy weight statuses were analyzed, and the results presented as percentages and as means ± SD (min–max). For both TRPA and income variables, quartile (Q) medians (Q1, Q3) were calculated, and the medians used to divide ranked data into two groups surrounded by the confidence interval (CI): Q1 (with 25% of the data below this) and Q3 (with 25% of data above this). Chi-square, Student's *t* and Fisher's exact tests were performed to analyze associations between metabolically healthy and unhealthy weight statuses, as well as the potentially related comorbidities, risk factors, total health costs and health costs ignoring productivity. Bonferroni adjustment of the descriptive statistics for the study population was performed, as the whole group and each group separately had been analyzed. Univariate and multivariable logistic regression analyses were conducted to estimate the odds ratios (ORs) for MUNW (reference category: MHNW), MHOV (reference category: MUOV) and MHO (reference category: MUO). For each multivariable analytical model, variables were based on statistical criteria (only variables with $P < 0.20$ on univariate analyses were considered). To evaluate the multicollinearity of variables within the model, variance inflation factors were measured for each independent variable. When the variance inflation factor was equal to 1, that variable was considered independent of the remaining predictors. Results were considered significant at the 5% critical level ($P < 0.05$). All analyses were performed with SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA).

Results

Prevalence of MHNW, MUNW, MHOV, MUOV, MHO and MUO

According to the Ortega et al. [7] definition, > 22% of participants to the EHES-LUX$_{2013–2015}$ had an MHOV profile, around 6% were MHO and almost 8% had an MUNW profile. The prevalence of the three other profiles was 15.6% for MUOV, 14.3% for MUO and 34.1% for MHNW [7] (Appendix A; see supplementary materials associated with this article online). Using the definition restricted to zero metabolic components to characterize metabolically healthy profiles, rates of prevalence were: 21.3% for MUNW and 20.4% for MHNW; 30.7% for MUOV and 7.4% [7] for MHOV; and 18.6% for MUO and 1.5% for MHO (Appendix A; see supplementary materials associated with this article online).

Finally, when each weight category was considered separately and cardiometabolic health was defined according to Ortega et al. [7], it appears that almost 20% of participants with normal weight had a metabolically unhealthy profile, whereas 60% of those with overweight and 30% with obesity had metabolically healthy profiles. General characteristics are detailed in Table 1.

Demographic, socioeconomic and lifestyle correlates

Univariate analyses are detailed in Appendices B1–B3. Multivariable logistic regression showed that, for each year of greater age, there were 6% greater odds of having MUNW than MHNW. There were also fourfold greater odds of having MUNW in men than in women. On the other hand, for every 100 METs of higher TRPA, there were 2% lower odds of having MUNW than MHNW. Also, for each year of greater age, there were 2% lesser chances of having a metabolically healthy profile in people with overweight, and 6% lesser chances in those with obesity. In addition, there was a threefold lesser chance of having MHOV and/or MHO in men than in women. For overweight people doing APA for at least 150 min/week, there was a two-fold greater chance of having a metabolically healthy profile (Fig. 1a–c).

As for our three models, there was no important collinearity. Variance inflation factors are detailed in Appendix C (see supplementary materials associated with this article online).

Associated comorbidities

Self-perceived health, longstanding illness and physical pain

Metabolically healthy people were more likely to perceive their health as good or very good (66%; $P < 0.0001$) and to not be experiencing any physical pain or discomfort (64%; $P = 0.03$), although no significant differences were observed between metabolically healthy and unhealthy profiles regarding self-perceived health and physical pain in either the normal-weight or overweight or obese participants (not statistically significant; Table 2). Also, MHOV profiles were less likely to be associated with longstanding illness than MUOV profiles (62%; $P = 0.0055$; Table 2).

Longstanding limitations in daily activities

People with metabolically healthy profiles were less likely to experience any limitations in performing their usual daily activities (66%; $P = 0.0008$), although no significant difference was observed within any weight category (normal weight, overweight or obesity). In terms of functional physical limitations, MHNW subjects seemed to have less difficulty walking half a kilometre with no aid compared with MUNW subjects (82%; $P = 0.002$).

Regarding limitations in personal-care activities, people with metabolically healthy profiles were less likely to have any difficulty getting in or out of a bed or chair (63%; $P = 0.02$) or dressing and undressing (63%; $P = 0.003$) than those with metabolically unhealthy profiles, although no significant difference was observed within the three weight categories. Daily limitations in terms of bathing or showering were not significantly different between those with metabolically healthy and unhealthy weight statuses.

However, participants with MUOV seemed to have more difficulty doing light housework than those with MHOV profiles (57%; $P = 0.03$). Also, metabolically healthy people were, in general, less likely to have any difficulty doing their shopping (63%; $P = 0.053$) or the occasional heavy housework (64%; $P = 0.07$; Table 3).

Chronic diseases

Several diseases were significantly associated with metabolically unhealthy weight categories. In terms of cardiometabolic comorbidities, those with MUNW profiles were three times more likely to have high cholesterol than MHNW, whereas the MHOV and MHO were two times less likely to have high cholesterol than the MUOV and MUO ($P < 0.0001$). While stroke prevalence was not significantly associated with either MUNW or MHNW profiles, no stroke cases were reported in participants with overweight and/or obesity. Gastrointestinal disorders such as stomach and duodenal ulcers were more likely with metabolically unhealthy than metabolically healthy profiles (65%; $P = 0.02$), but there was no significant difference according to weight category.

