Using bioelectrical impedance analysis in children and adolescents: pressing issues

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Abstract

Single- and multifrequency bioelectrical impedance analysis (BIA) have gained popularity as tools to assess body composition and health status of children and adolescents, but many questions and misconceptions remain. This review addresses pressing issues researchers and health care providers may encounter when using BIA in the young population. The importance of choosing population-specific and device-specific equations to estimate body composition as well as the use of BIA in longitudinal analysis are discussed. When specific equations are not available, raw bioimpedance values (i.e., resistance, reactance, and impedance) can be used to compute bioimpedance parameters, such as phase angle, impedance ratio, and bioelectrical impedance vector analysis. As interpreting these parameters is challenging, suggestions are provided on the use of reference data, cut-off points, and adjustment factors. Furthermore, unsolved technical and analytical issues are listed. Based on existing issues and potential for future development, a greater interaction between industry and academic researchers to improve the validity of BIA measurements among children and adolescents across their developmental stages is encouraged.

Introduction

Bioimpedance techniques are widely used to estimate body composition given their low cost, portability, ease of use, and lack of radiation exposure [1,2]. To briefly illustrate the physical principle involved, bioimpedance techniques measure the opposition (or impedance) of body tissues to the flow of an alternating electrical current (at one or more frequencies) applied to the skin surface through the contact with electrodes [3]. There are three main categories of bioimpedance techniques based on the range of frequencies available, including: single-frequency bioelectrical impedance analysis (SF-BIA; commonly at 50 kHz); multifrequency BIA (MF-BIA; with at least one low frequency [e.g., 5, 7.5 kHz] and one high frequency [e.g., 50, 100, 200, 500, 1000 kHz]); and bioimpedance spectroscopy (BIS; over the entire spectrum of frequencies from 5 to ~1,000 kHz) [4]. Due to differences in frequencies, the ability to estimate water compartments (i.e., intracellular water [ICW], extra-cellular water [ECW], and total body water [TBW]) varies across bioimpedance categories as reviewed elsewhere [2,4,5]. Furthermore, SF-BIA and MF-BIA use population-derived equations to predict body composition; on the other hand, BIS applies biophysical modelling to estimate body compartments.

The most commonly used bioimpedance techniques in the pediatric population are the SF-BIA and MF-BIA[6–9]. Despite being feasible and safe techniques, the absence of standardized protocols as well as incorrect interpretations of results may affect the validity of BIA measurements in children and adolescents [9,10]. In our experience, questions posed by researchers, medical industry, and health care providers working in pediatrics include choice of optimal BIA device and equations, longitudinal assessment, data interpretation approaches, and protocol standardization (**Figure 1**) [4,11,12]. Here, we aim to clarify these questions and raise awareness of issues one may encounter when employing BIA techniques (i.e., SF-BIA

and MF-BIA) in children and adolescents. We briefly discuss limitations of BIS devices in the pediatric population.

Choosing adequate bioimpedance devices and body composition predictive equations

Considered as a two-compartment method, SF-BIA indirectly estimates the content of fat mass (FM) and fat-free mass (FFM) using equations based on bioimpedance variables (e.g., reactance and resistance), demographics (e.g., age and sex), and anthropometric characteristics (e.g., weight and height) that are regressed against a reference indirect technique [13]. Two important assumptions underlying the SF-BIA method are that chemical composition of FFM, ICW to ECW ratio, and body shape are maintained constant; these assumptions must be met to produce accurate results [1,2]. However, these assumptions are violated during growth and maturation when rapid and substantial changes in water, protein, and mineral content, as well as in the length of limbs and trunk occur [1,14,15]. Changes in the content of ICW and ECW are also observed[16], influencing bioimpedance measurements as the SF-BIA technique is unable to distinguish between water compartments; it is therefore suggested to include a hydration factor that is specific to age and sex when developing FM and FFM predictive equations [1]. Moreover, equations should be chosen carefully as modifications in body composition and shape during growth differ between sexes, pubertal stages, ethnicity, degree of obesity, malnutrition, and illness [17,18]. As such, predictive equations must be constructed and validated in a population with similar characteristics to the one under investigation [1]. Although MF-BIA devices estimate both ICW and ECW content, body composition is also predicted using regression-derived, population-specific equations. In fact, not all researchers recognize the specificity of BIA equations. In a previous systematic review from our group, we observed that most equations applied to the pediatric population with obesity were constructed using data from adults or children with diverse

