Letters

Incidence of Metabolic Risk Factors Among Healthy Obese Adults

20-Year Follow-Up

There is growing evidence that obese adults without metabolic risk factor clustering (the so-called "healthy obese") progress to unhealthy obesity over time [1]. However, the pathophysiological changes underlying the long-term transition into an unhealthy obese state have not been well characterized. To inform clinical management of healthy obesity, we aimed to identify the metabolic risk factors responsible for this transition, as well as the timing of their onset.

Repeat clinical data were drawn from the Whitehall II cohort study of British adults. We grouped participants as normal-weight (body mass index [BMI] 18.5 to 24.9 kg/m^2), overweight (BMI 25 to 29 kg/m^2), or obese (BMI $\geq$30 kg/m^2), and as healthy [2] if they were free of any the following characteristics: high-density lipoprotein cholesterol <1.03 mmol/l (men) and <1.29 mmol/l (women); blood pressure $\geq$130/85 mm Hg or antihypertension medication use; fasting plasma glucose $\geq$5.6 mmol/l or diabetic medication use; triglycerides $\geq$1.7 mmol/l; and homeostatic model-assessed insulin resistance >2.83 (baseline 90th percentile value). Participants provided written

FIGURE 1 Incidence of Metabolic Risk Factors Among Initially Healthy Obese Compared With Initially Healthy Normal-Weight Adults Over 20 Years (n = 1,120)
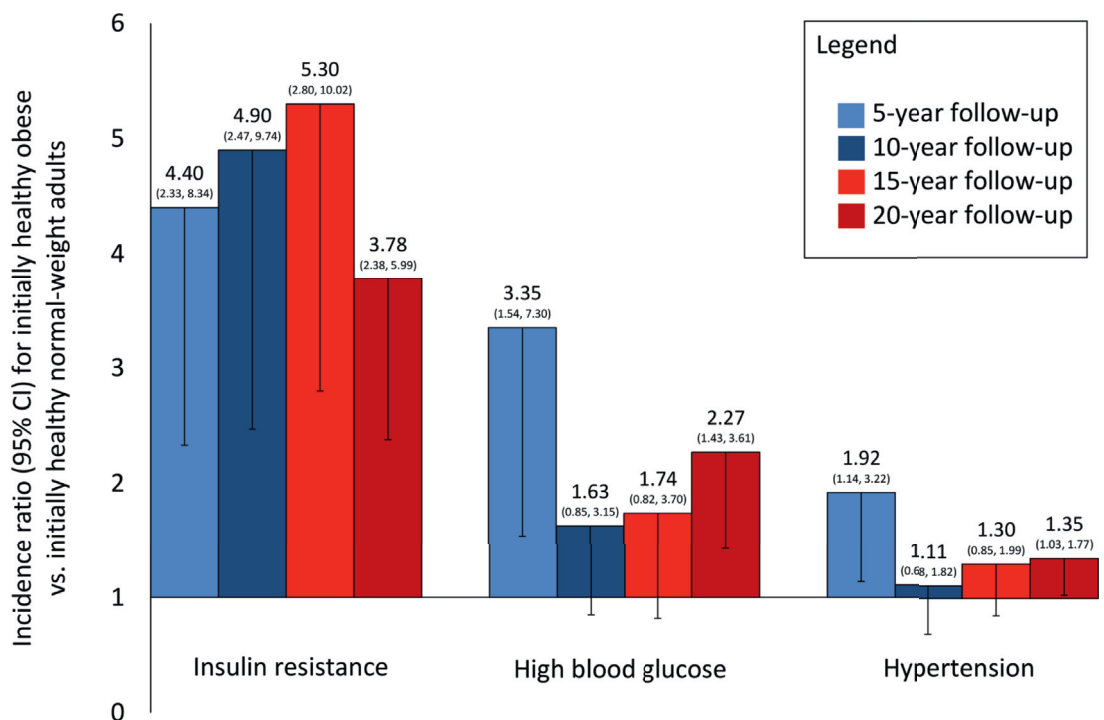
Results are incidence ratios and 95% confidence intervals (CI) for having each metabolic risk factor at follow-up, on the basis of Poisson regression models with robust error variances. Models are adjusted for age, sex, and ethnicity. Little difference in high-density lipoprotein cholesterol or triglycerides was observed between groups. Baseline healthy status is defined as having none of 5 metabolic risk factors (hypertension, low high-density lipoprotein cholesterol, high triglycerides, insulin resistance, and high blood glucose).

informed consent. The University College London research ethics committee provided ethical approval.

