CURRENT SCIENCE

Volume 125 Number 2 25 July 2023

EDITORIAL

Classifying 'Normal' in health and nutrition: complicated, confusing and controversial!

Clinicians classify individuals as normal or sick, as this distinction forms the basis of medical practice. For clinicians, defining abnormality helps assess the need for treatment, while in public health it helps assess disease burden (proportion of population with disease) (Catita, M. *et al*., *Philos. Ethics Humanit. Med.*, 2020, **15**(1), 3). To define abnormality, a 'cut-off' value is used, above or below which, the values of that parameter are termed abnormal. Definitions of normality have been criticized to being arbitrary and haphazard, leading to questioning medicine as an objective science (Koeslag, J. H., *S. Afr. Med. J.*, 1993, **83**(1), 47–50). Normality has been conceptualized or defined in different ways in health sciences. Typically, it can have a naturalistic or normative approach.

The commonly used statistical approach is an objective method based on mathematical concepts of mean and standard deviation (SD). As a convention, two standard deviations on either side of a mean (± 2 SD) are used as cut-offs to define normal, leaving 2.5% on either end of the spectrum as deficient or high (Jones, G. and Barker, A., *Clin. Biochem. Rev. Suppl.*, 2008, 1S93–1S97). There is nothing sacrosanct about 2 SD, except its conventionality. This approach gives us two cut-offs (high and low) with a range of values in between that is considered normal, acknowledging the variability involved. One of the best examples of this approach is the child growth standards recommended by WHO (de Onis, M. *et al*., *Food Nutr. Bull*., 2004, **25**, S15–S26).

Role of genetic influence and childhood environment on a child's nutritional status has been debated for long-nature versus nurture debate. Not discounting the role of genetic and familial influences, growth in the first five years of life is largely dependent on maternal nutrition and subsequent dietary habits including breast feeding of the child. Subject to remaining healthy and given the required nutrition, children across the globe have similar growth patterns. The child growth norms were revised by WHO in 2009 using height and weight data of children from Brazil, Ghana, India, Norway, Oman and the United States. The norms are different for girls and boys as there were biological differences (de Onis, M. *et al*., *WHO Arch. Pediatr.*, 2009, **16**, 47–53).

Other approaches involve relating the parameter of interest to a health status or outcome. Typically, one can compare the values of one parameter to another biological measure of the same construct. For example, body mass index (BMI) used to define levels of obesity is based on its association with the total body fat content or haemoglobin with ferritin levels. Another approach is when we identify cut-offs at which the risk of adverse outcome increases. Some examples are of under-five malnutrition and its association with risk of mortality (Gomez, F. *et al*., *J. Trop. Pediatr.* (*London*), 1956, **2**, 77–83) and levels of blood pressure and risk of acute stroke or cardiac event (Brown, M. J., *Lancet*, 2000, **355**, 653–654). However, as these studies also show that the risk of adverse outcome increases linearly as a continuum with no level at which risk is zero, cut-offs are subjective, rather than objective.

One of the problems with normality definitions is that many of the currently used normal values are based on historical recommendations that had a limited evidence base. The definition of anemia used even today comes from a WHO committee recommendation in 1968 (Blanc, B. *et al*., *WHO Tech. Rep. Ser.*, 1968, **405**, 1–40). The report itself said that the cut-offs were arbitrary, although these have been subsequently validated (Khusun, H. *et al*., *J. Nutr.*, 1999, **129**(9), 1669–1674). Beutler and Whalen identified 2 SD cut-offs for haemoglobin using data from two population level surveys including US-NHANES and after excluding people with chronic illnesses, men had approximately 1 g/dl higher value than women and blacks about 0.7–0.8 g/dl lower than whites (Beutler and Waalen, *Blood*, 2006, **107**(5), 1747–1750). The original WHO definition did not use any decimal and the above cut-off values differed from it by a few decimal points. Even a 0.5 g/dl difference in mean haemoglobin can impact the prevalence of anemia immensely.

Using population distribution to define normality has an inherent fallacy. In a population where everyone is 'abnormal' we will classify most as normal and vice versa. Rose (*Int. J. Epidemiol*., 2001, **30**, 427–432; 433–434) showed that the population distributions of systolic blood pressure of middle-aged men in two populations – Kenyan nomads and London civil servants – were very different; and using the concept of 2SD would result in two very different cut-offs of normality in these two populations. He argued that the blood pressure levels of the population of London had shifted to the right and that the population was 'sick' due to its modern lifestyle as compared to traditional lifestyle of the nomads. Using cut-offs from the London population to de-

fine hypertension would be self-defeating, converting abnormal into normal.

