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Influences of weight, age, gender, genetics, diseases, and ethnicity on bitterness perception: a narrative review of current methodological aspects

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Abstract

Background: Bitterness perception seems to be related to an enhanced intake of dietary fat and to a tendency to the development of diseases such as obesity. However, the exact factors for this possible contribution still need to be better investigated. So, gustatory perception of the bitter taste is a promising area of study because of its importance regarding food choices and consequently feeding behavior. Therefore, this short review focused on recent papers reporting correlations between bitter taste, anthropometric variables, obesity and other chronic diseases, age, gender, ethnicity, and genetics.

Methods: A survey was performed in MEDLINE (PubMed) and Scielo from September 2015 to January 2017. Only review articles, observational studies and clinical trials published in English and Portuguese over the last 15 years which met the objectives of the present study were considered. A total of 40 papers were evaluated.

Results: Two papers showed a positive correlation between bitter taste and obesity, one indicated that this correlation is influenced by the subject's age, one suggested a negative correlation, and two found no association. Age seems to be negatively correlated with the bitterness perceived, and female gender was associated with a stronger perception of bitterness. Genetics, mostly due to differences in TAS2R38 expression, influences sensitivity to the bitter taste, feeding behavior and also alcohol intake. Ethnicity, not only the subject's phenotypic or genotypic characteristics, seems to play a role in taste perception and nutritional diseases.

Conclusions: Age, gender, genetics and ethnicity seem to play a role in bitterness perception. Data about associations between bitterness perception and anthropometrics are conflicting.

Keywords: Bitter taste, Obesity, Genetic, Gustatory perception

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Background

Taste as we know involves a complex mixture of sensory stimuli (redundant) consisting not just of the taste itself but also of the olfaction and the tactile sensation of food. As the gustatory perception influences food preferences, the manner of how humans sense such tastes could be associated with an inappropriate feeding behavior and consequently to chronic diseases, such as obesity [1]. Furthermore, correlations between the bitter taste and obesity have been studied, since bitterness perception enhances the preference for sweet and high-fat foods, which are expected to be related to a higher energy consumption [2]. However, obesity could not be entirely explained by a higher consumption of food and by taste perception. In fact, obesity can affect energy metabolism and storage through changes in expression of polymorphisms or genes not related to taste [3, 4]. Other authors have argued that, at least, gustatory alterations contribute to the perpetuation and worsening of the weight gain [5]. However, although some studies have evaluated correlations between anthropometric variables and gustatory perception, no causative relationship has been reported.

There are five known tastes: sweet, salty, sour, bitter, and umami, which are sensed in the oral and nasal cavity by the TR1 and TR2 family receptors. For these two families, for example, the expression *Tas1r1* is used for taste receptor type 1, member 1 (italicised in lowercase for mice or rats) or *TAS1R1* (italicised in uppercase for humans). The corresponding proteins are reported in uppercase letters and are not italicised (for example, T1R1). When both human and rodent genes are referred to, one should use T...R (uppercase letters, not italicised, such as T2R) [1].

The expression of the T2R bitter taste receptor occurs at oral sites, on the whole epithelium of the gastrointestinal system, as well as in the lungs, pancreas and brain [6, 7]. Studies about genetics, genetic expression and sensory skills would help to understand these questions [8]. Yet, the lack of analysis of social, behavioral and ethnic factors does not permit to reach a solid conclusion [9].

Different methodologies are used to evaluate bitterness. The method using forced choice of paired comparisons intends to obtain more concise and valid results [10]. Tests with 6-n-propylthiouracil (PROP) seeking to detect "non-taster" and "taster" subjects are commonly employed in children because they do not require reading skills [11]. The Labeled Magnitude Scale (LMS) is based on semantic descriptors such as "weak" and "strong," inserted in the context of gustatory sensation. In conclusion, the protocol for the determination of gustatory sensation threshold can detect the taste threshold for the five different tastes [12] and the facial reactions related to bitterness. In this test, a camera and software detect hedonic characteristics of facial expressions, something particularly relevant since hedonia plays a role in appetite control and food ingestion [13, 14].

The aim of this narrative review was to report recent findings of association between bitterness perception, anthropometric variables, age, gender, ethnicity, obesity and other diseases, as well as the methodologies applied in the various studies.

