QATAR UNIVERSITY

COLLEGE OF HEALTH SCIENCE

Consanguinity among Autistic individuals:

Prevalence and Associations with Intellectual Disability and Epilepsy

BY

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A Thesis submitted to the faculty of the College of health science

in partial Fulfillments of the Requirements for the degree of

Master of Public Health

June 2019

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ABSTRACT

Background: Although autism is a global disorder, relatively little is known about the prevalence of consanguinity among autism spectrum disorder (ASD) individuals. Also, the relation of ASD comorbidities (Epilepsy and Intellectual Disability) to consanguinity have not been explored.

Aims: We aim to estimate the global prevalence of consanguinity among the ASD individuals and compare it that among different populations. In addition, we aim document the prevalence of epilepsy and ID in relation to consanguinity in individuals diagnosed with ASD in Qatar and to assess the association between epilepsy and ID and consanguinity and other potential socio-demographic factors, environmental and other clinical factors.

Methods: Meta-Analysis of observational studies reporting prevalence of consanguinity among ASD individuals from 8 countries were searched systematically in important databases including EMBASE, PubMed and Academic Search Complete. Individual studies were screened by two reviewers independently, extracted data and assessed the risk of bias using a risk of bias tool. Random Effect model was used to calculate pooled weighted estimates due to considerable heterogeneity. Subgroup analysis was also calculated.

Moreover, secondary data were analyzed using the cross-sectional study on profiles and correlates of ASD clinical sample in Qatar. Descriptive, univariable and multivariable analysis were conducted to estimate the prevalence of consanguinity, epilepsy and ID among ASD individuals in this cohort and assess association to other potential confounding determinants.

Results: The meta-analysis included 10 studies reporting prevalence of consanguinity among ASD cases. The pooled estimate of consanguinity among ASD cases was 24% (95%CI:17%-32%). Subgroup analysis by the study country led to a higher pooled estimate of consanguinity of 38% (95%CI:28%-49%) in the GCC countries compared to other than GCC countries with a pooled estimate of 16% (95%CI:11%-23%).

The cross-sectional included a total of 171 ASD cases. Male to female ratio 4:1 and mean age was 13.5 years. Epilepsy was reported by 19%. ID reported by 83% of the cases. 76.6% were nonverbal. Eighty-three percent of the families had one proband, 9.9% had 2 probands, and 7.1% had more than two. The association between epilepsy and ID among ASD patients and consanguinity was not statistically significant (P value >0.05) controlling for other potential risk factors.

Conclusion: The globally estimated pooled consanguinity prevalence among ASD patients was 24%, GCC countries showed a higher pooled prevalence (38%). The clinical sample used did not provide any evidence on association between both epilepsy and ID and consanguinity among ASD patients in Qatar. Further larger studies with much better large and representative sample may be required to confirm our results.

الملخص

الخلفية: على الرغم من أن طيف التوحد هو اضطراب عالمي، إلا أنه لايُعرف إلا القليل حول شيوع القرابة بين المرضى المصابين باضطراب طيف التوحد (ASD). كذلك، لم يتم استكشاف العلاقة بين الأمراض المصاحبة لاضطراب طيف التوحد (الصرع والإعاقة الذهنية) وبين القرابة.

الأهداف: نهدف إلى تقدير معدل الانتشار العالمي للقرابة بين الأطفال المصابين باضطراب طيف التوحد ومقارنته بين مختلف المجموعات السكانية. بالإضافة إلى ذلك، نهدف إلى توثيق معدل انتشار الصرع والإعاقة الذهنية فيما يتعلق بالقرابة عند الأطفال المشخصين باضطراب طيف التوحد في قطر وتقييم الارتباط بين الصرع والإعاقة الذهنية وبين القرابة وغيرها من العوامل الاجتماعية الديموغرافية والبيئية المحتملة والعوامل السريرية الأخرى.

الطرق: تم إجراء تحليل بشكل منهجي بطريقة التحليل البعد Meta-Analysis لدراسات المشاهدة التي تشير لمعدل انتشار القرابة بينحالات اضطراب طيف التوحد ضمن 8 بلدان في قواعد البيانات الرئيسية بما في ذلك Academic Search Complete و EMBASEو PubMed وقام اثنان من المراجعين بفحص الدراسات الفردية بشكل مستقل، واستخلاص البيانات وتقييم خطر الانحياز باستخدام أداة خطرالانحياز. ونظرًا لعدم التجانس المعتبر، تم حساب التقديرات الموزونة باستخدام نموذج التأثير العشوائي. كما تم حساب تحليل المجموعة الفرعية كذلك.

النتائج : التحليل البعدي (meta-analysis) على الملفات cross-sectional studyعلاوة على ذلك، تم تحليل البيانات الثانوية باستخدام دراسة مستعرضة الشخصية والارتباط لعينة سريرية لاضطراب طيف التوحد في قطر. وأجري تحليل وصفي و وحيد المتغير ومتعدد المتغيرات لتقدير معدل انتشار القربى والصرع والإعاقة الذهنية بين الأطفال المصابين باضطراب طيف التوحد ضمن هذه الجماعة وتقييم الارتباط مع غيرها من المحددات المربكة المحتملة.

تضمن دراسة 10 دراسات حول شيوع القرابة بين المرضى المصابين باضطراب طيف التوحد. إن تقدير نسبة القرابة عند المرضى المصابين باضطراب طيف التوحد كانت 24%. تحليل المجموعة الفرعية بحسب بلد الدراسة أدى إلى نسبة تقدير أعلى للقرابة بين مرضى طيف التوحد في دول الخليج مقارنة بغيرها من الدول (التي لا تتبع لدول الخليج)وذلك بنسبة 38% بنسبة 16%.

تضمنت171 حالة من مرضى طيف التوحد ،نسبة الرجال cross sectional study إن الدراسة المستعرضة للنساء كانت 4:1 ومعدل العمر الوسطي فيها 13.5سنة. تم الإبلاغ عن الإصابة بالصرع بنسبة 19%من الحالات ،والإعاقة الذهنية بنسبة 83% من الحالات. كما أن نسبة حالات التواصل الغير لفظي كانت 76% من الحالات، 83% من العائلات لديهم مصاب واحد ، 9.9% لديهم مصابيَن و 7.1% لديهم اكثر من مصابيَن.

العلاقة بين الصرع والإعاقة الذهنية بين المرضى المصابين بطيف التوحد والقرابة لم تكن ذو أهمية احصائية بعد السيطرة علي عوامل الخطر الأخرى المحتملة.

الاسستنتاج (النتيجة): إن تقدير معدل الانتشار العالمي للقرابة بين مرضى طيف التوحد كان بنسبة 24%. دول الخليج أظهرت تقديراً أعلى للقرابة بين المرضى المصابين بطيف التوحد 38%. إن العينة السريرية المستخدمة لهذه الدراسة لم تقدم أي دليل حول العلاقة بين كل من (كلا) الصرع والإعاقة الذهنية مع القرابة بين مرضى التوحد في قطر. قد تكون هناك حاجة لمزيد من الدراسات باستخدام عينة أكبر وأفضل تمثيلا من أجل تأكيد صحة نتائجنا

DEDICATION

This study is whole heartedly dedicated to my beloved parents, who were my source of inspiration, gave me strength when I thought of giving up and who continually provided their moral, spiritual, emotional, and financial support. To my beloved sisters; who stood next to me when things looked bleak, and to everyone in my life who touched my heart.

ACKNOWLEDGMENTS

I extend my sincere gratitude to my supervisor, Dr. Manar Elhassan, for her guidance throughout this research endeavor and for her invaluable input at every stage of this project, which have helped me to produce a product of which we can be proud of.

Furthermore, I thank Dr. Fouad Alshaban for his vital time and assistance throughout this study.

I am also grateful to my university faculty especially the program coordinator Prof.Lukman Thalib for their unfailing support and assistance.

I also thank Qatar University and in particular, the College of Health Sciences for providing the opportunity to conduct this research.

Last but not the least, I would like to thank my friends Ibrahem Abdlhakam and Aamna Hamid for their support.

