CESPU
INSTITUTO UNIVERSITÁRIO
DE CIÊNCIAS DA SAÚDE

Efeitos das cardiopatias congénitas no desenvolvimento neurocognitivo de crianças e jovens adultos – revisão sistemática da literatura

Sónia Alexandra Silva Machado

Dissertação de Mestrado em Psicologia da Saúde e Neuropsicologia

Orientação: Prof. Doutora Maria Emília Areias

Gandra, Setembro de 2019

Efeitos das cardiopatias congénitas no desenvolvimento neurocognitivo de crianças e jovens adultos – revisão sistemática da literatura

Sónia Alexandra Silva Machado

Dissertação apresentada no Instituto Universitário de Ciências da Saúde Instituto de Investigação e Formação Avançada em Ciências e Tecnologias da Saúde, para obtenção do grau de Mestre em Psicologia da Saúde e Neuropsicologia, sob orientação da Professora Doutora Maria Emília Areias

Gandra, Setembro de 2019

AGRADECIMENTOS

O meu sincero agradecimento a todos aqueles que amo, que fazem o favor de fazer parte da minha vida e que me apoiam e incentivam nesta aventura que é a vida.

ÍNDICE GERAL

LISTA DE CONTEÚDOS

RESUMO

As cardiopatias congênitas (CHD) têm origem em anomalias no desenvolvimento embriológico ou fetal do coração e nos grandes vasos.[1,2] A prevalência é de cerca de 8 por 1.000 nados vivos.[3]

As CC provocam uma circulação sanguínea fetal irregular, essencialmente no que respeita à distribuição e/ou privação de oxigénio, condição que influencia o bom desenvolvimento cerebral, que poderão ser preditores de anomalias no desenvolvimento neurocognitivo a longo prazo.

Na literatura encontramos alguns consensos e convergências, no que respeita aos domínios neurocognitivos mais afetados pela existência de cardiopatia congénita. A linguagem, as capacidades visuoespaciais, as funções executivas, a atenção, a memória e as funções sensoriomotoras são os domínios cognitivos mais representados nos estudos avaliados e selecionados para este trabalho.

Procuramos neste estudo sistematizar o estado da arte sobre a relação entre cardiopatia congénita e alterações neurocognitivas, analisando as implicações desta patologia no desenvolvimento e identificando os domínios mais afetados e as limitações associadas.

Esta dissertação consiste na realização de um artigo para submissão e publicação subordinado ao tema: Efeitos das cardiopatias congénitas no desenvolvimento neurocognitivo de crianças e jovens adultos.

P**alavras-Chave:** Alterações neurocognitivas; domínios neurocognitivos; cardiopatia congénita; crianças; jovens adultos.

ABSTRACT

Congenital heart diseases (CHD) have their origin in anomalies in the embryological or fetal development of the heart and great vessels.[1,2] The prevalence is about 8 per 1000 neonates.[3]

CHD cause an irregular blood flow in the fetus, especially in the distribution and/or oxygen privation, condition which influences the good cerebral development, which can be long term predictors of abnormalities in the neurocognitive development.

The literature is controversial regarding the neurocognitive domains most affected by the existence of congenital heart disease. In our review the selected studies report language, visuospatial capabilities, executive functions, attention, memory and sensorimotor functions as the most frequent cognitive domains in CHD.

In this stud we aim to identify and understand the relationship between congenital heart disease and neurocognitive changes. With the selected studies, we were able to analyze the implications of this pathology for development and identified the most affected domains and respective limitations in the lives of patients with CHD.

This essay consists in the production of an article for submission and publishing entitled: Effects of congenital heart disease on neurocognitive development of children and young adults.

Key-Words: Neurocognitive effects; neurocognitive domains; congenital heart disease; children; young adults.

PARTE I

Artigo para submissão em revista: ***Effects of congenital heart disease on neurocognitive development of children and young adults - a systematic review.***

Effects of congenital heart disease on neurocognitive development of children and young adults – a systematic review.

Sónia Machado[a,c], Bruno Peixoto[a,e], José Carlos Areias[b], Maria Emília Areias[a,b],

[a] Department of Social and Behavioral Sciences, Instituto Universitário de Ciências da Saúde, CESPU, Paredes, Portugal.

[b] Unidade de Investigação e Desenvolvimento Cardiovascular, Faculty of Medicine, University of Porto, Porto, Portugal.

[c] Instituto de Investigação e Formação Avançada em Ciências e Tecnologias da Saúde, IINFACTS. Paredes, Portugal.

[e] NeuroGen – Center for Health Technology and Services Research, CINTESIS. Porto, Portugal

Correspondence concerning this article should be addressed to Maria Emília Areias, Instituto Universitário de Ciências da Saúde, Rua Central de Gandra, 1317. 4585-116. Gandra (Portugal).Phone:+351-919309766. Email: metega@sapo.pt

Introduction: The main goal of this study was to undertake a systematic review of the literature on the characterization of the neurocognitive effects in children and young adults, with a diagnosis of congenital heart disease.

Methods: Research was done in Pubmed and Cinahl's data base aiming to identify random and controlled studies that tackled this connection. For that effect, there were used the following English keywords: *neurocognitive development; psychological adjustment; congenital heart disease; children and young adults.* A descriptive sum-up was made as well as the quality of all the selected studies for analysis was assessed.

Results: 10 publications were identified with randomized and controlled studies that were related to the objective of this work. The neurocognitive domains of the executive functions of memory and attention are the most mentioned aspects, by the investigators, as well as it was assessed the deficient areas in children, adolescents and young adults, conditions that affect their personal and social development.

Discussion and Conclusion: We can conclude that patients with congenital heart disease, especially those who have severe forms of disease and those that have been submitted to surgical procedures in childhood, present alterations in several cognitive domains, showing worse cognitive performance when compared with healthy children and adolescents. These modifications tend to affect psycho-social development, school performance as well as the growth and social integration. Therefore, future studies should examine if the limitations are sustained in adulthood and if they affect significantly the quality of life of this population.

Key-words: Neurocognitive effects; neurocognitive domains; congenital heart disease; children and young adults.

INTRODUCTION

Congenital heart diseases (CHD) have their origin in anomalies in the embryological or fetal development of the heart and great vessels.[1,2] The prevalence is about 8 per 1000 neonates.[3]

CHD can be classified, according to their severity, in mild, moderate and complex.[4] Mild CHD do not cause major restrictions in the patient's life, in most cases they are asymptomatic and do not require any surgical procedures. Most cases of moderate CHD, patients are symptomatic and may require surgical procedures in order to provide better life expectations and improve life quality. Complex CHD demand frequent medical monitoring and vigilance since these patients suffer major limitations in their everyday life, needing one or multiple surgical procedures. [4,5]

Clinically, CHD can also be classified as cyanotic and acyanotic.

Cyanotic CHD are characterized by low oxygen saturation in the blood.[6] Examples of cyanotic CHD are Tetralogy of Fallot (TOF) and Transposition of the Great Arteries (d-TGA). A surgical procedure after birth is mandatory in d-TGA and in TOF, increasing the chances of survival if it is performed during the first year of life.[7]

In Acyanotic CHD, on the other hand, there is a normal saturation of oxygen in arterial blood.[6] Examples of acyanotic CHD are Atrial Septal Defect (ASD), Ventricular Septal Defect (VSD),[7,8,9] Persistence of Ductus Arteriosus (PDA),[9,10] Aortic Stenosis (AS), Pulmonary Stenosis (PS) [9,10] and Coartation of the Aorta (CoA).[12]

Congenital Heart disease and Neuropsychological development

Congenital heart diseases may cause abnormal foetal blood flow, resulting in deprivation of oxygen and nutrients to the brain. This condition may influence cerebral growth, predicting abnormalities in the neurocognitive development, in the long run.

There is general agreement in literature about which are the cognitive domains that are most affected in congenital heart disease. Most of the selected studies highlight language, spatial-visual abilities, attention, memory, executive and sensory-motor functions as the affected cognitive domains. [5,12,13,14,15]

Most investigations concerning the effects of congenital heart disease on neurocognitive development have been carried out at school or preschool age, as it is difficult to assess

children at an earlier age with structured methodologies, particularly in cognitive domains with later maturation, being an example the executive functions.[14,16]

Several studies refer the presence of global cognitive deficits (attention, executive functions, visuospatial and visual motor abilities, learning disabilities, among others) in patients with CHD, with surgical intervention in early childhood. According to the authors, these disorders lead to school failure, poor social and general adjustment and neurocognitive vulnerabilities in adulthood. [13,16,17,18,19,20,21]

Bearing in mind the premise that CHD are complex pathologies associated with neurocognitive changes, a holistic and multidimensional view of health (physical, mental and social well-being) should increasingly be considered .[22]

Thus, this systematic review aimed to present the current state of scientific knowledge about the most prevalent neurocognitive disorders in children, adolescents and young adults with congenital heart diseases.

