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EDITORIAL

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Do we need dietary reference values for people with obesity?

The double burden of malnutrition – obesity and iron deficiency

Despite the rapid transition in the global nutrition landscape, malnutrition, which includes both undernutrition as well as overweight and obesity, or diet-related non-communicable diseases, remains a global problem. Millions of people suffer from different forms of malnutrition that can co-exist simultaneously within a population, a household or an individual (Bailey *et al.* 2015; WHO 2018) – a concept known as the double burden of malnutrition. Globally, progress has been made in addressing the double burden of malnutrition. However, progress is not equally spread across the different forms of malnutrition as the prevalence of overweight and obesity is still rising. Between 2000 and 2016, the prevalence of adult obesity has increased from 201.8 million (10.6%) to 393.5 million (15.1%) women and from 124.7 million (6.7%) to 284.1 million (11.1%) men (total: 13.1% of adults) (WHO 2020). In high-income countries, the prevalence of overweight and obesity is up to five times higher compared to low- and middle-income countries (LMICs) (Global Nutrition Report 2018, 2020). Nevertheless, obesity is also rising in LMICs (Ford *et al.* 2017). One of the key nutritional challenges in people with obesity is the co-existence of nutritional deficiencies such as iron deficiency that can progress to anaemia (Delisle 2018). Similar to obesity, no progress has been made in addressing the global prevalence of anaemia. In 2016, 613.2 million (32.8%) women of reproductive age suffered from anaemia. Globally, no country is on course either to reach the anaemia target of the 2025 global nutrition targets or to halt the rise in adult obesity (Global Nutrition Report 2020).

Notably, obesity and iron deficiency go hand in hand. From 1962 onwards, a growing number of researchers have observed that iron deficiency is more prevalent in people with obesity compared to their non-obese counterparts (Wenzel *et al.* 1962; Yanoff *et al.* 2007; Ausk & Ioannou 2008; Menzie *et al.* 2008; del Giudice *et al.* 2009; Tussing-Humphreys *et al.* 2009). The prevalence of iron deficiency ranges between 13% and 53% depending on the laboratory markers used and associated cut-off values (Benotti *et al.* 2020). Different mechanisms have been proposed that could explain the link between obesity and iron deficiency including (i) an inadequate dietary iron intake; (ii) higher requirements; and (iii) chronic low-grade inflammation. No differences have been observed in dietary iron intake between individuals with obesity and their non-obese counterparts (Menzie *et al.* 2008; Aeberli *et al.* 2009; Cepeda-Lopez *et al.* 2010; Cepeda-Lopez *et al.* 2011). However, iron requirements are higher in people with obesity due to increased blood volume (Cepeda-Lopez *et al.* 2019). Despite higher requirements, the chronic low-grade inflammation associated with obesity reduces iron absorption by increasing hepcidin levels (Tussing-Humphreys *et al.* 2010). In turn, the presence of iron deficiency within an individual with obesity can impair physical activity and further contribute to obesity due to the link between iron status, oxygen transport and physical activity (Cepeda-Lopez & Baye 2020). Based on the increases in iron requirements and decreases in iron absorption in people with obesity, it seems paradoxical to exclude inadequate dietary iron intake as a contributor to the development of iron deficiency based solely on the lack of difference in dietary iron intake between individuals with obesity and their non-obese counterparts. Rather than just comparing dietary intakes, it might be more useful to reconsider the dietary reference values for people with obesity.

Do we need specific dietary reference values for people with obesity?

Dietary references values have been proposed to identify populations that are at risk of under- or overconsumption. Nutrient intake is needed to ensure adequate growth and development, while reducing the

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risk of nutritional deficiencies. Nutritional requirements differ with age, sex and physiological conditions due to differences in velocity of growth, age-related changes in nutrient absorption, body function and functional capacity. Therefore, dietary reference values are available for different age and sex groups (EFSA 2020). However, research has shown that physiological conditions can differ between individuals and populations independent of age and gender. Although dietary reference values are rarely derived for patient populations, since most conditions have a more acute nature, obesity is a chronic progressive condition that is more than just a risk factor for other diseases (Bray *et al.* 2017). Due to its chronic nature, the underlying physiology of people with obesity is affected. Progressive adaptations include low-grade chronic inflammation, higher morbidity, increased blood volume, reduced hepatic blood flow and reduced renal clearance (Boullata 2010). These physiological conditions can contribute to the burden of nutritional deficiencies by affecting the absorption, distribution, metabolism and excretion of nutrients (Boullata 2010). Considering these physiological alterations, the question arises as to whether the available dietary reference values set for healthy individuals are sufficient to cover the needs of all population groups including people with obesity.

