International Journal of Obesity (2015) **39,** 82–84

www.nature.com/ijo

DEBATE

'Obesity paradox' misunderstands the biology of optimal weight throughout the life cycle

JB Dixon[1], GJ Egger[2], EA Finkelstein[3], JG Kral[4] and GW Lambert[1]

The 'obesity paradox' refers to observations that run counter to the thesis that normal weight (BMI 18.5–24.9 kg/m^2) provides the lowest mortality and higher weight is associated with greater mortality. We argue that the weight of lowest mortality is influenced by aging and chronic disease, with mortality advantage extending into the overweight and even class I obese ranges under some circumstances. A focus on quality nutrition, physical activity, fitness, and maintaining function in these weight ranges may be preferable to a focus on intentional weight loss, which has uncertain effects. The 'obesity paradox' is no 'paradox' if one defines and interprets 'ideal' weight appropriately.

International Journal of Obesity (2015) **39,** 82–84; doi:10.1038/ijo.2014.59

Keywords: healthy aging; reverse causation; obesity epidemic; survival advantage; body mass index

The 'obesity paradox' assumes that being overweight or even obese, measured by body mass index (BMI) cutoffs, provides mortality advantage compared to being 'normal' weight (BMI 18.5–24.9 kg/m^2). Perhaps the most convincing data come from population studies indicating that whereas obesity (BMI>30) is associated with higher all-cause mortality, overweight (BMI 25–29.9 kg/m^2) exhibits the lowest mortality risk. Both normal weight and class I obesity (BMI 30–34.9 kg/m^2) entail increased risk compared with overweight.[1] Yet, there is a clear linear rise in the prevalences of type 2 diabetes, hypertension and dyslipidemia throughout the normal, overweight and class I obese ranges.[2,3]

The response to the mortality findings is understandably met with a knee jerk 'it cannot be right', followed by suspicion and a range of more or less sophisticated reasons to dismiss the observations. Emphasis on the obesity epidemic, understandably focusing on the huge costs in terms of suffering and threats to the economy, subjugates any public health message proposing benefits of increased weight.

Yet, there are many cases where this is indeed the case. Hip fracture risk in post menopausal women reduces with increasing BMI.[4] And when it comes to mortality, there are consistent reports that overweight and class I obese individuals have a lower mortality than those of normal weight for a range of diseases and conditions. There is clear evidence for a fit-fat 'metabolically healthy' obese phenotype,[5] but conditions with lower risk include cardiac failure, type 2 diabetes,[6] peripheral vascular disease, acute coronary syndromes, hypertension with established coronary artery disease,[7] chronic kidney disease on maintenance haemodialysis, chronic obstructive pulmonary disease, and following coronary artery bypass graft surgery and valve surgery.[8] This list is dominated by common chronic conditions, which, ironically, are often targeted for intentional weight loss as a therapeutic strategy in overweight and obese individuals.

The premise tested by evolution is that energy reserves are needed in times of illness, increasing with age, sarcopenia and frailty. As median life expectancy increases, so do aging-related diseases, the foundations of which may have been laid down very early in life ('developmental origins of adult disease').

How do we reconcile these apparently paradoxical observations? We propose that there is no paradox. Rather, our current narrow, rigid view of 'normal' or 'optimal' weight is simplistic and biologically inappropriate. The concept that all adults have a weight or weight range that is associated with optimal health is reasonable, but the notion that this range is the same for all individuals, or over the lifecycle regardless of antecedents or context, is not.

The association between BMI and mortality is usually U-shaped with increasing risk at both low and high ends of the continuum, but the nadir, or optimal BMI for lowest mortality is not a constant and appears to vary with age, ethnicity and the presence of established disease. Human aging provides perhaps the most natural example of a shifting association between BMI and lowest mortality risk, as shown in Figure 1, with those over 70 years of age appearing to have an optimal BMI for mortality in the overweight and class I obese range, and any risks usually associated with even higher levels of obesity are attenuated or absent.[9–11] In addition, BMI above the normal range in older individuals may also be associated with better functional capacity, and reduced physical and cognitive decline.[9] The relationship between disease risk, mortality and BMI also varies considerably with ethnicity and race as seen when comparing disease risk in White, Asian and various indigenous populations.[12]