METHODS

We conducted this systematic review according to *Preferred Reporting Items for Systematic Review and Meta-Analysis'* declaration [24], and accordingly it is not an update of a previous review.

The research was performed using the PubMed and Cinahl's databases, and the following key-words: neurocognitive development* AND psychological adjustment* AND congenital heart disease* AND children* OR young* OR adult*.

We considered the following inclusion criteria: controlled and randomized studies that studied neurocognitive changes in children and young adults with a diagnosis of CHD, considered only full-text studies, dated 2005 onwards and written in Portuguese, Spanish or English.

We considered the following exclusion criteria: studies that do not conform to respect inclusion criteria, studies with animals and those that involve systematic reviews or meta- analyses.

The researchers reviewed all the titles and abstracts with the intent of erasing the duplicates and assess their relevancy, taking into consideration the defined criteria of inclusion and exclusion. A third reviewer was consulted whenever ambiguity was found, to decide on dissident cases in the selection of articles, as recommended of *Crochrane Collaboration`s recommendations.* [24]

Data were collected, verified and analyzed for their relevance, using a pre-developed table (Table 1), with extraction of the baseline characteristics of the studies in order to form descriptive summaries.

RESULTS

Based on this research strategy, we identified 43 articles, and performed a descriptive summary to assess their quality for inclusion in the analysis. Then, 24 articles were considered for reading and 14 were excluded (8 [25,26,27,28,29,30,31,32] because they were not related to the objective of this study, 5 [33,34,35,36,37] because the type of study was not consistent to the inclusion criteria and 1[38] because the article is written in Italian). Finally, 10[19,21,39,40,41,42,43,44,45,46] were selected.

Throughout the research, we decided to include two other articles[47,48] because we consider their analysis important to the interpretation of previous results, despite not stemming from the search with the keywords.

Then, 10 controlled and randomized studies, published between 2006 and 2018, were analysed. The details of the research are summarized in the flow diagram (Fig. 1).

<Figure 1>

The characteristics of the studies are shown in tables 1, 2 and 3. We did not perform a quantitative analysis of the data, as we considered that they were not sufficiently homogeneous.

In respect to the samples' characteristics, the majority of the studies present similar contexts, concerning age, gender, family-social situation and parent's academic studies. In six of the selected studies, the sample includes patients, whose ages vary from 9 to 16 years old. In the remaining studies, the sample includes children whose ages vary from 4 to 6 years old.

<Table 1>

Regarding the instruments, all studies (n = 10) used intelligence assessment batteries for children and young adults (either subscales of Wechsler Intelligence Scale for Children or subscales of Wechsler Adult Intelligence Scale) to assess the language, memory and attention domains; five evaluated the domains of attention, language and executive functions using a battery of tests devised for this purpose (Developmental Neuropsychological Assessment); five used the Trail Making Test and Stroop Test to evaluate executive functions, more specifically attention and inhibitory control and to evaluate the domains of memory and executive functions, four of the studies used the

Rey-Osterrieth Complex Figure Test. In addition to neurocognitive changes, behavioral assessments were found in three studies using a specific scale for this purpose, the Child Behavior Checklist.

<Table 2>

Analyzing the results of all studies, we can find some consensus regarding the prevailing deficits in cognitive functioning of CHD patients.

In seven studies, authors refer changes in attention abilities, that eventhough sometimes involve mild deficits, may negatively influence school performance, giving rise to a need for special education.[42]

In eight of the studies, changes in memory were found.

A study by Latal et al. showed that CHD patients undergoing cardiopulmonary bypass, compared to healthy children with similar sociodemographic characteristics, show a 10% reduction in hippocampal volume. In an attempt to understand the importance of this brain structure in the functioning of memory and in general intellectual performance, these authors verify a positive and significant association between intellectual performance and the areas of verbal comprehension and working memory, and these deficits tend to endure during adolescence, leading to limitations in adulthood.[45,47,48]

The largest consensus is on changes in executive functioning (n = 10). There are several studies reporting that changes in these abilities seem to condition school performance and social development of these children.[40] In addition, some researchers warn to the likelihood of these children to show behavior problems, aggressiveness, hyperactivity and impulsivity. This condition thus limits future life options.[44]

Difficulties in motor skills, speech, language and social cognition that may be related to neonatal and psychological adjustment variables, are also mentioned in some studies.[46]

<Table 3>

DISCUSSION AND CONCLUSION

Congenital heart diseases have a prevalence of 8 per 1000 to 1 per cent of neonates, and have been studied for long.[3] The increased rate of survival in last decades rendered possible the follow-up of these patients from childhood to adult life, extending the scope of scientific research to understanding the impact of sequelae on different biopsychosocial dimensions.

Therefore, the authors of this study found relevant, at this stage, to perform a systematic review of the literature, in order to gather scientific evidences on neurocognitive changes in CHD, and how they affect development and quality of life of patients.

The literature points to evidence of neurological alterations[16] and cognitive deficits, affecting attention, memory and executive functions, visuo-constructive and visuo-spatial abilities. Some studies show also retardation in expressive language and learning disabilities [11,13,17,18,19]

There is wide consensus on the literature in considering that deficits in executive functioning are good predictors of later neurocognitive development, school performance, social adjustment and quality of life of patients. These factors, altogether with parental overprotection and less exposure to physical activity, limit the potential for development of these children.[39,40,41,42,43,44,46]

Some authors report that prenatal diagnosis of CHD is associated with better outcomes in neuropsychological tests, as it allows early intervention and stimulation, and that a late diagnosis may be considered a risk factor to poor performance in executive function and social cognition, therefore stressing the importance of early diagnosis of CHD to reduce general sequelae of illness later on.[41]

Several studies point out that the individual outcomes of illness are influenced by some neonatal variables and the psychological adjustment of patients.[46,49,50]

In conclusion, the importance of this systematic revision was to enable a wide perspective on scientific evidence about the effects of CHD on neurocognitive performance, and how the later affects development and adjustment of patients along the life cycle.

Despite this main contribution, we must stress that in future it should be considered as a main objective to broaden the scope of the selected data, enabling a meta-analytic study, with deeper understanding of the consequences of these changes on the lives of patients with CHD.

Finally, we believe that future studies should focus on aspects that are relevant for clinicians that deal with the limitations of patients.

REFERENCES

1. Popelová J, Oechslin E, Kaemmerer H et al. Congenital Heart Disease in Adults (1ª Ed.) United Kingdom: Informa Health Care, Ltd.2008
2. Fauci A, Braunwald E, Kasper D et al. Harrison Medicina Interna – 17. Ed. – Rio de Janeiro: McGraw-Hill.2008
3. Schwedle G, Lindinger A, Lange PE, et al. Frequency and spectrum of congenital heart defects among live births in Germany: a study of the Competence Network fo Congenital Heart Defects. Clin Res Cardiol. 2011; 100: 1111-7.
4. Kovacs A, Sears S, Saidi, A. Biopsychological experiences of adults with congenital heart disease: Review of literature. American Heart Journal. 2005; 150 (2), 193-201.
5. Miatton M, De Wolf D, François K et al. Neurocognitive Consequences of Surgically Corrected Congenital Heart Defects: A Review. Neuropsychology Review. 2006; 16:65-85
6. Nousi D, Christou A. Factors affecting the quality of life in children with congenital heart disease. Health Science Journal, 2010; 4: 94 – 100.
7. Brickner M, Hillis L, Lange R. Congenital Heart Disease – Second of Two Parts. The New England Journal of Medicine. 2000; 342 (5), 334-342.
8. Bricner M, Hillis L, Lange R. Congenital Heart Disease – Second of Two Parts. The New England Journal of Medicine. 2000b; 342(5): 334-342.
9. Kasper D, Braunwald E, Fauci A et al. Harrison Medina Interna (16 ed.). Rio de Janeiro: McGraw-Hill Interamericana do Brasil Ltda.2006.
10. Arrend W, Armitage J, Drazen J, et al. Tratado de Medicina Interna/ editado por Golman L., Ausiello; (tradução de Ana Kemper et al.). – Rio de Janeiro: Elsevier. 2005.
11. Gerdes M, Flynn T. Clinical assessment of Neurobehavioral outcomes in infants and children with congenital heart disease. Progress in Pediatric Cardiology. 2010; 29:97-105.
12. Bellinger D, Newburger J. Neuropsychological, Psychological and quality of life outcomes in children and adolescents with congenital heart disease. Progress in Pediatric Cardiology. 2010; 29:87-92.

