A REVIEW OF CONGENITAL HEART DEFECTS IN CHILDREN WITH TRISOMY 21 OVER A 5-YEAR PERIOD AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine: School of Paediatrics and Child Health

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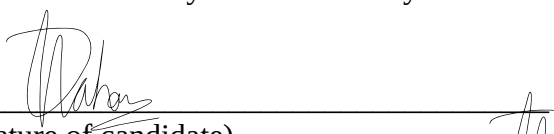
Johannesburg, 2020.

DECLARATION

I Raeesa Moosa Kara Mahomed declare that this Research Report is my own, unaided work. It is being submitted for the Degree of Master of Medicine: School of Paediatrics and Child Health at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



(Signature of candidate)

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I dedicate this report to

My Father
Dr Mahomed Moosa Kara Mahomed
My guide and mentor in medicine and life.

ABSTRACT

Background: In the first ten years of life, mortality in Trisomy 21 (T21) is strongly associated with the presence of Congenital Heart Defects (CHDs). There is currently a lack of local and regional data regarding the prevalence, management and outcomes of children with T21 and CHDs.
Objectives: To describe the prevalence, type and frequency of CHDs and review interventions (cardiac catheterisation and surgery) and survival post-surgery of children with CHDs in the T21 population at a South African facility, the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) Paediatric Cardiology Unit (PCU).
Methods: A retrospective, cross sectional, observational review of 177 participants at CMJAH PCU between January 2013 to December 2017 was performed. Data collected from the PCU database and clinical records included: demographics, echocardiographic diagnosis, details of Diagnostic Cardiac Catheterisation (DCC), Interventional Cardiac Catheterisation (ICC) and surgery required and performed, age at diagnosis and intervention as well as survival post-surgery.
Results: There were 128 participants with laboratory-confirmed T21 and CHD on echocardiography meeting inclusion criteria. The majority of participants were female (56.0%) and African (97.0%). The median age at presentation was six (IQR 9.75) months. The prevalence of CHDs was 77/128 (60.2%) and 58/77 (75.3%) had a single CHD. The most frequent CHD was an Atrioventricular Septal Defect (AVSD) (38%) (with or without another associated CHD). DCC was required in 60/77 (77.9%) participants and 25/60 (41.6%) were performed. The median age at DCC was 15 (IQR 15) months. One participant with isolated PDA required and underwent successful ICC for PDA closure at 17 months. Surgery was required in 60/77 (77.9%) of participants, while 15/60 (25.0%) surgeries were performed. Almost half of DDCs and surgeries not performed were due to participants lost to follow-up (40% and 45% respectively). The median age at first surgery was 31 (IQR 24) months. The most common surgery was an AVSD repair (73%). Post-surgery survival was 93.3% at hospital discharge, 3-week and 6-month follow-up and 86.7% at 1-year follow-up.
Conclusion: The prevalence, type and frequency of CHDs in the CMJAH T21 population is comparable to global data. The age at presentation was not optimal for early intervention, and there was further delay in catheterisation and surgery. Survival post-surgery compares favourably with other centres even though surgery was performed at a much later age than the age recommended for best outcome (six months). Early screening, diagnosis and intervention can prevent morbidity, mortality due to CHDs and may decrease the financial burden on the healthcare system.

ACKNOWLEDGEMENTS

I must acknowledge my supervisors Dr. Firoza Motara and Prof. Daynia Ballot for their patience, time, dedication and guidance, Dr Wiedaad Slemming for her assistance in preparing the paper for publication and lastly, the staff at the Paediatric Cardiology Department for the use of their database.

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NOMENCLATURE

ASD: Atrial Septal Defect secundum type
AVSD: Atrioventricular Septal Defect
CHD: Congenital Heart Defect
CMJAH: Charlotte Maxeke Johannesburg Academic Hospital
DCC: Diagnostic Cardiac Catheterisation
ICC: Interventional Cardiac Catheterisation
IQR: Interquartile Range
PCU: Paediatric Cardiology Unit
PDA: Patent Ductus Arteriosus
RCH: Red Cross War Memorial Children's Hospital
SA: South Africa
TOF: Tetralogy of Fallot
T21: Trisomy 21
USA: United States of America
VSD: Ventricular Septal Defect

A review of Congenital Heart Defects in children with Trisomy 21 over a 5-year period at Charlotte Maxeke Johannesburg Academic Hospital

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Abstract

Background: In the first ten years of life, mortality in Trisomy 21 (T21) is strongly associated with the presence of Congenital Heart Defects (CHDs). There is currently a lack of local and regional data regarding the prevalence, management and outcomes of children with T21 and CHDs.
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Conclusion: The prevalence, type and frequency of CHDs in the CMJAH T21 population is comparable to global data. The age at presentation was not optimal for early intervention, and there was further delay in catheterisation and surgery. Survival post-surgery compares favourably with other centres even though surgery was performed at a much later age than the age recommended for best outcome (six months). Early screening, diagnosis and intervention can prevent morbidity, mortality due to CHDs and may decrease the financial burden on the healthcare system.

Introduction

The leading chromosomal abnormality in humans is Trisomy 21 (T21) with an incidence between 1:750 and 1:1 000 live births.[1] The prevalence of children born with T21 has increased by as much as 25% over that last 30 years.[2] Worldwide, an estimated 40-60% of T21 individuals have an associated Congenital Heart Defect (CHD).[3] In South Africa (SA) untreated CHDs are the leading cause of mortality associated with birth defects and an estimated 8% of patients diagnosed with a CHD have confirmed T21.[4, 5]

Worldwide, CHDs in T21 predominantly presents with a single defect but multiple defects may occur. The CHD most commonly cited is an Atrioventricular Septal Defect (AVSD), with a prevalence between 15-48%.[6-8] Recent studies suggest that there is a geographical variation in frequencies of CHDs in T21. AVSD is most frequently described in the literature from United States of America (USA), western Europe and north Africa, Ventricular Septal Defect (VSD) is most frequent in Asia and Atrial Septal Defect (ASD) in Latin America.[7-12] There are very few studies from Africa and only one South African study describing CHDs among children with T21, performed in 2006 at Red Cross War Memorial Children's Hospital (RCH) in the Western Cape .[7, 10, 11, 13-17]

In the first ten years of life, mortality in T21 is strongly associated with the presence of CHDs.[18] Cardiopulmonary disease accounts for ~ 75% of morbidity and mortality in the T21 population.[19] Thus, CHDs and its complications are significant contributors to the cost of management of patients with T21. Recent literature has presented evidence of a shift in the distribution of CHDs in T21 toward defects that are more easily operable than preceding years, resulting in improved morbidity and mortality.[3, 6, 20] The decrease in incidence of CHDs in T21 as a result of selective abortion of T21 patients with CHDs (with the advent of amniocentesis and antenatal screening programs) may be the reason for the shift in distribution, but improved medical and surgical management has also resulted in improved operative outcomes.[18, 20]

South African public-sector hospitals have a shortage of human resources (cardiologists, cardiothoracic surgeons and nursing staff) as well as few referral specialist centres and intensive care units for post intervention care. This means interventions may not be performed timeously (due to extremely long waiting lists) or at all.[5] Historically, children with T21 were unlikely to receive intervention.[21] It was argued, that individuals with T21 were less likely to be employed or contribute to society, not only because they had perceived poorer short-term outcomes after surgery, but also in the long-term due to concurrent conditions, mental impairment, a higher risk of Alzheimer's dementia and a limited lifespan affecting their productivity. [5, 17, 21] With early identification and intervention, complications may be avoided.[17, 19] In addition, the cost of recurrent and prolonged hospital admissions due to these complications, or the financial cost to parents taking time off work may be much more draining on monetary and other resources than definitive management like surgery.[4, 5, 21] Evidence of survival and favourable outcome post-surgery has since been reported in literature worldwide and in SA, with no significant difference in burden to the health care system or survival post-surgery in T21 vs non-T21 patients.[3, 17, 22, 23]

There is currently a lack of local and regional data regarding the prevalence, management and outcomes of children with T21 and CHDs. The aim of this study was to describe the prevalence, type and frequency of CHDs as well review interventions (cardiac catheterisation and surgery) and survival post-surgery of children with CHDs in the T21 population at a South African facility, the CMJAH Paediatric Cardiology Unit (PCU).

Methods

Design
A retrospective, cross sectional, observational study, was carried out. Participants were drawn from the population of paediatric patients seen at the CMJAH PCU over a five-year period (January 2013 to December 2017).

Setting
CMJAH is a tertiary centre situated in Parktown, Johannesburg, SA. The hospital is a referral centre for a number of hospitals and clinics in the surrounding area. [24] The PCU at CMJAH sees on average ~ 2050 patients yearly.

All patients who had presented to any of the paediatric services at CMJAH with suspected or laboratory confirmed T21 (with polymerase chain reaction aneuploidy testing) were routinely referred to the CMJAH PCU for a screening echocardiographic assessment. Thereafter, any patient with a significant CHD underwent further intervention as required; this included diagnostic cardiac catheterisation (DCC), interventional cardiac catheterisation (ICC) and surgery (multiple interventions may have been required). All participants older than 9 months with an indirect assessment of pulmonary hypertension on echocardiogram or in whom DCC was deemed necessary by the unit, underwent DCC prior to surgery. Surgical repair was indicated in CHDs that were haemodynamically significant or could lead to significant morbidity and mortality. The patients were then followed up at specified intervals post intervention.

At the time of the study there were two trained paediatric cardiologists and one cardiology fellow working in the unit. Surgery was performed by the cardiothoracic surgery unit on site at CMJAH. The surgical team comprised three surgeons trained in repair of CHDs.

Data source
All relevant patient information was recorded onto the CMJAH PCU database on site by the principle cardiologist in the unit on presentation and updated at each follow up visit. The database comprises information of all patients who are assessed by the unit including data on demographics, comorbid conditions (e.g. T21), cardiac diagnosis on echocardiogram, cardiac catheterisation data and surgery performed. Further details of cardiac catheterisation, surgery, survival and outcome were recorded in patient records at the PCU.

Participants
There were 177 patients on the database with echocardiographic diagnosis of CHD and confirmed or suspected T21. This included both in-patients and out-patients. Participants between birth and 16 years with laboratory confirmed T21 were included in the study. Participants with a preceding cardiac diagnosis prior to referral to CMJAH PCU (e.g. referral from other hospitals for cardiac catheterisation only), participants with acquired heart disease, participants with incomplete information on clinical database and/or patient records (such as diagnostic and outcome data) and participants in whom no echocardiogram was done, were all excluded.