Dismissing sound observations carries great risk yet, as for many aspects of the global obesity epidemic, it seems that most lay people as well as professionals have firm opinions regarding causes, risks, management, and optimal targets for intentional weight loss. There is clearly a propensity to dismiss observations contrary to one's attitudes and beliefs. Fortunately, although after some delay, putative explanations for the apparent paradox of obesity have emerged. Understandable concerns regarding

[1]Baker IDI Heart & Diabetes Institute, Melbourne, Victoria, Australia; [2]School of Health & Human Sciences, Southern Cross University, Lismore, Balgowlah NSW, Australia; [3]Duke-NUS Graduate Medical School, Singapore, Singapore and [4]Department of Surgery, SUNY Downstate Medical Center, 450 Clarkson Avenue, Brooklyn, NY, USA. Correspondence: Professor JB Dixon, Clinical Obesity Research, Baker IDI Heart & Diabetes Institute, PO Box 6492 St Kilda Road Central, Melbourne, VIC 8008, Australia.
E-mail: john.dixon@bakeridi.edu.au
Received 18 December 2013; accepted 26 January 2014; accepted article preview online 15 April 2014; advance online publication, 20 May 2014

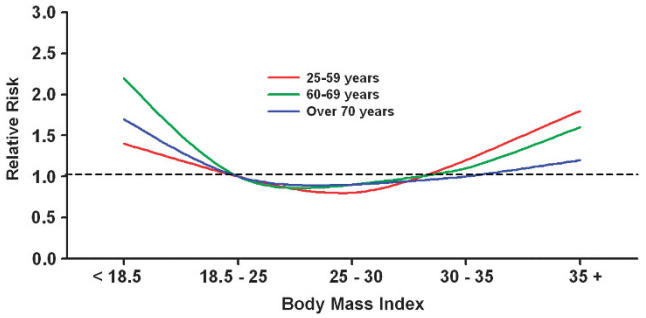

Figure 1. Relative risk of all-cause mortality across BMI categories, stratified by age group, based on NHANES I, II and III data. Adapted from Flegal *et al. JAMA.* 2005;293(15):1861–1867.

intentional versus unintentional weight loss (reverse causation),[10] and a selective survival bias effect were logical frontrunners. However, findings contrary to expectation are not necessarily caused by bias, and attempts to adjust for illness-related weight loss have found little evidence of such bias.[10] The durability and consistency of the data has generated a broader approach to understanding possible additional mechanisms that may be involved. Chronic diseases and aging are associated with reductions in lean body mass and especially muscle mass, lower bone mineral density, compromised nutrition, and impaired physical function—issues that may be greater in those of lower weight and attenuated in people with greater weight. Increased weight (including fatness) may provide advantages in aging and disease states through a number of possible mechanisms including: sparing lean body mass; reducing the impact of oxidative stress and inflammation; providing a favorable functional lipid/lipoprotein profile; stabilising hemodynamic function; sequestering fat-soluble environmental pollutants; reducing regional sympathetic activity; ischaemic pre-conditioning; an altered telomere length-weight association with aging; and favorable alterations of circulating peptides and adipokines with putative cardiovascular benefits.[13–17]

There are now many associations that may link increased fatness to possible benefit in certain populations, however the mechanisms remain highly speculative. Lower weight may therefore have a causal effect on mortality rather than being associated with bias. The importance of understanding the risks and benefits of increased weight and fatness in aging and its related diseases is critical for providing the most basic lifestyle advice and support to our growing aging communities. Consistent cross- species data indicate dietary restriction without malnutrition, and macronutrient protein to non-protein balance provides long-term survival benefits.[18,19] However, from an evolutionary perspective increased fatness with illness and aging may have had survival value when competition for scarce resources favored the young and the fit. There is little doubt that the shift towards individualized weight management advice and targets, based on a broad range of factors including ethnicity, age and health status, will replace the myopic view of a single ideal weight range for all.