13. Daliento L, Mapelli D, Volpel B. Measurement of Cognitive Outcome and Quality of Life in Congenital Heart Disease. Heart. 2006; 92:569-574.
14. Bellinger D, Newburger J. Neuropsychological, Psychological and quality of life outcomes in children and adolescents with congenital heart disease. Progress in Pediatric Cardiology. 2010; 29:87-92.
15. Calderon J, Bonnet D, Courtin C et al. Executive function and theory of mind in school-aged children after neonatal corretive cardiac surgery for transposition of great arteries. Development Medicine & Child Neurology. 2010; 52 (12), 1139-1144.
16. Chock V, Reddy V, Bernstein D et al. Neurologic events in neonates treated surgically for congenital heart disease. Journal of Perinatology. 2006; 26: 237-242.
17. Miatton M, De Wolf D, François K et al. Neuropsychological Performance in School- Aged Children with Surgically Corrected Congenital Heart Disease. Journal of Pedriatics. 2007; 151:73-78.
18. Brosig C, Mussatto K, Kuhn E et al. Neurodevelopmental Outcome in Preschool Survivors of Complex Congenital Heart Disease: Implications for Clinical Pratice. Journal of Pediatric Health Care.2007; 21 (1): 3-12.
19. Fuller S, Nord A, Gerdes M et al. Predictors of impaired neurodevelopmental outcomes at one year of age of age after infant cardiac surgery. European Journal of Cardio-Thoracic Surgery.2009; 36: 40-48.
20. Majner A, Limperopoulo C, Shevell M et al. Development and functional Outcomes at school Entry in Children with Congenital Heart Defects. Journal of Pediatrics. 2008; 153:55-60.
21. Murphy L, Compas B, Reeslund K et al. Cognitive and attentional functioning in adolescents and young adults with Tetralogy of Fallot and d-transposition of great arteries. Child Neuropsychol. 2017; 23(1), 99-110.
22. World Health Organization (WHO). WHOQOL: Measuring Quality of Life. Avalilable at https://www.who.int/healthinfo/survey/whoqol-qualityoflife/en/ (accessed 01 Setember 2019).
23. Moher D, Liberati A, Telzlaff J et al. The Prisma Group (2009). Preferred Reporting Items for Systematic Review and Meta-Analyses: The PRISMA Statement.PLoSMed6(7):e1000097.https://doi.org/10.1371/journal.pmed1000097

24. Cochrane Handbook for Systematic Reviews of Interventions. Avalilable at https://training.cochrane.org/handbook (accessed 01 Setember 2019).
25. Sterken C, Lemiere J, Van den Berghe G et al. Neurocognitive development after pediatric heart surgery. Pediatrics. 2016; 137(6).
26. Wray J, Long T, Radley-Smith R et al. Returning to school after heart or heart-lung transplantatiom: How well do children adjust? Transplantation. 2001; 72: 100-106.
27. Ishibashi N, Jonas R. Anomalies of ventrículo-arterial connections and immature brain development. Word J. Pediatr Congenit Heart Surg. 2016; 7(5): 611-613.
28. Puosi R, Korkman M, Sarajuuri A et al. Neurocognitive Development and behavioral outcome of 2-years-old children with univentricular heart. Journal of the International Neuropsychological Society. 2011; 17: 1094-1103.
29. Loeys B, Chen J, Neptune E et al. A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. Nature genetics. 2005; 37(3): 275-281.
30. Compas B, Jaser S, Reeslund K et al. Neurocognitive deficits in children with chronic health conditions. American Psychologist. 2017; 4: 326-338.
31. Charnay A, Antisdel-Lomaglio J, Zelko F et al. Congenital Central Hypoventilation Syndrome. Neurocognition already reduced in preschool-aged children.CHEST. 2016; 149 (3): 809-815.
32. Birca A, Vakorin V, Porayette P et al. Interplay of brain structure and function in neonatal congenital heart disease. Annals of Clinical and Translation Neurology. 2016; 3(9): 708-722.
33. Char D, Ramamoorthy C, Wise-Faberowski L. Cognitive dysfunction in children with heart desease: the role of anesthesia and sedation. Congenit Heart Dis. 2016; 11: 221-229.
34. Antonini T, Dreyer W, Caudle S. Neurodevelopmental functioning in children being evaluated for heart transplant prior to 2 years of age. Child Neuropsychology. 2016:1-15.
35. Calderon J, Bellinger D. Executive function deficits in congenital heart desease: why is intervention important? Cardiology in the young. 2015; 25: 1238-1246.
36. Donofrio M, Massaro A. Impacto f congenital heart desease on brain development and neurodevelopment outcomes. International Journal of Pediatrics. 2010; 2010:1-13.

37. Marino S, Lipkin P, Newburger J et al. Neurodevelopmental outcomes in children with congenital heart desease: Evaluation and management. American Heart Association. Circulation. 2012; 126: 1143-1172.
38. Amianto F, Beliicanta A, Bergui G et al. Crescere con una malatia cardiac congénita: outcome neurocognitiviti, psicopatologici e qualiatà di vita. Riv Psichiatr. 2013; 48(6): 415-431.
39. McCusker C, Doherty N, Molloy B et al. Determinants of neuropsychological and behavioural outcomes in early childhood survivors of congenital heart desease. Arch Dis Child. 2007; 92:137-141.
40. Calderon J, Bonnet D, Courtin C et al. Executive functions and theory of mind in school-aged children after neonatal corrective cardiac surgery for transposition of great arteries. Developmental Medicine & Child Neurology.2010; 52:1139-1144.
41. Calderon J. Angeart N, Moutier S et al. Impact of prenatal diagnosis on neurocognitive outcomes in children with transposition of great arteries. Journal of Pediatrics. July 2012; 161:94-98.
42. Schaefer C, Rhein M, Knirsch W et al. Neurodevelopmental outcome, psychological adjustment, and quality of life in adolescents with congenital heart disease. Developmental Medicine & Child Neurology. 2013; 55:1143-1149.
43. Matos S, Sarmento S, Moreira S et al. Impacto f fetal development on neurocognitive performance of adolescents with cyanotic and acyanotic congenital heart disease. Congenit Heart Dis. 2014; 9:373-381.
44. Sarrechia I, Miatton M, De Wolf D et al. Neurocognitive development and behaviour in school-aged children after surgery for univentricular or biventricular congenital heart disease. European Journal of Cardio-Thoracic Surgery. 2015; 1-8.
45. Latal B, Patel P, Liamlahi R et al. Hippocampal volume reduction is associated with intellectual functions in adolescents with congenital heart disease. Pediatric Research. 2016; 122: 1-7.
46. Areias M, Peixoto B, Santos I et al. Neurocognitive profiles in adolescents and young adults with congenital heart disease. Rev Port Cardiol. 2018: 1-9.
47. Von Rhein M, Buchmann A, Hagmann C et al. Brain volumes predict neurodevelopment in adelescents after surgery for congenital heart disease. Brain. 2014; 137: 268-276.

48. Von Rhein M, Scheer I, Loennecker T et al. Structural brain lesions in adolescents with congenital heart disease. Journal of Pediatrics. 2011; 158: 984-989.
49. Holst L, Kronborg J, Idorn L et al. Impact of congenital heart surgery on quality of life in children and adolescents with surgical corrected Ventricular Septal Defects, Tetralogy of Fallot, and Transposition of the Great Arteries. Cardiology in the Young, 2019:1-6.
50. Abda A, Bolduc ME, Tsimicalis A et al. Psychossocial Outcomes of children and Adolescents With Severe Congenital Heart Defects: A Systematic Review and Meta-Analysis. Journal of Pediatric Psychology, 2018, 1-15.

Figure.1 – Flux diagram

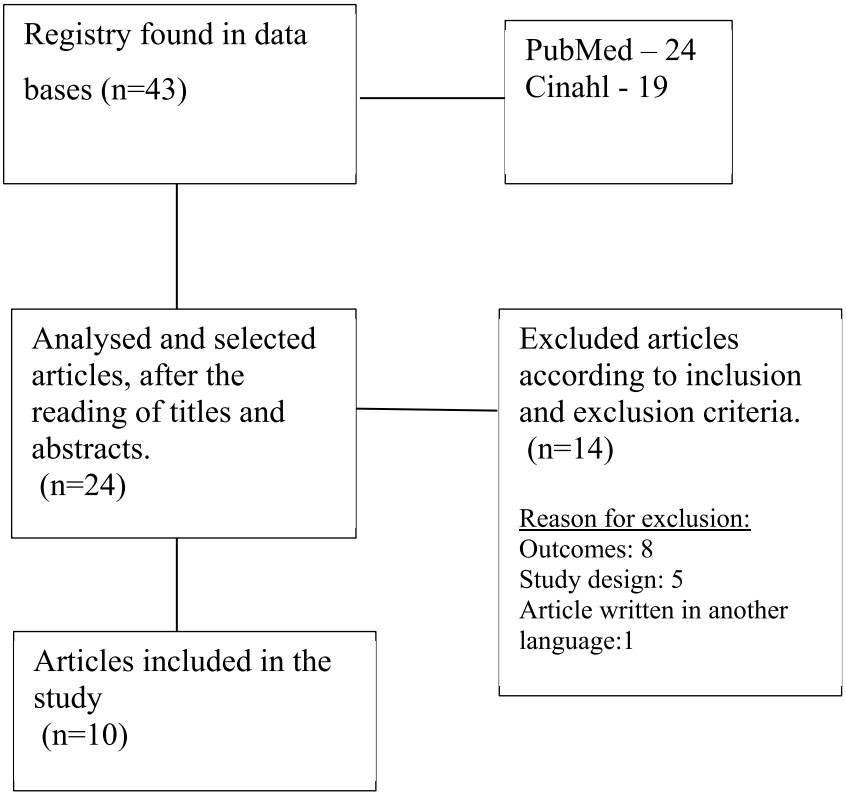

Table 1. Characteristics of included studies in systematic review of congenital heart disease and neurocognitve shifts outcome

Author(s)/ Year	Country	Population/ Sample	Sample selection criteria	Type of study	Total (n)	Instruments	Neurocognitive Shifts	Resultts
McCuster 2006 [39]	UK	Children diagnosed with heart disease, divided into 4 groups according to their clinical condition: 1 - 34 Closed acyanotic; 2 - 25 Open acyanotic; 3 - 19 Cyanotic-corrected condition; 4 - 12 Cyanotic-complex condition; Control groups: 1 -19 Condition of mild and self-correcting heart defect in childhood; 2 - 34 Acyanotic-closed;	Children 4 years old, attending school and undergoing at least 1 invasive surgical procedure, with corrective or palliative purpose;	Cross-sectional	90	NEPSY[d] WPPSI[k] CBCLc Maternal Worry Scale Parenting Focus Control Scale Family Environment Scale Significant Others Scale	All neurocognitive domains.	Patients with congenital heart disease, who undertook heart surgery, present a bigger risk of deficits in their neuropsychological development; have lower outcomes in all neurocognitive domains and alterations in their motor sensorial capacity,that may be connected to social and environmental factors, due to parental overprotection and minor exposure to situations involving physical activity.
Miatton 2007[17]	Belgium	Children with congenital heart disease (21-F; 22-M), divided into 2 groups: 1 - 26 Cyanotic condition; 2 - 17 Acyanotic condition; Control group with healthy children	Ghent University Hospital patients between 1995 and 1999, with birth weight greater than 2000g, no history of prenatal pathology, no other noncardiac malformations or genetic pathology, and who had undergone open heart surgery.	Cross-sectional	43	WISC [j] NEPSY[d]	Attention Sensorimotor domain Language Memory Executive Functions	Patients with congenital heart disease present a deficient neuropsychological profile marked by limitations in motor sensorial and language areas. Studies point out that 25% of children with congenital heart disease show a lower performance, than expected, in motor tasks. The FE and attention domains are also affected, but in a less expressive way.

Table 1. (Continued)

Author(s)/ Year	Country	Population/ Sample	Sample selection criteria	Type of study	Total (n)	Instruments	Neurocognitive Shifts	Resultts
Calderon 2010[40]	France	School age children (14-M; 7-F); Control group 21 children (12-M; 9-F) in the same age group.	Children undergoing corrective heart surgery in the neonatal period between January 2001 and April 2002 at the Necker Pediatric Hospital in Paris, patients diagnosed with intact ventricular septum or ventricular septal defect and who have undergone cardiac surgery using a single life support method, weighing = => 2.5. Kg at birth and not carrying other genetic pathologies and other heart problems.	Cross-sectional (single-center trial)	21	WISC[j] NEPSY[d] Stroop Task Columbia Mental Maturity Scale Corsi block Tapping Task	Sustained Attention Visuospatial capabilities Language Psychomotor development	Patients with congenital heart disease present results within the norm in intelligence tests and moderate deficits in FE domains. However, these executive alterations seem to condition the academic performance and the social development of these children.
Calderon 2012[41]	France	Children with congenital heart disease (67% M; 33% F). Control group: 45 healthy children with similar sociodemographic characteristics.	Children born between 2003 and 2005 in a pediatric hospital in Paris, diagnosed with intact ventricular septum or ventricular septal defect and who underwent cardiac surgery using a single life support method, with birth weight = or> a 2.5kg, not with genetic disorders or other heart problems. Children aged between 4 and 6 at the time of the assessment and whose mother tongue was French.	Prospective (single-center prospective study)	45	WISC[j] NEPSY[d] Columbia Mental Maturity Scale	Language Visuospatial capabilities Executive Functions	The prenatal congenital heart disease is associated to better results in neuropsychological tests. The patients present similar results to the controlled group in most of the cognitive functions, except in cognitive inhibition. The belated diagnosis is the risk factor in FE's performance and social cognition, areas that influence academic performance and social adaptation.

Table 1. (Continued)

Author(s)/ Year	Country	Population/ Sample	Sample selection criteria	Type of study	Total (n)	Instruments	Neurocognitive Shifts	Resultts
Schaefer 2013[42]	Switzerland	Teenagers with CC (34F; 25M) Control group: 40 healthy adolescents (22F; 18M) with a mean age of 13A and 18M	The children studied were selected after analysis of the database of the University Hospital of Zurich. Patients who underwent the first surgery between 1995 and 1998, with an average age at the time of surgery of 11 months. Parents would have to have a good command of the German language and children would be between 6 and 16 years old by the time they were tested. Children without a diagnosis of chromosomal or genetic syndrome and without congenital or acquired neurological disease.	Longitudinal	59	WISC[j] Beery test of visual motor integration FCR[e] ZNAl SDQ[g] KIDSCREEN	Visual perception Neuromotor integration Working Memory Reasoning Executive Functions	Patients with congenital heart disease present worse neurodevelopment performances, being the areas of reasoning, work memory, motor visual integration, visual perception and EF's the most affected, deficits that can last in time and influence academic performance and lead to the implementation of special educational measures.
Matos 2013[43]	Portugal	Children and adolescents with CHD (43M; 34F) Control Group: 16 Healthy Children and Adolescents (11M; 5F)	Participants in this study were selected from the Pediatric Cardiology Service at a Central Hospital in Porto.	cross-sectional (data was collected in a single moment)	77	WISCj FCR[f] Stroop TMT[h]	Divided and selective attention Visual and working memory Executive Functions (Appointment, planning, organization, problem solving, visual-constructive capabilities)	Patients with congenital heart disease present worse neuropsychological performances in all cognitive domains, with a higher prevalence in patients with cyanosis. The heart and fetal condition seems to influence the cerebral development, foretelling a cognitive dysfunction verified in adolescence, which may go on trough all life time.

Table 1. (Continued)

Author(s)/ Year	Country	Population/ Sample	Sample selection criteria	Type of study	Total (n)	Instruments	Neurocognitive Shifts	Resultts
Sarrechia 2015[44]	Belgium	Children evaluated after cardiac surgery, divided into: 1 - 17 Children with UVH (13M; 4F); 2-46 Children with BiVH (19M; 27F). Control group: 17 Healthy children (13M; 4F).	The sample was selected from two centers specialized in cardiac pathology from two Belgian hospitals. Patients undergoing cardiac surgery and with two diagnoses associated with CHD: 1) UVH (HLH / TA) and BiVH (ASD-II / VSD) and aged between 6 and 12 years. Patients with severe genetic disorders, developmental syndromes or mental retardation were excluded from the UVH group. Children with evidence of perinatal problems were excluded from the group of patients with biVH, gestational age less than 37 weeks, birth weight. less than 2000g, have other cardiac malformations, genetic changes or developmental syndrome.	cross-sectional	63	WISC[j] NEPSY[d] CBCL[c]	Attention Fine motor skills Visuospatial Processing Sensoromotor Memory Executive Functions	Patients with congenital heart disease present results within the expected in the intelligence domain, few alterations in attention, motor skills, spatial-visual information processing and memory. Some investigators alert to the presence of behavioural problems, aggressiveness, hyperactivity and impulsivity. This condition predicts the future results in their academic performance and future life.

