Stability of metabolically healthy obesity over 8 years: the English Longitudinal Study of Ageing

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Abstract

Objective: Metabolically healthy obesity possibly reflects a transitional stage before the onset of metabolic dysfunction, but few studies have characterised this transition. We examined the behavioural and biological characteristics of healthy obese adults that progressed to an unhealthy state over 8 years follow up.

Methods: Participants were 2422 men and women (aged 63.3 ± 7.7 years, 44.2% men) from the English Longitudinal Study of Ageing. Obesity was defined as body mass index ≥ 30 kg/m^2. Based on blood pressure, HDL-cholesterol, triglycerides, glycated haemoglobin, and C-reactive protein participants were classified as 'healthy' (0 or 1 metabolic abnormality) or 'unhealthy' (≥ 2 metabolic abnormalities).

Results: Over eight years follow-up, 44.5% of healthy obese had transitioned into an unhealthy state, compared to only 16.6% and 26.2% of healthy normal weight and overweight adults, respectively. Compared with healthy obese adults who remained stable, those who progressed to an unhealthy state were more likely to have high blood pressure (75.0% vs 37.0%, age- and sex-adjusted odds ratio [OR] 8.9, 95% confidence interval [CI] 4.7-17.0), high C-reactive protein (53.7% vs 17.0%, OR=8.6, 95% CI 4.1-18.0), high glycated haemoglobin (46.3% vs 5.9%, OR=13.8, 95% CI 6.1-31.2) and high triglycerides (45.4% vs 11.9%, OR=5.9, 95% CI 2.9-12.0) at follow-up, with excess risk remaining independent of lifestyle factors including self-reported physical activity. Progression to an unhealthy state was also linked with significant gains in waist circumference (B=2.7, 95% CI, 0.5 – 4.9 cm).

Conclusion: These data show that a healthy obesity phenotype is relatively unstable. Transition to an unhealthy state is characterised by multiple biological changes which are not fully explained by lifestyle risk factors.

Introduction

Population based studies have identified an obese phenotype that is not accompanied by adiposity associated cardio-metabolic risk factors. Termed 'metabolically healthy obesity', it is unclear if the healthy obese phenotype is a stable trait or a transitional stage prior to the onset of metabolic dysfunction.[1] This instability may explain the inconsistency in findings between studies with shorter and longer follow-up periods in relation to healthy obesity and risk of incident type 2 diabetes and cardiovascular disease (CVD).[2,3]

In particular, the characteristics of healthy obese participants that remain stable or develop metabolic abnormalities are poorly understood. In a recent cohort study, 67% of healthy obese adults maintained stable metabolic health profiles at 4 years follow-up, and these adults displayed lower waist circumference at baseline although no differences in physical activity, alcohol or smoking were observed.[4] In the Whitehall II study of British men and women, more than half of healthy obese adults progressed to an unhealthy obese state after 20 years.[5] The aim of the present study was to examine stability of healthy obesity over an 8 year follow-up period and to describe the metabolic and lifestyle profile of obese participants that progressed to an unhealthy state.

Materials and Methods

Study sample and procedures

The English Longitudinal Study of Ageing (ELSA) is an ongoing cohort study that contains a nationally representative sample of free-living men and women born on or before 29 February 1952.[6] Data collected at wave 2 (2004-05) were used as the baseline for present

68 analyses, as this was the first occasion clinical information was gathered. A clinical
69 assessment was repeated eight years later. Participants gave full informed written consent
70 to participate in the study and ethical approval was obtained from the London Multi-Centre
71 Research Ethics Committee.

72 Clinical Measurements at baseline and follow-up

73 Nurses collected anthropometric data (weight, height, waist circumference), blood pressure
74 (BP), and non-fasting blood samples using standard protocols at baseline and follow-up.
75 Body weight was measured using Tanita electronic scales without shoes and in light
76 clothing, and height was measured using a Stadiometer with the Frankfort plane in the
77 horizontal position. Body mass index (BMI) was calculated as weight (kilograms)/height
78 (meters) squared. Waist circumference was recorded twice mid-way between the iliac crest
79 and lower rib using measuring tape. An average of the first two measurements was used
80 provided these differed by no more than 3cm; otherwise a third reading was taken and the
81 two closest results utilised. Systolic and diastolic BP was measured with an Omron HEM-907
82 blood pressure monitor three times in the sitting position after 5-minute rest between each
83 reading. The initial reading was discarded and an average of the second and third BP
84 recordings was used for the present analyses. Blood samples were analyzed for C-reactive
85 protein (CRP), high density lipoprotein (HDL) cholesterol, triglycerides, and glycated
86 haemoglobin (HbA1c). Detailed information on the technicalities of the blood analysis, the
87 internal quality control, and the external quality assessment for the laboratory have been
88 described elsewhere.[7] Additional data were collected on physician diagnosed conditions
89 (hypertension, diabetes) and medication use.

