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Invited Commentary

Obesity, iron deficiency and anaemia: a complex relationship

Low- and middle-income countries are facing complex, overlapping and interconnected burdens of malnutrition. Those different forms of malnutrition can co-exist within the same individual, households and populations, and across the life course and can even paradoxically be linked[1]. Obesity (OB) and Fe deficiency (ID) are two of the commonest nutritional disorders in the world. A growing number of studies are showing that ID is common in individuals with overweight and OB (OW/OB)[2]. In this issue of *Public Health Nutrition*, Zheng *et al.* contribute to this growing body of evidence by showing that ID, anaemia and OB are all public health concerns among schoolchildren in Guangzhou, China. They showed that ID anaemia contributed to <10 % of the overall anaemia prevalence and that OB is associated with ID, but not with anaemia or ID anaemia.

OB, characterised by chronic low-grade inflammation, increases hepcidin, reduces Fe absorption and eventually leads to systemic ID and/or Fe-restricted erythropoiesis[3–5]. This reduction in Fe absorption in OW/OB subjects is paradoxical as it happens in spite of increased Fe requirements, partly due to increased blood volume[6]. Also striking is the finding that the enhancement of Fe absorption by ascorbic acid in OW/OB is one-half that in normal-weight women as illustrated in a recent stable isotope study in Switzerland[3]. Further confirmation of the OB–ID relationship comes from studies that have shown lower circulating hepcidin and increased Fe absorption after laparoscopic sleeve-gastrectomy[7].

Several studies have consistently found an association with the features of anaemia of inflammation, specifically, elevated serum ferritin and low serum Fe. However, contrary to anaemia of inflammation, Hb concentration is usually not lower in individuals with OW/OB compared with normal-weight persons[8]. This is consistent with the findings by Zheng *et al.* where OB was associated with ID, but not with anaemia, which may initially appear paradoxical. Only 8·9 % of the anaemia was related to ID, which is unsurprisingly given the complex aetiology of anaemia. This finding echoes findings from a more recent systematic analysis of national surveys that suggests that the proportion of anaemia associated with ID is much lower than the assumed 50 % and that other causes including hereditary blood disorders and infections such as hookworm and malaria may be important contributors[9].

While OB can contribute to ID, ID can in turn participate in OB-related pathogenesis. Given the intricate link between Fe status, O_2 transport and physical performance[10], ID in the OW/OB can exacerbate the already low physical performance, hence, aggravating OB. Over secretion of hepcidin can also lead to Fe sequestration in cells of the reticuloendothelial system, which could induce oxidative stress, endoplasmic reticulum stress, inflammation and adipose tissue endocrine dysfunction[10,11]. Increased intracellular Fe stores in subjects with OW/OB could also result in tissue damage (e.g. liver), increasing the risk for hepatic cancer[12,13], as well as neurodegenerative disorders[14]. For children, the combination of ID and OB can have dire consequences including impaired immune functions, poor cognitive and physical performance, as well as increased risk for non-communicable diseases in later life[15]. Consequently, ID monitoring, prevention and treatment programmes should not only be confined to settings where high levels are expected because of high prevalence of undernutrition as is often the case in low- and middle-income countries but also target areas where OW/OB is a concern.

A key challenge that needs to be addressed is the complexity of Fe status assessment in individuals with OW/OB[16]. Commonly used biochemical markers are often affected by dilution or inflammation[17]. For example, increased blood volume in the OW/OB can dilute serum Fe leading to an overestimation of hypoferraemia[6]. Inflammation can also confound serum ferritin, transferrin saturation and transferrin receptor measures[7,11,16]. Zheng *et al.* were able to assess several Fe metabolism biomarkers, but did not measure inflammation markers like C-reactive protein and α1-acid glycoprotein which are essential to apply correction to serum ferritin values[16,18]. Measurement of soluble transferrin receptor could have allowed calculation of total body Fe using the log ratio of soluble transferrin receptor:serum ferritin. Moreover, the regression-correction approach is one method to ameliorate inflammation-confounded estimates of population-level ID[11]. More research is needed to determine the validity of inflammation-corrected estimates in OW/OB populations.

The ever-growing risk of the co-occurrence of OB and ID and the urgency for effective double-duty actions to address it call for more studies like that of Zheng *et al.* However, future studies should consider, whenever

possible, a combination of Fe status biomarkers including measuring serum hepcidin and inflammatory markers like C-reactive protein and α1-acid glycoprotein to allow a more accurate interpretation. The definition of ID and interpretation of Fe status biomarkers in populations with high rates of OB are more complex and warrant further investigation. Commonly used strategies to control ID (e.g. Fe supplementation and fortification) may also need to be re-evaluated as they might not be effective in populations with high OW/OB prevalence.

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