Table 1. (Continued)

Author(s)/ Year	Country	Population/ Sample	Sample selection criteria	Type of study	Total (n)	Instruments	Neurocognitive Shifts	Resultts
Latal 2016[45,47,48]	Switzerland	Adolescents with CHD who survived cardiopulmonary bypass surgery in childhood, with a mean age of 13A and 8M (21M; 44F), 9 had brain lesions and 34 did not. Control group: 32 Healthy adolescents with similar sociodemographic characteristics..	Participants were selected at the Zurich Pediatric Hospital and had as an eligibility criterion that they underwent cardiopulmonary surgery in childhood, occurring between 1995 and 1998, without genetic changes, under 16 years of age at the time of the evaluation, without cochlear implants or pacemeker.	cross-sectional	48	WISC[j] FCR[f] Beery test of visual motor integration MRI[e]	Memory Language Executive Functions	Patients with previous surgical intervention and cerebral lesion have a 10% smaller and less larger hippocampus than the controlled group. This cerebral structure has significance in the functioning of memory domains and in most intellectual development, which demonstrated a positive and significant association with the results of intellectual performance in domains of verbal comprehension and work memory that according to the authors prevail through time.
Murphy 2017[21]	U.S.A	Children and young adults with CHD with a mean age of 16A (61% F; 39% M); Control group: 18 healthy children and young adults, siblings of children diagnosed with CHD, mean age 16A (56% F; 44% M)	Participants were identified through patient records from a Cardiology Clinic and selected when they went to the health facility for routine consultations. Inclusion criteria were: a) to have a diagnosis of d-TGA or TOF, requiring surgical intervention before 15 years of age; b) between 10 and 29 years old, without genetic, cognitive or developmental alterations. In the control group the same assumptions were considered, except for the clinical condition.	cross-sectional (data were collected using an online questionnaire and testing was performed in a single moment).	18	WISC[j] WAIS[i] CBCL[c] ABCL[a]	Attention Processing speed Visuospatial Processing Reasoning Working memory Executive Functions	Patients with childhood diagnosis of congenital heart disease present neurocognitive alterations identified and studied in infancy, including processing velocity in reasoning and work memory. These alterations predict bad social adaptation and neurocognitive vulnerabilities in adulthood.

Table 1. (Continued)

Author(s)/ Year	Country	Population/ Sample	Sample selection criteria	Type of study	Total (n)	Instruments	Neurocognitive Shifts	Resultts
Areias 2018[46]	Portugal	Patients with CHD (116M; 101F) with a mean age of 15Y. Control group: 80 children and young adults (35M; 45F) with a mean age of 16 Y.	The sample was selected from a public hospital and considered only patients who at the time of the interview were between 12 and 30 years old, who had an educational level that would allow them to answer the questions and who had a complete clinical record. The control group was selected in several schools and universities in the city of Porto and in demographic terms would have to have similar characteristics regarding the age, gender and educational level of the parents.	cross-sectional (data was collected in a single moment)	217	WISC[j] WAIS[i] FCR[f] Stroop Task TMT[h] BADS[b]	All neurocognitive domains.	Patients with congenital heart disease present lower neurocognitive performances in all neurocognitive domains when compared to their reference group. The areas of motor ability, speech, language, executive functions, social cognition and impulsive behavior are the most affected. These performances are connected with neonatal variables and psychological adjustment.

Legenda:

a) Adult Behavior Checklist

b) Behavioural Assessment of the Dysexecutive Syndrome

c) Child Behavior Checklist

d) Developmental neuropsychological assessment

e) Magnetic Resonance Imaging

f) Rey-Osterrieth Complex Figure Test

g) Strengths and Difficulties Questionnaire

h) Trail Making Test

i) Wechsler Adult Intelligence Scale

j) Wechsler Intelligence Scale for Children

k) Wechsler Preschool and Primary Scale of Intelligence

l)Zurich Neuromotor Assessment

Table 2. Instruments used in the included studies

	CBCL	NEPSY	FCR	TMT	WAIS	WISC	Stroop Test	Columbia Mental Maturity	Beery test of visual motor integration	Others*
McCuster 2006 [39]	✓	✓				✓				✓
Miatton 2007 [17]		✓				✓				
Calderon 2010 [40]		✓				✓	✓	✓		✓
Calderon 2012 [41]		✓				✓		✓		✓
Schaefer 2013 [42]			✓			✓			✓	✓
Matos 2013 [43]			✓	✓		✓	✓			✓
Sarrechia 2015 [44]	✓	✓				✓				
Latal 2016 [45,47,48]						✓			✓	✓
Murphy 2017 [21]	✓		✓		✓	✓				
Areias 2018 [46]			✓	✓	✓	✓	✓			✓

***Instruments used only in one studie**: ABCL; BADS; MRI ;SDQ; WPPSI ;ZNA; Maternal Worry Scale; Parenting Focus Control Scale; Family Environment Scale; Significant Others Scale; Corsi Block; Tapping Task; Kidscreen.

Table 3. Neurocognitive domains identified in the included studies

	Attention	Language	Memory	EF	Sensormotor domain	Visuo espacial capabilities	Psychomotor development	Visual perception	All neurocognitive domains
McCuster 2006 [39]									✓
Miatton 2007 [17]	✓	✓	✓	✓	✓				
Calderon 2010 [40]	✓	✓		✓		✓	✓		
Calderon 2012 [41]		✓		✓		✓			
Schaefer 2013 [42]			✓	✓	✓			✓	
Matos 2013 [43]	✓		✓	✓					
Sarrechia 2015 [44]	✓		✓	✓	✓	✓			
Latal 2016 [45,47,48]		✓	✓	✓					
Murphy 2017 [21]	✓		✓	✓	✓	✓			
Areias 2018 [46]									✓

ANEXOS

ANEXO I

Normas para submissão na *Revista Portuguesa de Cardiologia*

Revista Portuguesa de Cardiologia

INTRODUCTION

Revista Portuguesa de Cardiologia, órgão oficial da Sociedade Portuguesa de Cardiologia, foi fundada em 1982 com o objectivo de informar e formar os cardiologistas portugueses através da publicação de artigos científicos na área da arritmologia, cirurgia cardíaca, cuidados intensivos, doença coronária, ecocardiografia, electrofisiologia, hipertensão arterial, insuficiência cardíaca, métodos de imagem entre outros. Trata-se duma revista mensal de elevada qualidade científica e gráfica, publicada em português e em inglês desde 1999 o que permitiu a sua larga projecção no estrangeiro.

Types of article

The Journal accepts the following article types:

- Original Articles reporting clinical or basic research;
- Review Articles (including systematic reviews and meta-analyses) on clinical or basic science topics;
- Case Reports;
- Editorials, which are written at the invitation of the Editor and consist of commentary on articles published in the journal or on subjects of particular importance;
- Letters to the Editor, which consist of concise opinions on recently published articles;
- Images in Cardiology;
- Snapshots;
- Guidelines; and
- Current Perspectives.

Manuscripts submitted for publication should be prepared in accordance with the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" of the International Committee of Medical Journal Editors (ICMJE). This document is available at http://www.icmje.org/recommendations/.

Review Articles and Systematic Reviews

Review Articles should have a maximum of 5000 words, with a total of up to 15 tables and/or figures, and should be structured as follows: Abstract (maximum 250 words; unstructured); 3-10 keywords; Introduction; thematic sections at the discretion of the

authors; Conclusion(s); Acknowledgements, if any; References (up to 100); and figure legends, if any.

Systematic Reviews should be structured as Introduction, Methods, Results, Discussion and Conclusion(s). The subject should be clearly defined. The objective of a systematic review should be to produce an evidence-based conclusion. The Methods should give a clear indication of the literature search strategy, data extraction, grading of evidence and analysis.

Systematic Reviews should not normally exceed 4000 words, with a total of up to 6 tables and/or figures and up to 100 references.

Authors are strongly recommended to consult the PRISMA statement (http://www.prisma-statement.org/), which is intended to help improve the reporting of systematic reviews and meta-analyses.

Current Perspective

This type of manuscript is submitted upon invitation by the Editorial Board. It may cover a broad diversity of themes focusing on cardiology and healthcare: current or emerging problems, management and health policies, history of medicine, society issues and epidemiology, among others. An author who wishes to propose a manuscript in this section is requested to send an abstract to the Editor-in-Chief including the title and Author list for evaluation. The text should not exceed 1200 words, and up to 10 references, two tables or two figures are allowed. An abstract is not required.

Contact details for submission

You can send your manuscript at https://www.evise.com/profile/#/REPC/login

Language

This journal is published in Portuguese and in English language.

The title (and abstract and key words if applicable) must be submitted in both English and Portuguese.

Articles submitted to the Journal should be clearly written in Portuguese (from Portugal) and/or English of a reasonable standard. Text may be edited to maintain linguistic quality and to conform with standard American English.