90 Lifestyle risk factors at baseline

Health-related questions included cigarette smoking (current, previous or non-smoker), the frequency of participation in light, moderate, and vigorous physical activities (more than once per week, once per week, one to three times per month, hardly ever), and the frequency of alcohol intake (daily, 5-6/week, 3-4/week, 1-2/week, 1-2/month, once every couple of months, 1-2/year, never).

Statistical analyses

We used the conventional criteria to define obesity (BMI ≥ 30 kg/m^2) and overweight (BMI ≥ 25 and <30 kg/m^2). A healthy metabolic status was based on existing criteria,[8] and according to availability of data, defined as having less than two of the following metabolic risk factors: high BP (BP ≥130/85 mmHg, or hypertension diagnosis, or use of anti-hypertensive medication), impaired glycaemic control (HbA1c > 6.0% [42.1 mmol/mol] or doctor's diagnosed diabetes), systemic inflammation (CRP≥ 3mg/l), low HDL cholesterol (<1.03 mmol/l in men and <1.30 mmol/l in women), and high triacylglycerol (≥ 1.7 mmol/l). Participants were then categorized into four groups: 'healthy non-obese'; 'unhealthy non-obese'; 'healthy obese '; and 'unhealthy obese'. We categorised healthy obese participants into those that met criteria for healthy obesity both at baseline and at 8 years follow-up ('stable healthy obese') and those that developed ≥ 2 metabolic risk factors ('unstable healthy obese'). Differences in baseline characteristics between stable and unstable groups were tested using ANOVA and Chi-squared tests. Metabolic profiles at follow-up between stable and unstable groups were compared using logistic regression and general linear models to examine individual risk factors as categorical and continuous variables, respectively. In multivariable models we adjusted effect estimates for several covariates in a step-wise fashion: Model 1 contained age, sex, and baseline risk factor; Model 2 contained

additional behavioural and anthropometric covariates, including baseline smoking, alcohol, physical activity, and change in central obesity (waist circumference). We also examined the concept of 'weight cycling', which was defined as participants who experienced both weight gain (>5% gain in BMI) and weight loss (>5% reduction BMI) between examinations.[9] For these analyses we utilised data collected from baseline (wave 2; 2004-05), wave 4 (2008-09), and wave 6 (2012-13). Analyses were conducted using SPSS version 20.

Results

At baseline the sample consisted of 3851 individuals although loss to follow up resulted in a final analytic sample of 2442 men and women (aged 63.3 ± 7.7 yrs, 44.2% men). Participants excluded (drop-outs) did not differ in age, gender, or BMI, but were less physically active (23.8 vs 13.5%, $p<0.001$) and more likely to be metabolically unhealthy (46.2 vs 40.6% ≥ 2 risk factors, $p=0.001$) compared with included participants, respectively.

At baseline, 1206 participants were classified as healthy non-obese, 584 as unhealthy non-obese, 243 as healthy obese, and 389 as unhealthy obese. At follow-up, 44.5% of baseline healthy obese adults had transitioned into an unhealthy state, compared with 22% of healthy non-obese adults (Figure 1). We further categorised the non-obese into 'healthy normal weight' (n=530) and 'healthy overweight' (n=676); 16.6% and 26.2%, respectively, had transitioned into an unhealthy state at follow up. Adjusting for age and sex, healthy obese adults were four times as likely to transition into an unhealthy state compared with healthy normal weight adults (odds ratio = 4.00, 95% CI, 2.81 – 5.69). As expected, this association was weaker when the healthy obese were compared with the healthy

overweight (odds ratio = 2.30, 95% CI, 1.69 – 3.13). This likelihood remained unchanged after further adjustment for baseline lifestyle risk factors, including self reported physical activity, in relation to healthy normal weight (odds ratio=3.79, 95% CI, 2.60–5.51) or overweight (odds ratio = 2.30, 95% CI, 1.66 – 3.19) as the reference category. At baseline, 656 participants (n=70 healthy obese) had exceptional metabolic health (zero risk factors; 10.7% of obese adults vs 32.7% of non-obese adults). At follow-up, 325 (55.5%) of healthy non-obese and 19 (27.1%) of healthy obese remained free of any risk factors.