Participants with MUNW profiles had urinary incontinence four times more frequently ($P = 0.004$) than those with MHNW. There was also a tendency towards a greater prevalence of urinary incontinence with MUOV than with MHOV (73%; $P = 0.06$),

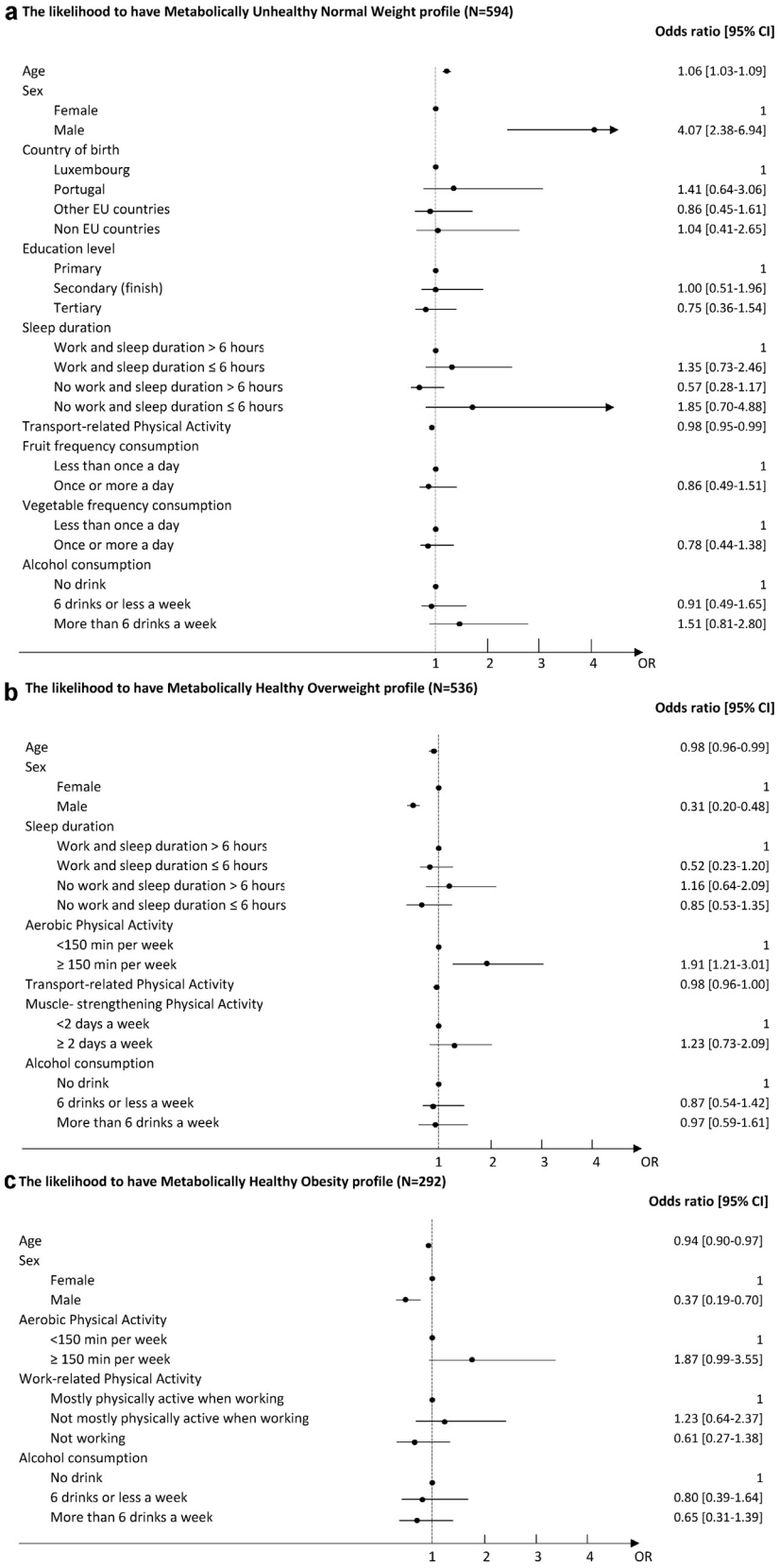

Fig. 1. Multivariable logistic predictive models for: (a) metabolically unhealthy normal weight vs. metabolically healthy normal weight; (b) metabolically healthy overweight vs. metabolically unhealthy overweight; and (c) metabolically healthy obesity vs. metabolically unhealthy obesity. Data are from the European Health Examination Survey in Luxembourg in 2013–2015 (EHES-LUX$_{2013–2015}$).

Table 2
Self-perceived health, longstanding illness and physical pain in people with metabolically healthy and unhealthy normal weight, overweight and obesity in the European Health Examination Survey in Luxembourg in 2013–2015.

	Total (n = 1422)			Normal weight (n = 594)			Overweight (n = 536)			Obesity (n = 292)		
	Unhealthy n = 534 (37.5%)	Healthy n = 888 (62.5%)	P[a]	Unhealthy n = 109 (18.3%)	Healthy n = 485 (81.7%)	P[a]	Unhealthy n = 222 (41.4%)	Healthy n = 314 (58.6%)	P[a]	Unhealthy n = 203 (69.5%)	Healthy n = 89 (30.5%)	P[a]
Self-perceived	(n = 533)	(n = 888)	< 0.0001	(n = 109)	(n = 485)	0.17	(n = 222)	(n = 314)	0.20	(n = 202)	(n = 89)	0.65
health (%)	34%	66%		17%	83%		40%	60%		71%	29%	
Very good to good	47%	53%		25%	75%		50%	50%		66%	34%	
Fair	50%	50%		25%	75%		41%	59%		74%	26%	
Bad to very bad												
Longstanding	(n = 533)	(n = 888)	< 0.0001	(n = 109)	(n = 485)	0.31	(n = 222)	(n = 314)	0.055	(n = 202)	(n = 89)	0.08
illness (%)	45%	55%		21%	79%		47%	53%		74%	26%	
Yes	33%	67%		17%	83%		38%	62%		65%	35%	
No												
Physical pain,	(n = 533)	(n = 887)	0.03	(n = 109)	(n = 485)	0.37	(n = 222)	(n = 314)	0.83	(n = 202)	(n = 89)	0.26
discomfort (%)	36%	64%		18%	82%		41%	59%		66%	34%	
None/very mild	39%	61%		18%	82%		39%	61%		75%	25%	
to mild	48%	52%		27%	73%		45%	55%		78%	22%	
Moderate												
Severe or very severe												

[a] $P < 0.025$ threshold significance value for individual analyses, based on Bonferroni correction (two comparisons) with $P < 0.05$ significance threshold.

whereas no significant relationship was observed in the prevalence of urinary incontinence between MUO and MHO.