Methodology

A survey was performed in MEDLINE (PubMed) and Scielo from September 2015 to January 2017. The following queries were used: "bitter taste and obesity," "bitter taste and anthropometry," "bitter taste and gender," "bitter taste and age," "bitter taste and genetic," "bitter taste and disease," and "bitter taste and ethnicity." Two researchers were chosen to perform the selection of the articles based on the objectives of the study. In case of disagreement, a third researcher was consulted. Only review articles, observational studies and clinical trials published in English and Portuguese over the last 15 years which met the objectives of the present study were considered. Articles cited in the papers found that fulfilled the inclusion selection criteria were also read in full. Thus, a total of 40 articles were included in the present review (see Table 1).

Results and discussion

Bitterness perception, obesity and anthropometric variables

Studies evaluating bitterness perception and obesity showed discrepant results. For example, using multiple linear regression, Martinez-Cordero et al. [15] did not observe correlations between bitterness perception and anthropometric variables, energy consumption or hormone levels. In their study, 14 solutions were diluted with different concentrations of quinine to quantify the sensitivity threshold of each subject. In this respect, the lower the concentration for bitterness perception, the lower the sensitivity threshold. Similarly, in a literature review, Nasser et al. [16] also did not report any difference between normal-weight and obese subjects regarding the perception of the four basic tastes. On the other hand, Garcia-Burgos and Zamora [13] evaluated the relationship between the facial reaction to the food bitterness and body mass index (BMI) and reported evidence of high levels of facial expression for bitterness in patients with a high BMI ($p = 0.07$). Lumeng et al. [17] detected a 6-point higher BMI percentile among taster subjects than among those unable to perceive bitterness (non-tasters) in a sample of low-income volunteers ($p = 0.0002$). Several studies also suggest that children incapable of sensing PROP

Table 1 Articles included in the present review

Topic	Authors	Results
Bitterness perception, obesity and anthropometric variables	Martinez-Cordero et al. 2015 [15]	No correlations between bitterness perception and anthropometric variables, energy consumption or hormone levels
	Nasser et al. 2001 [16]	No difference between normal-weight and obese subjects regarding the perception of the four basic tastes
	Garcia-Burgos et al. 2013 [13]	Evidence of high levels of facial expression for bitterness in patients with a high BMI
	Lumeng et al. 2008 [17]	Six-point higher BMI percentile among taster subjects than among those unable to perceive bitterness (non-tasters) in a sample of low income volunteers
	Keller et al. 2016 [18]	Children incapable of sensing PROP (non-tasters) prefer and ingest dietary fat and are more propense to obesity
	Choi S. et al. 2015 [19]	Subjects with a better perception of bitterness had a lower BMI and a lower energy consumption and lipid intake
	Avau et al. 2015 [21]	The nutrient chemosignalling of receptors located in the gustatory papillae and intestine (TAS2R, bitterness related), appeared to be a major precursor of obesity
	Simchen et al. 2006 [5]	Suggested that the sensitivity to bitterness is related to body weight and age. On the other hand, overweight subjects older than 65 years were more sensitive to bitterness
	Tepper et al. 2014 [22]	Inverse correlation between perception of PROP bitterness and energy consumption and/or BMI
	Goldstein et al. 2007 [23]	In pre-adolescent children, current energy intakes were negatively related to children's PROP status and positively related to maternal disinhibition
	Shafaie et al. 2013 [24]	Non-taster and medium taster women consume more daily energy than do supertaster women when eating in a buffet setting, which is a common type of dietary exposure
	Tepper 2002 [25]	The inverse association between PROP status and BMI reported earlier in men is also present in women and that this relationship becomes apparent when variables relevant to eating behavior in women are taken into consideration
	Drewnoswski et al. 2007 [26]	PROP responsiveness was not associated with diets lower in sugar and fat, more favorable plasma lipid profiles, or with lower body mass indexes
	Duffy et al. 2000. [27]	The association between genetic taste measures and acceptance of sweet and high-fat groups differed in women and men
	Baranowski et al. 2011 [28]	Sensitivity to the taste of 6-n-propylthiouracil was not related to intake of cruciferous vegetables
	O'Brien et al. 2013 [29]	Bitterness perception, as measured by TAS2R38 genotype or PROP taster status, does not appear to exert a significant effect on patterns of dietary intakes
	Johnston et al. 1966 [30]	Taster subjects might be taller than non-tasters
Bitterness perception and other diseases	Orsmark-Pietras et al. 2013 [34]	Significant correlations between expression of TAS2Rs and clinical markers of asthma severity were found in both adults and children
	Deshpande et al. 2010 [35]	Inhaled bitter tastants decreased airway obstruction in a mouse model of asthma
	Alves et al. 2011 [36]	Individuals that suffer stoke had difficulty in the perception of bitterness and sourness
	Cecchini et al. 2014 [37]	They found correlation between olfactory and taste performances in Parkinson's disease
	Nolano et al. 2008 [38]	Patients with Parkinson's and other cortical neurodegenerative diseases showed a decrease of olfactory and gustatory function compared to healthy subjects
	Reiter et al. 2006 [39]	Hepatic and renal (systemic) diseases can affect the function of chemoreceptors
	Doty et at. 1994 [40]	Cancer treatment can also directly impair the chemosensory processes, thus impairing stimulus transport (e.g., reducing mucus secretion) and modifying transduction mechanisms