There were no differences in demographic and behavioural characteristics between stable and unstable healthy obese adults at baseline, although a higher proportion of stable participants had zero risk factors and stable healthy obese displayed higher baseline levels of HDL-cholesterol, and lower triacylglycerol, and HbA1c (Table 1). At follow-up, all metabolic risk factors were more prevalent among unstable healthy obese compared with stable participants. Compared with healthy obese adults that remained stable, those that progressed to an unhealthy state also gained greater waist circumference at follow up (B=2.7; 95% CI, 0.5, 4.9 cm), although no increase in BMI was observed (B= 0.63; -0.02, 1.28 kg/m^2) after baseline adjustment. In the overall cohort 9.3% of study members were identified as 'weight cycling', although this was not associated with stability of metabolic health. Lifestyle risk factors remained similar at follow-up between stable and unstable healthy obese; for example, participation in vigorous physical activity (25.8% vs. 31.1%, p=0.43) and smoking (2.3% vs. 5.7%, p= 0.33) was comparable in stable and unstable, respectively, at follow-up. When we compared the characteristics of stable and unstable healthy overweight participants the results we largely similar to those presented for the healthy obese group.

Unstable healthy obese adults demonstrated higher HbA1c (B=0.22; 0.14, 0.30%), higher triglycerides (B=0.31; 0.16, 0.47 mmol/L), higher CRP (B=0.34; 0.20, 0.47 log units), and lower HDL cholesterol (B= -0.12; -0.19, -0.06mmol/L) at follow-up after baseline adjustments for each respective risk factor. When we adjusted these models for change in waist circumference the associations with HbA1c were marginally attenuated (B=0.19; 0.12, 0.27) but effect estimates for other biomarkers were unchanged. Further adjustments for lifestyle risk factors at baseline or follow-up did not influence the associations (data available on request).

We further examined the characteristics of unhealthy obese adults at baseline who remained unhealthy or became healthy at follow-up (Table 2). At follow-up, 23.1% of unhealthy obese had transitioned into a healthy state. There were few differences in baseline characteristics between those that remained unhealthy and became healthy, except that participants transitioning into a healthy state were more likely to consume alcohol regularly (Table 2). Compared with unhealthy obese adults that became healthy, those that remained unhealthy gained greater waist circumference (B=5.5; 95% CI, 3.3, 7.7 cm), and BMI (B= 1.3; 0.5, 2.0 kg/m^2) at follow up after baseline adjustment.

Discussion

The present study has several key findings. First, healthy obesity is a relatively unstable phenotype. Second, instability in healthy obesity was not attributable to self-reported lifestyle behaviours including physical activity, but we did observe greater increases in waist circumference that is likely to be reflective of adverse changes in visceral adiposity. Third,

important features of instability were also development of low grade systemic inflammation, impaired glycaemic control, and reduction in HDL-cholesterol.

Our findings relating to stability in healthy obesity over time are largely consistent with the limited available evidence.[4,5] However, when one considers defining metabolic health as "zero risk factors" we observed striking results; first, obese adults without any metabolic risk factors are rare (10.7% of obese participants); and second, obese adults who maintain zero risk factors over time are rarer still (2.9% of obese participants).

Only one previous study has examined the characteristics of stable and unstable healthy obese adults. Consistent with our findings, they showed no differences in self-reported physical activity, alcohol or smoking,[4] although the unstable healthy obese demonstrated higher waist circumference at baseline. Our results add to this evidence base by showing that unstable healthy obese adults developed greater increases in central adiposity and several metabolic risk factors over 8 years follow-up, one particularly notable factor being impaired glycaemic control. The unstable healthy obese displayed slightly elevated HbA1c levels at baseline compared with their stable counterparts, but also greater increases in this risk factor at follow up as our analyses were adjusted for baseline. Previous work has also demonstrated that weight cycling is associated with metabolic syndrome,[9, 10] although this findings was not replicated in our data possibly owing to limited follow up of body mass assessments over the 8 years. Several over feeding studies have demonstrated that healthy obese adults display different biological responses to moderate weight gain, such as increased adipose tissue capacity for lipogenesis[11] and favourable characteristics of subcutaneous adipose tissue that help prevent visceral fat depots.[12] Thus, more subtle

differences in metabolic function, that were not possible to measure in this study, may differentiate stable and unstable healthy obesity.

Several limitations should be noted. Participants with poorer metabolic health at baseline were less likely to complete follow up assessments. Thus, the proportion of unhealthy participants that transitioned into a healthy metabolic state at follow-up may be over-estimated. The use of self-report measures to assess lifestyle risk factors may have introduced bias. Indeed, we recently demonstrated differences in physical activity between healthy and unhealthy obese adults when using objective data but not for self report.[13] Thus, the results on self-reported physical activity in the present study may underestimate the associations, although a major bias is unlikely.

In summary, healthy obesity is a relatively unstable phenotype at high risk of developing vascular, inflammatory, glycaemic and lipidaemic abnormalities over time. A true healthy obese phenotype capable of maintaining exceptional metabolic health (zero risk factors) for a prolonged period appears to be exceptionally rare in the general population. Disease prevention strategies are therefore required in the healthy obese.

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Contributors

MH had full access to the data, and takes responsibility for the integrity and accuracy of the results. MH drafted the paper. All authors contributed to the concept and design of the study and critical revision of the manuscript.

Competing interests

The authors declare no competing interests.

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Figure caption

Figure 1. Progression of metabolic risk factors over 8 years follow up

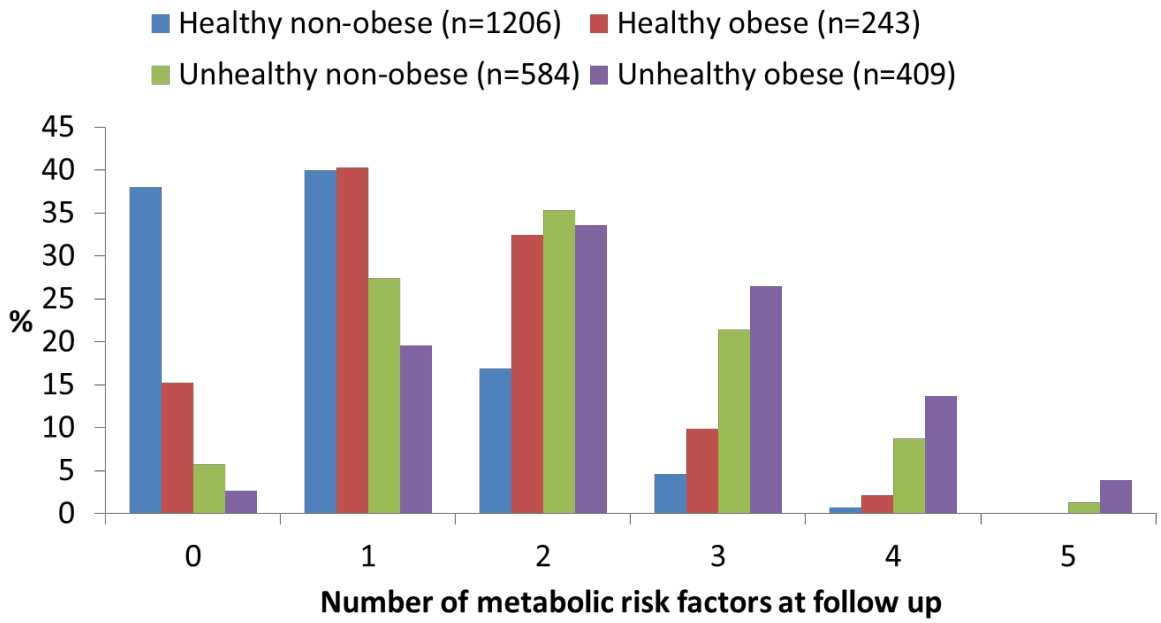

Table 1. Characteristics of healthy obese adults at baseline who remained healthy (stable) or became unhealthy (unstable) at follow-up.

