Risk Factors Associated with Congenital Heart Disease in Patients Presenting to Aljalila Cardiology Clinic between January 2020-May 2020: A Case Control Study

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ABSTRACT

Objective: To investigate the association of maternal diabetes, maternal smoking and syndromes with congenital heart disease (CHD) in patients attending Aljalila cardiology clinic between January 2020 and May of 2020.

Methods: A case control study to assess the association of maternal diabetes, maternal smoking and syndromes with CHD. All patients that presented to the clinic between January 2020 and May of 2020 were included. An interviewer administered questionnaire was used to record the presence of maternal diabetes, maternal smoking, and the type of syndrome and type of CHD. Patients with CHD were included in the case group and patients who did not have CHD were in the control group. Age, gender, and nationality were also collected from the hospital records. Fisher exact test and logistic regression was used to analyze the results.

Results: A total of 177 cases and 211 controls were recruited. All the risk factors increase the risk of CHD, with maternal diabetes (OR 6.3, 95% CI 2.7-14.6) having the strongest association, then syndromes (OR 5.1, 95% CI 2.3-11.3) and lastly maternal smoking (OR 4.0, 95% CI 1.0-16.3). The most common type of CHD is ventricular septal defect.

Conclusion: Maternal diabetes, maternal smoking and syndromes are significant risk factors of CHD in children visiting Aljalila cardiology clinic. Action needs to be taken in order to decrease these risk factors and so, decrease the incidence of CHD in the future. Clearly, more research is needed in order to identify other risk factors for patients in the United Arab Emirates (UAE).

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Introduction
Background
Congenital heart disease (CHD) is a defect in the heart that is present at birth, it can range from asymptomatic to life threatening [1]. Some risk factors of CHD have been identified, however in the majority of patients with CHD no risk factors have been found [2]. This is because a mixture of genetics and environmental factors play a role in the development of CHD [3].

CHD is the one of the most common types of congenital anomalies in children across the world [4], with a prevalence of 1% of live births worldwide [3,4]. This means that countries with a high fertility rate have a higher incidence and prevalence of CHD. These countries usually have a lower income per capita increasing the financial burden of healthcare [5]. In the United Arab Emirates (UAE), the second leading cause of death in children under the age of five is congenital anomalies, however no research has been done in the UAE to identify risk factors and the prevalence of these risk factors in children with CHD [6].

Some children with CHD often need lifelong treatment or surgeries. Hospitalizations of patients with CHD between the ages of 0-20 years old cost the United states 5.9 Billion dollars in 2009 [3,7]. The average cost per hospitalization for a patient with CHD is estimated to be a minimum of 25,000 dollars and the cost only rises with complicated CHD.

In severe cases of CHD, life expectancy can be shortened dramatically and there could be a great impact on the quality of life, stress on children and their families and impaired growth and development. The development of new methods to treat CHD has prolonged the life expectancy of these patients to 75 years, which is 4 years less than the life expectancy of unaffected individuals [8,9]. As a result of this, CHD is on the rise in the adult population, which opens up doors for new research on adult CHD [10]. Also, it means that more patients with CHD will reach reproductive years and so can pass on the disease to future generation, which would

increase the incidence of CHD in the future [11].

To decrease the incidence of CHD and its complications it is very important to gain better knowledge and understanding of potential risk factors and propose ways to decrease them. Also, implementing compulsory cheap methods of screenings for neonates can reduce complications by early detection and treatment, and so morbidity and mortality [12].

Some of the risk factors of CHD are maternal diabetes, maternal smoking and syndromes. Diabetes is a growing concern for the population of the UAE, with 17.4% of the adult population affected [13]. The incidence of diabetes in the UAE is rising much faster than anywhere else in the world with the number expected to double by 2040 [12,13]. A study conducted on UAE nationals in Abu Dhabi used biochemical tests to detect smoking in participants and proved that 42% of male participants and 9% of female participants smoked even though most didn't admit to smoking [1]. This is largely due to social stigma especially for females who smoke since most UAE nationals are Muslims. This result is much higher than the suspected WHO figure of 25% smokers for the Eastern Mediterranean regions and the number is only expected to rise [14,15]. No studies have been conducted in the UAE to investigate risk factors of CHD, therefore this study aims to investigate the association of the three risk factors with CHD.

Objectives
• To investigate the relationship between the three risk factors (maternal diabetes, maternal smoking, syndromes) and CHD in patients attending the cardiology clinic at Aljalila children's hospital.

