EJM
Erasmus Journal of Medicine

February 2018 • vol 7 - no 1

Erasmus Journal of Medicine: independent scientific journal

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Colophon

The Erasmus Journal of Medicine (EJM) is a scientific magazine by and for students, especially students of Erasmus MC University Medical Center Rotterdam. It was initiated by the MFVR (the medical students' organization of Erasmus MC). We strive to release the journal twice a year. It is published on paper (1250 copies) and on the EJM website (www.erasmusjournalofmedicine.nl).

The main purpose EJM is to encourage medical and research master students to conduct research (empirical studies or systematic reviews), report on this research, and become acquainted with the professional publishing process either as authors, reviewers or editors. A secondary purpose is to make the results of excellent student-driven research known to others.

The Journal accepts articles describing original research, systematic reviews, extended abstracts (summaries of recently conducted studies), calls from research projects for students to participate, opinion papers written by students, editorial comments, case reports, clinical lessons, clinical images, and letters to the editor.

The Erasmus Journal of Medicine is funded by Erasmus MC, through an unrestricted grant.

Publisher
Erasmus University Medical Center Rotterdam.

Formatting & Printing
BS Producties, Monnickendam

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Foreword

An Instrument To Familiarize Scientific Research

Medicine is a dynamic field. Medical doctors and specialists cannot simply lean on the knowledge they acquired in the past, but need to keep up with ongoing developments. Observational and experimental research is the major driving force for advanced knowledge. Therefore, medical students should not only learn the state-of-the-art, but also develop the research skills that they need to help move the field forward.

According to this vision, the Erasmus Journal of Medicine was raised as an instrument to familiarize medical students with scientific research. EJM is a journal by and for students: they submit as well as review manuscripts, and they form the core of the editorial board. Medical students are already invited to become involved in EJM activities in the first year of the bachelor phase. Supervision is provided by teachers, senior researchers and MDs.

During the 2017 annual congress of the The Netherlands Association for Medical Education (NVMO), EJM organised a round-table discussion, together with its sister-journal Radboud Annals of Medical Students. The participants, a mixture of students and teachers, were invited to bring forward ideas for the further development of our student journals. We obtained several interesting suggestions to involve a broader group of medical students via (extra-)curricular activities, such as workshops for student-reviewers and -editors, and even the creation of a national network. We will get started with these ideas!

The current issue of EJM addresses various topics, ranging from Postoperative pain management to ACE-inhibitors in paediatric heart failure and Quality of life in patients with psychotic disorders. We trust you will enjoy reading, and be stimulated to contribute to future issues as author, reviewer or editor.

Prof. Hans van Leeuwen, MD PhD
Dean

Prof. Eric Boersma, MSc, PhD, FESC
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Erasmus Journal of Medicine

Editorial comment

Efficacy of ACE inhibitors in pediatric heart failure caused by a congenital heart defect

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Congenital heart defects (CHD) are the most common cause of heart failure in children. The most effective treatment for CHD is surgery. Pharmacotherapy could be useful prior to surgery, furthermore it can be given as treatment for remaining heart failure post-surgery.

The systematic review of Korpershoek et al.1 assesses the evidence for the use of ACE inhibitors in paediatric heart failure. Since ACE inhibitors are an established treatment for adults with heart failure, performing this review appears to be appropriate. Their original aim was to perform a meta-analysis. Because of large differences in methodology of the selected studies performing a meta-analysis appeared to be impossible, and the authors chose to do a systematic review. They found 7 studies, 4 retrospective cohort studies, one case-control study and 2 randomized controlled trials (RCTs). All retrospective cohort studies, as well as one RCT2 found a beneficial effect of ACE inhibitors on the primary outcome criteria for heart failure.

The quality of a systematic review is always limited by the quality of the selected studies. All studies, except one RCT included a small number of patients and the retrospective cohort studies lacked a control group. Furthermore studies different outcome criteria and some studies had a very short follow-up period. Korpershoek et al. conclude, that ACE inhibitors are a potential pharmacotherapy for heart failure in children with CHD, but evidence for the efficacy of ACE-inhibitors is not strong, based on their review.

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Is varicella zoster vaccination truly inefficient?

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Immunosenescence is the term used for the gradual decrease in the efficacy of the immune system as age advances. Not only our brain, but also our immune cells become forgetful and have to be reminded from time to time. One way of reminding the immune system is by vaccination. For varicella zoster, an infection we almost all contract during childhood and responsible at later age for herpes zoster (HZ), vaccination is proven to be successful to prevent HZ in a large number elderly patients.
However, in the current issue of the journal Kwekkeboom argues against herpes zoster vaccination in the elderly based on the fact that vaccination, although effective, is inefficient and therefore not justifiable. A bold statement based mostly on costs. Zostavax, the vaccine used is expensive (€144,54 per vial). To be efficient number needed to treat (NNT) should therefore be low. Kwekkeboom doesn't mention NNT but instead states that costs exceed the limit regarded acceptable for preventive measures (€20,000 per quality adjusted life year). Yet, this limit is highly influenced by emotion. To prevent childhood leukemia, the Dutch government spend 440 million Euro to place 135 km of electronic powerlines below ground; estimated prevented cases of leukemia two per year at most.

Luckily, there is an alternative to vaccination: regular exposure to varicella infected children will also boost the immune system. All we need is larger families.

Essay

Herpes Zoster vaccination in Dutch people aged 50 years and above

An ethical measure?

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Summary

Background: **Use of Zostavax® vaccine might lower the incidence and symptoms of Herpes Zoster (HZ) and its common complication post herpetic neuralgia (PHN). Incidence increases from the age of 50. Therefore vaccination of Dutch people aged over 50 is considered. Is vaccination of this specific group efficient and ethical?**

Ethics and facts: **The seven criteria for the introduction of a vaccine as published by the Health Council of the Netherlands are used. Firstly, the disease is serious and the extent of the burden of disease is substantial. The incidences of HZ and PHN for people aged over 50 respectively are 7-8/1000 person-years and 2,9% and increase as the age increases. The EQ-5D-score for quality of life is 0.59 for HZ and 0.61-0.67 for PHN. Besides the vaccine is effective: in the first five years Zostavax® decreases the incidence of HZ and PHN with 51.3% and 66.5% respectively. Burden of disease in HZ decreases with 61,1% in the first five years. Thirdly, the vaccination is acceptable: Zostavax® does not significantly increase the amount of serious adverse events as compared to placebo injection. However, Zostavax® is not efficient: the costs, €21,716/QALY to €29,664/QALY, exceed the generally accepted limit of 20,000/QALY. Prioritizing goes beyond the scope of this article.**

Conclusion: **Zostavax® is effective and acceptably reduces the incidence and burden of disease in HZ and PHN. Nonetheless it is not efficient in promoting public health. I advise against introduction of HZ vaccination for all Dutch elderly, as long as the criterion of efficiency has not been met, and priority over other vaccines has not been established.**

Introduction

Herpes Zoster (HZ), in popular terms known as shingles, is caused by the Varicella Zoster Virus (VZV). Nearly all Dutch people have been infected with the virus during childhood [1]. Primary infection with VZV causes Varicella Zoster, or chicken pox [2]. After primary infection the virus goes dormant in the dorsal root and cranial nerve ganglia, where it is latently present [3]. If cellular immunity diminishes, for instance consequent to age, immunocompromising disease or medication, the virus might reactivate [2,4,5]. Reactivation manifests as rash and pain in one or more dermatomes and is called shingles [2,3]. A common complication of shingles is post herpetic neuralgia (PHN) [2,6], defined as pain lasting more than three months after diagnosis with HZ [7]. Rarer complications that may occur are encephalitis, myelitis, meningitis, retinitis and cranial or peripheral nerve involvement [8].

The incidence of HZ increases as the age of people increases and is twice as high at the age of 50 as during childhood [9,10]. This might be caused by diminished cellular immunity at older age [2,5]. In order to stimulate cellular immunity against VZV, the life-attenuated vaccine Zostavax® might be of use [11]. In the Netherlands this vaccine is licensed for people aged 50 years and older [12]. Since they are at high risk of being infected, it is considered to offer Herpes Zoster vaccination to all people aged over 50 in the Netherlands. This raises the following questions: is vaccination with Zostavax® of use, safe and effective? And, is vaccination of this specific risk group ethical?

Facts of Herpes Zoster and Zostavax®

In order to answer these questions, first of all it is important to get a clear picture of the need for vaccination; the incidence of and burden of disease due to HZ and PHN should be investigated. In addition, the value of vaccination should be assessed, taking into account the efficacy, adverse events and efficiency of Zostavax®.

Incidence and burden of disease

In the Netherlands the mean incidence of HZ is 3.2 per 1000 person-years [10]. From the age of 50, the incidence raises sharply:[10] 7-8/1000 person-years for people aged 50 years and older and 10-11/1000 person-years for elderly aged over 80 years old [9,10]. When it comes to burden of disease, a study investigated the quality of life in people with HZ using the EQ-5D-score; this score integrates problems due to mobility, self-care, usual activities, pain/discomfort and anxiety/depression.[13] HZ patients reported a mean EQ-5D-score of 0.59 (0= worst health 1= perfect health) [13]. Pain caused by HZ infection lasts for 32.5 days on average [13].

PHN is diagnosed in 2.6% of all HZ patients in the Netherlands

[6]. This percentage increases as the age increases: from 2.9% at the age of 55-64 till 9.0% for patients aged over 75 years old [6]. The pain experienced in PHN negatively influences mood, sleep, enjoyment of life and general activity, and thereby impairs the quality of life; the mean EQ-5D-score for PHN patients is 0.61-0.67 [13,14]. In less than half of the patients treatment results in a pain reduction of 50% or more; the mean NNT in current treatment strategies ranges from 2.1 to 4.8 [15].

Efficacy of Zostavax®

In people aged between 50-59 years old, Zostavax® reduces the incidence of HZ with 75.3% after one and a half years [16]. The vaccine's efficacy has also been studied in people aged over 60. In the first five years after vaccination, the use of Zostavax® significantly decreases the incidence of HZ by 51.3% in this age group. [17-19]. This decrease was significantly more pronounced in people aged between 60-69 than in those aged over 70, 63.9% vs. 37.6% [19]. In the seventh year after vaccination, the vaccine's efficacy to reduce the incidence of HZ falls. [17,20]. After seven years a reduction in incidence of 48.7% is seen [17,18], which falls to 21.1% at eleven years [17,20]. Vaccination reduces the burden of disease due to HZ, defined on the basis of severity and duration of pain, compared to placebo injection with a mean of 61.1% in the first five years after vaccination [17-19]. There was no significant difference in reduction between those aged 60-69 and those aged 70 years and older [19]. After five years the reduction in burden of disease decreased year by year [17,20], resulting in a reduction of 58.6% after seven years [17,18] and 37.3% after eleven years [18,20].
Vaccination with Zostavax® reduces the incidence of PHN with 66.5% after five years [17-19], with 64.9% after seven years [17,18] and with 35.4% after eleven years [17,20]. This reduction was only significant in the first two years [17,20]. The reduction did not significantly differ by age [19].

Safety of Zostavax®

Research has shown there is a larger amount of people with one or more adverse events after HZ vaccination than after placebo injection: RR 1.70 [21] or 73% vs. 42% [16]. This difference, however, mainly concerns adverse events on the site of injection, RR 2.99[21] or 64% vs. 14% [16], as erythema, swelling, pain/tenderness and pruritus [19,22]. Confirmed cases of HZ within 42 days after vaccination were reported significantly fewer in the vaccine group than in the placebo group, <0.1% vs. 0.1%. [23]. The hospitalization rate related to HZ was 0.2% in both groups [23]. Taking into consideration vaccine-related serious adverse events and vaccine-related mortality, research does not show a significant difference between vaccination and placebo groups [21,22].

Efficiency of Zostavax®

The cost-effectiveness of vaccination with Zostavax® has been assessed in two studies. Both studies based their results on implementation of HZ vaccination in the national influenza vaccination programme [24,25]. Van Lier et al. estimates the cost-effectiveness ratio (Incremental cost-effectiveness ratio (ICER)) €21,716/QALY for vaccination at the age of 70 years old and €38,519/QALY at the age of 60 years old [24]. De Boer et al. estimated the ICER at €29,664/QALY for vaccination of people aged 70 and €35,555/QALY for people aged 60 [25].

Ethics of Herpes Zoster vaccination

In order to investigate whether a particular vaccination programme is ethical or not, the Health Council of the Netherlands has published seven criteria (figure 1) [26]. By means of these criteria, I would like to discuss the ethical dilemma of proportionality, the conflict between the principles of beneficence and non-maleficence, when it comes to the implementation of Zostavax® in a vaccination programme for Dutch elderly. Furthermore, the ethical principle of justice and the problem of scarcity will be highlighted.

Figure 1. Seven criteria Health Council of the Netherlands (21)

Seven criteria Health Council of the Netherlands

Seriousness and extent of the disease burden

1 The infectious disease causes considerable disease burden within the population
- The infectious disease is serious for individuals, and:
- The infectious disease affects or has the potential to affect a large number of people.

Effectiveness of the vaccination

2 Vaccination may be expected to considerably reduce the disease burden within the population.
- The vaccine is effective for the prevention of disease or the reduction of symptoms.
- The necessary vaccination rate is attainable (if eradication or the creation of herd immunity is sought).

3 Any adverse reactions associated with vaccination are not sufficient to substantially diminish the public health benefit.

Acceptability of the vaccination

4 The inconvenience or discomfort that an individual may be expected to experience in connection with his/her personal vaccination is not disproportionate in relation to the health benefit for the individual concerned and the population as a whole.

5 The inconvenience or discomfort that an individual may be expected to experience in connection with the vaccination programme as a whole is not disproportionate in relation to the health benefit for the individual concerned and the population as a whole.

Efficiency of the vaccination

6 The ratio between the cost of vaccination and the associated health benefit compares favourably to the cost-benefit ratio associated with other means of reducing the relevant disease burden.

Priority of the vaccination

7 The provision of vaccination may be expected to serve an urgent or potentially urgent public health need.

Seriousness and extent of the disease burden

When we talk about the seriousness and extent of the disease burden we mean the seriousness of the infectious disease for individuals and its potential to affect a larger group of people [26]. In this touchstone, the principle of justice can be found: is there any difference between Dutch elderly and the remainder of the population that justifies offering the vaccine solely to elderly people? In the medical field, groups are distinguished on the basis of medical need. Above-mentioned incidence rates show HZ is a common disease in people aged over 50 and increases by age [9,10]. The quality of life is considerably impaired in HZ patients, with a mean EQ-5D-score of 0.59 and pain that lasts for 32.5 days on average [13]. In addition, the common complication of PHN [6], which cannot be treated well,[15] clearly impacts the quality of life [13,14]. The incidence of PHN also increases as the age increases [6].

Because of the huge increase in incidence from the age of 50 and because of the considerable burden of disease in HZ and PHN, it would be justified to only offer vaccination to elderly people, because they are in greater medical need than the remainder of the population.

Effectiveness

This criterion weighs up the vaccine's effectiveness in reducing the burden of disease in the population and the vaccine's negative effects on public health [26]. This carries us to the principles of beneficence and non-maleficence and how they are balanced, the proportionality. Zostavax® turns out to be an effective vaccine till five years after administration, as is evident from the reduction in HZ and PHN incidence rates and HZ burden of disease rate mentioned above [17-20]. Additionally, till eleven years after vaccination effectiveness can still be seen, though after the first five years this effect reduces year on year [17,20]. Seen from the point of beneficence, implementation of a HZ vaccination programme could be advocated: the possibility of promoting well-being is there and because of that there is a greater moral obligation to do so.

The vaccine might be able to promote well-being. However, what if vaccination meanwhile harms previously healthy people? That would advocate against introduction of the vaccine, since the old principle of non-maleficence would be at stake. The amount of (vaccine-related) serious adverse events, the number of (hospitalized) cases of HZ and the mortality due to vaccination with Zostavax®, though, does not increase compared to placebo injection [21-23]. More adverse events at the site of injection are found (64% vs. 14%) [16,22], but these are not serious adverse events. This means the health benefits are proportionally larger than the harmful health effects, which argues for introduction of the vaccine.

Acceptability

Acceptability is a term used to balance the inconvenience a person experiences due to the vaccination itself and the vaccine programme on the one hand, and the health benefit the person itself and the population in general experiences on the other hand [26]. It has already been stated the beneficial health effects are larger than the harmful health effects. As the incidence of HZ for persons aged over 50 is 7-8/1000 person-years [10], the chance a vaccinated person will experience health benefits is substantial. Therefore, the balance for the individual is reasonable.

Efficiency

With respect to efficiency, the cost-effectiveness of the vaccine compared to other therapies for HZ and PHN should be the subject of inquiry [26]. The fact is there are no other generally accepted measures to prevent HZ and PHN [27,28]. Besides, recent therapies for PHN – a common complication which, as stated above, evidently impairs quality of life - [13,14] are suboptimal [15]. This means the use of Zostavax® as a preventive measure could be justified.

One could object that the maximum acceptable cost used for the implementation of preventive measures is €20,000/QALY [29]. It is estimated that Zostavax® costs €21,716/QALY at the age of 70 years old and €38,519/QALY at the age of 60 years old [24], and thereby more than exceeds this limit. Raising this limit has been suggested [30]. Nonetheless, to date the costs of Zostavax® exceed the limit.

Priority

Finally a comparison should be made between the urgency of introduction of the HZ vaccine and that of other vaccines [26]. We all know there is a certain scarcity of financial resources, and consequently not all technically possible health beneficial measures can be implemented. Thus prioritizing is needed on the basis of urgency and cost-effectiveness. Comparing the different vaccination programmes the Government of the Netherlands considers, like rotavirus vaccination [31], goes beyond the scope of this essay: they should be all tested using the seven criteria, before comparison could be made. However, as has been argued before, it is evident there is considerable need for HZ vaccination.

Conclusion

To my opinion, Zostavax® is a useful, safe and effective vaccine in elderly aged over 50. The health benefits that are achieved outweigh the complaints about the little harm it causes on administration. However, the costs irrefutably exceed the generally accepted limit for efficiency. Besides it is unclear whether there are other vaccines that are more cost-effective and have a higher urgency for introduction into the vaccination programme of the national government. Furthermore, revaccination may be needed, because the vaccine's efficiency declines year on year. This may lead to an even greater expansion of the costs. Because of above-mentioned arguments I would, to date, not advise to offer Herpes Zoster vaccination to all people aged over 50 in the Netherlands. However, offering Zostavax® to specific high risk groups might be efficient and ethical, e.g. patients anticipating immunosuppressive medication; further investigation needs to be done. Lastly, if the Government of the Netherlands decides to raise the limit of the maximum accepted cost for preventive measures and if this vaccination programme turns out to be the most cost-effective and most urgent, I would certainly recommend implementation of this useful, safe and effective vaccine.

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Systematic Review

Evidence for the use of ACE-inhibitors in paediatric heart failure due to a congenital heart defect

A systematic review

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Abstract

Introduction: **Congenital heart defects (CHDs) are the most common cause of paediatric heart failure (HF). The consequences of HF can become serious and life-threatening, so most CHDs need to be corrected with surgery and/or catheter intervention. While waiting for surgery or to treat remaining HF after surgery, pharmacotherapy could be indicated. The objective of this review is to determine whether there is sufficient evidence for the use of angiotensin-converting enzyme inhibitors (ACE-inhibitors) in children with HF due to a CHD.**

Methods: **A search was conducted in Pubmed. The inclusion criteria were: paediatric patients, the patients had HF due to a CHD, and the drug intervention was any ACE-inhibitor or angiotensin receptor blocker (ARB). Reviews, editorials, articles not written in Dutch or English and articles with a follow-up of less than 14 days were excluded. Ventricular function, somatic growth/weight gain, feeding time, amount and route and respiratory rate were selected as primary outcomes.**

Results: **A total of seven articles, two randomized controlled trials (RCTs), four retrospective cohort studies and one retrospective case-control study, were included. The retrospective cohort studies showed favourable effects of ACE-inhibitors on echocardiographic, catheterisation and clinical parameters. One RCT also found effectiveness of ACE-inhibitors in reducing echocardiographic parameters, such as left ventricular hypertrophy and volume overload. The other RCT did not find favourable effects on clinical outcomes, such as somatic growth. In addition, the retrospective case-control study only found limited evidence of ACE-inhibitors on echocardiographic parameters.**

Conclusion: **The studies analysed in this review differ strongly in outcome measures, follow-up and conclusions. Hence, more well controlled RCT's with a longer follow-up period are needed to determine the long-term effects of ACE-inhibitors in children with HF due to a CHD.**

Introduction

Congenital heart defects (CHDs) are a serious cause of mortality and morbidity in paediatric patients. Worldwide approximately one million births with CHDs were reported in 2001 [1]. The birth prevalence has increased substantially in the last century, because of changes in diagnostic and screening methods, the survival of premature infants and the increase in maternal age. Along with the prevalence of CHDs, also the consequences of CHDs will continue to rise [2].

CHDs are the most common cause of paediatric heart failure (HF) [3].Approximately 20% of all patients with a CHD has HF [4]. Paediatric HF may occur at birth, because of fetal disease caused by for example structural abnormalities, and in children of older age (0-18 years) [5]. HF is a complex disease affecting multiple organ systems of the human body. In this review, paediatric HF will be defined as failure of the heart to deliver an adequate amount of blood to the systemic and/or pulmonary circulation, or to receive venous return because of a changed filling pressure. This results in difficulties for the heart, the circulation and the paediatric patient [6]. The consequences of HF can become severe and life-threatening (and can result in hospitalizations) [7]. According to the New York University Paediatric Heart Failure Index (NYU PHFI) the severity of paediatric HF can be assessed by several signs and symptoms. This index is proven to be a reliable and convenient instrument for measuring heart failure severity in children of all ages [8].

The main therapy for CHD is surgery and/or catheter intervention. While waiting for surgery or to treat remaining HF after surgery, pharmacotherapy could be indicated. Nowadays, the pharmacotherapy for children with HF and a CHD differs among physicians, because less research is done in children compared to adults with HF. Guidelines have been published by Kantor et al. (2013) in which recommendations for the medical treatment of children with HF are given [6]. Pharmacological treatment

of acute paediatric HF can include diuretic agents, vasopressin antagonist agents, inotropic agents and vasodilator agents including angiotensin-converting enzyme inhibitors (ACE-inhibitors). Some possibilities for the treatment of chronic HF are β-adrenergic antagonists, aldosterone antagonists, digoxin, ACE-inhibitors and angiotensin receptor blockers (ARBs) [6].
In adults with HF the effects of ACE-inhibitors and ARBs are well established, but the responses in children with HF are quite different [9]. For example, literature states that enalapril does not give hemodynamic improvement and promotion of somatic growth in single ventricle patients compared to adult patients with HF. This may be a result of differences in the activation of the renin-angiotensin-aldosterone system [10]. Regarding the pharmacokinetics of ACE-inhibitors in paediatric HF patients compared to adults, only limited studies can be found. These studies conclude less bioavailability and a shorter duration of action of enalapril in children with HF and that the oral enalapril dose should be calculated on the basis of body surface rather than on bodyweight basis [11,12]. Some retrospective studies have found a favourable effect of ACE-inhibitors on acute hemodynamic markers [13-16], but there is little knowledge about the long-term benefits of ACE-inhibitors in children. Therefore, the objective of this review is to determine whether there is sufficient evidence for the use of ACE-inhibitors in children with HF due to a CHD. This includes both children waiting for surgery and/or a catheter intervention as well as those suffering from remaining HF as a result of residual problems after such interventions.

Methods

Search strategy
This systematic review was implemented according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [17]. A PubMed database search was conducted on 22 September, 2016. We searched for articles that address the effect of ACE-inhibitors/ARBs in children with heart failure as consequence of a congenital heart disease. The exact search we performed was: ("Child"[Mesh] OR "Infant"[Mesh] OR "Infant, Newborn"[Mesh] OR "Adolescent"[Mesh] OR "Child"[tiab] OR "Infant"[tiab] OR "Newborn"[tiab] OR "Adolescent"[tiab]) AND ("Angiotensin-Converting Enzyme Inhibitors"[Mesh] OR "Angiotensin-Converting Enzyme Inhibitors"[tiab] OR "Enalapril"[Mesh] OR "Enalapril"[tiab] OR "Captopril"[Mesh] OR "Captopril"[tiab] OR "Angiotensin Receptor Antagonists"[Mesh] OR "Angiotensin Receptor Antagonists"[tiab] OR "Angiotensin Receptor Blockers"[tiab] OR "Angiotensin II Receptor Antagonists"[tiab] OR "Angiotensin II Receptor Blockers"[tiab]) AND ("Heart"[Mesh] OR "Heart"[tiab]). The term for ACE-inhibitors did not capture all relevant articles. Hence, we added terms for enalapril and captopril, which are most frequently reported in paediatric treatment with ACE-inhibitors [9].