Baseline characteristics	**Stable healthy obese (n= 135)**	**Unstable healthy obese (n= 108)**	**p-value**
Age (years, ± SD)	61.9 ± 7.1	62.4± 7.4	0.59
Men (%)	40.0	44.4	0.49
Vigorous physical activity at least once/week (%)	30.4	37.0	0.54
Current smoker (%)	7.4	13.0	0.15
At least one alcoholic drink/week (%)	70.0	65.3	0.62
Body mass index (kg/m^2)	32.7±2.8	32.8±3.3	0.73
Waist circumference (cm)	102.9 ± 13.2	104.9 ± 13.5	0.24
Systolic BP (mmHg)	132.2 ± 14.2	134.9 ± 14.9	0.16
Diastolic BP (mmHg)	77.1± 8.7	76.4 ± 7.7	0.49
HDL-cholesterol (mmol/l)	1.59±0.31	1.48±0.28	0.005
Triacylglycerol (mmol/l)	1.41±0.65	1.65±0.68	0.005
C-reactive protein (log unit)	1.09±0.57	1.19±0.59	0.19
HbA1C (%)	5.35±0.32	5.51±0.28	0.001
Zero metabolic risk factors (%)	35.6	20.4	0.01
Weight cycling	12.7	13.2	0.92
Metabolic risk factors at follow-up†			**Odds ratio (95% CI)‡ [stable (ref) vs. unstable]**
High blood pressure (%)	37.0	75.0	8.9 (4.7, 17.0)
Impaired glycaemic control (%)	5.9	46.3	13.8 (6.1, 31.2)
Low HDL-C (%)	0.7	11.1	15.9 (1.9, 132.5)
High triglycerides (%)	11.9	45.4	5.9 (2.9, 12.0)

Inflammation (%)	17.0	53.7	8.6 (4.1, 18.1)

† High blood pressure (clinic BP ≥130/85 mmHg, or hypertension diagnosis, or use of anti-hypertensive medication), impaired glycaemic control (HbA1c > 6.0% or doctor's diagnosed diabetes), systemic inflammation (C-reactive protein≥ 3mg/l), low HDL cholesterol (<1.03 mmol/l in men and <1.30 mmol/l in women), and high triacylglycerol (≥ 1.7 mmol/l).

‡ Odds ratio (OR) for having each risk factor for stable (ref) vs. unstable healthy obese adults; adjusted for age, sex, and baseline risk factor.

Table 2. Characteristics of unhealthy obese adults at baseline who remained unhealthy or became healthy at follow-up.

Baseline characteristics	**Remained unhealthy at follow-up (n= 299)**	**Became healthy at follow-up (n= 90)**	**p-value**
Age (years, ± SD)	62.3 ± 7.1	63.0± 7.1	0.38
Men (%)	39.5	34.4	0.39
Vigorous physical activity at least once/week (%)	22.7	26.7	0.73
Current smoker (%)	7.2	10.3	0.59
At least one alcoholic drink/week (%)	45.8	60.5	0.03
Body mass index (kg/m^2)	34.3 ± 3.7	33.5 ± 3.7	0.10
Waist circumference (cm)	107.5 ± 16.0	104.9 ± 8.3	0.15
Weight cycling (%)	9.8	7.5	0.54
Metabolic risk factors at follow-up†			**Odds ratio (95% CI)‡ [Healthy (ref) vs. unhealthy]**
High blood pressure (%)	85.3	52.2	6.3 (3.3, 12.2)
Impaired glycaemic control (%)	62.5	7.8	13.5 (5.5, 13.0)
Low HDL-C (%)	24.4	2.2	16.8 (3.9, 72.7)
High triglycerides (%)	56.5	7.8	20.9 (9.2, 47.8)
Inflammation (%)	54.5	17.8	7.5 (4.0, 13.8)

† High blood pressure (clinic BP ≥130/85 mmHg, or hypertension diagnosis, or use of anti-hypertensive medication), impaired glycaemic control (HbA1c > 6.0% or doctor's diagnosed diabetes), systemic inflammation (C-reactive protein≥ 3mg/l), low HDL cholesterol (<1.03 mmol/l in men and <1.30 mmol/l in women), and high triglycerides (≥ 1.7 mmol/l).

‡ Odds ratio (OR) for having each risk factor for remaining unhealthy (ref) vs. becoming healthy obese adults; adjusted for age, sex, and baseline risk factor.