weight status [8]. Furthermore, only those studies cross-validating their newly developed equations in an external group of children and adolescents with very similar characteristics to the study group (e.g., age, pubertal stage, body mass index [BMI], and body composition) reported satisfactory agreement between measurements obtained by BIA and reference techniques [8,19,20].

Another particularity of equations to estimate body composition using BIA is the high device specificity. Resistance and reactance measures are not interchangeable between devices or approaches, such as segmental vs. whole-body or SF-BIA vs. MF-BIA[21,22]. In fact, the ability of an electrical current to penetrate cell membranes is determined by its frequency; higher frequencies are required for full penetration, as cell membranes act as capacitors [22,23]. Given that bioimpedance parameters are used as independent variables in these regression equations, and a specific coefficient is given to each variable, raw BIA values obtained with a particular device cannot and should not be inputted into equations developed using a different device [24]. Indeed, validation studies have shown poor agreement between different BIA equations and reference methods to estimate body composition [7,25]. Considering the proprietary nature of regression models, some BIA devices are built with equations that are not fully disclosed by manufacturers (Table S1). Although it may pose a challenge when comparing the validity of body composition estimates across devices [24], this approach can prevent incorrect application of equations since they are not interchangeable between devices. Having said that, a greater issue is the lack of transparency about characteristics of the population used to build and validate these equations. Information on age alone is insufficient for researchers and health care providers to determine whether body composition outputs from BIA devices can be used appropriately in their studies, as discussed earlier.

Caution should therefore be taken when estimating body composition using BIA in children and adolescents as equations must be both population-specific and device-specific.

Cross-validation studies may be performed to evaluate the accuracy of equations if such criteria are not met; a more established method to assess body composition should be chosen as the reference standard [4]. In pediatric studies, a four-compartment (4-C) model may have a greater precision and accuracy to estimate body composition as the technique does not assume constant values for density and hydration [26]. However, even when cross-validation studies are conducted, a poor performance is still expected, especially at the individual level. A source of bias could be the use of reference techniques that do not match the ones employed when building predictive equations. Consequently, researchers often opt for developing a new equation that is therefore specific for their population and device. The bootstrapping method is a feasible option for external validation of predictive models in both pediatric and adult populations [27,28].

Although bioimpedance spectroscopy (BIS) is not the focus of our discussion, it is noteworthy that this different bioimpedance technique has also been employed in pediatric studies. Different from SF-BIA and MF-BIA, the BIS technique first uses impedance data using the Cole model to determine R_0 and R_∞ values that are then applied to equations based on the Hanai's mixture theory to estimate total body water volume and its sub-compartments (i.e., ECW and ICW) [5]. Because these models do not rely on predictive equations that are specific to a studied population, one could argue that the BIS technique can be used interchangeably across individuals with different age, health status, and body composition. However, resistivity coefficients used in the BIS modeling are constants related to the specific resistivity of body fluids that may differ between populations and cannot be universally applied. Previous studies have derived specific coefficients in preterm infants [29] and children aged 3-18 years of multi-ethnic origin [30,31]. Importantly, these resistivity coefficients are considered specific to the methods (i.e., algorithms) and protocols (i.e., right or left side of the body) used to generated them [32]. It is therefore recommended that

researchers conduct validation studies testing the accuracy of resistivity coefficients and estimated water volumes against a reference technique (e.g., $^{2}H_2O$ dilution). Despite these limitations, reference values for BIS measurements have been published recently from a sample of Belgian children and adolescents [33]. However, data obtained by other devices and in different populations still cannot be compared to this reference data.