In- and exclusion criteria
To complete our search we used the following inclusion criteria: the study population had to consist of paediatric patients, the patients had to have HF due to a CHD, and the drug intervention had to be any ACE-inhibitor or ARB. Articles were excluded if the follow-up of patients was less than 14 days, if they were reviews or editorials, and if they were written in a language other than English or Dutch.

Study selection
The resulting articles were screened by title and abstract by one reviewer. When titles and abstracts met the inclusion criteria, the full-text articles were assessed for eligibility independently by the two reviewers (BK and KvB). Disagreement in the assessment of the full-text articles was negotiated to achieve an agreement. When disagreement between the two reviewers remained, a third and fourth researcher were asked for advice (WJvG and WAH).

Outcome
The primary outcome measures were selected by using the NYU PHFI. We selected ventricular function, somatic growth/weight gain, respiratory rate and feeding time, amount and route as primary outcomes. The ventricular function was determined with a catheter and /or an echocardiogram.

Data analysis
When applicable and appropriate, meta-analysis and funnel-plots of the data of all articles would be performed.

Results

Overview of the articles
By using our method we found 559 articles in PubMed. After screening of title and abstract, 520 articles were excluded. The remaining 39 articles were assessed for eligibility by reading the full text.
Furthermore, we screened reference lists of reviewed articles and relevant studies to detect other valuable articles, but no relevant articles were found. The addition of the search term for ARBs did not result in any relevant articles for paediatric use, hence only ACE-inhibitors are discussed in this review. Eventually, seven articles met the inclusion criteria and were used in this review. Figure 1 shows the flowchart of the article search.

Study characteristics
Table 1 describes the study characteristics and populations. The studies included, contained two randomized controlled trials (RCTs), four retrospective cohort studies and one retrospective case-control study. Two studies used echocardiographic parameters, such as left ventricular end-diastolic dimension (LVDd) or shortening fraction (SF) as primary outcome measures.[18,19] One study used catheterisation for the measurement of the primary outcomes, for example end-diastolic pressure (EDP) or mean atrial pressure (MAP) [20]. Four studies used clinical features, such as weight gain and respiratory weight [20-23]. The follow-up duration ranged from 14 days to 3.4 years. Only children (age 0-18 years) were investigated in all studies with variation in age between 5 days and 16 years. A total of 341 paediatric patients with HF due to one or more CHDs participated in the studies. The smallest study contained 8 participants and the largest study 230, with a median of 20 participants.
Two studies investigated patients with single ventricle (SV) physiology [21,24] and three studies studied patients with left-to-right shunts (L-R shunts) [20,22,23]. The remaining two studies

Table 1 - Overview of included studies

Author year	Study design	Medication, Dose (mg/kg/d)	Number of Patients (Age Range)	Type of Congenital Heart Disease	Primary outcome measure	Follow-up Time	Results	Conclusions
Yim DLS et al., 2015	Single-centre retrospective cohort study	Enalapril (0.28; range 0.2-0.78) Lisinopril (0.25; 0.17 – 0.37) Captopril (0.94; 0.9 – 0.97)	17 (28-88 months); no controls	SV	Ventricular EDP (mmHg), mean pulmonary artery pressure (mmHg), mean atrial pressure (mmHg)	Median 9.4 months (IQR 7.3-19.1)	Median + IQR: ↓Ventricular EDP: 13 (12-16) to 10 (8-12) (p=0.002) ↓ MPAP: 16 (14-17) to 13 (11-15.5) (p=0.049) ↓ MAP: 12 (10-15) to 9 (7-10.5) (p=0.001)	Reduction in ventricular end-diastolic pressure, pulmonary artery pressure, and mean atrial pressure.
Hsu DT et al., 2010	Multi-centre double-blind randomized placebo-controlled trial	Enalapril (0.31 ± 0.13) Captopril (0.5-1)	115 treated (20.1 ± 8.9 days); 115 placebo (20.7 ± 9.1 days)	SV or unclassified	Weight-for-age z-score at 14 months of age	Until 14 months of age	Mean ± SE: -0.62 ± 0.13 (Enalapril) versus -0.42 ± 0.13 (Placebo) (p=0.28)	No favourable effect of enalapril on somatic growth, clinical outcomes or ventricular function in infants with single-ventricle physiology.
Knirsch W et al., 2010	Single-centre Retrospective case-control study	Enalapril (5-10 mg/m2/day)	12 treated (8.1 ± 4.7 years); 12 controls (6.0 ± 4.7 years)	MVR with an AVSD or MVP	LVEDD (z-score), LVPWD (z-score), IVS (z-score), SF (%)	1 year after start	Mean + SD: LVEDD: 1.73±1.27 (treated) versus -0.05±1.50 (control) LVPWD: -0.12±0.47 versus 0.37± 0.52 IVS:1.70±1.33 versus 0.80 ±1.04 SF: 38±6.1 versus 40 ±8.3	Limited evidence of ACE-inhibitors on improvement of echocardiographic parameters of left ventricular function could be shown.
Scammell AM et al., 1987	Single-centre retrospective cohort study	Captopril (2,47; max. 3.5)	18 (4 – 41 weeks); no controls	L-R shunts	Weight gain (g/day) Respiratory rate (breaths/min) Feeding score*	21 days Adenosine (0.14mg/kg/min)	Weight gain: -7 to +13 (p<0.001). Respiratory rate: 71 (±9) to 61 (±10) (p<0.05). Feeding score: 3.2 (±1.2) to 3.9 (±1.2).	Captopril has a favourable effect on heart failure in infancy when due to volume overload in the presence of a shunt with pulmonary hypertension.

included children suffering from mitral (MVR) or aortic valve regurgitation (AVR).[18,19] Captopril and enalapril were the most common prescribed ACE-inhibitors [18-24]. Lisinopril and cilazapril were prescribed for respectively six and nine patients [18,24]. In three studies, an ACE-inhibitor was the only treatment given [19,21,24]. In the other four studies, some or all patients also received diuretics and/or digoxin, which they were already using before starting with the ACE-inhibitor [18,20,22,23]. However, despite the use of diuretics and/or digoxin, these patients still developed HF.

Study results

Table 1 shows the results and conclusions of the seven studies. Yim et al. (2015), the most recent retrospective cohort study, showed a reduction of 23% in ventricular EDP (13 to 10 mmHg, p=0.002), a reduction of 19% in mean pulmonary artery pressure (16 to 13 mmHg, p=0.049) and a reduction of 25% in MAP (12 to 9 mmHg, p=0.001) in 17 patients with SV physiology without control group after use of enalapril, lisinopril or captopril for a period of 9.4 months (median) [24].

The older retrospective cohort studies used the clinical parameters weight gain, respiratory rate and feeding (route and amount) as primary outcome variables [20,22,23]. All these studies included patients with L-R shunts. Shaw et al. (1988) found a significant gain in weight of 112% (48 to 102 g/week, p<0.02) and a decrease of 12% in respiratory rate (68 to 60 breaths/min, p<0.05) after 20 patients used captopril for four weeks [22]. Scammell et al. (1987) found a significant gain of 186% in weight (-7 to +13 g/week, p<0.001) and a 14% decrease in respiratory rate (71 to 61 breaths/min) as well [23]. These findings suggest an improvement of paediatric HF symptoms in patients with a L-R shunt after using captopril. Scammel et al. also found a significant improvement in feeding score (3.2 to 3.9) in their study population consisting of 18 patients with no control group. The follow-up was 21 days.

Frenneaux et al. (1989) mentioned the advantage of enalapril, namely the once daily regimen in comparison to a three times daily regimen for captopril [20]. The study found a pronounced and sustained clinical improvement in six of the eight patients after two weeks, that was seen in the 9% gain of weight (mean 3.3 to 3.6 kg), the 20% decrease in respiratory rate (66 to 53 breaths/min), the lower amount of patients who needed nasogastric feeding (4 to 2 patients) and an increase of 18% in the mean daily feed volume (135 to 159 ml/kg/day). However, there was

Table 1 - Overview of included studies

Author year	Study design	Medication, Dose (mg/kg/d)	Number of Patients (Age Range)	Type of Congenital Heart Disease	Primary outcome measure	Follow-up Time	Results	Conclusions
Mori Y et al., 2000	Single-centre randomized controlled study	Cilazapril (0.03-0.04) Enalapril (0.15–0.4)	12 treated; 12 controls (0.3 – 16 years)	AVR or MVR, with (A) VSD or TGA	LVDd (z-score), LVDs (z-score), SF (%), PWT (z-score), LV mass (% of normal)	3.4 years	Mean ± SD: LVDd: -0.25 ± 0.33 (ACEi) versus 0.42 ± 0.48 (control) (p=0.0007) LVDs: -0.36 ± 0.49 versus 0.47 ± 0.56 (p=0.0009) SF: 0.03 ± 0.05 versus -0.02 ± 0.05 (p=0.02) PWT: -0.31 ± 0.31 versus 0.47 ± 0.56 (p=0.0004) LV mass: -72 ± 89 versus 37 ± 35 (p=0.0007)	Long-term treatment with ACE inhibitors is effective in reducing not only LV volume overload but also LV hypertrophy in the volume-overloaded heart in growing children.
Frenneaux M et al., 1989	Single-centre retrospective cohort study	Enalapril (0.26; range 0.12-0.43)	8 (4 days – 12 weeks); no controls	L-R shunts	Weight (kg) Respiratory rate (breaths/min) Feeding route (naso-gastric) Feeding amount (ml/kg/day)	14 days	Mean weight: 3.3 to 3.6. Mean respiratory rate: 66 to 53. Route: 4/7 to 2/7. Mean daily feed volume: 135 to 159.	This study suggests that enalapril may offer a new and exciting alternative treatment for severe heart failure in infancy, particularly in patients with large systemic-to-pulmonary shunts.
Shaw NJ et al., 1988	Single-centre retrospective cohort study	Captopril (1.3; range 0.88 – 2.5)	20 (1 – 7 months); no controls	L-R shunt	Weight gain (g/week) Respiratory rate (breaths/min)	4 weeks (weight gain); 3 days after maximum dose had been achieved (respiratory rate)	Weight gain: 48 to 102 (p<0.02). Respiratory rate: 68 to 60 (p<0.05).	The main objective indications of improvement in the control of cardiac failure have been better weight gain and decreased respiratory rate.

* Feeding score: 1 = all nasogastric tube feeds; 2 = all feeds completed by tube; 3 = some feeds completed by tube; 4 = "slow" or "reluctant" with feeds; 5 = "fed well".
SV = single ventricle; AVSD = atrioventricular septal defect; MVP = mitral valve prolapse; MVR = mitral valve regurgitation; AVR = aortic valve regurgitation; VSD = ventricular septum defect; TGA = transposition of the great arteries; L-R shunts = left-to-right shunt/systemic-to-pulmonary shunt; EDP = end-diastolic pressure; MPAP = mean pulmonary artery pressure; MAP = mean atrial pressure; LVEDD = left ventricular end-diastolic diameter; LVPWD = left ventricular posterior wall diameter; IVS = interventricular septum diameter; SF = shortening fraction; LVDd = left ventricular end-diastolic dimension; LVDs = left ventricular end-systolic dimension; PWT = posterior wall thickness; LV mass = left ventricle mass.

no mentioning of significance or control group.

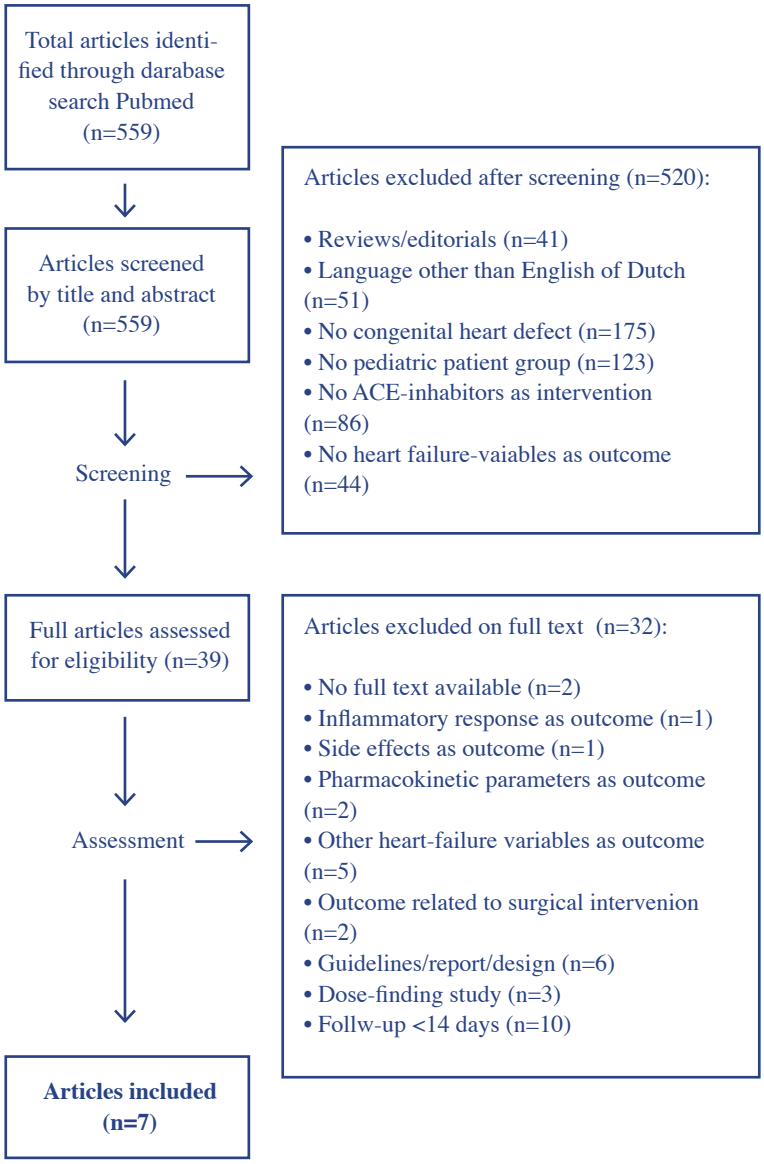
Knirsch et al. (2010) found a decrease in left ventricular end-diastolic diameter (LVEDD) and posterior wall diameter (LVPWD) after one month of treatment and remained stable for a year although there was no statistically significant improvement compared to the control group [19]. Both the ACE-inhibitors group and the control group consisted of 12 patients. LVEDD decreased from 1.73 to -0.05 (z-score), LVPWD increased from -0.12 to 0.37 (z-score) and other echocardiographic parameters including interventricular septum diameter (IVS) and SF remained stable during follow-up. The follow-up was after one month and again after one year.

The remaining two studies showed results of RCTs with different design and outcome measures. Mori et al. (2000) included 24 patients with AVR or MVR of which 12 patients were part of the control group [18]. The follow-up period was 3.4 years for the use of cilazapril or enalapril. The study found significant favourable changes in LVDd and left ventricular end-systolic dimensions (LVDs), posterior wall thickness (PWT), SF and LV mass comparing the ACE-inhibitor group with the placebo group: LVDd -0.25 versus 0.42 (p=0.0007), LVDs -0.36 versus 0.47 (p=0.0009), SF 0.03 versus -0.02 (p=0.02), PWT -0.31 versus 0.47 (p=0.0004) and LV mass -72 versus 37 (p=0.0007). Hence, the conclusion states that long-term treatment with ACE-inhibitors is effective in reducing LV volume overload and LV hypertrophy in children with HF due to AVR or MVR. The RCT of Hsu et al. (2010) did not show a favourable effect of enalapril on somatic growth, clinical outcomes or ventricular function in children with SV physiology. This RCT included 230 patients from which 185 completed the trial until they were 14 months of age. The enalapril group eventually contained 91 patients and the placebo-controlled group contained 94 patients. The weight-for-age z-score, used as primary outcome measure, did not show significance between the enalapril and placebo group (-0.62 versus -0.42, p=0.28) [21].

Discussion

Our study suggests that there is little well-substantiated evidence for the use of ACE-inhibitors for children with HF due to a CHD. In adults, the pathophysiology of HF is well investigated. Angiotensin II is a vasoconstrictor, activates the adrenergic nervous system, causes myocardial remodelling including hypertrophy of myocytes and is the most important regulator of myocardial fibrinolysis [25,26]. These mechanisms result in chronic HF

Figure 1- Flow chart of the article selection process.



and could be treated with ACE-inhibitors. In several large studies in adults, ACE-inhibitors have demonstrated to contribute to the reduction of mortality, hospital admission and quality of life [27,28]. Because of the efficacy of ACE-inhibitors in adults, there were high expectations on their use in children. However, paediatric HF frequently is acute and the responses to therapy including ACE-inhibitors are different as will be discussed subsequently [9].

All the retrospective cohort studies [20,22-24] reported a favourable effect of ACE-inhibitors on the primary outcome measures for HF in paediatric patients with a CHD, including SV physiology, MVR and L-R shunts. Shaw et al. (1988) and Scammell et al. (1987) both found a significant gain in weight and a significant decrease in respiratory rate after the use of captopril [22,23]. These findings suggest an improvement of paediatric HF in patients with a L-R shunt after using captopril, but this should be carefully interpreted since these two studies do not have a control group and the patient groups consisted of 20 respectively 18 patients with a short follow-up of 4 versus 3 weeks. Frenneaux et al. (1989) suggested that enalapril may offer an exciting alternative treatment for paediatric HF in patients with L-R shunts because of the pronounced and sustained improvements in weight gain, respiratory rate and feeding amount [20]. In this study no control group was included, the patient group consisted of 8 patients and the follow-up was only 14 days, so caution is needed. Knirsch et al. (2010) found limited improvement of echocardiographic parameters in paediatric patients with MVR compared to the control group without an ACE-inhibitor after 1 year, but this was not statistically significant [19]. The remaining two RCTs [18,21] differed in study design, outcome measures and conclusions. Mori et al. (2000) stated that ACE-inhibitors significantly reduce left ventricular volume overload and hypertrophy in paediatric HF due to AVR or MVR after a relatively long follow-up of 3.4 years [18]. Hsu et al. (2010) did not show a favourable and significant effect of enalapril on somatic growth, clinical outcomes and ventricular function in children with SV physiology after one year of follow-up [21].

Of the seven included studies, five found a significant and favourable effect of ACE-inhibitors regarding heart failure [18,20,22-24]. Four of these five studies were retrospectively analysed after a short follow-up without a control group [20,22-24]. Only the RCT of Mori et al. (2000) found a significant improvement in echocardiographic findings compared to a control group. The studies of Knirsch et al. (2010) and Hsu et al. (2010) did not find a significant improvement of heart failure due to ACE-inhibitors [19,21]. The studies of Mori et al. (2000) and Hsu et al. (2010) have the highest quality based on the number of included patients, presence of a control group, follow-up time and study design. We believe that ACE-inhibitors have little beneficial effect in children with HF due to a CHD based on the outcome measures. Since the included studies use one or more different ACE-inhibitors, have a different follow-up period and different outcomes it is difficult to draw a single unifying conclusion about the efficacy of ACE-inhibitors in the treatment of children with HF due to a CHD.

Comparison to existing literature

Momma K. (2006) reviewed the use of ACE-inhibitors in children with HF. She concluded that myocardial dysfunction and valvular insufficiency are effectively treated with ACE-inhibitors, and left-to-right shunts only when surgery was not indicated /possible [9].

Kantor et al. (2013) then developed guidelines and recommendations to assist physicians in the treatment of paediatric HF [6]. Their article includes one strong recommendation about the use of ACE-inhibitor therapy: its use is indicated in children with primary a disease of the left ventricular heart muscle. Nothing is mentioned about HF caused by other diseases as CHDs. In general they advise to give ACE-inhibitors after stabilization with diuretics, and follow-up is needed to assess renal function, especially in children under the age of 4 months.

Both previously published reviews recommend the use of ACE-inhibitors in paediatric HF, although with different indications.

Limitations

This review has several limitations. Many studies use a different definition of heart failure and different outcome measures, because heart failure is a complex disease. In our review, we focused on studies with echocardiographic/catheterisation parameters, weight gain, feeding time or respiratory rate as outcome measures. We excluded studies that used other outcome measures for HF than ventricular function, somatic growth/weight gain, feeding time, amount and route and respiratory rate. Thus, we could have excluded studies that might have been important to our research question. Moreover, all studies, apart from the RCT of Hsu et al. (2010), included a small number of patients and the retrospective cohort studies did not include a control group. The small amount of patients and the absence of control groups make it hard to draw conclusions from the studies. Furthermore, we only used PubMed as a source of articles which also limited the number of results. We did not perform a meta-analysis because of the heterogeneity in outcome measures and patient groups. The patient groups consisted of few patients as well. This resulted in less comparability of the studies.

Conclusion

In conclusion, more multicentre randomized placebo-controlled studies with a longer follow-up period are needed to determine the long-term effects of ACE-inhibitors in children with HF due to a CHD. Eventually, surgery or catheter intervention is needed to treat the children with a CHD, but until then they will need another useful intervention to relief their symptoms of HF and to grow strong for surgery. In addition, children who suffer from HF due to a remaining heart defect, such as a persistent VSD or valvular insufficiency, also need interventions to relief their symptoms. ACE-inhibitors are a potential pharmacological intervention for these patients, but evidence for the effects of ACE-inhibitors is not strong enough so far.

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Systematic Review

The impact of endometriosis on women's sexuality

a systematic review and meta-analysis

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Abstract

Objective: **10-15% of women at a reproductive age is affected by endometriosis and this condition could affect their sexuality. The aim of this study is to review the current knowledge on sexual function of women suffering from endometriosis.**
***Methods*: A systematic search in Medline was conducted by means of the Mesh terms "Endometriosis", "Sexual Dysfunctions", "Psychological", "Physiological" and "Sexual Behaviour". English written articles were included when they addressed the impact of endometriosis on sexual function and when they were published within the last 10 years.**
Results: **Based on the Mesh terms, 224 articles were found published between 2006 and 2016 from which 13 were included for analysis. Others were excluded when there was no full-text version available, when the treatment or diagnostics were investigated or when the article missed sexuality or endometriosis. Meta-analysis resulted in 44.8% of the women experienced dyspareunia, 51.1% suffered from sexual dysfunction and 33.5%-71% experiencing a negative effect on their sexual quality of life.**
Conclusion: **Almost half of the women with endometriosis experience a moderate to severe level of dyspareunia and/or sexual dysfunction. Most of the women stated that endometriosis has a negative impact on their relationships and sexual quality of life.**

Introduction

Endometriosis is a benign oestrogen-dependent chronic progressive gynaecological disorder affecting 10-15% of all women of reproductive age and 20-50% of the infertile women [1-3]. It is characterized by ectopic endometrial glands and stroma outside the uterus causing a chronic inflammatory response [4]. The ectopic endometrial tissue prefers locations as the ovaries, pelvic peritoneum, rectovaginal septum and the bladder [4]. Endometriosis can be distinguished into different stages, stages I-IV, with advancing severity. Deep infiltrating endometriosis (DIE) is defined as endometriosis infiltrating deeper than 5mm under the peritoneum [5]. Clinical symptoms associated with endometriosis are dysmenorrhea, non-cyclic pain, dyspareunia, dysuria, dyschezia, chronic pelvic pain and sub- or infertility and therefore reduces the quality of life considerably [6]. Especially DIE has been validated to affect sexual function drastically, whereby dyspareunia is one of the most common complaints [7,8]. Dyspareunia is defined as a genital pain experienced immediately before, during or after sexual intercourse which can be categorized in deep and superficial [9]. The severity of dyspareunia is often measured by means of the Visual Analogue Scale (VAS), a pain scale from 0-10 in which 0 corresponds to no symptoms and 10 to the worst pain imaginable [10]. Sexual dysfunction can be determined with different questionnaires. The most used questionnaires are the FSFI and FSDS. FSFI (Female Sexual Function Index) is a questionnaire with 19 items assessing the key dimensions of sexual function in women [11]. FSDS (Female Sexual Distress Scale) measures sexual related personal stress in women to assess sexual dysfunction and distress [12]. As stated before, sexual function could be negatively influenced by endometriosis with a great impact on the quality of life. Although the effect of endometriosis on sexual function has been analysed frequently in literature, there is no consensus about this effect. Therefore, the aim of this article is to review the current knowledge on sexual function affecting women suffering from endometriosis. This article is relevant for all specialists dealing with endometriosis to acknowledge the impact of endometriosis on sexuality.

Methods

Information sources and search strategy
On December 22 2016, a systematic search in Medline was conducted. Medline was searched using Mesh Terms.

Inclusion criteria
Articles were included when they were in English and about the impact of endometriosis on sexuality. No age limits were conducted.

Exclusion criteria
Articles were excluded when no full-text version was available via Erasmus MC or older than 10 years. Articles that solely investigated the effect of treatment or the effectiveness of diagnostics were also excluded. Further exclusion criteria were missing of sexuality or endometriosis. Non English articles were excluded.

The articles were screened by three independent investigators on title and abstract. Each investigator screened the articles on

eligibility based on the exclusion criteria. When one investigator was unsure about an article or when the opinions of the investigators didn't agree, concession was reached by discussion.

The remaining articles were read completely to assess if they met the inclusion criteria. The references of the articles were screened to make sure no important articles were missed.

Statistical analysis

A statistical analysis was performed when three or more articles used the same questionnaire and scoring system. For the comparison of results averages with standard deviations were converted into percentages considered that the results were conform normal distribution. Therefore, the z-score was used in a z-score to percentile calculator.

The statistical analysis was done with the programme OpenMeta[Analyst] using a one arm PR. For the analysis a 95% confidence interval was used.

Results

Search screening and selection

The search in Medline resulted in 224 articles based on the used Mesh Terms. Of these 224 articles, 77 were excluded because of no full-text availability and 45 articles were excluded because they were outdated (older than 10 years).

There were 91 articles excluded based on the exclusion criteria. 52 articles were excluded since they were solely about the effect of treatment. 13 articles were excluded because they solely investigated the best method for diagnosing endometriosis. 17 articles were excluded for absence of sexuality, 5 for absence of endometriosis and 3 were not written in English (Figure 1).

This resulted in 12 articles which were fully read. Of these articles one was excluded for minimality of sexuality and two articles were included based on references. Therefore, the final selection contained 13 articles as shown in Table 1.

Design and characteristics of articles

Four articles had a cross-sectional design [8,13-15]. Three articles were qualitative studies based on interviews with patients [16-18]. Two articles were based on a case-control design [7,19]. Furthermore, one article was a cohort study [20], one was a narrative review [21], one was a multivariate analysis [22] and one was a research article [23].

The studies were performed in Europe [7,8,17-23], Turkey [13], Australia [16], China [14] and Brazil [15]. Five studies [14,19,20,22,23] used a VAS score to determine the severity of dyspareunia. Three studies [14,15,20] used the FSFI (Female Sexual Function Index) to determine sexual dysfunction and two studies [7,8] used the SHOW-Q (Sexual Health Outcomes in Women Questionnaire), a simplified version of the FSFI questionnaire. Other articles also used the FSDS (Female Sexual Distress Scale) [20] or SRS (Sexual Self-Rating Scale) [19] questionnaire.

Stages of endometriosis

9 articles described the stage of endometriosis in the patients. Three articles included only patients with DIE (deep infiltrating endometriosis) [7,8,15]. Other articles looked at patients with different stages of endometriosis [17,20,22]. One article included only patients with a stage IV endometriosis [13]. One article looked at differences between stages I/II or stages III/IV and whether the women had DIE or not [14]. One article compared women with or without rectovaginal lesions [19].

Dyspareunia

Ten articles looked at the amount of women with dyspareunia and the influence of dyspareunia. Dyspareunia is for many women with endometriosis an important problem in their sex life [8,17]. One article reported that 5/30 women ended their relationship because of dyspareunia and avoidance of intercourse due to pain [18].

Another article stated that most of the women avoided intercourse because of pain [17]. Analysis of VAS scores of six articles [14,15,19,20,22,23] resulted in an overall percentage of 44.8% (95%CI, 26.9% - 62.7%) of the women with a VAS score above 5 (Figure 2). A score above five is defined as moderate to severe pain. One article used VRS instead of VAS and found that 75.8% of the women with endometriosis had dyspareunia [13].

Figure 1 - Flow chart of systematic search

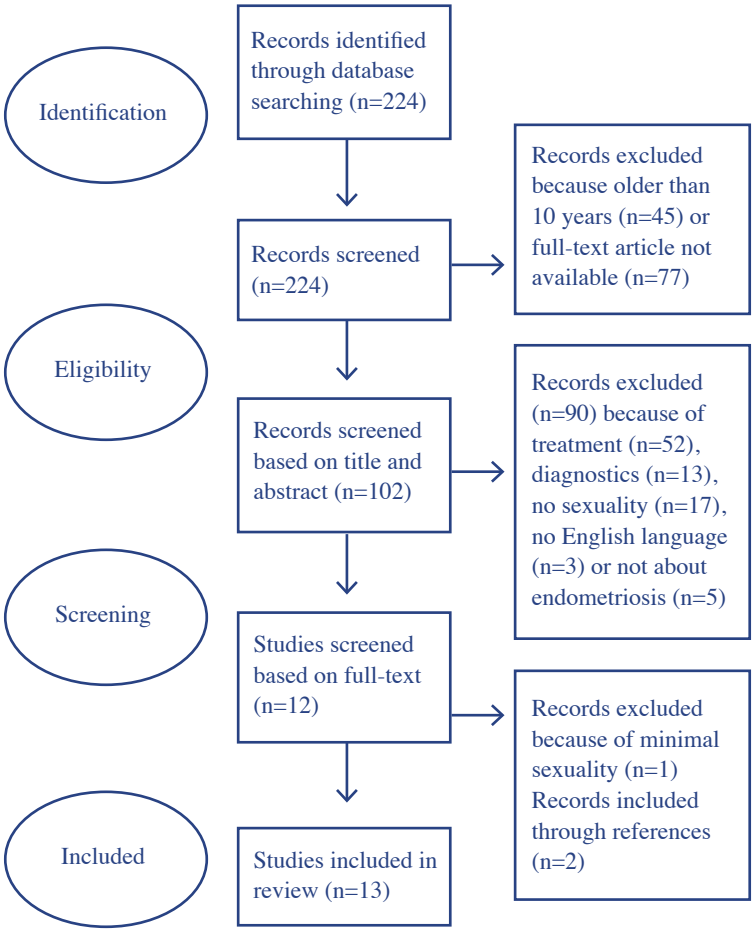
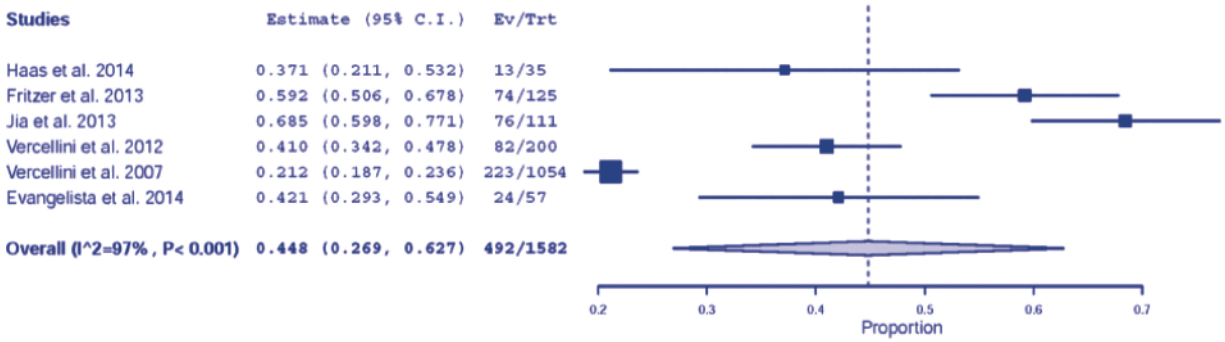


Table 1 - Characteristics of the included studies

Author, year of publication	Study aim	Study type	Sample	Scoring system(s)	Findings
Kiykac Altinbas (2015) Turkey	To assess the impact of severe endometriosis on the quality of life	Prospective cross-sectional study	33 Turkish women with stage IV endometriosis	VAS1, VRS2, WHOQOL-BREF4	No correlations between quality of life and VRS and VAS scores in patients with dyspareunia ($p > 0.05$). 75.8% of the patients with dyspareunia. 53.1% with decreased libido. 39.4% frequency of sexual intercourse less than twice a week.
Di Donato (2014) Italy	To compare sexual function between patients with deep infiltrating endometriosis and healthy women	Case control	182 women with DIE	SHOW-Q5	Sexual function significantly impaired compared to healthy women. 58% (105/182) of DIE patients reported affection of sexual function, compared to 1% (2/182) in control ($p < 0.0001$). Sexual desire was absent or less than one or two times per month in 45% (82/182) of women with DIE compared to 14% (26/182) in control ($p < 0.0001$). 49.9% scored low on the orgasm scale.
Moradi (2014) Australia	To explore experiences of the impact of endometriosis and whether there are differences across three age groups.	Qualitative	35 women. 23 with endometriosis and 12 without endometriosis	Semi-structured focus group discussions	Negative impacts on their sexual relationships because of pain during or after sex, Lesser frequency because of bleeding during or after sex and failure to have orgasm. Anxiousness about initiating a new relationship or staying single
Haas (2014) Switserland	To evaluate the course of endometriosis from the premenopausal to the postmenopausal period	Research	35 women with endometriosis in menopause	Questionnaire and VAS	71.4% had already dyspareunia premenopausally, and it persisted postmenopausally in 54.3%. Before the menopause 37.8% had a VAS score above 5 and after the menopause 17.4%. 80% reported affected sexual life in the premenopausal period, compared to 54.3% in the postmenopausal period.
Fauconnier (2013) France	Compare patient descriptions of endometriosis with the physicans' descriptions	Qualitative	41 women with endometriosis	Interviews	Clinicians identified three while the patients identified five themes.
Fritzer (2013) Germany	To evaluate the prevalence and the impact of sexual dysfunction, sexual distress and interpersonal relationships in patients with endometriosis.	Multicenter cohort study	125 women with endometriosis with dyspareunia	FSFI7, FSFD8, NAS9 and self-administered questionnaire	97patients with female sexual distress and 40 patients with sexual dysfunction. Significant correlations between sexual dysfunction and pain by sexual intercourse ($p < 0.01$ /$p < 0.01$), a lower number of episodes of sexual intercourse per month ($p < 0.01$), greater feelings of guilt towards the partner ($p < 0.01$) and fewer feelings of feminity ($p < 0.01$). 38 had a primary motivation for sexual intercourse to conceive and 46% stated that satisfying the partner was primary motivation. 66% of the women is afraid of pain by sexual intercourse. NAS during intercourse: 6.5 (SD 2.7) with FSD10, 5.2 (SD 2.3) without FSD ($p<0.01$).
Jia (2013) China	To estimate the prevalence and associated factors of female sexual dysfunction in endometriosis	Cross sectional	111 women with endometriosis before laparoscopy	FSFI (simplified) and VAS	The prevalence of female sexual dysfunction was 73% Patients with moderate-to-severe pelvic pain had a 3.4-fold higher risk of having sexual dysfunction. Stage III or IV had a 4.4-fold higher risk of having sexual dysfunction 68,5% of the women with endometriosis had a VAS score >5
Culley (2013) United Kingdom	To review the current knowledge on the social and psychological impact of endo-metriosis	Critical narrative review	5757 women with endometriosis	Varies per article	33.5% to 71% reported negatively affected sex lives. Subsequently avoidance or limiting of sexual intercourse.
Vercellini (2012) Italy	To assess the impact of rectovaginal endo-metriosis on pain at intercourse and sexual functioning	Case control	300 women: 100 with rectovaginal and 100 with no recto-vaginal endometriosis and 100 controls	VAS and SRS11	Deep dyspareunia by 67% in the rectovaginal endometriosis group Deep dyspareunia by 53% in the peritoneal and/or ovarian endometriosis group. No significant difference in overall SRS score was detected between women in the two endometriosis groups.
Denny (2007) United Kingdom	To determine the impact of endometriosis associated dys-pareunia on the lives and relation-ships	Qualtitative	30 women with endometriosis	Semi-structured interviews	Dyspareunia by 86%. 69% experienced pain for several hours after intercourse. 18 women avoided sex because of pain. 5 women had ceased to be sexually active. 3 women experienced pain but did not avoid intercourse Partners were very supportive, but there were tensions and arguments caused by the lack of sexual relations.
Vercellini (2007) Italy	Analyse association between patients characteristics, lesion type, disease stage and severity of pain symptoms.	Multivariate analysis	1054 women with endometriosis	Questionnaire and VAS	A strong association was found between posterior cul-de-sac lesions and pain at intercourse. A correlation between endometriosis stage and severity of symptoms was observed only for dysmenorrhoea and non-menstrual pain 21.2% had moderate/severe pain.
Evangelista (2014) Brazil	To assess the sexual function in women with deep infiltrating endometriosis	Observational, cross-sectional prospective	95 women; 57 with DIE and 38 as control	FSFI and VAS	Patients with endometriosis had more pain in intercourse than controls FSFI score patients 3.4 ± 1.8, control 4.5 ± 1.7 ($p=0.001$) VAS scores patients 4.3 ± 3.3, control 3.30 ± 3.1 ($p=0.007$)
Montanari (2013) Italy	To evaluate sexual function in women with deep infiltrating endometriosis and to study the impact on sexual function.	Cross-sectional	182 women with DIE	SHOW-Q and VAS	61.54% of women with DIE had low frequency of sexual intercourse. 71.43 % of women with DIE low sexual activity SHOW-Q showed poor sexual functioning. Affected were libido and orgasm. 20.68% of the women had severe pain dyspareunia. They had significant impaired orgasm ($p=0.006$), satisfaction ($p=0.013$) and desire ($p=0.050$).

1. VAS: Visual Analogue Scale. 2. VRS: Verbal Rating Scale. 3. QoL: Quality of Life. 4. WHOQOL-BREF: World Health Organization Quality of Life Assessment-BREF. 5. SHOW-Q: Sexual Health Outcomes in Women Questionnaire. 6. DIE: Deep Infiltrating Endometriosis. 7. FSFI: Female Sexual Function Index. 8. FSDS: Female Sexual Distress Scale. 9. NAS: Numeric Analogue Scale. 10. FSD: Female Sexual Dysfunction. 11. SRS: Sexual Self-Rating Scale.

Figure 2 - Meta-analysis of dyspareunia (VAS>5)



Remarkably, pain symptoms mostly decrease below a VAS score of 5 after the menopause [23]. Before the menopause 37.8% of the women had a VAS score above 5 and after the menopause only 17.4% of the women experienced moderate to severe pain [23].

Sexual Dysfunction

Nine articles discussed the sexual dysfunction among women with endometriosis. Besides the measurement of sexual dysfunction with the FSFI questionnaire, some articles also looked at other aspects of sexual dysfunction. One article stated that 53.1% of the women had a decreased libido [13]. Another article stated that 78% of the women experienced sexual distress scored with FSDS [20]. Besides that, 26% to 48.9% of the women experienced a failure to have an orgasm [7,8,16,19.

One article stated that 80% of the women felt that their sexual life had been influenced by the endometriosis[23]. There were three articles that used the FSFI questionnaire to determine the presence of sexual dysfunction among the women [14,15,20]. Analysis of the results gave an overall percentage of 51.1% (95% CI, 11.2%-91.1%) of the women with sexual dysfunction. Sexual dysfunction is determined as a FSFI score below 26.55 (Figure 3).

In another article was stated that there was a significant difference in prevalence of sexual dysfunction in women with moderate to severe pelvic pain, DIE or an advanced stage of endometriosis compared to other women with endometriosis [14].

Relationships

Five articles discussed the influence of endometriosis on relationships.

During interviews in several articles [16,18] women described a negative impact of endometriosis on their relationship. Endometriosis affects the relationship because of pain during or after sex or causes a lesser frequency of sex because of bleeding [16]. Some women had a relationship breakup because of sexual problems in their relationship [16,18].

Most partners were described as supportive but a number of women spoke about tensions and arguments caused by the lack of sexual relations, especially younger women in less developed relationships [18]. Older women replaced penetrative sex by other alternatives [18].

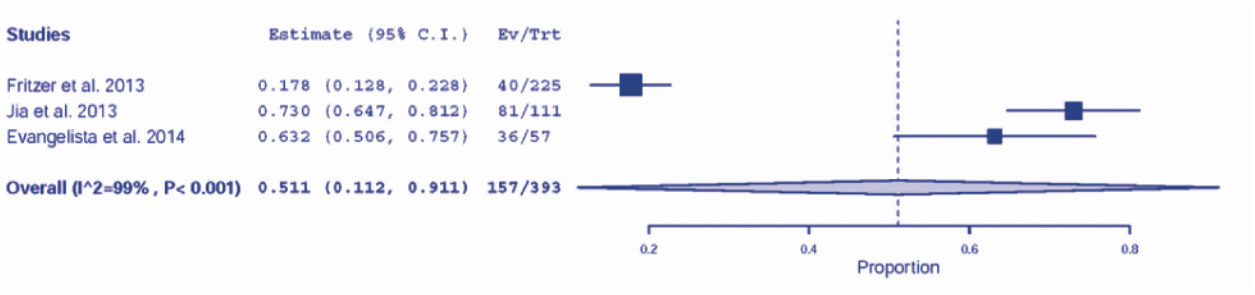
33.5% to 71% of the women experienced a negative influence on their sex life resulting in avoidance of intercourse or decrease in frequency of sex [13,18,21]. In one article 19% of the women said that they are not sexually active due to endometriosis [18].

One article [20] discovered that 46% of the women endures intercourse despite feeling pain to satisfy their partner and 30% of the women have feelings of being a bad wife because they experienced pain during intercourse.

Discussion

The impact of endometriosis on sexuality has never been reviewed. Therefore, a systematic review with meta-analysis was set up. The findings showed that endometriosis had a negative influence on the sexuality of women. This negative influence was caused by dyspareunia, failure to have an orgasm and/or sexual dysfunction. Relationships were also negatively influenced by endometriosis because of pain.

Figure 3 - Meta-analysis of sexual dysfunction (FSFI <26,55)



Multiple articles investigated the prevalence of dyspareunia among women with endometriosis [24-29]. Besides that, there were also a lot of articles about the influence of endometriosis on sexuality [30-34]. These articles stated that endometriosis had a negative influence on sexuality, in the form of sexual dysfunction, as found in our review. The impact of endometriosis on relationships is less frequently investigated. However, these articles found a negative impact on relationships and sex lives, as found in our review.

The amount of impact of endometriosis on sexuality differed between the articles. Bigger study groups mostly scored a lower percentage of women with negative impact on sexuality compared to the smaller study groups. This can be caused by bigger populations or too much selection bias in the smaller studies. Therefore, the negative influence of endometriosis on the whole population is most likely lower than the percentages found in this review.
Most of the women that participated in the studies were recruited from specialised endometriosis clinics for women with severe problems caused by endometriosis. These women don't represent the total population of women with endometriosis and are more likely to give higher impact scores. Hence, a selection bias in the smaller patient populations can't be excluded.

This study could be limited by differences between study groups and studies. Some studies specified their study groups to one or two stages of endometriosis, DIE or specific lesion types. Therefore, there could be differences in the impact of endometriosis between the analysed women.

Furthermore, there has to be awareness that this study can be biased because of publication limitations. For this article we only found studies that proved that endometriosis has a negative impact on the sexuality of women, but there is a possibility that unpublished studies have found no impact on sexuality at all.

Another possible limitation of this study is the absence of a quality assessment. There was no quality assessment performed due to large variation between study types. Therefore, it was difficult to set up correct criteria for a quality assessment that measured each study type equally. In our opinion the articles are of comparable quality with no studies of significant poor quality.

For the conversion of the results for the meta-analysis, results without percentages were converted considering a normal distribution of the average using the standard deviation. This was based on the assumption of a normal distribution, but the true distribution was not stated in the articles.

Despite the differences in articles, there was an ability to perform two meta-analyses on the results from several articles. Furthermore, this study showed that endometriosis influences sexuality based on a systematic review. This type of analysis has not been performed before.

Future research should be focused on patient populations that are more representative for the entire endometriosis population. Besides that more attention should be paid to the emotional impact of endometriosis on women their lives. This can be achieved with a quantification of the emotional impact using a standard tool or questionnaire. A better understanding of the extent of this disease by physicians will lead to an improved quality of life for women with endometriosis.

Conclusion

From the results there can be concluded that almost half of the women with endometriosis experience a moderate to severe dyspareunia, a failure to have an orgasm and sexual dysfunction. Most of the women stated that endometriosis has a negative impact on their relationships and sex life. Further research with women representative for the whole population with endometriosis is recommended.

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The influence of social support on symptom-severity and quality of life in patients with psychotic disorders

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Abstract

Objective: **To address the question whether social support has a significant influence on symptom-severity and quality of life in patients with a psychotic disorder.**
Methods: **We systematically searched the PubMed database for studies reporting the influence of social support on symptom-severity or quality of life in patients with a psychotic disorder.**
Results: **Eight studies were included in this review. Four studies examined the influence of social support on symptom-severity. Two of these studies found a significant influence. Another four studies examined the influence of social support on quality of life and all found a significant influence.**
Conclusions: **Social support seems to have a significant influence on symptom-severity. Social support does have a significant influence on quality of life. We suggest further research on the influence of social support on symptom-severity, because social support can be clinically relevant in improving treatment and recovery of patients with a psychotic disorder.**

Keywords

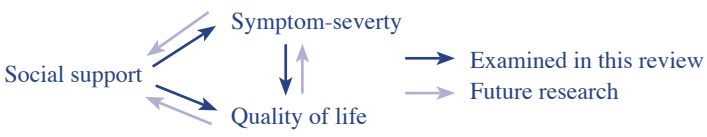
Psychotic disorder • Social support • Symptoms • Quality of life • Emotions

Introduction

Psychotic disorders make up a significant part of the field of Psychiatry. The lifetime prevalence of psychotic disorders is 3.06% [1]. Psychotic disorders have a tremendous impact on the patients life, because they cause disturbances in thinking, perception and emotions [2]. This makes it a burdensome illness for the patient and his or her environment. There is no long-term cure yet and therefore psychotic disorders often require chronic treatment, which contributes to high costs of these kind of illnesses [2]. Research has already shown that it is possible to achieve recovery in patients with schizophrenia [3]. Yet little is known about the way in which recovery can be achieved. However, we do know that family care significantly improves psychosocial functioning in patients with schizophrenia [4]. Therefore, we sought to investigate the influence of social support on patients with a psychotic disorder. Social support typically refers to the functions performed for the individual by significant others [5]. The most frequently mentioned functions are emotional, informational and instrumental assistance [5]. A previous study has described two definitions of recovery [6]. One was based on individual subjective feelings and personal journey of recovery and the other on scientific and clinical models involving objective symptoms of the illness. To implement these definitions of recovery in this study, symptom-severity is used to address the objective definition and quality of life is used to address the subjective definition of recovery. We tested the following hypotheses (Figure 1):

1) Social support has no significant influence on symptom-severity in patients with a psychotic disorder.
2) Social support has no significant influence on quality of life in patients with a psychotic disorder.
3) Symptom-severity has no significant influence on quality of life in patients with a psychotic disorder.

Figure 1 - Relationship between social support, symptom-severity and quality of life



We conducted a systematic review to address the following research question: What is the influence of social support on symptom-severity and quality of life in patients with psychotic disorders?

Methods

Search strategy

On January 7th 2017, we searched the PubMed electronic database for studies using the following Medical Subject Headings [MeSH] terms and title/abstract terms [Tiab]:
"Schizophrenia Spectrum and Other Psychotic Disorders"[Mesh] AND ("Social Support"[Mesh] OR "Social Network*"[Tiab] OR "Social Support"[Tiab])
AND ("emotions"[MeSH] OR "emotion*"[Tiab])

The different categories of social support (emotional/informational/practical) can be measured in various ways. As emotions make up an important part of social support, "Emotions"[MeSH] and "emotion*"[Tiab] were added to the search key to prevent exclusion of relevant studies.

To keep this search updated, we performed the same PubMed search again on November 3rd 2017. Nowadays, more attention is paid to prevent or fight stigmatization towards psychiatric patients. However, research has shown that stigmatization still is a common problem in patients with psychotic disorders [7]. Therefore, we decided to perform the search without restrictions in publication year.

Selection criteria

Both authors independently read the title and abstract of the studies that were obtained by the search term, to decide whether a study could be included in this systematic review. To be eligible, a study had to include all of the following criteria:

I. Patients in the study were diagnosed with a psychotic disorder (psychosis/schizophrenia/schizoaffective disorder)
II. Quality of life or symptom-severity of the psychotic disorder was measured during the study
III. Social support was measured during the study
IV. The influence of social support on symptom-severity or quality of life was examined in the study

We excluded a study when:

I. The type of publication was a systematic review
II. The type of measurement of social support was not mentioned
III. The type of measurement of symptom-severity or quality of life was not mentioned
IV. The study was not written in English

If the title and abstract seemed eligible to us, we read the full text to ensure that the in- and exclusion criteria were still met.

We approved the measurement of social support via the perspective of relatives. As we wanted to create a general overview of the influence of social support in patients with psychotic disorders, we did not apply additional criteria about follow-up and the way in which the psychotic disorder was diagnosed in the studies (e.g. DSM or ICD), any diagnosis was adequate. The flowchart of the selection process is visible in Figure 2.

Analysis

First we produced an overview of the characteristics of the included studies. After that we compared their results. We assessed the quality of the included studies with the Quality Assessment Tool for Observational Cohort and Cross-sectional studies by the National Health Institute (NIH) [8]. This tool consists of 14 questions and points can be scored for each question that can be answered with Yes. The maximum score for cohort studies is 14. For cross-sectional studies we lowered this score to 11, because questions about follow-up are not applicable because of the study design. We applied the following cut-off points: to be rated as a good quality study, cohort studies had to score a minimum of 9 points, cross-sectional studies had to score at least 6 points. Calculating the ratios of the scores made it possible to compare the quality of all the included studies. Our primary outcomes were the influence of social support on symptom-severity in patients with a psychotic disorder and the influence of social support on quality of life in these patients. The primary outcomes were described separately. Our secondary outcome was the influence of symptom-severity on quality of life. An Excel spreadsheet with confidence interval calculator was used to calculate missing confidence intervals. This calculator was downloaded on January 22th 2017 [9].

Figure 2 - Flowchart of the search strategy and results

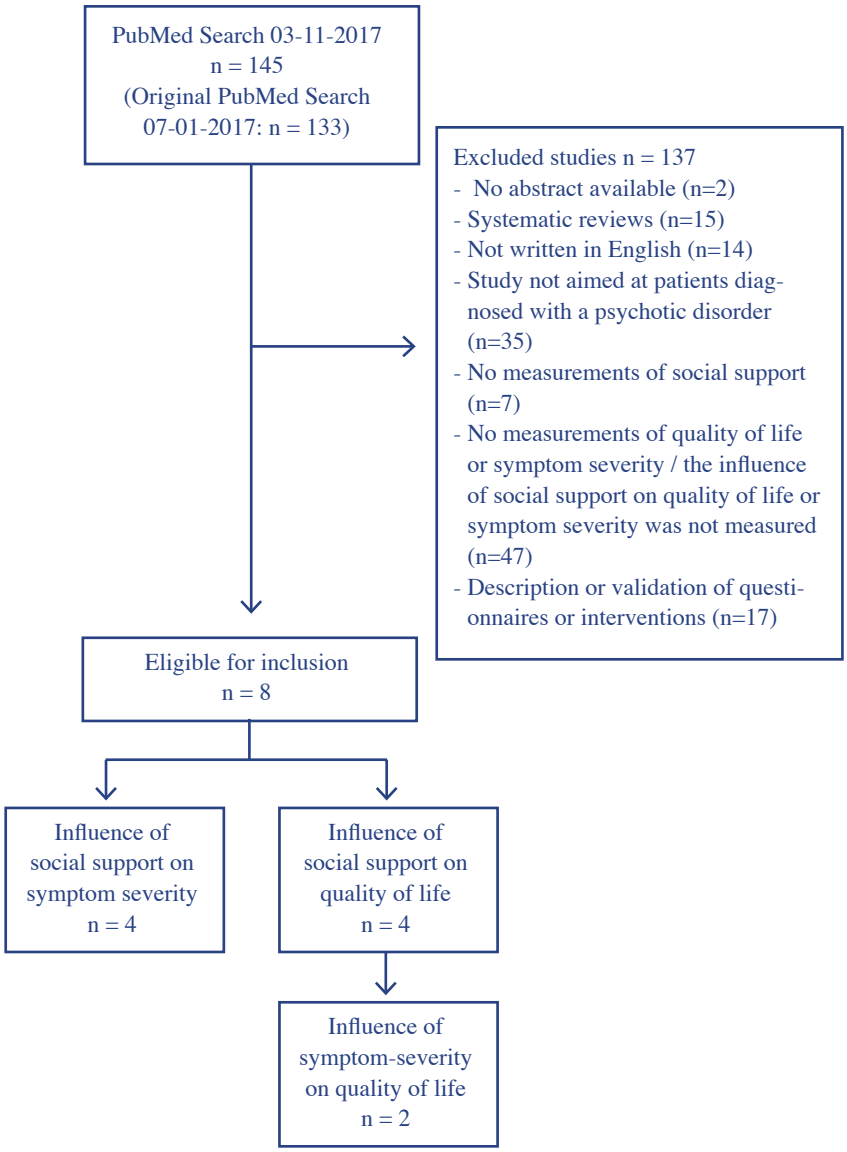


Table 1 - Characteristics of included studies

Author	Study type	Country	Follow-up	Patient population cohort	Relatives population cohort	Mean age patients (SD)	Social support measure	Symptom-severity measure	Quality of life measure	Psychotic disorder
Sündermann et al., 2014	Cross-sectional study	England	-	N = 38	-	32.3 (9.6)	MDSS[A]	SANS[B], SAPS[C]	-	First-episode psychosis
Tempier et al., 2013	Cohort study	England	18 months*	N = 123	-	26.3 (6.1)	SOS[D]	PANSS[E], GAF[F]	-	Early episode psychosis
Ritsner et al., 2012	Prospective longitudinal cohort study	Israel	10 years**	N = 108	-	48.1 (9.3)	MSPSS[G]	PANSS[E]	Q-LES-Q[H]	Schizophrenia and Schizoaffective disorder
Roe et al., 2011	Cross-sectional study	Israel	-	N = 159	-	23.3 (7.9)	MSPSS[G]	Modified BPRS-E[I]	MANSA[J]	Schizophrenia and Schizoaffective disorder
Ritsner et al., 2006	Longitudinal cohort study	Israel	16 months***	N = 148	-	38.2 (9.5)	MSPSS[G]	PANSS[E]	Q-LES-Q[H]	Schizophrenia
Greenberg et al., 2006	Cross-sectional study	United States of America	-	N = 122	N = 203	44.1 (8.3)	FMSS[K], CFI[L], PAI[M]	-	SWLS[N]	Schizophrenia
Kohn-Wood et al., 2005	Cross-sectional study	United States of America	-	N = 49	N = 49	44.8 (14.0)	Was measured via an index developed and used in a previous study	BPRS[O]	-	Chronic psychotic illness
Bentsen et al., 1998	Cross-sectional study	Norway	-	N = 47	N = 72	28.5 (6.5)	CFI[L]	PANSS[E]	-	Schizophrenia or related psychosis

[A] MDSS: Multidimensional support scale
[B] SANS: Scale for the Assessment of Negative Symptoms
[C] SAPS: Scale for the Assessment of Positive Symptoms
[D] SOS: Significant Others Scale
[E] PANSS: Positive and Negative Syndrome Scale
[F] GAF: Global Assessment of Functioning
[G] MSPSS: Multidimensional scale of perceived social support
[H] Q-LES-Q: Quality of Life Enjoyment and Life Satisfaction Questionnaire
[I] Modified BPRS-E: Brief Psychiatric Rating Scale Expanded
[J] MANSA: Manchester short assessment of quality of life
[K] FMSS: Five-Minute Speech Sample
[L] CFI: Camberwell Family Interview
[M] PAI: Positive Affect Index
[N] SWLS: Satisfaction with Life Scale (self and present life subscale)
[O] BPRS: Brief Psychiatric Rating Scale

* 18 months after admission to hospital
** 10 years after hospital discharge
*** maximum of 16 months after hospital admission

Results

Description of studies

The PubMed search on January 7th 2017 produced 133 publications. After we applied the in- and exclusion criteria, 8 studies remained to be used in this analysis. The PubMed search on November 3rd 2017 produced 145 publications. This had no consequences for the amount of included studies, based on the in- and exclusion criteria. 8 studies remained to be included in this analysis (Figure 2). We described the included studies in Table 1. The studies used many different questionnaires to measure social support, symptom severity and/or quality of life. A description of these questionnaires is added in Appendix 1.

The results of the quality assessment are shown in Table 2. All studies were rated as good quality scores. The studies of Roe et al. and Kohn-Wood et al. scored the lowest on quality with both having a ratio of 0.55. Tempier et al. had the highest quality, with a ratio of 0.86.

Hypothesis 1: Influence of social support on symptom-severity

Subjects

Four out of eight studies examined the influence of social support on symptom-severity. All these studies consisted of a patient population cohort and were performed in Western Europe or the United States of America [10-13]. Two studies included a

Table 2 - Results of the Quality Assessment (NIH Quality Assessment Tool for Observational Cohort and Cross-sectional studies)

Study	Quality	Score	Ratio
Sündermann et al., 2014	Good	8 / 11	0.73
Tempier et al., 2013	Good	12 / 14	0.86
Roe et al., 2011	Good	10 / 14	0.71
Ritsner et al., 2006	Good	6 / 11	0.55
Greenberg et al., 2006	Good	10 / 14	0.71
Kohn-Wood et al., 2005	Good	8 / 11	0.73
Bentsen et al., 1998	Good	6 / 11	0.55

relatives population cohort [12, 13]. The total number of patients varied from 38 [10] to 123 patients [11]. The majority of patients was male in all studies. The mean age of the patients varied from 26.3 years (SD 6.1) [11] to 44.8 years (SD 14.0) [12]. Two studies did not have a follow-up period [12, 13] and two studies did not mention how diagnoses were reached [10, 11]. In the two studies that did mention diagnosis, the diagnosis was reached by using the Diagnostic and Statistical Manual of Mental Disorders-III-revised (DSM-III-r) [13] or the Operational Criteria Checklist for Psychotic Illness (OPCRIT) [12].

Social support

One study measured social support using the Multidimensional Support Scale (MDSS) and found a mean score of 13.9 (SD 3.9) [10]. Another study measured social support using an index developed and used in a previous study [12]. The mean score found in this study was 2.0 (SD 2.4). A third study measured social support using the Camberwell Family Interview (CFI) and found a mean score of 2.8 (SD1.1) [13]. The last study divided social support into practical and emotional support. Both practical and emotional support were measured using the Significant Others Scale (SOS) [11]. The mean perceived support score found in this study was 4.59 (SD 1.80).

Symptom-severity

Symptom-severity among patients was measured in all four studies. One study measured the symptoms using the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) [10]. This study found a mean SAPS and SANS score of respectively 2.9 (SD 4.3) and 5.8 (SD5.5). Two studies measured the symptoms using the Positive and Negative Syndrome Scale (PANSS) [11,13]. One of these studies found a mean remission duration of 7.32 months (SD 4.73) [11], whereas the other study did not mention the found PANSS score [13]. The fourth study measured the symptoms using the Brief Psychiatric Rating Scale (BPRS) and found a mean score of 147 (SD 14.1) [12].

Influence of social support on symptom-severity

Two studies found no significant influence of social support on symptom-severity (p=0.09 and p= not available) [12, 13]. Another study found the same result for practical support (p=0.07), however, this study did find a significant influence of emotional support on symptom severity (p<0.01) [11]. The fourth study found a significant influence of social support on symptom-severity (p<0,005) [10]. All above mentioned results are summarized in Table 3.

Hypothesis 2: Influence of social support on quality of life

Subjects

Four out of eight studies examined the influence of social support on quality of life. Three of the studies were performed in Israel [14-16], the fourth one was performed in the United States of America [17]. All studies consisted of a patient population cohort and one study included a relatives population cohort [17]. The total number of patients varied from 108 [15] to 159 patients [16]. The majority of patients was male in all studies. The mean age of the patients varied from 23.3 years (SD 7.9) [16] to 48.1 years (SD 9.3) [15]. Two studies consisted of a follow-up period [14, 15] and only one study mentioned the way their patients were diagnosed with their illness (DSM-IV) [15].

Social support

Three studies measured social support using the Multidimensional scale of perceived social support (MSPSS) [14-16]. One of these studies found a social support score of 57.39 (SD 16.78) at initial assessment. At follow-up, the score was 61.94 (SD 74.15) [15]. The other two studies gave no description of the social support scores [14,16]. The fourth study measured social support via the Five-Minute Speech Sample (FMSS), CFI and Positive Affect Index (PAI) [17]. This study gave no descriptives of the social support scores.

Table 3 - Summary of the results examining the influence of social support on symptom-severity

Author	Social support	Symptom-severity	Influence of social support on symptom-severity	p-value
Sündermann et al., 2013	MDSS: Satisfaction with social support- friends and family	SAPS 2.9 (SD 4.3), (0-15)	Social support – SAPS: -0,35 Social support – SANS: -0,38 (spearman's rank correlations)	p < 0,005 p < 0,005
Tempier et al., 2013	Mean 13.9 (SD 3.9), (6-18) Mean perceived support score 4.59 (SD 1.80), (4.27-4.91)	SANS 5.8 (SD 5.5), (0-19) 7.32 (SD 4.73)*, (6.48-8.16)	Perceived emotional support had a significant influence on symptom-severity. Perceived practical support did not have a significant influence on symptom-severity. (Poisson models)	p < 0,01 p = 0,07
Kohn-Wood et al., 2005	Mean 2.0 (SD 2.4)**, (0-12)	BPRS Mean 147 (SD 14.1), (31-162)	Correlation between social support and function/symptom severity as measured by BPRS 0.24 (Pearson's R correlation)	p = 0.09
Bentsen et al., 1998	Mean level of warmth expressed by relatives was 2.8 (SD 1.1), (2.54-3.06)	PANSS scores not described	No significant correlation between emotional warmth and PANSS (Bivariate tests)	Not available

* Symptom-severity was expressed as mean remission duration, this was the number of months in which the patient was symptom free.
** Was measured via an index developed and used in a previous study

Table 4 - Summary of the results examining the influence of social support on quality of life

Author	Social support	Quality of life	Influence of social support on symptom-severity	p-value
Ritsner et al., 2012	Initial assessment: 57.39 (SD 16.78), (54.19-60.59) Follow-up: 61.94 (SD 74.15), (47.80-76.08)	Q-LES-Q scores not available	Increase in social support over a 10 year follow up period significantly improved Q-LES-Q domain scores (Regression models)	p = 0.001
Roe et al., 2011	MSPSS scores not available	MANSA scores not available	Social support was significantly positively correlated with quality of life; r = 0.31 (Pearson correlation)	p < 0.001
Ritsner et al., 2006	MSPSS scores not available	Baseline 3.4 (SD 0.7), (3.29-3.51) Follow-up 3.5 (SD 0.7), (3.39-3.61) (significantly improved; p < 0.05)	Social support was associated with improvement in the quality of life index (Multiple Regression Analysis)	p = 0.023
Greenberg et al., 2006	FMSS, CFI and PAI scores not available	SWLS scores not available	Maternal warmth had a significant correlation with life satisfaction of the patient; 0.26 (Pearson correlation)	p < 0.01

Quality of life

Quality of life among the patients was measured in all four studies. One study used the Satisfaction with Life Scale (SWLS) [17]. This study did not mention the SWLS scores. Another study measured quality of life using the Manchester Short Assessment of Quality of Life (MANSA) and did not mention the scores as well (16). Two studies measured quality of life using the Quality of Life Enjoyment and Life Satisfaction Questionnaire (Q-LES-Q) [14, 15]. One of these studies found a quality of life score of 3.4 (SD 0.7) at baseline. At follow-up, the score was 3.5 (SD 0.7) [14]. The other study that used the Q-LES-Q did not mention the quality of life scores [15].

Influence of social support on quality of life

One study found that an increase in social support over a 10 year follow-up period significantly improved the quality of life of the patients (p=0.001) [15]. Another study found a significant correlation between social support and quality of life (p<0.001; r=0.31) [16]. The third study found a significant association between social support and quality of life (p=0.023) [14]. The last study found a significant correlation between maternal warmth and life satisfaction of the patient (p<0.01) [17]. All above mentioned results are summarized in Table 4.

Hypothesis 3: Influence of symptom-severity on quality of life

Subjects

In two out of eight studies, the relation between symptom-severity and quality of life was examined [15, 16]. Both studies were performed in Israel and consisted of a patient cohort. The number of patients varied from 108 [15] to 159 (16). The majority of patients was male in both studies. The mean age of the patients was 48.1 years (SD 9.3) in one study [15] and 23.3 years (SD 7.9) in the other study [16].Only one study had a follow-up period [15].

Symptom-severity

One study measured symptom-severity using the PANSS [15]. The negative symptom score in this study was 28.6 (SD 8.4) at baseline and 26.4 (SD 6.4) at follow-up. The positive symptom score was 11.6 (SD 4.5) at baseline and 11.3 (SD 4.0) at follow-up. The other study measured symptom severity using the modified BPRS-Expanded (BPRS-E) and did not mention the symptom-severity scores [16].

Quality of Life

One study measured quality of life using the Q-LES-Q and did not mention the scores [15]. The other study measured quality of life using the MANSA and did not mention the scores [16].

Influence of symptom-severity on quality of life

One study found that changes in the negative symptoms measured by PANSS did not contribute to changes in general quality of life (p=0.097) [15]. The other study found a significant negative correlation between total score of symptoms and quality of life (p<0.05; r= -0.20) [16]. All above mentioned results are summarized in Table 5.

Discussion

In this study we performed a literature review to examine the influence of social support on symptom-severity and quality of life. We expected a significant influence of social support on both features of recovery. However, we only found partial support for these hypotheses.

Hypothesis 1: Social support has a significant influence on symptom-severity in patients with a psychotic disorder.

Two out of four studies that examined social support and symptom-severity found a significant influence of social support on symptom-severity. Despite the contradicting results, we think that social support could have a significant influence on symptom-severity in patients with a psychotic disorder. The study of Bentsen et al did not find a significant influence of social support on symptom-severity [13]. A potential reason for this could be the fact that social support was measured as levels of warmth, which is a specific and small part of social support. A broader definition of social support could possibly lead to significant outcomes in this study. The study of Kohn-Wood et al did not find a significant influence of social support on symptom-severity either [12]. A potential reason for this could be the fact that social support was measured in the context of rural areas, where there is a lack of community resources. Moreover, the quality of the studies that did not find a significant influence of social support on symptom-severity was considerably lower than the quality of

Table 5 - Summary of the results examining the influence of symptom-severity on quality of life

Author	Social support	Quality of life	Influence of social support on symptom-severity	p-value
Ritsner et al., 2012	Negative symptoms - Baseline 28.6 (SD 8.4), (27.00-30.20) - Follow-up 26.4 (SD 6.4), (25.18-27.62) Positive symptoms - Baseline 11.6 (SD 4.5), (10.74-12.46) - Follow up 11.3 (SD 4.0), (10.54-12.06)	Q-LES-Q scores not available	Changes in the PANSS negative symptoms did not contribute to changes in general quality of life. The influence of changes in the PANSS positive symptoms on quality of life were not mentioned. (Multiple Regression Analysis)	P = 0.097
Roe et al., 2011	Modified BPRS-E scores not available.	MANSA scores not available	A significant negative correlation was found between total score of symptoms and quality of life; r = -0.20 (Pearson Correlation)	p < 0.05

the studies that did find a significant influence. On the other hand, it is also possible that social support is not linked to symptom-severity directly, but that this relation is moderated by different factors, for example loneliness or anxiety. This could explain the fact that the two studies did not find a significant influence of social support on symptom-severity. Further research should investigate these possible moderators, because this could influence the importance of social support in the treatment of patients with a psychotic disorder. Now treatment is mainly focused on medication, new data could raise the importance of social support in treatment schedules.

Hypothesis 2: Social support has a significant influence on quality of life in patients with a psychotic disorder.
All four studies that examined social support and quality of life found a significant influence of social support on quality of life. These findings support the hypothesis. Previous research has already shown that loneliness has a significant negative influence on quality of life in patients with a psychotic disorder [18] and that social support can decrease the feeling of loneliness [19]. These findings suggest an indirect influence of social support on quality of life. However, the results of this review suggest that quality of life is directly and significantly influenced by social support.

Hypothesis 3: Symptom-severity has a significant influence on quality of life in patients with a psychotic disorder
Two studies examined symptom-severity and quality of life. One study did not find a significant influence of symptom-severity on quality of life. The other study did find a significant negative correlation between symptom-severity and quality of life, which corresponds to this hypothesis. However, due to lack of data on this topic, it is impossible to draw any conclusions for this hypothesis yet. We did not apply specific in- or exclusion criteria to select studies that examined the influence of symptom-severity on quality of life. We only included studies that examined the influence of social support on symptom-severity or quality of life. If these studies looked at the influence of symptom-severity on quality of life as well, we mentioned it in the secondary analysis. Further research should focus on the relation between symptom-severity and quality of life without the interference of social support. This will possibly lead to more studies, which will increase the quality of the analysis and the possibility to draw any conclusions. Furthermore, we only looked at the influence of symptom-severity on quality of life, further research should also examine the influence of quality of life on symptom-severity.

Limitations
A limitation of our study is the fact that we only searched the electronic database PubMed. Another limitation is that patients in this study had to be diagnosed with a psychotic disorder. However, this is a broad term and does not distinguish between the type, duration and the amount of psychoses. This could decrease the applicability of the results. Furthermore, there is heterogeneity between the included studies. To measure each of the items (social support/symptom-severity/quality of life), many different questionnaires were used, which makes comparability of the results difficult.

Another limitation of this study was the content of the included studies. In five studies, parts of the data were missing. This could be an obstacle in the process of analyzing and comparing the outcomes of the different studies. Moreover, five of the included studies were cross-sectional studies, which means that there was no follow-up. Follow-up provides insight in the moments of measurement. For example, it makes a difference whether symptoms or social support are measured right after a psychosis or later in the process of recovery. Furthermore, all studies had relatively small patient population cohorts. The study of Sündermann et al for example, did not have enough power to find a significant influence because of this [10]. Besides a lack of power, small patient population cohorts potentially limit the generalizability of findings. Finally, a majority of the studies used self-reported questionnaires, which increases the risk of potential recall bias in patients and their relatives.

For future studies, the reporting of follow-up could increase the comparability of study results. The study of Tempier et al made a distinction between emotional support and practical support [11]. Emotional support had a significant influence on symptom-severity, whereas practical support did not have a significant influence on symptom-severity. This finding suggests further research into the different kinds of social support and their effectivity on recovery in patients with a psychotic disorder. In order to improve the social support network of a patient, it is important to know which factors of social support have the most impact on the recovery of a psychotic disorder. This knowledge could contribute to a more effective and patient specific treatment of psychotic

disorders. Furthermore, the antipsychotic medications can cause adverse effects, such as weight gain, Diabetes Mellitus Type 2 or myocarditis [20]. A more prominent role of social support in the treatment of psychotic disorders could lead to a decrease in the prescription of antipsychotic medication, which will result in lower medical costs and less side effects. Finally, we only examined the influence of social support on symptom-severity and quality of life. As shown in Figure 1, the influences probably also work the other way around, which is linked to endogeneity. Further research could investigate whether symptom-severity or quality of life influence social support and if there is a correlation between symptom-severity and quality of life.

Conclusions

The findings of this review do not support the hypothesis that social support has a significant influence on symptom-severity. There was no consensus between the four studies that examined social support and symptom-severity: two studies showed a significant influence, while the other two did not. Despite the fact that hypothesis one was not supported fully by the results of this review, we do think that social support can have a clinically relevant influence on symptom-severity. Therefore we suggest further research into this matter which could lead to the implementation of social support in the treatment of patients with a psychotic disorder. The prescribed drugs together with social support as a part of the treatment will decrease the symptom-severity in these patients. The findings of this review do support the hypothesis that social support has a significant influence on quality of life in patients with psychotic disorders. All four studies that examined this relation found a significant influence. Therefore, we think that social support should be implemented in the treatment of psychotic disorders, to improve the recovery of those patients and to create a treatment that suits the individual patient.

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Appendix 1

Social Support
MDSS
The Multidimensional Support Scale (MDSS) is a self-report scale measuring the availability of social support and the perceived adequacy and satisfaction with it from three different groups: Relatives and close friends, people with a similar life or lifestyle (for example patients suffering from the same illness), and mental health professionals [10]. Availability of support is measured by the total frequency of supportive behavior (scored 1-4: never, sometimes, usually or always), perceived adequacy is measured by the satisfaction patients have with that frequency (scored 1-3: would have liked more, would have liked less, it was just right).

SOS
The Significant Others Scale (SOS) identifies the relationship between the patient and the people who supply practical and emotional support; mostly family, friends and fellow workers [11]. It is a self-report scale and is made out of four questions that are rated from 1 (never) to 7 (always). Out of these 4 questions, two measure the practical part of social support and the other two measure the emotional part of social support.

MSPSS
The multidimensional scale of perceived social support (MSPSS) is developed to measure social support [14-16]. This psychometric tool pays attention to emotional support and the degree of satisfaction with perceived social support from significant others (family, friends etc.). The questionnaire consists of 12 items, in which each question is answered on a 7-point scale, (1=totally disagree, 7=totally agree). A higher score implies a higher level of social support.

FMSS
The Five-Minute Speech Sample (FMSS) determines expressed emotion via an alternative and brief method. In the included study of Greenberg et al, the mother of the patient had to speak about the relationship she had with her daughter [17]. The instructions were to speak five minutes long without being interrupted.

CFI
The Camberwell Family Interview (CFI) is a tool to gain information about the circumstances in which the person of interest lives at home and the three months prior to the person's admission for psychiatric nursing [13, 17]. This information is obtained via a two-hour semi-structured interview, in which the level of warmth is measured through the tone of the voice, the level of spontaneity during the expression of empathy, sympathy and concern. To rate the level of warmth, a 5-point scale is used (1 implying no warmth, 5 implying a higher level of warmth).

PAI
The Positive Affect Index (PAI) is a tool used to measure the quality of the relationship between mother and adult child [17]. The mother answers the questions on this 10-item self-report questionnaire. The answers are rated on a 6-point scale, (1=not at all, 6=extremely). The minimum score is 10 and the maximum score is 60. A higher score implies a greater quality of the relationship.

Symptom severity
SANS
The Scale for the Assessment of Negative Symptoms (SANS) is used to measure negative symptoms in schizophrenia [10]. Negative symptoms are defined as affected or reduced emotions or behavior as compared to healthy people. The scale is divided into 5 categories in which symptoms are rated on a 5-point scale (0=absent, 5=severe). Higher scores imply more symptom severity.

SAPS
The Scale for the Assessment of Positive Symptoms (SAPS) is very similar to the SANS [10]. It is a scale that is used to measure the positive symptoms in patients with schizophrenia. Positive symptoms are defined as psychotic symptoms that are normally not seen in healthy people. The SAPS is divided into 4 different categories in which symptoms are rated on a 5-point scale (0=absent, 5=severe). A higher score indicates more severe psychotic symptoms.

PANSS
The Positive and Negative Syndrome Scale (PANSS) is used to measure symptom severity in patients diagnosed with schizophrenia [11, 13-15]. In an interview, 30 (positive and negative) symptoms are rated on a rated on a 7-point scale. The minimum total PANSS score is 30, the maximum score is 210.

GAF
The Global Assessment of Functioning (GAF) is used to measure the psychological, social and professional functioning of people [11]. The scale is included in the DSM-IV and is divided into 10 different categories of functioning [1-10, 11-20, etc. 91-100]. A score around 100 implies 'normal' functioning, a lower score indicates more psychological or social problems. A score of 0 indicates insufficient information to draw any conclusions.

BPRS
The Brief Psychiatric Rating Scale (BPRS) is a universally popular method to measure the psychiatric outcome and clinical psychopharmacology in people with schizophrenic disorders. The BPRS can be used to measure symptom-severity as well. The included study of Kohn-Wood et al used a 24-itemed BPRS, however the original version consists of 18 items [12]. Clinical analysis of interview responses and clinically judged behavioral ratings make up the total score. A higher score means that the patient experiences more or worse symptoms.

Modified BPRS-E
The modified version of the Brief Psychiatric Rating Scale-Expanded (BPRS-E) consisted of 15 items to measure symptom severity [16]. The original version of the BPRS-E contains 24 items. The questions are rated on a 7-point Likert scale (1=not present, 7=extremely severe).

Quality of life
Q-LES-Q
The Quality of Life Enjoyment and Life Satisfaction Questionnaire (Q-LES-Q) is used to measure the sensed quality of life [14, 15]. The 93-itemed self-report questionnaire is divided into 10 summary categories. All of the items are scored on a 5-point scale (1=not at all, 5=all the time). A higher score implies an advanced enjoyment and satisfaction with certain life categories.

MANSA
The Manchester Short Assessment of Quality of Life (MANSA) is a shortened version of the Lancaster Questionnaire Life Quality Profile (LQLP) [16]. The 12-itemed questionnaire measures satisfaction with life in general. All of the items are rated on a 7 point scale (1= totally disagree, 7=totally agree). A higher score implies a great quality of life.

SWLS
The Satisfaction With Life Scale (SWLS) measures the general life satisfaction perceived by a person [17]. The SWLS is a self-reported questionnaire that consists of 6 items that are rated on a 5-point scale (0 implying not at all, 5 implying a great deal). The minimum score is 0 and the maximum score is 30. A higher score implies higher levels of satisfaction.

Systematic Review and meta-analysis of the association between preoperative anaemia and various postoperative morbidities after cardiac surgery

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Abstract

Objectives: **We performed a systematic review and meta-analysis of observational studies to examine the incidence of postoperative morbidities, comparing preoperative anaemic patients with non-anaemic patients, after cardiac surgery.**
Methods: **We included studies concerning preoperative anaemia, postoperative morbidities and cardiac surgery. We used the Newcastle-Ottawa Scale with one extra criterion we defined urselves to assess the methodological quality of the included studies. The primary outcome measures were: renal failure, stroke, myocardial infarction and atrial fibrillatin. Data are presented as odds ratios (OR) with 95 per cent confidenceinterval (C.I.).**
Results: **After adjusting various exclusion criteria we included 5 studies with a total of 12107 patients. Anaemia was significantly associated with an increased incidence of renal failure (OR 3.27, 95%C.I. 2.86 to 3.75; $I^2 = 0$ per cent; P<0.001), stroke (OR 1.98, 95%C.I. 1.46 to 2.69; $I^2 = 0$ per cent; P<0.001) and atrial fibrillation (OR 1.192, 95%C.I. 1.07 to 1.33; $I^2 = 0$ per cent; P=0.001), but not significantly with myocardial infarction (OR 1.06, 95%C.I. 0.75 to 1.49; $I^2 = 0$ per cent; P=0.763).**
Conclusion: **Preoperative anaemia is significantly associated with a higher incidence in renal failure, stroke and atrial fibrillation. More attention should be paid to preoperative anaemia in patients undergoing cardiac surgery in order to try to prevent postoperative renal failure, stroke and atrial fibrillation.**

Introduction

Preoperative anaemia is a common and potentially correctable condition in patients undergoing surgery. Patients with anaemia have an insufficient number of red blood cells leading to an inadequate oxygen-carrying capacity to meet the body's physiological needs [1]. De population prevalence of anaemia varies with age and comorbidity [2]. Data from the US National Surgery Quality Improvement Program (NSQIP) database shows a 30.4% prevalence of anaemia in all patients undergoing surgery [3]. Preoperative anaemia is strongly predictive for both mortality and surgical complications [3]. A recently published meta-analysis already describes an association between anaemia and an increased risk of death for patients undergoing cardiac surgery, so we decided to elaborate on the possible adverse outcomes after cardiac surgery with patients having preoperative anaemia [4].

We performed a systematic review and meta-analysis of observational studies to examine the incidence of postoperative morbidities, comparing preoperative anaemic patients with non-anaemic patients, after cardiac surgery.

Methods

Search strategy

We have searched the PubMed database on the 23th of December 2016. The search strategy we used for PubMed: ("Preoperative Period"[Mj] OR preoperat*[Ti] OR Pre-operat* [Ti]) AND ("Anemia"[Mj] OR Anemia*[Ti] OR Anaemia* [Ti]) AND ("Comorbidity"[Mj] OR Comorbid* OR Morbidit*) AND English[lang]

Study selection criteria

First, non-English-language articles were excluded from any further screening. Articles that were not Full Text (Free and Erasmus MC) online available were also excluded from further title and abstract screening. On the remaining articles two medical students together performed a title and abstract screening. Articles were excluded if they: were systematic reviews in design, concerned various treatment, were mortality studies, only reported oncology outcomes, included patients under 18 years old, were non-patients studies and if they were non-cardiac studies. Based on full text screening we assessed the remaining articles for eligibility. Based on full text screening articles were excluded if patients were not classified by their preoperative haemoglobin level into an anaemic and non-anaemic research cohort or if an article included less than 100 patients.

We used the Newcastle-Ottawa Scale (NOS) to assess the methodological quality of the included studies [5]. We added an

extra criterion to the NOS score: correct use of the international definition (definition according to the World Health Organisation (WHO) of anaemia (female: haemoglobin <12 g/dl, male: <13 g/dl) [6]. We could assign a maximum of 10 points to each study: 9 points for selection of cohorts, comparability of cohorts and assessment of outcomes and 1 point for correct use of the international WHO definition of anaemia. We excluded studies scoring less than 6 points.

Data extraction

Variables we identified for this study were: study characteristics, patient characteristics (number of male/female patients in included study, number of patients with and without preoperative anaemia, surgery procedure specification), definition of anaemia in g/dl and patient outcomes (renal failure, stroke, myocardial infraction and atrial fibrillation). We entered the collected information into a Microsoft Word (2010) database. Both authors both read all included articles identify and collect the previously named necessary determinants for this systematic review.

Clinical outcomes

The primary outcome measures were: the incidence of renal failure, stroke, myocardial infarction and atrial fibrillation within 30 days after surgery or before hospital discharge, depending on the author's definitions.

Statistical analysis

We used OpenMeta[Analyst] Windows 8 (current version) for all statistical analyses. First, we indexed the clinical outcomes concerning our primary outcome measures of all included studies. We considered a P-value < 0.10 to indicate the statistical significance of heterogeneity. We would use a fixed effects model (Mantel-Haenszel method) if we did not find significant heterogeneity. When finding heterogeneity, we would use a random effects model. We assessed between-study statistical heterogeneity by I^2 tests to indicate the presence of heterogeneity. To summarize the used models and found results we compose forest plots. Findings are presented as odds ratios (ORs) with 95 percent confidence interval (95% C.I.), calculated by OpenMeta[Analyst]. In analysing the results, we consider a P-value <0.05 as significant.

Results

Study selection

We identified a total of 65 articles after online search strategy, of which 9 were not Full Text (Free and Erasmus MC) online available. After title and abstract screening 9 studies remained: 10 articles were excluded because they were systematic reviews, 3 were mortality studies, 12 concerned various treatment, 2 only contained oncology outcomes, 2 included participants under 18 years old, 1 was a non-patient study and 17 were non-cardiac studies. After full text screening 4 more studies were excluded, so we included a total of 5 observational articles in our systematic review and meta-analysis (Table 1).

Characteristics of included studies

In Table 2 characteristics of all included studies are summarized.

Our studies included a total of 12107 patients. Four studies reported renal failure as one of their main outcomes, five studies reported stroke, four studies reported myocardial infarction and three studies reported atrial fibrillation as an outcome measure. All studies were performed between 2006 and 2014. Not all studies applied the same criteria for anaemia: three studies applied the WHO criteria for anaemia (Haemoglobin <13g/dl (= 8,07 mmol/L) for men and haemoglobin <12g/dl (= 7,45 mmol/L) for women [6]), one study considered a haemoglobin level <12.5 g/dl as anaemic and one study considered a haemoglobin level <12g/dl as anaemic. None of the studies described that they corrected the anaemic status of the patients preoperatively.

Table 1 - Flowchart of article selection

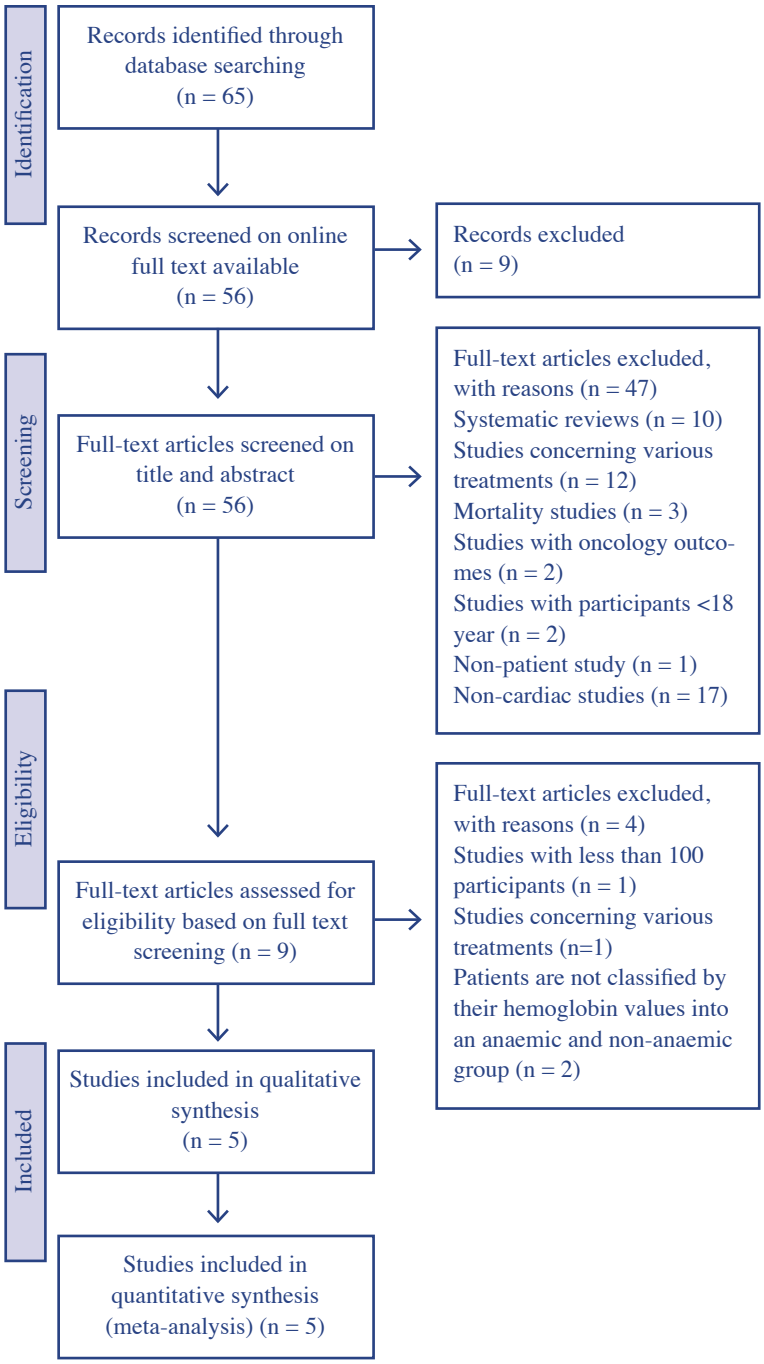


Table 2 - Characteristics of included studies

Reference	Study design	Surgery	Total incl. patients	No. incl. female	No. incl. male	No. with anaemia	No. without anaemia	Definition of anaemia (g/dl)*	Outcomes reported (morbidities)				
									Kidney failure	Stroke	Myocardial infarction	Atrial fibrillation	NOS-score
Miceli, A. et al.	Observational cohort study	CABG, Single valve surgery, combined procedure, aortic surgery	7738	1936	5802	1856	5882	< 13 (M) < 12 (F)	Yes	Yes	Yes	Yes	8
Zhang, L. et al.	Observational cohort study	CABG	655	156	499	223	432	< 13 (M) < 12 (F)	Yes	Yes	Yes	No	8
Carrasca I.Y. et al.	Prospective cohort study	Coronary, valvular and mixed surgery	227	101	126	95	132	< 13 (M) < 12 (F)	No	Yes	Perioperative AMI**	Yes	7
Karkouti, K. et al.	Multicenter cohort study	CABG, single valve replacement, various bypass procedures	3500 (204 dropped out during study period)	804	2492	774	2512	< 12.5	Yes	Yes	No	No	6
Cladellas, M. et al.	Observational cohort study	Valve replacement	201	114	87	42	159	< 12	Yes	Yes	Yes	Yes	6

* Haemoglobin level below which patients were considered anemic.
** Perioperative acute myocardial infraction (AMI)

Primary outcomes

Renal failure

Four studies including 11877 patients reported postoperative re-nal failure as a clinical outcome measure (Table 2). All four stu-dies individually reported a significant outcome.To analyse the outcome measure 'Renal failure' we have used a fixedeffects model. Anaemia was significantlyassociated with an increased incidence of postoperative renal failure (OR 3.27% C.I. 2.86 to 3.75; $I^2 = 0$ per cent; P<0.001) (Fig.1)..

Stroke

Five studies including 12107 patients reported postoperative stroke as a clinical outcome measure (Table 2). Two out of fiv included studies individually reported a significantoutcome. To analyse the outcome measure 'Stroke' we have used a fixedeffects model. Anaemia was significantlyassociated with an increased incidence of postoperative stroke (OR 1.98%C.I. 1.46 to 2.69; $I^2 = 0$ per cent; P=0.001) (Fig.2).

Myocardial infarction

Four studies including 8821 patients reported postoperative myocardial infarction as a clinical outcome measure (Table 2). On forehand no studies reported a significantoutcome. To analyse the outcome measure 'Myocardial infarction' we have used a fixedeffects model. Anaemia was not significantlyassociated with an increased incidence of postoperative myocardial infarc-tion (OR 1.06%C.I. 0.75 to 1.49; $I^2 = 0$ per cent; P=0.763) (Fig.3).

Atrial fibrillation

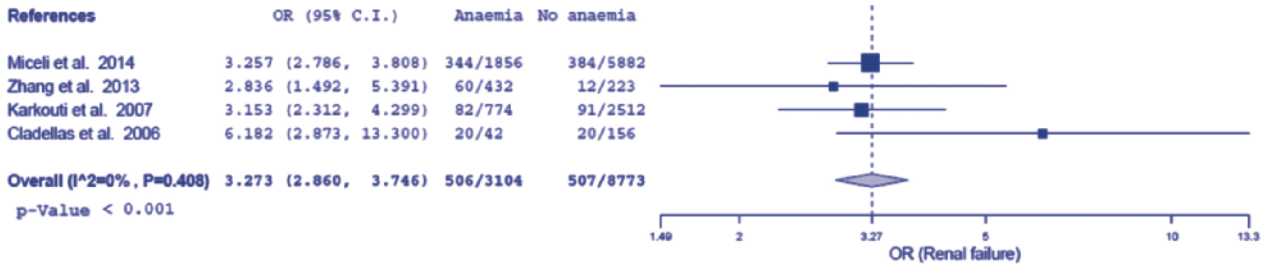
Three studies including 8166 patients reported postoperative atrial fibrillationas a clinical outcome measure (Table 2). One of the three studies individually reported a significantoutcome. To analyse the outcome measure 'Atrial fibrillation we have used a fixedeffects model. Anaemia was significantlyassociated with an increased incidence of postoperative atrial fibrillation(OR 1.19, 95%C.I. 1.07 to 1.33; $I^2 = 0$ per cent; P=0.001) (Fig.4).

Discussion

We can conclude that preoperative anaemia is significantly associated with renal failure, stroke and atrial fibrillation. Myocardial infarction was not significantly associated with preoperative anaemia.

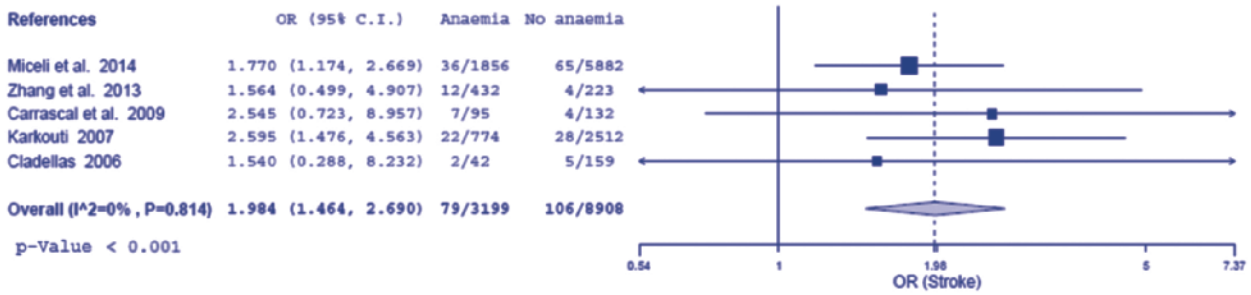
All four studies assessing renal failure independently showed a significant higher incidence of renal failure in the anaemic patient cohort compared to the non-anaemic cohort, after cardiac surgery [7-10]. Also all five studies [7-11] assessing stroke independently showed a higher incidence of stroke in the anaemic cohort compared to the non-anaemic cohort: two studies [7,9] independently showed a significant association and three studies [8,10,11] did not show a significant association. Nevertheless, our systematic review and meta-analysis showed a significant association. We observed the same phenomenon in the atrial fibrillation analysis: one study [7] independently showed a significant association and two other studies [10,11] did not, but our systematic review and meta-analysis found a significant result. In contrast with the previous described outcome measures preoperative anaemia was not significantly associated with myocardial infarction. Only one study [7] showed a decreased incidence of myocardial infarction and three other studies [8,10,11] showed a non-significant association between preoperative anaemia and myocardial infarction. We found it surprising that our systematic review and meta-analysis did not find significant higher odds ratio of myocardial infarction in anaemic patients compared to non-anaemic patients after cardiac surgery. Since having anaemia implicates that a person has less oxygen delivery capacity, which would lead more easily to a lack of oxygen in myocardial tissue [12-13]. We expected a higher odds ratio of myocardial infarction in anaemic patients. As 87.7 per cent of patients in the myocardial infarction was contributed by one single study we believe that interpreting the myocardial infarction outcome data should be done carefully [7].

Figure 1 - Forest plot of renal failure



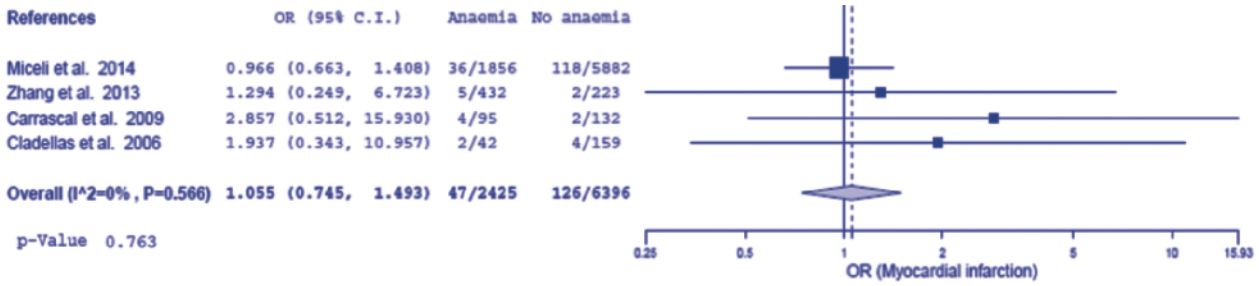
Forest plot of renal failure in anaemic versus non-anaemic patients. Sizes of the squares indicate the weight of each study according to sample size. For the meta-analysis we used a fixed effects model. Odds ratios are shown with 95 per cent C.I.

Figure 2 - Forest plot of stroke



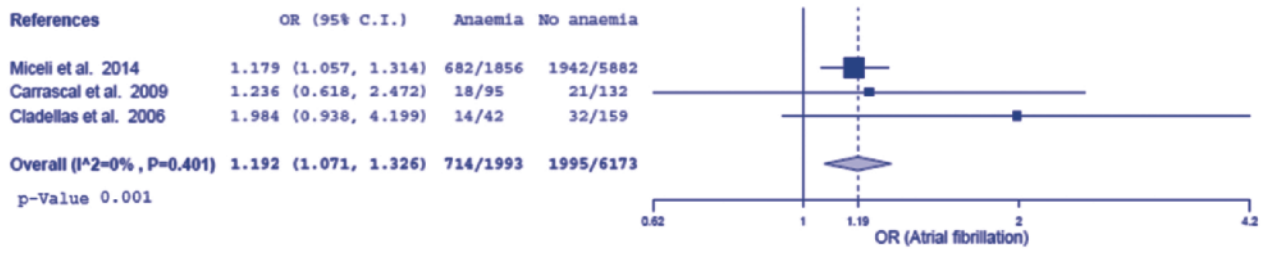
Forest plot of stroke, according to the author's definition of anaemia. Sizes of the squares indicate the weight of each study according to sample size. For the meta-analysis we used a fixed effects model. Odds ratios are shown with 95 per cent C.I.

Figure 3 - Forest plot of myocardial infarction



Forest plot of myocardial infarction, according to the author's definition of anaemia. Sizes of the squares indicate the weight of each study according to sample size. For the meta-analysis we used a fixed effects model. Odds ratios are shown with 95 per cent C.I.

Figure 4 - Forest plot of atrial fibrillation



Forest plot of atrial fibrillation, according to the author's definition of anaemia. Sizes of the squares indicate the weight of each study according to sample size. For the meta-analysis we used a fixed effects model. Odds ratios are shown with 95 per cent C.I.

We cannot confirm whether there is a causal relationship between preoperative anaemia and postoperative outcomes, since we only observed the incidence of morbidities and not the pathophysiology of anaemia and renal failure, stroke, myocardial infarction and atrial fibrillation.

Clinical relevance

By performing this systematic review and meta-analysis we want to draw attention to the extent of the problem of preoperative anaemia. We try to ensure that all healthcare professionals are on the alert for occurring previously described morbidities in anaemic patients after cardiac surgery, since we observed a higher incidence of described morbidities in anaemic patients. It would be even better to correct the anaemic status of the patient prior to surgery. We expect that at early discovery some morbidities might be preventable and damage can be limited.

Study limitations

Not all included studies applied the WHO criteria for anaemia. Three out of five included studies applied the WHO criteria (Haemoglobin <13g/dl for men and haemoglobin <12g/dl for women) one study considered a haemoglobin level <12,5 g/dl as anaemic and one study considered a haemoglobin level <12g/dl as anaemic (table 2). This means that in our systematic review and meta-analysis we miss a part of the anaemic patient cohort that is probably added to the non-anaemic patient cohort.

One of the NOS-score criteria was the following: "Demonstration that outcome of interest was not present at start of study [5]." We noticed that some included studies describing the incidence of postoperative morbidities include patients that already suffer from some morbidities at baseline of the study or have suffered from one of these morbidities before. Not all studies have adjusted for this baseline characteristic. We expect that this patient group has a higher risk of suffering from postoperative morbidities after cardiac surgery. However, we were not able to find data describing whether anaemic patients with morbidities at baseline or in their medical history have an increased risk of getting the same postoperative morbidity after cardiac surgery compared to anaemic patients with no documented medical history. We suggest that more research should be done on this topic to assess the influence of preoperative morbidities on the risk of getting postoperative morbidities.

Our study examined the incidence of postoperative morbidities, comparing anaemic patients with non-anaemic patients after cardiac surgery. Despite that, we included one study that did not report postoperative myocardial infarction, but perioperative myocardial infarction. We do not expect this study to influence the result of our systematic review and meta-analysis.

The strength of this study is that for all analyses we were able to use a fixed effects model, since we observed a high level of between-study homogeneity. Heterogeneity was not a source of bias.

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The prevalence of mutations of the aryl hydrocarbon receptor interacting protein (AIP) in sporadic and familial isolated GH-secreting pituitary adenomas

A systematic review

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Abstract

Objective: **Familial isolated pituitary adenomas (FIPA) and sporadic pituitary adenomas cause acromegaly if they are of the GH-secreting type. The aryl hydrocarbon receptor interacting protein (AIP) mutation is known to be involved in tumorigenesis and behaviour of pituitary adenomas. Knowledge of the prevalence of the AIP mutation could be clinically relevant.**

Methods: **Studies that sequenced for the AIP mutation in patients with GH-secreting FIPA or sporadic pituitary adenomas were included.**

Results: **10 studies were included. AIP mutations had a mean appearance in 45 of 84 patients (54%) with familial isolated GH-secreting pituitary adenomas compared to 55 of 675 patients (8%) with sporadic pituitary adenomas. Secondary outcomes show that patients with AIP mutations are often younger at diagnosis than patients without the mutation.**

Conclusions: **We suggest screening for all patients with GH-secreting FIPA and screening for sporadic GH-secreting pituitary adenoma patients who were under the age of 30 years at diagnosis.**

Introduction

The mystery of the pathophysiology of pituitary adenomas is not yet completely solved. The majority of pituitary adenomas occur sporadically, but familial cases are increasingly being recognized.[1] One of these familial syndromes is termed familial isolated pituitary adenomas (FIPA). FIPA, an autosomal dominant disease, causes 2% of all pituitary adenomas. The occurrence of FIPA is homogeneous or heterogeneous. In the homogenous type, all affected family members have the same type of pituitary adenoma. Patients within the same family can also be affected by different pituitary adenomas, so called heterogeneous families. [2] FIPA is characterized by predominance of prolactinomas and GH-secreting tumours [3]. GH-secreting tumours cause acromegaly in adults and gigantism in children. FIPA patients are younger at diagnosis than patients with sporadic pituitary adenomas [3].

Several studies are investigating the DNA in tissues of pituitary adenomas. The aryl hydrocarbon receptor interacting protein gene (AIP gene) is found to be involved in pituitary tumorigenesis [4]. This gene contains six exons and is located on chromosome 11q13.1 [2]. These exons are encoding a 330 amino acid protein with 3 typical tetratricopeptide repeat (TPR) domains and a final extended alpha helix [5]. All kinds of AIP mutations have been identified: deletions, insertions, segmental duplications, nonsense, missense, splice-site and promoter mutations [6]. Large deletions and a promoter mutation also have been described [7]. Analysis of tumoral DNA has shown a loss of heterozygosity, this suggests that the AIP mutation may function as a tumour suppressor gene [4,8]. Other theories discuss the possibility that the AIP mutation may act on the cell surface, causin g changes in integrin function [9]. Leontiou, et al. found that the mutated AIP protein lost its ability to stop cell proliferation [8].

Even though there are a lot of uncertainties concerning the pathophysiology of the AIP mutation, AIP mutations influences the behaviour of the pituitary adenoma clearly. Clinical features have been published frequently. AIP mutations can occur in homogeneous and heterogeneous FIPA [2]. FIPA patients with AIP mutations are significantly younger at diagnosis than patients who do not have this mutation [5]. The mean maximal diameter of the adenomas in the patients with the AIP mutation is significantly larger in comparison to patient without the mutation [2]. Studies also suggest that pituitary adenomas associated with AIP mutations are more aggressive [9,10]. Furthermore, patients

with AIP mutations appear to be less sensitive to the effects of somatostatin analogs than patients without the mutation.[8] AIP mutations are frequently found in patients with FIPA. The mutation appears to be less frequent in patients with sporadic pituitary adenomas [3,11,12]. The prevalence of the AIP mutation appears to be higher in patients with GH-secreting pituitary adenomas than in patients with other tumour types [13]. Due to the fact that adenomas in patients with the AIP mutation occur to be more aggressive, knowledge of the prevalence of this mutation may be clinically relevant. This review discusses the prevalence of the AIP gene mutation in patients with GH-secreting FIPA and sporadic pituitary adenomas.

Methods

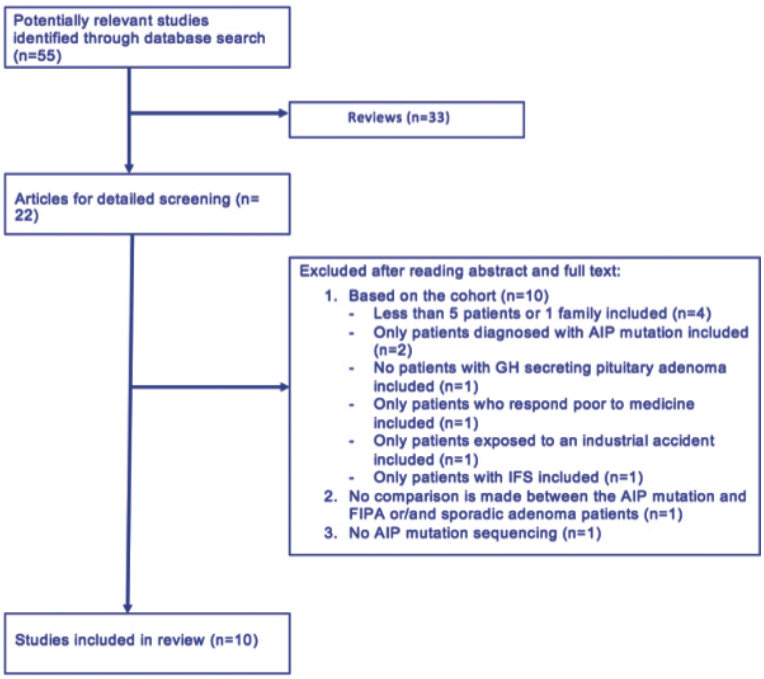
Data search strategy

A systematic literature search of the PubMed database was used to find relevant articles. The medical subject heading [MESH] used was "Pituitary Neoplasms/genetics" in combination with the keywords AIP AND (FIPA OR sporadic). In order to avoid bias we did not limit the date of publication or location. The language was restricted to articles published in English. Only Erasmus MC available or Free Full text articles were included.

Inclusion criteria

All study types were included except reviews. Articles were included if they had patients with GH-secreting pituitary adenomas in their cohorts. Studies that analysed the presence of the aryl hydrocarbon receptor interacting protein (AIP) mutation in patients were included. These studies were only included if they subdivided their population in sporadic adenomas and/or familial isolated pituitary adenomas (FIPA) and sorted them by type of hormone-secreting adenoma.

Figure 1- Flow diagram of literature search and full text screening.



Exclusion criteria

Studies with cohorts less than 5 patients with pituitary adenomas or less than 2 families know with FIPA were excluded. Cohorts without patients with GH-secreting adenomas were excluded. Furthermore, studies that made a selection inclusion of patients in their cohort based on a certain characteristic were excluded. Studies that focussed on the relation between prevalence of the AIP mutation and symptoms of the disease or histology of the tumour tissue were excluded. Studies that did not sequence the patient's DNA for the AIP mutation were excluded.

Selection

Study selection began by screening the titles and abstracts for inclusion. Then the full articles of studies that were considered relevant were investigated. Two students selected the articles independently. Disagreements were solved by an independent third reviewer, who made the final decision.

Quality assessment for studies

We assessed the quality of the included studies using the Newcastle-Ottawa Quality Assessment Scale for cohort studies. All studies scored 5 to 7 points on the scale. Lacking points were mostly applicable to follow-up, which is not necessarily relevant. All studies can be considered as high quality.

Outcomes

Primary outcomes are the prevalence of the AIP mutation in the cohort with GH-secreting FIPA patients and the prevalence of the mutation in the cohort with GH-secreting sporadic pituitary adenomas. Secondary outcomes include age at diagnosis.

Results

Search results

The database search outcome contained 55 articles. After excluding 33 reviews, detailed screening was performed. 10 studies complied with the requirements. The literature search and detailed screening progress is shown in the flow diagram in figure 1.

Data analysis

All included studies used direct sequencing of the AIP gene to find mutations. First, the AIP coding region (exons 1-6) and intron-exon junctions were amplified by using PCR. 2 studies applied splice sites and the 1200 bp promoter region [14,15]. After sequencing, 5 studies used MPLA to search for mutations apart from the AIP gene region [11,15-17]. Outcomes were brought together into an Excel form for analysis.

Primary outcomes

The remaining 10 studies described 759 patients with GH-secreting adenomas, of whom 84 patients had FIPA and 675 had sporadic adenomas. Results are shown in table 1. The incidence of AIP mutations in patients with familial isolated GH- secreting adenomas was various from 39% to 100% among 5 studies. In patients with sporadic GH-secreting adenomas, AIP mutations occurred in 0% to 20% cases. AIP mutations had a mean appearance in 45 of 84 patients (54%) with familial isolated GH-secreting pituitary adenomas compared to 55 of 675 patients (8%) with sporadic pituitary adenomas (odds ratio = 13.01 [95%

Table 1 - Occurrence of AIP mutations in GH-secreting adenoma patients with FIPA or sporadic pituitary tumours in cohorts of the included studies.

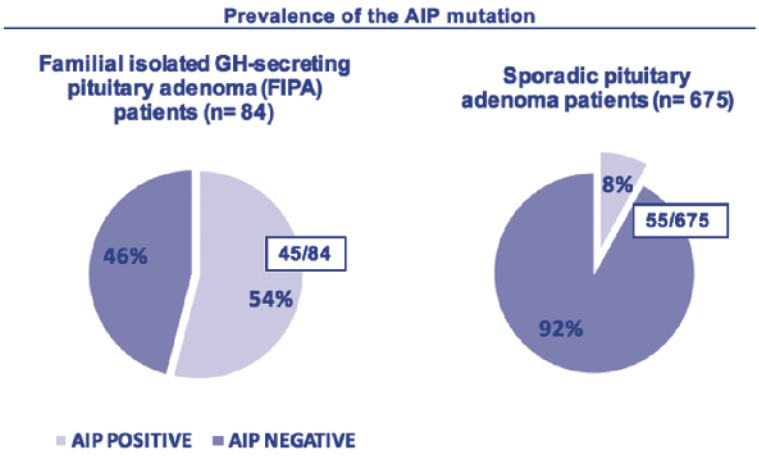
	Number of FIPA patients	Number of FIPA patients with GH-secreting pituitary adenoma	AIP mutation positive FIPA patients with GH-secreting pituitary adenoma	Number of sporadic patients	Number of sporadic patients with GH-secreting pituitary adenoma	AIP mutation positive sporadic patients with GH-secreting pituitary adenoma
	n	n	% (n)	n	n	% (n)
Rostomyan, et al. 2015	28	28	64% (18)	115	115	20% (23)
Preda, et al. 2014				127	48	8% (4)
Cai, et al. 2013	16	6	50% (3)	216	80	6% (5)
Cazabat, et al. 2012				443	148	4% (6)
Tichomirowa, et al. 2011				163	83	13% (11)
Kasuki Jomori de Pinho, et al. 2010	11	6	83% (5)			
Igreja, et al. 2010	90	41	39% (16)			
Georgitsi, et al. 2008				36	7	14% (1)
Cazabat, et al. 2007				154	154	3% (5)
Iwata, et al. 2007	3	3	100% (3)	40	40	0% (0)
Total			54% (45)			8% (55)

CI, 7.81-21.66], P<0.0001). The distribution of AIP mutations in GH-secreting FIPA and sporadic GH-secreting pituitary adenoma patients is shown in figure 2.

Secondary outcomes

Acromegaly seemed to occur generally in AIP mutation positive FIPA families. Three studies showed an incidence of acromegaly in 15% to 31% of families with AIP mutation positive patients. In these studies, GH-secreting adenomas were only found in FIPA families with AIP mutation [17]. Among sporadic patients with acromegaly, GH-secreting adenomas were mostly diagnosed at a young age. No AIP mutations were found in patients with onset of clinical symptoms after the age of 40 [13,17]. Two studies verified that sporadic acromegaly patients with AIP mutations were significant younger than patients without AIP mutation ($p < 0.01$ and $p = 0.005$) [7,13].

Figure 2- Prevalence of AIP mutations in patients with GH-secreting FIPA and sporadic GH-secreting pituitary adenomas.



Discussion

Our data suggests that 54% of the familial isolated patients with GH-secreting FIPA are positive for the AIP mutation. In GH-secreting familial isolated pituitary adenomas, the appearance of AIP mutations varied from 39% to 100%. Pituitary adenomas in patients with AIP mutations turn out to be more aggressive and bigger. From these results we conclude that it will be useful to screen patients with GH-secreting FIPA for the AIP mutation. Due to the aggressive character of these adenomas, treatment might be adjusted when the patient is positive for the AIP mutation.

In this review, a low (8%) prevalence of AIP mutations was found in patients with sporadic GH-secreting pituitary adenomas. Patients with sporadic pituitary adenomas that carried the AIP mutation, were found to be significant younger at diagnosis than patients without the mutation [7,13]. We suggest that screening in sporadic pituitary adenoma patients could be clinically useful when presenting at a young age (<30 years).

Although all included studies were considered high quality, some articles still contained limitations that might have influenced our results. First, the studies were performed in different medical centres. Some academic medical centres only treat complicated adenomas. Due to the fact that pituitary adenomas with AIP mutations behave more aggressive and have a poor response to medication, the distribution of types of adenomas could result in a higher percentage of AIP positive patients. To minimalize bias we only used numbers of patients instead of the percentages each study showed. Second, the prevalence of AIP mutations in sporadic patients was higher in studies using a cohort with mostly young aged (<30 years) patients [10,14,18]. Studies using a varied aged cohort, showed the lowest rates of AIP mutations in sporadic patients with GH-secreting adenomas [7,11,13]. In Cazabat et al., all AIP mutations were found in sporadic patients younger than 40. They proposed to limit AIP testing to patients diagnosed before the age of 40 [13]. Preda, et al. revealed a low presence of the AIP mutation in patients under the age of 40 with sporadic GH-secreting adenomas [17]. However, their study used a single-centre cohort with a limited number of patients. Further research is needed to prove if screening is effective in these young patients. This could be accomplished by performing a clinical trial.

Conclusion

54% of the patients with a GH-secreting familial isolated pituitary (FIPA) adenoma carry the AIP mutation. Therefore, we suggest DNA screening for the AIP mutation in this patient population. DNA screening for the AIP mutation in sporadic GH-secreting adenomas might be useful in patient populations < 30 years old. Further research is needed to prove the relevance of screening this patient population.

Acknowledgements

The authors thank prof. W.W. de Herder for his supervision and support.

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Risk Factors for Venous Thromboembolism in Adolescents: *A Case Report, Case Series and Systematic Review*

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Intended to be submitted to Erasmus Journal of Medicine

Abstract

Introduction: **In general, the incidence of pediatric venous thromboembolism (VTE) is increasing. In childhood, VTE especially occurs in infancy and adolescence. Pediatric thrombosis is a multifactorial disease. However, the incidence, sites and risk factors of VTE are largely unknown in adolescence. The objective of this study is to determine the incidence, sites and risk factors regarding VTE in adolescents aged 13 to 18 years.**

Methods: **As of January 2016, patients (13 to 18 years old) diagnosed with VTE in the Sophia Children's Hospital Erasmus Medical Center in Rotterdam, the Netherlands, were selected through the use of lists containing daily registered patients of the Department of Pediatric Hematology. Additional information about these patients was collected from the electronic patient file. This information included, amongst others, the sites and risk factors for VTE. An online literature research was performed in PubMed. The relevant information for this systematic review concerned epidemiological data (incidence or prevalence), locations of and risk factors for venous thromboembolism in adolescents.**

Results: **In the case series, ten patients with VTE were included. The most common site of VTE was the vena jugularis (33%). The most important risk factors were the presence of a central venous catheter (24%), surgery (19%) and the use of oral contraceptives (14%). Three studies were included in the literature study of this systematic review. The results of these three studies were combined. In this combined analysis, it is found that the most common site of VTE was the venous system of the lower extremities (86 out of 158 patients, 54%). Furthermore, the most important risk factors for VTE were immobilization (52 out of 158 patients, 33%); obesity (40 out of 158 patients, 25%) and surgery (36 out of 158 patients, 23%). 116 out of the 158 included patients had two or more risk factors (73%).**

In the literature, no specific information was found regarding the incidence or prevalence of VTE in adolescents exclusively.

Conclusions: **The incidence of VTE in adolescents exclusively remains largely unknown. Based on this research, we find that VTE is most commonly located in the lower extremities in adolescents. The cause of VTE in adolescents is usually multifactorial. The identified most important risk factors are immobility, obesity and surgery.**

Introduction

Case report

A 16 year-old Caucasian girl with Down syndrome was presented to the hematology department with thoracic pain. She had a history of obesity (BMI 29,94). A heterozygous factor V Leiden mutation was found through thrombophilia-screening. Congenital heart disease has not been identified in this patient. An oral contraceptive was prescribed a month prior because of her menorrhagia.

In the hospital, the doctors found an increased level of D-dimer (4 microgram/ml [normal <0,5]) and the chest-CT showed pulmonary embolisms in the left lower lobe and the right upper lobe. Indications for right ventricle overload were present on the electrocardiogram.

This young girl was in need of oxygen, so she was ventilated with a non-rebreathing mask. The pulmonary embolisms were treated with nadroparin 5700 IE (twice daily). The vitamin K antagonist phenprocoumon (3-2-1 mg) was started the next day. Furthermore, the girl needed to stop with the oral contraceptives. The patient had a good clinical response. The total duration of the anticoagulation therapy was three months.

Background

Venous thromboembolism (VTE) consists of pulmonary embolism (PE) and deep venous thrombosis (DVT).[1] For adult patients, PE and DVT frequently are identified as significant causes of morbidity and mortality [2]. However, it seems that recognition of this disease in both neonatal and pediatric practice has increased steadily during the past two decades.[3] Even though the awareness of VTE in childhood is rising, the incidence rates of PE are likely to be underestimated due to the fact that PE is frequently clinically silent and/or presents with symptoms resem-

bling underlying diseases. Furthermore, the incidence rates are presumably rising due to improvements in pediatric care, in particular through the use of central venous catheters (CVCs). Finally, the diagnostic techniques for VTE have improved as well.[4]

In adulthood, an important number of first-time VTE seems to be idiopathic. However, the majority of VTE cases in both neonates and childhood are secondary events. This reflects the growing exposure of children to various risk factors, which often co-exist. Many of these risk factors appear in tertiary care settings. The increasing incidence of VTE reflects the growing number of neonates and children who now survive complex medical and surgical interventions [3]. For neonates, which are newborns less than four weeks old, the risk factors for VTE are well known. The most important risk factor for VTE in neonates is the use of CVCs. Other known risk factors are infection or sepsis, asphyxia, congenital heart disease and surgery. Neonatal VTE is most commonly located in the upper venous system, due to the fact that it is almost exclusively catheter-associated [5].

However, the risk factors for VTE in adolescents are not well explored. Increasing the knowledge in the potential thrombotic risk factors is of great importance in order to take efficient measures to prevent VTE. Therefore, the objective of this systematic review is to describe the epidemiology, sites and risk factors of VTE in adolescents.

Methods

This study consists of a retrospective case-series and literature search.

Data collection Case Series

With the use of day lists, which are property of the Department of Pediatric Hematology from the Sophia Children's Hospital Erasmus Medical Center in Rotterdam, the Netherlands, three authors have selected the cases used for the case series in this article. Day lists are overviews containing medical information and personal data of the patients that were admitted to the Department of Pediatric Hematology on a specific day. Medical information included the diagnosis and (a short) medical history of the admitted patients. Personal data included name, patient-number, sex and date of birth. Every single patient selected by the authors had VTE in the period from January 2016 to September 2016 and was between 13 and 18 years of age (adolescent) at the time of the diagnosis. Patients with DVT and/or PE were eligible for this analysis. Additional information on the selected cases was collected from the electronic patient file program named ELPADO. This included information about possible risk factors for VTE, such as immobility, recent surgery, malignancy, the use of oral contraceptives or the presence of a CVC. Specifically regarding VTE, details about age at diagnosis, thrombophilic risk factors and the site of VTE were collected. In the Erasmus Medical Center, all children and adolescents, up to the age of 16 years, are screened for thrombophilia.

Literature search

Search methods for identification of studies

An electronic database, PubMed, was used to identify published studies. On 14 September 2016, the authors have performed a literature search in PubMed, using the search term: ((“venous thrombosis”[MeSH Terms] OR (“venous”[All Fields] AND “thrombosis”[All Fields]) OR “venous thrombosis”[All Fields] OR (“deep”[All Fields] AND “vein”[All Fields] AND “thrombosis”[All Fields]) OR “deep vein thrombosis” [All Fields]) AND (“thromboembolism”[MeSH Terms] OR “thromboembolism”[All Fields])) AND “risk factors”[All Fields] AND “adolescent”[All Fields] NOT “adults”[All Fields] AND (“2006/09/18”[PDat] : “2016/09/14”[PDat] AND English[lang]). Additional information on the epidemiology of VTE in adolescents was found through references in the included studies.

Criteria for considering studies for this systematic review

Titles and abstracts were independently examined by three authors in order to keep selection bias to a minimum. If no decision could be made based on title or abstract, full text articles were obtained. Any disagreements were resolved through discussion until a total consensus was reached.

In order to be included, studies had to focus on the epidemiology and/or risk factors regarding VTE in adolescents.

The language of publication of the studies was restricted to English. Studies published between September 2006 and September 2016 were included. At last, the additional filter “Children (MB)” was used. The pre-defined inclusion criteria, used for the systematic review, are defined in Table 1.

Data extraction and outcome measures

Three authors have independently extracted data from the studies. The authors composed a table with the main characteristics of the studies with the use of this data. The outcomes of interest, relevant for this systematic review, were epidemiological data (incidence and prevalence) regarding, locations of, and risk factors for VTE in adolescents.

Table 1 - inclusion criteria for the systematic review

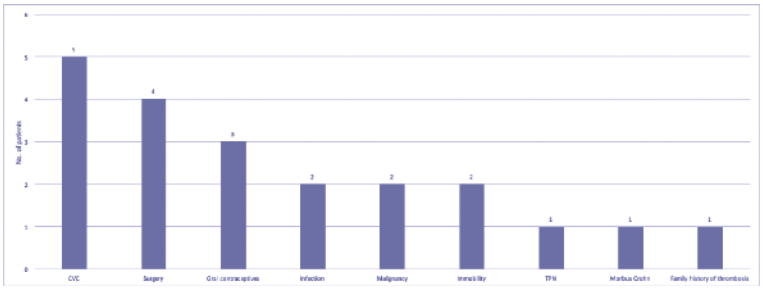
Patient	Adolescents (13-18 years of age) with an objectively confirmed VTE
Intervention	N/A
Comparison	No thrombosis
Outcome	Studies were included if they reported ≥ 1 of the following priority outcomes: • VTE • DVT • PE • Incidence • Prevalence • Epidemiology • Risk factors
Study design	(Retrospective) Registration studies Systematic Reviews Cohort studies
Date and language of publication	Studies from September 2006 until September 2016 English publications only

Table 2 - Case series: patient characteristics

	Age (years)	Sex (M/F)	Site of VTE	Risk factors
Pat. no.1	13	M	Upper venous	Surgery
			system	CVC
			Vena iliaca	
			communis	
Pat. no. 2	14	F	Vena jugularis	Obesity
				Immobility
				Morbus Crohn
				Surgery
Pat. no. 3	17	F	Vena cava	Malignancy
			superior	CVC
			Vena subclavia	
Pat. no. 4	15	F	CVST	Malignancy
				Oral contraceptives
Pat. no. 5	17	M	Vena jugularis	TPN
			interna and	CVC
			externa	Infection
			Vena subclavia	
Pat. no. 6	17	F	DVT	Surgery
				Oral contraceptives
				Obesity
				Family history of
				thrombosis
Pat. no. 7	16	F	Vena jugularis	Surgery
				CVC
Pat. no. 8	17	F	CVST	
Pat.no. 9	13	M	Upper venous	Immobility
			system	Infection / Sepsis
				CVC
Pat. no. 10	16	F	PE	Oral contraceptives

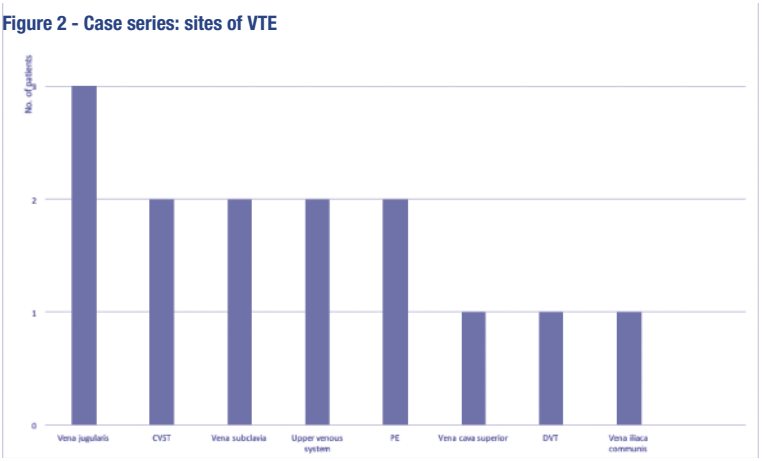
Abbreviations: Pat. no.: Patient number, CVST: cerebral venous sinus thrombosis, PE: pulmonary embolism, TPN: total parenteral nutrition, CVC: central venous catheter, F: female en M: male

Figure 1 - Case series: risk factors for VTE



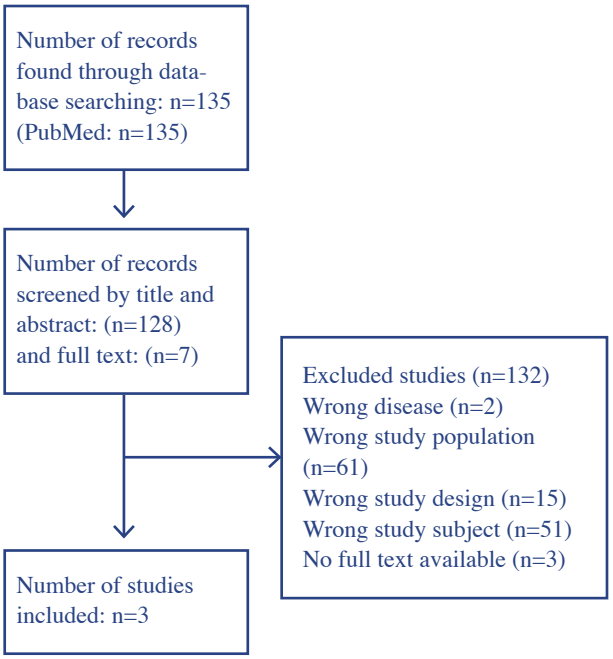
Abbreviations: CVC: central venous catheter, TPN: total parenteral nutrition

Figure 2 - Case series: sites of VTE



Abbreviations: CVST: cerebral venous sinus thrombosis, PE: pulmonary embolism, DVT: deep vein thrombosis

Figure 3 - Systematic review flow diagram. This flow diagram shows inclusion and exclusion of the publications found through the literature search.



Results

Case series

Ten patients with a VTE were selected. The included patients can be found in table 2. The mean age of the selected patients was 15,5 year. Of these ten patients, 3 were male (33%). Some of these patients were hospitalized because of their VTE, while others developed VTE during their stay and/or treatment on the Department of Pediatric Hematology.

Most patients had more than one risk factor. The most important risk factors were CVC (24%), surgery (19%) and oral contraceptives (14%). Other risk factors can be found in figure 1. Out of the 10 patients, 3 (33%) patients had thrombosis in the vena jugularis. Other sites of VTE can be found in figure 2.

Literature study

Search results

With the electronic database search in PubMed, the authors found 135 articles. Of these articles, 128 were screened by title and abstract and 7 by full text. In total, 132 publications were excluded on the basis of this screening. The flow diagram of this electronic database search can be found in figure 3.

Incidence of VTE

In the literature, no information regarding the incidence of VTE in adolescents exclusively was found. Information about the incidence of VTE during childhood can be found in the discussion of this systematic review.

Table 3 - Main characteristics of the studies

	1. Ishola, et al. (1)	2. Biss, et al. (2)	3. Samkova, et al. (3)
Median age (range)	16 years (12-20)	15 years (12-17)	16 years (14-18)
Number of patients, n	64	76	18
Male, n (%)	32 (50%)	41 (54%)	2 (11%)
DVT, n (%)	57 (89%)	65 (86%)	14 (78%)
Site of DVT, n (%)			
Lower extremities	32 (50%)	43 (57%)	11 (61%)
Upper extremities	17 (27%)	5 (7%)	2 (11%)
Head/CVST	11 (17%)	12 (16%)	N/A
Abdomen	5 (8%)	N/A	N/A
IVC	N/A	2 (3%)	N/A
Intracardiac	N/A	1 (1%)	N/A
Multiple sites	N/A	2 (3%)	2 (11%)
PE, n (%)	17 (27%)	11 (15%)	6 (33%)
Risk factor, n (%)			
Obesity	30 (47%)	7 (9%)	3 (17%)
Surgery	17 (27%)	14 (18%)	5 (28%)
CVC	17 (27%)	5 (7%)	N/A
Infection	17 (27%)	N/A	1 (6%)
Immobility	14 (22%)	34 (45%)	4 (22%)
Autoimmune	13 (20%)	4 (5%)	N/A
Family history of VTE	13 (20%)	9 (12%)	N/A
Inherited Thrombophilia	12 (19%)	17 (22%)	7 (39%)
Acquired Thrombophilia	N/A	4 (5%)	N/A
Personal history of VTE	5 (8%)	N/A	N/A
Malignancy	5 (8%)	15 (20%)	N/A
Oral contraceptives	4 (6%)	8 (11%)	12 (67%)
Tobacco	4 (6%)	N/A	N/A
Trauma	2 (3%)	2 (3%)	1 (6%)
CHD	N/A	1 (1%)	N/A
RF ≥ 2	52 (81%)	46 (61%)	18 (100%)

Abbreviations: DVT: deep vein thrombosis, IVC: inferior vena cava, CVST: cerebral venous sinus thrombosis, PE: pulmonary embolism, CVC: central venous catheter, CHD: congenital heart disease

Summary of the studies

Table 3 shows the main characteristics of the three included studies.

Study 1

In the study of Ishola et al., data was collected from medical records from the Texas Children's Hospital, United States of America (USA) [6]. Sixty-four adolescents, aged between 12 and 20 years (median age: 16 years), met the study requirements. Thirty-two of these patients were male (50%).

Sites of VTE

Out of the 64 adolescents, 57 had DVT (89%). The most common localization of DVT was the lower extremities; 32 patients had DVT localized in a deep vein of the lower limbs (50%). Seventeen of the patients (27%) had DVT in an extremity of the upper body. Finally, 17 (27%) of the patients had an embolism in a pulmonary vein.

Risk factors for VTE

In this study, the most common risk factor was obesity; 30 out of 64 adolescents were obese (47%). Furthermore, 17 patients suffered from infection (37%) and another 17 had underwent surgery (37%). Fourteen of the patients had a relatively reduced mobility (22%) and malignancy was a risk factor in 5 patients (8%). Four of the included adolescents had DVT after using oral contraceptives (6%).

Thrombophilic risk factors were also common. Fifty of the 64 adolescents were tested for thrombophilic risk factors. Of these 50, 12 had a thrombophilic risk factor (24%), which is 19% of all the included adolescents. The most frequent inherited risk factor was the Factor V Leiden mutation. Seven of the tested patients tested positive for this mutation (14%). This equals 11% of the total number of included patients. Of the 64 adolescents, 52 had 2 or more risk factors (81%).

Study 2

In the study from Biss et al., data was collected from eight tertiary centers in the United Kingdom (UK) [7]. Seventy-six adolescents met the study criteria, of which 41 were male (54%). Median age of the included patients was 15 years (ranging from 12 to 17 years).

Sites of VTE

Sixty-five of the 76 adolescents suffered from DVT; this equals 86% of the total number of included patients. Forty-three had DVT primary localized in a deep vein of the lower limbs (57%), 11 experienced a PE (14%).

Risk factors for VTE

In this study, the most occurring risk factor was immobility: 34 of the 76 patients had a reduced mobility (45%). Furthermore, 20% of the adolescents had a malignancy (n=15) and 18% acquired VTE after a recent surgery (n=14). Finally, 8 adolescents got DVT after using oral contraceptives (11%).

Forty-three of the 76 adolescents were tested for thrombophilia. Of these 43 patients, 22 had no abnormalities (51%), 17 had an inherited thrombophilia (40%) and 4 had an acquired form of thrombophilia (9%).

Out of the 76 patients, respectively 27 (36%), 31 (41%) and 15 (20%) had one, two or three or more thrombotic risk factors at the time of their VTE. Three patients (4%) had no thrombotic risk factor identified.

Study 3

Data in the study from Samkova et al. was collected from patients admitted to the Department of Paediatrics of University Hospital Hradec Kralovec (Czech Republic) [8]. Only adolescents with a symptomatic DVT and/or PE were included. Eighteen adolescents met the study criteria; the mean age of these patients was 16 years, ranging from 14 to 18 years. Sixteen of the patients were female (89%), 2 were male.

Site of VTE

Of the 18 patients, 9 had DVT diagnosed in one of the deep veins of the lower body (50%), 6 patients experienced a PE (33%) and 3 (17%) had DVT localized in a deep vein of the upper body. Other, less common, sites of VTE study can be found in table 3.

Risk factors for VTE

Out of the 16 girls, 12 (75%) used oral contraceptives. Therefore, the use of oral contraceptives is the most frequent risk factor

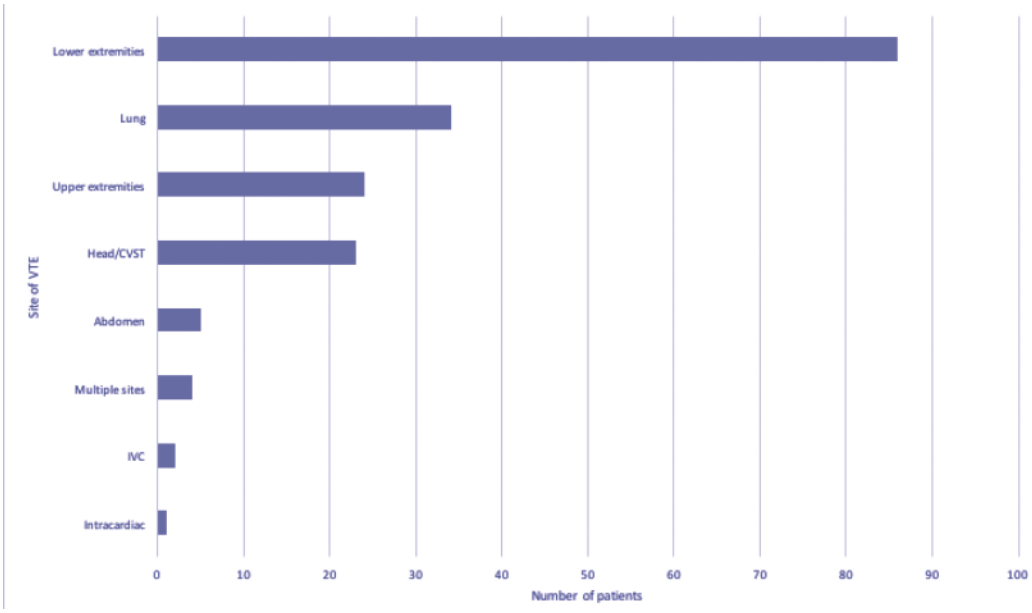
in this study. All girls had one or more additional risk factor(s): 5 had underwent surgery (28%) and 4 had a reduced mobility (22%).
The most frequent inherited thrombophilic risk factor was the Factor V Leiden mutation: 28% of the patients had this mutation (n=5). Furthermore, 10 of the 18 patients (56%) had elevated levels of factor VIII.
100% of the patients had 2 or more risk factors. The mean number of both acquired and inherited risk factors is 2,6. Additional risk factors for VTE in adolescents can be found in table 3.

Combined results
The results of these three studies were combined. There were 158 adolescents included in this combined analysis, of which 75 were male (47.5%). The mean age was 15,7 years, ranging from 12 to 20 years.

Sites of VTE
136 of the 158 adolescents suffered from DVT (87%). The most common place of DVT was the deep venous system of the lower extremities: this occurred in 86 of the 158 adolescents (54%). 34 had a pulmonary embolism (22%) and 24 had thrombosis in a deep vein in an extremity of the upper body (15%). Other sites of DVT can be found in figure 4.

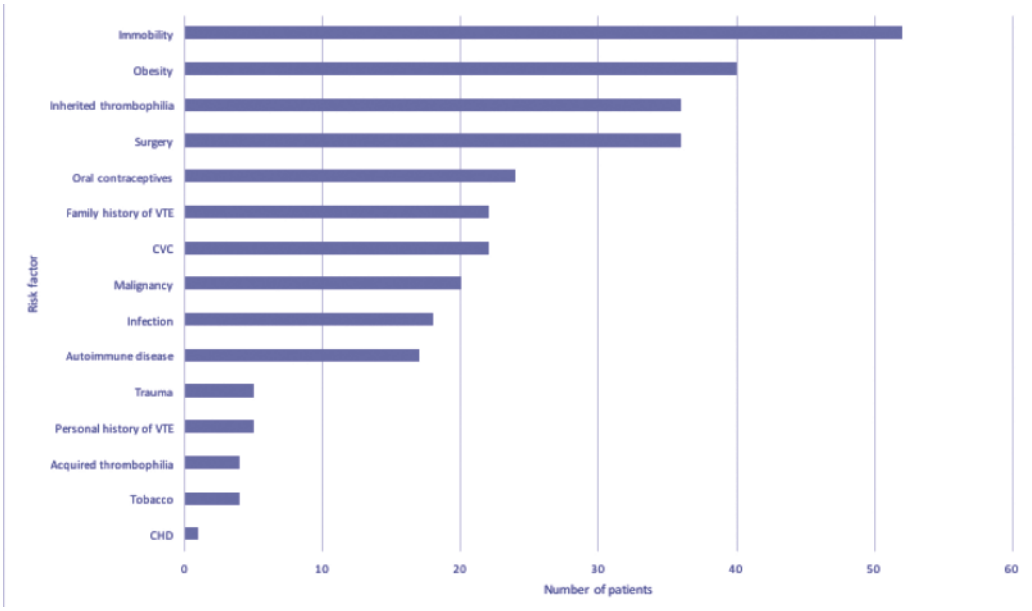
Risk factors for VTE
The most frequent risk factor was immobility: 52 of the 158 adolescents were (relatively) immobile at the time of the diagnosis (33%). Further frequent risk factors were obesity (n=40; 25%); surgery (n=36; 23%) and an inherited thrombophilia (n=29; 21%). Malignancy was a risk factor in 20 patients (12%) and

Figure 4 - Sites of VTE in adolescents



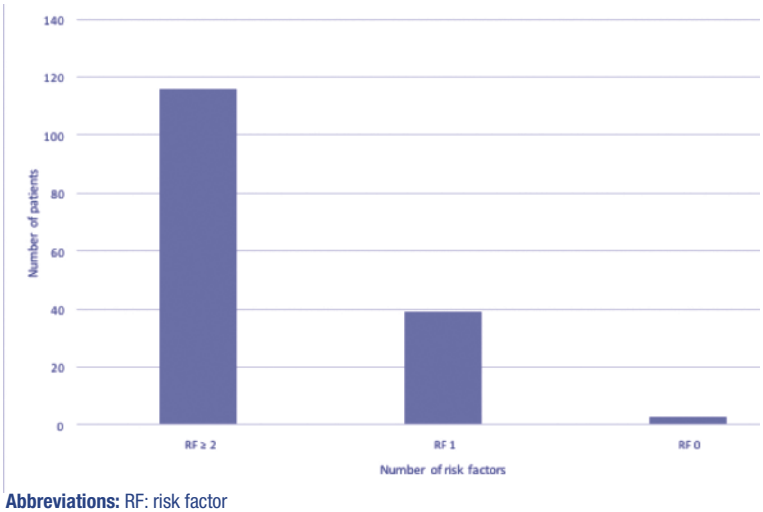
Abbreviations:
CVST: cerebral venous sinus thrombosis, IVC: inferior vena cava

Figure 5 - Risk factors for VTE in adolescents



Abbreviations:
VTE: venous thromboembolism, CVC: central venous catheter, CHD: congenital heart disease

Figure 6 - Number of risk factors per patient



Abbreviations: RF: risk factor

the use of oral contraceptives was the cause of DVT in 24 patients (15%). Additional risk factors for VTE in adolescents can be found in figure 5.

Number of risk factors

Of the 158 adolescents, 3 had no thrombotic risk factors (2%), 39 had one risk factor (25%) and 116 (73%) had two or more risk factors (see figure 6).

Discussion

This study showed that the precise incidence of VTE in adolescents remains unknown. Furthermore, in contrast to neonates, in whom VTE is usually localized in the upper venous system, VTE in adolescents is mostly located in the lower extremities. Finally, VTE in adolescents usually has a multifactorial cause. The most important risk factors are immobility, obesity and surgery. In neonates, however, VTE is mostly catheter-related [5].

Incidence of VTE

No literature was found about the incidence of VTE in adolescents only. During childhood, the incidence of VTE is estimated to be 0.7 to 10.9 per 100.000 in the general population. The incidence of VTE is higher in hospitalized children: 5.3 per 10.000 [2,5,9]. A bimodal distribution of VTE events has been found, with the majority of the VTE occurring in neonates and adolescents [2,10]. The higher incidence in adolescents is partly due to the transition to a more adult-like coagulation profile [11]. It seems that the incidence of VTE during childhood is increasing. The incidence is increasing due to multiple factors. First of all, a combination of improvements in medical care are leading to improved survival in children with potentially prothrombotic conditions, such as malignancy and congenital heart defects. Secondly, the awareness of VTE in children has increased among healthcare workers. At last, the diagnostic techniques for VTE have improved. These factors each seem to have their own contribution to the increased incidence of VTE in adolescents.[7]

Sites of VTE

Neonatal VTE is mostly located in the upper venous system, due to the fact that neonatal VTE is almost exclusively caused by the presence of a CVC [5]. For adolescents, a variety of sites for VTE have been reported. VTE in adolescents is mostly found in the lower extremities (54% of the cases) [6,7]. Other sites of VTE in adolescents are the head-and-neck region, the abdomen, the inferior vena cava, the cerebral venous sinus and inside the heart (intracardiac) [6,7]. In our case series, however, the most common site of VTE was the upper venous system, as the majority of the VTE was catheter-related. This is probably because Erasmus Medical Center is a tertiary care center with a lot of patients in the intensive care unit and a high use of extracorporeal membrane oxygenation. Furthermore, the case series only included ten patients. Presumably not all adolescent patients diagnosed with VTE in the period from January 2016 to September 2016 were included in the case series. Most thrombi were diagnosed in the hospital, but some were diagnosed in secondary care centers. Those patients were seen in the outpatient clinic of the Sophia Children's Hospital. Children with hematological problems (in- and outpatient) under the supervision of the pediatric hematologists, are placed on the hematology day list. Probably not all patients, especially the outpatients, will be mentioned on that list. Thus more adolescents might have developed thrombosis in the Sophia Children's hospital that year.

Risk factors for VTE

VTE in adolescents often has a multifactorial cause. The majority of the patients had two or more risk factors or co-morbidities at the time of diagnosis [6,7]. Only 2% of the patients had no thrombotic risk factor identified [7].

Presence of a CVC is, according to the international literature, an important risk factor and is associated with up to 27% of VTE in adolescents. According to Ishola et al., other significant risk factors for VTE in adolescents were surgery, infection, immobility and obesity.[6] In this study, obesity was by far the most notable risk factor. Ishola et al. describe that obesity was associated with nearly half of the VTEs documented in the population used for their study. Out of the 30 subjects with obesity, additional risk factors were found in all but one subject. When compared to non-obese patients (17%), PE was often found in obese patients (35%) [6]. However, according to Biss et. al, obesity was a less significant risk factor for VTE in adolescents [7]. This is possibly due to the fact that there are less obese children in the UK compared to the USA [12]. This might be true for the Netherlands, as well.

Additional risk factors for VTE are, among other things, inherited or acquired thrombophilia, family history of VTE, and the use of oral contraceptives.

Limitations of the study

There are some limitations in this systematic review. First of all, there are only few studies which report about VTE in adolescents. Studies about risk factors in adults and children have been performed, but there are only a few studies about risk factors for VTE in adolescents exclusively.

Another limitation is the lack of standardization of definitions of some risk factors, for example 'obesity' and 'immobility'. Furthermore, the age range of the adolescents is different for each study.

The retrospective character of the studies is also a limitation. Probably not all adolescents have been included. In addition, one of the studies was performed in a Children's hospital. But not every adolescent will be seen by a pediatrician. Especially the older adolescents are sent to the regular hospital. Therefore, some adolescents might not be included in the study.

At last, in the studies from Ishola, et. al and Biss et al., the adolescents were tested for (inherited or acquired) thrombophilia. However, not every adolescent included in the studies was tested. In the study by Ishola et al., only 50 out of the 64 adolescents were tested for thrombophilic risk factors. Only 43 out of the 76 adolescents in the study by Biss et al. were tested. Because of the fact that not all adolescents were tested for inherited or acquired thrombophilia, the percentage of patients with a thrombophilic risk factor was very high. Probably only the adolescents with a family history of VTE were tested for thrombophilia. Therefore, this percentage is not representative for clinical practice.

Generalizability of the study

The results of this systematic review are probably generalizable for the Netherlands. This is due to the fact that the studies were performed in tertiary care settings. The healthcare in these settings is most highly comparable with the Dutch healthcare. However, in the USA, there are probably more obese children than in the Netherlands [12]. In the Netherlands the incidence of obesity among children and adolescents is rising. The relationship between VTE and obesity is an additional reason for the prevention of obesity during childhood.

Conclusions and recommendations

No studies have reported about the incidence of VTE in adolescents exclusively. Little information regarding the incidence of VTE during childhood was found. In the studies regarding the incidence of VTE during childhood, the patients weren't divided in different age groups. Therefore, it is recommended to conduct studies regarding the incidence of VTE in adolescents aged 13 to 18 years.

Although VTE in children and adolescents is an uncommon event, it is important to have knowledge of the risk factors in this group of patients. Knowledge about these risk factors can be used in the prevention of VTE in adolescents.

VTE in adolescents is usually caused by a combination of risk factors. Important risk factors in adolescents are immobility, obesity and surgery. However, only few studies have been performed in adolescents exclusively.

This suggests that there is a strong need for a thorough and detailed assessment of risk factors in this population. In order to fully understand the role of the various risk factors, it seems likely that these studies will need to be executed in different clinical settings. Additional knowledge about this subject may facilitate the development of risk-factor-modifying strategies to prevent (recurrence of) VTE in adolescents.

Currently there are no evidence-based guidelines for thromboprophylaxis in children and adolescents. It is not recommended to use chemical thromboprophylaxis in unselected hospitalized adolescents due to the lack of evidence of efficacy and safety and the low prevalence of VTE in this age group. However, chemical and/or mechanical thromboprophylaxis can be considered in selected hospitalized adolescents, such as obese and/or immobilized patients with a malignancy or a recent surgery.

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Postoperative Pain Management in Adolescents after Scoliosis Surgery *A Systematic Literature Search*

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Acknowledgments
We like to thank Dr. Jurgen de Graaff, Pediatric Anesthesiologist at the Department of Anesthesiology, Erasmus University Medical Center, Rotterdam, The Netherlands, for being our supervisor and for helping us write this article.

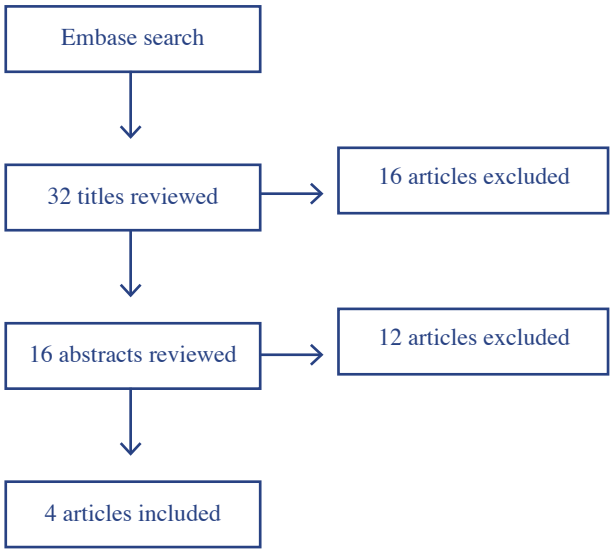
Clinical Scenario:
A fifteen-year-old, otherwise healthy girl undergoes a spinal correctional surgery. She will receive two bars alongside her spinal column from the fifth thoracic vertebrae through the fifth lumbar vertebrae. This type of surgery is very painful and good postoperative analgesia is essential.

Clinical question:
The standard protocol at the Erasmus Medical Centre for postoperative pain management after scoliosis surgery in adolescents is epidural analgesia [1]. In some cases, combined with intravenous morphine. The risks involved, such as a higher risk of infection, limit the placement of epidural catheters by surgeons after surgery. Also, the use of intravenous morphine comes with certain risks and side effects, for example risk of respiratory depression. Therefore, we performed a literature study to investigate the following question "What is the best post-operative pain management after scoliosis surgery in healthy adolescents?".

Literature search:
We searched Embase® using the following terms: 'scoliosis' AND 'analgesia' AND 'postoperative pain' AND 'postoperative analgesia' AND [adolescent]/lim (limited to age adelescents) until the date 10/04/2016. Our search generated 32 articles. These 32 articles were reviewed by title by the two authors. We searched for articles about idiopathic scoliosis surgery in adolescents and the pain management post-operative. We then reviewed the abstracts of sixteen publications. We included articles about pain management and we looked specifically for randomized controlled trials and large population size cohort studies. We excluded articles that were not primarily about the post-operative pain management or that did not use a specific (drug) therapy. Four publications met our criteria (Table 1, Figure 1).

Critical appraisal of the articles:
The following pain management methods were found in our literature search; continuous epidural analgesia (CEA), patient controlled analgesia (PCA), the use of acetaminophen (paracetamol) and the use of additional Gabapentin.

Figure 1 - Flowchart of methodology



Sucato et al. performed a retrospective cohort study entitled: "Postoperative Analgesia Following Surgical Correction for Adolescent Idiopathic Scoliosis: A Comparison of Continuous Epidural Analgesia and Patient-Controlled Analgesia" [2]. The authors did a retrospective cohort study with 613 patients, 413 patients in the Continuous Epidural (CEA) group and 200 in the Patient Controlled Analgesia (PCA) group. PCA involves the patient in pain administering their own pain-relieving solution using a controlled infusion pump. The results of this study have to be reviewed with some scepticism, since the group sizes are non-comparable (200 vs 413 patients) the risk of sample selection bias is very high. We could not find any reason for the patients to be in one of those two groups, whether this was by the choice of the surgeon, on historical grounds, or on indication by the anaesthesiologist. The CEA protocol used continuous infusion of hydromorphone and bupivacaine at 0.1 to 0.2 mL/kg/h. The PCA protocol used morphine 0.02 to 0.03 mg/kg or meperidine 0.2 to 0.3 mg/kg. The primary outcome was pain measured using Visual Analogue Scale (VAS) scores at different moments after surgery and adverse effects of the analgesia post-operative. The average of all pain scores, scores at individual time points and the average maximum score were all significantly better (1.3 vs. 1.9, $P<0.0001$) in the CEA group when compared to the PCA group. The need to temporarily stop and then restart the pain manage-

ment and premature permanent discontinuation, however were both greater in the CEA group. As for the known complications associated with epidural use, no neurologic injuries occurred in both groups. In the CEA group however, three people (0.7%) suffered from respiratory depression caused by the morphine, resulting in the discontinuation of the CEA therapy. In the PCA group, this adverse reaction did not occur. The authors also mention a large down side of CEA; in 8% of their patients in the CEA group the catheter was not placed correctly, resulting in inadequate analgesia. With the use of PCA this risk is much smaller and therefore it has a much more reliable continuous average pain relief capability than CEA.

In the article "Effects of Pre-emptive Analgesia Using Continuous Subcutaneous morphine for Postoperative Pain in Scoliosis Surgery" by Machida et al. [3] the authors evaluated the efficacy and safety of continuous subcutaneous morphine administration for post-operative analgesia after scoliosis surgery. A long butterfly needle placed subcutaneously over the lateral deltoid muscle during surgery, which was moved to the sternum after surgery, over which the continuous subcutaneous morphine was given. This subcutaneous technique is not the standard in The Netherlands, and is considered very unreliable because of the drug absorption and distribution by this method and the more variable pain relief reached in patients. The population of their randomized controlled trial consisted of 30 patients in the subcutaneous morphine group, and twenty patients in the control group who did not receive morphine. This is a questionable distribution of patients in a controlled trial, the intervention group is 150% the size of the placebo group, which could lead to less reliable statistical outcomes. The verbal response score (VRS) and visual analog pain scale (VAS) were used as measurement of pain after surgery. Primary outcome was measured as the average of VRS and VAS pain scores in the first 72 hours after surgery. The secondary outcome was the number of times the patient requested supplemental analgesics. In their results, Machida et al. show that "VRS and VAS measurements were significantly lower in the continuous subcutaneous morphine group compared with the control group" [3]. But also show that supplemental analgesic consumption was lower in the morphine group compared to the control group. As for the known complications associated with morphine use, respiratory depression and constipation, there was no significant difference between the groups. In the last few years, epidural analgesia has become the standard in the pain management after scoliosis surgery, but there are several downsides to this method. For instance, the time it takes for the agent to become effective after epidural administration is 1-2 hours [4]. Also the need to stop the analgesia temporarily to monitor neurologic function is a downside of CEA. The use of subcutaneous or iv morphine overcomes these disadvantages.

Hiller et al. [5] studied the effect of Acetaminophen (Paracetamol) on analgesia mainly in adolescents, by performing a double blinded randomized controlled trial with 36 patients. The primary aim of this study was to determine what the pain-relieving capacity of acetaminophen was, which is part of the pain medication protocol used in the Erasmus MC [1]. Standard post-operative pain management in the Erasmus MC is two epidural catheters. Both catheters contain a 0.1 ml/kg ropivacaine 0.2% and clonidine 1-2 mcg/kg bolus solution initially. After a bolus is given both catheters receive a continuous solution of 0.2% ropivacaine with 0.5 mcg/ml sufentanyl. Continuous analgesia is limited to 6 ml/h per catheter. In addition, Paracetamol is given the first 3 days 90 mg/kg/day. Here on after Paracetamol is given 60 mg/kg daily, additionally diclofenac is given 3 mg/kg. If standard given analgesia is not sufficient clonidine 1mcg/kg can be given every 12 hours. The secondary aim was to determine whether there was an opioid sparing effect. Patients were randomized into two groups. One group received acetaminophen by iv for 15 minutes with a maximum of 1.5 g, the other group received a placebo. The primary outcome of this study was that analgesia was clinically significant improved ($p<0.05$) after acetaminophen had been given. However, the secondary outcome showed that there was no difference in opioid consumption. The secondary results suggest that the opioid consumption was not reduced during the use of iv acetaminophen. The reason for this might be the use of remifentanil during surgery. Hiller et al. [5] describe that the use of intraoperative remifentanil is associated with a higher pain score and with greater opioid consumption post-operatively. Furthermore, the expected lower opioid consumption was based on adult studies, which they mention in their discussion [6]. The unexpected outcome of non-lower opioid consumption might be explained by this.

The primary aim of the randomized controlled trial by Mayell et al. [7]. Analgesic effects of gabapentin after scoliosis surgery in children was to determine whether a single dose of gabapentin pre-operatively would decrease the consumption of opioids post-operatively. The secondary aim of this study was to evaluate whether gabapentin reduced pain scores and drug absorption. Sample sizes were calculated a priori, using a 0.05 two tailed alpha test and a study power of 0.8, resulting in a total of sixteen patients required to show a reduction in morphine consumption of 25%. Patients were randomized into two groups. One group received a 600 mg capsule of gabapentin 1 hour before surgery. The other group received a placebo. For post-operative pain management both groups received morphine via PCA pump at 10 mcg/kg/h, 15 g/24h paracetamol (acetaminophen) for basic pain medication, and ondansetron for nausea and vomiting. Both outcomes in this study were not statistically significant. They found that gabapentin did not decrease opioid consumption and decreased pain sensation. An important limitation for this study is the choice of 600 mg gabapentin. The given dose might have been inadequate for this population and surgical setting. A higher dose might have produced more adequate results. The authors of a recent systematic review in Anesthesiology found a recommended dosage of 1200 mg gabapentin in adults for sufficient post-operative pain management [8]. Secondly, Mayell et al. describe an interpatient variability in drug absorption mostly because gabapentin is absorbed by amino acid carriers limited to a relatively small part of the duodenum. This causes a variation in analgesic effect of gabapentin [8].

Discussion:

Two important factors for the evidence of an article are the study design and the population size. A randomized controlled trial has more power than a retrospective cohort study, due to the larger risk of statistical bias. In our article however, the study with the largest population is a retrospective cohort study and the rando-

Systematic Literature search

Table 1 - Overview of evidence

Author	Year of publication	Country	Study Design	Population size	Comparison	Primary Outcome	Result	Secundary Outcome	Result	Conclusion
Sucato et al.	2005	United States	Retrospective cohort	613	Continuous Epidural Analgesia vs. Patient-	The average of VRS and VAS pain scores	1.3 vs. 1.9 (P<0.0001)	The average maximum pain score	2.6 vs. 3.2 (P<0.05)	Less fluctuation in pain and less maximum pain with CEA
Machida et al.	2004	Japan	Controlled Trial	50	Controlled Analgesia Continuous Subcutaneous Morphine vs. Control	VAS-scores	8h: 2.3 vs. 8.4 24h: 2.2 vs. 6.5 48h: 1.7 vs. 3.8 72h: 0.9 vs. 2.5	Number of times supplemental analgetics were required	24h: 1.2 vs. 3.8 48h: 0.5 vs. 2.6 72h: 0.4 vs. 1.3	Pain scores and analgetica consumption lower with CSM
Miller et al.	2012	Finland	Randomized Controlled Trial	36	Acetaminophen vs.	Patients with VAS pain score ≥6	39% vs. 72% (P<0.05)	Percentage of hours with VAS ≥6	8.7% vs. 17.8% (P<0.05)	Less patients with VAS pain score 6 or more in the acetaminophen group
Mayell et al.	2014	Canada	Randomized Controlled Trial	36	Placebo Gabapentin vs. Placebo	Morphine consumption (mg/kg)	1h: 0.087 vs. 0.121 4h: 0.24 vs. 0.35 8h: 0.44 vs. 0.56 24h: 1.29 vs. 146	Time to rescue analgesia	25.5 minutes vs. 24 minutes	No statistically significant reduction in opioid consumption with gabapentin and no difference in secondary outcomes

* Haemoglobin level below which patients were considered anemic.
** Perioperative acute myocardial infraction (AMI)

mized controlled trials have a smaller population size. However, the RCT's have a larger clinical effect, due to their statistically significant group sizes. In our article, we wanted to focus on the best post-operative pain management after scoliosis surgery, therefore we included all the articles equally. In the article of Machida et al. a valid point is made, epidural analgesia has a higher potency and the delivery is efficient, therefore the epidural analgesia method is commonly used after scoliosis surgery. Sucato et al. described analgesia by PCA as the safest method. However, they also found that over time the patients who were given CEA had significantly less pain at all time periods in comparison with patients who had PCA [2]. After excluding those patients who had initial CEA treatment stopped due to excessive pain, the patients in the CEA group had on average half the pain scores compared to the PCA groups. The use of gabapentin in the dosage of 600 mg as shown by Mayell et al. [7] has no significant effect on postoperative opioid consumption. When considering other literature on this topic, Rusy et al. [9] described an opioid sparing effect administering one dose of 15mg/kg preoperatively and three times a day post operatively for 5 days. This showed that the use of gabapentin could be effective in postoperative pain management when used in interval dosages, or when given in dosages of 1200 mg [8].

Bottom line:
We advise continuous epidural analgesia (CEA) to be the primary post-operative pain management. In addition, acetaminophen (paracetamol) should be given to improve pain scores, which is already the standard pain management protocol in our institution, the Erasmus MC. Secondary the use of additional Gabapentin cannot be verified at this time, further research has to be done to include or exclude Gabapentin in post-operative pain management in this type of surgery and to establish in what dosage.

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Instructions for EJM authors

When the paper is taken into review, it will be sent out to two external reviewers, a student and a staff member of Erasmus MC. Based upon these reviewers comments, their recommendations and the opinion of the editorial team, a decision will be made: reject, major revision, minor revision, accept with or without minor changes.

The paper will then be returned to the corresponding author, along with the recommendation. We try to return papers within 3 weeks after submission. When a paper is rejected, it cannot be resubmitted, but we encourage resubmissions when we recommend major or minor changes to a paper. Resubmitted paper will be reviewed again by the same reviewers and editorial team.

Before a paper can be accepted for publication, we will need a statement that the staff member that supervised your work agrees with the submission of your paper. Moreover, we need a signed Copyright Transfer Agreement (CTA) and a signed Conflict of Interest statement. When your research project involves patients or volunteers, we need a statement in the paper that the research protocol has been reviewed by a Medical Ethics Committee. Failure to provide this information at an early stage of the submission may impair the review process.

When a paper is accepted for publication, it will often be forwarded to our language editing and restructuring editors. They will each in turn give recommendations and ask the author adapt the paper accordingly. When this phase is completed, the paper will be forwarded to the publisher. Page proofs will be sent to the author for a final check.

Formatting instructions

Entry format - Papers should be submitted by email, to ejm@erasmusmc.nl. Word 2007 files are preferred for the initial submission. The file should include all figures and tables.

Title page - The title page should clearly identify the authors, the institute where the research project was carried out, as well as the staff member who supervised the project. The corresponding author name (first name and family name), email address, student id, should be clearly indicated. In case of multiple authors, state functions and departments only in superscript in alphabetical order.

Example:
First name A.G. Family name[a] and First name W.F. Family name[a] Supervisor: First name R. Lastname[b]
[a] Medical students, Erasmus MC University Medical Center Rotterdam, the Netherlands
[b] Dept. of Internal Medicine, Erasmus MC University Medical Center Rotterdam, the Netherlands
Correspondence: First name A.G. Family name, email: FirstnameFamilyname@me.com.

Structure - Please use the following sections in all papers (except in comments and opinion papers): Abstract, Introduction, Methods, Results, Discussion, References, Tables, Figures.

References - Number references in order of appearance. References should have the following format:
Rothwell, P. M. Medical and surgical management of symptomatic carotid stenosis. Int J Stroke. 2006; 1: 140-149. (I.e. year;vol:ppp-ppp) In case of more than 3 authors, name the first 3 and insert "et al.". Limit the number of references to 30. References should appear in the text as follows: "… treatment is of proven benefit.[1]"

Tables and figures - Tables and illustrations (both numbered in Arabic numerals) should be prepared on separate pages. Number tables and figures separately and consecutively. Tables require a heading and figures a legend, also prepared on a separate page and should be formatted with a text editor (example). Figures should be submitted electronically. B/w half-tone and color illustrations must have a final resolution of 300 dpi after scaling, line drawings one of 800-1,200 dpi (jpg and tiff is an acceptable format). Please note that all color-figures will be converted to gray tones. Please adapt graphs to suit this format, i.e. make use of dotted and dashed lines and hatched bars instead of colored items.. The final submission should contain figures as JPG or TIFF files.

Page layout
- Standard margins
- no headers or footers
- no columns
- left align (ragged right)
- font: 12pt Arial
- single line spacing
- main headings 14 pt bold; subheading 12 point italic
- indent every paragraph, except after headings, tables, bulleted lists or figures

Other formatting
- number all tables and figures sequentially
- place tables and figures at the end of article; insert captions at correct locations in body text
- no text boxes
- no footnotes or end notes
- do not submit figures with text as drawing objects (they cannot be edited)
- limit the use of italics and do not use italics for simple emphasis; do not italicize quotations; quotation marks are sufficient
- do not use italics for commonly understood Latin expressions such as "in vitro"
- use italics for other foreign words, such as expressions in Dutch
- no "sub-paragraphs"
- no hyphenation (afbreking)

Language
US English spelling and punctuation

The template for authors

Introduction

1. *What is the health-related problem that your research helps to solve?*

2. *What is your strategy to solve the problem?*

3. *What is your research question/hypothesis?*
   Whether a question or a hypothesis, state it in terms of 2 items:
   • variables: the measurable/observable independent and outcome variables that you measured/observed and
   • relationships: the relationships between those variables that your data analyses were designed to determine.

4. *The core concept of the methods you used to answer the research question*
   Briefly describe the core concept of the methods at the end of the Introduction section. This helps readers to understand the complex details that are then presented in the Methods section

Methods section

Organize the details of the Methods section under subheadings. Possible subheadings:

What was studied and study design (subheading)

Describe the details of
– what was studied: sample from a patient/animal population, and
– the design of the study: case-series, cohort study, case-control study, randomized trial, etc.

Data collection (subheading)

Describe the details of how the data was collected/observed

Note
Observable variables will be credible only if qualified observers and validated instruments were used to assess them. Examples of observable variables include patient symptoms, subject responses to open interviews/ questionnaires, ultrasound/MRI/CT images, assessments of articles in a literature review etc. In such cases, build credibility in the Methods section; report "who" observed and interpreted the data. For example, "An experienced radiologist interpreted the images."

Note
When reporting on decisions/judgments that were made, use the "we" form—take responsibility for what you did.

Note
The Methods section reports historical facts and must be in past tense.

Data analysis (subheading)

Results section

5. *The core concept of the Results*
   Briefly describe the core concept of the results in a short paragraph at the beginning of the Results section. This helps readers to understand the details that follow. Note just as in the Methods section, this section reports historical facts and must be in past tense.

Then organize the details of your Results under sub-headings, for example:

Patient/animal characteristics
Data
Statistical results

Discussion section

Structure your Discussion to focus on 4 core concepts (6, 7, 8, and 9 below).

6. *The answer to your research question*
   Present this right at the top of the Discussion section—the very first sentence, a present tense statement that expresses—to the best of your knowledge—how the world works as related to your research question/hypothesis. It is a direct answer to the question/hypothesis stated in the Introduction.
7. *Support that answer?*
   a) how your factual findings, (expressed in past tense), support your answer.
   b) relating the findings of others to your answer.
   c) theoretical considerations that support your answer.

Limitations (subheading)

8. *The limitations to that answer*
   Focus explicitly on limitations related to possible confounders:
   • sample size
   • specific locations/medical centers of your study,
   • possible ethnic/cultural variables,
   • uncontrolled patient/subject characteristics and
   • underlying assumptions.

Conclusions (subheading)

The Conclusion is not a summary, but should focus on the consequences of your work. Structure this subsection using separate paragraphs that state 2 main messages (9 and 10)

9. *What are the practical/theoretical consequences of your answer?*
   The value—relevance— of your work: how it helps to solve the problem described at the beginning of the Introduction.
10. *What is a next step to help solve the original problem?*
    • a new research question to be answered
    • a refinement of the present study to reduce limitations
    • a protocol to implement the findings in the clinic

Advice to the reviewers of EJM

For the convenience of our future contributors and our readers, we publish here the advice we give to our reviewers.

In the process of reviewing a paper, please refer to the following points:

- Your first step should be to evaluate your relationship with the authors. To ensure the credibility of the process, reviewers should not have a conflict of interest with the authors. If this is a case, the paper should be appointed to other reviewers. Please keep us informed whether conflict of interest is an issue for you as an appointed reviewer.
- Is this work relevant and interesting for EJM?
- Are the objectives appropriate and clearly stated?
- Are the data valid?
- Are the conclusions valid and properly supported?
- Is the already existing work described adequately?
- Paper structure/organization; is this logical?
- Does abstract clearly convey meaning of the paper?
- Is the paper well written and can be easily understood? (Please keep in mind that students don't have the experience to reed throughout the paper very quickly and to understand everything in a research paper at the first glance)
- Are all sections really needed, or could they be shortened?
- Is the science reliable? Please, be aware of ethical issues such as plagiarism!

Comments should be detailed and specific. Mentoring the authors includes helping authors improve their paper under review even if these papers will/could not be accepted for publication in our journal. By careful reviewing, you will help improving the quality of papers published elsewhere too. Avoid vague complaints and provide appropriate citations if authors are unaware of the relevant work.

Please consider a manuscript received for reviewing as a confidential document and do not discuss the content of this paper with others. To maintain the validity of this process, you should never contact the authors about the paper under review.

The review process serves two important goals: providing guidance to the authors to improve the quality of their paper, and providing the editor or editorial board with valuable recommendations regarding the acceptance or rejection of the peer-reviewed papers (along the whole spectrum of major revision- minor revision- rejection). So it is important that you give comments to the authors, and to the editor in separate sections. Please use the provided form, because this makes life easier for you, the editor and the authors.

EJM is committed to rapid editorial decisions and publication. We request that reviewers return their comments within the time indicated at invitation. If any unanticipated difficulties arise that may prevent you from submitting the review on time, contact us by sending an email to the editorial office at ejm@erasmusmc.nl. You are welcome to contact us if you have any questions.

For more information about guidelines for the review process, please visit our website: www.erasmusmc.nl/ejm. We also recommend you to view the presentations of the EJM workshop on our website. Here you can find instructions about how to scan through a paper and grab its essence, and how to structure your comments to the authors and to the editor.

Januari 2017, Editorial board of Erasmus Journal of Medicine.

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