Arthrosis prevalence was significantly different in metabolically healthy vs. unhealthy profiles ($P = 0.001$), although no significant relationship was observed within the three weight categories.

Self-reported sleep apnoea was significantly more frequent with metabolically unhealthy profiles (65%; $P = 0.002$), but no significant relationship was detected across the three weight categories. However, when the BQ score was applied, significant weight-category-related differences were observed for sleep apnoea risk, which was more prevalent in the MUHN than in the MHNW, and less prevalent in the MHOV and MHO compared with MUOV and MUO ($P < 0.0001$). Nevertheless, having hypertension and obesity in the BQ may interfere with the diagnosis of healthy/unhealthy phenotypes.

According to PHQ-9 scores, participants with MUOV profiles were more likely to report depressive symptoms than those with MHOV profiles (52%; $P = 0.06$ for a statistical tendency).

Finally, no significant relationship was observed between a cardiometabolically healthy or unhealthy weight status and coronary heart disease, myocardial infarction, cirrhosis or other liver disease, osteoporosis, rheumatoid arthritis, lower-back disorders, asthma and chronic anxiety (Table 4).

Direct and indirect costs of disease

The direct and indirect costs of disease (healthcare-related costs + cost of productivity loss) were lower for participants with metabolically healthy profiles in general, with differences of up to € 3000 (cost of metabolically unhealthy profiles = € 4563 vs. cost of metabolically healthy profiles = € 2739; $P = 0.02$). Within the different BMI groups, the direct and indirect costs of disease were generally lower for those showing metabolically healthy profiles, although the results were not statistically significant except for obesity (costs of MUO = € 6400 vs. MHO = € 3533; $P = 0.056$; Table 5).

Discussion

The present work suggests that a non-negligible number of people displayed MUNW (8%), MHOV (22%) and MHO (6%) profiles between 2013 and 2015 in Luxembourg. This was the first attempt to investigate this specific issue in the Grand Duchy of Luxembourg in a nationally representative sample of adult residents aged 25–64 years. One-fifth of those with normal weight displayed metabolically unhealthy profiles. On the other hand, around one-third of those with obesity and two-thirds of those with overweight showed metabolically healthy profiles.

Investigating metabolically unhealthy profiles within the normal-weight category is usually neglected despite the importance of treating and preventing their complications. Indeed, just like people with MUOV or MUO profiles, those with MUNW similarly show high levels of non-alcoholic fatty liver disease, high abdominal-visceral obesity, low leg-fat adiposity, insulin resistance and/or low cardiorespiratory fitness, all of which are major risk factors of cardiometabolic disorders [35]. As such, they need to be properly managed, particularly in terms of body composition, to prevent future complications [35]. It is also crucial to investigate metabolically healthy profiles in the overweight and obesity categories to better characterize those who are not necessarily in need of intervention, but who may need to preserve their cardiometabolic health [6,8,9,12], whereas people with MUOV and MUO are already generally being properly managed.

Age and gender (male) were significantly associated with metabolically unhealthy profiles independently of weight status. Aerobic exercise was significantly associated with the MHNW profile, and TRPA was significantly associated with the MHOV profile. Distinguishing between the physical-activity categories to investigate the relationship between weight status and cardiometabolic health was an innovative approach applied in the present study.

This work also highlights the idea that people with metabolically unhealthy profiles are more likely to have poorer perceived health, functional physical limitations, metabolic, gastrointestinal and renal complications, arthrosis, sleep apnoea and depression, all independently of their weight status. Yet, very few studies have previously explored the relationships between metabolically healthy and unhealthy weight statuses and such a wide range of health conditions. Instead, the majority of studies have focused on the relationship with cardiometabolic health and found controversial results.

In addition, our present findings reveal that any direct and indirect costs of disease are more likely to be associated with

Table 3
Longstanding limitations in daily activities in people with metabolically healthy and unhealthy normal weight, overweight and obesity in the European Health Examination Survey in Luxembourg in 2013–2015.

