



# Revista da ASSOCIAÇÃO MÉDICA BRASILEIRA

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## Review article

# Homocysteine: cardiovascular risk factor in children and adolescents?☆

Adriana Amorim De Farias Leal<sup>a,\*</sup>, Ástrid Camêlo Palmeira<sup>a</sup>,  
Gabiella Menezes Almeida De Castro<sup>b</sup>, Mônica Oliveira Da Silva Simões<sup>b</sup>,  
Alessandra Teixeira Ramos<sup>b</sup>, Carla Campos Muniz Medeiros<sup>b</sup>

<sup>a</sup> Post-graduation Program in Public Health, Universidade Estadual da Paraíba, Campina Grande, PB, Brazil

<sup>b</sup> Department of Pharmacy, Universidade Estadual da Paraíba, Campina Grande, PB, Brazil

### ARTICLE INFO

#### Article history:

Received 23 May 2012

Accepted 27 May 2013

Available online 30 October 2013

#### Keywords:

Homocysteine

Cardiovascular diseases

Child

Adolescent

### ABSTRACT

The aim of this study was to identify publications in literature that investigated Homocysteine (He) as a risk factor for CVD among children and adolescents. An active search for information in LILACS, IBECs, Science Direct, Medline and Cochrane Library databases was conducted using the following combination of keywords “homocysteine”, “cardiovascular diseases”, “child” and “adolescent”. Fifteen articles were analyzed showing direct relationship with increasing age (8 studies) and male gender (10 studies), and an inverse relationship with serum vitamins B6, B12 and folate levels. Thus, the results suggest that more research must be carried through in order to determine in a more coherent way the causes of the hiperhomocisteinemia in the pediatric population, guiding for an adequate diet, rich in nutrients necessary to favor the metabolism of the He.

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### Homocisteína: fator de risco cardiovascular em crianças e adolescentes?

#### RESUMO

O objetivo do estudo foi identificar na literatura publicações que investigaram a Homocisteína (He) como um fator de risco para doenças cardiovasculares na faixa etária de crianças e adolescentes. Realizou-se uma busca ativa de informações nas bases de dados LILACS e IBECs, Science Direct, Medline e Biblioteca Cochrane, utilizando-se a combinação dos descritores “homocysteine”, “cardiovascular diseases”, “child” e “adolescent”. Foram analisados 15 artigos, os quais apontaram relação direta dos níveis de He com o sexo masculino (10 estudos) e com o aumento da idade (8 estudos), e uma relação inversa com os níveis séricos das vitaminas B6, B12 e folatos (10 estudos). Sugere-se que sejam realizadas mais

#### Palavras-chave:

Homocisteína

Doenças cardiovasculares

Crianças

Adolescentes

☆ Study conducted at Centro de Obesidade Infantil, Instituto de Saúde Elpidio de Almeida, Campina Grande, PB, Brazil.

\* Corresponding author.

E-mail: [adriana-aaf@uol.com.br](mailto:adriana-aaf@uol.com.br) (A. Amorim De Farias Leal)

pesquisas a fim de determinar de maneira mais coerente as causas da hiperhomocisteinemia na população pediátrica, orientando para uma dieta adequada e rica em nutrientes necessários para favorecer o metabolismo da He.

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## Introduction

Cardiovascular diseases (CVD) are a major public health problem for being the leading cause of death and disability, affecting adults in full productive age, resulting in loss of potential years of life and producing high costs for the public health system.<sup>1</sup>

Some risk factors for the development of CVD are well known, such as age, male gender, dyslipidemia, smoking, systemic hypertension, diabetes mellitus, obesity, sedentary lifestyle and genetic factors or parental history of atherosclerotic diseases.<sup>2</sup> Currently, high levels of plasma homocysteine (hyperhomocysteinemia) have been associated with increased cardiovascular mortality rates, especially in the adult population.<sup>3</sup>

The pathogenesis of the vascular lesion caused by hyperhomocysteinemia (HHe) includes endothelial cell lesion, vascular smooth muscle growth, increased platelet adhesiveness, increased LDL-cholesterol oxidation with deposition on the vascular wall and direct activation of the coagulation cascade.<sup>4</sup>

In this context, interest in homocysteine (He) as a causal risk factor for CVD in childhood was stimulated by the observation that over 50% of children with genetic disorder of homocystinuria died prematurely from vascular diseases, as well as the fact of high levels of He being associated with physiologic and nutritional factors.<sup>5</sup>

Thus, to determine the prevalence of cardiovascular risk factors in early childhood should be a priority among preventive measures, because atherogenesis may precede by many years its clinical manifestations, such as acute myocardial infarction (AMI) and stroke.<sup>6</sup> Therefore, this study is a systematic literature review of publications that have investigated He as a risk factor for CVD in the age group composed of children and adolescents.