Longitudinal body composition assessment with bioimpedance

Another common question is whether BIA can be used for longitudinal assessment of body composition in children and adolescents. Previous studies have shown small differences between changes in body composition estimated by SF-BIA devices at 50 kHz and dual-energy x-ray absorptiometry (DXA), suggesting that they are as accurate as DXA is to track 12-month changes in FM and FFM when using the BC-418 device (Tanita Corp., Tokyo, Japan) with the manufacturer's undisclosed equation in one study [34] as well as RJL devices (i.e., 101Q, 106, and Quantum II; RJL Systems, Detroit, United States) with the Lewy et al. [35] equation for African American children or the Suprasongsin et al. [36] equation for Caucasian children in another study [37]. However, it remains unclear how much variation in the hydration of FFM, ICW and ECW content, and body shape would be necessary to affect longitudinal measurements of body composition by BIA. When appropriate equations are employed, it should be noted that changes in BIA measurements must be greater than the minimal detectable change (which can be estimated from precision values) to be considered significant [4]. For example, one systematic review described coefficients of variation for repeated measures of body fat percentage by different BIA devices ranging from 1.7% to 22.2% in healthy subjects aged <18 years [7]. Thus, awareness of potential measurement errors as well as standardization of pre-test and test procedures are required. Additionally, future studies will

confirm the accuracy of SF-BIA and MF-BIA equations to estimate body composition longitudinally, particularly for longer follow-up periods.

The utility of raw bioimpedance values in pediatric populations

Given the concerns presented above, raw bioimpedance values (i.e., resistance, reactance, and impedance) obtained by SF-BIA, MF-BIA, and BIS can be used as an alternative to estimating body composition, if published equations do not meet the population and device-specific criteria. These raw variables can be used to calculate parameters, such as phase angle, impedance ratio at 200/5 kHz (by MF-BIA and BIS only), and bioelectrical impedance vector analysis (BIVA) [4]. Several studies have evaluated the associations of these parameters to prognostic factors and clinical outcomes in pediatrics [38–40]. For instance, the risk of developing sepsis in a pediatric intensive care unit increased as phase angle (measured at 50 kHz by a SF-BIA) and height-adjusted reactance (Xc/H) decreased in children aged one month to 6 years [40]. Another study showed that a low phase angle at 50 kHz using a BIS device was associated with longer stay in the pediatric intensive care unit after cardiac surgery in children with congenital heart diseases [41]. Using the classical BIVA model in severe acute malnutrition with raw impedance values obtained by a MF-BIA at 50 kHz, studies have shown that children with oedema and non-oedema plot differently in BIVA graphs, and changes in hydration status towards loss of water content can be observed during treatment in children with oedema [42,43]. Hydration status was also evaluated by the BIVA model in adolescents with cystic fibrosis using a SF-BIA at 50 kHz [44] and children with neurologic impairments using a MF-BIA at 50 kHz [45]. Thus, bioimpedance parameters appear to be clinically meaningful given their associations with adverse outcomes and disturbances of hydration.

Interpretation of bioimpedance parameters in clinical and research settings

While the determination of both BIA and BIS parameters (i.e., phase angle, impedance ratio, and BIVA) is free of inherent errors related to predictive equations and assumptions as they use raw bioimpedance data, interpretation of these parameters is challenging in clinical and research settings. The first reason is that isolated measurements of phase angle or BIVA are meaningless when reference data stratified by age, sex, and body mass index are unavailable [4]. Furthermore, cut-off points to identify abnormalities in these parameters are population- and device-specific and should not be used in conditions differing from the ones when they were generated. For example, one study has shown that phase angle measured at 50 kHz with two different MF-BIA devices from the same manufacturer differed between supine and standing positions as well as sex in children and adolescents [46]. A recent study further evaluated the influence of body positions on BIS measures using the same device in young children; it was found that all raw bioimpedance values (R_0 and R_∞, impedance at the characteristic frequency, and resistance, reactance and impedance at 50 kHz) were greater in supine than standing positions [47]. Although converting impedance parameters to standardized scores (i.e., Z-scores) may be a superior approach in adults [48,49], there is still limited evidence of its prognostic significance and clinically meaningful values in the pediatric population [50]. Also, not all BIA devices generate these raw measurements and parameters as outputs (Table S1) [4]; thus, the choice of device has a role in determining the applicability of the technique in research and clinical settings. Moreover, although some manufacturers claim their devices are not intended for use in pediatrics because validation studies in this population have not yet been performed, assessment of raw BIA measurements in children and adolescents is still possible with these devices as long as the internal quality check has been disabled.

Unsolved technical and analytical issues

Despite the growing body of studies applying BIA methods, some technical issues remain unsolved. These include optimal location for electrodes placement in infants and young children to minimize electrical interference at the measuring site, impact of food intake prior to examination, and effects of a full bladder during examination on BIA results [11,12]. Standing BIA devices may also require some modifications to their existing structure to allow assessment of children of varied age and body shape (**Figure 2**). For instance, a BIS device called SOZO® Digital Health Platform (ImpediMed Inc, Carlsbad, United States) allows measurements to be obtained in a seated position as per manufacturer's instructions [51]. Although research is needed to support the use of bioimpedance techniques in the seated position, it may be a simple and helpful adaptation for use in pediatric assessment. Additionally, it is not clear whether phase angle measured at 50 kHz best depicts cell mass and cellular health in the pediatric population [52]. Using a BIS device, Brantlov et al. tested whether raw bioimpedance values as well as bioimpedance parameters measured at the characteristic frequency (i.e., frequency at which reactance reaches its maximum) were superior to measures obtained at the commonly used frequency of 50 kHz to distinguish a small sample of children with nephrotic syndrome from healthy controls [39]. The authors observed differences between groups for most values/parameters independent of the frequency used; future larger studies are needed to confirm or expand upon these findings in different clinical populations and using other devices. Uncertainties also exist regarding the use of whole-body and segmental BIA approaches, mainly due to the great diversity of technical specifications of available devices and adjustments for body shape. For example, one study reported that height-adjusted resistance (H^2/R) of the whole-body, measured by a segmental MF-BIA at 500 kHz, predicted FFM with a greater accuracy than H^2/R assessed by a whole-body SF-BIA at 50 kHz [53]. Other studies found that segmental impedance obtained

237 at a frequency of 50 kHz with a MF-BIA best predicted both whole-body FFM (obtained by a
238 4-C model) and segmental FFM (using DXA) when adjusted for segment length [54,55].
239 However, associations of segmental impedance values to whole-body and segmental body fat
240 were significant only after correcting segmental impedance for both segment length and
241 cross-sectional area (i.e., "specific resistivity") [54,55]. In an attempt to also improve the BIVA
242 model among the pediatric population using a MF-BIA device, Wells et al. reported that
243 variations in FM and FFM were best predicted when BIVA parameters at 50 kHz adjusted for
244 body surface (known as the "BIVA specific") were combined with conventional BIA and
245 body weight [56]. The proposed equation, however, should not be applied to other populations
246 and are also device specific as any other BIA parameter.
247 Interpretating raw bioimpedance values obtained at different frequencies is not
248 straight forward as several segments are available to choose from (e.g., right limbs, left limbs,
249 trunk). One approach, already employed in pediatric studies, is to combine segmental
250 measurements at the whole-body level by summing the resistance values for each segment
251 either with SF-BIA or MF-BIA devices [53,55]. It has also been suggested that averaging
252 bioimpedance values from the left and right sides of the body would be appropriate in adults
253 [57]. To test this method in a pediatric cohort with obesity, we calculated differences in
254 resistance measured at 50 kHz between the left and right sides of the body using the seca
255 mBCA 525 MF-BIA device (Seca GmbH & Co. Kg., Hamburg, Germany) in a small sample
256 of children of an ongoing study in our lab (n = 10; age range = 10.0 to 16.8 year); we found
257 differences ranging from 2.3 Ω to 28.6 Ω between sides. Despite test procedures being
258 standardized, it is likely that small deviations in the placement of electrodes, with different
259 distances between the current and voltage electrodes, have led to asymmetrical resistance
260 measurements. In clinical populations, lateral variations in resistance may occur in conditions
261 associated with unilateral oedema (e.g., lymphedema) and significant body asymmetry (e.g.,

unilateral hemiparesis, amputations, and neuromuscular conditions) [58]. Future studies are therefore required to test whether summing of individual segments or averaging sides best correct for variations in electrode placement and body shape [57].

Conclusion

In view of our discussion, we extend the call for additional research made by experts in the field of pediatric body composition assessment [59] and encourage a greater interaction between industry and academic researchers to solve above-mentioned issues (**Figure 3**). The ultimate goal is to enhance accuracy and promote BIA measurements in children and adolescents beyond research settings.

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Conflict of Interest

C.E.O declares no competing financial interests. MCG reports receiving honoraria from Abbott Nutrition and Nestle Health Science, outside the scope of the submitted work. M.J.M is employed by Seca gmbh & co. kg. A.M.H. has received grant funding from Rhythm pharmaceuticals and Levo therapeutics outside the scope of the submitted work. C.M.P. reports receiving honoraria and/or paid consultancy from Abbott Nutrition, Nutricia, Nestle Health Science, Fresenius Kabi, Pfizer, and Helsinn outside the scope of the submitted work.

Author Contributions

CEO. and CMP, designed research; CEO, conducted research; CEO, writing – original draft preparation; CEO, CMG., MJM, AMH, CMP, writing – review and editing. All authors have read and approved the final manuscript.

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FIGURE LEGENDS

Figure 1. Selected frequently asked questions about the use of bioelectrical impedance analysis in pediatrics. *Abbreviations:* BIA, bioelectrical impedance analysis; BIVA, bioelectrical impedance vector analysis; DXA, dual energy x-ray absorptiometry; FFM, fat-free mass; FM, fat mass; MF-BIA, multifrequency bioelectrical impedance analysis; SF-BIA, single-frequency bioelectrical impedance analysis; TBW, total body water.

Figure 2. Assessment of bioimpedance parameters using standing devices is challenging in children across their developmental stages. A) As depicted above, younger children would be unable to place their hands in the proper location to complete a bioimpedance test. B) Modifications to the device' structure would be necessary to accommodate children of varied age and body shape.

Figure 3. A SWOT analysis for the use of bioelectrical impedance analysis (BIA) in children and adolescents. Strengths, weakness, opportunities, and threats are described to guide researchers and industry in their decision-making processes with the ultimate goal of improving the utility of BIA in pediatrics. *Abbreviations:* BIA, bioelectrical impedance analysis; BIVA, bioelectrical impedance vector analysis.


What does BIA measure? And what does it estimate?
•BIA measures the electrical response of the body to an electric current applied by single- or multifrequency devices
•It estimates TBW, FFM, and FM or other parameters using SF-BIA and MF-BIA predictive equations
How to choose the right device?
•Choose a device that also provides raw bioimpedance measurements as outputs (e.g., resistance, reactance, and impedance) in addition to the body composition parameters
How do you select an equation to estimate body composition?
•Ideally, equations should match:
- the characteristics of the population being evaluated (e.g., age, sex, sexual maturation, ethnicity, health status, obesity degree)
- the device being used (e.g., brand, model/version, frequency, whole-body or segmental, supine/standing)
If available equations are not population-specific or device-specific, how to proceed?
•Perform a cross-validation study
•Choose a reference standard measuring body composition at the same level (e.g., multicompartment, DXA, dilution method)
•Use agreement analysis to evaluate the validity of the selected equations. A guide is provided in Earthman (4)
•If agreement analysis is not satisfactory, develop a new equation and test its external validity using an external sample or the bootstrapping method
What alternatives to body composition assessment exist when using BIA?
•Raw BIA measurements can be used, such as resistance, reactance, and impedance
•These measurements can be adjusted by height or used to compute BIA parameters, including phase angle, impedance ratio, and BIVA
What protocol to follow?
•We advise following the guidance provided by Lyons-Reid et al (11) and Brantlov et al. (12) until a standard protocol for the pediatric population is established; or, if available, the study protocol by the device's manufacturer
•Use the same protocol for all subjects and during all follow-up visits
•When deviations from the recommendations are necessary, record modifications and report them in future publications

Figure 1

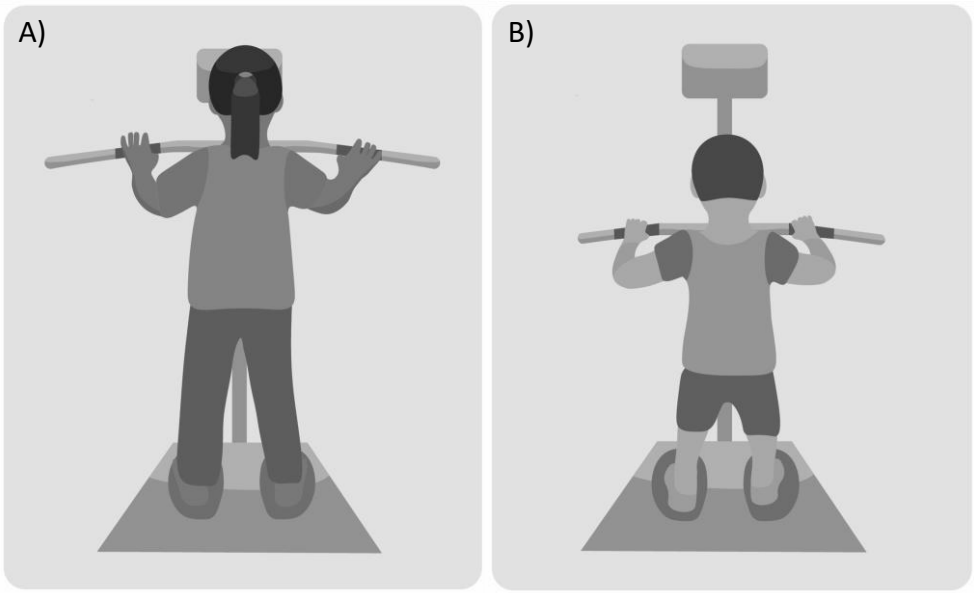

Figure 2

	Helpful to improve the utility of BIA in pediatrics	**Harmful** to improve the utility of BIA in pediatrics
Internal origin attributes of the BIA method	**STRENGTHS** • Low cost • Portable • Ease of use • Non-invasive • No radiation exposure	**WEAKNESS** • Doubly indirect method • Assumptions may be violated by rapid changes in hydration and body shape • Equations must be population-specific and device-specific • Manufacturers may not provide details on how equations have been constructed (e.g., population, reference standard) • Devices may not generate raw BIA outputs • Inability to compare bioimpedance data across devices, especially between those that used different reference methods • Lack of protocol standardization
External origin attributes of environment	**OPPORTUNITIES** • Solve technical issues • Investigate the validity of longitudinal BIA measurements and the specific BIVA • Examine the predictive ability of phase angle measured at different frequencies • Compute reference data for BIA estimates that are device-specific and population-specific • Establish a standard protocol • Improve reporting of procedures • Develop partnerships between industry and academic researchers	**THREATS** • Conflict of interests • Costs • Standard reference methods are not free of error • Interindividual variability between testing subjects

Figure 3