THE FATE OF THE NEOAORTIC ROOT FOLLOWING THE ARTERIAL SWITCH FOR TRANSPOSITION

by

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Abstract

This study looks at the fate of the neoaortic root following the arterial switch for transposition. The study aims to address the hypothesis; is there variability in the fate of the neoaortic root described in the literature? And whether this may, in part, be determined by the operative approach used at the arterial switch. The study also aims to assess whether patients who underwent the arterial switch during childhood in Birmingham demonstrate progressive neoaortic root dilatation on serial CMR imaging into adulthood and their incidence of aortic dissection and surgical reintervention. The first section of the study is a narrative review which follows after findings that there is heterogeneity in the data of reporting the outcomes of the neoaortic root. The second section reports a clinical dataset from Queen Elizabeth Hospital Birmingham, showing the collection of neoaortic root measurements of 205 patients following arterial switch for transposition at Birmingham Children’s Hospital

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1. Introduction

1.1 Transposition of the great arteries (TGA)

1.1.1 What is transposition?

Transposition of the great arteries (TGA), otherwise known as D-transposition, or more simply as transposition, is a congenital heart defect where neonates are born with atrioventricular concordance and ventriculoarterial discordance (D-TGA) (Fricke 2020). Transposition occurs in around 5% of all children with a congenital heart defect. This makes it the second most common cyanotic congenital heart defect after tetralogy of Fallot (Szymanski et al, 2023). Whilst the aetiology of TGA remains unknown, it has been reported that the defect is more prevalent in males, with a 2:1 male-to-female ratio (Warnes., 2006). It has also been stipulated that there are certain risk factors for a fetus to develop this defect, such as viral illness or poor nutrition of the mother during pregnancy, the mother being over 40 years of age, or the mother experiencing diabetes or alcoholism during the pregnancy (Szymanski et al, 2023). Contrary to many other forms of CHD, TGA is rarely associated with an underlying genetic cause (Yasuhara and Garg., 2021).

When babies are born with TGA, they usually become cyanotic very quickly after birth when they transition from fetal to post-natal circulation. During fetal circulation, they receive oxygen from the placenta and umbilical cord; after birth, this changes to where inhalation by the lungs saturates the blood with oxygen to be pumped around the body and delivered to cells (Szymanski et al, 2023).

Neonates with TGA have a ‘transposition’ of the aorta and the main pulmonary artery, leading to the systemic and pulmonary circulation being parallel rather than series (Szymanski et al, 2023). In normal postnatal circulation, the oxygenated blood from the lungs travels to the left atrium, to the left ventricle and is pumped by the heart out of the aorta and around the body to provide oxygen to cells; however, in neonates with TGA, the oxygenated blood is redirected back to the vascular bed of the lungs via the pulmonary artery, meaning the oxygen is not supplied to the cells of the body (Van der Palen, 2021). Furthermore, in TGA, when deoxygenated blood from the body travels into the right atrium and ventricle, it is then pumped back to the body through the aorta, leading to the appearance of cyanosis. This is opposed to normal circulation, where the deoxygenated blood leaves the right ventricle through the pulmonary artery to be saturated with oxygen in the lungs (Van der Palen, 2021). These parallel circuits of blood flow are determined because of the abnormal connections present in TGA where the left ventricle is connected to the pulmonary artery, and the right ventricle is connected to the aorta (Allen et al., 2008).

The chances of survival of the neonate with TGA increase if they are born with a patent ductus arteriosus (PDA), atrial septal defect (ASD) or ventricular septal defect (VSD). These allow the deoxygenated and oxygenated blood to mix between the parallel systemic and pulmonary circulations (Fricke 2020), acting as left-to-right shunts, providing a way for oxygenated blood to reach the organs and tissues that are supplied oxygen via systemic circulation (Planche, Lacour-Gayer and Serraf., 1998). However, it remains that children born with TGA who do not have it surgically corrected have a mortality rate of around 30% by the end of week one, 50% by the end of month one and 90-95% by the end of their first year of life (Allen et al., 2008, Fricke 2020). Conversely, when neonates with TGA are diagnosed and operated on early, the chance of long-term survival is over 90% (Allen et al., 2008).

1.1.2 TGA subtypes

Whilst nearly 70% of TGA occurrences are isolated lesions, TGA can also be associated with other defects. These can include ventricular septal defects (VSD), atrial septal defects (ASD), patent ductus arteriosus (PDA), and left ventricular outflow tract obstruction (LVOTO) which are the most common associated defects (Van der Palen, 2021). Less common cardiac defects that occur with TGA are aortic arch abnormalities, such as coarctation, pulmonary valve abnormalities, such as asymmetrical three-leaflet, stenosis or bi-leaflet valve, and ventricular defects such as ventricular hypoplasia and atresia of the atrioventricular valve (Rigby, 2021). Double outlet right ventricle (DORV) is another type of TGA, where patients often also have a subpulmonary VSD; this combination is called Taussig-Bing anomaly. Individuals with Taussig-Bing often have associated aortic arch abnormalities (Van der Palen, 2021). The presence of associated defects is an important consideration when determining the surgical correction of TGA (Van der Palen, 2021).

1.1.3 Correction of TGA

As previously mentioned, a neonate born with TGA may be able to mix systemic and pulmonary circulation if they have a VSD, ASD or PDA, which facilitates this by acting as a shunt. Unfortunately, this is not enough to sustain life in neonates, who need corrective surgery for this. If these defects are not present or minimal and thus cannot allow sufficient mixing of circulation, the neonate will suffer systemic acidosis, leading to fatal hypoxia. Ideally, TGA is detected prenatally so that delivery can be planned in a specialist centre and early treatment can be given to avoid cardiovascular collapse.

Immediate treatment to ensure sufficient and continuous flow between circulations includes the administration of E1 prostaglandins, which keep the arterial duct open, allowing the mixing of deoxygenated and oxygenated blood (Van der Palen, 2021). A balloon atrial septostomy can also create an opening between the atria, allowing an additional or alternative route for mixing systemic and pulmonary circulation (Van der Palen, 2021).

Whilst a balloon atrial septostomy and E1 prostaglandins contribute to the sustainment of the child in the short term, surgical correction of the TGA is necessary to allow long-term survival (Van der Palen, 2021).

1.2 The arterial switch operation (ASO)

Before the arterial switch operation (ASO), there were palliative operations, such as the atrial switch, which aimed to correct the transposition. The atrial switch operation was well-established and popular among surgeons, who viewed the operative procedure as safer than the ASO when Adib Jatene introduced it in 1975 (Jatene et al., 1975). The operative mortality of ASO was very high, at 30-60%, until the late 1980s (Hutter et al., 2002). Around this time, the mortality dropped due to the simplification of the ASO by introducing the trapdoor technique for coronary translocation by Brawn and Mee in Melbourne’s Royal Children’s Hospital (Brawn and Mee, 1988). Between 1983 and 1989, this hospital's mortality rate dropped to 1.6% (Brawn and Mee, 1988).

The ASO is very successful in the short term, with an early mortality rate of just 1-3% (Fricke et al., 2012, Lo Rito et al., 2015). However, many adverse long-term outcomes are associated with the ASO such as neoaortic root dilatation, neoaortic root regurgitation, coronary artery stenosis and neo-pulmonary stenosis (Lim et al., 2013). These can result in required reoperation (Fricke and Konstantinov, 2019). This seems particularly prevalent in patients who experience TGA with associated defects such as VSD, Taussig-Bing anomaly, concomitant arch and late presentation of TGA with IVS (Fricke and Konstantinov, 2019).

1.3 Neoaortic root dilatation and regurgitation

Aortic root dilatation is when the aortic root increases in diameter, it ‘dilates’. In the normal population, the risk of progressive dilatation of the aortic root is increased by being male, smoking, suffering renal failure, having high diastolic blood pressure, any previous infections surrounding the heart, occurrence of atherosclerosis and left ventricular wall abnormalities (McMahon et al., 2004; Isselbacher, 2005; Nataf and Lansac, 2006).

After the ASO, the dilatation of the neo-aorta is a common finding (Fricke and Konstantinov, 2019). This is undesirable as it can lead to aortic regurgitation. Aortic regurgitation occurs when the expansion of the neoaortic root means that when the neoaortic valve is closing, the valve leaflets cannot meet fully, preventing the valve from being closed completely. In normal circumstances, when the left ventricle contracts, oxygenated blood is pumped out of the heart through the aorta under high pressure, being transported to tissues and organs. However, during neoaortic root dilatation the neoaortic valve is not functioning optimally, and a backflow of blood often happens during diastole (Dewaswala and Chait, 2022). It is dangerous because it reduces the volume of blood pumped to the body's cells, ultimately reducing the oxygen they receive. Over time the aortic regurgitation can lead to impairment of the left ventricle. The volume overload of the left ventricle can cause eccentric hypertrophy, resulting in a decline of the ejection fraction and, thus, decreased systolic function. As cardiac function drops, symptoms of heart failure may develop (Dewaswala and Chait, 2022).

Furthermore, when the aortic root dilatation is severe it can lead to dissection, with tearing or rupture of the aortic root, which is life-threatening or, if chronic, can cause the bulging and stretching of the aorta, often known as an aortic root aneurysm.

Laplace's law states that:

"The tension on the wall of a sphere is the product of the pressure times the radius of the chamber, and the tension is inversely related to the thickness of the wall" (Gilbert-Kawai and Wittenburg, 2014).

This suggests that as the aortic root becomes more dilated, there is increased pressure on the wall of the aorta, and thus, the wall tension rises. The findings of many observational studies follow this and it has been demonstrated that increased aortic root dilatation increases the chances of dissection and aortic aneurysm (Nataf and Lansac, 2006). Furthermore, as aortic aneurysms expand the rising tension placed on the wall means the occurrence of rupture increases (Coady et al., 1999; Davies et al., 2002; Nistri et al., 2005).

Aortic regurgitation and aortic root aneurysms can present with the symptoms of fatigue, shortness of breath; especially when exercising, mild chest pains, ankle swelling and heart palpitations, or it can be that no symptoms are noticed (Dewaswala and Chait, 2022). On the contrary, when aortic root aneurysms tear or rupture, the pain is noticeable and intense. This can be felt in the chest and radiate to the back, with severe shortness of breath experienced, fainting and problems with swallowing (Levy et al., 2022). However, neoaortic dissection in patients with repaired TGA is rare, suggesting that it is less prone to the effects of chronic dilatation.

Once the neoaortic root is dilated, it may stabilise or continue to grow, but it will not shrink independently. Thus, if the aortic regurgitation is severe, it may be necessary to undergo further surgical correction to increase the functionality of the neoaortic valve.

1.4 Neoaortic root reoperation

When severe neoaortic root dilatation occurs, with or without secondary neoaortic regurgitation, the patients often undergo reoperation to their neoaortic root to correct it and prevent further complications. There are two main approaches to neoaortic root reoperations. The ‘radical’ approach is when the neoaortic root, or the valve, is replaced completely. The ‘conservative’ approach aims to spare the neoaortic valve but must still replace the rest of the neoaortic root (Nataf and Lansac, 2006). Koolbergen and colleagues (2014) stated that for their Leiden cohort, the freedom from neoaortic root reoperation was 99.3% at five years, 97.3% at fifteen years and 95.0% at twenty-five years.

1.5 What do we know about the fate of the neoaortic root following ASO?

In 2006, Nataf and Lansac stated that when the native aortic diameter increases to 6cm, the cumulative risk of experiencing either dissection, rupture or death is 14.1%. The individual occurrence is that the risk of dissection is 3.7%, rupture is 3.6% and death is 10.8% per year. Whilst these measurements are valuable predictors for the native aortic root, they cannot be used as absolute guidelines for the neo-aorta as the aortic and neoaortic roots are physiologically different. Whilst the ASO is often known as an “anatomical repair”, the neoaortic root began as the pulmonary root, meaning the wall tissue composition may differ from a normal aortic root. The reverse is also true; the neo-pulmonary root is anatomically different from the normal pulmonary root (Stamm, Anderson and Ho, 1998). The pulmonary root is not made to withstand the high pressures of systemic circulation (Stamm, Anderson and Ho, 1998). The neoaortic root, therefore, may respond differently to the aortic root when continuously faced with these high pressures.