To illustrate these concerns, we recalculated the current dietary reference values of iron for people with obesity using a simple factorial approach. We adapted the estimated average requirement (EAR) for adult men and women proposed by the Institute of Medicine based upon changes in overall iron absorption and bodyweight for different obesity classes [Class 1: body mass index (BMI) between 30.0 and 34.9 kg/m^2; Class 2: BMI between 35.0 and 39.9 kg/m^2; and Class 3: BMI above 40.0 kg/m^2]. The EARs for iron depend on basal iron loss [bodyweight (kg) * 0.014 mg/kg/day], menstrual iron loss (0.51 mg/day) and overall iron absorption (18%)[1] (Institute of Medicine 2001). For basal iron loss, we calculated the requirement with the bodyweight that corresponded to the lower limit BMI of the different obesity classes. Therefore, we used the median height for adult men (175.6 cm) and women (161.9 cm) in the US as reported in *NHANES* 2011–2014 and calculated the corresponding weight for BMI 30, 35 and 40 kg/m^2 (Green *et al.* 1968; Fryar *et al.* 2016). According to our knowledge, no data are available regarding menstrual iron loss specifically in subjects with obesity. Therefore, we maintained the value of 0.51 mg/day for pre-menopausal women. For iron absorption, we used mean haem and non-haem iron absorption that was measured in a group of obese women before bariatric surgery (haem iron: 23.9%; non-haem iron: 11.1%) in combination with the original iron bioavailability fractions to obtain an overall absorption value of 12.38% (Ruz *et al.* 2012).

The adapted EARs per obesity class are summarised in Table 1. According to the adapted EARs, the requirements are higher per obesity class for both men and women. For obesity Class 1, the EARs increased by 75.0%, 60.5% and 78.0% for men, pre- and post-menopausal women, respectively, compared to the EARs set for the healthy adult population (6, 8.1 and 5 mg/day for men, pre- and post-menopausal women, respectively). For obesity Class 2, the EARs increased by 103.3%, 79.0% and 106.0% for men, pre- and post-menopausal women, respectively. For obesity Class 3, the EARs increased by 133.3%, 97.5% and 138.0% for men, pre- and post-menopausal women, respectively.

Table 1 The revised estimated average requirements (EARs) for iron per obesity class

	Men	Pre-menopausal women	Post-menopausal women
Healthy adult			
EAR (mg/day)	6	8.1	5
Obesity Class 1: ≥30 kg/m^2			
Weight (kg)	92.5	78.6	78.6
Basal loss (mg/day)	1.30	1.10	1.10
Menstrual iron loss (mg/day)	–	0.51	–
Iron absorption	0.1238	0.1238	0.1238
EAR (mg/day)	10.5	13.0	8.9
Obesity Class 2: ≥35 kg/m^2			
Weight (kg)	107.9	91.7	91.7
Basal loss (mg/day)	1.51	1.28	1.28
Menstrual iron loss (mg/day)	–	0.51	–
Iron absorption	0.1238	0.1238	0.1238
EAR (mg/day)	12.2	14.5	10.3
Obesity Class 3: ≥40 kg/m^2			
Weight (kg)	123.3	104.9	104.9
Basal loss (mg/day)	1.73	1.47	1.47
Menstrual iron loss (mg/day)	–	0.51	–
Iron absorption	0.1238	0.1238	0.1238
EAR (mg/day)	14.0	16.0	11.9

[1]Formulation to determine iron absorption = {[fraction non-haem iron (0.9) × bioavailability non-haem iron (0.168)] + [fraction haem iron (0.1) × bioavailability haem iron (0.25)]} × 100 = 17.6 ≈ 18.

Higher iron requirements, as indicated by the revised EARs, might explain why individuals with obesity suffer more from iron deficiency, while their dietary iron intake is not lower than individuals with normal weight, as mentioned above. On the contrary, they support the idea that dietary iron intake should be higher in people with obesity. Moreover, these distinct differences in requirements might indicate that the current diets are potentially inadequate for people with obesity. A nutrient-poor diet in combination with chronic inflammation could further worsen micronutrient status in obesity. As a consequence, a triple challenge of undernutrition (*i.e.* micronutrient deficiencies), overnutrition (*i.e.* obesity) and inflammation implies a major threat for metabolic health. Especially, when the different malnutrition forms could exacerbate each other and worsen the overall burden of malnutrition (Wells *et al.* 2020). Nonetheless, clinical investigations in people with obesity are needed to verify these assumptions. Importantly, the concept is not solely applicable to iron. Other vitamin and mineral deficiencies (*e.g.* vitamin B12) have also been associated with obesity (Kaidar-Person *et al.* 2008a; Kaidar-Person *et al.* 2008b), for which the same concept of higher requirements could also apply.

Conclusion

In the face of all malnutrition challenges, the question arises as to whether we are paying sufficient attention to obesity and its related nutritional problems. We would like to say yes, but the reality is that the prevalence and worldwide spread of obesity have never been higher. Moreover, available research suggests the presence of serious nutritional challenges in obesity. In particular, the co-existence of nutritional deficiencies and obesity is often neglected among malnutrition challenges. In fact, nutrition financial resources are predominantly collected through undernutrition programs, while the financial resources needed for addressing malnutrition related to obesity keep growing (Hawkes *et al.* 2020). In an increasingly obese world, more attention is urgently needed to address existing obesity and its related nutritional problems rather than focusing solely on obesity prevention. In the context of dietary reference values, research is necessary to test whether the available dietary reference values fulfil the requirements of people with obesity in the light of the physiological alterations. This means allocating financial resources to investigate the physiological alterations in people with obesity, to study nutrikinetics (*i.e.* absorption, distribution, metabolism and excretion of nutrients) in people with obesity, to analyse dietary requirements in the light of the nutrikinetic findings and to explore prevention and treatment options while collaborating with all involved parties ranging from policymakers to the nutrition community.

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