Submission checklist

You can use this list to carry out a final check of your submission before you send it to the journal for review. Please check the relevant section in this Guide for Authors for more details.

Ensure that the following items are present:

One author has been designated as the corresponding author with contact details:

- E-mail address
- Full postal address

All necessary files have been uploaded:

Manuscript:

- Include keywords
- All figures (include relevant captions)
- All tables (including titles, description, footnotes)
- Ensure all figure and table citations in the text match the files provided
- Indicate clearly if color should be used for any figures in print

Graphical Abstracts / Highlights files (where applicable)

Supplemental files (where applicable)

Further considerations

- Manuscript has been 'spell checked' and 'grammar checked'
- All references mentioned in the Reference List are cited in the text, and vice versa
- **Permission has been obtained for use of copyrighted material from other sources (including the Internet)**
- A competing interests statement is provided, even if the authors have no competing interests to declare
- Journal policies detailed in this guide have been reviewed
- Referee suggestions and contact details provided, based on journal requirements

For further information, visit our Support Center.

BEFORE YOU BEGIN

Ethics in publishing

Please see our information pages on Ethics in publishing and Ethical guidelines for journal publication.

Human and animal rights

If the work involves the use of human subjects, the author should ensure that the work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.Â The privacy rights of human subjects must always be observed. A statement must be included to the effect that the study was conducted in accordance with the

amendedÂ Declaration of Helsinki, that the local institutional review board or independent ethics committee approved the protocol, and that written informed consent was obtained from all patients. The name of the committee, the name of the chairperson of the committee (or the person who approved the protocol), the date of approval and the approval number should follow this statement in the Methods section. For multicenter studies, a list of the relevant approvals may be provided in a separate document to be published as supplementary material.

All animal experiments should comply with the ARRIVE guidelines and should be carried out in accordance with the U.K. Animals (Scientific Procedures) Act, 1986 and associated guidelines, EU Directive 2010/63/EU for animal experiments, or the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978) and the authors should clearly indicate in the manuscript that such guidelines have been followed.

Declaration of interest

All authors must disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding.

Authors must disclose any interests in two places: 1. A summary declaration of interest statement in the title page file (if double-blind) or the manuscript file (if single-blind). If there are no interests to declare then please state this: 'Declarations of interest: none'. This summary statement will be ultimately published if the article is accepted. 2. Detailed disclosures as part of a separate Declaration of Interest form, which forms part of the journal's official records. It is important for potential interests to be declared in both places and that the information matches. More information.

Submission declaration and verification

Submission of an article implies that the work described has not been published previously (except in the form of an abstract or as part of a published lecture or academic thesis, see 'Multiple, redundant or concurrent publication' section of our ethics policy for more information), that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including

electronically without the written consent of the copyright-holder. To verify originality, your article may be checked by the originality detection service Crossref Similarity Check.

Autorship

All authors should have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted, and (4)Â all authors should agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Changes to authorship

Authors are expected to consider carefully the list and order of authors **before** submitting their manuscript and provide the definitive list of authors at the time of the original submission. Any addition, deletion or rearrangement of author names in the authorship list should be made only **before** the manuscript has been accepted and only if approved by the journal Editor. To request such a change, the Editor must receive the following from the **corresponding author**: (a) the reason for the change in author list and (b) written confirmation (e-mail, letter) from all authors that they agree with the addition, removal or rearrangement. In the case of addition or removal of authors, this includes confirmation from the author being added or removed.

Only in exceptional circumstances will the Editor consider the addition, deletion or rearrangement of authors **after** the manuscript has been accepted. While the Editor considers the request, publication of the manuscript will be suspended. If the manuscript has already been published in an online issue, any requests approved by the Editor will result in a corrigendum.

Clinical trial results

In line with the position of the International Committee of Medical Journal Editors, the journal will not consider results posted in the same clinical trials registry in which primary registration resides to be prior publication if the results posted are presented in the form of a brief structured (less than 500 words) abstract or table. However, divulging results in other circumstances (e.g., investors' meetings) is discouraged and may jeopardise consideration of the manuscript. Authors should fully disclose all posting in registries of results of the same or closely related work.

Reporting clinical trials

Randomized controlled trials should be presented according to the CONSORT guidelines. At manuscript submission, authors must provide the CONSORT checklist accompanied by a flow diagram that illustrates the progress of patients through the trial, including recruitment, enrollment, randomization, withdrawal and completion, and a detailed description of the randomization procedure. The CONSORT checklist and template flow diagram are available online.

Registration of clinical trials

Registration in a public trials registry is a condition for publication of clinical trials in this journal in accordance with International Committee of Medical Journal Editorsrecommendations. Trials must register at or before the onset of patient enrolment. The clinical trial registration number should be included at the end of the abstract of the article. A clinical trial is defined as any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects of health outcomes. Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example drugs, surgical procedures, devices, behavioural treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. Purely observational studies (those in which the assignment of the medical intervention is not at the discretion of the investigator) will not require registration.

Copyright

Upon acceptance of an article, authors will be asked to complete a 'Journal Publishing Agreement' (see more information on this). An e-mail will be sent to the corresponding author confirming receipt of the manuscript together with a 'Journal Publishing Agreement' form or a link to the online version of this agreement. Copyright of manuscripts is retained by the Portuguese Society of Cardiology.

Author rights

As an author you (or your employer or institution) have certain rights to reuse your work. More information.

Elsevier supports responsible sharing

Find out how you can share your research published in Elsevier journals.

Role of the funding source

You are requested to identify who provided financial support for the conduct of the research and/or preparation of the article and to briefly describe the role of the sponsor(s), if any, in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. If the funding source(s) had no such involvement then this should be stated.

If no funding has been provided for the research, please include the following sentence:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Funding body agreements and policies

Elsevier has established a number of agreements with funding bodies which allow authors to comply with their funder's open access policies. Some funding bodies will reimburse the author for the Open Access Publication Fee. Details of existing agreements are available online.

Open access

This is an open access journal: all articles will be immediately and permanently free for everyone to read and download.Â Permitted third party (re)use is defined by the following Creative Commons user licenses:

Creative Commons Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)

For non-commercial purposes, lets others distribute and copy the article, and to include in a collective work (such as an anthology), as long as they credit the author(s) and provided they do not alter or modify the article.

No fee is payable by the author as publishing costs are covered by the society.

Elsevier Researcher Academy

Researcher Academy is a free e-learning platform designed to support early and mid-career researchers throughout their research journey. The "Learn" environment at Researcher Academy offers several interactive modules, webinars, downloadable guides and resources to guide you through the process of writing for research and going through peer review. Feel free to use these free resources to improve your submission and navigate the publication process with ease.

Language (usage and editing services)

Please write your text in good American English. Authors who feel their English language manuscript may require editing to eliminate possible grammatical or spelling errors and to conform to correct scientific English may wish to use the English Language Editing serviceavailable from Elsevier's WebShop.

Informed consent and patient details

Studies on patients or volunteers require ethics committee approval and informed consent, which should be documented in the paper. Appropriate consents, permissions and releases must be obtained where an author wishes to include case details or other personal information or images of patients and any other individuals in an Elsevier publication. Written consents must be retained by the author but copies should not be provided to the journal. Only if specifically requested by the journal in exceptional circumstances (for example if a legal issue arises) the author must provide copies of the consents or evidence that such consents have been obtained. For more information, please review the Elsevier Policy on the Use of Images or Personal Information of Patients or other Individuals. Unless you have written permission from the patient (or, where applicable, the next of kin), the personal details of any patient included in any part of the article and in any supplementary materials (including all illustrations and videos) must be removed before submission.

Submission

Our online submission system guides you stepwise through the process of entering your article details and uploading your files. The system converts your article files to a single PDF file used in the peer-review process. Editable files (e.g., Word, LaTeX) are required to typeset your article for final publication. All correspondence, including notification of the Editor's decision and requests for revision, is sent by e-mail.

Submit your article

Please submit your article via https://www.evise.com/profile/#/REPC/login

Referees

Please submit the names and institutional e-mail addresses of several potential referees. For more details, visit our Support site. Note that the editor retains the sole right to decide whether or not the suggested reviewers are used.

PREPARATION

Peer review

This journal operates a rigorous single blind peer review process, in which manuscripts are sent to external reviewers selected from an extensive database. All contributions will be initially assessed by the editor for suitability for the journal. Papers deemed suitable are then typically sent to a minimum of two independent expert reviewers to assess the scientific quality of the paper. The Editor is responsible for the final decision regarding

acceptance or rejection of articles. The Editor's decision is final. More information on types of peer review.