Various studies have conflicting results on the neoaortic root's fate after the ASO. Some suggest that neoaortic root dilatation and aortic regurgitation are stable over time. In contrast, others suggest a progressive increase in the dilatation and extent of aortic regurgitation (Schwartz et al., 2004; Losay et al., 2006; Bove et al., 2008).

The evolution of the neoaortic root following the ASO needs to be clearly defined, and the mechanism of dilatation of the neoaortic root is unknown (McMahon et al., 2004). As data on late follow-up becomes available, this must be used to understand the neoaortic root in more detail to identify and assess the trend in the neoaortic root following the ASO.

1.6 Project components, aims and hypotheses

This project encompasses two main components. The first is a systematic review of the literature on the fate of the neoaortic root after the arterial switch for transposition. The second includes the collection and analysis of a clinical data set which examines the late outcomes of the neoaortic root in a cohort of patients who have undergone arterial switch at a single institution, Birmingham Children's Hospital, to describe the changes in dimensions that occur over time.

Aims:

1. To conduct a systematic review of the literature on the fate of the neoaortic root after the arterial switch for transposition.
2. To examine the late outcomes of the neoaortic root in a cohort of patients who have undergone arterial switch at a single institution to describe the changes in dimensions that occur over time.

Hypotheses:

1. There is variability in the fate of the neoaortic root described in the literature. This may, in part, be determined by the operative approach used at the arterial switch.
2. Patients who underwent arterial switch during childhood in Birmingham will demonstrate progressive neoaortic root dilatation on serial CMR imaging into adulthood but with a low incidence of aortic dissection or surgical reintervention.

2. A narrative review of the long-term fate of the neoaortic root following arterial switch operation for transposition.

2.1 Introduction

The domain to be studied was the arterial switch operation which has become the standard approach for the surgical management of transposition in most centres worldwide. However, there is evidence that the neoaortic root may dilate over time and require reintervention. In this chapter, I conducted a narrative review of the literature to assess the long-term outcomes of the neoaortic root following arterial switch for transposition, the rate and extent of neoaortic dilatation, and the need for reintervention.

2.2 Methods

2.2.1 The subject of the review

Review title: A narrative review of the long-term fate of the neoaortic root following the arterial switch operation for transposition.

Review question: What is the long-term fate of the neoaortic root following the arterial switch for transposition?

This review was carried out as recommended in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2022). The arterial switch operation for transposition was defined as the anatomical correction of ventricular-arterial discordance by translocating the great arteries so that the left ventricle supplies the neo-aorta and the right ventricle supplies the neo-pulmonary artery (Jatene et al., 1975).

2.2.2 The search strategy

An extensive literature search strategy was applied to the electronic databases PubMed, EMBASE and LILACS. The search strategy included only terms relating to or describing the outcome of the intervention. The PubMed search terms were adapted for use with the other bibliographic databases in combination with database-specific filters (Table 1). All studies published before the date the searches were run were sought.

Table 1: Search strategies utilised for the various databases.

Database name	Search strategy applied
PubMed	#1 = transposition of great vessels [mh] OR transposition of the great vessels [tiab] OR transposition of the great arteries [tiab] OR d-transposition [tiab] OR d-loop transposition [tiab] #2 = arterial switch operation [mh] OR arterial switch [tiab] #3 = #1 AND #2 #4 = animals [mh] NOT humans [mh] #5 = #3 NOT #4 #6 = neoaort* [tw] OR aort* [tw] #7 = #5 AND #6 *mh,* Medical Subject Heading (MeSH) term ('exploded'); *tw,* text word; *tiab*, title or abstract.
EMBASE	#1 = exp great vessels transposition OR transposition of the great arteries.mp OR transposition of the great vessels.mp OR d-transposition.mp OR d-loop transposition.mp #2 = arterial switch.mp #3 = #1 AND #2 #4 = neoaort*.mp OR aort*.mp #5 = #3 AND #4 *exp,* MeSH heading exploded*; mp,* title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword.
LILACS	LILACS #1 = tw:(transposition OR transposición OR transposição) #2 = tw:(arterial switch OR Jatene) #3 = #1 AND #2 *tw,* text word.

2.2.3 The inclusion/exclusion criteria and outcomes considered

The types of study to be included were any studies with data on the long-term outcomes of the neoaortic root after the arterial switch operation for transposition. The long-term outcomes were defined as a median follow-up of at least five years after arterial switch operation.

The exclusion criteria for study type were case reports, case series, opinion pieces, and commentaries. Any study documenting patients with a median follow-up of less than five years was excluded. There were no exclusions applied for the coronary relocation operative technique used. There were also no language restrictions. There were no restrictions on the publication dates of the studies.

The main outcome assessed in this review was the change in the size of the neoaortic root over time, with the additional outcomes being a need for surgical reintervention to the neoaortic root and the frequency and categorisation of neoaortic valve regurgitation.

2.2.4 Study screening

The titles and abstracts of the studies retrieved using the search strategy were screened independently by two review authors (myself and Dr Stoll) to identify studies which met the inclusion criteria. Any discrepancies were highlighted and discussed, consulting a third reviewer (Mr Drury) if an agreement could not be reached. The full texts of the included studies were then retrieved and assessed for eligibility by myself and my supervisors. If a paper could not be retrieved, the authors of the paper were contacted. If the authors did not respond in the following months, the paper was excluded.

A key was utilised to code the reasons for exclusion. Any disagreements over the eligibility of particular studies were resolved through consensus.

2.2.5 Data extraction

A standardised, pre-piloted form was used to extract data from the included studies to assess study quality and evidence synthesis. The extracted information included: study setting; study population and participant demographics and baseline characteristics; details of the intervention and type of surgery; outcomes, and neoaortic root measurements. Data extraction was performed by myself, although ideally, it would have been repeated independently by a second reviewer to improve data quality.

2.2.6 Assessment of bias

I independently assessed the risk of bias in included studies by considering the following characteristics in accordance with the Newcastle-Ottawa scale for determining the quality of non-randomised studies (Hartling et al, 2009).

For each study, the categories for risk of bias were 'Good', 'Fair' or 'Poor quality', assessed in the following domains:

a) Selection
b) Comparability
c) Outcome/Exposure

A study was awarded a maximum of one star for each numbered item within the Selection and Outcome/Exposure categories and a maximum of two stars for the Comparability section.

Case-control and cohort studies were judged by slightly different criteria as per the Agency for Healthcare Research and Quality (US) (Hartling et al., 2012). This is documented in Appendix 1.

2.2.7 A narrative review

Whilst I set out to complete a systematic review with meta-analysis, the methods of reporting of not just the neoaortic root measurements, but also the reported patients, timings and outcomes, method of cross-sectional imaging, calculations used for body surface area, definitions of TGA subtypes and the way of assessing neoaortic regurgitation was highly heterogeneous. A meta-analysis could not be performed as it would not have given reproducible or reliable results. Therefore, a narrative review has been done.

2.3 Results

2.3.1 An overview of the papers included

Three databases were screened using the search strategy detailed in the methods. There were 1767 records found, 599 of these were duplicates, leaving 1168 papers. There were 151 studies that made it to full-text screening, these papers had authors affiliated with eighty-four centres in thirty-three different countries. Seven of the studies were multi-centred. At full-text screening, 124 studies were excluded, 57% due to the absence of neoaortic root measurements and 21% because the cohort was the same as in another study from the same centre, with the other study containing more recent data. The remaining reasons are described in Figure 1. There were twenty-seven papers that passed all screening stages. The authors of these papers were affiliated with forty centres in twenty-six countries. Just one paper was a multicentre study. The key findings of the final studies are documented in Table 2 and described in the next section.

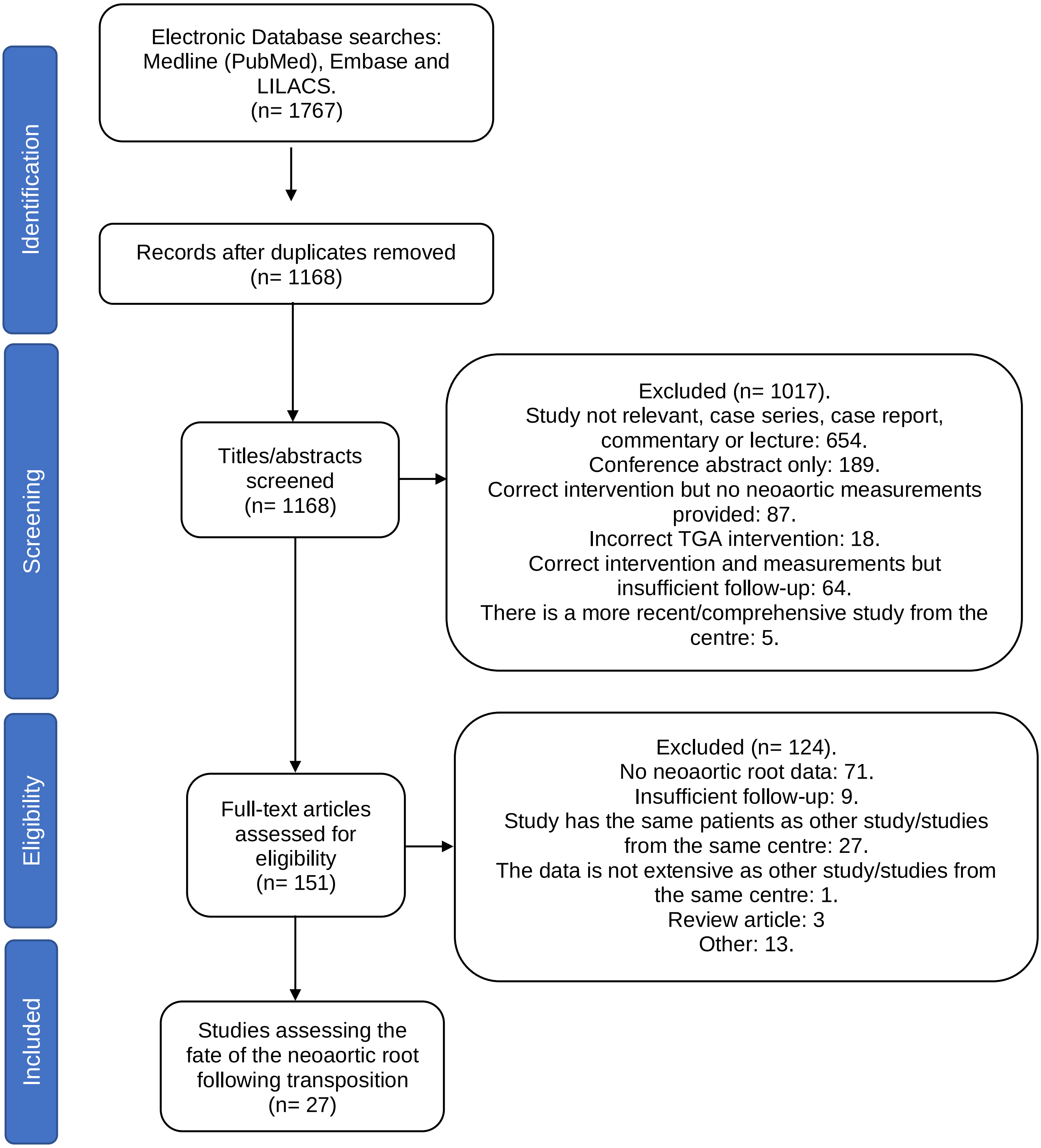

Figure 1: Flow diagram according to PRISMA standards detailing databases searched, records found, inclusion and exclusion of papers following the screening on title/abstract and full-text, and the final number of papers for inclusion.

Table 2: Summary of key data from the 27 articles included.