Data Collection
The study was a secondary analysis of the existing patient database at CMJAH PCU and review of patient records. Data were entered into a MS Excel spreadsheet and variables included demographic data (gender, ethnicity, age at assessment), echocardiographic diagnosis (presence of CHD, type of CHD, single defect vs multiple defects), intervention (need for cardiac catheterisation (DCC, ICC or both), need for surgery, number that underwent intervention if required, age at intervention and survival to hospital discharge, at first, second and third follow-up visit post intervention (3 weeks, 6

months and 1 year). Details of echocardiographic data, intervention data and outcome as well as any missing variables on the database were collected from patient records.

Statistical Analysis
Data were and analysed using SPSS Statistics 25. The median and interquartile range (IQR) of continuous variables were reported as distribution was skewed, while the frequencies and percentages of categorical variables were reported.

Ethics
The study was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (Clearance Certificate No. M180919) and submitted to the National Health Research Database.

Results

There were 128 participants in the final study sample (See Fig. 1.).

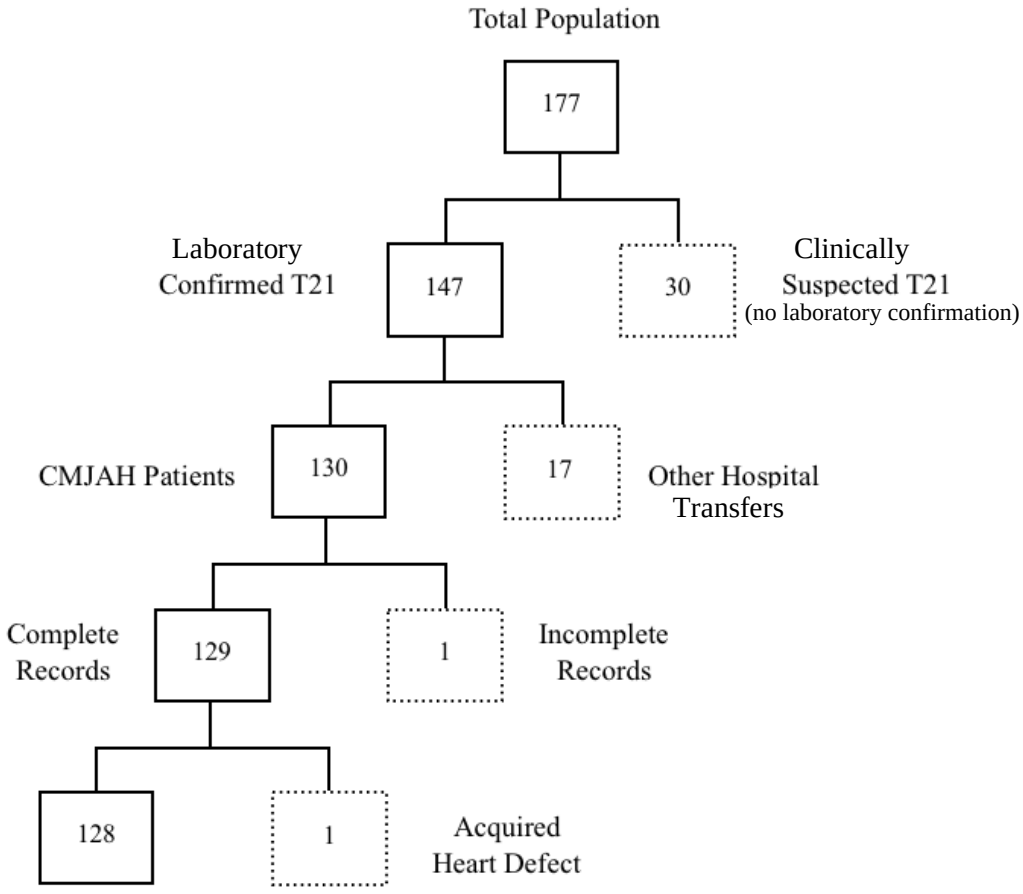

Fig. 1. Flow diagram of final sample and exclusion criteria (CMJAH: Charlotte Maxeke Johannesburg Academic Hospital; T21: Trisomy 21)

Description of study sample
The majority of participants were female (56.0%) and of African ethnicity (97.0%). The median age at presentation was six (IQR 9.75) months. There were 77/128 (60.2%) participants who had a CHD on echocardiography; 58/77 (75.3%) had a single CHD while 19/77 (24.7%) had multiple CHDs. The types of CHD are described in Table 1. The frequency of individual types of CHD in

total (summation of single plus multiple) are summarised in Figure 2. AVSD (complete or partial) was reported as a single CHD. ASD refers to ASD secundum type.

Table 1: Type of congenital heart defect

Single defect (*N* = 58)	*n* (%)
AVSD	28 (48.3)
VSD	14 (24.1)
PDA	11 (19.0)
ASD	4 (6.9)
TOF	1 (1.7)
Multiple defects (*N* = 19)	*n* (%)
AVSD/PDA	8 (42.1)
AVSD/ASD	1 (5.3)
AVSD/TOF	1 (5.3)
VSD/PDA	5 (26.3)
VSD/ASD	1 (5.3)
VSD/ASD/PDA	1 (5.3)
ASD/PDA	1 (5.3)
ASD/Other*	1 (5.3)

AVSD = Atrioventricular Septal Defect; PDA = Patent Ductus Arteriosus; VSD = Ventricular Septal Defect; ASD = Atrial Septal Defect secundum type; TOF = Tetralogy of Fallot.
* Other includes peripheral pulmonary stenosis

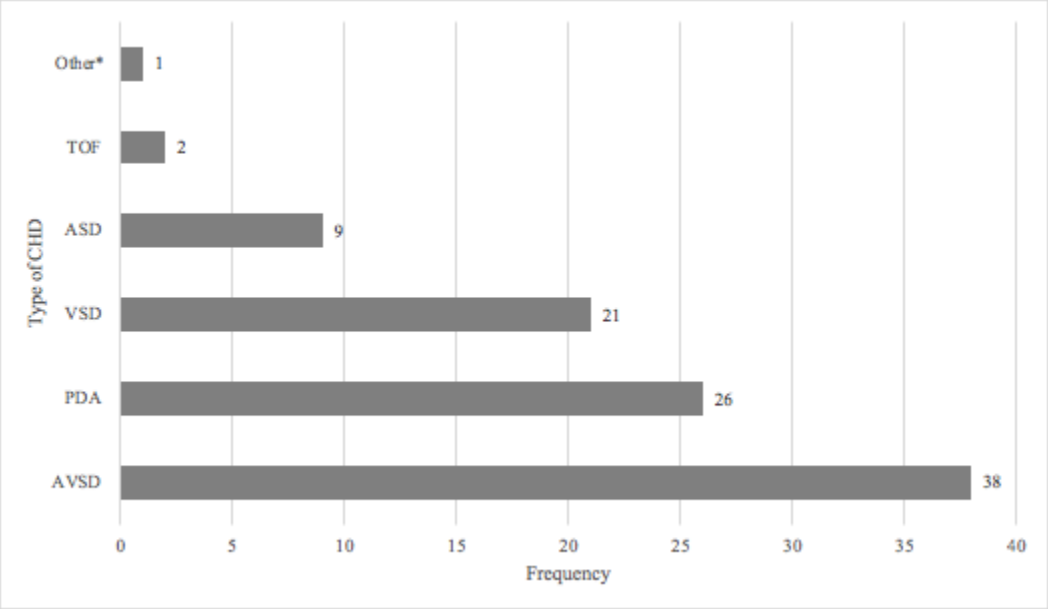

Fig. 2: Frequency of congenital heart defects in total (single plus multiple)
(AVSD = Atrioventricular Septal Defect; PDA = Patent Ductus Arteriosus; VSD = Ventricular Septal Defect; ASD = Atrial Septal Defect secundum type; TOF = Tetralogy of Fallot. * Other includes peripheral pulmonary stenosis)

Intervention - Cardiac Catheterisation

A total of 60/77 (77.9%) participants with a CHD required DCC and 25/60 (41.6%) received DCC. Details of DCC is presented in Table 2. One participant with AVSD underwent surgery without requiring DCC.

Table 2: Diagnostic cardiac catheterisation by type of congenital heart defect

Single Defect	Required	Done	Awaiting	Lost to Follow-up†	Demised‡
AVSD (*n* = 28)	**27 (96.0%)**	12/27 (44.4%)	0/27 (0.0%)	12/27 (44.4%)	3/27 (11.1%)
VSD (*n* = 14)	**12 (85.7%)**	2/12 (16.7%)	4/12 (33.3%)	5/12 (41.7%)	1/12 (8.3%)
PDA (*n* = 11)	**3 (27.3%)**	2/3 (66.7%)	0/3 (0.0%)	1/3 (33.3%)	0/3 (0.0%)
ASD (*n* = 4)	**1 (25.0%)**	0/1 (0.0%)	0/1 (0.0%)	1/1 (100.0%)	0/1 (0.0%)
TOF (*n* = 1)	**1 (100.0%)**	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	1/1 (100.0%)
Multiple Defects	Required	Done	Awaiting	Lost to Follow-up†	Demised‡
AVSD/PDA (*n* = 8)	**8 (100.0%)**	5/8 (62.5%)	0/8 (0.0%)	3/8 (37.5%)	0/8 (0.0%)
AVSD/ASD (*n* = 1)	**1 (100.0%)**	1/1 (100.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)
AVSD/TOF (*n* = 1)	**1 (100.0%)**	1/1 (100.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)
VSD/PDA (*n* = 5)	**3 (60.0%)**	2/3 (66.7%)	0/3 (0.0%)	1/3 (33.3%)	0/3 (0.0%)
VSD/ASD (*n* = 1)	**1 (100.0%)**	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	1/1 (100.0%)
VSD/ASD/PDA (*n* = 1)	**1 (100.0%)**	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	1/1 (100.0%)
ASD/PDA (*n* = 1)	**1 (100.0%)**	0/1 (0.0%)	0/1 (0.0%)	1/1 (100.0%)	0/1 (0.0%)
ASD/Other* (*n* = 1)	**0 (0.0%)**	0/0 (0.0%)	0/0 (0.0%)	0/0 (0.0%)	0/0 (0.0%)
Total	**60**	**25/60 (41.7%)**	**4/60 (6.7%)**	**24/60 (40.0%)**	**7/60 (11.7%)**

AVSD = Atrioventricular Septal Defect; PDA = Patent Ductus Arteriosus; VSD = Ventricular Septal Defect; ASD = Atrial Septal Defect secundum type; TOF = Tetralogy of Fallot.
* Other includes peripheral pulmonary stenosis
† Lost to follow-up before diagnostic cardiac catheterisation
‡ Demised before diagnostic cardiac catheterisation

The median age at presentation of participants in whom DCC was done was 7 (IQR 7.5) months and the median age at DCC was 15 (IQR 15) months. A second DCC was required and performed in 3/77 (3.9%) of participants; both with an AVSD type CHD.

