News & Views

Metabolically healthy obesity and NAFLD

Giovanni Targher and Christopher D. Byrne

Giovanni Targher is at the Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, University of Verona, and at Azienda Ospedaliera Universitaria Integrata, Piazzale A. Stefani 1, Verona 37126, Italy.

Christopher D. Byrne is at Nutrition and Metabolism, Faculty of Medicine, University of Southampton, Southampton, UK; and Southampton National Institute for Health Research Biomedical Research Centre, University Hospital Southampton, Tremona Road, Southampton, SO166YD, UK.

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Correspondence to G.T.
giovanni.targher@univr.it

Standfirst (51 words)
Obesity is a risk factor for several noncommunicable diseases, but some individuals with obesity remain metabolically healthy throughout life; whether these individuals are at risk of developing NAFLD is uncertain. In a new study, Chang *et al.* showed a statistically significant, graded relationship between BMI and NAFLD in metabolically healthy individuals.

Obesity is known to be an important risk factor for a whole range of noncommunicable diseases that include type 2 diabetes mellitus (T2DM), chronic obstructive sleep apnoea, various types of cancers (*e.g.*, colorectal cancer, oesophagus and breast cancer after the menopause) and NAFLD. Although the fact that obesity increases risk of certain diseases is well accepted by clinicians, evidence has shown that some individuals who are obese are also metabolically healthy: so-called metabolically healthy obesity (MHO).

In a recent retrospective cohort study involving metabolically healthy individuals, Chang *et al.* found that BMI categories are positively associated with an increased incidence of NAFLD, suggesting that the obese phenotype, regardless of metabolic abnormalities, might increase the risk of developing NAFLD[1].

Increasing evidence suggests that BMI, the most common proxy measure used to help categorize overweight or obesity, is an imprecise measure of body-fat-related risk of noncommunicable diseases. Rather, other features associated with overweight or obesity, such as visceral fat mass, adipose tissue inflammation, adipose tissue function, or factors such as insulin resistance and metabolic syndrome components, might be the key pathogenetic aspects that mediate increased risk of noncommunicable diseases in individuals with overweight or obesity (TABLE 1). Nevertheless, the concept of MHO has gained much interest in the scientific community.

MHO is a complex, emerging phenotype with risks intermediate between metabolically healthy individuals with normal-weight and individuals who are metabolically abnormal with obesity (MAO). Compared with metabolically healthy individuals with normal-weight, persons with obesity are at increased risk of all-cause and cause-specific mortality and cardiovascular disease events even in the absence of metabolic abnormalities, suggesting that there is no healthy pattern of increased weight[2-4]. However, compared with their peers who are MAO, individuals with MHO have lower risk of all-cause and cause-specific mortality[2-4]. Furthermore, studies suggest that individuals with MHO have similar insulin sensitivity to lean individuals, as well as lower liver fat content and lower intimal-medial thickness of the carotid artery compared with individuals who are MAO[5,6]. Agreement on a universally accepted definition of MHO, however, would improve the design of future studies and would facilitate comparisons between studies.

Obesity is a much stronger risk factor for T2DM than for cardiovascular disease, suggesting that there could be differential effects of fat mass, fat function or other obesity-related cardiometabolic risk factors in these two different noncommunicable diseases. Researchers have increasingly been investigating relationships between obesity and NAFLD, and the consequent negative effects of NAFLD on risk of T2DM and cardiovascular disease. Although NAFLD has been known for many years to increase the risk of developing chronic liver

disease and hepatocellular carcinoma, it is now evident that NAFLD is also an important risk factor for extrahepatic diseases, such as cardiovascular disease and T2DM[7].

Previously, one study examined the cross-sectional association between obesity and NAFLD using data from a large Korean occupational cohort, and showed that the prevalence of ultrasonography-diagnosed NAFLD amongst 945 individuals with MHO was 45%[8]. Using data from the same occupational cohort, Chang *et al*. have now developed the work further and have undertaken a retrospective cohort study to examine relationships between BMI categories and incident NAFLD, having excluded patients who were metabolically abnormal at baseline (defined as having no metabolic syndrome components and a homeostasis model assessment of insulin resistance of less than 2.5)[1]. The researchers studied 77,425 men and women who were free of NAFLD, with the presence of NAFLD again determined using ultrasonography. During the 4.5 years of follow-up, 10,340 participants developed NAFLD. In a multivariable adjusted regression model, the hazard ratios for incident NAFLD, comparing participants who were overweight and obese with participants with normal-weight were 2.15 (95% CI 2.06–2.26) and 3.55 (95% CI 3.37–3.74), respectively. Importantly, increasing baseline BMI showed a strong and approximately linear positive relationship with the incidence of NAFLD, suggesting that any amount of excess body fat increased the risk of developing NAFLD[1].