First author and year of publication	Number of patients	TGA subtype	Operative repair technique	Absolute or indexed measurements of the neo-aorta	Z scores	Annual growth	AR ≥ moderate	Reoper-ation to neo-aorta
Takada, 2021	36	29 D-TGA. 7 TBA.		Aortic valve annulus: AR group= 30 ± 6.0 mm. Non-AR group= 24 ± 4.6 mm. SoV: AR group= 47 ± 6.7 mm. Non-AR group= 39 ± 6.7 mm. STJ: AR group= 31 ± 8.6 mm. Non-AR group= 24 ± 4.8 mm. Asc aorta: AR group= 29 ± 5.2 mm. Non-AR group= 24 ± 3.1 mm.		SoV (mm indexed): AR group= 24 ± 5. Non-AR group= 20 ± 4.	Mild-moderate: 7 Moderate-severe: 2	3
Van der Palen, 2019	345	TGA-IVS: 230. TGA-VSD: 89. DORV-SP-VSD: 26.	Double button: 197 (57.1%). Single trapdoor, single button: 96 (27.8%). Double trapdoor: 31 (9.0%). Other or unknown: 21 (6.1%).			Annulus: 0.39 ± 0.06 mm. SoV: 0.63 ± 0.09 mm. STJ: 0.54 ± 0.11 mm.	33	10

Martins, 2019	157	TGA IVS: 93. TGA VSD: 41. TGA VSD CoAo: 21. TGA subpulmonary stenosis: 2.		SoV: Cusp to commissure: 25.62 ± 6.02 (mm/BSA$^{0.5}$). Cusp to cusp: 27.15 ± 3.20 (/BSA$^{0.5}$).	SoV: 2.94 ± 1.51.		7	1
Cheung, 2019	21			Aortic valve annulus: 14.41 mm/m^2 SoV: 19.88 mm/m^2 STJ: 17.41 mm/m^2 Asc aorta: 17.88 mm/m^2			2	
Oda, 2019	145	IVS: 79. VSD: 46. DORV: 20. Coarctation of the aorta: 19. LVOTO: 12. Bicuspid native pulmonary valve: 1.	Punch only: 71 (49.0%). Trapdoor only: 60 (41.3%). Punch and trapdoor: 13 (9.0%). Yacoub: 1 (0.7%).	Aortic valve annulus: Frontal view: 30.19 ± 1.2. mm. Lateral view: 30.6 ± 1.0 mm. SoV: Frontal view: 46.9 ± 1.1 mm. Lateral view: 47.4 ± 1.3 mm.		SoV: 0.0046 to 0.029 z score. Annulus: 0.0046 to 0.029 z score.		
Martins, 2018	127	Simple TGA: 84. Complex TGA: 43.	Lecompte: 122. (Coronary reimplantation never trapdoor, always in sinuses of Valsalva.)		Valve annulus: Simple: 1.8 ± 1.0. Complex: 2.2 ± 1.3.		24	2

Vida, 2017	111	D-TGA: 99. DORV TGA: 12.	Trapdoor: 50. Lecompte: 97.	Aortic valve annulus: 29.6 mm median (27–34.6 IQR). SoV: 46 mm median (42–48 IQR).	Valve annulus: 3.9 median. SoV: 6.6 median.		54	126
Di Salvo, 2017	105	D-TGA with VSD: 24. D-TGA with gothic arch: 46. D-TGA with no gothic arch: 59.	Posterior translocation of the ascending aorta.	SoV: GA group: 27.4 ± 7.5 mm. NGA group: 21.2 ± 6.9 mm.				0
Shepard, 2016	220	D-TGA: 205. TGA-VSD: 94. TGA with subvalvar or valvar PS: 23. TGA with subvalvar or valvar AS: 19. TGA with coarctation: 25. TGA-DORV: 15.		SoV: A-P diameter: 2.68 ± 0.39 (cm/BSA$^{0.5}$). Lateral diameter: 2.87 ± 0.40 (cm/BSA$^{0.5}$). Asc aorta: A-P diameter: 1.73 ± 0.32 (cm/BSA$^{0.5}$). Lateral diameter: 1.73 ± 0.32 (cm/BSA$^{0.5}$).	SoV: 3.54 ± 1.91 (-0.84 - 9.37). Asc aorta: -0.26 ± 1.91 (-5.13 - 7.41).	SoV: 0.03 z score.	16	39
Baruteau, 2016	220	Isolated ventricular	Lecompte and direct transfer.		SoV: ≥ 3: 53 patients. ≥ 5: 19 patients.		28	42

		septal defect: 174. Multiple ventricular septal defects: 29. Aortic arch obstruction: 64.						
Morgan, 2017	66	TGA/IVS: 35. TGA/VSD: 20. TGA with aortic arch anomaly: 9. Taussig-Bing: 2.	Lecompte.	SoV: 23 ± 6 mm/m^2				
Biglino, 2014	18		Lecompte.	Aortic valve annulus: Cross sectional area 7.3 ± 2.3 cm^2			0	0
Raju, 2013	32	Simple TGA: 14. Complex TGA: 14. Taussig-Bing: 4.						15
Voges, 2013	51	Simple TGA: 40. (11 had additional	Lecompte: 48.	SoV: 6.03 ± 2.41 cm/m^2 Asc aorta: 3.41 ± 1.44 cm/m^2			5	

		septal defects).						
Ruys, 2013	24	Baseline Characterist-ics given for original cohort of 30: Simple TGA: 17. (TGA with IVS: 16. TGA with VSD without patch: 1). Complex TGA: 13. (TGA with VSD with patch: 7. TGA with DORV and/or aortic pathology: 6).	Lecompte in 70% of cases.	SoV: MRI: Mean diameter 39 mm (30-49). Echo: 33 ± 6 mm.			1	0
Co-Vu, 2013	124	Simple: 50. TGA with coexisting lessions: 74. (VSD: 37.			Aortic valve annulus: ≥2.5: 67 patients. SoV: ≥2.5: 88 patients.	SoV: 0.16cm, 0.08 z score. Annulus: 0.09cm, 0.0002 z score.	17	0

		Nonusual coronary artery pattern: 20. Coarctation of the aorta: 14. DORV morphology: 11. Bicommissu-ral pulmonary valve: 7. LVOTO: 2).						
Pees, 2013	52		Lecompte and direct transfer.	Aortic valve annulus: 21.8 ± 5.7 mm. SoV: 27.6 ± 7.6 mm. STJ: 23.7 ± 7.5 mm. Asc aorta: 22.34 ± 7.4 mm.	Aortic valve annulus: 2.64 ± 1.24. SoV: 2.33 ± 1.3. STJ: 2.41 ± 1.65. Asc aorta: 1.33 ± 2.17.			
Kempny, 2012	145	TGA with IVS: 95. TGA with VSD: 49. Taussig-Bing: 1. Aortic coarctation: 12.	Lecompte: 128.	SoV: >45 mm: 3 patients. Maximum size was 49 mm. SoV of moderate/severe AR patients: 39.5 ± 5.5 mm. SoV of none/mild AR patients: 35.0 ± 5.2 mm.			8	4

Jhang, 2012	240	TGA with IVS: 137. Taussig-Bing: 18. VSD: 100. Posterior TGA: 1. Arch obstruction: 16. Pulmonary stenosis: 9. Bicuspid pulmonary valve: 12.	Trapdoor.		Aortic valve annulus: ≥3: 44 patients. SoV: ≥3: 74 patients. STJ: ≥3: 12 patients.		6	2
Bove, 2008	93	TGA with IVS: 62. TGA with VSD: 31. (8 had Taussig-Bing).	Direct: TGA/IVS group: 35. TGA/VSD group: 20. Trapdoor: TGA/IVS group: 27. TGA/VSD group: 11.		Aortic valve annulus: IVS: Mean 1.45 ± 1.83. > 3: 10 patients. VSD: Mean 3.17 ± 2.03. > 3: 15 patients. SoV: IVS: Mean 1.96 ± 1.57. > 3: 16 patients. VSD: Mean 3.25 ± 1.59. > 3: 16 patients. STJ:	Annulus: IVS group: 1.83 mm, 0.25 ± 0.65 z score. VSD group: 2.54 mm, 0.41 ± 1.15 z score. SoV: IVS group: 2.38 mm, 0.04 ± 0.8 z score. VSD group: 3.27 mm, 0.10 ± 0.73 z score. STJ:	1	5

					IVS: Mean 0.18 ± 1.42. > 3: 4 patients. VSD: Mean 0.70 ± 1.65. > 3: 2 patients.	IVS group: 1.74 mm, 0.17 ± 0.67 z score. VSD group: 2.19 mm , 0.13 ± 1.12 z score.		
Marino, 2006	82	TGA with IVS: 52. TGA with VSD or DORV: 30.	Lecompte. Coronary buttons were excised with a button of aortic wall and reimplanted the posterior great vessel.	Aortic valve annulus: Post-op: 0.93 ± 0.34 cm. 0-2 yrs: 1.19 ± 0.25 cm. 2-4 yrs: 1.37 ± 0.23 cm. 4-6 yrs: 1.55 ± 0.30 cm. 6-8 yrs: 1.73 ± 0.32 cm. 8-10 yrs: 1.80 ± 0.36 cm. 10-12 yrs: 1.99 ± 0.44 cm. 12-14 yrs: 2.08 ± 0.34 cm. 14-17 yrs: 2.30 ± 0.50 cm. SoV: Post-op: 1.23 ± 0.44 cm. 0-2 yrs: 1.63 ± 0.35 cm. 2-4 yrs: 1.88 ± 0.36 cm. 4-6 yrs: 2.12 ± 0.33 cm. 6-8 yrs: 2.39 ± 0.46 cm. 8-10 yrs: 2.52 ± 0.50 cm. 10-12 yrs: 2.72 ± 0.54 cm. 12-14 yrs: 2.84 ± 0.35 cm. 14-17 yrs: 3.32 ± 0.73 cm. STJ: Post-op: 0.97 ± 0.42 cm. 0-2 yrs: 1.27 ± 0.30 cm. 2-4 yrs: 1.50 ± 0.33 cm. 4-6 yrs: 1.74 ± 0.39 cm.	SoV: 1 year post ASO: > 2: 49 patients. 5 years post ASO: > 2: 32 patients.	SoV: 0.11 cm, 0.10 z score. STJ: 0.10 cm, 0.08 z score. Basal hinge points: 0.08 cm, 0.02 z score.	4	10

				6-8 yrs: 1.93 ± 0.41 cm. 8-10 yrs: 2.02 ± 0.38 cm. 10-12 yrs: 2.16 ± 0.49 cm. 12-14 yrs: 2.38 ± 0.32 cm. 14-17 yrs: 2.52 ± 0.26 cm.				
McMahon, 2004	119	Simple D-TGA: 73. D-TGA/VSD: 36. DORV/subp-ulmonary VSD: 10.	Trapdoor: 69.		SoV: 1-6 months after ASO: 1.3 (-1.45-7.4). 10 years after ASO: 3.4 (0.98-10.3). Annulus: 1-6 months after ASO: 0.94 (-2.7-5.6). 10 years after ASO: 1.6 (-2.4 to 4.6). Anastomosis: 1-6 months after ASO: - 0.52 (-2.68-1.3). 10 years after ASO: 0.54 (-2.1-2.7).	SoV: 0.21 z score.	3	3
Hövels-Gürich, 2003	60	TGA with IVS: 47.	Direct.	Aortic valve annulus: Median 20mm at latest follow-up (range 12-31 mm, IQR 5 mm).		No growth for diameters observed.	1	3

		TGA with VSD: 13. (TGA with aortic isthmic stenosis: 3).		21mm 5 yrs prior (range 16-31 mm, IQR 5 mm). SoV: Median 27mm (range 17-36 mm, IQR 6 mm). 32mm 5 yrs prior (range 24-44 mm, IQR 6 mm).		Z scores decreased between mid-term and present evaluation.		
, 2001	144	Simple TGA: 97. TGA with VSD: 47. (Taussig-Bing: 16 Coarctation of the aorta: 8. Interrupted aortic arch: 1. TGA with atrioventric-ular septal defect and cor triatriatum: 1).	Trapdoor.		Aortic annulus: 0-4 months: 0.63 ± 2.20. 5-12 months: 2.56 ± 2.30. 1-5yrs: 2.40 ± 2.55. 6-10yrs: 1.07 ± 2.14. 11-15yrs: 1.26 ± 2.05. >15yrs: 1.29 ± 2.41. SoV: 0-4 months: 0.22 ± 0.94. 5-12 months: 1.76 ± 1.08. 1-5yrs: 2.28 ± 1.11. 6-10yrs: 1.86 ± 1.03. 11-15yrs: 1.53 ± 1.02.		2	4

					>15yrs: 1.53 ± 1.22. Anastomosis: 0-4 months: -0.64 ± 0.98. 5-12 months: 0.83 ± 1.49. 1-5yrs: 1.33 ± 1.35. 6-10yrs: 1.69 ± 1.39. 11-15yrs: 1.63 ± 1.53. >15yrs: 2.11 ± 2.54.			
Vera, 2021	74	TGA with IVS: 6. Complex TGA: 33. TGA with VSD: 22. TGA with VSD and coarctation: 11.	Trapdoor.	SoV: 21.6 ± 5 mm.	SoV: 2.24 ± 1.9.		5	5
Loke, 2019	42	TGA with IVS: 31. TGA with VSD: 7. DORV: 4.	Lecompte.	SoV: 573 ± 151 mm^2/m^2 Asc aorta: Prox-AscAo area: 436 ± 164 mm^2/m^2 MidAscAo area: 229 ± 79 mm^2/m^2				2

Villalba, 2016	224	Simple TGA: 122. Complex: 77. (With coarctation: 4. With LVOTO: 2). Taussig-Bing: 25. (With coarctation: 9).			SoV: 27 patients dilated with a mean of 3.5 ± 0.8. Range: 2.1 - 5.		23	15
Fricke, 2020	11			SoV: Mean 4.0 cm pre- and post-pregnancy.			Pre- and post-pregnancy: 1	2
Stoll, 2018	15	TGA with intact ventricular septum: 10. TGA with ventricular septal defects: 3. Complex TGA with associated cardiovascu-lar lesions: 2.		SoV: Pre-pregnancy: 33 ± 5.0 mm. Post-pregnancy: 34 ± 5.0 mm.	SoV: Pre-pregnancy n=15 people. Non-normalised: 1.85 ± 1.96. Normalised for BSA: 1.35 ± 1.80. Post-pregnancy n=12 people. Non-normalised: 2.19 ± 1.86.		2	

		(1 RVOTO, 1 coarctation of aorta).			Normalised for BSA: 1.73 ± 1.76.			