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Chapter 1: Introduction

1.1 Background

Autism Spectrum Disorder (ASD) or autistic disorder is a complex neurodevelopmental syndrome that affects the person's capability to socially interact with others, communicate and reply to stimulations in their environments (Elsabbagh et al., 2012). ASD is presently considered as one of the most frequent morbidities of childhood and presents in different levels of severity (El-Baz et al., 2016). It is has been estimated that out of every 1000 child, 3–6 of them would have autism worldwide and the prevalence is higher in males compared to females (El-Baz et al., 2016). However, the magnitude of autism in the Gulf Cooperation Council (GCC) region is still unclear as epidemiological research into this area is considered to be relatively new (Salhia, Al-Nasser, Taher, Al-Khathaami, & El-Metwally, 2014). Studies have found that autism prevalence is 0.6%in the Kingdom of Saudi Arabia (Hemdi & Daley, 2017), 1.4% in Oman (Al-Farsi et al., 2011) and 1.1% in Qatar (Qatar-tribune 2018). Studies in the United Kingdom and America estimated the economic burden of autism to be more than several billion US dollars (Ganz, 2007; Knapp, Romeo, & Beecham, 2009).

Although neonatal and prenatal risk factors were the focus of numerous epidemiological studies over 40 years, Autism etiology is still unknown (Gardener, Spiegelman, & Buka, 2011). As many risk factors were related to ASD, family history of ASD, high paternal and maternal age (>35years), were also related to a noteworthy increase in the risk of autism (El-Baz, Ismael, & El-Din, 2011). Other factors like exposure to lead, mercury as well as radiation has been proposed as possible causes of autism (El-Baz et al., 2016). A number of theories about the pathogenesis proposed

the interaction between different genetic predispositions and environmental factors (Tchaconas & Adesman, 2013).

One of the factors that have been linked to autism and is related to genetic is consanguinity. Consanguinity can be defined as the "relation between two people who share a common ancestor" (Dahdouh, Taleb, Blecha, & Benyamina, 2016); constructed between individuals who are biologically related (Dahdouh et al., 2016). Almost 20% of the world's population lives in societies that favor consanguineous unions such as Northern Africa and South Asia (Dahdouh et al., 2016). In Qatar, consanguinity is estimated to be 54% (Bener & Hussain, 2006). Many medical complications are known in consanguineous marriages such as malformations (Jaber et al., 2005) and rare recessive genetic disorders (Bittles, 2008), in addition to disorders of complex inheritance, like psychiatric disorders (Mansour et al., 2010; Musante & Ropers, 2014; Sharkia, Azem, Kaiyal, Zelnik, & Mahajnah, 2010).

ASD is associated with high rates of other disorders comorbidity, for example, anxiety disorders, fears and phobias, mood disorders, attention deficit hyperactive disorder (ADHD) and epilepsy (Ghaziuddin, Ghaziuddin, & Greden, 2002; Leyfer et al., 2006; LoVullo & Matson, 2009; Simonoff et al., 2008; Smith & Matson, 2010a, 2010b, 2010c). Recently, researchers started to acknowledge, and emphasis on comorbidity in individuals with ASD (LoVullo & Matson, 2009; Smith & Matson, 2010c). The co-occurrence of epilepsy and ASD is well recognized (Canitano, 2007; Spence & Schneider, 2009; R. Tuchman & Rapin, 2002). Epilepsy prevalence in persons with ASD have roughly varied between 5% to 46% (Spence & Schneider, 2009). Rates of ASD and comorbid ADHD differ widely, with estimates ranging from 14 to 78% (Amr et al., 2012; Gjevik, Eldevik, Fjæran-Granum, & Sponheim,

2011; Holtmann, Bölte, & Poustka, 2007). These estimations put ADHD as one of the most frequent comorbid disorders in individuals with ASD.

About one third of youth with ASD had intellectual skills in the Intellectual Disability (ID) range as stated by the latest Centers for Disease Control and Prevention (CDC) report, (with additional 23 % in the marginal range), although estimations through studies range broadly, from 26 to 68 % (Centers for Disease Control and, 2012; Fombonne, 2005; Yeargin-Allsopp et al., 2003).

With the growing worldwide prevalence of ASD, as well as in Qatar (1.4%), research should have rapidly progressed efforts to improved understand the increase in it is incidence and co morbidities. The overall prevalence of consanguinity among ASD patients and it is association with ASD comorbidities have not been fully explored, thus it is vital to investigate such association.

1.2 Aims

This study aims to estimate the global prevalence of consanguinity among the ASD individuals and compare it that among different populations (Meta-analysis). In addition, the aim is to document the prevalence of epilepsy and ID in relation to consanguinity in individuals diagnosed with ASD in Qatar and to assess the association between epilepsy and ID and consanguinity and other potential socio-demographic factors, environmental and other clinical factors (Cross-sectional study).

1.3 Research Questions

- What is the global prevalence of consanguinity among ASD?
- Is consanguineous marriage associated with increasing occurrence of ID and Epilepsy among ASD individuals in Qatar?

Chapter 2 Literature Review

2.1 Autism Spectrum Disorder (ASD)

Autism Spectrum Disorder (ASD) or autistic disorder is a complex neurodevelopmental syndrome that affects the person's capability to socially interact with others, communicate and reply to stimulations in their environments (Elsabbagh et al., 2012). Autism symptoms commonly appear in the first two years of life, but it can be diagnosed at any age (NIMH). There are several conditions come under autism spectrum disorder that can be diagnosed separately as indicated by American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-IV): Asperger syndrome, pervasive developmental disorder not otherwise specified (PDD-NOS) and autistic disorder (CDC). In the most recent form of American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM 5), Autistic Disorder, Asperger's Disorder and PDD-NOS are replaced by the diagnosis of Autism Spectrum Disorder (Autism Society).

ASD can result in important communication, behavioral and social challenges. Individuals with ASD may behave, communicate, learn and interact in different ways than other people. AS ASD problem-solving, educational and thinking capabilities varied from talented to severely confronted, some of them need a large amount of assistance in their everyday lives, while others need less (CDC).

2.2 Burden of ASD

2.2.1 Global

ASD is currently considered as one of the most common neurodevelopmental childhood disorder and presents in various degrees of severity (El-Baz et al., 2016). It is has been estimated that out of every 1000 child, 3–6 of them would have autism

worldwide and the prevalence is higher in males compared to females (El-Baz et al., 2016). In 2012, a review comparing ASD prevalence in various parts of the world, researchers reported the median global prevalence as approximately 1 in 161 (62/10,000) for all pervasive developmental disorders and 1 in 588 (17/10,000) for autistic disorder (Elsabbagh et al., 2012). The inconstancy between countries and regions and the growth in estimates over time may be related to the change in diagnostic criteria and approaches as well as the increasing autism awareness throughout the world (Elsabbagh et al., 2012). In the United Kingdom 2006, the prevalence of all ASDs in 9-10-year-olds children was 116.1/10,000, however, in 2014, 1 out of every 100 children has ASD as reported by the National Autistic Society (Baird et al., 2006). In Brazil A pilot study was conducted and stated a prevalence rate of 27/10,000 (Paula, Ribeiro, Fombonne, & Mercadante, 2011); while in Quito and Ecuador the prevalence of ASD in schoolchildren was observed to be 11/10,000 persons (Dekkers, Groot, Mosquera, Zúniga, & Delfos, 2015). In Canada, ASD rank as one of the widely recognized developmental disabilities, with a prevalence rate of 1.2%, in children aged 1 to 17 years in 2014 to 2015 (Diallo et al., 2018).

2.2.2 Asia

Elsabbagh et al, 2012 conducted a review of the epidemiological studies about ASD done in the Western Pacific region (in addition to Japan and China), and she found that that prevalence rates ranged from 2.8/10 000 to 94/10 000 (median value of 11.6/10 000) (Elsabbagh et al., 2012). A subsequent study in China included children aged 2–6 years, also stated a prevalence of 11.0 per 10,000 children (Zhang & Ji,

2005). Another study from Indonesia reported a prevalence of 11.7 per 10,000 (Wignyosumarto, Mukhlas, & Shirataki, 1992).