Patients with NAFLD are known to have an increased risk of both liver-related and cardiovascular disease mortality[7], but it is unclear how BMI in this patient group influences risk of NAFLD-related mortality. Controversy persists among researchers as to the optimum BMI for lowest mortality in the general population. Optimal BMI levels will probably vary by age, ethnicity and the proportion of people with comorbidity (such as NAFLD) in different populations. A detailed meta-analysis of 230 prospective studies with 3.74 million deaths among >30 million participants has also provided further evidence that adiposity (measured by BMI) increases the risk of premature mortality[9], in which the lowest mortality was observed at a BMI of approximately 25 kg/m^2. The relative effect of different BMIs on health in people with different comorbidities such as NAFLD, however, needs clarification. This information would be extremely helpful both for health-care professionals and for the patients with these comorbidities. Owing to the occurrence of secular trends in BMI over time that also influence the relationship between BMI and mortality outcomes, contemporaneous data (rather than historical evidence) is needed to better understand relationships between BMI and noncommunicable diseases such as NAFLD. Recently, one interesting study in a Danish cohort clearly demonstrated that the BMI associated with lowest all-cause mortality had increased by 3.3 kg/m^2 between 1976 and 2013[10]. Given that BMI measurement is a crude proxy for the adiposity levels in an individual and has different implications in the presence or absence of other metabolic risk factors, one option for redefining healthy BMI categories for adults would be to use standardized BMI-for-age z-scores based on contemporary population distributions for men and women (separately) of different ethnicity and age groups, similar to the z-score approach used to identify obesity among children. Furthermore, as weight gain often occurs in individuals at different times during life, there are major challenges to find effective ways to prevent weight gain, support weight loss and prevent weight regain in order to influence risk of developing NAFLD.

In conclusion, Chang *et al*. showed that increasing BMI is independently associated with an increased incidence of NAFLD in a cohort of strictly defined metabolically healthy men and women[1]. The study adds to the increasing body of evidence that overweight and obesity are much stronger risk factors for NAFLD than for other noncommunicable diseases, such as cardiovascular disease.

Future large prospective studies are needed to examine the transition between MHO and MAO phenotypes and whether genetics and lifestyle factors play a part in both development and reversal of such phenotypes. Furthermore, additional research is also needed to better elucidate how the transition between MHO and MAO phenotypes might affect the severity of NAFLD histology. Finally, future inquiries should also target genetic studies to investigate why certain individuals with obesity do not seem to develop the metabolic abnormalities associated with obesity.

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Competing interests statement
The authors declare no competing financial interests.
Author Contributions
Both authors have contributed equally to write this article.

1. Chang, Y. *et al*. Metabolically healthy obesity and the development of nonalcoholic fatty liver disease. *Am. J. Gastroenterol*. http://dx.doi.org/10.1038/ajg.2016.178 (2016).
2. Bergman, R.N. *et al*. Abdominal obesity: role in the pathophysiology of metabolic disease and cardiovascular risk. *Am. J. Med*. **120**, S3-S8 (2007).
3. Kramer, C.K., Zinman, B. & Retnakaran, R. Are metabolically healthy overweight and obesity benign conditions?: a systematic review and meta-analysis. *Ann. Intern. Med*. **159**, 758-769 (2013).
4. Roberson, L.L. *et al*. Beyond BMI: the "metabolically healthy obese" phenotype & its association with clinical/ subclinical cardiovascular disease and all-cause mortality – a systematic review. *BMC. Public Health* **14**, 14 (2014).
5. Ortega, F.B. *et al*. The intriguing metabolically healthy but obese phenotype: cardiovascular prognosis and role of fitness. *Eur. Heart. J*. **34**, 389-397 (2013).
6. Stefan, N. *et al*. Identification and characterization of metabolically benign obesity in humans. *Arch. Intern. Med*. **168**, 1609-1616 (2008).
7. Byrne, C.D. & Targher, G. NAFLD: a multisystem disease. *J. Hepatol*. **62**, S47-S64 (2015).
8. Sung, K.C., Cha, S.C., Sung, J.W., So, M.S. & Byrne, C.D. Metabolically healthy obese subjects are at risk of fatty liver but not pre-clinical atherosclerosis. *Nutr. Metab. Cardiovasc. Dis.* **24**, 256-262 (2014).
9. Aune, D. *et al*. Body mass index and all-cause mortality: a systematic review and nonlinear dose-response meta-analysis of 230 prospective studies with 3.74 million deaths among 30.3 million participants. *BMJ* **353**, i2156 (2016).

10. Afzal, S., Tybjærg-Hansen, A., Jensen, G.B. & Nordestgaard, B.G. Change in body mass index associated with lowest mortality in Denmark, 1976-2013. *JAMA* **315**, 1989-1996 (2016).

Table 1| Main differences of typical metabolically healthy and metabolically abnormal obese patients in comparison with lean metabolically healthy individuals.

Factor	**Metabolic status**	
	Metabolically healthy obese	**Metabolically abnormal obese**
Fat distribution	Subcutaneous fat > visceral fat	Visceral fat > subcutaneous fat
Muscle mass	Slightly increased muscle mass	Decreased muscle loss (sarcopenia)
Insulin sensitivity	Normal	Insulin resistant
Glycaemia	Normal	Dysglycaemia
Lipid metabolism	Normal	Atherogenic dyslipidaemia
Blood pressure	Normal	Hypertension
Cardiovascular risk	Low to mild	Moderate to high
Liver disease risk	Nonalcoholic fatty liver (NAFL)	NASH

Author biographies

Giovanni Targher, M.D. is an Associate Professor and Senior Consultant at the Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, University of Verona, and at Azienda Ospedaliera Universitaria Integrata, Verona, Italy. His main research interests are NAFLD and its relationships with cardiovascular diseases and other extra-hepatic complications.

Chris Byrne is Chair of Endocrinology & Metabolism at the University of Southampton, UK. He specializes in the management of patients with diabetes and liver disease and was Expert Diabetologist Advisor to the UK National Institute for Care Excellence (NICE) NAFLD Guideline Development Group. He has published extensively on metabolic syndrome and NAFLD.