2.3.2 A narrative synthesis of the findings

Takada et al. (2021) measured the neoaortic root in 36 patients, divided on the presence of AR at the latest follow-up: 9 patients had AR (7 mild-moderate and two moderate-severe) at a mean interval of 21 years (range: 18-24 years). In the AR group, the aortic valve annulus, sinus of Valsalva, STJ, and ascending aorta were all significantly larger than in the non-AR group. Three patients required surgical aortic valve replacement for AR. The authors do not describe the operative technique used at the arterial switch.

In 2019, Van der Palen and co-authors published measurements for the growth of the neoaortic root over time for their cohort of 345 patients. In adulthood, the average annual growth of the sinus of Valsalva, STJ and aortic valve annulus significantly exceeded normal. Thirty-three patients developed moderate AR, and ten required reoperations, with the primary indications being root dilatation (n=4) and root dilatation with AR (n=6). They found that complex TGA anatomy and neoaortic root growth were risk factors for AR ≥ moderate. TGA-VSD, DORV-SP-VSD and male gender were independent risk factors for root dilatation. The operative techniques were identified for 127 patients; a single trapdoor with a single button in 96 and a double trapdoor in 31.

At the Necker–Enfants Malades Hospital in Paris, Martins and colleagues (2019) measured the neoaortic root cusp-to-commissure and neoaortic root cusp-to-cusp for 157 patients, with the cusp-to-cusp measurement being slightly larger

(27.15 ± 3.20 mm normalised to BSA). The average neoaortic root z score was 2.94 ± 1.51, with a large range of −0.34 to 7.01 and a non-significant increase with age. Thirty-four patients experienced mild-severe AR, including 7 with moderate-severe. One patient required reoperation, a Bentall procedure for severe neoaortic dilatation and regurgitation. The coronary technique was not documented in this work. Through univariate and multivariate analyses, the authors found TGA-VSD, TGA-VSD with coarctation of the aorta and dysplastic neoaortic valve anomaly correlated with increased root dilatation and higher incidence of AR.

In Hong-Kong, China the neoaortic root was measured in 21 patients with an average interval of ASO to imaging 21.5 ± 2.3 years (Cheung et al.,2019). Indexed measurements were compared to a cohort of 36 healthy patients. For all neoaortic measurements (sinus of Valsalva, SJT, aortic valve annulus and ascending aorta), the TGA cohort had a significantly larger neoaortic root size than the control group. Fourteen patients in the TGA cohort had mild AR, and 2 had ≥ moderate. They do not give information on the operative technique used for ASO.

Oda et al. (2019) have a cohort of 145 patients. The ASO coronary techniques utilised were punch only for 71 patients, trapdoor only for 60 patients, punch and trapdoor for 13 patients and Yacoub for one patient. Neoaortic root measurements were taken at frontal and lateral views, with the lateral view giving slightly larger measurements in both the neoaortic valve annulus and sinus of

Valsalva. Twenty-one patients had AR, but the severity was not categorised. The annual growth of the neoaortic root was documented as progressive during somatic growth, then stabilising without normalisation in adulthood. Their multivariable analysis revealed DORV, neoaortic valve insufficiency, and VSD as significant predictors of sinus of Valsalva dilatation, and DORV and neoaortic valve insufficiency as significant predictors of a neoaortic annulus dilatation.

Martins and colleagues (2018) looked at 127 patients in Belo Horizonte, Brazil. 84 patients had simple TGA and 43 had complex TGA. The complex TGA patients had a higher average neoaortic valve annulus z score than simple TGA patients (2.2 ± 1.3 and 1.8 ± 1.0, respectively). There was a higher rate of moderate AR in the complex TGA (19/43) population compared to the simple TGA population (5/84). The authors give mean z scores and ages for all patients according to their AR classification. Those with moderate AR had an average z score of 2.60 ± 1.40 with an average age of 9.81 ± 4.21 yrs. The authors conclude that the larger the aortic annulus, the higher the regurgitation grade ($p < 0.001$). They describe the coronary relocation technique as "always in Sinuses of Valsalva"; the trapdoor technique was not used.

A paper by Vida and colleagues published in 2017 included neoaortic root data from 17 centres. This multicentre study looked at a cohort of 111 patients requiring reoperations after the ASO for transposition. In the 111 patients, there were 126 reoperations performed (aortic valve replacement: 38, LVOTO relief: 17, aortic valve plasty: 14, coronary ostium relocation: 11, CABG: 11, Bentall's procedure: 11, supravalvar aortic enlargement: 10, supravalvar aortic plasty (reduction): 10, switchback operation: 4, ascending aorta replacement: 1, orthotopic heart transplantation: 1). Seventeen patients required more than one reoperation. 44% of DORV-TGA patients required more than one reoperation, compared to 14% of D-TGA patients. Indexed measurements of the neoaortic valve annulus and sinus of Valsalva were given alongside z scores for the overall cohort and patients divided by subtype. There was no significant difference between DORV-TGA and D-TGA patients. The trapdoor technique was used on 50 patients, whilst the other 97 had the traditional Lecompte manoeuvre.

Di Salvo et al. (2017) looked at 105 patients in Riyadh, Saudi Arabia. They divided the patients into those with gothic arch (n=46) and those without (n=59). The sinus of Valsalva of the gothic arch group was significantly larger than that of the group without (27.4 ± 7.5 mm vs 21.2 ± 6.9 mm, $p<0.0001$). No neoaortic root reoperations were required. When commenting on the operative technique, they state that translocation of the ascending aorta was performed posteriorly. No comment is made on z scores, annual growth or aortic regurgitation.

In Boston, Shepard et al. (2016) looked at a cohort of 220. For all patients, the sinus of Valsalva and ascending aorta dimensions were measured and normalised for body surface area. Annual growth was assessed in 66 patients with the sinus of Valsalva and was positively associated with an increase in the time since ASO (0.03 z score increase per year, 95% CI 0.002–0.06; $p=0.035$). At multivariable analysis, male sex (OR, 4.27; 95% CI, 1.6–11.47; $P=0.0039$) and higher neoaortic root AP diameter z score (OR, 1.36 for each unit increase; 95% CI, 1.05–1.77; P=0.0207) were identified as risk factors for neoaortic root dilatation. Seventy-two patients experienced mild AR, and 16 had ≥ moderate AR. The authors document 39 neoaortic reoperations in the population. They do not document the ASO coronary technique.

Sinus of Valsalva measurements were given for 220 TGA-complex patients in a paper by Baruteau et al. (2016). All patients had direct transfer in their ASO. Fifty-three patients had a z score ≥3 (24.1%), and a z score of ≥ 5 was given to 19 patients (8.6%). Forty-two reoperations occurred in the cohort. These were aortic valve repair or replacement (15), Bentall procedure (6), and re-coarctation repair (15), and of those that underwent re-coarctation repair, 40% (6 patients) had undergone unsuccessful aortic arch balloon angioplasty. They note that 12.7% of patients experience at least moderate AR. Male sex (p=0.025), aortic arch obstruction (p=0.022), aortopulmonary diameter mismatch (p=0.034) and previous aortic arch repair (p=0.021) were identified as risk factors for dilatation at univariate analysis.

Morgan and colleagues (2017) document 66 patients with an average age at follow-up of 14.3 ± 3.6 years. The mean indexed measurements for the sinus of Valsalva were 23 ± 6 mm/m2. They do not document z scores. The authors state that all patients underwent Lecompte but do not go into further detail. TGA-IVS occurred in 53% of patients (35), TGA-VSD occurred in 30% of patients (20), 14%

of patients (9) had TGA with an aortic arch anomaly, and 2% had Taussig-Bing (2 patients).

Eighteen patients were assessed by Biglino et al. (2014). They do not identify the subtype of TGA the patients have. They also do not identify the coronary reimplantation technique in the arterial switch. The mean cross-sectional area of the aortic valve annulus was 7.3 cm^2 (SD 2.3). No patients experienced moderate AR. However, four patients had trivial AR. No patients needed required reoperation.

In 2013, 32 patients registered at the Mayo Clinic in Rochester, Minnesota had their neoaortic roots measured (Raju et al., 2013). All patients had at least one reoperation; the mean age was 6.7 ± 1.4 years. Ten of the first re-operations related to the neoaortic root; 4 AVR, two valve-sparing neoaortic root replacements, 1 Bentall procedure, one aortic valve repair, one patch aortoplasty, one relief of LVOT and two re-coarctation procedures. Twelve patients had at least two reoperations, at a mean age of 10.8 ± 13.4 years. 2 of these were AVRs, and 1 was a stent re-coarctation procedure. Three patients had a third reoperation. However, none of these were related to the neoaortic root. 11.3 ± 6.1 years was the mean age at the third reoperation. Before reoperation, three patients had a dilated neoaortic root, although the measurement was not stated. Four patients had a dilated root post-reoperation, ranging from 31 – 41 mm. They state that the Lecompte manoeuvre was applied in 70% of cases.

Co-Vu and colleagues (2013) took neoaortic root measurements from 124 patients. More patients developed a sinus of Valsalva z score above 2.5 compared to a neoaortic valve annulus z score of 2.5 (88 and 67, respectively). The probability of being free from a neoaortic root diameter z score of 2.5 or higher at 1, 5, 10, and 15 years after ASO was 84%, 67%, 47%, and 32%. The neoaortic valve annulus remained relatively stable over time, increasing proportionately to somatic growth, whilst the dilation of the sinus of Valsalva appears to be progressive over time and disproportionate to somatic growth. They do not comment on operative technique at the arterial switch.

In Vienna, Austria, Pees, Laufer and Michel-Behnke (2013) assessed the aortic root of 52 patients, all of whom had a direct coronary transfer in the arterial switch. They compared the patients to a healthy control group. The ASO group had a significantly greater degree of increase during somatic growth than the control group for all four neoaortic measurements and in all subdivided years post-operative to ASO (<1 year, 1 – 5 years, > 5 years). Three patients had AR, but the severity was not given. These patients were slightly younger at ASO (age 4.3 +/- 3.8 days) than those without aortic regurgitation (age 11.2 +/- 22.8 days) and had a higher average neoaortic valve z score.

Kempny and colleagues (2012) measured the neoaortic root of 145 patients using echocardiography and MRI. 54% of patients had a dilated sinus of Valsalva, whilst 11% had a dilated STJ. One patient required aortic root replacement. There was a low prevalence of significant aortic root dilatation (7 moderate, one severe), which the authors suggested demonstrated neoaortic dilatation that was not rapidly progressive in early adulthood. Patients with moderate or severe AR had a significantly larger aortic sinus diameter than those with mild or no AR (39.5 ± 5.5 and 35.0 ± 5.2 mm, respectively, p=0.049). The Lecompte manoeuvre was performed in all patients, but no other information was given.