	Total $n=1422$			Normal weight $n=594$			Overweight $n=536$			Obesity $n=292$		
	Unhealthy $n=534$ (37.5%)	Healthy $n=888$ (62.5%)	P^a	Unhealthy $n=109$ (18.3%)	Healthy $n=485$ (81.7%)	P^a	Unhealthy $n=222$ (41.4%)	Healthy $n=314$ (58.6%)	P^a	Unhealthy $n=203$ (69.5%)	Healthy $n=89$ (30.5%)	P^a
Longstanding limitations	$n=533$	$n=887$	0.0008	$n=109$	$n=485$	0.08	$n=222$	$n=314$	0.94	$n=202$	$n=88$	0.34
in daily activities	45%	55%		18%	82%		44%	56%		67%	33%	
Severe limitations	45%	55%		26%	74%		42%	58%		76%	24%	
Limitations, but not severe	34%	66%		17%	83%		41%	59%		67%	33%	
No limitations at all												
Functional physical limitations												
Walking half a kilometre	$n=533$	$n=886$	<0.0001	$n=109$	$n=484$	0.002	$n=222$	$n=313$	1.00	$n=202$	$n=89$	0.83
with no aid	37%	63%		18%	82%		42%	58%		69%	31%	
No difficulty	63%	37%		67%	33%		43%	57%		72%	28%	
Some difficulty												
Walking up or down 12 steps	$n=533$	$n=886$	<0.0001	$n=109$	$n=484$	0.009	$n=222$	$n=313$	0.78	$n=202$	$n=89$	0.44
No difficulty	36%	64%		18%	82%		41%	59%		69%	31%	
Some difficulty	57%	43%		44%	56%		44%	56%		74%	26%	
Personal-care activity limitations												
Getting in & out of a bed or chair	$n=533$	$n=886$	0.02	$n=109$	$n=484$	0.15	$n=222$	$n=313$	0.91 (FE)	$n=202$	$n=89$	0.79
No difficulty	37%	63%		18%	82%		42%	58%		70%		
Some difficulty	56%	44%		50%	50%		43%	57%		67%	30%	
											33%	
Dressing & undressing	$n=533$	$n=886$	0.003	$n=109$	$n=484$	0.23	$n=222$	$n=313$	0.40 (FE)	$n=202$	$n=89$	0.62 (FE)
No difficulty	37%	63%		18%	82%		41%	59%		69%	31%	
Some difficulty	62%	38%		40%	60%		54%	46%		75%	25%	
Using toilets	$n=533$	$n=886$	0.68 (FE)	$n=109$	$n=484$	0.18 (FE)	$n=222$	$n=313$	0.17	$n=202$	$n=89$	0.03 (FE)
No difficulty	37%	63%		18%	482%		41%	59%		70%	30%	
Some difficulty	50%	50%		100%	0%		100%	0%		0%	3 (100%	
Bathing or showering	$n=533$	$n=886$	0.12	$n=109$	$n=484$	NA	$n=222$	$n=313$	0.72 (FE)	$n=202$	$n=89$	0.70 (FE)
No difficulty	37%	63%		18%	82%		41%	59%		70%	30%	
Some difficulty	56%	44%		0 (/)	0 (/)		50%	50%		63%	37%	
Limitation in household activities												
Preparing meals	$n=533$	$n=887$	0.35 (FE)	$n=109$	$n=484$	0.25 (FE)	$n=222$	$n=314$	0.43 (FE)	$n=202$	$n=89$	0.42 (FE)
No difficulty	37%	63%		18%	482%		41%	59%		70%	30%	
Some difficulty	53%	47%		50%	50%		57%	43%		50%	50%	
Do not need to do	42%	58%		14%	86%		53%	47%		50%	50%	
Shopping	$n=533$	$n=886$	0.053 (FE)	$n=109$	$n=484$	0.23 (FE)	$n=222$	$n=314$	0.78 (FE)	$n=202$	$n=89$	0.89 (FE)
No difficulty	37%	63%		18%	82%		41%	59%		70%	30%	
Some difficulty	58%	42%		33%	67%		56%	44%		64%	36%	
Do not need to do	57%	43%		50%	50%		33%	67%		100%	0%	
Doing light housework	$n=533$	$n=887$	0.04 (FE)	$n=109$	$n=484$	1.00 (FE)	$n=222$	$n=314$	0.03 (FE)	$n=202$	$n=89$	0.63(FE)
No difficulty	37%	63%		19%	81%		41%	59%		70%	30%	
Some difficulty	47%	53%		0%	100%		57%	43%		56%	44%	
Do not need to do	83%	17%		0%	100%		100%	0%		100%	0%	
Doing occasional heavy	$n=533$	$n=887$	0.07 (FE)	$n=109$	$n=484$	0.66 (FE)	$n=222$	$n=314$	0.60 (FE)	$n=202$	$n=89$	0.61 (FE)
housework	37%	64%		18%	82%		42%	58%		69%	31%	
No difficulty	45%	55%		24%	76%		35%	65%		70%	30%	
Some difficulty	55%	45%		0%	100%		40%	60%		100%	0%	
Do not need to do												

FE: Fisher's exact test.
[a] $P<0.025$ threshold significance value for individual analyses based on Bonferroni correction (two comparisons) with $P<0.05$ significance threshold.

cardiometabolic health in general than with weight status. To our knowledge, this is the first population-based study to consider such a health-economics approach in the field.

Prevalence

Depending on the studied population and definitions adopted, previous prevalence estimates of metabolically healthy/unhealthy weight status have varied from 8% to 24% for MUNW, and from 3% to 75% for MHOV and MHO [5,7,36,37]. The wide ranges observed may be due to the differing definitions used to investigate the prevalence of these weight statuses. In fact, no consensus has yet been established to permit a standardized definition, and various definitions are still used by different authors, thereby preventing full comparability of their findings. Nevertheless, in spite of the multitude of definitions previously used, our present findings are in agreement with the available literature [5,7,36,37]. Our study chose the Ortega et al. [7] definition to define metabolically unhealthy profiles because of its restrictive features, including no more than two cardiometabolic abnormalities and the widespread use of this threshold in the current literature [9]. However, as the Ortega et al. definition stipulates that people with metabolically unhealthy profiles represent those with ≥ 2 cardiometabolic abnormalities, it is therefore not unusual to find participants with some such disorders, in particular diabetes, despite being metabolically healthy (Table 4). Indeed, of our 76 participants with diabetes, six showed metabolically healthy profiles according to Ortega's definition; of these six, two women with a mean age of 47.5 years had an average BMI of 25.1 kg/m^2 and mean waist circumference of 91 cm. However, none of them had elevated blood pressure or coronary disease, although three had high cholesterol levels, and one had depression and cirrhosis.

Nevertheless, it seems inappropriate to consider subjects as metabolically healthy when they have diabetes and/or coronary

Table 4
Presence of chronic disease in the past 12 months in people with metabolically healthy and unhealthy normal weight, overweight and obesity in the European Health Examination Survey in Luxembourg in 2013–2015.

	Total ($n=1422$)			Normal weight ($n=594$)			Overweight ($n=536$)			Obesity ($n=292$)		
	Unhealthy $n=534$ (37.5%)	Healthy $n=888$ (62.5%)	*P*	Unhealthy $n=109$ (18.3%)	Healthy $n=485$ (81.7%)	*P*	Unhealthy $n=222$ (41.4%)	Healthy $n=314$ (58.6%)	*P*	Unhealthy $n=203$ (69.5%)	Healthy $n=89$ (30.5%)	*P*
Cardiometabolic comorbidities												
Arterial hypertension	$n=534$	$n=886$	<0.0001	$n=109$	$n=484$	<0.0001	$n=222$	$n=313$	<0.0001	$n=203$	$n=89$	<0.0001
Yes	68%	32%		51%	49%		61%	39%		85%	15%	
No	26%	74%		13%	87%		33%	67%		53%	47%	
High cholesterol	$n=534$	$n=888$	<0.0001	$n=109$	$n=485$	<0.0001	$n=222$	$n=314$	<0.0001	$n=203$	$n=89$	<0.0001
Yes	65%	35%		43%	57%		64%	36%		84%	16%	
No	19%	81%		11%	89%		23%	77%		46%	54%	
Diabetes	$n=534$	$n=886$	<0.0001	$n=109$	$n=484$	<0.0001	$n=222$	$n=313$	<0.0001	$n=203$	n=89	<0.0001
Yes	92%	8%		71%	29%		94%	6%		98%	2%	
No	35%	65%		17%	83%		40%	60%		64%	36%	
Coronary heart disease	$n=533$	$n=887$	0.18	$n=109$	$n=485$	0.33 (FE)	$n=222$	$n=313$	0.70 (FE)	$n=202$	$n=89$	1.0 (FE)
Yes	53%	47%		50%	50%		29%	71%		75%	25%	
No	37%	63%		18%	82%		42%	58%		69%	31%	
Myocardial infarction	$n=533$	$n=888$	0.43 (FE)	$n=109$	$n=485$	0.33 (FE)	$n=222$	$n=314$	1.0 (FE)	$n=202$	$n=89$	1.0 (FE)
Yes	57%	43%		50%	50%		50%	50%		66%	33%	
No	37%	63%		18%	82%		41%	59%		70%	31%	
Stroke	$n=533$	$n=888$	0.37 (FE)	$n=109$	$n=485$	0.18 (FE)	$n=222$	$n=314$	NA	$n=202$	$n=89$	NA
Yes	100%	0%		100%	0%		NA	NA		NA	NA	
No	37%	63%		18%	82%		41%	59%		69%	31%	
Gastrointestinal disease												
Stomach or duodenal ulcer	$n=533$	$n=888$	0.02	$n=109$	$n=485$	1.0 (FE)	$n=222$	$n=314$	0.10 (FE)	$n=202$	$n=89$	0.31 (FE)
Yes	65%	35%		0%	100%		70%	30%		100%	0%	
No	37%	63%		18%	82%		41%	59%		69%	31%	
Liver disease												
Cirrhosis or others	$n=533$	$n=888$	0.35	$n=109$	$n=485$	0.67 (FE)	$n=222$	$n=314$	0.25 (FE)	n=60%	$n=89$	0.64 (FE)
Yes	46%	54%		22%	78%		58%	42%		170%	40%	
No	37%	63%		18%	82%		41%	59%			30%	
Renal disease												
Urinary incontinence	$n=533$	$n=888$	0.0003	$n=109$	$n=485$	0.004	$n=222$	$n=314$	0.058	$n=202$	$n=89$	0.95
Yes	63%	37%		47%	53%		73%	27%		70%	30%	
No	37%	63%		18%	82%		41%	59%		69%	31%	
Osteoarticular diseases												
Osteoporosis	$n=533$	$n=888$	0.99	$n=109$	$n=485$	0.39 (FE)	$n=222$	$n=314$	0.76 (FE)	$n=202$	$n=89$	0.46 (FE)
Yes	38%	62%		25%	75%		46%	54%		56%	44%	
No	37%	63%		18%	82%		41%	59%		70%	30%	
Arthrosis	$n=533$	$n=888$	0.001	$n=109$	$n=485$	0.33	$n=222$	$n=314$	0.94	$n=202$	$n=89$	0.08
Yes	47%	53%		22%	78%		42%	58%		77.2%	22.8%	
No	36%	64%		18%	82%		41%	59%		67%	33%	
Rheumatoid arthritis	$n=532$	$n=888$	0.08	$n=109$	$n=485$	0.77 (FE)	$n=222$	$n=314$	0.88	$n=201$	$n=89$	0.57
Yes	47%	53%		20%	80%		40%	60%		74%	26%	
No	37%	63%		18%	82%		41%	59%		69%	31%	
Lower-back disorders	$n=533$	$n=888$	0.19	$n=109$	$n=485$	0.10	$n=222$	$n=314$	0.26	$n=202$	$n=89$	0.84
Yes	40%	60%		23%	77%		37%	63%		70%	30%	
No	37%	63%		17%	83%		43%	57%		69%	31%	
Respiratory diseases												
Asthma	$n=534$	$n=888$	0.24	$n=109$	$n=485$	0.80 (FE)	$n=222$	$n=314$	0.09	$n=203$	$n=89$	0.51 (FE)
Yes	31%	69%		15%	85%		27%	73%		82%	18%	
No	38%	62%		19%	81%		42%	58%		70%	31%	
Sleep apnoea (self-reported)	$n=534$	$n=888$	0.002	$n=109$	$n=485$	0.45 (FE)	$n=222$	$n=314$	0.74 (FE)	$n=203$	$n=89$	0.20 (FE)
Yes	65%	35%		33%	67%		33%	67%		84%	16%	
No	37%	63%		18%	82%		42%	58%		68%	32%	
Sleep apnoea (BQ scores)	$n=534$	$n=888$	<0.0001	$n=109$	$n=485$	<0.0001	$n=222$	$n=314$	<0.0001	$n=203$	$n=89$	<0.0001
Yes	66%	34%		45%	55%		59%	41%		84%	16%	
No	29%	71%		15%	85%		35%	65%		58%	42%	
Mental disorders												
Chronic anxiety	$n=534$	$n=888$	0.22	$n=109$	$n=485$	0.42	$n=222$	$n=314$	0.27	$n=202$	$n=89$	0.91
Yes	45%	55%		11%	89%		52%	48%		71%	29%	
No	37%	63%		18%	82%		41%	59%		69%	31%	
Depression (PHQ-9 scores)	$n=533$	$n=887$	0.33	$n=109$	$n=484$	0.91 (FE)	$n=222$	$n=314$	0.06	$n=202$	$n=89$	0.08
No depression (0–4)	37%	63%		19%	81%		39%	61%		73%	27%	
Mild to moderate (5–14)	40%	60%		17%	83%		52%	48%		60%	40%	
Moderately severe to severe (15–27)	47%	53%		17%	83%		50%	50%		58%	42%	

FE: Fisher's exact test; NA: not available; BQ: Berlin Questionnaire.

heart disease, myocardial infarction and/or stroke. Indeed, there is no agreement on how to deal with this group of people, and it may be an important limitation if they are considered metabolically healthy. A definition restricted to zero metabolic components to characterize metabolically healthy phenotypes (and ≥ 1 abnormality for unhealthy phenotypes) would be more sensitive than the Ortega et al. [7] definition to determine metabolically unhealthy profiles within the three categories of weight.