Samadi et al. found that the Iranian prevalence for five-year old was 6.26 per 10,000 (Samadi, Mahmoodizadeh, & McConkey, 2012). Dahlia Saab submitted a study about National Prevalence and Correlates of Autism in Lebanon and reported that the ASD prevalence in Lebanon is 1.48%, with a little predominance of male gender (Saab, Chaaya, & Boustany, 2018).

2.2.3 Gulf Cooperation Council (GCC) region

The Gulf Cooperation Council (GCC) countries it consists of 6 countries: Saudi Arabia, United Arab Emirates (UAE), Kuwait, Sultanate of Oman, Qatar and Bahrain, which are located in the Arab peninsula. However, the magnitude of autism in the Gulf Cooperation Council (GCC) region is still unclear as epidemiological research into this area is considered to be relatively new (Salhia et al., 2014). In Oman, a cross-sectional study estimated the prevalence of ASD, indicated an overall prevalence of 1.4 cases per 10,000 children aged 0-14 years (5). In United Arab Emirates the weighted prevalence was estimated to be 29 per 10,000, while in the Kingdom of Saudi Arabia the ASD prevalence reported was 0.6% (Eapen, Mabrouk, Zoubeidi, & Yunis, 2007; Hemdi & Daley, 2017).

2.2.4 Qatar

After personal communication with Dr. Alshaban, he told about a study conducted by Hamad Bin Khalifa University's Qatar Biomedical Research Institute (QBRI). They did screen for primary school in Qatar (93 schools) using lifetime social communication questionnaire for children aged 5-12 years to detect the high

functioning ASD children. Also, they recruited ASD individuals from all special need centers in Qatar and results showed that prevalence of ASD in Qatar 1.4 for both (1 in 87 children). The result of this prevalence study is in process of publication under title: Prevalence and Correlate of Autism Spectrum in Qatar, A National Study (Alshaban et al., 2019, in press).

2.3 Autism risk factors and consanguinity

Many risk factors have been associated with ASD such as: multiple birth, congenital malformation, delayed initiation of breastfeeding, birth injury or trauma, umbilical-cord complications, low birth weight, maternal hemorrhage, ABO or Rh incompatibility, summer birth, small for gestational age, fetal distress, feeding difficulties, neonatal anemia meconium aspiration, hyperbilirubinemia and low 5-minute Apgar score (Gardener et al., 2011; Salhia et al., 2014; Wassink, Brzustowicz, Bartlett, & Szatmari, 2004). Instrumental methods of delivery, postnatal hypoxia, jaundice, positive family history and high paternal and maternal age (>35 years) were also related to a noteworthy upsurge in the risk of autism (El-Baz et al., 2011). Other factors like lead exposure, mercury and radiation have been proposed as possible causes of autism (El-Baz et al., 2016).

Although neonatal and prenatal exposures were the concentration of several epidemiological studies for more than 40 years, Autism etiology is still unknown (Gardener et al., 2011). Numerous theories about the pathogenesis suggested the interface between various genetic predispositions and environmental factors with strong and clear genetic influences (Tchaconas & Adesman, 2013). Studies of twin pairs, families, high-risk infant siblings and populations have estimated correspondence rates and separation of the disorder within families. The concordance

rate was reported as 5-30% in siblings and as 60-70% in monozygous twins; this is in agreement with a recurrence rate of 18% in infant siblings and of 33% in multiplex families which revealed by a recent large prospective study (Bailey et al., 1995; Ozonoff et al., 2011). One of the factors that have been linked to autism and is related to genetic is consanguinity. Consanguinity can be defined as the "relation between two people who share a common ancestor" (Dahdouh et al., 2016), constructed between individuals who are biologically related (Dahdouh et al., 2016). It is categorized as 1st, 2nd and 3rd degree. The 1st being the closest kinship. About 8.5% of children have consanguineous parents and almost 20% of the world's population lives in societies that favor consanguineous unions in Southern coast of the Mediterranean, throughout the Middle East and South-East Asia and Northern Africa. According to available data among the population of these countries (Dahdouh et al., 2016).

The situation in the Middle East region and Qatar is more profound, where consanguinity is estimated to be as high as 54% (Bener & Hussain, 2006). Medical complications are well recognized in consanguineous marriages; these contain both malformations (Jaber et al., 2005) and rare recessive genetic disorders (Bittles, 2008), in addition to disorders of complex inheritance, like psychiatric disorders (Mansour et al., 2010; Musante & Ropers, 2014; Sharkia et al., 2010).

Few pieces of literature studied the association between ASD and consanguinity. Some studies yielded a significant relation while other did not. In India, a case-control study studied the consanguinity as a risk of Autism. The study concluded that consanguinity increases the ASD risk (odds ratio= 3.22) (Mamidala et al., 2015). In Lebanon, a pilot study was conducted to study the association between autism and

multiple risk factors, including consanguinity, older parents age, unhappy maternal feeling during pregnancy and previous childhood infection (Hamadé et al., 2013). The results came out indicating a significant relationship with the entire factor except consanguinity (Hamadé et al., 2013). Even though the overall prevalence of consanguineous marriage in Lebanon was high (35.5%) they expanded the explanation about the situation by saying that consanguinity was found to increase the risk of autism and it needs more research studies with bigger sample size to evaluate its significant correlation with autism (Hamadé et al., 2013). Furthermore, Al-Salehi and colleagues discovered that nearly 33% of autistic children in Saudi Arabia were an outcome of consanguineous marriage (Salhia et al., 2014) and that autism is related to consanguinity as consanguinity was reported by 28.6% of patients from Saudi (Salhia et al., 2014). A study examines the consanguinity in ASD children in Qatar and reported that 83% of their cohort had one proband, 9.9% with two probands, and 7.1% with over two, however, the impact of consanguinity as a hazard factor was not observed to be significant (Alshaban et al., 2017).

2.4 Autism Comorbidities

ASD is associated with high rates of other disorders comorbidity, for example, anxiety disorders, fears and phobias, mood disorders, attention deficit hyperactive disorder (ADHD) and epilepsy (Ghaziuddin et al., 2002; Leyfer et al., 2006; LoVullo & Matson, 2009; Simonoff et al., 2008; Smith & Matson, 2010a, 2010b, 2010c). Researchers started to acknowledge and emphasis on comorbidity in individuals with ASD recently (LoVullo & Matson, 2009; Smith & Matson, 2010c). Davignon et al, 2018 studied the frequency of psychiatric and medical comorbidities in a large population of ASD individuals. 13% of their cohort were diagnosed with ID (5%

sever, 9% moderate, 15% mild, 69% unspecified, 2% profound). ID prevalence increased with age (11%, 12% and 19% in age group of 14–17-year-olds, 18–21-year-olds and 22–25-year-olds respectively) and higher among women (20%) than men (11%). 34 % of ASD patients had a co-occurring psychiatric condition. ADHD was the most common (15 %) followed by anxiety (14 %), depression (10 %), and bipolar disorder (6 %). Most psychiatric conditions were significantly higher in the ASD individuals than in each comparison group, and the majority of medical conditions in the ASD group were significantly higher than in the ADHD and control groups (Davignon, Qian, Massolo, & Croen, 2018). Croen et al 2015 studied 1507 adults with ASD to assess the range comorbidity among them. Around one-fifth (19.2%) of adults with ASD also had an intellectual disability diagnosis. 54% of them were diagnosed with a psychiatric condition: anxiety (29%), depression (26%), bipolar disorder (11%), obsessive–compulsive disorder and schizophrenia (8% each). Adults with autism had significantly high rates of all main psychiatric disorders including anxiety, depression, obsessive–compulsive disorder, schizophrenia, bipolar disorder, and suicide attempts. Approximately all medical conditions were significantly higher in adults with ASD, such as immune conditions, sleep disorders, seizure and diabetes (Croen et al., 2015). Isaac S. Kohane and his colleges evaluated comorbidity magnitude of ASD in young adults and children using electronic health records in four hospitals in the Boston area (Kohane et al., 2012). They discovered that among ASD patients, 19.44% also had epilepsy, 2.43% had schizophrenia, 0.83% had inflammatory bowel, 11.74% had bowel disorders, central nervous system anomalies 12.45%, type 1 diabetes mellitus 0.79%, muscular dystrophy 0.47% and 1.12% had sleep disorders (Kohane et al., 2012). Another study assessed the frequency of

current The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-IV) comorbidities that comorbid ASD in a special school for adolescents and children demonstrating the wide area of intellectual degrees and common ASD subgroups (Gjevik et al., 2011). The study concludes that 72% of study populations were diagnosed with a minimum of one comorbid disorder. Forty-one percent had anxiety disorders and 31% had ADHD. In older children, obsessive-compulsive disorder was more common, while oppositional defiant disorder/conduct disorder were more common in pervasive developmental disorder (Gjevik et al., 2011).