Research Question: Do genetic syndromes, diabetic or smoking mothers constitute important risk factors for CHD in patients who attended Aljalila children's hospital cardiology clinic, between January and May of 2020?

Alternative Hypothesis: There is an association between maternal diabetes, maternal smoking, syndromes, and CHD.

Null Hypothesis: There is no association between maternal diabetes, maternal smoking, syndromes and CHD.

Methods
Study Design and Setting: A case control study to investigate the three risk factors and their association with the development of CHD. This study design was used because there are several risk factors to be investigated and a small sample size can be used compared to a retrospective cohort study. Data was obtained from a pediatric cardiology clinic in a tertiary hospital (Aljalila Childrens hospital) in Dubai, UAE between January, and May of 2020. Most patients visiting this clinic were referred from primary or secondary hospitals.

Study Subjects: All patients presenting to the cardiology clinic in Aljalila Childrens specialty hospital between January and May of 2020. The sampling method is time frame sampling and convenience sampling since all the patients attended the same outpatient department [16]. The patients with CHD were allocated to the case group and patients that do not have CHD were in the controls group. A total of 388 participants were recruited, 177 cases and 211 controls and so the power of this study is 87%. The minimum sample size for a power of 80% is 129 per group. This equation [16] was used to estimate the minimum sample size: $N = Z^2 \alpha/2 \ P(1-P) = 129 \ B^2$

The values used in the equation was taken from 'Cardiovascular malformations in infants of diabetic mothers' [17].

Case Definition: Patients between 0-18 years of age that that were diagnosed as having CHD in Aljalila cardiology clinic between January and May of 2020. Diagnosis was made using standard methods in the clinic which consisted of auscultation, echocardiogram, ECG and chest x-rays. Controls are children between 0-18 years who presented to the clinic between January and May of 2018 and were diagnosed with other heart conditions that were not CHD or were normal.

Study Variables: Sociodemographic factors such as age, gender and nationality were collected from all study subjects. The exposure variables collected were presence of maternal pregestational or gestational diabetes, maternal smoking, and the type of genetic syndrome in the child. The type of CHD was also recorded.

Ethical Consideration: Patients information will be kept in the hospital and no patient will be identified in the results. Also, the patients are minors so an explanation of the research was given to mothers to gain verbal consent. This research project has been approved by the Mohammed Bin Rashid University Institutional Review Board (IRB) committee (MBRU-IRB-SRP2-18-037) and Aljalila Childrens specialty Hospital.

Data Sources and Statistical Methods: Data on the risk factors (presence of maternal diabetes, maternal smoking, type of syndrome) was collected by the attending physician from the patients' parents using an interviewer- administered questionnaire and recorded on a printed table. All patients with syndromes underwent genetic testing in the hospital not in the cardiology clinic, if the results of the test were not reported yet during data collection the type of syndrome was recorded as unidentified. Demographic data such as gender, age and nationality were taken from the hospital records by the researcher. Data was then inputted into a Microsoft excel data sheet and transferred to SPSS statistics 24 package to be analyzed. Chi- squared and the exact-fisher test was used to determine association and find the p-value. Univariate analysis and multivariate analysis (logistic regression) was used to calculate odds ratio. The p-value used was <0.05 to determine statistical significance and all tests were performed two-sided. Other categorical data collected, type of syndromes and type of CHD was recorded in a frequency table. Age was categorized into 4 groups (below 1 year, between 1-1.9 years, between 2-13 years, above 13 years). There was no missing information.

Results
Participants
Analysis was based on all patients that presented to the clinic between January and May of 2020, a total of 388 participants between the ages of 0-18 years, 177 were cases and 211 were controls. Both groups were comparable on gender and nationality but not in age.

Descriptive data
Of the cases, 86 (48.7%) are females and 91 (51.3%) are males. There are 62 patients (35.0%) under 1 year, 35(19.0%) between 1-1.9 years, 78 (44.0%) between 2 and 13 years and only 2 (1.1%) over 13 years. The percentage of UAE locals in the cases was 66.1% and non-UAE locals was 33.9% (Table 1).

Of the controls, 96 (45.5%) are females and 115 (54.5%) are males. There are 36 (17.1%) of controls under 1 year, 41(19.4%) between 1-1.9 years, 124(58.8%) between 2 and 13 years and

8(3.8%) older than 13. UAE nationals account for 81.9% of controls and non-UAE locals account for 18.0% (Table 1).