## Methods

The study methodology was the active search for information in LILACS and IBECs (Virtual Health Library), Science Direct, Medline and Cochrane Library databases, using the following combination of keywords "homocysteine", "cardiovascular diseases", "child" and "adolescent". There was a query to the DeCS service (Keywords in Health Sciences) of the Virtual Health Library for standardization of keywords used in the search. Studies conducted in the last 15 years were screened (from 1997 to 2011), in Brazil and abroad, without restriction as for the language of publications, in which the assessment of plasma homocysteine concentrations was an independent variable of interest in the analysis of risk for cardiovascular diseases by restricting the age group of children and/or adolescents (0-19 years).

The inclusion criteria were: (1) only original studies, full text available online; (2) samples that included children and adolescents (0-19 years); (3) cross-sectional, case-control and/or cohort studies. Theses/dissertations, review articles, meta-analyses and experimental studies with animal models were excluded. These criteria were used to increase the comparability of findings between studies.

Data were extracted independently by three of the authors. Disagreements were resolved by consensus among authors. The first screening was performed including the following combination of keywords "homocysteine" and "cardiovascular diseases" and "child" and "homocysteine" and "cardiovascular diseases" and "adolescent", in which the authors sought to identify abstracts in duplicate, delete references of abstracts without full article available, literature reviews and dissertations. In a second step, only publications of studies that investigated the topic of interest with samples composed of children and adolescents were selected. In the third step, the references of articles selected were reviewed in order to capture manuscripts not found in the search.

## Results

A total of 678 studies were identified and obtained by the first screening. In the previous analysis, 663 studies were excluded (Fig. 1). After the other two steps of the search strategy adopted, 15 studies were selected, which met the pre-established inclusion and exclusion criteria, and, upon completing their reading, all were included in the final sample of this study.

Table 1 shows the characterization of articles according to the first author's name, country where the study was conducted, publication year, journal name, study type, sample, objectives and main results.

All studies showed He as a dependent variable, whose plasma concentration was compared to folate, vitamin B12 and cobalamin concentrations, and to lipid and glucose profiles, as well as to other demographic and clinical variables and those related to lifestyle (age, gender, BMI, blood pressure, genetic polymorphism and parental history of CVD).

In most studies, boys had total He values higher than girls<sup>8-11,15-17,19-21</sup> with mean values of He for boys ranging from 5.22-13.30  $\mu\text{mol/L}$ , and for girls from 4.84-10.4  $\mu\text{mol/L}$ . Nevertheless, in only one study, no differences were observed between genders in relation to He concentrations.<sup>18</sup>

It is noteworthy that three studies found a strong relationship between serum He levels and parental history of CVD.<sup>7,12,13</sup> It is also interesting that eight studies showed a directly proportional relationship that either increased He levels and increasing age.<sup>9,11,14,16-18,20,21</sup> Eight studies evaluated the association between He and serum folate and vitamin B12 concentrations.<sup>9,10,13,15,17,18,20,21</sup> Only one study evaluated the relationship between He levels and genetic polymorphisms.<sup>18</sup>