Only one participant with isolated PDA required and underwent successful ICC for PDA closure at 17 months of age.

Intervention - Surgery

A total of 60/77 (77.9%) of participants were eligible for surgery, while 15/60 (25.0%) surgeries were performed. Details of surgical intervention in each type of CHD category is shown in Table 3.

Table 3: Surgical intervention by type of congenital heart defect

Single Defect	Required	Done	Awaiting	Lost to Follow-up†	Demised‡
AVSD (*n* = 28)	**28 (100.0%)**	7/28 (25.5%)	5/28 (17.9%)	12/28 (42.9)	4/28 (14.3%)
VSD (*n* = 14)	**11 (78.6%)**	1/11 (9.0%)	4/11 (36.4%)	5/11 (45.5%)	1/11(9.0%)
PDA (*n* = 11)	**3 (27.3%)**	1/3 (33.3%)	0/3 (0.0%)	2/3 (66.7%)	0/3 (0.0%)
ASD (*n* = 4)	**1 (25.0%)**	0/1 (0.0%)	0/1 (0.0%)	1/1 (100.0%)	0/1 (0.0%)
TOF (*n* = 1)	**1 (100.0%)**	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	1/1 (100.0%)
Multiple Defects	Required	Done	Awaiting	Lost to Follow-up†	Demised‡
AVSD/PDA (*n* = 8)	**8 (100.0%)**	3/8 (37.5%)	1/8 (12.5%)	4 (50.0%)	0/8 (0.0%)
AVSD/ASD (*n* = 1)	**1 (100.0%)**	1/1 (100.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)
AVSD/TOF (*n* = 1)	**1 (100.0%)**	0/1 (0.0%)	0/1 (0.0%)	1/1 (100.0%)	0/1 (0.0%)
VSD/PDA (*n* = 5)	**3 (60.0%)**	2/3 (66.7%)	0/3 (0.0%)	1/3 (33.3%)	0/3 (0.0%)
VSD/ASD (*n* = 1)	**1 (100.0%)**	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	1/1 (100.0%)
VSD/ASD/PDA (*n* = 1)	**1 (100.0%)**	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	1/1 (100.0%)
ASD/PDA (*n* = 1)	**1 (100.0%)**	0/1 (0.0%)	0/1 (0.0%)	1/1 (100.0%)	0/1 (0.0%)
ASD/Other* (*n* = 1)	**0 (0.0%)**	0/0 (0.0%)	0/0 (0.0%)	0/0 (0.0%)	0/0 (0.0%)
Total	**60**	**15/60 (25.0%)**	**10/60 (16.7%)**	**27/60 (45.0%)**	**8/60 (13.3%)**

AVSD = Atrioventricular Septal Defect; PDA = Patent Ductus Arteriosus; VSD = Ventricular Septal Defect; ASD = Atrial Septal Defect secundum type; TOF = Tetralogy of Fallot.
* Other includes peripheral pulmonary stenosis
† Lost to follow-up before surgery
‡ Demised before surgery

Of participants who had surgery, the median age at presentation was 8 (IQR 18) months and the median age at first surgery was 31 (IQR 24) months. Only 2/77 (2.6%) participants with a CHD required follow up surgery and a second surgery was performed on only one of the two participants (both with AVSD and PDA) at 44 months. The median age at presentation and death of participants who demised before surgery was 2.5 (IQR 7.5) months and 12.5 (IQR 18) months respectively.

The majority (*n*=11, 73.3%*)* of the surgeries performed were AVSD repair (three with PDA ligation), followed in descending frequency by VSD repair (*n*=3, 20.0%; two with PDA ligation) and isolated PDA ligation (*n*=1, 6,7%). The majority of single PDA's did not require surgery as spontaneous closure was confirmed with echocardiography, the defect was haemodynamically insignificant in size or ICC was performed with device closure. Similarly, a small number of participants with single VSD, single ASD and VSD/PDA also had defects that did not require surgery.

Figure 3 represents total numbers of interventions required and outcomes for DCC and surgery in all CHDs.

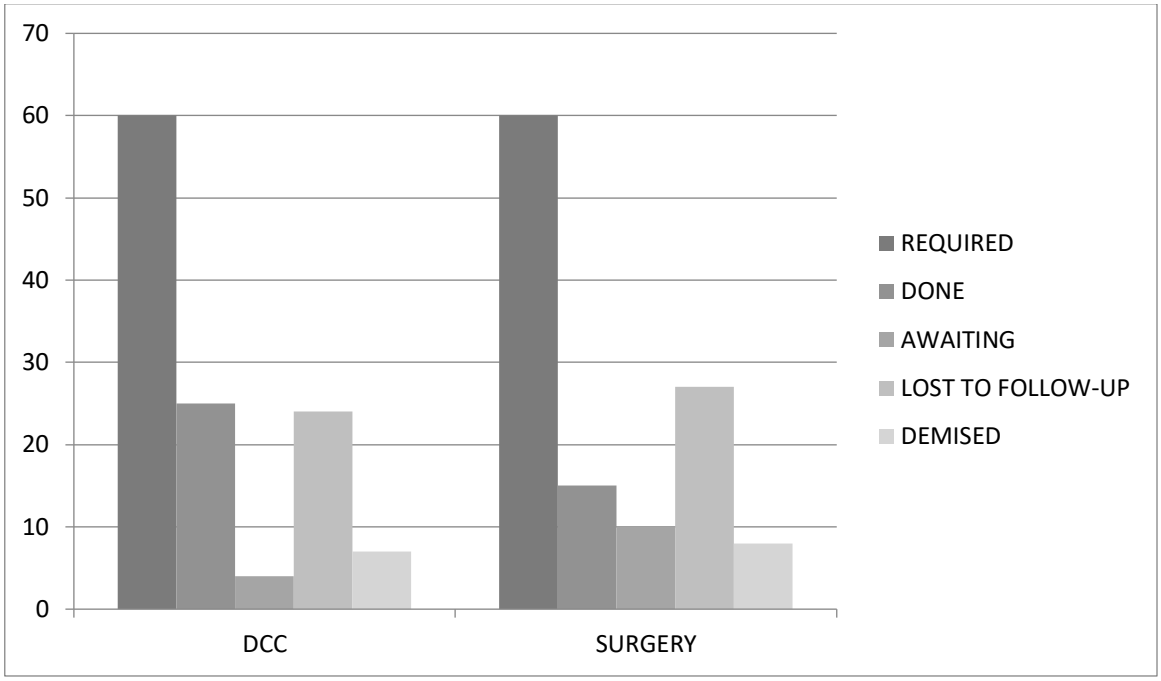

Fig. 3: Details of intervention required – all congenital heart defects in total (DCC = Diagnostic Cardiac Catheterisation)

Survival Post-Intervention

Survival to one year follow up post ICC was reported in one participant with PDA who underwent closure with a duct occluder device. Post-surgery survival is presented in Table 4. Only one participant required a second surgery and the participant survived to one year follow up.

Table 4: Post surgery survival

	Hospital discharge	3 weeks	6 months	1 year
Alive	14 (93.3%)	14 (93.3%)	14 (93.3%)	13 (86.7%)
Demised	1 (6.7%)	1 (6.7%)	1 (6.7%)	2 (13.3%)

Eleven patients demised during the study period; eight participants pre-surgery (see Table 3), two post-surgery (see Table 4) and lastly, one with a VSD who did not require surgery.

Discussion

This study was the first to describe CHDs in the paediatric South African T21 population in Gauteng. The study found that the prevalence of CHDs in the T21 study population was 60.2% which is comparable with that found in literature worldwide of between 40-60%.[3] More than a third of participants screened had a normal heart on echocardiography.

In this study, the most common CHD recorded was a single AVSD; AVSD was also reported most frequent in the RCH study as well as T21 populations of USA, western Europe and north Africa.[7-11, 17, 25] Table 5 compares the frequency of CHDs in this study to literature from other African countries and worldwide. A single CHD was reported in just over 75% of participants, equal to Morocco and more common than Algeria (68%), Ethiopia (66%), Libya (65%) and Nigeria (45%)[10, 11, 13, 15, 16].

Table 5: Comparison of congenital heart defects in Africa and worldwide

Country	Congenital heart defect %						
	AVSD	**PDA**	**VSD**	**ASD**	**TOF**	**CoA**	**Other**
South Africa*	39.2	26.8	21.6	9.3	2.1	0.0	1.0
Algeria[13]	44	6	17	7	4	1	21
Egypt[14]	16.4	4.4	39.8	12.6	2	0.5	24.3
Ethiopia[16]	18.6	36.5	19.9	19.0	2.6	1.9	1.5
Libya[10]	19	4	12	24	2	1	39
Morocco[11]	30	17	22	20	5	1	5
Nigeria [15]	18	17	16	27	11	0	11
Sudan[7]	48	7	23	5	6	0	11
Brazil[8]	15.1	6.6	12.7	42.1	2	0	21.5
USA[6, 25]	45	7	35	8	4	1	1

AVSD = Atrioventricular Septal Defect; PDA = Patent Ductus Arteriosus; VSD = Ventricular Septal Defect; ASD = Atrial Septal Defect secundum; TOF = Tetralogy of Fallot; CoA = Coarctation of the Aorta; USA = United States of America.
*Charlotte Maxeke Johannesburg Academic Hospital study

The majority of participants with a CHD required a DCC to assess eligibility for surgery. Of the single CHDs, AVSD required catheterisation in almost all cases and almost 100% of participants with multiple CHDs required catheterisation. Less than half of DCC's required were performed, but loss of participants to follow-up pre-DCC was the primary reason for DCC not performed. The waiting time to first DCC was nine months.

There is a paucity of details about DCC being required or performed in other studies reviewed. Only one study performed in Sudan commented on DCC required for five participants. All participants who required DCC had an AVSD and DCC was performed after one year of age to assess anatomy not visualised on ECHO and to measure pulmonary artery pressure and vascular resistance. However, findings with relation to surgery or survival of these participants was not further discussed.[7] Details of DCC not discussed in other studies may be due to differences in unit policy' where DCC is not required prior to surgery. Alternatively, diagnosis on ECHO for surgical eligibility may have been sufficient in those study populations if surgery was performed at a younger age prior to the development of complications or on less complex lesions. [3, 17]

Since the introduction of ICC, device closure of defects like PDA and ASD is now standard practice.[26] However, only one participant in this study had a device closure.