The benefits of intentional weight loss on mortality are unclear. Outcomes after bariatric surgery, performed in individuals with a BMI >35 kg/m^2, and more usually >40 kg/m^2, provide the only sound evidence that intentional weight loss reduces mortality, while improving health-related quality of life and obesity-related comorbidity.[20,21] However, one bariatric surgical study failed to demonstrate a mortality advantage and, of potential importance, this was in an older, high risk, and male-dominated US Veteran Affairs population.[22] The effect of any intentional weight loss on mortality in the overweight and class I obese BMI ranges is unknown. Intentional weight loss is broadly recommended for overweight and obese individuals, especially those with increased cardiovascular risk and type 2 diabetes, and the beneficial effects on hypertension, dyslipidemia, glucose homeostasis, sleep and functional outcomes have been documented, but the influence on hard cardiovascular outcomes and mortality has not. Furthermore, the importance of choice of method for achieving intentional weight loss has not been adequately addressed. The large prospective 'Look Ahead' study, which examined the effect of an intensive weight loss-focused lifestyle program in overweight and obese individuals with type 2 diabetes, was prematurely terminated on the basis of a futility analysis that found the intensive program did not reduce the risk of cardiovascular events.[23] The Look Ahead findings may suggest a mismatch between improved cardiovascular risk. Several longitudinal studies have also found weight loss, rather than weight stability or even weight gain, is associated with increased mortality in overweight and obese individuals with type 2 diabetes and/or suspected cardiovascular disease.[24,25]

While the data regarding the risks of diabetes and cardiovascular morbidity with increasing BMI are overwhelming, there has been limited attention paid to the possibility of an altered BMI nadir or optimal weight for all-cause and cardiovascular mortality in those with established disease. The concept of variance in optimal weight range is not implausible and has significant clinical implications, and so warrants careful evaluation.

Future research will need a convergent epidemiological, clinical, and preclinical approach to examine the array of important questions generated by a variable optimal weight range, and uncertainty regarding when and how to utilize intentional weight loss. More focused epidemiological population and cohort studies looking at weight, weight trajectory and health, using the appropriate methods to assess bias and causality, are needed.[10,26,27] Additional carefully designed longitudinal clinical studies that assess the influence of body composition, nutritional status, and a range of established and novel risk factors on morbidity and mortality with aging and in specific disease states are also required. Randomized trials of comparable modalities will be needed to examine effects of intentional weight loss in aging and related diseases focusing on functional and hard clinical outcomes and side-effects such as dietary restraint stress, rather than making inferences from risk factor changes. The identification of a range of novel putative factors that may generate risk-benefit differences in lean compared with overweight-obese individuals will require detailed human physiological studies verified in animals to examine effects on aging and in specific diseases.

There is no 'obesity paradox' to explain, if we accept the premise that varying ideal weight ranges apply to individuals over different stages of the life span, accordingly allowing us to abandon the rigid biologically implausible concept of a single 'ideal weight' (for height) or weight range. Perhaps lifestyle advice should focus less on biologically difficult to achieve intentional weight loss for those in the overweight and class I obese range, and instead focus more on quality nutrition, physical activity, fitness and maintaining function in chronic disease states and with aging.

CONFLICT OF INTEREST

JD has received research funding and support from Allergan Inc. He is on the Optifast® Medical Advisory Board for Nestlé Australia and has received consultancy fees from Allergan Inc, Metagenics, and iNova Pharmaceuticals. EF has acted as a consultant for Allergan Inc. in the past and currently does consulting work for Jenny Craig and Vivus Inc. G.L.'s laboratory currently receives commercial research grant funding from Medtronic (formerly ARDIAN Inc.), Servier Australia, Abbott (formerly Solvay) and Allergan Inc.; he has acted as a consultant for Medtronic and has received honoraria or travel support for presentations from Pfizer, Wyeth Pharmaceuticals, Servier and Medtronic. GE and JK have no conflict of interest to declare.