There was a total of 13 different syndromes with different types of genetic inheritance. Between the 5 most common types of CHD, atrial septal defects (ASD) and ventricular septal defects (VSD) were the most common with a prevalence of 31% and 32%, respectively (Figure 1).

Maternal age is a cofounding factor as the older a mother is the more likely she is to have diabetes and a child with CHD.
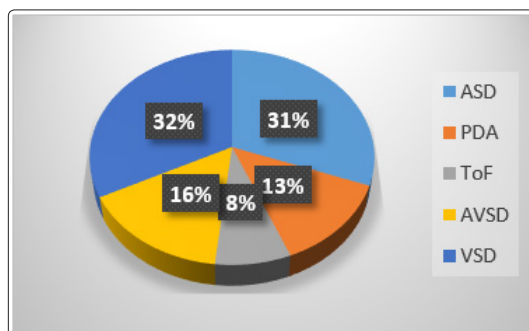
Figure 1: A pie chart to show the percentage of types of CHD amongst the five most common types in cases. Atrial septal defect (ASD), patent ductus arteriosus (PDA), tetralogy of fallot (ToF), atria-ventricular septal defect (AVSD), ventricular septal defect (VSD)

Outcome Data

Amongst cases 28 (15.8%) have syndromes with the most common type of syndrome being down syndrome (DS). 17 patients have DS which constituted 45.9% of all syndromes, with 16 patients in the cases (94.1%) compared to 1 patient in the controls (5.9%). Atrio-ventricular septal defects (AVSD) was the most common type of CHD in these patients with 7 (43.8%) having this type of CHD. Amongst controls 9 (4.3%) have syndromes, marfans syndrome is the most common with 2(22.2%) patients.

Table 1: Characteristics and exposures to certain risk factors of all patients attending Aljalila hospital cardiology clinic Dubai, UAE between January, and May 2020

		All-n (%)	Case	Control
All- n(%)		388	177 (45.6)	211 (54.4)
Gender- n(%)				
	Male	201 (51.8)	86 (42.8)	115 (57.2)
	Female	187 (48.2)	91 (48.7)	96 (51.3)
Age group- n(%)				
	<1 year	98 (25.3)	62(63.3)	36(36.7)
	1-1.9 years	76 (19.6)	35(46.1)	41(53.9)
	2-13 years	202 (52.1)	78(38.6)	124(61.4)
	>13 years	10 (2.6)	2(20.0)	8(80.0)
Nationality- n(%)				
	UAE locals	290 (74.7)	117 (40.3)	173 (49.7)
	Non-UAE locals	98 (25.3)	60 (61.2)	38 (38.8)
Syndromes- n(%)/ Types of syndromes				
	Yes	37 (9.5)	28 (75.7)	9 (24.3)
	DS	17 (45.9)	16(94.1)	1 (5.9)
	Digeorge	2 (5.4)	2 (100.0)	0 (0.0)
	Edward	2 (5.4)	2 (100.0)	0 (0.0)
	Marfan	2 (5.4)	0 (0.0)	2 (100.0)
	Others	14 (37.8)	8 (57.1)	6 (42.9)
	No syndromes	351 (90.5)	149 (42.2)	202 (57.8)
Maternal diabetes- n(%)				
	Yes	38(9.8)	30(78.9)	8(21.1)
	No	350(90.3)	147(42.0)	203(58.0)
Maternal smoking- n(%)				
	Yes	10(2.6)	7(70.0)	3(30.0)
	No	378(97.4)	107(28.3)	208(55.0)

Categorical variables are presented as frequencies (%). Down syndrome(DS)

Maternal smoking was only in found in non-UAE nationals which explains the low prevalence of 10(2.5%) in this population, of which 7(70%) were in the cases and 3(30%) in the controls. As for diabetes 32 (11.0%) of UAE nationals had maternal diabetes mirroring the increase in diabetes in the local population of the UAE [5]. Only 6 (6%) of non-nationals had diabetes. Amongst cases, 30 (17%) were exposed to maternal diabetes but among controls only 8 (3.8%) were exposed.

Table 2: Odds ratio and the p-value of three risk factors using univariate and multivariate analysis on all patients that attended Aljalila Childrens hospital between January- May 2020

Exposures	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P- value
Maternal diabetes	5.2 (2.3-11.6)	0.00	6.3 (2.7-14.6)	0.00
Maternal smoking	2.9 (0.7-11.2)	0.11	4.1 (1.004-16.3)	0.04
Syndromes	4.2 (1.9-9.2)	0.00	5.1 (2.3-11.4)	0.00

95% Confidence interval is stated in a range. P Value of under 0.05 is taken as statistically significant

There is no association between maternal diabetes and the type of CHD. 2 patients in the cases group (1.1%) had two out of the three exposures which were maternal diabetes and syndromes.

Main Results
Using SPSS, univariate analysis was calculated (Table 2). The Odds ratio(OR) for maternal smoking is 2.9 (95% CI 0.7-11.2) and the p value is 0.11, so we can conclude that smoking is not a risk factor as it exceeds the cut off point for statistical significance (0.05). Maternal diabetes is a risk factor because OR is 5.2 (95%CI 2.3-11.6) and the p value is 0.00, which proves that there statistical significance. Syndromes has an OR of 4.2 (95%CI 1.9-9.2) so it is also a risk factor of CHD (p-value 0.00). The OR for DS was 20.9 (95% CI 2.7-159.0) which proves the huge association of DS with CHD, as the risk of CHD is 20 times higher in DS patients (p-value 0.00). Patients with DS are 17.9 times more likely to develop AVSD (OR 17.9 95% CI 5.6-57.0) (p-value 0.00).

Simple logistic regression was used to explain the association of the risk factors with CHD. The fitness of the model was 19.5%, which shows that 19.5% of cases were explained by the age and the three risk factors adjusted over gender. The OR for maternal diabetes was 6.3 (95% CI 2.7-14.6) and the p-value was 0.00 which is significant and so proves that maternal diabetes increases the risk of CHD by 6.3 times. The OR for maternal smoking was 4.0 (95% CI 1.004-16.3) with a p-value of 0.049 which shows that it is just under the cut off point for statistical significance and so it is a risk factor. The OR for syndromes is 5.1 (95% CI 2.3-11.3) with a p-value of 0.00 and so it is a risk factor. There was no significant difference in the gender (p-value 0.13) between cases and controls. However, the difference in age between the cases and controls was significant with an average of 41% of the cases being younger than the controls since OR was 0.59 (95% CI 0.46-0.76) and the p-value was 0.00.

Discussion
Summary of Major Findings
This is the first study in the UAE to establish an association between these risk factors and CHD. There is a strong association between each of these risk factors and CHD. Children of diabetic mothers have the highest risk with a 6.3 times higher risk of having CHD. Children with syndromes have a 5.1 times higher chance of having CHD compared to controls, and maternal smoking increases the risk of CHD by 4.0 times. There is a significant difference in the age of the cases and control with 41% of the controls being younger than the cases. VSD was the most common

CHD (32%) among the five most common types of CHD.

Comparison with Previous Studies
The most common type of CHD in this study was VSD, which is also the most common type of CHD in the world according to the Centre of disease control [18,19].

In this study, the OR of maternal diabetes is 6.3 (95% CI 2.7-14.6) which is like a prospective cohort study done on a very big study sample of 192,618 participants between 1995-2000, that showed a relative risk of 5.0 (95% CI 3.3-7.8) [20]. Some studies suggest that children of diabetic mothers are screened more for CHD and so some silent types of CHD are discovered earlier than in other individuals [2,21].

A lot of studies have been done to prove an association between down syndrome (DS) and CHD, however not much studies on other types of syndromes were done. The OR of DS in the study was 20.9 (95% CI 2.7-159.0) which proves a very strong association. A meta-analysis study that compared gender for the prevalence of CHD in patients with DS, found that CHD is present in 40-60% [22] of patients with down syndrome and that females are more likely to have AVSD compared to males with DS (OR 1.5 CI 1.2-1.9) [17]. In this study the most common CHD in DS patients was AVSD with an OR of 17.9 (95% CI 5.6-57.0).

In this study, the OR for maternal smoking was 4.0 (95% CI 1.0-16.3). In comparison, another study proved no association between all types of CHD combined and smoking [11], however when separating the different types of CHD, an association was found for truncus abnormalities (OR 1.2 95% CI 1.0-1.5), atrial septal defects (OR 1.6 95% CI 1.0-2.6), and Patent Ductus Arteriosus (OR 1.30 95% CI 1.05-1.62). A case-control study on the effects of maternal smoking in the first trimester proved an association with an OR of 1.2 (95% CI 1.1-1.2), it also proved that the association is stronger in mothers older than 35 and those that smoked more cigarettes daily [23,24].