Cross-tabulations were used to describe incidence of each of these 5 metabolic risk factors at 5- (1997 to 1999), 10- (2002 to 2004), 15- (2007 to 2009), and 20-year (2012 to 2014) follow-ups for healthy normal-weight, overweight, or obese participants at baseline (1992 to 1994). Poisson regression models with robust error variances were used to estimate age-, sex-, and ethnicity-adjusted incidence ratios and 95% confidence intervals for having each metabolic risk factor at follow-up for healthy obese compared with healthy normal-weight adults at baseline.

Among 2,878 adults with anthropometric and metabolic risk factor data at each time point, 1,120 adults (39 to 61 years of age; 68% male) were free of all metabolic risk factors at baseline. This initially healthy status was progressively rarer among those in higher BMI groups, representing 51.5%, 25.8%, and 13.4% of normal-weight, overweight, and obese adults, respectively. Of the healthy obese participants, 57.1% had at least 1 metabolic risk factor at the 5-year follow-up, with corresponding proportions being 64.3% at 10 years and 78.6% at 20 years. These proportions were smaller (32.8%, 46.7%, and 60.3%) among initially healthy normal-weight participants.

After 5 years (Figure 1), relative to initially healthy normal-weight adults, initially healthy obese adults were 4.40 times more likely to be insulin resistant, 3.35 times more likely to have high blood glucose, and 1.92 times more likely to be hypertensive (all $p < 0.05$). Incident insulin resistance remained higher over all subsequent follow-ups among baseline healthy obese compared with healthy normal-weight adults. Case numbers were small for 20-year incidence of low high-density lipoprotein cholesterol (2 cases) and high triglycerides (3 cases) among healthy obese adults, with little difference in risk compared with healthy normal-weight adults over time. Additional data are available on request.

The risk of developing insulin resistance, high blood glucose, and hypertension was 2 to 5 times higher among initially healthy obese adults compared with their healthy normal-weight counterparts, and these changes were evident after only 5 years of follow-up. There was little difference in progression to dyslipidemia. However, the key factor explaining the long-term decline of healthy obesity was insulin resistance, which was consistently most common among healthy obese adults over time.

Healthy obese adults are known to experience an elevated future risk of type 2 diabetes (3) and cardiovascular disease (4) compared with healthy normal-weight counterparts. That insulin resistance is an established indicator of future impaired glucose metabolism (5) may explain their much higher incidence of type 2 diabetes (relative risk near 4.0) (3) and slightly higher incidence of cardiovascular disease (relative risk near 1.2) (4), given that earlier onset of risk factors leads to a greater cumulated exposure and higher disease risk. Overall, our findings suggest that healthy obesity is strongly linked with future insulin resistance that subsequently induces cardiometabolic pathology.

*Joshua A. Bell, MSc
Mark Hamer, PhD
G. David Batty, DSc
Archana Singh-Manoux, PhD
Séverine Sabia, PhD
Mika Kivimäki, PhD

*Department of Epidemiology & Public Health
University College London
1-19 Torrington Place
London, United Kingdom WC1E 6BT
E-mail: joshua.bell.11@ucl.ac.uk
http://dx.doi.org/10.1016/j.jacc.2015.06.014

REFERENCES

1. Bell JA, Hamer M, Sabia S, et al. The natural course of healthy obesity over 20 years. J Am Coll Cardiol 2015;65:101–2.

2. 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.

3. Bell JA, Kivimaki M, Hamer M. Metabolically healthy obesity and risk of incident type 2 diabetes: a meta-analysis of prospective cohort studies. Obes Rev 2014;15:504–15.

4. 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.