Table 5
Metabolically healthy and unhealthy weight statuses: Direct and indirect costs of disease[a]

Phenotypes	EHES-LUX$_{2013–2015}$ (n = 1422)			Normal weight (n = 594)			Overweight (n = 536)			Obesity (n = 292)		
	MU n = 534 (37.5%)	MH n = 888 (62.5%)	P	MUNW n = 109 (18.3%)	MHNW n = 485 (81.7%)	P	MUOV n = 222 (41.4%)	MHOV n = 314 (58.6%)	P	MUO n = 203 (69.5%)	MHO n = 89 (30.5%)	P
Direct & indirect costs of disease	€ 4563	€ 2739	0.02	€ 2754	€ 2484	0.76	€ 3751	€ 2905	0.48	€ 6400	€ 3533	0.056
Healthcare-related costs	€ 1260	€ 954	0.19	€ 826	€ 885	0.77	€ 1303	€ 1105	0.66	€ 1441	€ 800	0.02
Cost of productivity loss	€ 3303	€ 1786	0.04	€ 1929	€ 1598	0.66	€ 2449	€ 1803	0.37	€ 4959	€ 2733	0.11

EHES-LUX$_{2013–2015}$: European Health Examination Survey in Luxembourg in 2013–2015; MU/MH: metabolically unhealthy/healthy; MUNW/MHNW: metabolically unhealthy/healthy normal weight; MUOV/MHOV: metabolically unhealthy/healthy overweight; MUO/MHO: metabolically unhealthy/healthy obesity.
[a] Healthcare-related costs + cost of productivity loss.

Finally, due to the lack of available data, it was not possible to test more-sensitive definitions based on inflammation and/or insulin resistance [5].

Correlates

MUNW and MUO increased with age in the present study, which is in line with work previously conducted in American and Korean adult populations [5,37]. Our findings also indicate that metabolically unhealthy profiles may be more common in men than in women, which is consistent with the study by Lee et al. [37] in the Korean population. Wildman et al. [5] also reported that around 30% of MUNW profiles are present in US men and 21% in women, and about 29% of MHO profiles are in men and 35.4% in women.

Certain authors have emphasized the negative impact of sedentary behaviours, such as weekly television-viewing times, on cardiometabolic health in individuals with MHO [17]. Others, however, observed no significant difference between MHO and MUO in screen-watching time (albeit television, videos and computers), but found a significant positive impact of physical activity instead [18,38].

Our present findings are in line with the work of Fung et al. [39], which highlighted the important role played by cardiorespiratory fitness to preserve metabolic health in overweight people. Our findings corroborate the notion that regular APA is positively associated with MHOV. It was also observed that only 100 METs of TRPA can lower the risk of developing MUNW.

Regarding the role of dietary habits in the development of metabolically healthy and unhealthy weight statuses, no consensus has yet been established in the literature. While certain authors have shown that dietary composition did not differ between the MHO and MUO [19,20], others found a significant positive impact of a "healthy dietary pattern" on cardiometabolic health in obesity [21,38]. However, our study could find no significant associations with dietary habits (fruit, vegetable and/or alcohol consumption) after adjusting for other correlates.

Comorbidities

Cardiovascular (CV) risk factors and diseases are the most frequently investigated comorbidities in relation to MHO and MUO in the literature. However, the previously published findings have been rather controversial. Appleton et al. [40] found MUO to be a risk factor for T2D, but not for CV diseases. Hinnouho et al. [41] showed an increased risk of CV diseases in both MUO and MHO, but a lower risk of T2D in MHO.

Although less well investigated, the relationship between CV disturbances and the MUNW profile is now an emerging issue. Dyslipidaemia, hyperglycaemia and hypertension especially appear to also arise in people with normal weight, which is in agreement with our findings [5]. However, Yoo et al. [42] observed more arterial stiffness and carotid atherosclerosis in Koreans who were MUNW than in those who were MHO. In the present work, no significant link was observed with CV diseases, most likely due to limited statistical power, rendering this something to be assessed in larger studies including more subjects.

Regarding the relationship between metabolically healthy and unhealthy profiles and mental health, our findings suggest that feelings of well-being, anxiety and depression may be significantly associated with unhealthy metabolic profiles rather than weight status [14]. Hamer et al. [15] found a significant relationship between depression and both MHO and MUO, with higher depression rates in the MUO. On the other hand, our findings were somewhat in favour of depression with MUOV profiles.

Our present study also investigated the relationships between metabolically healthy and unhealthy weight statuses and other health issues less widely explored in the literature, such as functional physical limitations, and found significantly fewer such limitations with MHNW profiles compared with MUNW, as previously reported by Bouchard et al. [13].

Furthermore, our study found that individuals with metabolically healthy profiles, regardless of weight status, were more likely to report a better perceived health status, fewer stomach or duodenal ulcers, and less sleep apnoea, arthrosis, physical pain, and limitations in daily and personal activities because of a health problem. To our knowledge, these findings represent novel observations in the literature.

