

49 486 individuals; 41 210 participants had a haemoglobin value, 8087 of whom were included. Compared with existing WHO cutoffs, the study cutoffs for haemoglobin were lower at all ages, usually by 10–20 g/L, but more so in children of both sexes aged 1–2 years and in girls aged 10 years or older.

Addo et al. (20), evaluated and analysed data collected from 30 household, population-based nutrition surveys of children aged 6 to 59 months and nonpregnant women aged 15 to 49 years during 2005 to 2016 across 25 countries. To define a healthy population, persons with iron deficiency (ferritin <12 µg/L for children or <15 µg/L for women), vitamin A deficiency (retinol-binding protein or retinol <20.1 µg/dL), inflammation (c-reactive protein >5 mg/L or α-1-acid glycoprotein >1 g/L), or known malaria were excluded. Survey-specific, pooled haemoglobin 5th percentile cutoffs were estimated. A total of 79 950 individuals were included in the original surveys. The final healthy sample was 13 445 children (39.9% of the original sample of 33 699 children: 6750 [50.2%] boys, mean [standard deviation, SD] age 32.9 [16.0] months) and 25 880 women (56.0% of the original sample of 46 251 women, mean [SD] age 31.0 [9.5] years). Survey-specific haemoglobin 5th percentiles among children ranged from 79.0 g/L (95% CI = 75.4–82.6 g/L in Pakistan) to 112.3 g/L (95% CI = 111.4–113.3 g/L in the United States of America), and among women from 88.3 g/L (95% CI = 77.7–98.8 g/L in Gujarat, India) to 120.9 g/L (95% CI = 120.0–121.7 g/L in the United States of America). Inter-survey variance around the haemoglobin 5th percentile was low (3.5% for women and 3.6% for children). Pooled 5th percentile estimates were 96.5 g/L (95% CI = 92.6–100.4 g/L) for children and 108.1 g/dL (95% CI = 103.5–112.7 g/L) for women. The authors concluded that current WHO cutoffs to define anaemia are higher than the pooled 5th percentile of haemoglobin among the biochemically healthy individuals in this study.

In addition to data from Braat et al., data from the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) study and from INTERBIO-21st, an extension aimed at improving the characterization of the fetal growth restriction, were analysed to propose haemoglobin cutoffs for pregnancy by trimester (21, 22). The INTERGROWTH-21st project was carried out between 2009 and 2016 across eight diverse, geographically delimited, urban areas. At each visit, information was collected about the pregnancy, as well as the results of blood tests taken as part of routine antenatal care. All study sites assessed haemoglobin concentration from venous blood samples using commercially available methods (23). Measurement of ferritin and other iron biomarkers were not available. The gestational age-specific percentiles for maternal haemoglobin proposed were based on prospective study throughout pregnancy of 3502 healthy, well-nourished women from eight countries, whose healthy babies were followed up to 2 years of age. The highest median maternal haemoglobin concentration was at 14 weeks of gestation (121.4 g/L) and the lowest was between 31 and 32 weeks of gestation (114.6 g/L), but values rose progressively thereafter to a median concentration of 118.7 g/L at 40 weeks of gestation.

The INTERBIO-21st study comprised two components: fetal study and neonatal study. The fetal component monitored fetal growth from early pregnancy (14 weeks) up to delivery, whereas the neonatal component monitored these infants up to 2 years. Among the variables collected were detailed biological parameters (e.g. haemoglobin) of the mothers and documentation of maternal and fetal outcomes (24). The authors concluded that, when compared to a reference value of 110 g/L, women with haemoglobin levels below 95 g/L had an increased risk of adverse neonatal outcomes, which doubled with haemoglobin values below 80 g/L. A U-shaped relationship between maternal haemoglobin and adverse neonatal outcomes was also demonstrated, with an increased risk of adverse neonatal outcomes among women with haemoglobin concentrations of 140 g/L or more (22).

The limitations of the INTERGROWTH project are the lack of haemoglobin data collected at <14 weeks of gestation and the lack of data on ferritin, which gives rise to the possibility that women with iron deficiency may have been included in the sample. Also, most of the included women received iron and folic acid supplementation as standard care.

As noted by the WHO guidance published in 1989, although anaemia is often graded as mild, moderate, and severe, the haemoglobin values for these three categories vary and are arbitrary (14). The 1989 guidance considered anaemia to be mild, moderate, or severe when haemoglobin concentrations were above 80%, between 80% and 60%, or less than 60% of the cutoffs, respectively. According to the 1989 guidance, given the relatively small differences between age and sex groups, mild anaemia was diagnosed when the haemoglobin concentration was above 100 g/L but below the cutoff, moderate anaemia when the concentration was