REFERENCES

1 Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA* 2013; **309**: 71–82.
2 Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes Care* 1994; **17**: 961–969.
3 Brown CD, Higgins M, Donato KA, Rohde FC, Garrison R, Obarzanek E *et al.* Body mass index and the prevalence of hypertension and dyslipidemia. *Obes Res* 2000; **8**: 605–619.
4 Armstrong ME, Spencer EA, Cairns BJ, Banks E, Pirie K, Green J *et al.* Body mass index and physical activity in relation to the incidence of hip fracture in postmenopausal women. *J Bone Miner Res* 2011; **26**: 1330–1338.
5 Bouchard DR, Langlois MF, Brochu M, Dionne IJ, Baillargeon JP. Metabolically healthy obese women and functional capacity. *Metab Syndr Relat Disord* 2011; **9**: 225–229.
6 Carnethon MR, De Chavez PJ, Biggs ML, Lewis CE, Pankow JS, Bertoni AG *et al.* Association of weight status with mortality in adults with incident diabetes. *JAMA* 2012; **308**: 581–590.
7 Uretsky S, Messerli FH, Bangalore S, Champion A, Cooper-Dehoff RM, Zhou Q *et al.* Obesity paradox in patients with hypertension and coronary artery disease. *Am J Med* 2007; **120**: 863–870.
8 Morse SA, Gulati R, Reisin E. The obesity paradox and cardiovascular disease. *Curr Hypertens Rep* 2010; **12**: 120–126.
9 Oreopoulos A, Kalantar-Zadeh K, Sharma AM, Fonarow GC. The obesity paradox in the elderly: potential mechanisms and clinical implications. *Clin Geriatr Med* 2009; **25**: 643–659 viii.
10 Flegal KM, Graubard BI, Williamson DF, Cooper RS. Reverse causation and illness-related weight loss in observational studies of body weight and mortality. *Am J Epidemiol* 2011; **173**: 1–9.
11 Andres R, Elahi D, Tobin JD, Muller DC, Brant L. Impact of age on weight goals. *Ann Intern Med* 1985; **103**(Pt 2): 1030–1033.
12 WHO. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004; **363**: 157–163.
13 O'Carroll AM, Lolait SJ, Harris LE, Pope GR. The apelin receptor APJ: journey from an orphan to a multifaceted regulator of homeostasis. *J Endocrinol* 2013; **219**: R13–R35.
14 Kalantar-Zadeh K, Kopple JD. Obesity paradox in patients on maintenance dialysis. *Contrib Nephrol* 2006; **151**: 57–69.
15 Hong NS, Kim KS, Lee IK, Lind PM, Lind L, Jacobs DR *et al.* The association between obesity and mortality in the elderly differs by serum concentrations of persistent organic pollutants: a possible explanation for the obesity paradox. *Int J Obes (Lond)* 2012; **36**: 1170–1175.
16 Ozeke O, Ozer C, Gungor M, Celenk MK, Dincer H, Ilicin G. Chronic intermittent hypoxia caused by obstructive sleep apnea may play an important role in explaining the morbidity-mortality paradox of obesity. *Med Hypotheses* 2011; **76**: 61–63.
17 Lee M, Martin H, Firpo MA, Demerath EW. Inverse association between adiposity and telomere length: The Fels Longitudinal Study. *Am J Hum Biol* 2011; **23**: 100–106.
18 Simpson SJ, Raubenheimer D. Macronutrient balance and lifespan. *Aging (Albany NY)* 2009; **1**: 875–880.
19 Masoro EJ. Overview of caloric restriction and ageing. *Mech Ageing Dev* 2005; **126**: 913–922.
20 Sjostrom L, Narbro K, Sjostrom CD, Karason K, Larsson B, Wedel H *et al.* Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med* 2007; **357**: 741–752.
21 Adams TD, Gress RE, Smith SC, Halverson RC, Simper SC, Rosamond WD *et al.* Long-term mortality after gastric bypass surgery. *N Engl J Med* 2007; **357**: 753–761.
22 Maciejewski ML, Livingston EH, Smith VA, Kavee AL, Kahwati LC, Henderson WG *et al.* Survival among high-risk patients after bariatric surgery. *JAMA* 2011; **305**: 2419–2426.
23 Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M *et al.* Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013; **369**: 145–154.
24 Myers J, Lata K, Chowdhury S, McAuley P, Jain N, Froelicher V. The obesity paradox and weight loss. *Am J Med* 2011; **124**: 924–930.
25 Doehner W, Erdmann E, Cairns R, Clark AL, Dormandy JA, Ferrannini E *et al.* Inverse relation of body weight and weight change with mortality and morbidity in patients with type 2 diabetes and cardiovascular co-morbidity: an analysis of the PROactive study population. *Int J Cardiol* 2012; **162**: 20–26.
26 Stevens J, Juhaeri, Cai J. Changes in body mass index prior to baseline among participants who are ill or who die during the early years of follow-up. *Am J Epidemiol* 2001; **153**: 946–953.
27 Zheng H, Tumin D, Qian Z. Obesity and mortality risk: new findings from body mass index trajectories. *Am J Epidemiol* 2013; **178**: 1591–1599.