Work by Jhang and colleagues in Seoul, Korea (2012) documents the measurements for 240 patients, with a median follow-up of 79 months, ranging from 12 months to 19.5 years. The authors compare patient results straight after ASO to results at the latest follow-up. Twenty-five patients had a neoaortic valve annulus z score > 3 between 1 and 6 months after ASO. By the latest follow-up, this had increased to 44 patients with a z score > 3. 37 patients had a z score > 3 for sinus of Valsalva z score after ASO, and then at the latest follow-up, this was 74 patients. The STJ 4 had z scores > 3 after ASO and 12 patients at the latest follow-up. After ASO, just three patients had AR of moderate severity, however, at latest follow-up, this had increased to 6 patients, 5 with moderate and 1 with severe. 2 patients required reoperations due to their AR. All patients underwent the trapdoor technique for coronary relocation.

Bove et al. (2008) took measurements from 93 patients, 61 with IVS and 31 with VSD. They found that when looking at the differences in mean z scores of IVS and VSD patients, the neoaortic valve annulus, the sinus of Valsalva, and the STJ had significantly different mean z scores for the different TGA subtypes (neoaortic valve annulus p<0.0001, sinus of Valsalva p<0.0001, STJ p=0.01).

Similarly, they document the influence of neoaortic valve dysfunction on the z scores of the above three measurements, and note the annual growth by AR grade. Just one patient experienced AR ≥ moderate. Five patients underwent a reoperation; 4 had balloon dilatation, and 1 had neoaortic valve and root plasty. They document that VSD ($p=0.05$) and AR ≥ mild ($p=0.02$) were determinants for a z score > three at the sinus of Valsalva. In this cohort, fifty-five patients underwent direct coronary transfer (35 with IVS, 20 with VSD), and 38 underwent trapdoor (27 IVS and 11 with VSD).

Marino and colleagues (2006) looked at 82 patients; however, only 76 had sufficient imaging available to assess their neoaortic roots. They provide indexed measurements for the neoaortic valve annulus, sinus of Valsalva and STJ before the ASO and after the ASO, as well as in 2-year increments between ages 0 to 17 years. The authors find progressive dilation of the neoaortic root out of proportion to somatic growth. The random effect variable of time is statistically significant for all three measurements ($p < 0.0001$). Root dilation was associated with VSD ($p = 0.058$). No association was found between progressive root dilation and AR. The authors describe the operative technique used at the arterial switch as coronary buttons were utilised in all cases.

In 2004, McMahon and fellow researchers measured the neoaortic root in 119 patients. They found that the neoaortic valve annulus and sinus of Valsalva annual growth followed an abnormal distribution during the study period (McMahon et al., 2004). They found the sinus of Valsalva enlargement rate was highest in the first six months after ASO and then decreased to a mean increase of 0.21 z scores per year. Three patients required aortic homograft; these patients were the only patients with≥ moderate AR. The authors do not give risk factors for neoaortic dilatation however they do link neoaortic dilatation to AR, stating that a neoaortic root z score >5 had a significantly greater risk of developing ≥ mild AR than those with a z score of 3–5 (p < 0.001). The coronary transfer in this cohort varied depending on the coronary anatomy, with the trap door technique used in 69 patients (58%).

Ho¨vels-Gu¨rich and colleagues (2003) assessed the neoaortic root of 60 patients in Aachen, Germany. They note the measurements at the latest follow-up (patient age 10.5 +/- 1.6 years) and five years before the latest follow-up (patient age 5.3 +/- 1.6 years). Whilst the neoaortic valve annulus measurements are not significantly different at the latest and midterm follow-up (p=0.09), the measurements for the sinus of Valsalva are significantly different (p<0.0001), showing a decrease at present evaluation. A significant reduction is also demonstrated for z scores measurements (p<0.0001). Just one patient had ≥ moderate AR at present evaluation. Three reoperations were required, all to correct aortic coarctation. Direct coronary transfer was utilised for all patients in the ASO.

In 2001, Hutter et al. looked at 144 patients, all of whom had the trapdoor technique performed during the arterial switch. The authors give the mean z scores for the neoaortic valve annulus and sinus of Valsalva in six different age categories. However, the number of observations at these different ages varies from just 28 observations to 163 observations. All z scores show a rapid increase in the first year of life, the neoaortic valve and sinus of Valsalva decrease after this, whereas the anastomosis increases further but at a decreased rate. Risk factors for dilatation were TGA-VSD (p=0.027), coarctation (p<0.0001) and a P/A size ratio greater than 1.5 (p=0.04) at the neoaortic valve annulus. At the sinus of Valsalva, the risk factors for dilatation were TGA-VSD (p=0.05) and coarctation (p=0.011). Just two patients experienced AR ≥ moderate in this cohort.

74 patients in Malaga had their neoaortic roots measured, with 70 having complete follow-up available (Vera et al., 2021). All patients in this cohort had the trapdoor technique performed during ASO. In this retrospective study, the type of imagining is not described. They give the mean indexed and z score for the sinus of Valsalva and state that 32% of patients had a z score above 3. 7.6% of the patients (5 patients) had AR ≥ moderate but the number of patients with lesser degrees of AR is not quantified. Five reoperations were performed in the cohort: 2 balloon angioplasties, one aortic valve replacement and one subaortic stenosis repair.

In Washington, 2019, Loke and fellow researchers measure the neoaortic roots of 42 patients. They stated that all patients had the Lecompte manoeuvre but did not go into further detail on operative techniques. They give the indexed measurements for the sinus of Valsalva and ascending aorta for 38 patients, given in mm per m^2 of body surface area. They state that two patients required reoperations related to the neoaortic root, these were both LVOTO repairs; Konno procedures. The development of AR is not commented on.

Villalba et al. (2016) look at 224 patients with an average ASO to imagining interval of 7.6 +/- 5.4 years. The authors do not document the coronary artery translocation method used in the arterial switch. 6 of the 15 patients with moderate AR had dilated neoaortic root (p=0.0000), whilst 4 of the eight patients with severe AR had dilated neoaortic root. (0.0008). At univariable and multivariable analysis, significant AR was associated with neoaortic dilatation (p=0.000 in both). Aortic neo-root dilation was associated with prior LV preparation (p = 0.009), initial surgical stage (p = 0.002), and longer follow-up time (p = 0.0000). There were 15 reoperations necessary for this cohort, with a large range of operative procedure types.

In Melbourne, Fricke et al. (2020) looked at a cohort of eleven women post-pregnancy who had undergone ASO in childhood. Eight patients had pre- and post-pregnancy data available. Pre-pregnancy imaging was performed at a mean of twenty-two months before delivery (range 6-65 months), and postpartum imaging was performed at a mean of 18 months postpartum (range 2-44 months). The mean neoaortic root size was 4.0 cm both pre- and post-pregnancy. Two patients experienced progression of their AR severity postpartum; one progressed from trivial to mild AR, and one progressed from moderate/severe to severe AR. 2 patients required reoperation; 1 aortic valve replacement and one aortic root replacement. Fricke and colleagues do not describe the operative technique used at the arterial switch.

In Birmingham, data was collected on the sinus of Valsalva of women pre- and post-pregnancy from an obstetrics-cardiology clinic and a level 1 congenital cardiology centre (Stoll et al. 2018). Dr Stoll and colleagues documented the sinus of Valsalva of 15 women pre-pregnancy and attained imaging for 12 of these women post-pregnancy too. There was no change in the indexed measurements of the neoaortic root for these 12 women. 36% had mild neoaortic root dilatation pre-pregnancy, but none developed progressive dilatation in the first-year post-partum. Post-pregnancy z scores were larger than those pre-pregnancy. Z scores for patients with neoaortic root dilatation were larger than those without neoaortic root dilatation, both pre-and post-pregnancy. After pregnancy, one woman progressed from no AR to mild AR. None of the women experienced severe AR, and just 2 had moderate AR. The coronary relocation technique in the arterial switch was not described. No risk factors for neoaortic dilatation were given, and no information regarding reoperation was provided.

2.3.3 Heterogeneity in the methods of reporting

As can be seen in the previous sections, the twenty-seven included studies display variation in the way the patient cohort is selected, the cross-sectional imaging method used for the neoaortic root, the way measurements are taken and the results described.

Vida and colleagues (2017) have selected a patient cohort of only those who have undergone one or multiple reoperations. They have 111 patients, with 126 reoperations performed overall. Fricke and colleagues (2020) and Stoll and colleagues (2018) look at neoaortic root dilatation after pregnancy. The selection of patients in the included studies is described in more detail in section 2.3.2.

Twenty-three studies state the TGA sub-type of the patients in their cohort. However, as seen in Table 2 the way of stating this varies between papers. Most studies comment on whether the patients have TGA-IVS or TGA-VSD. Some studies also include the number of patients with additional defects, either giving the overall number of patients with additional defects or splitting them into categories such as double outlet right ventricle (DORV), subpulmonary stenosis, coarctation of the aorta, left ventricular outflow tract obstruction (LVOTO) or bicuspid native pulmonary valve. Other studies report ‘simple’ and ‘complex’ TGA, but few state the inclusion and exclusion criteria for their definitions of simplex and complex, or reference the standards on which their definitions are based. The studies that do define simple and complex vary in their definition. Most include Taussig-Bing anomaly or arch abnormalities within ‘complex’, while others document these patients separately or exclude them from their study. The paper by Takada and colleagues (2021) simply states the number of patients with D-TGA and the number with Taussig-Bing anomaly.

Twenty-one studies provide information on the operative technique at the arterial switch. For a few of these studies, only some of the patients are accounted for e.g. McMahon and colleagues (2004) note that 69/119 patients had the trapdoor technique, but they do not comment on the other patients. No studies provided neoaortic root measurements whilst dividing the cohort according to operative technique. Four of the studies state that all patients had a direct coronary transfer, and three studies stated all patients had the trapdoor utilised at ASO.

The measurements of the neoaortic root also differ. Studies give absolute values or measurements indexed to body surface area (19 studies), z scores (15 studies), and neoaortic root growth per year (9 studies). Fourteen studies only utilise one method of reporting, eleven use two methods and two studies use all methods. Within the included studies the provided neoaortic measurements vary from being given as means with standard deviation, median with interquartile range or occasionally as the number of patients that fall into a set category e.g. those with roots > 30mm. A range of imaging techniques were utilised throughout the included studies, with some studies using a combination. These included MRI, CT and echocardiography. The imaging of the neoaortic root was performed in a wide variety of ways. The frontal and lateral view were used by studies such as those written by Oda and colleagues (2019) and Shepard and colleagues (2016). Loke and colleagues (2019) and Biglino and colleagues (2014) gave the neoaortic root measurements as cross-sectional areas. Other studies give the measurements of the cusp to commissure, cusp to cusp or anteroposterior (A-P) diameter. Table 3 documents the risk of bias in the studies.

Table 3: Newcastle-Ottawa scale for assessing the quality of the 27 included non-randomised studies.

Identifier	Study design	Selection				Comparability		Outcome/Exposure			Total	Study quality
		1	2	3	4	1	2	1	2	3		
Takada, 2021	Case-control	*a	*a	b	*a	*a	*b	*a	*a	*a	8/9	Good
Van der Palen, 2019	Cohort	*b	-	*a	*a	*a	*b	*b	*a	*b	8/9	Good
Martins, 2019	Cohort	*b	-	*a	b	*a	-	*b	*a	*b	6/9	Fair
Cheung, 2019	Case-control	*a	*a	*a	*a	*a	*b	*a	*a	*b	8/9	Good
Oda, 2019	Cohort	*b	-	*a	*a	*a	-	*a	*a	*a	7/9	Fair
Martins, 2018	Case-control	*a	b	*a	*a	*a	*b	*a	*a	c	7/9	Good
Vida, 2017	Cohort	c	-	*a	b	*a	*b	*b	b	*a	5/9	Poor
Di Salvo, 2017	Cohort	c	*a	*a	b	*a	*b	*a	*a	d	6/9	Fair
Shepard, 2016	Cohort	*b	b	*a	b	*a	*b	*a	*a	*b	7/9	Fair
Baruteau, 2016	Cohort	*b	-	*a	b	*a	*b	*a	*a	*b	7/9	Fair
Morgan, 2017	Case-control	*a	*a	b	*a	*a	*b	*a	*a	*a	8/9	Good
Biglino, 2014	Case-control	*a	b	*a	*a	*a	*b	*a	*a	*b	8/9	Good
Raju, 2013	Cohort	*b	b	*a	b	*a	*b	*b	*a	*b	7/9	Fair
Voges, 2013	Case-control	*a	*a	b	*a	*a	*b	*a	*a	*a	8/9	Good
Ruys, 2013	Case-control	*a	b	*a	*a	*a	-	*a	*a	*b	7/9	Fair
Co-Vu, 2013	Cohort	*b	-	b	*a	*a	*b	*b	b	*a	6/9	Fair
Pees, 2013	Case-control	*a	*a	*a	*a	*a	*b	*a	*a	c	8/9	Good
Kempny, 2012	Cohort	*b	-	*a	*a	*a	-	*a	*a	*b	7/9	Fair
Jhang, 2012	Cohort	*a	-	*a	b	*a	*b	*a	*a	*b	7/9	Fair
Bove, 2008	Cohort	*a	b	*a	b	*a	*b	*b	*a	*b	7/9	Fair
Marino, 2006	Cohort	*b	-	*a	*a	*a	*b	*b	b	*a	7/9	Good
McMahon, 2004	Cohort	*a	-	*a	*a	*a	-	*a	*a	*b	7/9	Fair
Ho ̈vels-Gu ̈rich, 2003	Cohort	*a	-	*a	b	*a	*b	*b	b	c	5/7	Poor
Hutter, 2001	Cohort	*b	b	*a	*a	*a	*b	*b	*a	*b	8/9	Good
Vera, 2021	Cohort	*a	-	*a	b	*a	*b	*b	b	*a	6/9	Fair

Loke, 2019	Case-control	*a	*a	*a	*a	*a	*b	*a	b	*a	8/9	Good
Villalba, 2016	Cohort	*a	b	*a	b	*a	-	*b	*a	*b	6/9	Fair
Fricke, 2020	Cohort	*b	-	*a	b	*a	*b	*a	b	*a	6/9	Fair
Stoll, 2018	Cohort	*b	-	*a	b	*a	*b	*a	*a	*a	7/9	Fair

2.4 Discussion

2.4.1 The success of the review search

The search strategy performed, documented in the methods includes search terms and phrases relevant to the long-term fate of the neoaortic root and the arterial switch. The search terms are set to an expanded format but also as free text words. This is the method of constructing a search detailed by Tawfik et al., (2019) whereby they outline that search strategies should have relevant terms as both MeSH terms and also as free text terms. They also advise not to utilise any search terms for the outcomes of the review, e.g. dilatation, aortic regurgitation, neoaortic reoperation (Tawfik et al., 2019). This reasoning was considered and applied to the search. Unfortunately, restricting the outcome terms prevents papers being captured that may only state ‘root dilatation’ or ‘secondary aortic regurgitation’. However, it could be stated that if these papers contained data relevant to the study, they would contain the current search terms and so would have already been captured, thus it would be unnecessary to extend the search as it would not retrieve a higher number of relevant studies, but would provide many more papers to screen.

The PubMed search line 6 “neoaort* [tw] OR aort* [tw]” ensures all studies that mention the neoaortic root are captured, as well as those that may have referred to it as the aortic root. It may have been useful to substitute “neoaor*” for “neo?aort*” which would retrieve papers where the authors have hyphenated to ‘neo-aortic’ as well as the ‘neoaortic’ papers. This would have been useful in ensuring no studies were missed (Salvador-Olivan, Marco-Cuenca and Arquero-Aviles, 2019).

There were three electronic databases used for this review. This is in line with another ongoing review in this field published on Prospero by Edington et al, in 2021 (PROSPERO CRD42021292532), which also documents their plan to use just three databases. However, using only three may have caused us to miss papers (Salvador-Olivan, Marco-Cuenca and Arquero-Aviles, 2019). This may be the reason the two other groups who are looking at the long-term outcomes of the neo-aorta after arterial switch decided to apply their search to a higher number of databases (Notenboom et al, 2021, PROSPERO CRD42021279179, and Jacquemyn et al, 2022 PROSPERO CRD42022373214). Whilst these studies have not been published yet to peer-reviewed journals, in order to offer analysis as extensive as theirs is it important to consider the number of sources searched and thus when publishing my review it may be worth searching further sources.

The use of grey literature was not applied to this review, this was due to grey literature not being peer assessed, which is a significant disadvantage of grey literature outlined by Pappas and Williams (2011). Despite this, grey literature can also add value to the work through the retrieval of papers that may describe negative results that the authors decided not to disseminate, thus reducing publication bias and offering a more realistic picture of the subject of review (Paez, 2017).

2.4.2 The use of the Newcastle-Ottawa scale as a tool for bias testing of non-randomised studies

The Newcastle-Ottawa scale is one of the most popular and commonly known, scales for assessing the quality of non-randomised studies (Stang, 2010 and Luchini et al, 2017). This tool was appropriate for assessing the long-term fate of the neoaortic root following the arterial switch as it facilitated a smooth comparison and transition when assessing the case-control and the cohort studies. The Newcastle-Ottawa being validated for multiple types of non-randomised study is an advantage over many other tools for bias testing, and for the current study prevents the use of multiple tools for one review (Wells et al, 2012).

It is described in the methods that as this review has progressed, the results found meant that a narrative synthesis of findings would be more appropriate than a meta-analysis. The Newcastle-Ottawa scale is a tool validated and most often used for assessing the quality of studies for inclusion in meta-analysis, not narrative review, so it may be incorrect to compare using the same criteria (Luchini et al., 2017 and Frampton et al., 2022).

2.4.3 Heterogeneity in the reporting of findings

Heterogeneity in the results has led to a narrative review of the literature instead of a meta-analysis. Heterogeneity is noticed in the follow-up period, which for inclusion in the review was 5 years or above, as defining ‘long-term follow-up’. Most papers, whilst stating they reported long-term follow-up, either did not define this or had different definitions. Often when stating the follow-up this was stated as an average among all patients, which could therefore within itself contain a large variety of follow-up lengths. Hence unless explicitly stated, it could not be assumed that all patients in the cohort were reporting ‘long-term’ follow-up. The information could not be separated to give the neoaortic roots of only those patients monitored for the required amount of time. In addition to this, when the average follow-up was noted for the cohort, it would be inaccurate to then state all neoaortic root measurements as relating to that specific follow-up period because of the large variety of time periods this could encompass or the extreme values that could offset the average.

Heterogeneity arose in the measurement of the neoaortic root and the methods of reporting. Physicians used varying forms of scanning including MRI, CT, echocardiography, or a mixture of all to assess the neoaortic root. They also measured at different places on the neoaortic root itself, with not all papers noting the places measured. The presence of aortic regurgitation also varied among the papers, as did the ways of calculating patient body surface area. A few papers reported z scores when giving the neoaortic root measurements whilst others did not.

Furthermore, a few studies only looked at certain cohorts who had multiple reoperations or a specific subtype only. This is not representative of a whole population. In addition to this, some studies included different morphology in their classification of simple and complex TGA, e.g. some included Taussig-Bing, and some did not.

2.4.4 Association of neoaortic root growth with time

Whilst meta-analysis was not able to commence, and results could not be compiled, as previously mentioned, the narrative review does provide information on the trends of the studies included. Whilst it would not be fair to collate these into one measurement, the comparison of the findings found, and how this compares to normal is useful in contributing to the literature and current knowledge in this area.

There is a mixture of conclusions reached about the growth of the neoaortic root over time. Some studies state that there is an increase in the growth of the neoaortic root during somatic growth but that this stabilises in adulthood, without normalisation (McMahon et al., 2004, Oda et al., 2019 and Van der Palen et al., 2019). Alternatively, Hövels-Gürich and colleagues (2003) state that the diameters of the neoaortic root and neoaortic valve annulus do not increase between mid-term (5.3 +/- 1.6 years) and present evaluation (10.5 +/- 1.6 years follow up). The median age at the arterial switch for this cohort was 7.1 +/- 5.1 days and so both the present and mid-term evaluation occurred in the somatic growth phase. This contradicts the previously mentioned findings. Martins and colleagues (2019) document that there is a non-significant z score increase between the first (2.5 z score), second (3.0 z score) and third (3.3 z score) decades of life, whilst Shepard et al. (2016) also concluded an insignificant association between the neoaortic dimensions and time.

Out of all studies, most came to the conclusion that measurements of the neo-aorta increase rapidly and then slow or level out with age. In some studies this reduction in rate reaches the same as normal aortic root growth, in others it does not slow quite as much as normal. This appears to happen at a range of ages too. Some studies state that the neoaortic growth slows to normal after one year following the arterial switch operation, others state that it slows to near normal after this time. Other studies state that between ages 0-18 the growth of the neoaortic root remains at an abnormal rate, and slows once the patient has reached adulthood. Overall though it is universally found in these papers that the diameter of the neo-aorta remains higher than normal, despite the point in time that the growth slows to a normal rate.

2.4.5 Addressing the aim and hypothesis

The introduction states the aim of this section was ‘To conduct a systematic review of the literature on the fate of the neoaortic root after the arterial switch for transposition.’ The hypothesis was ‘There is variability in the fate of the neoaortic root described in the literature. This may, in part, be determined by the operative approach used at the arterial switch.’

Whilst the aim of the study was not met as a narrative review took the place of the originally planned systematic review. The papers did not document how the operative technique at arterial switch operation impacted the studies. And as meta-analysis could not be done these conclusions were not able to be made.

3. Investigating the long-term fate of the neoaortic root after the ASO for transposition- outcomes of a single centre utilising the trapdoor surgical technique, a retrospective cohort study.

3.1 Introduction

Birmingham Children's Hospital used a standardised management and operative technique for the arterial switch since 1988, the trapdoor technique. This presents an opportunity to investigate the long-term outcomes of the arterial switch at this institution, specifically the neoaortic root following the arterial switch for TGA.

3.2 Methods

3.2.1 Data collection

Data were independently retrieved from a clinical database. Patients who underwent the arterial switch operation at Birmingham Children's Hospital had their follow-up in adulthood retrospectively analysed. Data was collected from this cohort of patients from scans taken at Queen Elizabeth Hospital Birmingham when the patients were aged 16 and over. The primary focus for data collection was the neoaortic root measurements, either as indexed measurements or normalised for body surface area. The neoaortic regurgitation classification of the patients was also noted if such data was available. Patient date of birth, date of arterial switch, and reoperation status were collected. All data was stored securely and analysed in a fully anonymised format.

3.2.2 Exclusions

Only patients were included who had the arterial switch performed at Birmingham Children's Hospital performed for transposition, then followed up at Queen Elizabeth Hospital Birmingham. Echocardiographic measurements were excluded. Patients were excluded if the age at arterial switch operation was later than the cut-off of one year.

3.2.3 Ethical considerations

This study was registered with Birmingham Women's and Children's Research & Development office (BWC/LA/Drury/10, 04/10/2021) and in accordance with UK National Research Ethics Service guidance, neither individual informed consent nor formal research ethics committee review was required as the study was undertaken by the direct clinical care team using information previously collected in the course of routine care.

3.2.4 Data analysis

All data were analysed in a fully anonymised format. The captured data was adjusted accordingly to allow analysis in RStudio.

3.3 Results

3.3.1 Summary of the patient population

Cross-sectional imagining (MRI or CT) was available for a total number of 210 patients who had the arterial switch performed at Birmingham Children's Hospital for transposition, using the trapdoor operative repair technique. All patients were followed up in adulthood at Queen Elizabeth Hospital Birmingham.

There were 5 patients excluded from the study due to the age at arterial switch operation being later than one year, leaving data on 205 patients. 3 patients died during the follow-up period; these patients all had follow-up data available before death. The median age at ASO was 8 days (5-18 days). There were 129 patients with TGA-IVS, 50 TGA-VSD and 26 complex patients. A total number of 473 scans were available (205 patients had one scan, 118 patients had two scans, 74 had three, 45 had four, 19 had five, 8 had 6, 2 had seven, 1 had eight and 1 had nine, no patients had ten available scans). Of the total scans, 18 were CT scans, the rest were MRI. The measurements were not all performed by one specialist.

3.3.2 Findings at latest follow-up

The neoaortic root findings at the latest follow-up are stated in Table 4. Three patients were excluded from this as they had no scans prior to the neoaortic reoperation. At the latest follow-up there were 7 CT scans and 195 MRI scans. There were no scans that measured the neoaortic valve annulus in the complex TGA subgroup.

Table 4: Neoaortic measurements at latest follow-up, median (IQR

	Overall	TGA-IVS	TGA-VSD	Complex
Total number of patients	202	127	50	25
Age at ASO, days	8.0 (5.0-17.0),	7 (5.0-11.0)	15.5 (6.8-24.8)	11.0 (5.5-44.0)
Interval between ASO and latest follow-up, years	20.8 (18.0-24.9),	20.7 (17.8-25.1)	20.5 (18.0-24.3)	22.8 (18.1-25.6)
Aortic valve annulus, cm	2.5 (2.1-3.05),	2.5 (2.1-2.7)	3.1 (2.1-3.25)	N/A
Sinus of Valsalva, cm	4.0 (3.6-4.4)	4.2 (3.5-4.2)	4.0 (3.6-4.2)	4.4 (4.0-4.7)
<40mm, n (%)	96 (50.5),	66 (56.4)	24 (50)	6 (24)
40-44mm, n (%)	56 (29.5)	33 (28.2)	16 (33.3)	8 (32)
45-49mm, n (%)	24 (12.6)	13 (11.1)	4 (8.3)	7 (28)
≥50mm, n (%)	13 (6.8)	5 (4.3)	4 (8.3)	4 (16)
Sinotubular junction, cm	2.7 (2.4-3.2)	3 (2.4-3.3)	2.8 (2.3-3.7)	2.8 (2.5-2.9)
Mid-ascending aorta, cm	2.4 (2.2-2.8)	2.7 (2.2-2.7)	2.4 (2.1-2.8)	2.7 (2.1-3.0)

3.3.3 Changes over time

In order to assess change over time, the cross-sectional imaging findings were mapped on scatter plots, with scans belonging to the same patients connected by coloured lines to depict changes in individuals.

Figure 2 shows the neoaortic root in cm over time, divided by gender. At first glance it is obvious there are more male patients than female patients, and more scans are available for males than females, represented by the number of points on the plots.

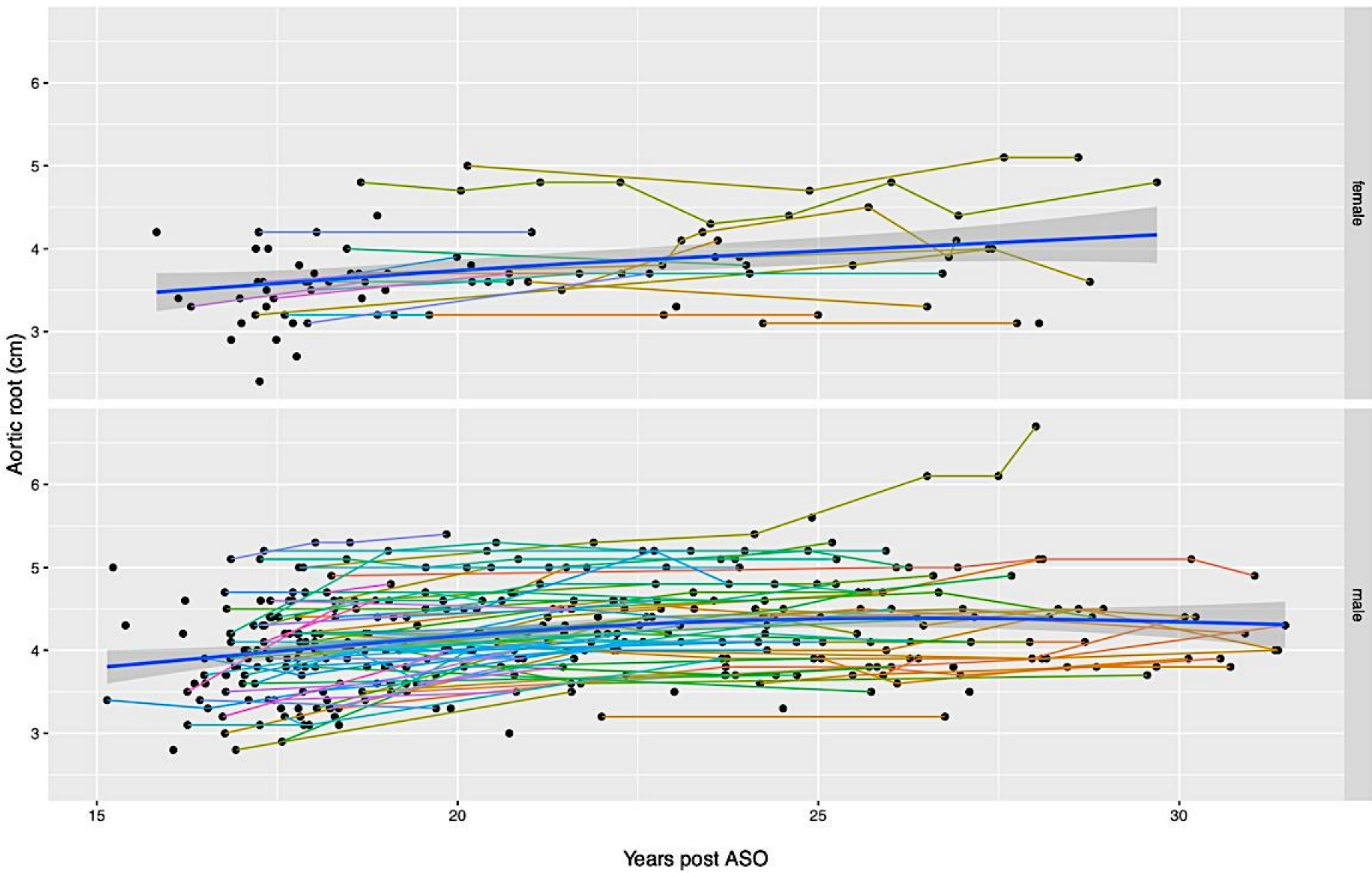

Figure 2: The diameter of the neoaortic root (sinus of Valsalva) over time by gender.

Figure 3 shows the neoaortic valve annulus in cm over time, divided by gender. It is clear there are much fewer measurements taken of this than the neoaortic root measurements. There is huge range in both males and females.

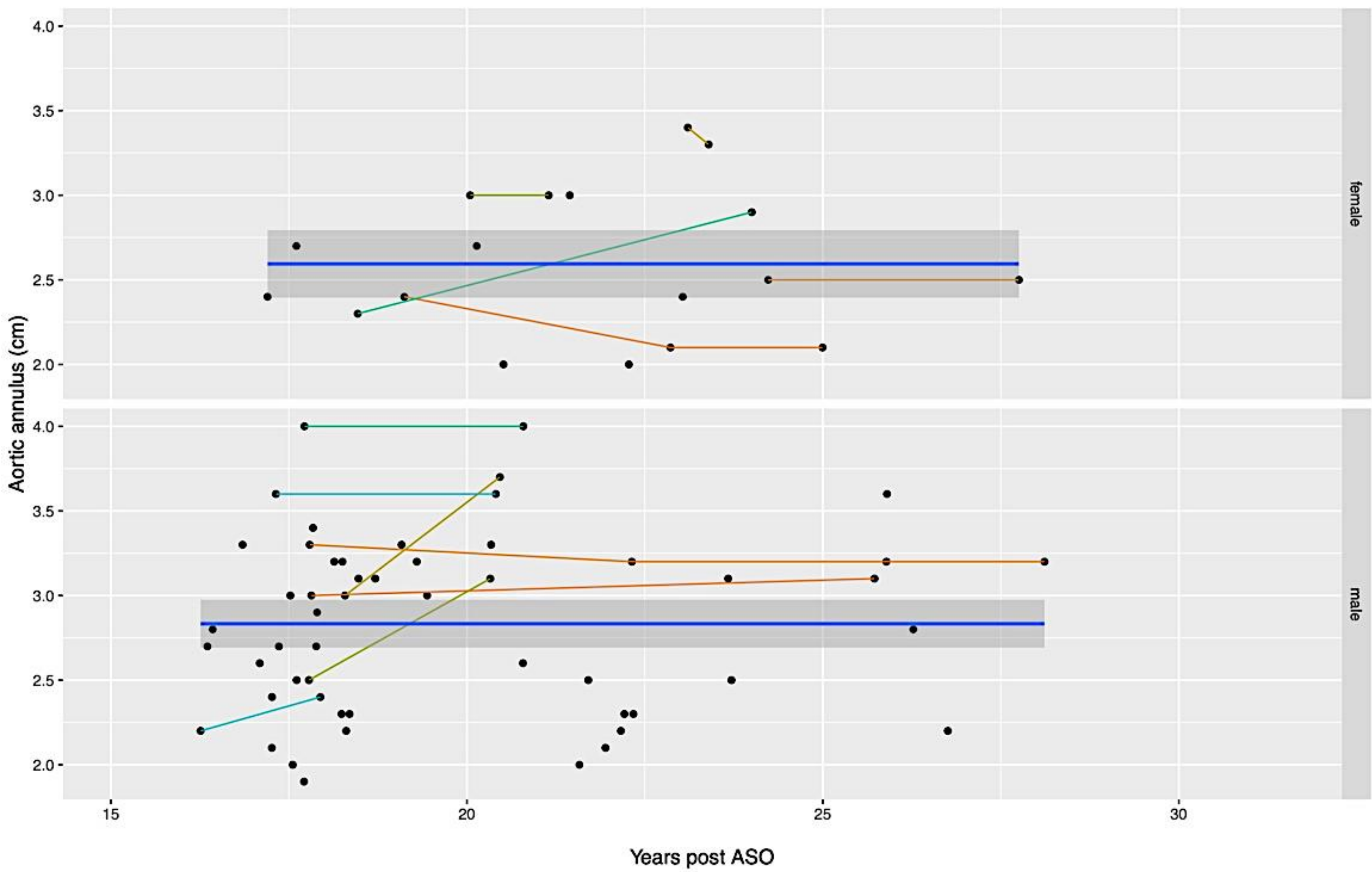

Figure 3: The diameter in cm of the neoaortic annulus over time by gender.

Figure 4 shows the sino-tubular junction in cm over time, divided by gender. Once again there are fewer measurements for this than provided for the neoaortic root.

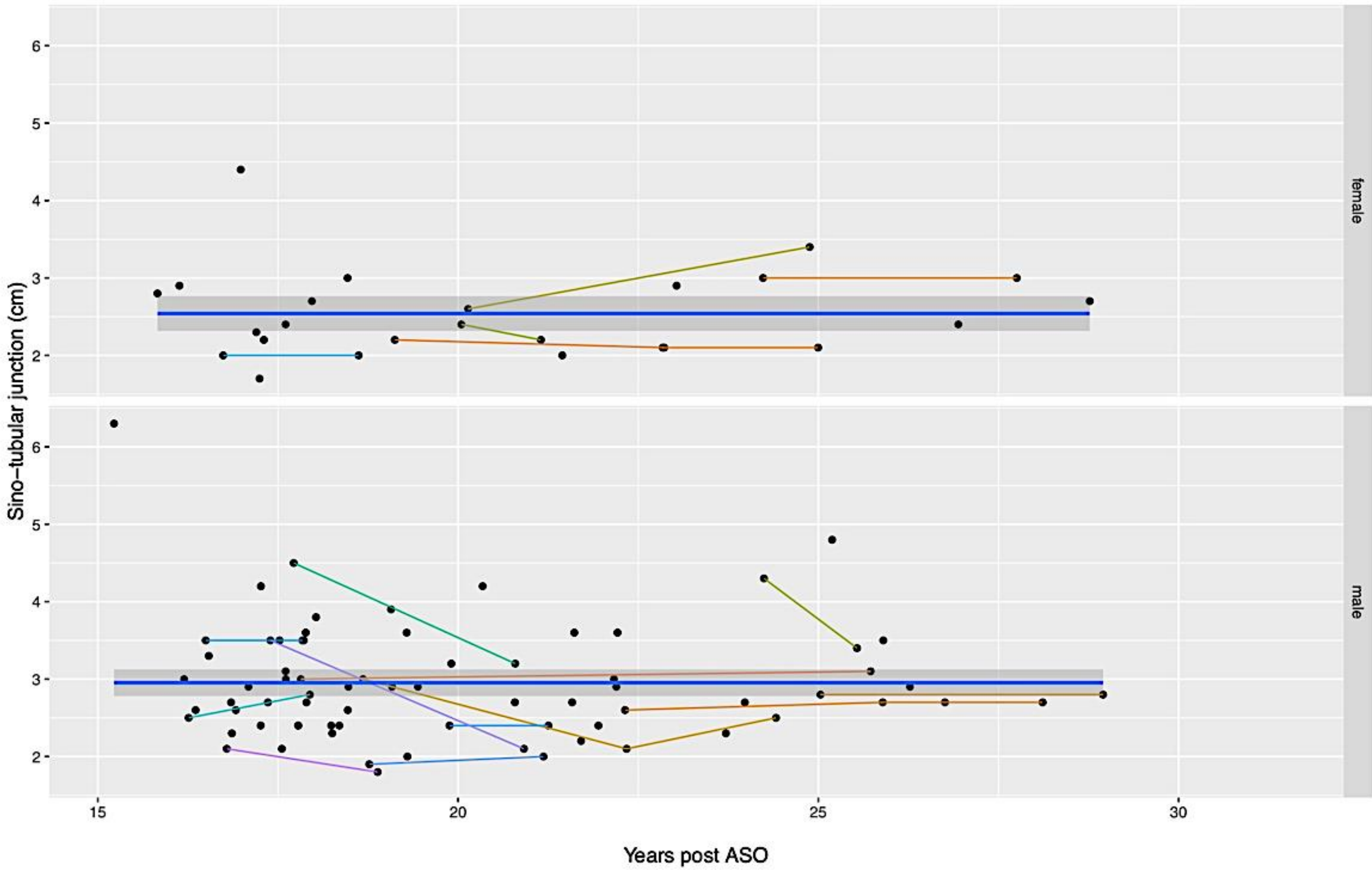

Figure 4: The diameter in cm of the sino-tubular junction over time by gender.