**Table 1 – Characteristics of screened studies.**

Study/country/ publication year	Journal	Design	Sample	Objective(s)	Main results
Greenlund KJ/United States/1999 <sup>7</sup>	Circulation Journal	Cross-sectional	1,137 children and adolescents (5-17 years)	To examine the plasma He levels and its association with parental history of CVD.	Elevated He levels have been observed in children with positive parental history of CVD
Osganian SK/United States/1999 <sup>8</sup>	JAMA	Cross-sectional	3,524 adolescents (13-14 years)	To describe the distribution of serum He concentrations among students.	The average He concentration was significantly higher for boys; Serum He was not significantly associated with serum lipids or parental history of CVD; He concentrations were lower in children and increased proportionally with age; In adolescents aged 15 years, He concentrations were higher in boys;
De Laet C/United States/1999 <sup>9</sup>	American Journal of Clinical Nutrition	Cross-sectional	647 children and adolescents (5-19 years)	To establish the He distribution in a total population of healthy students and determine the relationship between He, folate and vitamin B12.	Boys had higher plasma He levels than girls; Plasma He levels were positively associated with body weight and height and to systolic and diastolic blood pressure, but not related to lipid profile;
Shen MH/Taiwan/2002 <sup>10</sup>	Clinical Biochemistry	Cross-sectional	1,235 adolescents (12-15 years)	To examine the association between plasma He levels, folate and vitamin B12, and cardiovascular risk factors among children in Taiwan.	The total He concentrations for boys and girls began to diverge at the age of 10 years and increased in adolescence, and boys showed higher concentrations; – Differences in total He concentrations between ethnic categories were found in the group of girls and were higher in non-Hispanic African American girls;
Must A/United States/2003 <sup>11</sup>	The Journal of Nutrition	Cross-sectional	2,027 children and adolescents (4-19 years)	To describe the total He distribution in a sample of children and adolescents in the U.S., and assess the different He concentrations between gender, age and ethnic categories.	There was association between total He and parental history of stroke and high blood pressure or systolic blood pressure in male adolescents; – There was no significant association between total He and the percentage of glycated hemoglobin A1c in boys and girls;
Gillium RF/United States/2004 <sup>12</sup>	Annals of Epidemiology	Cross-sectional	941 adolescents (12-16 years)	To describe the distribution and assess the association between total He concentration and variables associated with the syndrome of insulin resistance in adolescents.	Children with parental history of CVD had higher serum He levels than those without such history;
Casanueva V/Chile/2003 <sup>13</sup>	Revista Médica del Chile	Case-Control	80 children and adolescents (6-15 years)	To measure serum He, folic acid and vitamin B12 levels in children with and without parental history of CVD.	In both sexes, total He concentrations increased with age; – Plasma folate was considered a dependent predictor of total He
Beynum IM/Holland/2005 <sup>14</sup>	American Journal of Clinical Nutrition	Cross-sectional	234 children and adolescents (0-19 years)	To describe total He and its predictors in Dutch children.	The averages of total He were elevated in both groups and were higher in boys than in girls; – Triglyceride, LDL cholesterol and insulin resistance were higher in overweight adolescents, and HDL cholesterol was higher in the group with normal weight;
Brasileiro RS/Brazil/2005 <sup>15</sup>	Nutrición Hospitalaria	Case-Control	239 adolescents (15-19 years)	To test the hypothesis that overweight adolescents had higher total He concentrations than adolescents with normal weight and explore the association between plasma He levels with folic acid, vitamin B12 and some risk factors for CVD in both groups.	

– Table 1 (Continued)

Study/country/ publication year	Journal	Design	Sample	Objective(s)	Main results
Papandreou D/Greece/2006 <sup>16</sup>	Clinical Nutrition	Cross-sectional	524 children and adolescents (6-15 years)	To investigate the distribution and determinants of total serum He levels in healthy Greek children.	Homocysteine levels were increasing with age and boys showed total He levels higher than girls; – Age and folate levels were the most significant and independent determinants associated with total He;
Papandreou D/Greece/2006 <sup>17</sup>	British Journal of Nutrition	Cross-sectional	520 children and adolescents from 6-15 years of age	To provide a set of specific data for total He levels and determine the relationship between He and folic acid, vitamin B12, age, BMI, blood pressure and diet in a Greek pediatric population.	The highest mean Hct concentration was found in boys; He concentrations were lower in children and increased in proportion to age; There was correlation between He levels and age, serum folate, BMI and systolic blood pressure; He concentrations were significantly influenced by age and folate and cobalamin concentrations; – No differences were observed between genders in relation to He concentrations;
Huemer M/Austria/2006 <sup>18</sup>	Pediatrics Research	Cross-sectional	264 healthy children and adolescents aged from 2-17 years	To investigate total He concentrations and the relationship between He and folate, cobalamin, genetic polymorphisms and other clinical variables.	The prevalence of high He levels was higher in boys than in girls; – The prevalence of high serum lipids was higher in girls than in boys; He concentrations increased progressively with age and were higher in boys than in girls;
Villarreal E/Colombia/2008 <sup>19</sup>	Biomédica	Cross-sectional	600 children aged from 5-14 years	To determine the lipid profile, He and PCR, and identify the relationship between these markers with gender, age and type of school.	
Kerr MA/England/2009 <sup>20</sup>	Pediatrics	Cross-sectional	2,127 youth aged from 4-18 years	To investigate age, gender, and lifestyle factors as determinants of folate, vitamin B12 and He in British children and adolescents and propose reference ranges by age for these biomarkers.	
Akanji AO/Kuwait/2010 <sup>21</sup>	Nutrition, Metabolism & Cardiovascular Diseases	Cross-sectional	774 healthy adolescents (316 boys, 458 girls) aged from 10-19 years	To investigate age, gender and body mass as determinants of folate, vitamin B12 and He levels in Arab adolescents and propose reference ranges by age and gender for these biomarkers.	There was a relationship between age and increased He levels; Boys had significantly higher total He levels;