The main justification for having different cut-offs for different population groups in nutrition and cardiometabolic disease domain is that the body composition varies by non-modifiable factors like sex, genetics, ethnicity, etc. (Molarius, A. *et al*., *Int. J. Obes.*, 1999, **23**, 116–125; Misra, A. *et al.*, *Nutrition*, 2005, **21**, 969–976). It also varies by the type of diet and levels of physical activity; but these are modifiable risk factors and should not be considered while defining obesity. While the BMI cut-offs for obesity remain the same for both sexes, men with waist circumference ≥ 94 cm and women with waist circumference ≥ 80 cm are considered to be at higher risk of cardio-metabolic diseases (Lean, M. E. J. *et al.*, *BMJ*, 1995, 158–161) based on studies comparing waist circumference with body fat or BMI or its ability to differentiate those with and without cardio-metabolic conditions. It is quite possible that if we apply a normative approach, we will find gender differences in many health parameters. However, that does not by itself justify the use of different cut-offs. Women are known to have social disadvantages in intra-household food and work distribution, which, impact the biological parameters. Thus, using population distribution for definition of cut-offs legitimizes this social discrimination. Cut-offs for waist-hip ratio as a cardiac risk marker differ by sex, as women have evolved to possess wider hips to aid them during childbirth. For hypertension, the current wisdom is that different cut-offs by sex or population groups are not warranted. Recently relaxation in cut-offs for older adults for blood pressure and BMI have been proposed with acceptance of it as a physiological change rather than a pathological status (James *et al*., *JAMA*, 2014, **311**(5), 507–520; Javed, A. A. *et al*., *Int. J. Obes.* (*London*), **46**(5), 1027–1035). This addresses a criticism, that common formulations of normality commit a fallacy, as they characterize the 'normal' as a state of the individual and not as an ongoing process within it (Rudnick, A., *Philos. Med.*, 2000, **25**(5), 569–580).

There are some issues in defining normality that have no clear answers. For example, at what magnitude of differences between two subgroups should one go for a different cut-off? How do we define the subgroups? Nation, state, district are artificial geographical boundaries, which by themselves do not justify a subgroup without a biological basis. There has always been a tension between having a global standard (for ease of use and comparison) and local applicability.

If normality is defined biologically, it should be time independent, while a normative approach is likely to change over time. For many conditions/parameters, the cut-offs for normality have changed over the years. These have been done usually to classify more people as abnormal. This has occurred with better recognition of risk and as a society, our eagerness to intervene earlier to save more lives. In the case of hypercholesterolemia, initial cut-off of 240 mg/dl was based on its distribution in the US population, while the revised cut-off of 180 mg/dl was based on risk of cardiovascular disease (Carleton, R. A., *Am. J. Clin. Pathol*., 1983, **79**(3), 402). Such changes have been criticized as attempts by vested interests such as the pharmaceutical industries to put more people on medicines. Following the downward revision in definition and indication for surgical treatment for obesity among Asians (Misra, A. *et al.*, *J. Assoc. Phys. India*, 2009, **57**, 163–170), bariatric surgery has tripled in the last 10 years, inviting criticism of commercial interests affecting decisions of abnormality (Ohta, M. *et al*., *Obes. Surg*., 2022, **32**(9), 2994–3004).

A finding from a population survey of haemoglobin among children and adolescents which found mean values for haemoglobin lower by 1–2 g/dl as compared to the WHO norms has led to suggestions that cut-off for anemia in Indian children needs to be revised downwards (Sachdev, H. S. *et al*., *Lancet Glob. Health*, 2021, **9**(6), e822–e831).

While we await revised WHO recommendations on anemia cut-offs (Garcia-Casal, M. N. *et al*., *Ann. N. Y. Acad. Sci*., 2019, **1450**, 5–14), it is important to note that studies have shown that the Indian diet is deficient in iron across all socio-economic groups, iron bioavailability in food is poor, which is worsened by recurrent infections or worm infestations (Anand, T. *et al.*, *Nutrition*, 2014, **30**(7–8), 764–770). Therefore, just as the London example mentioned earlier, Indian population is 'sick', whose haemoglobin distribution curve has deviated to the left and should not be used it to frame normality. Not giving iron supplements to mothers and children with lower haemoglobin (by WHO criteria) can have serious adverse consequences, as it is well known that haemoglobin level falls only in later stages of iron deficiency after depletion of iron stores.

Public health experts recommend doing away with the use of cut-offs. They recommend looking at the population distribution by using mean and SD (Institute of Medicine (US), 2003; https://www.ncbi.nlm.nih.gov/books/NBK221225/, accessed on 26 June 2023). Any population level intervention should be aimed at the whole population (irrespective of whether they are normal or abnormal) and its impact should be measured by the change in the population mean. While this sidesteps the issue of normality, we do need a cut-off to decide who will get treated.

Multiple approaches have been used to define normality including biological and statistical. However, there is always an element of arbitrariness in the way cut-offs are decided as they are a compromise between convenience, science, and the need to be uniform across groups. With increasing automation, the rationale of convenience of a single cut-off for subgroups becomes weaker. The cut-offs could and should be revisited from time to time if evidence questioning it emerges. However, the mere presence of a difference in mean or distribution does not justify a need for a different cut-off, as these differences may be measuring inequities rather than inequalities.

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