Only a quarter of participants who required surgery had surgery performed. This compares unfavourably with the study from Morocco where more than 60% of surgeries required were performed. [11] Most of the surgeries performed in the unit were AVSD repairs, in keeping with the most frequent CHD reported in the unit, and similar to surgeries performed at other centres worldwide.[3, 17] The majority of surgeries not performed were due to participants lost to follow-up.

The recommended age for surgery (chiefly AVSD repair) in T21 with CHDs for optimal survival is before six months.[23] The median age at surgery (31 months) in the study participants was more

than two years later than the recommended age for surgery and none were performed before 12 months (waiting time 23 months). In comparison, surgery was performed earlier at RCH (nine months), which could be explained by the better availability of specialised cardiothoracic surgeons or surgical facilities at RCH.[17] Surgery was also performed earlier in studies in Europe (six months) and the USA (five months) which may be due to earlier screening and diagnosis of CHDs or the greater availability of resources in high-income settings for surgical repair.[3, 23] Early repair of CHDs precludes the need for DCC to assess pulmonary vasoreactivity. The median age at presentation in this study was six months, thus early surgical repair was not a feasible option.

Many factors may have contributed to the delay and non-performance of interventions at CMJAH PCU. The main factor was the large number of participants lost to follow-up pre-DCC and pre-surgery. There may have been multiple causes for participants lost to follow-up including: socioeconomic constraints or participant mobility preventing attendance at clinic, reluctance by family of participants to undergo intervention, non-cardiac co-morbidities resulting in demise/non-attendance pre-intervention or demise due to CHDs. Another factor contributing to delay and non-performance of interventions was likely the shortage of resources. Resource shortages included an insufficient number of paediatric cardiologists and cardiothoracic surgeons for the number of patients and also a lack of finances to provide surgical equipment, devices and theatre time.

Historically, non-T21 children were prioritised over T21 children for surgery.[21] Surgery was likely not performed in T21 children due to the higher association of non-CHD co-morbidities, the shorter perceived life span of T21 individuals and the possibility of complexity of CHDs in T21 requiring repair.[5] However, it has been shown that children with T21 and AVSD (the commonest CHD requiring repair) have a defect more favourable to surgical repair compared to non-T21 children with AVSD.[23] Recent literature shows that T21 does not confer higher risk to surgery.[3, 23, 27] In 2014 a review article of the USA national clinical database confirmed that T21 showed no greater risk in mortality for surgical repair in all CHDs commonly found in T21 individuals.[3] The lifespan of individuals with T21 has also improved significantly over the last years (to an average of 60 years).[18] The 20-year survival rate of individuals with T21 has been reported as high as 88%.[28] Furthermore, the study at RCH looked specifically at the burden on resources of the management of CHDs in T21 and found the admission rate post-surgery to be much lower than admission rate pre-surgery in T21. The burden on resources was thus less after surgical correction of CHDs in T21 and highlighted no significant difference in resource use when compared to non-T21 participants.[17] The literature thus supports strongly advocating for early surgery in T21 children with CHDs.

The high survival rates after six-month and one-year follow-up in this study, compares favourably to post-surgical survival rates in African studies; Morocco 79% and Nigeria 81.1%.[11, 15] At RCH survival to hospital discharge was almost equal to this study (90%).[17] In the first world the 30 day mortality rate post primary repair has been reported as low as 5.3% (Germany) and the in-hospital mortality rate 1.9% (USA) both significantly lower than non-T21 participants.[2, 23] The survival rate of participants post-surgery in this study may have been affected by the development of complications of the CHD worsened by the delay in surgery (e.g. pulmonary hypertension, worsening cardiac function) or the presence of other non-CHD related complications (e.g. chronic lung disease).

Limitations

The study was limited by the small sample size which did not allow for trend analysis. Sixteen percent of participants with clinically suspected T21 were not confirmed with PCR aneuploidy testing and therefore excluded. It is possible that some children with T21 were not referred for screening echocardiography due to missed clinical signs of T21 and thus excluded.

It is also a limitation of this study that the population statistics could not be calculated, as population data on T21 patients were not available. Details of outcome related to participants lost to follow-up were not assessed. The cause of death of the participants was not recorded; therefore, it is unknown what effect co-morbidities may have had on the survival rate and whether death was primarily due to CHDs. There was no data collected on what effect surgery performed at a later age than recommended might have had on survival rate. More studies, with larger sample sizes and longer duration of follow-up, at different centres in SA are needed in order to get a full understanding of CHDs in T21 in SA.

Conclusions and recommendations

This study is the second review of children with T21 and CHDs in SA. The prevalence of CHDs in children with T21 is comparable to global studies and confirmed that single AVSD type CHD was most common in the CMJAH T21 population. The age at presentation and diagnosis of participants was not optimal for early intervention, and there was further delay in catheterisation and surgery. Measures need to be implemented to identify and rectify the large number of participants lost to follow-up contributing to the delay and non-performance of interventions. An increase in surgical resources may also assist in timeous intervention. Survival post-surgery compares favourably with other centres even though surgery was performed at a much later age than the age recommended for best outcome.

Our findings suggest that surgical repair in children with T21 and CHDs has a favourable outcome and thus should be performed. Early screening, diagnosis and intervention can prevent not only morbidity and mortality due to CHDs and the complications of CHDs, but also may decrease the financial burden on the healthcare system.

Acknowledgements. I must acknowledge my co-authors Dr. Firoza Motara and Prof. Daynia Ballot for their patience, time, dedication and guidance, Dr. Wiedaad Slemming for her support and assistance in the submission of this paper for publication and lastly the staff at the Paediatric Cardiology Department for the use of their database.

Conflict of Interest. None

Author Contributions. RM and FM were responsible for protocol, study design, conceptualization, data collection and analysis, article and study documents and were supported by DB.

Funding sources. Self-funded by principle author.

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APPENDIX 1 – APPROVED PROTOCOL

A REVIEW OF CONGENITAL HEART DEFECTS IN CHILDREN WITH TRISOMY 21 OVER A 5-YEAR PERIOD AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

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Introduction

Trisomy 21 (T21) is the leading chromosomal abnormality in humans with an incidence ranging between 1:750 and 1:1000 live births.[1] T21, or Down Syndrome, was first described in 1867 by the English Physician John Langdon Haydon Down.[2] The prevalence of children born with T21 has increased significantly over that last 30 years, by as much as 25%.[3]

In his paper, Down reported on a group of children under his care who showed a typical physical appearance, intellectual disability and other associated defects. He postulated a common underlying cause for these defects, that was not race related but rather independent of ethnic origin.[2] In the 1930's, Waardenburg and Bleyer were the first to discover the underlying cause of Down Syndrome to be a form of chromosomal abnormality (non-disjunction). It was later in 1959, when two independent authors, Jerome Lejeune and Patricia Jacobs, definitively determined the underlying defect to be trisomy (or triplication) of the 21st chromosome.[4]

T21 manifests in multi-systemic defects affecting the neurological, pulmonary, gastrointestinal, immunological, endocrine and cardiovascular systems. Down described the circulation of the identified group of children in his care as "feeble", but it was Garrod who first formed the association between congenital heart defects (CHD) and T21. [2, 5] The incidence of CHD in the T21 population is significantly higher than that of the general population. Worldwide, an estimate of between 40-60% of T21 individuals have an associated CHD. [6]

In South Africa, the incidence of CHD in the general population is between 0.6 - 0.8 per 1000 live births (~ 11 000 per year). [7] Untreated CHD in South African children is the leading cause of birth defect associated mortality.[7] According to the South African Medical Journal, 8 % of patients diagnosed with CHD have confirmed T21.[8] These numbers show that the burden of CHD in T21 patients is a significant factor and warrants further study and investigation.

Worldwide, CHD in T21 predominately presents with a single defect but multiple defects may be present in the individual. The most frequent defect, classically described in text, is an Atrioventricular Septal Defect (AVSD), with a prevalence between 31-47%.[9] Most data in literature is derived from population groups in the United States of America (USA), Europe and Asia. This prevalence however has been shown to vary between different countries; with a predominance of a single Atrial Septal Defect (ASD) in the Mexican (38%) population, Ventricular Septal Defect (VSD) in India (26%) and Patent Ductus Arteriosus (PDA) in a study from Guatemala (28%). [10, 11]

According to Benhaourech et al in the Cardiovascular Journal of Africa, there is lack of literature describing CHD in T21 in Africa. In Benhaourech et al.'s study, based in Morocco, AVSD was the commonest defect with a prevalence of 29.9%.[12] The African population has also been described in literature from Libya and Sudan. Sudan reported a 48% prevalence of AVSD, which is close in comparison to countries like USA, China and Italy.[13] Libya reported a predominance of ASD (24%) like that of Latin America.[10] In Brazil, a country with similar socioeconomic factors to SA, the commonest lesion described was that of ASD (42%).[14] These studies suggest that there is some geographical variation in frequency of CHD in T21: AVSD in USA, western Europe and north Africa, VSD in Asia and ASD in Latin America. However, to our knowledge no South African literature describing type and frequency of CHD in T21 is available.

Recent literature has further presented evidence of a shift in the distribution of CHD in the USA and Europe. [9] There has been a shift toward defects that are more easily operable then preceding years. [6, 9,15] The shift of frequencies away from complex cardiac lesions may be the reason of a more favourable outcome in patients with T21 and CHD. This may be as a result of selective abortion of T21 patients with complex congenital heart lesions (with the advent of amniocentesis

and antenatal screening programs) but improved medical and surgical management has also made its mark.[15, 16]

Ongoing medical advances have improved the outcome and long-term survival in the T21 cardiac population significantly in developed countries, with a decrease in mortality from 13% in the 1980's to 4% in the early 2000's. [16]

In the South African Health Sector resource constraints play a large role in allocation of specialist services, e.g. cardiac surgery. [7] In Johannesburg for example, the public-sector hospitals have a shortage of human resources (cardiologists, cardiothoracic surgeons and nursing staff) as well as few referral specialist centres and intensive care units for post intervention care. This means that not all patients who require intervention may receive it timeously (due to extremely long waiting lists) or at all. [8]

Deciding on which patients receive these costly interventions is often made by perceived long term medical outcomes. Historically, T21 individuals were unlikely to receive intervention ahead of their normal counterparts.[17] The rationale for T21 patients not being operated upon, was based on the principle of distributive justice (especially in the low resource setting). It was argued, that individuals with T21 were less likely to be employed or contribute to society, not only because they had perceived poorer short-term outcomes after surgery, but also in the long-term due to concurrent conditions, mental impairment, a higher risk of Alzheimer's dementia and a limited lifespan affecting their productivity. [8, 17, 18] Thus, T21 patients were deemed not to be good candidates for surgical repair.

Contrary to this belief, evidence of survival and favourable outcome post-surgery has since been reported in the literature:
In a study in 2014 by Evans et al, better post-operative outcomes were reported in T21 patients who underwent AVSD repair when compared to patients without T21. [2] In 2010, a national database analysis of American patients reported no significant difference in post-operative mortality in T21 patients verses non-T21 patients. [6] An article in The Journal of Thoracic and Cardiovascular Surgery, proved that Down Syndrome was not a risk factor for surgical repair.[19] It showed no significant difference in survival in T21 patients with classic AVSD repair post-surgery. It was further suggested that surgery in T21 should be done before 6 months of age, prior to the development of pulmonary vascular disease (a common complication of CHD in T21).[19]

In the first ten years of life, mortality in T21 is strongly associated with the presence of CHD.[16] CHD may lead to further cardiopulmonary compromise (pulmonary hypertension, cor pulmonale, recurrent lower respiratory infections, cardiac failure) and cardiopulmonary disease accounts for ~ 75% of morbidity and mortality in the T21 population. [20] Thus, CHD and its complications are significant contributors to the cost of management of patients with T21. With early identification and intervention, complications may be avoided.[18, 20] In addition, the cost of recurrent and prolonged hospital admissions due to these complications, or the financial cost to parents taking time off work may be much more draining on monetary and other resources then definitive management like surgery.[7, 8, 17]

Thus, it would follow, that denying intervention to patients with T21 is not justifiable, even in low resource settings. Furthermore, surgery should be performed in a timeous manner to prevent the development of complications which may worsen morbidity and mortality.

Justification for the study

The reason for the increased incidence of CHD in T21 compared to the general population is not yet known. It may thus be of benefit to compare the incidence in the South African T21 population to

neighbouring countries and their counterparts. The data collected may further enable research of the causative factors which may affect frequency and prevalence (e. g. environmental and sociodemographic vs genetic and ethnic determinants). In the South African context, with a diverse ethnic population and being geographically distant from all countries previously described, much is to be learned about the frequency and distribution of CHD in T21. It is important to be aware of the frequency and distribution of CHD in our South African population to make informed decisions regarding prognosis post intervention in these patients.

In conclusion, inadequate data is available describing CHD, the types of lesions, their frequency and the outcomes after intervention in the South African T21 CHD population.
The Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) Cardiology Unit, being a leading centre and important referral centre, may serve as a good predictor of provincial data and may be used for comparison with similar studies carried out at other centres in other provinces and worldwide. Thus, the aim of my study is to describe the type, frequency, intervention and outcomes of CHD in the T21 population at a South African paediatric cardiac facility, CMJAH Cardiology Unit. The study would serve as a valuable resource, as well as form a basis for further research into CHD in the South African T21 paediatric population.

Aim

To review CHD in patients with T21 seen at the paediatric cardiology unit at CMJAH over a 5-year period (between 2012 and 2016).

Objectives

1. To describe the type and frequency of CHD in children with T21 seen at the CMJAH paediatric cardiology unit from 2012 to 2016.

2. To evaluate interventions in T21 children with CHD at CMJAH paediatric cardiology unit from 2012 to 2016.
   A. to determine the number of patients who required intervention (cardiac catheterisation [diagnostic, interventional] and/or surgery)
   B. to determine the survival rate of patients that underwent cardiac catheterisation and/or surgery to hospital discharge, at first, second and third follow up visit (3 weeks, 6 months and 1 year respectively)

Study Design

This is a retrospective, observational study, to be carried out at the Paediatric Cardiology Unit at the CMJAH.

Study population

CMJAH is a highly specialised centre situated in Parktown, Johannesburg, South Africa. The hospital provides a wide range of services including secondary and tertiary level care. The hospital is also a referral centre for a number of hospitals and clinics in the surrounding area. [21]

The paediatric cardiology unit at CMJAH sees on average ~2050 patients yearly. Patients are referred as in-patients and out-patients from the hospital and it also receives referrals from other centres. Subjects will be drawn from the population of paediatric patients seen at the CMJAH paediatric cardiology unit over a five-year period (between 2012 to 2016).

Management of CHD patients with T21 at CMJAH

All patients who present to any of the paediatric services at CMJAH with suspected or laboratory confirmed T21 (with polymerase chain reaction aneuploidy testing) are routinely referred to the CMJAH paediatric cardiology unit for a screening echocardiographic assessment. This includes both patients admitted to the wards and those seen by the unit as out-patients. Thereafter, any patient with significant CHD may undergo further intervention as required; this includes cardiac catheterisation and if indicated, surgery (multiple interventions may be required). The patients are then followed up at specified intervals (three weeks, six months and one year) post intervention. All relevant patient information is recorded onto the CMJAH cardiology database by Dr Motara (principle cardiologist in the unit) on presentation and updated at each follow up visit.

This study will specifically look at patients presenting with echocardiographic diagnosis of CHD and laboratory confirmed T21.

A cursory review of the database shows the sample size to be between 150-200 subjects with the following inclusion and exclusion criteria:

Inclusion:

1. All children between the ages of 0 and 16 years with laboratory confirmed karyotyping T21 will be included in the study.

Exclusion:

1. Patients with T21 with a preceding cardiac diagnosis prior to referral to CMJAH cardiac unit (e.g. referral from another centre for cardiac catheterisation).
2. Any T21 patient with acquired heart disease.
3. Any study subject with incomplete information on clinical database and patient records (including demographics, type of lesion etc.).
4. Any patient with T21 in whom no echocardiogram was done.

Methods

This study is a secondary analysis of an existing patient database at CMJAH. The CMJAH paediatric cardiology database will be accessed on site to collect the relevant data required. Patient records will also be accessed to provide additional data that may be required, not accessible on the aforementioned database. Data will be transferred onto Data Collection Sheets. (see attached) This data will include: demographics (gender, ethnicity, age at assessment), echocardiographic diagnosis (presence of CHD, type of CHD, single defect vs multiple defects), intervention (need for cardiac catheterisation [diagnostic, interventional, both], need for surgery, number that underwent intervention if required, age at intervention), survival to hospital discharge, at first, second and third unit follow up post intervention (3 weeks, 6 months and 1 year).

Data Analysis

The data will then be computed using both continuous and categorical variables and recorded onto data collection sheets (see attached). The variables will be transferred onto an excel spread sheet and will be analysed using a statistics programme (STATA 15). The frequency and percentages of the categorical variables will be analysed and compared for statistical significance using the chi-squared test. Continuous variables will be analysed assessing the standard deviation, mean, median or range, and compared using the unpaired t test or Mann-Whitney U test where appropriate.

Limitations

Limitations to the study include patients with incomplete records and incomplete data on the clinical databases. Another possible limitation is that not all T21 patients may be referred to the CMJAH cardiology unit and thus may not receive a screening echo, these patients can therefore not be included. It is also a limitation of the study that the population statistics (of e. g. frequency and type of CHD, as well as prevalence) cannot be calculated, as population data on T21 patients is not available.

Ethical Considerations

This is a retrospective study, using a clinical database and thus will not require informed consent to be obtained. The confidentiality of subjects will be protected as no names, patient record numbers or birth dates will be reported in the study. Patients will be assigned a patient number to maintain anonymity.

Permission will be attained from the hospital director of CMJAH to carry out the study. I will apply for ethics approval from the Human Research Ethics Committee of the University of the Witwatersrand for my study as well as submit my protocol online for assessment to the National Health Research Database.

Timing

	DEC	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	JAN
Literature Review														
Preparing Protocol														
Protocol assessment														
Ethics Application														
Collecting Data														
Data Analysis														
Writing up														

Funding

All costs of transport to CMJAH to access the databases, printing and photocopying of paper will be funded by the candidate. An estimate of R500 will be required. No additional costs are anticipated.

Data Collection Sheet
Patient no:

Demographics				
Age at assessment				
Gender	Male	Female	Ambiguous	
Ethnicity	African	Caucasian	Indian	Other

Echocardiographic diagnosis						
Presence of cardiac defect	YES	NO				
No of lesions	Single	Multiple				
Type of lesion	AVSD	VSD	ASD	TOF	PDA	OTHER

OTHER LESION:

Intervention: Diagnostic Catheterisation		
Diagnostic Catheterisation required	YES	NO
Diagnostic Catheterisation done	YES	NO
Age at intervention (Diagnostic Catheterisation)		

Intervention: Interventional Catheterisation		
Interventional Catheterisation required	YES	NO
Interventional Catheterisation done	YES	NO
Age at intervention (Interventional Catheterisation)		

First Surgical Intervention		
Surgery required	YES	NO
Surgery done	YES	NO
Age at intervention (First Surgery)		

Second Surgical Intervention		
Surgery required	YES	NO
Surgery done	YES	NO
Age at intervention (Second Surgery)		

Third Surgical Intervention		
Surgery required	YES	NO
Surgery done	YES	NO
Age at intervention (Third Surgery)		

Outcome		
Survival to hospital discharge	YES	NO
Survival at 1st follow up (3 weeks)	YES	NO
Survival at second follow up (6 months)	YES	NO
Survival at third follow up (1 year)	YES	NO

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APPENDIX 2 – ETHICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Raeesa Mahomed et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180919

NAME: (Principal Investigator)	Dr Raeesa Mahomed et al
DEPARTMENT:	Paediatric Cardiology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	A review of congenital heart defects in children with trisomy 21 over a 5-year period at Charlotte Maxeke Johannesburg Academic Hospital
DATE CONSIDERED:	28/09/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Firoza Motara
APPROVED BY:	Dr C Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	16/10/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