5. Tabák AG, Jokela M, Akbaraly TN, et al. Trajectories of glycaemia, insulin sensitivity, and insulin secretion before diagnosis of type 2 diabetes: an analysis from the Whitehall II study. Lancet 2009;373:2215-21.

The Value of Cardiac Magnetic Resonance Imaging in Evaluation of Pediatric Patients for Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy

In the March 17, 2015 issue of the *Journal*, Etoom et al. (1) reported interesting findings about the role of cardiovascular magnetic resonance (CMR) for diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) in children. The results of Etoom et al. (1) are unique in that there are few other studies on children with ARVD/C. For the revised Task Force Criteria (TFC), only 9 of 108 (8%) probands were diagnosed in subjects between 12 and 18 years of age (mean 38 ± 13 years of age) (2,3). The study subjects of Etoom et al. (1) averaged 13.8 ± 3.2 years of age, without a given age range. As such, the extrapolation of the revised TFC to children studied by Etoom et al. must be considered experimental.

A particularly vexing problem is trying to "validate" CMR for ARVD/C while also using CMR to diagnose ARVD/C. For Etoom et al. (1), there was no independent anatomic comparator for CMR, because echocardiography had little or no contribution to the diagnosis (only 2 patients met major echocardiographic criteria). The children described by Etoom et al. (1) had large right ventricles (mean right ventricular [RV] end-diastolic volume 118 mL/m^2), suggesting severe disease. Although CMR is well suited to identify RV abnormalities in that setting, it is surprising that echocardiography was unable to capture these findings.

There are a number of other challenges that the authors faced in applying the revised TFC. Their paper reports that minor diagnostic criteria were equally represented in all groups and therefore not included in the statistical model. However, T-wave inversions in the precordial leads cannot be counted in children ≤14 years of age, because this is a nonspecific finding at this age (3). The authors should specify an age cutoff in their analyses. Genetic testing was only performed in 49 of 142 study subjects. Less specific 1994 TFC were used for endomyocardial biopsy. Finally, the authors combined patients who met the TFC (≥4 diagnostic points) with patients who had only 3 diagnostic points. We do not think that patients with 3 points should be classified as definite ARVD/C, especially in family members who receive a major criterion (2 points) merely by their family history (3).

In our own transatlantic series of >1,000 patients with ARVD/C, only 4 of 416 probands were present in patients <13 years of age (4). In our experience, children with ARVD/C typically have electrocardiographic and Holter abnormalities before CMR changes. Structural abnormalities in children with ARVD/C are often mild, and involve focal subtricuspid dyskinesia with preserved global function rather than severe RV enlargement. As such, we do not routinely advise CMR in children <10 years of age. In addition, a high percentage of false positive interpretation of CMRs from referring centers in the North American study suggests that misinterpretation of CMRs is common (2).

Nevertheless, Etoom et al. (1) have raised an important question of applicability of revised TFC in children. Their patient population is worthy of more in-depth study due to the early age at which they have expressed disease, perhaps representing an aggressive form of disease that is otherwise not commonly seen.

Anneline S.J.M. te Riele, MD
Frank I. Marcus, MD
Cynthia A. James, PhD
Brittney A. Murray, MS
Crystal Tichnell, MD
Stefan L. Zimmerman, MD
Ihab R. Kamel, MD, PhD
Jane Crosson, MD
Maarten J.M. Cramer, MD, PhD
Birgitta K. Velthuis, MD, PhD
Richard N.W. Hauer, MD, PhD
Harikrishna Tandri, MD
David A. Bluemke, MD, PhD
*Hugh Calkins, MD
*Sheikh Zayed Tower - Room 7125R
The Johns Hopkins Hospital
1800 Orleans Street
Baltimore, Maryland 21287
E-mail: hcalkins@jhmi.edu
http://dx.doi.org/10.1016/j.jacc.2015.04.082

REFERENCES

1. Etoom Y, Govindapillai S, Hamilton R, et al. Importance of CMR within the task force criteria for the diagnosis of ARVC in children and adolescents. J Am Coll Cardiol 2015;65:987-95.

2. Marcus FI, Zareba W, Calkins H, et al. Arrhythmogenic right ventricular cardiomyopathy/dysplasia clinical presentation and diagnostic evaluation: