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The Obesity Paradox – Some Methodological Considerations and Potential Physiological Mechanisms

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The World Health Organization (WHO) estimates that over the past two decades, the incidence of obesity has tripled in developing countries, and it is predicted that there will be 2.3 billion overweight and 700 million obese individuals worldwide by 2015 [1]. This metabolic disorder is amongst the most significant public health problems faced by health services across the globe. Overweight is defined as a (BMI) of 25 to 29.9 kg/m^2 and obesity as a BMI >30 kg/m^2. Overweight and obesity are both associated with increased morbidity and mortality, with even greater risk noted in extremely obese individuals with BMI>35 kg/m^2 [2].

Media outlets worldwide, reported a recently published systematic review and meta-analysis by Flegal et al. from the U.S. Centre for Disease Control [3], which reports Hazard Ratios (HR's) of all-cause mortality for overweight and obesity relative to normal weight in the general population. 97 studies were included in the analysis which provided a sample size of more than 2.88 million individuals and more than 270,000 deaths. The findings from this analysis were that, relative to normal weight (defined as BMI of 18.5-<25), grades 2 and 3 obesity were associated with significantly higher all-cause mortality. Grade 1 obesity overall was not associated with higher mortality and overweight was associated with significantly lower all-cause mortality (HR, 0.94 (CI, 0.91-0.96)). The findings remained consistent following adjustment for smoking status, pre-existing disease, or weight and height reporting method. The study did not report or investigate physiological mechanisms for their findings.

The part of this study that stirred media interest was the research findings which suggest that being overweight confers the benefit of increased life expectancy. This is not a unique discovery. Previous corroborative studies identify a phenomenon termed "the obesity paradox"; wherein, overweight and obese subjects with established coronary artery disease, heart failure and hypertension and chronic obstructive pulmonary disease demonstrate an improved mortality risk [4-9]. These studies suggest that even though overweight and obesity increase the risk of disease development, once the disease develops, overweight and obese have better short and long term clinical outcomes when compared with leaner counterparts [10]. Although some authors have proposed potentially contributing factors, the underlying physiological mechanisms explaining the "obesity paradox" remain to be determined.

It has been well identified that development and distribution of body fat is closely regulated by gonadal function [11]. Women have higher body fat and tend to store body fat in the gluteofemoral region, whilst men tend have greater visceral body fat deposition. Following menopause, women develop a redistribution of body fat similar with the male profile with subsequent abolishment of protective oestrogenic effects [12]. This sex difference in body fat distribution has been identified as the main determinant of differing metabolic profiles and cardiovascular disease risk between men and women [11,12]. Indeed, the risk of developing obesity related diseases is significantly lower in premenopausal women compared to men, a difference which is negated following menopause [12]. A number of large scale studies have shown that between 30-50% of ageing obese men with type 2 diabetes have below the minimum normal testosterone threshold for men, [13-15] even when adjusted for age [16]. Systematic review of the topic has shown that High testosterone levels are associated with higher risk of type 2 diabetes in women but with lower risk in men [16]. The same review reported that men with higher testosterone levels had 42% lower risk of developing type 2 diabetes [16].

Further to existing sex hormone differences, It is postulated that being underweight is associated with an increased catabolic state with elevated levels of cytokines and imbalance in cortisol/dehydroepiandrosterone ratio [10,17] which may heighten hazard ratios relative to overweight and obese. In addition, adipose tissue is innervated with tumour necrosis factor-α receptors, which may help clear the circulating interleukin-1 and other cytokines conferring protective effects against mortality in heart failure and patients with cancer and other chronic illnesses [18,19]. Decreased natriuretic peptide levels have also been shown in obese patients with existing heart failure [19,20]. Visceral fat expansion can increase the clearance of active natriuretic peptides by means of an increased expression of clearance receptors on adipocytes, and in this way, it may contribute to the activity of the cardiac endocrine system [21], perhaps explaining, in part, why the 'obesity paradox' is more comprehensively described in heart failure studies.

Even though BMI is the most commonly used index for measuring obesity, in epidemiological and clinical studies, it does not always accurately reflect the true at-risk body fatness. In the recent past, many studies using other anthropometric measures, such as Waist Circumference (WC), Waist-To-Hip Ratio (WHR), percent body fat (%BF), and weight-to-height ratio, which take body-fat distribution into consideration, especially abdominal adiposity, have shown to perform better in predicting CV risk than BMI [4,17]. In fact, studies which do not corroborate the 'obesity paradox' phenomenon [22-24] usually employ other methods of body composition assessment. The fact remains that BMI measurement does not account for differences in sex, age, race or cardio-respiratory fitness levels between individuals. A recent study by McCauley et al. in men with documented or suspected coronary heart disease, cardiorespiratory fitness was found to greatly modify the relation of adiposity to mortality [25]. Also bearing in mind that BMI can a rather poor measure body composition in athletic and muscular individuals [26] simply using BMI to assess mortality risk in patients with or without existing CHD may be misleading unless fitness is considered.

To conclude, the so called "obesity paradox" characterisation has been around for the past decade in clinical medicine and

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epidemiological studies though explanation of this phenomenon has been largely ignored. When interpreting epidemiological identification of this occurrence, it must be considered that there are also a number of studies that do not support the finding. Furthermore, statistical error may be inherent when one considers the method of classifying obesity. BMI measurement may contribute in inaccuracies in epidemiological studies where waist-hip ratio and radiographic techniques provide a better alternative, particularly when cardiorespiratory fitness may be a compounding factor. If the "obesity paradox" does exist then the most likely physiological explanation centres around the metabolic interaction between sex hormones, adipocytes and cellular metabolism, the identification of which are masked behind the cluster of metabolic dysfunctions of the metabolic syndrome. To further identify or refute the presence of the "obesity paradox" researchers should consider methodological classification of overweight and obesity in addition to a multi-disciplinary approach to underlying physiological mechanisms.

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