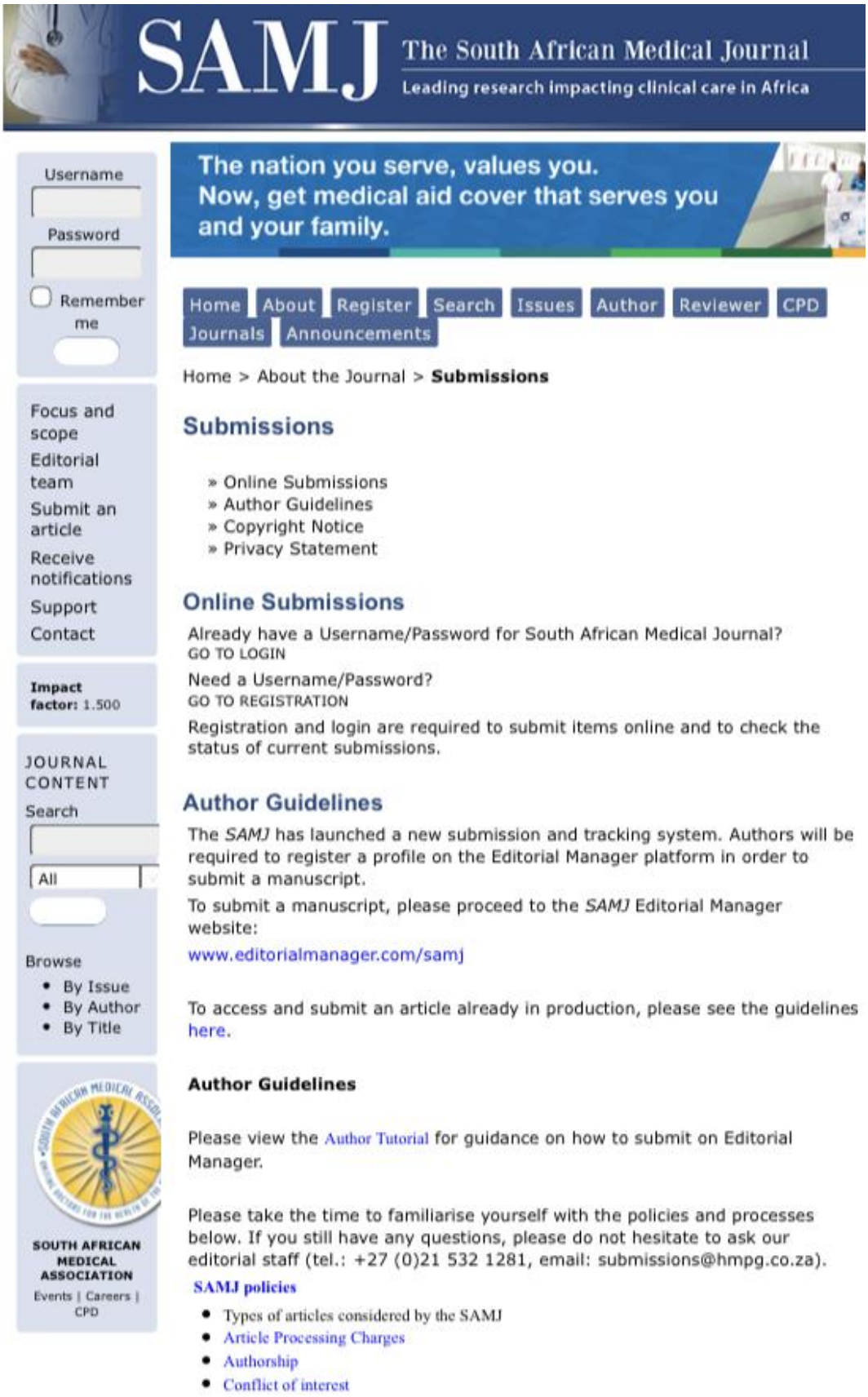
To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed September and will therefore be due in the month of September each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

20/10/2018
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX 3 – AUTHOR GUIDELINES



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- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
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- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state ‘none’.
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SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:

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**NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. ‘188del11’ can be glossed as ‘an 11 bp deletion at nucleotide 188.’

- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

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Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text .

Structured abstract

- This should be 250-400 words, with the following recommended headings:
    - **Background:** why the study is being done and how it relates to other published work.
    - **Objectives:** what the study intends to find out
    - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
    - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
    - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
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All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

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- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

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- Start with description of the population and sample. Include key characteristics of comparison groups.
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This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

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A review of Congenital Heart Defects in children with Trisomy 21 over a 5- year period at Charlotte Maxeke Johannesburg Academic Hospital R Mahomed, MBBCh; D Ballot, MBBCh, FCPaed (SA), PhD; F Motara, MBBCh, FCPaed (SA), Cert. Cardiology Paed (SA) Department of Paediatrics and Child Health, University of the Witwatersrand and Charlotte Maxeke

Johannesburg Academic Hospital, Johannesburg, South Africa Corresponding author: R Mahomed (raem1690@yahoo.co.uk) Abstract Background: In the first ten years of life, mortality in Trisomy 21 (T21) is strongly associated with the presence of Congenital Heart Defects (CHDs). There is currently a lack of local and regional data regarding the prevalence, management and outcomes of children with T21 and CHDs. Objectives: To describe the prevalence, type and frequency of CHDs and review interventions (cardiac catheterisation and surgery) and survival post-surgery of children with CHDs in the T21 population at a South African facility, the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) Paediatric Cardiology Unit (PCU). Methods: A retrospective, cross sectional, observational review of 177 participants at CMJAH PCU between January 2013 to December 2017 was performed. Data collected from the PCU database and clinical records included: demographics, echocardiographic diagnosis, details of Diagnostic Cardiac Catheterisation (DCC), Interventional Cardiac Catheterisation (ICC) and surgery required and performed, age at diagnosis and intervention as well as survival post-surgery. Results: There were 128 participants with laboratory-confirmed T21 and CHD on echocardiography meeting inclusion criteria. The majority of participants were female (56.0%) and African (97.0%). The median age at presentation was six (IQR 9.75) months. The prevalence of CHDs was 60.2% and 58/77 (75.3%) had a single CHD. The most frequent CHD was an Atrioventricular Septal Defect (AVSD) (38%) (with or without another associated CHD). DCC was required in 60/77 (77.9%) participants and 25/60 (41.6%) were performed. The median age at DCC was 15 (IQR 15) months. One participant with isolated PDA required and underwent successful ICC for PDA closure at 17 months. Surgery was required in 60/77 (77.9%) of participants, while 15/60 (25.0%) surgeries were performed. Almost half of DDCs and surgeries not performed were due to participants lost to follow-up (40% and 45% respectively). The median age at first surgery was 31 (IQR 24) months. The most performed surgery was an AVSD repair (73%). Post-surgery survival was 93.3% at hospital discharge, 3-week and 6-month follow-up and 86.7% at 1-year follow-up. Conclusion: The prevalence, type and frequency of CHDs in the CMJAH T21 population is comparable to global data. Participants presented and were diagnosed at an optimal age but catheterisation and surgery were delayed. Survival post-surgery compares favourably with other centres even though surgery was performed at a much later age than the age recommended for best outcome (six months). Early screening, diagnosis and intervention can prevent morbidity, mortality due to CHDs and may decrease the financial burden on the healthcare system. Introduction The leading chromosomal abnormality in humans is Trisomy 21 (T21) with an incidence between 1:750 and 1:1 000 live births.[1] The prevalence of children born with T21 has increased by as much as 25% over that last 30 years.[2] Worldwide, an estimated 40-60% of T21 individuals have an associated Congenital Heart Defect (CHD).[3] In South Africa (SA) untreated CHDs are the leading cause of mortality associated with birth defects and an estimated 8% of patients diagnosed with a CHD have confirmed T21.[4, 5] Worldwide, CHDs in T21 predominantly presents with a single defect but multiple defects may occur. The defect most commonly cited is an Atrioventricular Septal Defect (AVSD), with a prevalence between 31-47%. [6] Recent studies suggest that there is a geographical variation in frequencies of CHDs in T21. AVSD is most frequently described in the literature from United States of America (USA), western Europe and north Africa, Ventricular Septal Defect (VSD) is most frequent in Asia and Atrial Septal Defect (ASD) in Latin America.[7-12] There are very few studies from Africa and only one South African study describing CHDs among children with T21,

performed in 2006 at Red Cross War Memorial Children's Hospital (RCH) in the Western Cape .[8, 9, 11, 13-17] In the first ten years of life, mortality in T21 is strongly associated with the presence of CHDs.[18] Cardiopulmonary disease accounts for ~ 75% of

morbidity and mortality in the T21 population.[19] Thus, CHDs and its complications are significant contributors to the cost of management of patients with T21. Recent literature has presented evidence of a shift in the distribution of CHDs in T21 toward defects that are more easily operable then preceding years, resulting in improved morbidity and mortality.[3, 6, 20] The decrease in incidence of CHDs in T21 as a result of selective abortion of T21 patients with CHDs (with the advent of amniocentesis and antenatal screening programs) may be the reason for the shift in distribution, but improved medical and surgical management has also resulted in improved operative outcomes.[18, 20] South African public-sector hospitals have a shortage of human resources (cardiologists, cardiothoracic surgeons and nursing staff) as well as few referral specialist centres and intensive care units for post intervention care. This means interventions may not be performed timeously (due to extremely long waiting lists) or at all.[5] Historically, children with T21 were unlikely to receive intervention.[21] It was argued, that individuals with T21 were less likely to be employed or contribute to society, not only because they had perceived poorer short-term outcomes after surgery, but also in the long- term due to concurrent conditions, mental impairment, a higher risk of Alzheimer's dementia and a limited lifespan affecting their productivity. [5, 17, 21] With early identification and intervention, complications may be avoided.[17, 19] In addition, the cost of recurrent and prolonged hospital admissions due to these complications, or the financial cost to parents taking time off work may be much more draining on monetary and other resources then definitive management like surgery.[4, 5, 21] Evidence of survival and favourable outcome post- surgery has since been reported in literature worldwide and in SA, with no significant difference in burden to the health care system or survival post-surgery in T21 vs non-T21 patients.[3, 17, 22, 23] There is currently a lack of local and regional data regarding the prevalence, management and outcomes of children with T21 and CHDs. The aim of this study was to describe the prevalence, type and frequency of CHDs as well review interventions (cardiac catheterisation and surgery) and survival post-surgery of children with CHDs in the T21 population at a South African facility, the CMJAH Paediatric Cardiology Unit (PCU). Methods Design A retrospective, cross sectional, observational study, was carried out. Participants were drawn from the population of paediatric patients seen at the CMJAH PCU over a five-year period (January 2013 to December 2017). Setting CMJAH is a tertiary centre situated in Parktown, Johannesburg, SA. The hospital is a referral centre for a number of hospitals and clinics in the surrounding area. [24] The PCU at CMJAH sees on average ~ 2050 patients yearly. All patients who had presented to any of the paediatric services at CMJAH with suspected or laboratory confirmed T21 (with polymerase chain reaction aneuploidy testing) were routinely referred to the CMJAH PCU for a screening echocardiographic assessment. Thereafter, any patient with a significant CHD underwent further intervention as required; this included diagnostic cardiac catheterisation (DCC), interventional cardiac catheterisation (ICC) and surgery (multiple interventions may have been required). All participants older than 9 months with an indirect assessment of pulmonary hypertension on echocardiogram or in whom DCC was deemed necessary by the unit, underwent DCC prior to surgery. Surgical repair was indicated in CHDs that were haemodynamically significant or could lead to significant morbidity and mortality. The patients were then followed up at specified intervals post intervention. At the time of the study there were two trained paediatric cardiologists and one cardiology fellow working in the unit. Surgery was performed by the cardiothoracic surgery unit on site at CMJAH. The surgical team comprised three surgeons trained in repair of CHDs. Data source All relevant patient information was recorded onto the CMJAH PCU database on site by the principle cardiologist in the unit on presentation and updated at each follow up visit. The database comprises information of all patients who are assessed by the unit including data on