Table 1 Articles included in the present review *(Continued)*

Topic	Authors	Results
Bitterness perception and age	Glendinning, 1994 [41]	Bitter taste thresholds varied independently of toxicity thresholds, indicating that the bitter rejection response is just as likely to be elicited by a harmless bitter food as it is by a harmful one
	Correa et al. 2013 [42]	Children up to 8 years of age showed a larger number of fungiform gustatory papillae than adults
	Doty et al. 2009 [43]	Women have better sensory perception than men, especially regarding the perception of bitterness
	Mennella et al. 2010 [46]	Age modifies the genotype–phenotype relationship for the TAS2R38 bitterness receptor rendering the palate less sensitive to this taste along the years
Bitterness perception and sex	Padiglia et al. 2010 [47]	Differences in palate between genders is specifically due to hormonal influences on the salivary components
	Khataan et al. 2009 [48]	Differences between palates appear to be mainly due to hormonal differences rather than to genetic identity
	Duffy et al. 1998 [49]	Bitterness perception is also affected by pregnancy, when the palate becomes more sensitive
	Melis et al. 2013 [50]	Not find any difference between genders, mainly regarding the quantitation of gustatory papillae located on the tongue
Bitterness perception and genetics	Boxer et al. 2015 [52]	Evidence that bitter taste sensitivity to PROP exists as a broad range, and not exclusively as non-tasters, medium tasters, and supertasters
	Hayes et al. 2011 [53]	TAS2R3, TAS2R4 and TAS2R5 receptors explain some variability in the perception of coffee bitterness
	Joseph et al. 2016 [54]	Inborn differences in bitter sensitivity may affect childhood dietary sugar intake with long-term health consequences
	Mennella et al. 2005 [55]	Variations in a taste receptor gene accounted for a major portion of individual differences in PROP bitterness perception in both children and adults
	Connors et al. 2001 [57]	Examined the ways that people managed values in making food choices in various contexts
	Hwang et al. 2016 [58]	An overlap of genetic variance between perceptions of sweetness and bitterness from a variety of stimuli, which includes PROP when considering the TAS2R38 diplotype
	Risso et al. 2016 [59]	Individuals with higher bitterness perception would be protected against smoking due to intolerance to the bitter taste of tobacco
Bitterness perception and ethnicity	Rozin et al. 2006 [61]	Cultural characteristics are supposed to be determinants of food preference

(non-tasters) prefer and ingest dietary fat and are more propense to obesity [18]. Choi et al. [19], using PROP or chili pepper in the test, reported that subjects with a better perception of bitterness had a lower BMI and a lower energy consumption and lipid intake ($p < 0.03$, $p < 0.001$ and $p < 0.001$, respectively). For Tepper et al. [20], tasters may show lower preference for foods with accentuated bitterness and sweet and spicy taste, and for the astringency of alcohol and texture of fats [20].

In a study with animal modeling, Avau et al. [21] observed that the nutrient chemosignalling of receptors located in the gustatory papillae and intestine (TAS2R, bitterness related) appeared to be a major precursor of obesity. Rats with a deficiency in the signaling pathway were less propense to obesity. mRNA expression for TAS2R suggested a direct effect of a bitter agonist on adipocyte metabolism [21].

Other articles investigated associations between bitterness and anthropometric variables, mainly weight, height and BMI. Simchen et al. [5] suggested that the sensitivity to bitterness is related to body weight and age. In subjects younger than 65 years, bitterness perception among overweight individuals (BMI > 28 kg/m^2) was inferior to that reported by subjects of normal weight (BMI < 28 kg/m^2). On the other hand, overweight subjects older than 65 years were more sensitive to bitterness ($p = 0.015$) [5]. Similarly, Tepper et al. [22] suggested an inverse correlation between perception of PROP bitterness and energy consumption and/or BMI [23–25]. However, this same study group highlighted that other factors may have a role in the definition of the affinity for the taste

of PROP, of food perception and food preferences, as well as in diet behavior and body mass [26–29].

Johnston et al. [30] reported that "taster" subjects might be taller than "non-tasters." This finding was attributed to the lower consumption of goitrogenic food by tasters, i.e., of compounds with a bitter taste that preclude thyroid function, essential to the subject's growth. Another study suggests that reduced taste sensitivity to PROP has been associated with preferences for foods with more calories and lower circulating endocannabinoid levels in subjects with normal BMI ($p = 0.00012$) and higher BMI and lower circulating endocannabinoids in subjects with obesity and that were supertasters than in obese non-tasters ($p = 0.023$, $p = 0.003$). Those results might suggest that lower concentration of circulating endocannabinoids should be an adaptative mechanism to counteract excess of fat accumulation and PROP taste sensitivity is associated with food preferences and may determine long-term metabolic changes and body composition [31]. Also, Tomassini et al. [32] showed that taste sensitivity to PROP is associated with endocannabinoid (2-arachidonoylglycerol (2-AG), anandamide (AEA)) plasma levels in normal-weight individuals. They found that AEA and 2-AG have lower concentrations in the plasma of non-tasters than in supertaster subjects (AEA, $p = 0.034$; 2-AG, $p = 0.003$). Also, a more disinhibited eating behavior was found in non-tasters ($p = 0.02$). This behavior may be compensated in part, on lean subjects, by the decrease of peripheral endocannabinoids that downregulate the hunger–energy intake circuitry [32].

No article explored correlations between bitter taste and other anthropometric variables such as the abdominal circumference and body composition of each subject. The evaluation of BMI-only may be biased when the purpose is to assess body adiposity [33, 13], showing that association with other methods is preferable.

Bitterness perception and other diseases

Some diseases were associated with changes in bitterness perception, due to the disease itself or because of the medications necessary for their treatment. Cancer and neurological, hepatic and renal diseases are included. So far, it was thought that bitterness receptors (TAS2R) were located exclusively on the tongue [34]. However, it has been shown that these receptors are present in other organs of the human body, such as the lungs [35]. Therefore, considering that their stimulation would induce bronchodilation, they may be an alternative target for the treatment of asthma [34].

Neurological diseases commonly affect taste perception. For example, a study comparing 36 patients with stroke and 30 control subjects reported that the stroke group had difficulty in the perception of bitterness and sourness [36]. Similarly, patients with Parkinson's and other cortical neurodegenerative diseases showed a decrease of olfactory and gustatory function compared to healthy subjects [37, 38].

Furthermore, hepatic and renal (systemic) diseases can affect the function of chemoreceptors. Such dysfunction may be related to the severity and complications of the disease, the accumulation of toxic metabolites [39], the nutritional status and the effects of medication (angiotensin-converting enzyme inhibitors) [40]. Several pharmaceuticals do not show such clear association depending on the dose used, drug combinations, drug–nutrient interaction and main disease. In general, cancer treatment can also directly impair the chemosensory processes, thus impairing stimulus transport (e.g., reducing mucus secretion) and modifying transduction mechanisms [40].

Bitterness perception and age

Bitterness perception changes with age and is considered to be a protective mechanism against the ingestion of potentially harmful substances [41]. Nevertheless, genetic chemoreceptors that modulate taste perception change along life and when in contact with several stimuli, chronic conditions and environmental influences. Correa et al. [42] observed that children up to 8 years of age showed a larger number of fungiform gustatory papillae than adults ($p = 0.025$) [42, 43]. The National Institutes of Health (NIH) offers a toolset for the assessment of bitterness perception. In their validation study, the LMS was applied to 2557 North-American subjects of English and Spanish descent ranging in age from 12 to 85 years. According to the average rates observed for each age group, the authors concluded that the older the subject's age, the lower the intensity of bitterness perception [42, 43]. Confirming that, Whissell-Buechy et al. [44] found that PTC sensitivity declines at an average rate of 0.027 dilution steps of the solution test per year or 0.272 per decade. In another study, Mennella et al. [45] showed that age modifies the genotype–phenotype relationship for the TAS2R38 bitterness receptor, rendering the palate less sensitive to this taste along the years.

Bitterness perception and gender

Studies showed that perception can be different between men and women, though both have same gene expression about bitterness. According to Doty and Leslie [43], women have better sensory perception than men, especially regarding the perception of bitterness, and have a strong tendency to be supertasters [22, 23]. Also, sexual hormones seem to have some relationship with taste perception. An association between the PTC genotypes and timing of the pubertal period was found. A study showed that taster girls arrived at each stage of

development earlier than non-taster girls ($p = 0.01$). Otherwise, taster boys reached each stage later than non-taster boys ($p = 0.02$) [46]. In addition to the interaction between genotype and environment, a complex association between hormones and chemoreceptor functions has been suggested to exist in women [46]. Padiglia et al. [47] stated that differences in palate between genders are specifically due to hormonal influences on the salivary components [47, 48]. Furthermore, both men and women express the TAS2R38 gene, thus having the same amount of bitterness receptors. Therefore, differences between palates appear to be mainly due to hormonal differences rather than to genetic identity [47, 48]. Bitterness perception is also affected by pregnancy, when the palate becomes more sensitive. Such modification occurs as a protective mechanism, considering that bitterness is mostly recognized as something harmful to the organism [49]. Nevertheless, some authors did not find any difference between genders, mainly regarding the quantitation of gustatory papillae located on the tongue [50].

Bitterness perception and genetics

Human beings have about 25 genes coding for the receptors of bitterness perception expressed by gustatory cells [51]. These receptors constitute a family of proteins called T2R [52]. Several authors have pointed out that single nucleotide polymorphisms (SNP) in the receptors of bitter taste can modify the perception of tastes and diversify the food preferences. Hayes et al. [53] showed that TAS2R3, TAS2R4 and TAS2R5 receptors explain some variability in the perception of coffee bitterness. In their study, the variation of a TAS2R19 polymorphism for orange juice with no sugar was associated with an increase of bitterness perception and a feeling of displeasure. Also, an association was observed between TAS2R16 (SNP) and TAS2R38 and high alcohol consumption [53]. Furthermore, the TAS2R38 receptor appears to be involved in greater sugar addition and in the choice of cereals and beverages with high sugar levels among sensitive children than among those less sensitive to bitterness [54, 55]. In a study with 22 subjects considered tasters, the individual differences in the expression of the TASR38 were examined to test the hypotheses that the abundance of allele-specific gene expression accounts for the variation in human bitter taste perception and dietary intake of bitter-tasting foods. The result was that the expression varied widely and was positively correlated with ratings of bitterness intensity of PROP ($p = 0.007$) and with broccoli juice ($p = 0.004$). The study did not find correlations with the control solutions (carrot juice, $p = 0.47$; NaCl, $p = 0.68$; caffeine, $p = 0.24$; and urea, $p = 0.47$) [56].

Recent studies have claimed that the role of genetics in taste perception would be better elucidated in studies on children, considering that adults are already under a higher cultural influence of the society where they live [57]. A study evaluating sweetness and bitterness perception of eight different compounds in a sample of twin teenagers showed that up to one quarter of the genetic variation in the perception of sweetness is shared by at least half, or more, of the genetic variance in sucrose octa-acetate, quinine and caffeine. And, after adjustment of the TAS2R38 diplotype, 15% of the genetic variation in sweetness perception is also shared with PROP perception, suggesting that the human perception of sweetness and bitterness is linked by shared genes, and the extent of overlap depends on particular taste stimuli [58].

A study that evaluated the genetic variation in the bitter taste TAS2R38 receptor and the smoking behavior showed that the TAS2R38 haplotypes are associated with cigarette smoking in Americans of European descent, but not in the Afro-American population. Also, individuals with higher bitterness perception would be protected against smoking due to intolerance to the bitter taste of tobacco [59]. Furthermore, a group studied different phenotyping and data analysis strategies using TAS2R38-PROP association. The results show that data collection can have an impact on the power to detect chemosensory perception that can be affected by genotypic variation [60].

Despite the large number of publications on this subject, this is an area that needs further investigation since there are still conflicting reports in the literature and data that are beyond our comprehension.

Bitterness perception and ethnicity

Food preference and diet intake are complex phenotypical manifestations influenced by various factors such as social and cultural stimuli, socioeconomic condition, ethnicity and individual characteristics (i.e., body weight, gender and health status) [18], even as Rozin et al. [61] suggested that cultural characteristics are the determinants of food preference, mainly because they affect how food is prepared [13, 17, 61]. In a review of the literature, Keller et al. [18] considered that the sensitivity to the bitter taste of PROP may be a marker of childhood obesity, although only in some populations. Different reports of food consumption were obtained, even when the subjects had similar phenotypes and genotypes.

Choi et al. [19] detected statistically significant differences in the perceived intensity of bitter taste between Afro-Americans, white people, Hispanics and Asians ($p < 0.026$). In the USA, approximately 20 to 25% of the population is estimated to have low sensitivity to the bitter taste (non-tasters). Regarding the

ethnic groups of the study sample, 32% of Afro-Americans, 35% of white people, 30% of Hispanics and 18.5% of Asians were classified as non-tasters [19]. Whissell-Buechy et al. compared the results of a PTC sensitivity test (tasters and non-tasters frequencies) in a three-generational longitudinal study from Berkeley, California and London. As the major result, they found a decrease in frequency of Berkeley non-tasters to about half the frequency found in the London data, when group by group comparisons were made. They concluded that there is a significant difference in phenotypic frequencies [44]. Finally, ethnic differences regarding gender, access to food and socioeconomic status can explain discrepancies in the results of studies of bitterness perception [18].

Conclusion

Eight of the eligible studies evaluated associations between bitterness perception and obesity or BMI. Two of them found no correlations [15, 16]. Among the other six, two showed that the greater the severity of obesity, the greater the perception of bitterness [13, 17], and one found an inverse correlation [22]. Furthermore, it is possible that the association between bitter taste and obesity is affected by age [5] and that children that are incapable of perceiving the PROP taste tend to ingest more dietary fat and to be obese [18]. Finally, one study involving an animal model showed that chemosensory signaling of receptors for the bitter taste elicited by nutrients may be involved in obesity [21]. Since BMI only may not be adequate for an accurate nutritional and medical characterization of obesity, studies that explore and find correlations between abdominal circumference, body composition (i.e., Bioelectrical Impedance Analysis), skinfold and bitterness perception are crucial.

We did not find discrepancies regarding the association between age and bitterness perception. The selected studies indicate that receptors of and sensitivity to bitter taste are reduced along life, resulting in a low tolerance threshold among children [48, 43, 46]. Regarding gender, three articles reported that women are more sensitive to bitter taste also during pregnancy [22, 23, 43], and one did not find differences between genders regarding the number of gustatory papillae [50]. Different genetic expression, mainly of TAS2R38 and changes in the sensitivity to bitterness sensitivity, have been reported, influencing eating behavior and food preference, including alcohol ingestion [52, 53, 62]. Ethnic or cultural differences should always be considered because they appear to be crucial factors for food preference, justifying the discrepant results observed in the selected studies. Furthermore, bitterness perception may be associated with other diseases in addition to obesity, considering the genetic expression of TAS2Rs in distinct parts of the human organism, which appears to trigger pathological processes [34]. Finally, neurological and chronic systemic diseases and the use of medications affect the gustatory ability [39].

Abbreviations

BMI: Body mass index; LMS: Labeled Magnitude Scale; PROP: 6-n-propylthiouracil; SNP: Single nucleotide polymorphisms; T2R: Taste receptor type two family; TAS2R: Taste receptor type two—animals and humans

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Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Authors' contributions

SS, AA and MAS did the search in the databases and participate in the writing of the initial draft; CMML and CFCB evaluated if the articles were eligible or not; SFCC was consulted when CMML and CFCB disagreed during the selection of the articles; JSM critically reviewed the final draft; and JHS and ENI conceived the study, participated in its design and coordination, and helped to draft the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All procedures involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Review Board of our institution (protocol HCRP 924/2015).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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