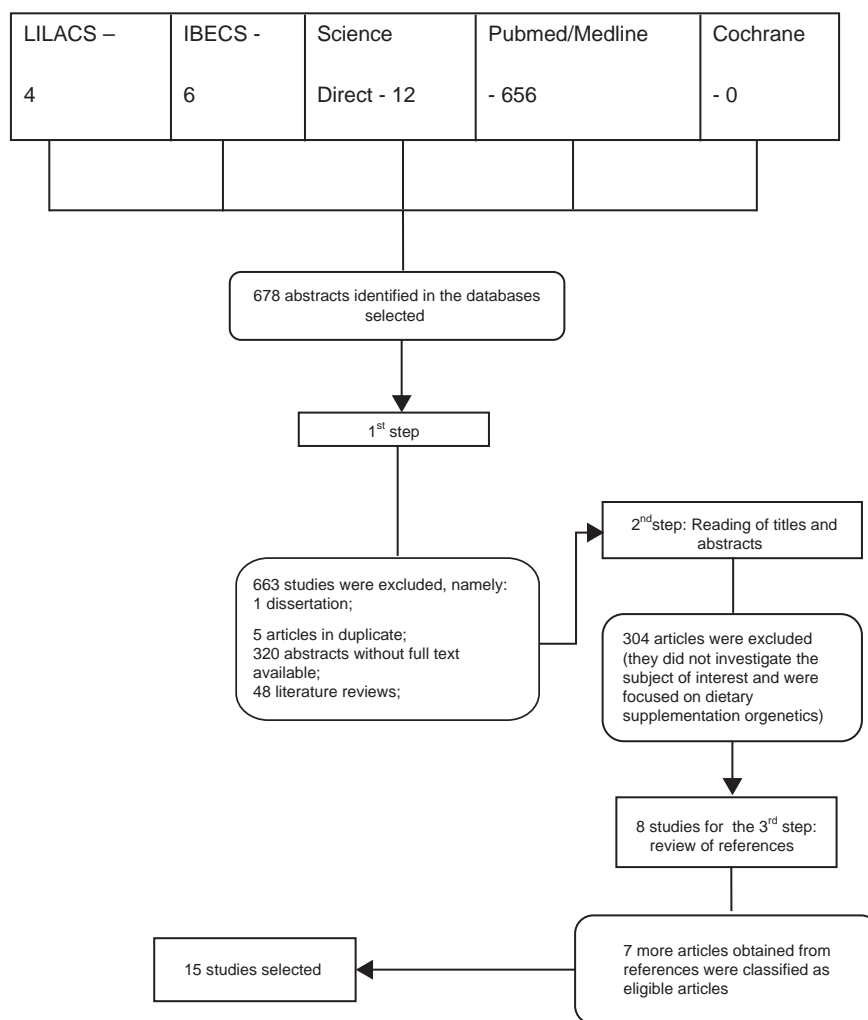


Fig. 1 - Search strategy flowchart.

## Discussion

The aim of this study was to make a literature review on the relationship between He and cardiovascular risk among children and adolescents. Epidemiological studies have shown that HHe is an important risk factor for the development of vascular disease.<sup>22</sup> Noteworthy is the fact that 30-35% of individuals with CVD present normocholesterolemia, but more than 40% of patients with primary disease of the coronary artery, cerebrovascular or peripheral vascular have HHe.<sup>23</sup>

Nevertheless, none of the articles evaluated pointed He as an independent cardiovascular risk factor in children and adolescents. The interest in He as a causal factor began from the observation that over 50% of children with genetic disorder of homocysteinuria died prematurely from vascular diseases.<sup>24</sup> The study by Huemer et al.<sup>18</sup> found a significant association in subjects who had high He concentrations and the MTHFR 677T allele. In adults, genotypes MTHFR 677T and MTHFR 677T/1298C are associated with HHe and CVD.<sup>25</sup>

In addition to genetic disorders, folate and vitamin B12 levels are inversely related to plasma homocysteine concentration.<sup>26</sup> Intracellular He metabolism occurs through

two-way remethylation, which is responsible for the conversion of He into methionine, and a one-way transsulfuration, which converts He into cysteine. In the remethylation process, folate and vitamin B12 act as coenzymes, or co-substrates, and in the transsulfuration process, in turn, vitamin B6 act as coenzyme.<sup>2,27</sup> Accordingly, the studies included in this review assessed He and these substrates, and found an inverse relationship.