demographics, comorbid conditions (e.g. T21), cardiac diagnosis on echocardiogram, cardiac catheterisation data and surgery performed. Further details of cardiac catheterisation, surgery, survival and outcome were recorded in patient records at the PCU. Participants There were 177 patients on the database with echocardiographic diagnosis of CHD and confirmed or suspected T21. This included both in-patients and out- patients. Participants between birth and 16 years with laboratory confirmed karyotyping T21 were included in the study. Participants with a preceding cardiac diagnosis prior to referral to CMJAH PCU (e.g. referral from other hospitals for cardiac catheterisation only), participants with acquired heart disease, participants with incomplete information on clinical database and/or patient records (such as diagnostic and outcome data) and participants in whom no echocardiogram was done, were all excluded. Data Collection The study was a secondary analysis of the existing patient database at CMJAH PCU and review of patient records. Data were entered into a MS Excel spreadsheet and variables included demographic data (gender, ethnicity, age at assessment), echocardiographic diagnosis (presence of CHD, type of CHD, single defect vs multiple defects), intervention (need for cardiac catheterisation (DCC, ICC or both), need for surgery, number that underwent intervention if required, age at intervention and survival to hospital discharge, at first, second and third follow- up visit post intervention (3 weeks, 6 months and 1 year). Details of echocardiographic data, intervention data

and outcome as well as any missing variables on the database were collected from patient records. Statistical Analysis Data were and analysed using SPSS Statistics 25. The median and interquartile range (IQR) of continuous variables were reported as distribution was skewed, while the frequencies and percentages of categorical variables were reported. Ethics The study was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (Clearance Certificate No. M180919) and submitted to the National Health Research Database for institutional approval. Results There were 128 participants in the final study sample (See Fig. 1.). Laboratory Clinically (no laboratory confirmation) Transfers Fig. 1. Flow diagram of final sample and exclusion criteria (CMJAH: Charlotte Maxeke Johannesburg Academic Hospital; T21: Trisomy 21) Description of study sample The majority of participants were female (56.0%) and of African ethnicity (97.0%). The median age at presentation was six (IQR 9.75) months. There were 77/128 (60.2%) participants who had a CHD on echocardiography; 58/77 (75.3%) had a single CHD while 19/77 (24.7%) had multiple CHDs. The types of CHD are described in Table 1. The frequency of individual types of CHD in total (summation of single plus multiple) are summarised in Figure 2. AVSD was reported as a single CHD comprising ASD primum and VSD. ASD refers to ASD secundum type. Table 1: Type of congenital heart defect Single defect (N = 58) n (%) AVSD 28 (48.3) VSD 14 (24.1) PDA 11 (19.0) ASD 4 (6.9) TOF 1 (1.7) Multiple defects (N = 19) n (%) AVSD/PDA 8 (42.1) AVSD/ASD 1 (5.3) AVSD/TOF 1 (5.3) VSD/PDA 5 (26.3) VSD/ASD 1 (5.3) VSD /ASD/PDA 1 (5.3) ASD/ PDA 1 (5.3) ASD/Other* 1 (5.3) AVSD = Atrioventricular Septal Defect; PDA = Patent Ductus Arteriosus; VSD = Ventricular Septal Defect; ASD = Atrial Septal Defect secundum type; TOF = Tetralogy of Fallot. * Other includes peripheral pulmonary stenosis Fig. 2: Frequency of congenital heart defects in total (single plus multiple) (AVSD = Atrioventricular Septal Defect; PDA = Patent Ductus Arteriosus; VSD = Ventricular Septal Defect; ASD = Atrial Septal Defect secundum type; TOF = Tetralogy of Fallot. * Other includes peripheral pulmonary stenosis) Intervention - Cardiac Catheterisation A total of 60/77 (77.9%) participants with a CHD required DCC and 25/60 (41.6%) received DCC. Details of DCC is presented in Table 2. One participant with AVSD underwent surgery without requiring DCC. Table 2: Diagnostic cardiac catheterisation by type of congenital heart defect Single Defect Required Done Awaiting Lost to Demised‡ Follow-up† AVSD (n = 28) VSD (n = 14)

PDA (n = 11) ASD (n = 4) TOF (n = 1) 27 (96.0%) 12/27 (44.4%) 0/27 (0.0%) 12/27 (44.4%) 12 (85.7%) 2/12 (16.7%) 4/12 (33.3%) 5/12 (41.7%) 3 (27.3%) 2/3 (66.7%) 0/3 (0.0%) 1/3 (33.3%) 1 (25.0%) 0/1 (0.0%) 0/1 (0.0%) 1/1 (100.0%) 1 (100.0%) 0/1 (0.0%) 0/1 (0.0%) 0/1 (0.0%) 3/27 (11.1%) 1/12 (8.3%) 0/3 (0.0%) 0/1 (0.0%) 1/1 (100.0%) Multiple Defects Required Done Awaiting Lost to Follow-up† Demised‡ AVSD/PDA (n = 8) 8 (100.0%) 5/8 (62.5%) 0/8 (0.0%) 3/8 (37.5%) 0/8 (0.0%) AVSD /ASD (n = 1) AVSD/TOF (n = 1) VSD/PDA (n = 5) VSD/ASD (n = 1) VSD/ ASD /PDA (n = 1) ASD/PDA (n = 1) ASD/ Other* (n = 1) 1 (100.0%) 1/1 (100.0%) 0/1 (0.0%) 1 (100.0%) 1/1 (100.0%) 0/1 (0.0%) 3 (60.0%) 2/3 (66.7%) 0/3 (0.0%) 1 (100.0%) 0/1 (0.0%) 0/1 (0.0%) 1 (100.0%) 0/1 (0.0%) 0/1 (0.0%) 1 (100.0%) 0/1 (0.0%) 0/1 (0.0%) 0 (0.0%) 0/0 (0.0%) 0/0 (0.0%) 0/1 (0.0%) 0/1 (0.0%) 0/1 (0.0%) 0/1 (0.0%) 1/3 (33.3%) 0/3 (0.0%) 0/1 (0.0%) 1/1 (100.0%) 0/1 (0.0%) 1/1 (100.0%) 1/1 (100.0%) 0/1 (0.0%) 0/0 (0.0%) 0/0 (0.0%) Total 60 25/60 (41.7%) 4/60 (6.7%) 24/60 (40.0%) 7/60 (11.7%) AVSD = Atrioventricular Septal Defect; PDA = Patent Ductus Arteriosus; VSD = Ventricular Septal Defect; ASD = Atrial Septal Defect secundum type; TOF = Tetralogy of Fallot. * Other includes peripheral pulmonary stenosis † Lost to follow-up before diagnostic cardiac catheterisation ‡ Demised before diagnostic cardiac catheterisation The median age at presentation of participants in whom DCC was done was 7 (IQR 7.5) months and the median age at DCC was 15 (IQR 15) months. A second DCC was required and performed in 3/77 (3.9%) of participants; both with an AVSD type CHD. Only one participant with isolated PDA required and underwent successful ICC for PDA closure at 17 months of age. Intervention - Surgery A total of 60/77 (77.9%) of participants were eligible for surgery, while 15/60 (25.0%) surgeries were performed. Details of surgical intervention in each type of CHD category is shown in Table 3. Table 3: Surgical intervention by type of congenital heart defect Single Defect Required Done Awaiting Lost to Demised‡ Follow-up† AVSD (n = 28) VSD (n = 14) PDA (n = 11) ASD (n = 4) 28 (100.0%) 7/28 (25.5%) 11 (78.6%) 1/11 (9.0%) 3 (27.3%) 1/3 (33.3%) 1 (25.0%) 0/1 (0.0%) 5/28 (17.9%) 4/11 (36.4%) 0/3 (0.0%) 0/1 (0.0%) 12/28 (42.9) 5/11 (45.5%) 2/3 (66.7%) 1/1 (100.0%) 4/28 (14.3%) 1/11(9.0%) 0/3 (0.0%) 0/1 (0.0%) TOF (n = 1) 1 (100.0%) 0/1 (0.0%) 0/1 (0.0%) 0/1 (0.0%) 1/1 (100.0%) Multiple Defects Required Done Awaiting Lost to Demised‡ Follow-up† AVSD/PDA (n = 8) AVSD /ASD (n = 1) AVSD/TOF (n = 1) VSD/PDA (n = 5) VSD/ASD (n = 1) VSD/ ASD /PDA (n = 1) ASD/PDA (n = 1) ASD/ Other* (n = 1) Total 8 (100.0%) 1 (100.0%) 1 (100.0%) 3 (60.0%) 1 (100.0%) 1 (100.0%) 1 (100.0%) 0 (0.0%) 60 3/8 (37.5%) 1/8 (12.5%) 4 (50.0%) 0/8 (0.0%) 1/1 (100.0%) 0/1 (0.0%) 0/1 (0.0%) 0/1 (0.0%) 0/1 (0.0%) 0/1 (0.0%) 0/1 (0.0%) 1/1 (100.0%) 0/1 (0.0%) 2/3 (66.7%) 0/3 (0.0%) 1/3 (33.3%) 0/3 (0.0%) 0/1 (0.0%) 0/1 (0.0%) 0/1 (0.0%) 1/1 (100.0%) 0/1 (0.0%) 0/1 (0.0%) 0/1 (0.0%) 1/1 (100.0%) 0/1 (0.0%) 0/1 (0.0%) 1/1 (100.0%) 0/1 (0.0%) 0/0 (0.0%) 0/0 (0.0%) 0/0 (0.0%) 0/0 (0.0%) 15/60 (25.0%) 10/60 (16.7%) 27/60 (45.0%) 8/60 (13.3%) AVSD = Atrioventricular Septal Defect; PDA = Patent Ductus Arteriosus; VSD = Ventricular Septal Defect; ASD = Atrial Septal Defect secundum type; TOF = Tetralogy of Fallot. * Other includes peripheral pulmonary stenosis † Lost to follow-up before surgery ‡ Demised before surgery Of participants who had surgery, the median age of presentation was 8 (IQR 18) months and the median age at first surgery was 31 (IQR