Peer reviewers will respond to the Editor within 30 days recommending acceptance, revision or rejection. The Editor will decide within 10 days whether to accept the manuscript without modification, to send the reviewers' comments to the authors for modification, or to reject it. When modifications are proposed, the authors have 30 days (which can be extended on request) to submit a revised version of the manuscript, incorporating the comments of the reviewers and the Editor. Any amendments should be highlighted in a different colour. The Editor will decide within 10 days whether to accept the new version, reject it, or send it for further review by one or more reviewers.

Letters to the Editor and Editorials will be reviewed by the Editorial Board, but external peer review may also be requested.

Use of word processing software

It is important that the file be saved in the native format of the word processor used. The text should be in single-column format. Keep the layout of the text as simple as possible. Most formatting codes will be removed and replaced on processing the article. In particular, do not use the word processor's options to justify text or to hyphenate words. However, do use bold face, italics, subscripts, superscripts etc. When preparing tables, if you are using a table grid, use only one grid for each individual table and not a grid for each row. If no grid is used, use tabs, not spaces, to align columns. The electronic text should be prepared in a way very similar to that of conventional manuscripts (see also the Guide to Publishing with Elsevier). Note that source files of figures, tables and text graphics will be required whether or not you embed your figures in the text. See also the section on Electronic artwork.

To avoid unnecessary errors you are strongly advised to use the 'spell-check' and 'grammar-check' functions of your word processor.

Article structure

Subdivision

Divide your article into clearly defined sections. Each subsection is given a brief heading. Each heading should appear on its own separate line. Subsections should be used as much as possible when cross-referencing text: refer to the subsection by heading as opposed to simply 'the text'. Use generic names of drugs (first letter: lowercase) whenever possible. Registered trade names (first letter: uppercase) should be marked with the superscript registration symbol ® or ™ when they are first mentioned.

The Journal recommends the guidelines for publication of the EQUATOR network (http://www.equator-network.org), including the CONSORT statement and its extensions for randomized trials (http://www.consort-statement.org/), STROBE for observational (cohort, case-control and cross-sectional) studies (http://www.strobe-statement.org/), STARD for diagnostic accuracy studies (http://www.stard-statement.org/), PRISMA for systematic reviews and meta-analyses (http://www.prisma-statement.org/), SQUIRE for quality improvement studies (http://www.squire-statement.org/) and CARE for case reports (http://www.care-statement.org/). Reporting of the statistical aspects of studies should be in accordance with the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines (http://www.equator-network.org/reporting-guidelines/sampl/).

Introduction

State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results.

Material and methods

Provide sufficient details to allow the work to be reproduced by an independent researcher. Methods that are already published should be summarized, and indicated by a reference. If quoting directly from a previously published method, use quotation marks and also cite the source. Any modifications to existing methods should also be described.

Results

Results should be clear and concise.

Discussion

This should explore the significance of the results of the work, not repeat them. A combined Results and Discussion section is often appropriate. Avoid extensive citations and discussion of published literature.

Conclusions

The main conclusions of the study may be presented in a short Conclusions section, which may stand alone or form a subsection of a Discussion or Results and Discussion section.

Cover letter and Essential title page information

Submission of an article must include a cover letter with the following information:

1. a brief description of the article's significance and/or interest;

2. a declaration of originality, specifying that none of the paper's contents have been published or are under consideration elsewhere;
3. a declaration that all authors have read and approved the manuscript;
4. a full disclosure of any potential conflict of interest for any of the authors;
5. and which manuscript type is being submitted for publication.

Title page must contain the following information:

• ***Title.*** Concise and informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible. Preferably not exceed 12 words. It may also include a subtitle of up to 4 words.

• ***Author names and affiliations.*** Please clearly indicate the given name(s) and family name(s) of each author and check that all names are accurately spelled. You can add your name between parentheses in your own script behind the English transliteration. Present the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lower-case superscript letter immediately after the author's name and in front of the appropriate address. Provide the full postal address of each affiliation, including the country name and, if available, the e-mail address of each author.

• ***Corresponding author.*** Clearly indicate who will handle correspondence at all stages of refereeing and publication, also post-publication. This responsibility includes answering any future queries about Methodology and Materials. **Ensure that the e-mail address is given and that contact details are kept up to date by the corresponding author.**

• ***Present/permanent address.*** If an author has moved since the work described in the article was done, or was visiting at the time, a 'Present address' (or 'Permanent address') may be indicated as a footnote to that author's name. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes.

• ***Word count*** of the manuscript text.

Structured abstract

A structured abstract, by means of appropriate headings, should provide the context or background for the research and should state its purpose, basic procedures (selection of study subjects or laboratory animals, observational and analytical methods), main findings (giving specific effect sizes and their statistical significance, if possible), and

principal conclusions. It should emphasize new and important aspects of the study or observations.

Abstracts for all article types should not contain any references. Abbreviations should be avoided or kept to a minimum.

The headings will consist of: Introduction and Objectives, Methods, Results and Conclusion(s))

Keywords

Immediately after the abstract, provideÂ the keywords, using British spelling and avoiding general and plural terms and multiple concepts (avoid, for example, 'and', 'of'). Be sparing with abbreviations: only abbreviations firmly established in the field may be eligible. Keywords should ideally be selected from the list of MeSH terms available at www.nlm.nih.gov/mesh/. These keywords will be used for indexing purposes.

Abreviaturas

Abbreviations should be used only if the term occurs more than three times. An abbreviated term must be written out in full the first time it appears, followed by the abbreviation in parentheses, and only the abbreviation should be used thereafter. Example: "... acute coronary syndrome (ACS) is ... suffered ACS ... ACS occurs...."

All abbreviations in tables and figures must be accompanied by the full form of the term. Abbreviations should not be used in the abstract, titles, headings or subheadings.

Ensure consistency of abbreviations throughout the article.

Acknowledgements

Collate acknowledgements in a separate section at the end of the article before the references and do not, therefore, include them on the title page, as a footnote to the title or otherwise. List here those individuals who provided help during the research (e.g., providing language help, writing assistance or proof reading the article, etc.)

Units

Follow internationally accepted rules and conventions: use the international system of units (SI). If other units are mentioned, please give their equivalent in SI.

Numbers less than 10 should normally be written as words and numbers 10 and greater should be written as Arabic numerals. A number that begins a sentence should be written as words.

Artwork

Image manipulation

Whilst it is accepted that authors sometimes need to manipulate images for clarity, manipulation for purposes of deception or fraud will be seen as scientific ethical abuse and will be dealt with accordingly. For graphical images, this journal is applying the following policy: no specific feature within an image may be enhanced, obscured, moved, removed, or introduced. Adjustments of brightness, contrast, or color balance are acceptable if and as long as they do not obscure or eliminate any information present in the original. Nonlinear adjustments (e.g. changes to gamma settings) must be disclosed in the figure legend.

Electronic artwork

General points

• Make sure you use uniform lettering and sizing of your original artwork.
• Embed the used fonts if the application provides that option.
• Aim to use the following fonts in your illustrations: Arial, Courier, Times New Roman, Symbol, or use fonts that look similar.
• Relevant details should be indicated using arrows in colours contrasting with the background.
• Number the illustrations according to their sequence in the text.
• Use a logical naming convention for your artwork files.
• Provide captions to illustrations separately.
• Size the illustrations close to the desired dimensions of the published version.
• Submit each illustration as a separate file.

A detailed guide on electronic artwork is available.

You are urged to visit this site; some excerpts from the detailed information are given here.

Formats

If your electronic artwork is created in a Microsoft Office application (Word, PowerPoint, Excel) then please supply 'as is' in the native document format. Regardless of the application used other than Microsoft Office, when your electronic artwork is finalized, please 'Save as' or convert the images to one of the following formats (note the resolution requirements for line drawings, halftones, and line/halftone combinations given below):

EPS (or PDF): Vector drawings, embed all used fonts.

TIFF (or JPEG): Color or grayscale photographs (halftones), keep to a minimum of 300 dpi.

TIFF (or JPEG): Bitmapped (pure black & white pixels) line drawings, keep to a minimum of 1000 dpi.
TIFF (or JPEG): Combinations bitmapped line/half-tone (color or grayscale), keep to a minimum of 500 dpi.
Please do not:
• Supply files that are optimized for screen use (e.g., GIF, BMP, PICT, WPG); these typically have a low number of pixels and limited set of colors;
• Supply files that are too low in resolution;
• Submit graphics that are disproportionately large for the content.

Color artwork

Please make sure that artwork files are in an acceptable format (TIFF (or JPEG), EPS (or PDF) or MS Office files) and with the correct resolution. If, together with your accepted article, you submit usable color figures then, at no additional charge, these figures will appear in color online (e.g., ScienceDirect and other sites) in addition to color reproduction in print. Further information on the preparation of electronic artwork.