Moreover, E Simonoff, found that 70% of their cohort had one comorbid disorder and 41% had two or more. The most widely recognized comorbidities were ADHD (28.2%), social anxiety disorder (29.2%), and oppositional defiant disorder (28.1%). Eighty-four percent of the ADHD patients, received a second comorbid diagnosis (Simonoff et al., 2008).

In the Arab region, research was conducted to study the frequency of comorbid psychiatric disorders in a cohort of ASD children enrolled from: Egypt, Saudi Arabia and Jordan (Amr et al., 2012). The results found that 63% of the children had at least one comorbidity. The most frequently described comorbidities were ADHD (31.6%), major depressive disorder (13.3%), anxiety disorders (58.3%) and conduct disorders (23.3%) (Amr et al., 2012).

In Egypt, a study reported that 90% of cases were associated with one or more comorbid conditions and the presence of more than one comorbidity was usually associated with male sex and severe type of autism, 72.5% of studied cases suffered from comorbid tics (40% occurred in severe autism), 25% presented with associated

ADHD, 20% suffered from oppositional defiant disorder (ODD) as comorbid conditions, 37.5% had comorbid obsessive compulsive disorder (OCD), and 5% suffered from comorbid general anxiety disorder (Elbahaaey, Elkholy, Tobar, & El-Boraie, 2016).

2.4.1 Autism, Epilepsy and Intellectual Disability

Epilepsy, a frequent ASD comorbidity, is defined as a chronic neurologic disorder characterized by repeated spontaneous epileptic seizures (Engel Jr, 2006). Epilepsy is occurred mainly in young children or individuals over the age of 65 years; but it can happen at any time. Several risk factors are reported to be associated to epilepsy such as positive family history of epilepsy, sex, febrile and abnormal neonatal history, head trauma and low education (Vozikis, Goulionis, & Nikolakis, 2012). The co-occurrence of ASD and epilepsy is well recognized (Canitano, 2007; Spence & Schneider, 2009; R. Tuchman & Rapin, 2002). Epilepsy prevalence estimations in individuals with ASD have varied from 5% to 46% (Spence & Schneider, 2009). The variation is due to factors like concurrent intellectual disability (ID) (Amiet et al., 2008; Jokiranta et al., 2014; Woolfenden, Sarkozy, Ridley, Coory, & Williams, 2012), severe language dysfunction (R. F. Tuchman, Rapin, & Shinnar, 1991), female gender (Amiet et al., 2008; Danielsson, Gillberg, Billstedt, Gillberg, & Olsson, 2005) and age (Hara, 2007; Rossi, Posar, & Parmeggiani, 2000; Volkmar & Nelson, 1990), which are all related to the risk of epilepsy in ASD. Amiet et al, in a meta-analysis on epilepsy and autism, revealed an association with intellectual disability; epilepsy was found in 21.5% of individuals with autism who correspondingly had intellectual disability and 8% of individuals without intellectual disability (Amiet et al., 2008).

The associations between autism and epilepsy continue to be argued. Mannion et al. (2013) found that a comorbid diagnosis of epilepsy was reported by 10.1% of ASD children and adolescents (Mannion & Leader, 2013). 22% of individuals with ASD had epilepsy by the age of 21 years as reported by Bolton et al. (2011) who followed up 150 children diagnosed with ASD (Bolton et al., 2011). Pavone et al, 2004 reported a lower rate of epilepsy, approximately 6% in children with autism without additional neurological disorders (Bolton et al., 2011).

Intellectual Disability (ID) is a disorder characterized by below average intellectual functioning (IQ<70) in combination with substantial restrictions in adaptive functioning. ID can happen as an isolated condition or accompanied with neurological signs, malformations, seizures, impairment of the special senses and behavioral disturbances (Simonoff et al., 2008). Several prenatal and perinatal factors have been associated with increased risk of ID; advanced maternal age, low maternal education, multiparity, maternal alcohol or tobacco use, maternal diabetes or hypertension, maternal epilepsy, preterm birth, low birth weight and male sex (Huang, Zhu, Qu, & Mu, 2016). In the latest Centers for Disease Control and Prevention (CDC) report, 31% of children with ASD had intellectual abilities in the ID range (with another 23 % in the borderline range), although estimations through studies range broadly, from 26% to 68 % (Ghaziuddin et al., 2002; Leyfer et al., 2006; LoVullo & Matson, 2009). The prevalence data demonstrates broadly inconsistent numbers in an overlap between ID and ASD. Bryson et al. (2008) reported that 28% of persons with ID also showed autism (Bryson, Bradley, Thompson, & Wainwright, 2008). De Bildt et al. (2004), using DSM-IV-TR criteria for Pervasive Developmental Disorder, stated a 16.7% occurrence rate of ID comorbidity (De Bildt et al., 2004).

With the emergent global prevalence of ASD, as well as in Qatar (1.4%), research should have rapidly advanced efforts to better understand the rise in occurrence and it is co morbidities. The weight of autism in GCC region is still unclear as epidemiological research into this area is relatively new, so we need to further investigate the prevalence, risk factors and characteristics of ASD in the region. Consanguinity is most commonly associated with rare recessive conditions, and some of the ASD genes are likely to be of this type. The relationship of consanguinity to autism spectrum disorder (ASD) risk has not been fully explored, thus it is important to study the association of consanguinity with ASD. Also, ASD is a lifelong neurodevelopmental disorder with high rates of comorbidities. Nonetheless, it is only recently researchers have begun to recognize and focus on comorbidities in individuals with ASD.

Chapter 3: The meta-analysis

3.1 Methods

3.1.1 Guidelines

Meta-Analysis of Observational Studies in Epidemiology guidelines will be applied in conducting the meta-analysis. We used the (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) PRISMA statement criteria in reporting our systematic review (Moher, Liberati, Tetzlaff, & Altman, 2009).

3.1.2 Protocol and Registration

We submitted a registration for this review in the International Prospective Register of systematic reviews (PROSPERO). The registration number is: 123474.

3.1.3 Search databases

An electronic search was conducted in PubMed, EMBASE, and Academic Search Complete to gather articles published up to Oct. 2018, with no date restriction.

3.1.4 Search strategy

The objective of the literature search is to identify all epidemiological studies that had estimated the global prevalence of consanguinity among the ASD individuals and compare it that among different populations. The search term was ((autism) or (autistic disorder)) and ((consanguinity) or (consanguineous marriage)), the search identified 60 studies in PubMed, 117 in Embase and 21 in Academic Search Complete. Additional 14 records were added from other sources (Fig 3). The systematic search did not identify any systematic review or meta-analysis about consanguinity prevalence among ASD individuals.

3.1.5 Inclusion criteria

- English-language studies.
- Patients with Autism.
- Consanguinity prevalence measured by any definition.

3.1.6 Exclusion criteria

- Overlap of databases.
- Not addressing ASD patients, separately (not relevant).

3.1.7 Study Selection

Title and abstracts of the included studies were reviewed, and duplicates studies were removed using Endnote. The Author and Dr. Ibrahem Abdalhakam; a research associate at Diabetes, Obesity and Metabolic Research Unit at Qatar Metabolic Institute, Hamad Medical Corporation, reviewed independently extracted information from articles (Table 2). The agreement between the two reviewers was measured and the PRISMA and data extraction table produced by both of them was found similar.