Direct and indirect costs of disease

Overweight, obesity and their potential related health comorbidities have been widely associated in the literature with both direct healthcare-related costs and the indirect costs of productivity loss, mostly due to more years of life with physical and mental disability, as well as more days spent sick in bed and on long-term sick leaves, more absenteeism from work, decreased live expectancy before retirement and/or earlier pensions [4]. However, as far as the present authors are aware, this is the first study to investigate the relationship between metabolically healthy and unhealthy weight statuses and the direct and indirect costs of disease. The present findings suggest that the relationship between weight status and health expenditure is more intricate than a simple weight consideration, given the fact that the cost of disease was significantly higher amongst the metabolically unhealthy profiles independently of weight status. Nevertheless, the differences observed in terms of cost should be interpreted with caution because of assumptions made for both resource use and unit costs due to the lack of national data. Future studies need to use more detailed resources such as questionnaires and, ideally,

local unit costs. Medication costs were not included in this study, but should also be included in any future ones.

Conclusion

Our study confirms the need for a paradigm shift in body-weight management, with a focus on cardiometabolic health rather than just body weight [43]. In fact, whatever the weight status, people can develop a metabolically unhealthy profile and be more likely to experience adverse health outcomes, with higher healthcare and loss-of-productivity costs. Conversely, a large proportion of people with overweight and/or obesity may have a metabolically healthy profile. From a public-health perspective, interventions focused on improving cardiometabolic health may also be cost-saving and more cost-effective than those focused solely on BMI categories. Finally, as this was a cross-sectional study, no conclusions as to causal relationships could be drawn. For that, further investigations would need to be performed in longitudinal studies.

Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary materials (Appendices A–D) associated with this article can be found at http://www.sciencedirect.com at https://doi.org/10.1016/j.diabet.2017.11.007.

References

[1] Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. BMC Public Health 2009;9:88. http://dx.doi.org/10.1186/1471-2458-9-88.

[2] Shields M, Shooshtari S. Determinants of self-perceived health. Health reports 2001;13:35–52.

[3] Pataky Z, Armand S, Muller-Pinget S, Golay A, Allet L. Effects of obesity on functional capacity. Obesity (Silver Spring) 2014;22:56–62. http://dx.doi.org/10.1002/oby.20514.

[4] Popkin BM, Kim S, Rusev ER, Du S, Zizza C. Measuring the full economic costs of diet, physical activity and obesity-related chronic diseases. Obes Rev 2006;7:271–93. http://dx.doi.org/10.1111/j.1467-789X.2006.00230.x.

[5] Wildman RP, Muntner P, Reynolds K, McGinn AP, Rajpathak S, Wylie-Rosett J, et al. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999–2004). Arch Intern Med 2008;168:1617–24. http://dx.doi.org/10.1001/archinte.168.15.1617.

[6] Karelis AD. Metabolically healthy but obese individuals. Lancet 2008; 372:1281–3. http://dx.doi.org/10.1016/s0140-6736(08)61531-7.

[7] Ortega FB, Lee DC, Katzmarzyk PT, Ruiz JR, Sui X, Church TS, et al. The intriguing metabolically healthy but obese phenotype: cardiovascular prognosis and role of fitness. Eur Heart J 2013;34:389–97. http://dx.doi.org/10.1093/eurheartj/ehs174.

[8] Mathew H, Farr OM, Mantzoros CS. Metabolic health and weight: understanding metabolically unhealthy normal weight or metabolically healthy obese patients. Metabolism 2016;65:73–80. http://dx.doi.org/10.1016/j.metabol.2015.10.019.

[9] Stefan N, Haring HU, Hu FB, Schulze MB. Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications. Lancet Diabetes Endocrinol 2013;1:152–62. http://dx.doi.org/10.1016/S2213-8587(13)70062-7.

[10] Jokela M, Hamer M, Singh-Manoux A, Batty GD, Kivimaki M. Association of metabolically healthy obesity with depressive symptoms: pooled analysis of eight studies. Mol Psychiatry 2014;19:910–4. http://dx.doi.org/10.1038/mp.2013.162.

[11] Liu J, Xu C, Ying L, Zang S, Zhuang Z, Lv H, et al. Relationship of serum uric acid level with non-alcoholic fatty liver disease and its inflammation progression in non-obese adults. Hepatol Res 2017;47:E104–12. http://dx.doi.org/10.1111/hepr.12734.

[12] Karelis AD, Messier V, Brochu M, Rabasa-Lhoret R. Metabolically healthy but obese women: effect of an energy-restricted diet. Diabetologia 2008;51:1752–4. http://dx.doi.org/10.1007/s00125-008-1038-4.

[13] Bouchard DR, Langlois MF, Brochu M, Dionne IJ, Baillargeon JP. Metabolically healthy obese women and functional capacity. Metab Syndr Relat Disord 2011;9:225–9. http://dx.doi.org/10.1089/met.2010.0101.

[14] Phillips CM, Perry IJ. Depressive symptoms, anxiety and well-being among metabolic health obese subtypes. Psychoneuroendocrinology 2015;62:47–53. http://dx.doi.org/10.1016/j.psyneuen.2015.07.168.

[15] Hamer M, Batty GD, Kivimaki M. Risk of future depression in people who are obese but metabolically healthy: the English longitudinal study of ageing. Mol Psychiatry 2012;17:940–5. http://dx.doi.org/10.1038/mp.2012.30.

[16] Lin L, Peng K, Du R, Huang X, Lu J, Xu Y, et al. Metabolically healthy obesity and incident chronic kidney disease: the role of systemic inflammation in a prospective study. Obesity (Silver Spring) 2017. http://dx.doi.org/10.1002/oby.21768.

[17] Bell JA, Kivimaki M, Batty GD, Hamer M. Metabolically healthy obesity: what is the role of sedentary behaviour? Prev Med 2014;62:35–7. http://dx.doi.org/10.1016/j.ypmed.2014.01.028.

[18] Camhi SM, Waring ME, Sisson SB, Hayman LL, Must A. Physical activity and screen time in metabolically healthy obese phenotypes in adolescents and adults. J Obes 2013;2013:984613. http://dx.doi.org/10.1155/2013/984613.