Figure captions

Ensure that each illustration has a caption. Supply captions separately, not attached to the figure. A caption should comprise a brief title (**not** on the figure itself) and a description of the illustration. Keep text in the illustrations themselves to a minimum but explain all symbols and abbreviations used written out in full and in alphabetical order. Different panels in a figure should be identified by capital letters (Figure 1A, Figure 2C, Figure 3A and B, etc. in the text and (A), (B), (C-E), etc. in the captions).

Text graphics

Text graphics may be embedded in the text at the appropriate position. See further under Electronic artwork.

Tables

Please submit tables as editable text and not as images. Tables can be placed either next to the relevant text in the article, or on separate page(s) at the end. Number tables consecutively in accordance with their appearance in the text and place any table notes below the table body. Be sparing in the use of tables and ensure that the data presented in them do not duplicate results described elsewhere in the article. Please avoid using vertical rules and shading in table cells.

All abbreviations used in the table must be written out in full, in alphabetical order, in the table legend immediately below the table. Footnotes may be used if necessary,

indicated by superscript lower-case letters ([a], [b], [c] etc.) in the table and in the legend. Asterisks (*, **, *** etc.) may be used to indicate p values only. If a table contains a reference cited in the text, it should be cited with the name of the first author and "et al." followed by the reference number without space (e.g. Millard et al.[9]).

References

Citation in text

Please ensure that every reference cited in the text is also present in the reference list (and vice versa). Any references cited in the abstract must be given in full. Unpublished results and personal communications are not recommended in the reference list, but may be mentioned in the text. If these references are included in the reference list they should follow the standard reference style of the journal and should include a substitution of the publication date with either 'Unpublished results' or 'Personal communication'. Citation of a reference as 'in press' implies that the item has been accepted for publication.

Reference links

Increased discoverability of research and high quality peer review are ensured by online links to the sources cited. In order to allow us to create links to abstracting and indexing services, such as Scopus, CrossRef and PubMed, please ensure that data provided in the references are correct. Please note that incorrect surnames, journal/book titles, publication year and pagination may prevent link creation. When copying references, please be careful as they may already contain errors. Use of the DOI is highly encouraged.

A DOI is guaranteed never to change, so you can use it as a permanent link to any electronic article. An example of a citation using DOI for an article not yet in an issue is: VanDecar J.C., Russo R.M., James D.E., Ambeh W.B., Franke M. (2003). Aseismic continuation of the Lesser Antilles slab beneath northeastern Venezuela. Journal of Geophysical Research, https://doi.org/10.1029/2001JB000884. Please note the format of such citations should be in the same style as all other references in the paper.

Web references

As a minimum, the full URL should be given and the date when the reference was last accessed. Any further information, if known (DOI, author names, dates, reference to a source publication, etc.), should also be given. Web references can be listed separately (e.g., after the reference list) under a different heading if desired, or can be included in the reference list.

Data references

This journal encourages you to cite underlying or relevant datasets in your manuscript by citing them in your text and including a data reference in your Reference List. Data references should include the following elements: author name(s), dataset title, data repository, version (where available), year, and global persistent identifier. Add [dataset] immediately before the reference so we can properly identify it as a data reference. This identifier will not appear in your published article.

References in a special issue

Please ensure that the words 'this issue' are added to any references in the list (and any citations in the text) to other articles in the same Special Issue.

Reference style

Text: Indicate references by superscript numbers in the text. The actual authors can be referred to, but the reference number(s) must always be given.

List: Number the references in the list in the order in which they appear in the text.

Examples:

Reference to a journal publication:

17. Sousa PJ, Gonçalves PA, Marques H, et al. Radiação na AngioTC cardíaca: preditores de maior dose utilizada e sua redução ao longo do tempo. Rev Port Cardiol. 2010;**29**:1655-65.

Reference to a journal publication with an article number:

2. Van der Geer J, Hanraads JAJ, Lupton RA. The art of writing a scientific article. *Heliyon*. 2018;**19**:e00205. https://doi.org/10.1016/j.heliyon.2018.e00205.

Reference to a book:

30. Cohn PF. Silent myocardial ischemia and infarction. 3rd ed. New York: Mansel Dekker; 1993.

Reference to a chapter in an edited book:

23. Nabel EG, Nabel GJ. Gene therapy for cardiovascular disease. In: Haber E, editor. Molecular cardiovascular medicine. New York: Scientific American;1995.p.79-96.

Reference to a website:

12. Portuguese Registry on Acute Coronary Syndromes (ProACS). Available at: http://www.clinicaltrials.gov/identifier NCT01642329 [accessed 26 October 2013].

Reference to a dataset:

[dataset] 5. Oguro M, Imahiro S, Saito S, Nakashizuka T. Mortality data for Japanese oak wilt disease and surrounding forest compositions, Mendeley Data, v1;

2015. https://doi.org/10.17632/xwj98nb39r.1.

Note shortened form for last page number. e.g., 51–9, and that for more than 3 authors the first 6 should be listed followed by 'et al.' For further details you are referred to 'Uniform Requirements for Manuscripts submitted to Biomedical Journals' (J Am Med Assoc 1997;**277**:927–34)(see also Samples of Formatted References).

Journal abbreviations source

Journal names should be abbreviated according to the PubMed list.

Video

Elsevier accepts video material and animation sequences to support and enhance your scientific research. Authors who have video or animation files that they wish to submit with their article are strongly encouraged to include links to these within the body of the article. This can be done in the same way as a figure or table by referring to the video or animation content and noting in the body text where it should be placed. All submitted files should be properly labeled so that they directly relate to the video file's content. In order to ensure that your video or animation material is directly usable, please provide the file in one of our recommended file formats with a preferred maximum size of 150 MB per file, 1 GB in total. Video and animation files supplied will be published online in the electronic version of your article in Elsevier Web products, including ScienceDirect. Please supply 'stills' with your files: you can choose any frame from the video or animation or make a separate image. These will be used instead of standard icons and will personalize the link to your video data. For more detailed instructions please visit our video instruction pages. Note: since video and animation cannot be embedded in the print version of the journal, please provide text for both the electronic and the print version for the portions of the article that refer to this content.

Supplementary material

Supplementary material such as applications, images and sound clips, can be published with your article to enhance it. Submitted supplementary items are published exactly as they are received (Excel or PowerPoint files will appear as such online). Please submit your material together with the article and supply a concise, descriptive caption for each supplementary file. If you wish to make changes to supplementary material during any stage of the process, please make sure to provide an updated file. Do not annotate any corrections on a previous version. Please switch off the 'Track Changes' option in Microsoft Office files as these will appear in the published version.

Data deposit and linking

Elsevier encourages and supports authors to share raw data sets underpinning their research publication where appropriate and enables interlinking of articles and data. More information on depositing, sharing and using research data.

AFTER ACCEPTANCE

Proofs

One set of page proofs (as PDF files) will be sent by e-mail to the corresponding author (if we do not have an e-mail address then paper proofs will be sent by post) or, a link will be provided in the e-mail so that authors can download the files themselves. Elsevier now provides authors with PDF proofs which can be annotated; for this you will need to download the free Adobe Reader, version 9 (or higher). Instructions on how to annotate PDF files will accompany the proofs (also given online). The exact system requirements are given at the Adobe site.

If you do not wish to use the PDF annotations function, you may list the corrections (including replies to the Query Form) and return them to Elsevier in an e-mail. Please list your corrections quoting line number. If, for any reason, this is not possible, then mark the corrections and any other comments (including replies to the Query Form) on a printout of your proof and scan the pages and return via e-mail. Please use this proof only for checking the typesetting, editing, completeness and correctness of the text, tables and figures. Significant changes to the article as accepted for publication will only be considered at this stage with permission from the Editor. We will do everything possible to get your article published quickly and accurately. It is important to ensure that all corrections are sent back to us in one communication: please check carefully before replying, as inclusion of any subsequent corrections cannot be guaranteed. Proofreading is solely your responsibility.

Offprints

The corresponding author will be notified and receive a link to the published version of the open access article on ScienceDirect. This link is in the form of an article DOI link which can be shared via email and social networks. For an extra charge, paper offprints can be ordered via the offprint order form which is sent once the article is accepted for publication. Both corresponding and co-authors may order offprints at any time via Elsevier's Webshop. Authors requiring printed copies of multiple articles may use Elsevier Webshop's 'Create Your Own Book' service to collate multiple articles within a single cover.

AUTHOR INQUIRIES

Visit the Elsevier Support Center to find the answers you need. Here you will find everything from Frequently Asked Questions to ways to get in touch.

You can also check the status of your submitted article or find out when your accepted article will be published.