3.1.8 Data extraction

We identified 10 publications from 8 different countries (KSA (2 studies), Lebanon (2 studies), Qatar, Bahrain, Egypt, Jordan, Iran, and Israel). All were peer-reviewed, published in English between 2009 and 2018, and reported the prevalence of consanguinity in ASD individuals.

3.1.9 Data Collection Process

A standardized data abstraction form was applied to collect the following information from eligible studies: first author, year, country, study design, total sample size, sample size of ASD cases and consanguinity cases (Table 2).

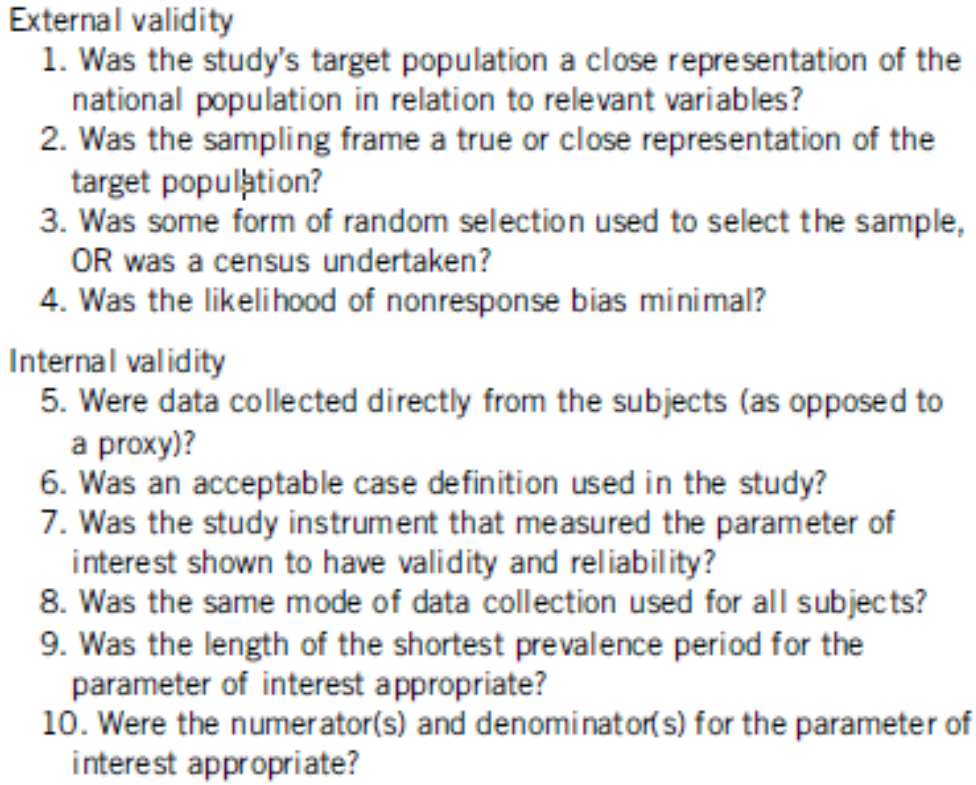
3.1.10 Quality of the data

A risk of bias is the risk of having a systematic error , or having results deviated from the truth (Viswanathan et al., 2012), Many tools were established to evaluate the data quality (risk of bias) in systematic reviews and meta-analysis , some of them are checklist where certain questions are asked and answered yes or no , while others are scales where the give a certain score for each component and then the overall score calculated to give the final score (Higgins et al.).

We used a tool established by Hoy et al. (2012) to assess the quality of studies involved, since this tool is specifically designed for assessing systematic review of the prevalence studies (Hoy et al., 2012). This tool included two main categories which are internal and external validity (Figure 1). Internal validity refers to degree of which the design and study methodology steps that used have the minimum possible bias. While external validity refers to the ability to generalize the results to the larger population (Friis, 2010).

The tool has ten different bias components, the first three items assessed the risk of selection bias, item four assess the non-response bias, from five to nine it was all about measurement bias, and the last item was about meta-analysis bias (Wang et al., 2017) (Figure 1).

To apply this tool, a score of Y (yes) or N (no) was assigned for each component of the tool to compute the quality scores. In computing the scores "Yes" score was considered as equivalent to one point, and "No" was equivalent to zero. Then these scores are summed was used (range from 0 to 10). The following classification created by Hoy et al. (2012) to classify the studies as high, moderate, or low risk of bias: Scoring 8 and above indicate having a low risk of bias, a result of 6 or 7 indicate moderate risk and having score equal or less than 5 indicate there is a high risk (Wang et al., 2017).


External validity

1. Was the study's target population a close representation of the national population in relation to relevant variables?
2. Was the sampling frame a true or close representation of the target population?
3. Was some form of random selection used to select the sample, OR was a census undertaken?
4. Was the likelihood of nonresponse bias minimal?

Internal validity

5. Were data collected directly from the subjects (as opposed to a proxy)?
6. Was an acceptable case definition used in the study?
7. Was the study instrument that measured the parameter of interest shown to have validity and reliability?
8. Was the same mode of data collection used for all subjects?
9. Was the length of the shortest prevalence period for the parameter of interest appropriate?
10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?

Figure 1. Hoy's Tool Items of Risk of Bias Assessment

3.1.11 Statistical Analysis

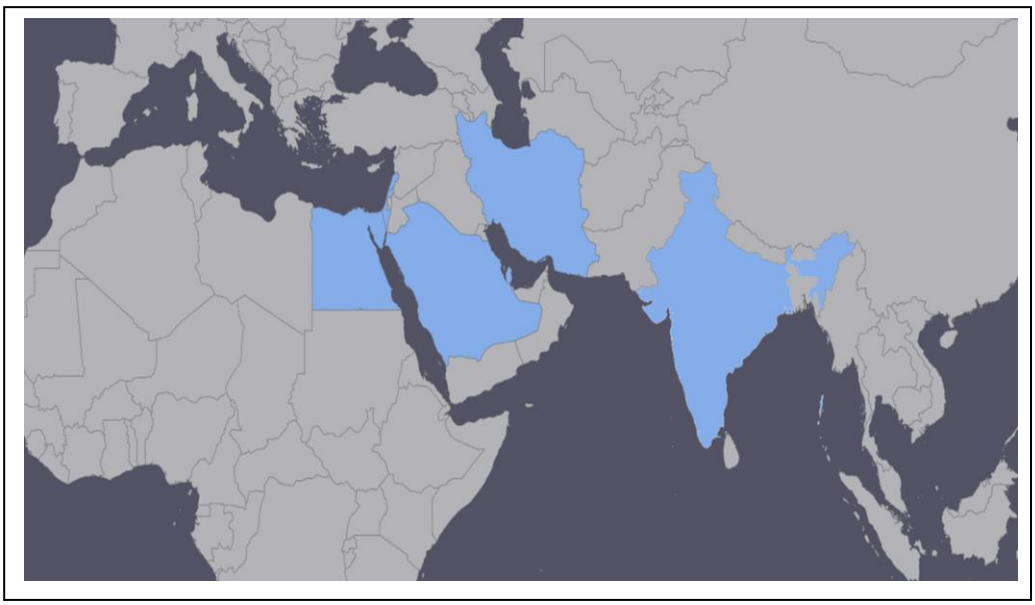
Overall pooled effect size was calculated using appropriate model. Statistical heterogeneity was tested by the Cochran Q statistic and reported as I^2. Random effect model was used because there was significant heterogeneity among studies. Funnel and Hunter plots were generated to examine publication bias. Comprehensive Meta-Analysis software, MetaXl version 5.3 and Revman 5.3 were used for all analyses. Also, we did subgroup analysis by country and study design.

3.2 Results

3.2.1 Qualitative Summary

10 publications were identified based on our inclusion criteria from 8 different countries, 4 of them were from the GCC (KSA (2 studies), Qatar, Bahrain) and the rest were from: Lebanon (2 studies), Egypt, Jordan, Iran, and Israel). Figure 2 show the geographic location of the included studies.

Seven of the included articles used a case control study design, and three were used cross sectional study design. Studies varied in ASD cases as it ranged between 49 - 500, and the total ASD cases in all studies were 1581 (Table 2). All studies address consanguinity among the ASD children despite the variation in the methods.



- Qatar
- India
- Iran
- KSA
- Lebanon
- Israel
- Egypt
- Bahrain

Figure 2. Geographic location of included studies

Table 1

Included Studies

Author	Year	Country	Study design
Farida El-Baz	2011	Egypt	case-control
Fouad Alshaban	2017	Qatar	cross-sectional
Saleh M. Al- Salehi	2009	KSA	cross-sectional
Aline Hamadé	2013	Lebanon	case-control
Muhammad Mahajnah	2015	Israel	cross-sectional
Madhu P. Mamidala	2015	India	case-control
A.M. Al-Ansari	2012	Bahrain	case-control
Dikran Richard Guisso	2018	Lebanon	case-control
Roksana Sasanfar	2010	Iran	case-control
Adnan Amin Alsulaimani	2014	KSA	case-control

Each of the 10 included studies are narratively summarized below as part of the systematic review.

Farida El-Baz et al. (2011) conducted a study in Egypt that included 100 autistic patients. At 1.5 years of age, 46% of them had autistic symptoms and at 2 years of age 32%. Fifty-five percent experienced moderate to severe intellectual disability (IQ=

20–70), 36% lower than normal intellectual function (IQ= 71–89), 13% were outcome of consanguineous marriage and 9% average intellectual function (IQ= 90–109). Advanced mother age (>35 years) at birth was reported by 23% of autistic children paralleled to only 9.5% of controls (P value 0.001). Paternal age at delivery time (> 35years) was higher in the cases group than in the controls group (91% and 83.5% respectively) which was statistically significant (P value < 0.001). A statistically significant association of positive family history with the risk of autism was found (16 % of their sample). All developmental milestones studied were delayed among autistic children compared to control group (P value < 0.001). Birth factors (low birth weight history and outcome of caesarian section) and postnatal factors (hypoxia, resuscitation, and jaundice) were statistically significant as risk factors for autism.

In Saudi Arabia, Saleh M. Al - Salehi & Elham H. Al-Hifthy et al. (2009) studied 49 ASD children in Saudi Arabia for reasons of referral and clinical characteristics. Their average age was 6.3 years, females were older, and 14 children were outcome of consanguineous marriage. Five patients had no speech and 5 had a history of language deterioration around the age of 18–24 months. Before the age of three, 42 patients had experienced symptoms. Chromosomal abnormality was found in one patient. Other comorbidity of seizure disorder was reported by 11 patients, mental retardation by 27 patients and hyperactivity and impulsiveness by 22 patients. Glucose 6 Phosphate Deficiency (G6PD) was found in 2 patients and cerebral paralysis and Tourette in patient each. Twenty - five patients took psychotropic medicines and 14 patients came from consanguineous marriages, which considered high percentage (29%), but it does not have a good reflection as their sample size was small.

Aline Hamadé et al. (2012) conducted a study on autism correlates in the Lebanese population in Lebanon. Their sample size was 86 autism cases from specialized schools and control group involve 172 school kids. They reported a significant association between autism and male gender, advanced parents age, unhappy maternal emotion throughout gestation, living around industrial area and history of infection during childhood (OR= 3.38, 1.27, 5.77, 6.58 and 8.85 respectively). Consanguinity was reported by 11 patients (13%). Maternal and paternal age were not associated significantly (28.84 and 29.38 for cases and 34.84 and 35.43 for controls, respectively).

Muhammad Mahajnah et al. (2015) collected demographic and clinical characteristics of two hundred ASD children from Arab and Jewish sectors in Israel that were evaluated in two child development centers. After that, they compared these tow ethnics group in terms of incidence and medical co - morbidity of autism. These children's psychiatric comorbidity and medical profile was similar to the studies published around the world. The Israel's Jewish sector autism prevalence was like that of the Arab sector in this study. Consanguinity (9%), incidence of mental retardation, autistic family members and severe autistic manifestations observed more in Arab patients ($P < 0.05$), while milder forms (such as Asperger syndrome and PDD-NOS) were more common in the Jewish sector. Genetic and cultural factors could explain this discrepancy.

In India, Madhu P. Mamidala has been studying India's consanguinity and association with autism spectrum disorder. They included 500 ASD kids and 500 controls between the ages of 2 and 10. The male - to - female ratio was calculated as 4:1. Consanguinity level was significant among ASD cases compared to controls (P <

0.0001). Univariate analysis showed that consanguineous marriage is an ASD risk factor (OR= 3.22, 95% CI—2.07, 4.62, P < 0.0001). LBW was considered as a significant risk factor for ASD (OR= 2.02), when they include consanguinity in the multivariate analysis.

A.M. Al - Ansari et al (2012) conducted a study to identify the prevalence of autistic disorder in Bahrain and to assess some of the characteristics of the population and family. A case-control design was used to select 100 children who were diagnosed with DSM-IV TR autistic disorder during the period 2000–2010. An equal number of controls were selected, matched for sex and age group that had been diagnosed with nocturnal enuresis and no psychopathology. The prevalence of autistic disorder was more in males with a male: female sex ratio of 4:1 and reported at 4.3 per 10,000 populations. Consanguinity was reported by 29 cases. Caesarean section delivery was significantly more in cases than controls and had mothers suffering prenatal complications. Bahrain's prevalence estimate is comparable with previous reports using similar methods. Autistic disorder may be associated with obstetric complications and delivery of the caesarean section.

Dikran Richard Guisso et al (2018) conduct a study on the association of pregnancy and natal complications with other ASD factors in children from Lebanon between 2 and 18 years old. One-hundred and thirty-six children with ASD from the Special Kids Clinic as well as 178 controls recruited from Beirut were interviewed. Consanguinity was reported by 14% of the cases. Difficulties in feeding postpartum, male gender, maternal infections / complications during pregnancy, consanguinity, psychiatric disorder family history were risk factors for ASD. ASD was negatively

associated with being born first / second and maternal psychological support during pregnancy.

Roksana Sasanfar et al (2010), recruited 179 children with autism and 1611 matched control children from Iran to investigate the association between autism and parents age. Nine controls groups on sex, parental education, consanguineous marriage, birth order, province of residence and urbanism were matched in each case. The model of Cox regression was used to perform on matched data conditional logistical regression. They found a significant relationship between advanced father age, but not mother age, and bigger risk of autism. Higher - educated parents had high risk of having autistic children with a parental age dose - response effect based on overall effect of parental age and education analysis. Consanguinity was reported by 58 cases.

Dr. Adnan Amin Alsulaimani et al (2012) conducted a study to interpret the psychometric, clinical and epidemiological aspects of a cohort of children with autism from KSA to conclude potential risk factors for autism. They enrolled 60 ASD cases diagnosed based DSM - IV - TR criteria. During June 2011 to May 2013, cases were recruited from the mental health clinic integrated into the Pediatric Clinic, Prince Mansour Military Hospital. The control group consisted of one hundred and twenty healthy children. They have been recruited from various ambulatory clinics. For each case, 2 control subjects were recruited and matched in habitat, gender, age and environment. no statistically significant variance between controls and cases with respect to their weight, age, height, mother's age at delivery time and birth order, whereas father's age at delivery time was lower in controls compared to cases, which was statistically significant. Fifty - five percent of autistic child parents were consanguineous at first degree compared to just 36.7% of controls (p value= 0.019).

In addition, 39% of autistic children had positive family history of psychiatric disease compared to just 18.3 percent of controls (p value= 0.03). 36.9 percent compared to only 11.7% of families of autistic patient cases and controls, respectively, had a positive family history of autism (p value= 0.0001).