The change in body surface area of the patients over time in m^2 is demonstrated in Figure 5. This shows that over time both populations increase in both surface area on average.

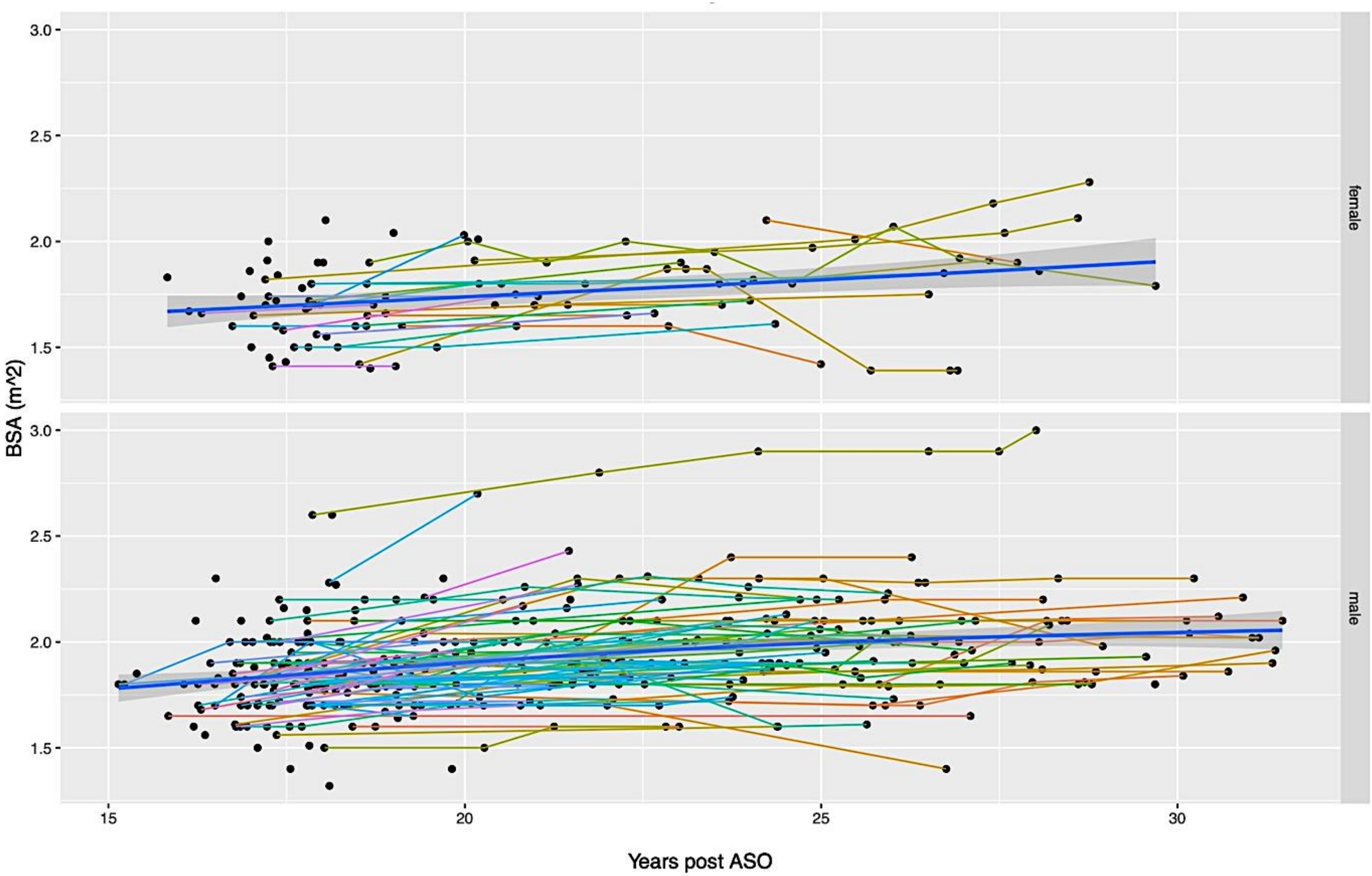

Figure 5: The BSA in metres squared of the cohort assessed, over time, by gender.

3.4 Discussion

When looking at the neoaortic root there is later follow-up available for males > 30 years, compared to <30 years for females. In both males and females, the starting points range greatly. Overall, the neoaortic roots for males are larger than for females in this cohort. With years post-ASO both women and men seem to increase with age, however, the male cohort appears to level off more than the females. One male patient represented by a green line at the top of the plot, appears to progress rapidly after 24 years, reaching a maximum of 6.6cm at approximately 28 years post-ASO.

Similarly, in this cohort the average starting point for male neoaortic valve annulus measurements is slightly larger than for females at around 2.8 cm compared to 2.6cm, respectively. Male patients have a later follow-up available than females for the neoaortic valve annulus. The maximum neoaortic valve annulus measurement seen for women was 3.4cm as opposed to the higher 4.0cm for males. Their lowest measurements were similar, with the male cohort being slightly smaller at 1.9cm and the female cohort with 2.0cm. There is a larger range of measurements for male patients. The trend lines in both males and females appear to show no progression over time.

Trends similar to this are also shown in the sino-tubular junction. There are more measurements for males than for females. Both the trendlines how no progression over time. Males start with higher measurements than females at around 3cm compared to 2.5cm. There is also a larger range of measurements depicted in the male population than the female population. The length of follow-up available is similar in both cases.

The body surface area plot features trend lines that are similar in this plot as those in Figure 2, where the female and male cohort slowly increase over time and the male cohort appears to plateau past 30 years. The follow-up for females is not given after around 29 years. Males have a larger range of body surface area measurements and reach higher body surface areas than females for this patient cohort. One patient has a substantially higher body surface area compared to the other patients, represented at the top of the male cohort plot with a green line.

4. Conclusions

4.1 Contribution to knowledge in this field

The narrative review demonstrates the heterogeneity in the measurement and reporting of the neoaortic root following transposition. Whilst it is clear that authors are striving to capture the fate of the neoaortic root following the arterial swtich for transposition, the work cannot truly be compared to other literature in the field due to the large variety of ways the neoaortic root is measured and reported by the studies. The Birmingham cohort provides long-term data following the arterial switch at an institution performing just trapdoor techniques. The latest follow up is documented providing measurements for the sinus of Valsalva, neoaortic valve annulus, sino-tubular junction and mid-ascending aorta. The latest follow up reaches a maximum of approximately 30 years post ASO.

4.2 Study limitations

The study limitations include the absence of grey literature in the narrative review, which was done because grey literature is not peer-assessed, generally meaning the data is less reliable. However, within the grey-literature, there will still be data which is correct and reliable, which would be useful for the review.

Secondly, there is no second screener for the data extraction which increases the risk of bias. This would be needed for publication as stated in the Cochrane guidelines.

Furthermore, the data from the narrative review is mostly from high-income countries (HICs) due to the highly complex nature of the procedure meaning it is performed in specialist centres. As there is more data from HIC populations bias is automatically introduced, as there are fewer patients in the cohorts from a range of backgrounds. This could also mean that maybe in the LMICs with specialist centres that perform this procedure, there may not be as much funding for research, and thus, less research is produced, and then their results are not seen in this review.

4.3 Future work

This includes a standardised way of reporting the neoaortic root measurements. For example, a questionnaire sheet. This way the method of reporting the neoaortic root measurements can become standardised and future work can be compared, allowing conclusions to be drawn.

The clinical dataset would benefit from continued follow-up as the patients advance and further analysis e.g. regression analysis.

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Appendices

Appendix 1: Newcastle-Ottawa scale

Cohort studies are judged as outlined below. For every numbered item in the selection, comparability and outcome the option which attains the study a star is marked with * at the end.

Selection

1. Representativeness of the exposed cohort
   a) Truly representative of the average population characteristics of individuals with TGA in the community *
   b) Somewhat representative of the average population characteristics of individuals with TGA in the community *
   c) A selected group of users, e.g., nurses, volunteers
   d) No description of the derivation of the cohort

2. Selection of the non-exposed cohort
   a) Drawn from the same community as the exposed cohort *
   b) Drawn from a different source
   c) No description of the derivation of the non-exposed cohort

3. Ascertainment of neoaortic measurements
   a) Secure records (e.g. surgical records) *
   b) Structured interview *

c) Written self-report

d) No description

4. Demonstration that outcome of interest was not present at the start of the study

a) Yes *

b) No

Comparability

1. Comparability of cases on the basis of the design or analysis

   a) Study controls for at least one variable (including age, sex, comorbidities, etc.)*

   b) Study controls for more than one variable (including age, sex, comorbidities etc.) *

Outcome

1. Assessment of outcome

a) Independent blind assessment *

b) Record linkage *

c) Self-report

d) No description

2. Was follow-up long enough for outcomes to occur

a) Yes (mean: ≥ 5 years) *

b) No

3. Adequacy of follow-up of cohorts

   a) Complete follow-up - all subjects accounted for *

   b) Subjects lost to follow-up unlikely to introduce bias - small number lost - ≤ 25% lost to follow-up, or description provided of those lost *

   c) Follow-up rate < 75 % and no description of those lost

   d) No statement

While many categories are the same, case-control studies are graded differently. Once again, the options that grant the study a star are denoted *.

Selection

1. Is the case definition adequate?

   a) Yes, with independent validation *

   b) Yes e.g. record linkage or based on self-reports

   c) No description

2. Representativeness of the cases

   a) Consecutive or obviously representative series of cases *

   b) Potential for selection biases or not stated

3. Selection of controls

a) Community controls *

b) Hospital controls

c) No description

4. Definition of controls

a) No history of disease (endpoint) *

b) No description of source

Comparability

1. Comparability of cases and controls on the basis of the design or analysis

a) Study controls for at least one variable (including age, sex, comorbidities etc.) *

b) Study controls for more than one variable (including age, sex, comorbidities, etc.) *

Exposure

1. Ascertainment of neoaortic measurements

a) Secure record (e.g. surgical records) *

b) Structured interview where blind to case/control status *

c) Interview not blinded to case/control status

d) Written self-report or medical report only

e) No description

2. Same method of ascertainment for cases and controls

a) Yes *

b) No

3. Non-response rate

a) Same rate for both groups *

b) Non-respondents described

c) Rate different and no designation

A quality grade was assigned to the studies based on how many stars were awarded in each category. ‘Good’ studies attained ≥ 3 stars for Selection, two stars for Comparability and ≥ 2 stars for Outcome/Exposure. ‘Fair’ studies achieved two stars for Selection, ≥ 1 for Comparability and ≥2 for Outcome/Exposure. ‘Poor’ was assigned to studies with 0-1 stars for Selection, 0 for Comparability and 0-1 for Outcome/Exposure.