Data of this review are in agreement with literature, since He levels were higher in males. The cause for the higher He levels in males may be related to different rates of formation of this amino acid associated with increased creatine synthesis and increased muscle mass found in men. Assessing the differences in the methionine cycle with stable isotopes in men and women, Fukagawa et al.<sup>28</sup> observed that the transmethylation and remethylation rates of homocysteine were higher in women than in men. The authors suggested that the difference between men and women regarding the need and use of remethylation rate would be responsible for the increased remethylation rate observed in women. It is also possible that estrogens would provide reduced homocysteine levels; however, the mechanisms by which estrogens would cause a reduction in homocysteine levels are still unknown.<sup>29,30</sup>

Eight of the 15 studies analyzed showed that the He levels in adolescents (aged over 10 years) were higher than in children. Homocysteine levels increase with age, regardless of gender. This is secondary to the decreased levels of vitamin cofactors, resulting in reduced enzymatic activity in the metabolic pathway or to the coexistence of renal disease.<sup>31</sup> In 1998, the study by Bydlowski et al.<sup>32</sup> reported that children tend to have lower He levels, and these levels tend to increase with age. The decrease in production or in enzymatic activity for the He metabolism, renal dysfunction, or decreased bioavailability of vitamins (B6, B12 and folate), may explain this phenomenon.<sup>27</sup>

In this review, three studies have evaluated the association between He and a positive parental history for CVD, which emphasized the history of stroke and high systolic and/or diastolic blood pressure. This is alarming, considering the strong relationship between He and atherogenic mechanisms, since in all the articles analyzed, He was identified as an independent risk factor for cardiovascular diseases, regardless of age group in the three continents covered by the studies (America, Europe and Asia). A systematic review with meta-analysis on He and cardiovascular risk developed by Humphrey et al.<sup>24</sup> concluded that high He levels may independently and moderately increase by about 20% the risks of developing CVD. In addition, other studies, also using meta-analysis techniques, assessed the benefits of reducing serum He concentrations and found that the decrease of 3-5  $\mu\text{mol/L}$  in serum He levels can reduce the incidence of deep vein thrombosis and stroke.<sup>33,34</sup>

Thus, the study by Brasileiro et al.<sup>15</sup> stands out, whose sample consisted of adolescents with and without excess weight and whose results showed higher He levels in the overweight ones. Therefore, it could be inferred that, despite the pathophysiological mechanisms by which HHe can promote atherothrombosis are not well defined, vascular lesion defined by the action of He includes endothelial cell lesion, vascular smooth muscle growth, increased oxidation of LDL cholesterol with direct deposition on the vascular wall and increased platelet adhesiveness, phenomena also observed in overweight individuals.<sup>35,36</sup>

On the other hand, the findings of this review indicate the need for further studies, correlating He with other variables such as renal function and insulin resistance. Only one article proposed assessing the relationship between He and glycated hemoglobin A1c levels; however, it found no significant association. Nevertheless, it would be necessary to investigate insulin levels which have an inverse relationship with He levels, since insulin contributes to decrease the serum He levels because it stimulates the biosynthesis of the hepatic cystathionine  $\beta$ -synthase enzyme, which is responsible for He degradation in the transsulfuration pathway.<sup>37</sup> Finally, it is also important to evaluate the renal function, since kidneys contain significant amounts of enzymes involved in the transsulfuration and remethylation process, playing an important role in He metabolism and clearance.<sup>38</sup>

## Conclusions

The results of the reviewed articles were quite homogeneous, emphasizing the relationship between high He levels and

increased age and male gender. However, high levels of He were not related to the determination of cardiovascular risk in this population at none of the studies evaluated. Thus, the results of this review suggest that further studies should be conducted, especially in Brazil, since it has high morbidity and mortality rates from cardiovascular causes, especially case-control or cohort studies on the issue proposed, in order to more accurately determine the causes of HHe in the pediatric population.

## Conflicts of interest

The authors declare no conflicts of interest.

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