

Letters

The Natural Course of Healthy Obesity Over 20 Years



Intense interest surrounds the “healthy” obese phenotype, which is defined as obesity in the absence of metabolic risk factor clustering (1). Efforts to understand the cardiovascular consequences of healthy obesity are ongoing (2); however, its conceptual validity and clinical value rest on the assumption that it is a stable physiological state, rather than a transient phase of obesity-associated metabolic deterioration. Therefore, a fundamental question is whether healthy obese adults maintain this metabolically healthy profile over the long term or naturally transition into unhealthy obesity over time. Few studies have examined this; in those that have, durations of follow-up have been modest, with none exceeding 10 years (3,4). Accordingly, we aimed to describe the natural course of healthy obesity over 2 decades in a large population-based study.

The Whitehall II cohort study of British government workers provided objectively measured anthropometric and metabolic risk factor data. “Obese” was defined as body mass index ≥ 30 kg/m². “Metabolically healthy” was defined as having < 2 of the following: high-density lipoprotein cholesterol level < 1.03 mmol/l (men) and < 1.29 mmol/l (women); blood pressure $\geq 130/85$ mm Hg or use of antihypertensive medication; fasting plasma glucose level ≥ 5.6 mmol/l or use of antidiabetic medication; triacylglycerol level ≥ 1.7 mmol/l; and homeostatic model assessment of insulin resistance > 2.87 (baseline 90th percentile value) (1).

Participants with data on obesity and metabolic status at baseline and all follow-up examinations were analyzed. Cross-tabulations were used to describe the proportion of participants according to their baseline (1992/1994) obesity and metabolic status in each category after 5-year (1997/1999), 10-year (2002/2004), 15-year (2007/2009), and 20-year (2012/2014) follow-up examinations. Log binomial models were used to estimate age-, sex-, and ethnicity-adjusted prevalence ratios with 95% confidence intervals for unhealthy obesity at each

follow-up, excluding unhealthy obese adults at baseline.

Descriptive analyses were repeated using maximum samples of healthy obese adults on the basis of duration of follow-up, allowing different baseline and follow-up points across the 20-year period. For example, the 15-year healthy obese sample included transitions from 1992/1994, to 2007/2009, or from 1997/1999 to 2012/2014. Analyses were performed using SPSS software version 19.0 (IBM, Armonk, New York), with $p < 0.05$ indicating statistical significance.

Our primary sample ($n = 2,521$; 39 to 62 years of age; 75% male) included 66 healthy obese adults at baseline (36.5% of the obese). Of these subjects, 21 (31.8%) were unhealthy obese after 5 years, and 27 (40.9%), 23 (34.8%), and 34 (51.5%) were unhealthy obese after 10, 15, and 20 years, respectively (Table 1). The proportion of healthy obese adults who were healthy nonobese at follow-up was 6.1%, 4.5%, 6.1%, and 10.6% after 5, 10, 15, and 20 years respectively.

The age-, sex-, and ethnicity-adjusted prevalence of unhealthy obesity after 5 years was 11.80 (95% confidence interval [CI]: 7.28 to 19.11) times higher in baseline healthy obese adults compared with healthy nonobese subjects. The corresponding prevalence ratio was 8.09 (95% CI: 5.54 to 11.81) after 10 years, 6.64 (95% CI: 4.43 to 9.96) after 15 years, and 7.74 (95% CI: 5.53 to 10.85) after 20 years.

Subsidiary analyses using maximum samples produced similar results. Of the 389 healthy obese adults with 5-year data, 35.2% were unhealthy obese after 5 years. This proportion was 34.7% after 10 years (sample $n = 317$), 37.9% after 15 years (sample $n = 224$), and 48.1% after 20 years (sample $n = 106$).

After 20 years, approximately one-half of healthy obese adults were unhealthy obese, and only 10% were healthy nonobese. Healthy obese adults were nearly 8 times more likely to progress to an unhealthy obese state after 20 years than healthy nonobese adults, and these subjects were consistently more likely to make this adverse transition than unhealthy nonobese adults. Progressions from healthy to unhealthy obesity also increased steadily with increasing follow-up duration when using maximum samples of healthy obese adults over the follow-up period.

Some evidence suggests that stability is associated with a more favorable fat distribution in the form

TABLE 1 Changes in Metabolic and Obesity Status Over 20 Years of Follow-Up Among Adults Between 39 and 62 Years of Age at Baseline in the Whitehall II Cohort Study of British Government Workers (N = 2,521)

Status at Baseline	Status at Follow-Up				Prevalence Ratio for Being Unhealthy Obese at Follow-Up* (95% CI)
	Healthy Nonobese	Unhealthy Nonobese	Healthy Obese	Unhealthy Obese	
5-Year Follow-Up					
Healthy nonobese (n = 1,677)	1,350 (80.5)	234 (14)	52 (3.1)	41 (2.4)	1.00
Unhealthy nonobese (n = 663)	249 (37.6)	331 (49.9)	24 (3.6)	59 (8.9)	3.97 (2.67-5.90)
Healthy obese (n = 66)	4 (6.1)	0 (0)	41 (62.1)	21 (31.8)	11.80 (7.28-19.11)
Unhealthy obese (n = 115)	9 (7.8)	9 (7.8)	20 (17.4)	77 (67)	
10-Year Follow-Up					
Healthy nonobese (n = 1,677)	1,199 (71.5)	325 (19.4)	76 (4.5)	77 (4.6)	1.00
Unhealthy nonobese (n = 663)	197 (29.7)	348 (52.5)	14 (2.1)	104 (15.7)	3.70 (2.77-4.93)
Healthy obese (n = 66)	3 (4.5)	1 (1.5)	35 (53)	27 (40.9)	8.09 (5.54-11.81)
Unhealthy obese (n = 115)	10 (8.7)	9 (7.8)	21 (18.3)	75 (65.2)	
15-Year Follow-Up					
Healthy nonobese (n = 1,677)	1,237 (73.8)	276 (16.5)	82 (4.9)	82 (4.9)	1.00
Unhealthy nonobese (n = 663)	232 (35)	311 (46.9)	23 (3.5)	97 (14.6)	3.23 (2.42-4.30)
Healthy obese (n = 66)	4 (6.1)	3 (4.5)	36 (54.5)	23 (34.8)	6.64 (4.43-9.96)
Unhealthy obese (n = 115)	12 (10.4)	4 (3.5)	22 (19.1)	77 (67)	
20-Year Follow-Up					
Healthy nonobese (n = 1,677)	1,128 (67.3)	372 (22.2)	76 (4.5)	101 (6)	1.00
Unhealthy nonobese (n = 663)	203 (30.6)	336 (50.7)	20 (3)	104 (15.7)	2.78 (2.14-3.62)
Healthy obese (n = 66)	7 (10.6)	0 (0)	25 (37.9)	34 (51.5)	7.74 (5.53-10.85)
Unhealthy obese (n = 115)	10 (8.7)	15 (13)	21 (18.3)	69 (60)	

Values are n (%) or prevalence ratio (95% CI). *Models exclude unhealthy obese subjects at baseline (remaining n = 2,406) and are adjusted for age, sex, and ethnicity. CI = confidence interval.

of lower waist circumference (4), and thus it may be possible to increase stability in healthy obesity over time. However, our results, which were obtained with a longer, more detailed follow-up than any previous study, suggest that long-term stability is the exception, not the norm. The natural course of healthy obesity is progression to metabolic deterioration.

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REFERENCES

1. Wildman RP, Muntner P, Reynolds K, 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.
2. Kramer CK, Zinman B, Retnakaran R. Are metabolically healthy overweight and obesity benign conditions? A systematic review and meta-analysis. *Ann Intern Med* 2013;159:758-69.
3. Soriguer F, Gutiérrez-Repiso C, Rubio-Martín E, et al. Metabolically healthy but obese, a matter of time? Findings from the prospective Pizarra study. *J Clin Endocrinol Metab* 2013;98:2318-25.
4. Appleton SL, Seaborn CJ, Visvanathan R, et al. Diabetes and cardiovascular disease outcomes in the metabolically healthy obese phenotype: a cohort study. *Diabetes Care* 2013;36:2388-94.