Fouad Alshaban et al (2017) conceived a study in Qatar to define ASD clinical characteristics and its correlates. ASD patients (171 patients) have been recruited from the Shafallah Center for Children with Special Needs. The analysis involved the subsequent factors: sex, nationality, consanguinity, socioeconomic status, age, comorbidity and prenatal and postnatal complications. Out of the 171 patients, 80% were males (male to female ratio of 4:1). Consanguinity was reported by 69 cases. Also, 83% of families with one proband, 9.9% had 2 probands, and 7.1% with more than two. Intellectual disability was found in 83%, epilepsy in 18.8% and 76.6% of patients were nonverbal.

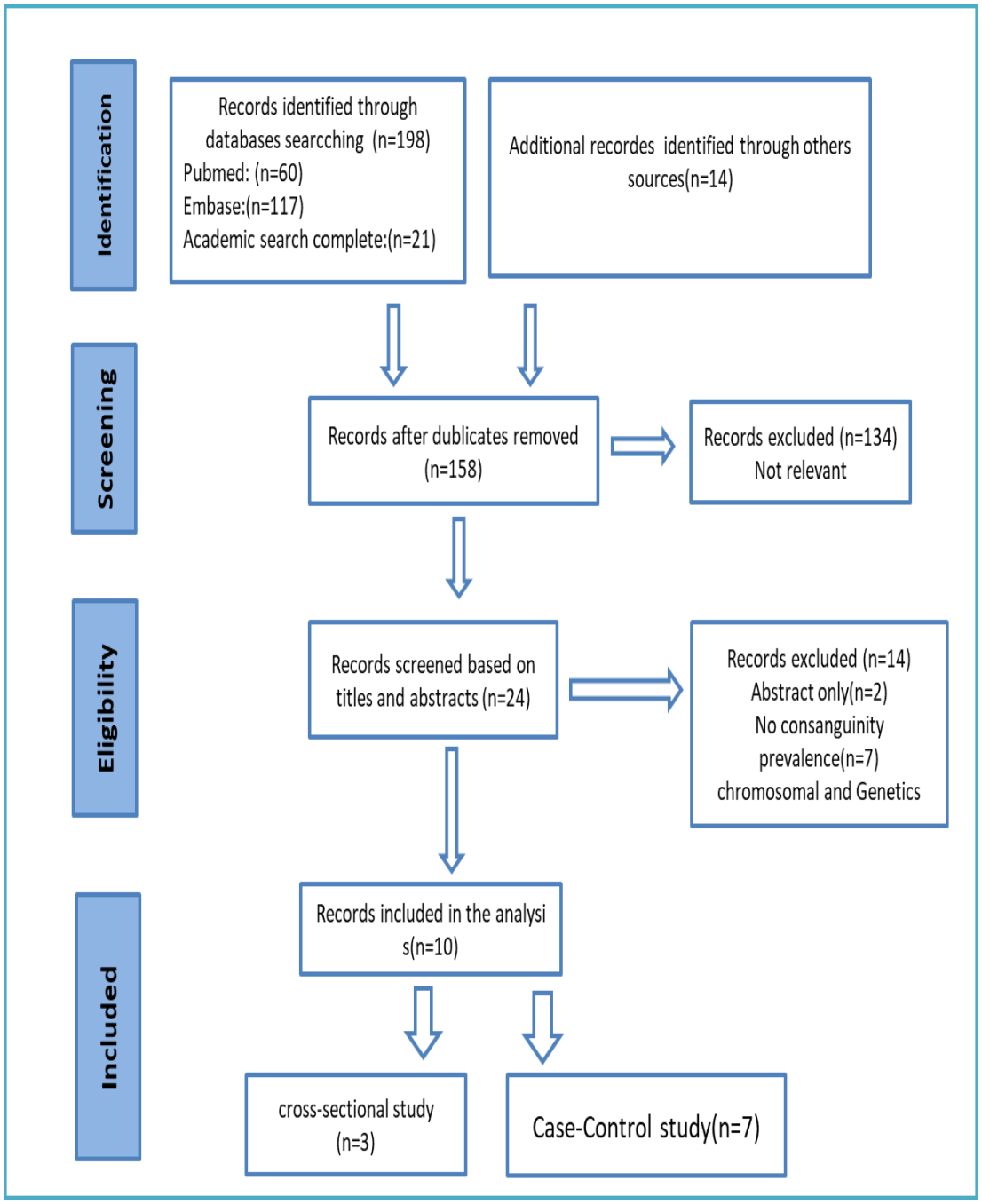


Figure 3. PRISMA Flowchart Diagram

Table 2

Characteristics of the included studies

Author	Farida El-Baz et al	Fouad Alshaban et al	SALEH M.AL-SALEHI et al
Random sampling	No	No	No
Population	Clinical	specialized schools	Clinical
Total sample size	300	171	49
Sample size, ASD/consanguineous	100/13	171/69	49/14
Sample size, Control/consanguineous	200/43	NA	NA
Consanguinity measurement/degrees	self-reported/Not reported	self-reported/Not reported	self-reported/Not reported
ASD Age ratio	2 to 13 years	not specified	mean age 6.3 years
ASD Gender ratio	males (82%) and females (18%)	80% males and 20% females	37 males and 12 females
Diagnosis tool	DSM-IV-TR criteria	DSM-IV	DSM-IV criteria

Table 2

Characteristics of the included studies (Continued)

Author	A.M. Al-Ansari et al	Dikran Richard Guisso et al
Random sampling	Yes	Yes
Total sample size	200	314
Population	Clinical	Clinical
Sample size of ASD/consanguineous	100/29	136/19
Sample size of Control/consanguineous	100/NA	178/13
Consanguinity measurement/Degrees	self-reported/reported	self-reported/Not reported
ASD Age ratio	2–27 years	2–18 years
ASD Gender ratio	male to female ratio 4:1	males (64%)
Diagnosis tool	DSM-IV	DSM-IV, DSM-V

Table 2

Characteristics of the included studies (Continued)

Author	Roksana Sasanfar et al	Adnan Amin Alsulaimani et al
Random sampling	No	No
Total sample size	1790	180
Population		Clinical
Sample size of ASD/consanguineous	179/58	60/33
Sample size of Control/consanguineous	549354/167001	120/44
Consanguinity measurement/Degrees	self-reported/Not reported	self-reported/reported
ASD Age ratio	5- 11 years	19m to 96m
ASD Gender ratio	male to female ratio was 4:1	males (76.7%) and females (23.3%)
Diagnosis tool	child psychiatrist's	DSM-IV-TR criteria

3.2.2 Risk of Bias

Of the 10 studies involved in our study, 2 (20%) articles met all the ten quality criteria (Dikran,Fadi,Dahila et al 2018, Madhu P. Mamidala et al 2015), 7 (70%) studies have low risk of bias (Saleh M. Al-Salehi et al 2009, Aline Hamadé et al 2013, Muhammad Mahajnah et al 2015, Roksana Sasanfar et al 2010, Adnan Amin Alsulaimani et al 2014 , A.M. Al-Ansari et al 2012 and Farida El-Baz et al 2011) and one study has moderate risk of bias (Fouad Alshaban et al 2017).

In regards to the external validity five of the studies get a full score (4/4) (Aline Hamadé et al 2013, Muhammad Mahajnah et al 2015, Madhu P. Mamidala et al 2015, A.M. Al-Ansari et al 2012 and Dikran Richard Guisso et al 2018) while the other five can be considered to have a good external validity (Farida El-Baz et al 2011, Fouad Alshaban et al 2017, Saleh M. Al-Salehi et al 2009, Roksana Sasanfar et al 2010 and Adnan Amin Alsulaimani et al 2014). Based on question 3 of the external validity; was some form of random selection used to select the sample or was a census undertaken? 50% of studies rated poorly for having a random assignment of the sample population (Farida El-Baz et al 2011, Fouad Alshaban et al 2017, Saleh M. Al-Salehi et al 2009, Roksana Sasanfar et al 2010 and Adnan Amin Alsulaimani et al 2014). All the studies have representative sample of the whole national population and the target population.

Regarding the internal validity, 30% of the studies had errors in the numerator and denominator for the parameter of interest (Fouad Alshaban et al 2017, Saleh M. Al-Salehi et al 2009 and Aline Hamadé et al 2013). Moreover, all of them had an acceptable definition of the cases and used similar method in data collection from all

patients which lead to increased validity and reliability. Figure 3 and 4 shows a plot and summary of risk of bias results.