Implications on Public Health
This study identifies patients that have an increased risk of developing CHD, and so helps implement more vigorous screening for them in order to detect problems early to prevent complications. A simple noninvasive pulse oximeter can help identify these patients in the first days of life [25, 26]. This study proves a rising concern for maternal diabetes and its implications on the health of children in the UAE. Foetuses of pregnant diabetic women

should be screened more carefully to detect any problems during pregnancy and to allow healthcare professionals time to plan the treatment early. It also proves how vital it is to raise awareness about the dangers of smoking during pregnancy and the potentially dangerous implications it can have on the fetus. In addition, this shows that all children with syndromes should be screened for CHD to allow early detection and treatment.

Limitations
This study is the only study that assesses risk factors of CHD in the UAE however it has several limitations: (1) controls are taken from the same clinic as the cases because of limited availability of hospital records from other departments, this would have an effect on the results because there might be a higher incidence of the risk factors in the controls compared to the general population, which will bias the results towards the null hypothesis (OR 1), (2) a significant difference was found between the age groups of the cases and control which proves a sampling bias which decreases external validity, this is mostly due to the nature of the studied illness which is present at birth and is usually discovered in infancy or early childhood, however it should not affect the results much as CHD is a lifelong condition and so patients can present at any age, but the exposure status doesn't change (3) all patients presenting to the hospital with syndromes were referred to the cardiology clinic and so are screened more carefully than other individuals which might bias the results towards the null hypothesis, (4) smoking is considered unacceptable in Muslim countries and so some mothers might not admit to smoking because of the social desirability effect, this will cause a non-differential misclassification bias which will bias the results towards the null hypothesis (5) smoking is of very low prevalence in women in the UAE so a bigger sample size is needed to get enough data on maternal smoking, (6) more risk factors such as maternal age should have been collected however because of the clinical setting of the data collection this was not possible, (7) data such as ethnicity and socioeconomic background was not collected.

Strengths
This is the only study in the UAE to test risk factors related to CHD and so provides novel data for more research in the future. There is no recall bias even though it is a retrospective case control study because the risk factors assessed were diabetes, which is a chronic illness and smoking which is a lifestyle habit. Even if mothers had pregestational diabetes it is unlikely that they forgot.

Generalizability
This study is not externally valid due to the sampling method used, which was convenience sampling as all data was collected from one tertiary care hospital in the Dubai which limits generalizability to other secondary or primary health care facilities across the UAE. Also, the control group was taken from the same clinic and so they do not represent the general population as they might have a higher prevalence of the exposure within this group compared to the general population.

Areas for Future Research
Sampling bias was introduced into this study because a significant difference exists between the age of the cases and control and so a paired-matching method of the cases to the controls can be used in future research to limit this bias, however due to the small number of patients attending the clinic this was not possible. Some risk factors for CHD have been identified such as maternal age and autoimmune disease [2,3,4] which could be investigated further in the UAE as there are no studies done on them. There are also a lot of suspected risk factors that need to be investigated in order

to determine their association, for example the drug paroxetine was changed by the FDA from a pregnancy category C drug to a category D drug for its potential to cause CHD [4,9,20]. There is also some rising concern for potential paternal risk factors for CHD as it has been proven that the risk of some syndromes increase with paternal age [12]. Some studies assess the risk of different types of CHD with different risk factors. Other studies investigate the timing of certain exposures during pregnancy with the risk of developing CHD such as medications given to the mother. Another important area of research is the association of different types of syndromes with CHD, as not much research has been done in this field. Also since medical treatment has improved greatly over the past several years, there is a growing number of adults with CHD, and so more research is needed to support treatment of these individuals. Information on glycemic control in pregnant mothers could be taken to test the association of poorly controlled diabetes with CHD. In this study, there was a non-differential misclassification bias due to the probability of mothers not reporting smoking and so biochemical tests could be used to test all mother for smoking. Another study proves that smokers are much more likely to have other unhealthy lifestyle behaviors than non-smokers [13] and so future research can investigate other maternal lifestyle factors. Clearly, a lot more research is needed to identify and decrease risk factors in susceptible individuals and any information collected is novel data since studies in the UAE on CHD are scarce.

Conclusion
This study is the first study in the UAE investigating risk factors of CHD. A huge association between maternal diabetes, maternal smoking, syndromes, and CHD was found. These findings illustrate important risk factors of CHD in patients in the UAE, and so provide an insight for healthcare professionals to help reduce risk factors and so the incidence of CHD.

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