24) months. Only 2/77 (2.6%) participants with a CHD required follow up surgery and a second surgery was performed on only one of the two participants (both with AVSD and PDA) at 44 months. The median age at presentation and death of participants who demised before surgery was 2.5 (IQR 7.5) months and 12.5 (IQR 18) months respectively. The majority (n=11, 73.3%) of the surgeries performed were AVSD repair (three with PDA ligation), followed in descending frequency by VSD repair (n=3, 20.0%; two with PDA ligation) and isolated PDA ligation (n=1, 6,7%). The majority of single

PDA's did not require surgery as spontaneous closure was confirmed with echocardiography, the defect was haemodynamically insignificant in size or ICC was performed with device closure. Similarly, a small number of participants with single VSD, single ASD and VSD/PDA also had defects that did not require surgery. Figure 3 represents total numbers of interventions required and outcomes for DCC and surgery in all CHDs. 70 60 50 REQUIRED 40 DONE 30 AWAITING LOST TO FOLLOW-UP 20 DEMISED 10 0 DCC SURGERY Fig. 3: Details of intervention required – all congenital heart defects in total (DCC = Diagnostic Cardiac Catheterisation) Survival Post-Intervention Survival to one year follow up post ICC was reported in one participant with PDA who underwent closure with a duct occluder device. Post-surgery survival is presented in Table 4. Only one participant required a second surgery and the participant survived to one year follow up. Table 4: Post surgery survival Hospital discharge 3 weeks 6 months 1 year Alive 14 (93.3%) 14 (93.3%) Demised 1 (6.7%) 1 (6.7%) 14 (93.3%) 1 (6.7%) 13 (86.7%) 2 (13.3%) Eleven patients demised during the study period; eight participants pre-surgery (see Table 3), two post-surgery (see Table 4) and lastly, one with a VSD who did not require surgery. Discussion This study was the first to describe CHDs in the paediatric South African T21 population in Gauteng. The study found that the prevalence of CHDs in the T21 study population was 60.2% which is comparable with that found in literature worldwide of between 40- 60%.[3] More than a third of participants screened had a normal heart on echocardiography. In this study, the most common CHD recorded was a single AVSD; AVSD was also reported most frequent in the RCH study as well as T21 populations of USA, western Europe and north Africa.[7-11, 17, 25] Table 5 compares the frequency of CHDs in this study to literature from other African countries and worldwide. A single CHD was reported in just over 75% of participants, equal to Morocco and more common than Algeria (68%), Ethiopia (66%), Libya (65%) and Nigeria (45%)[9, 11, 13, 15, 16] . Table 5: Comparison of congenital heart defects in Africa and worldwide Country Congenital heart defect % AVSD PDA VSD ASD TOF CoA Other South Africa* 39.2 26.8 21.6 9.3 2.1 0.0 Algeria[13] 44 6 17 7 4 1 Egypt[14] 16.4 4.4 39.8 12.6 2 0.5 Ethiopia[16] 18.6 36.5 19.9 19.0 2.6 1.9 Libya[9] 19 4 12 24 2 1 Morocco[11] 30 17 22 20 5 1 Nigeria [15] 18 17 16 27 11 0 Sudan[8] 48 7 23 5 6 0 Brazil[10] 15.1 6.6 12.7 42.1 2 0 USA[6, 25] 45 7 35 8 4 1 1.0 21 24.3 1.5 39 5 11 11 21.5 1 AVSD = Atrioventricular Septal Defect; PDA = Patent Ductus Arteriosus; VSD = Ventricular Septal Defect; ASD = Atrial Septal Defect secundum; TOF = Tetralogy of Fallot; CoA = Coarctation of the Aorta; USA = United States of America. *Charlotte Maxeke Johannesburg Academic Hospital study The majority of participants with a CHD required a DCC to assess eligibility for surgery. Of the single CHDs, AVSD required catheterisation in almost all cases and almost 100% of participants with multiple CHDs required catheterisation. Less than half of DCC's required were performed, but loss of participants to follow-up pre-DCC was the primary reason for DCC not performed. The waiting time to first DCC was nine months. There is a paucity of details about DCC being required or performed in other studies reviewed. Only one study performed in Sudan commented on DCC required for five participants. All participants who required DCC had an AVSD and DCC was performed after one year of age to assess anatomy not visualised on ECHO and to measure pulmonary artery pressure and vascular resistance. However, findings with relation to surgery or survival of these participants was not further discussed.[8] Details of DCC not discussed in other studies may be due to differences in unit policy' where DCC is not required prior to surgery. Alternatively, diagnosis on ECHO for surgical eligibility may have been sufficient in those study populations if surgery was performed at a younger age prior to the development of complications or on less complex lesions. [3, 17] Since the introduction of ICC, closure of defects like PDA and ASD is now standard practice.[26] However, only one participant in this study had a device closure. Only a quarter of participants who required surgery had surgery performed. This compares unfavourably with the study from Morocco where more than 60% of surgeries required were performed. [11] Most of the surgeries performed in the unit were AVSD repair, in keeping with the most frequent CHD reported in the unit, and similar to surgeries performed at other centres worldwide.[3, 17] The majority of surgeries not performed were due to participants lost to follow- up. The recommended age for surgery in T21 with CHDs for optimal survival is before six months.[23] The median age at surgery (31 months) in the study participants was more than two years later than the recommended age for surgery and none were performed before 12 months (waiting time 23 months). In comparison, surgery was performed earlier at RCH (nine months), which could be explained by the better availability of specialised cardiothoracic surgeons or surgical facilities at RCH.[17] Surgery was also performed earlier in studies in Europe (six months) and the USA (five months) which may be due to earlier screening and diagnosis of CHDs or the greater availability of resources in high-income settings for surgical repair.[3, 23] Early repair of CHDs precludes the need for DCC to assess pulmonary vasoreactivity. Median age of presentation in this study was six months, thus

early surgical repair is a feasible option. Many factors may have contributed to the delay and non-performance of interventions at CMJAH PCU. The main factor was the large number of participants lost to follow-up pre-DCC and pre-surgery. There may have been multiple causes for participants lost to follow-up including: socioeconomic constraints or participant mobility preventing attendance at clinic, reluctance by family of participants to undergo intervention, non-cardiac co-morbidities resulting in demise/non-attendance pre-intervention or demise due to CHDs. Another factor contributing to delay and non- performance of interventions was likely the shortage of resources. Resource shortages included an insufficient number of paediatric cardiologists and cardiothoracic surgeons for the number of patients and also a lack of finances to provide surgical equipment, devices and theatre time. Historically, non-T21 children were prioritised over T21 children for surgery.[21] Surgery was likely not performed in T21 children due to the higher association of non-CHD co-morbidities, the shorter perceived life span of T21 individuals and the possibility of complexity of CHDs in T21 requiring repair.[5] However, it has been shown that children with T21 and AVSD (the commonest CHD requiring repair) have a defect more favourable to surgical repair compared to non-T21 children with AVSD.[23] Literature also proven that T21 does not confer higher risk to surgery.[3, 23, 27] In 2014 a review article of the USA national clinical database confirmed that T21 showed no greater risk in mortality for surgical repair in all CHDs commonly found in T21 individuals.[3] The lifespan of individuals with T21 has also improved significantly over the last years (to an average of 60 years).[18] The 20-year survival rate of individuals with T21 has been reported as high as 88%.[28] Furthermore, the study at RCH looked specifically at the burden on resources of the management of CHDs in T21 and found the admission rate post-surgery to be much lower than admission rate pre-surgery in T21. The burden on resources was thus less after surgical correction of CHDs in T21 and highlighted no significant difference in resource use when compared to non-T21 participants.[17] The literature thus supports strongly advocating for early surgery in T21 children with CHDs. The high survival rates after six-month and one-year follow-up in this study, compares favourably to post-surgical survival rates in African studies; Morocco 79% and Nigeria 81.1%.[11, 15] At RCH survival to hospital discharge was almost equal to this study (90%).[17] In the first world the 30 day mortality rate post primary repair has been reported as low as 5.3% (Germany) and the in-hospital mortality rate 1.9% (USA) both significantly lower than non-T21 participants.[2, 23] The survival rate of participants post-surgery in this study may have been affected by the development of complications of the CHD worsened by the delay in surgery (e.g. pulmonary hypertension, worsening cardiac function)

or the presence of other non-CHD related complications (e.g. chronic lung disease). Limitations The study was limited by the small sample size which did not allow for trend analysis. Sixteen percent of participants with clinically suspected T21 were not confirmed with PCR aneuploidy testing and therefore excluded. It is possible that some children with T21 were not referred for screening echocardiography due to missed clinical signs of T21 and thus excluded. It is also a limitation of this study that the population statistics could not be calculated, as population data on T21 patients were not available. Details of outcome related to participants lost to follow-up were not assessed. The cause of death of participants was not recorded; therefore, it is unknown what effect co-morbidities may have had on the survival rate and whether death was primarily due to CHDs. There was no data collected on what effect surgery performed at a later age than recommended might have had on survival rate. More studies, with larger sample sizes and longer duration of follow-up, at different centres in SA are needed in order to get a full understanding of CHDs in T21 in SA. Conclusions and recommendations This study is the second review of children with T21 and CHDs in SA. The prevalence of CHDs in children with T21 is comparable to global studies and confirmed that single AVSD type CHD was most common in the CMJAH T21 population. Although initial presentation and diagnosis for T21 participants was optimal, ongoing management including early catheterisation and early surgery were delayed. Measures need to be implemented to rectify the large number of participants lost to follow-up, contributing primarily to the delay and non- performance of interventions. Survival post-surgery compares favourably with other centres even though surgery was performed at a much later age than the age recommended for best outcome. Our findings suggest that children with T21 should be prioritised for surgery to be performed at an early age prior to the development of complications to ensure the best chance of survival. Early screening, diagnosis and intervention can prevent not only morbidity and mortality due to CHDs and the complications of CHDs, but also may decrease the financial burden on the healthcare system. Acknowledgements. I must acknowledge my co-authors Dr. Firoza Motara and Prof. Daynia Ballot for their patience, time, dedication and guidance, Dr. Wiedaad Slemming for her support and assistance in the submission of this paper for publication and lastly the staff at the Paediatric Cardiology Department for the use of their database. Conflict of Interest. None Author Contributions. RM and FM were responsible for protocol, study design, conceptualization, data collection and analysis, article and study documents and were supported by DB. Funding sources. Self-funded by principle author.