[19] Hankinson AL, Daviglus ML, Van Horn L, Chan Q, Brown I, Holmes E, et al. Diet composition and activity level of at risk and metabolically healthy obese American adults. Obesity (Silver Spring) 2013;21:637–43. http://dx.doi.org/10.1002/oby.20257.

[20] Kimokoti RW, Judd SE, Shikany JM, Newby PK. Food intake does not differ between obese women who are metabolically healthy or abnormal. J Nutr 2014;144:2018–26. http://dx.doi.org/10.3945/jn.114.198341.

[21] Camhi SM, Whitney Evans E, Hayman LL, Lichtenstein AH, Must A. Healthy eating index and metabolically healthy obesity in U.S. adolescents and adults. Prev Med 2015;77:23–7. http://dx.doi.org/10.1016/j.ypmed.2015.04.023.

[22] Ruiz-Castell M, Kandala NB, Kuemmerle A, Schritz A, Barre J, Delagardelle C, et al. Hypertension burden in Luxembourg: Individual risk factors and geographic variations, 2013 to 2015 European Health Examination Survey. Medicine 2016;95:e4758. http://dx.doi.org/10.1097/MD.0000000000004758.

[23] Tolonen H. EHES Manual l. Part B. In: Fieldwork procedures 2016. Helsinki, Finland: National Institute for Health and Welfare; 2013.

[24] Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640–5. http://dx.doi.org/10.1161/CIRCULATIONAHA.109.192644.

[25] Bluher S, Schwarz P. Metabolically healthy obesity from childhood to adulthood - Does weight status alone matter? Metabolism 2014;63:1084–92. http://dx.doi.org/10.1016/j.metabol.2014.06.009.

[26] Finger JD, Tafforeau J, Gisle L, Oja L, Ziese T, Thelen J, et al. Development of the European Health Interview Survey-Physical Activity Questionnaire (EHIS-PAQ) to monitor physical activity in the European Union. Arch Public Health 2015;73:59. http://dx.doi.org/10.1186/s13690-015-0110-z.

[27] United States Department of Health and Human Services OoDPaHPPAGfA. Be active, healthy and happy; 2008 [Available at: https://health.gov/PAGUIDELINES/pdf/paguide.pdf; accessed October 2016].

[28] Hirshkowitz M, Whiton K, Albert SM, Alessi C, Bruni O, DonCarlos L, et al. National Sleep Foundation's sleep time duration recommendations: methodology and results summary. Sleep Health 2015;1:40–3. http://dx.doi.org/10.1016/j.sleh.2014.12.010.

[29] Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Ann Internal Med 1999;131:485–91.

[30] Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Internal Med 2001;16:606–13.

[31] Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. Chicago: Oxford university press; 2015.

[32] Caisse nationale de santé. Luxembourg Nomenclature des actes et services des médecins; 2017 [Available at: http://www.cns.public.lu/fr/legislations/ammd_dent/cns-ammd-med-tableau.html; accessed 06.02.2017].

[33] Hakkaart-van Roijen L, Van der Linden N, Bouwmans C, Kanters T, Tan SS. Kostenhandleiding Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. opdracht van Zorginstituut Nederland. Geactualiseerde versie; 2015.
[34] Mihaylova B, Briggs A, O'Hagan A, Thompson SG. Review of statistical methods for analysing healthcare resources and costs. Health Econ 2011;20:897–916. http://dx.doi.org/10.1002/hec.1653.
[35] Stefan N, Schick F, Haring HU. Causes, characteristics, and consequences of metabolically unhealthy normal weight in humans. Cell Metab 2017;26:292–300. http://dx.doi.org/10.1016/j.cmet.2017.07.008.
[36] Rey-Lopez JP, de Rezende LF, Pastor-Valero M, Tess BH. The prevalence of metabolically healthy obesity: a systematic review and critical evaluation of the definitions used. Obes Rev 2014;15:781–90. http://dx.doi.org/10.1111/obr.12198.
[37] Lee K. Metabolically obese but normal weight (MONW) and metabolically healthy but obese (MHO) phenotypes in Koreans: characteristics and health behaviors. Asia Pacific J Clin Nutrit 2009;18:280–4.
[38] Phillips CM, Dillon C, Harrington JM, McCarthy VJ, Kearney PM, Fitzgerald AP, et al. Defining metabolically healthy obesity: role of dietary and lifestyle factors. PLoS One 2013;8:e76188. http://dx.doi.org/10.1371/journal.pone.0076188.
[39] Fung MD, Canning KL, Mirdamadi P, Ardern CI, Kuk JL. Lifestyle and weight predictors of a healthy overweight profile over a 20-year follow-up. Obesity (Silver Spring) 2015;23:1320–5. http://dx.doi.org/10.1002/oby.21087.
[40] Appleton SL, Seaborn CJ, Visvanathan R, Hill CL, Gill TK, Taylor AW, et al. Diabetes and cardiovascular disease outcomes in the metabolically healthy obese phenotype: a cohort study. Diabetes care 2013;36:2388–94. http://dx.doi.org/10.2337/dc12-1971.
[41] Hinnouho GM, Czernichow S, Dugravot A, Nabi H, Brunner EJ, Kivimaki M, et al. Metabolically healthy obesity and the risk of cardiovascular disease and type 2 diabetes: the Whitehall II cohort study. Eur Heart J 2015;36:551–9. http://dx.doi.org/10.1093/eurheartj/ehu123.
[42] Yoo HJ, Hwang SY, Hong HC, Choi HY, Seo JA, Kim SG, et al. Association of metabolically abnormal but normal weight (MANW) and metabolically healthy but obese (MHO) individuals with arterial stiffness and carotid atherosclerosis. Atherosclerosis 2014;234:218–23. http://dx.doi.org/10.1016/j.atherosclerosis.2014.02.033.
[43] Mensinger JL, Calogero RM, Stranges S, Tylka TL. A weight-neutral versus weight-loss approach for health promotion in women with high BMI: a randomized-controlled trial. Appetite 2016;105:364–74. http://dx.doi.org/10.1016/j.appet.2016.06.006.