Having studies with no, low and moderate risk of bias is due to establishing highly selective inclusion criteria to include studies in meta-analysis, as well as most of the studies had similar characteristics and measurements. Since we are investigating specific exposure in a specific population, all studiers considered were answered Y (Yes). Regarding the sampling frame question, all of studies were representative of the target population, so all of them got Y(Yes) for this question.

When evaluating the non-response of participants (question 4), none of the studies had non-response problem, so there was low risk of non-response bias. Forty percent of the studies used medical records to collect the data, while the rest collect data directly from the participants (Question 5). All studies showed validity and reliability as they used standardized tool for ASD diagnosis (Question 7). Regarding question on whether the prevalence changes with time (question 9), all the studies got Y (Yes) as ASD prevalence changes through time.

Table 3

Tool for Assessing Risk of Bias

First Author (Year)	External validity				Internal validity						Quality Score	Risk of Bias
	1	2	3	4	5	6	7	8	9	10		
Dikran et al,2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	NO
Hamadé et al,2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	9	LOW
Fouad et al,2017(Qatar)	Y	Y	N	Y	N	Y	Y	Y	Y	N	7	MODERATE
Saleh.M.Al-Salehi et al,2009	Y	Y	N	Y	Y	Y	Y	Y	Y	N	8	LOW
Muhammed Mahajnah et al,2014	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9	LOW
Madhu P. Mamidala et al, 2015	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	NO
A.M.AL-Ansari et al,2012	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9	LOW
Roksana Sasanfar et al,2012	Y	Y	N	Y	N	Y	Y	Y	Y	Y	8	LOW
Farida et al,2011	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	9	LOW
Dr.Adnan et al,2014	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	9	LOW

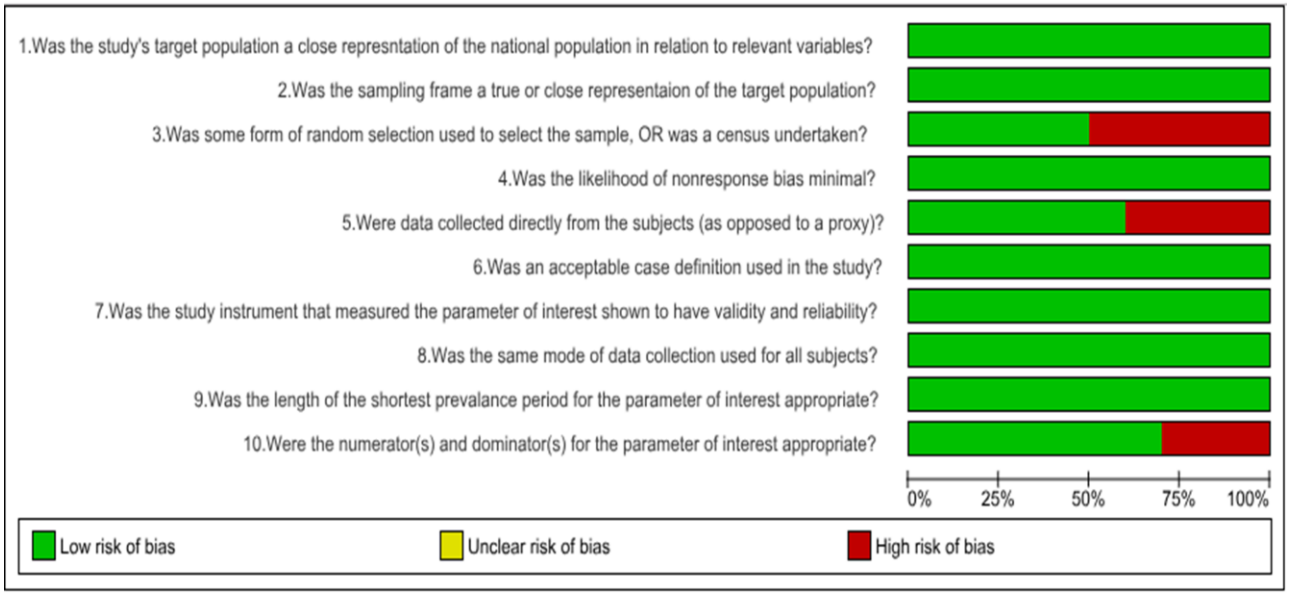


Figure 4. Risk of Bias graph

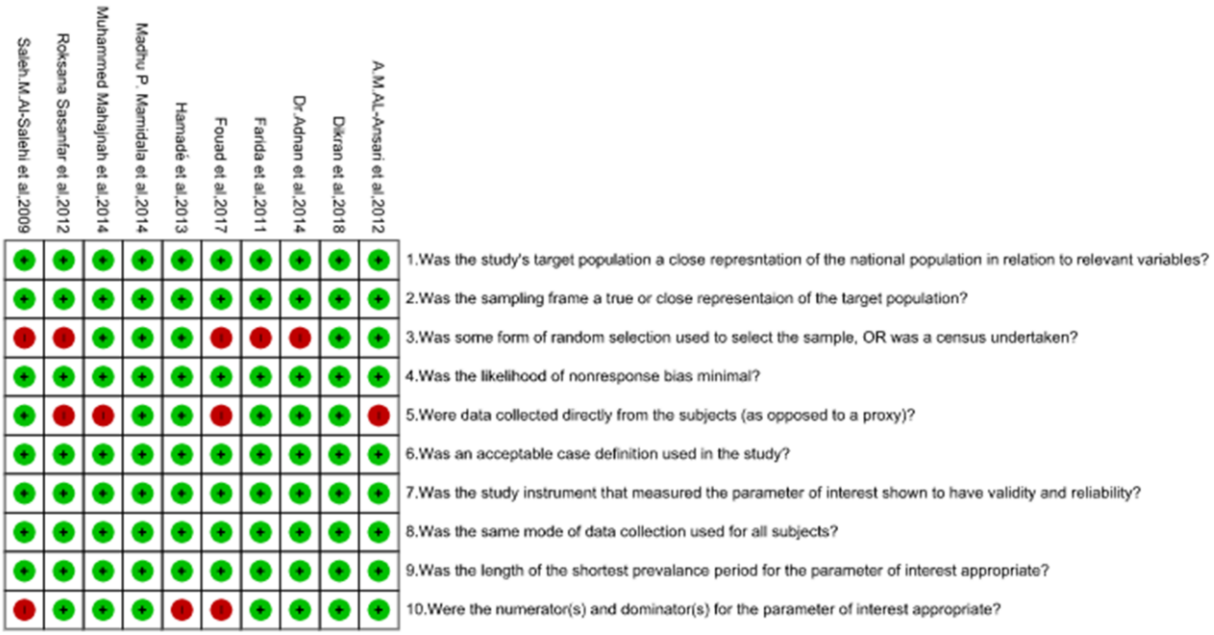


Figure 5. Risk of Bias summary

3.2.3 Heterogeneity Assessments

There are variations in the objectives and aims between the included studies in this meta-analysis. From the total included studies, we calculated pooled prevalence of consanguinity among ASD patients. There was significant heterogeneity among these studies (Q value= 113.3, P value<0.001, I^2 = 92%). As there is high heterogeneity, the random effect model was used to estimate the pooled prevalence.

The pooled prevalence for cross-sectional studies was 23% (95% CI:4%-50%), there was a high heterogeneity across studies (Q value=54.8, P value=0.001, I^2 = 96%). For case-control studies the estimated pooled prevalence was 23.3% (95% CI: 15.8%-33%), there was significant heterogeneity (Q value= 58.9, P value<0.001, I^2 = 89%).

In GCC countries, the estimated pooled prevalence of consanguinity among ASD patients was 38% (95% CI: 28%-49%), and there was considerable heterogeneity detected between these studies (Q value=12.7, P value = 0.01, I^2 = 76%). While for the pooled prevalence for the other than GCC countries was 16.2% (95% CI: 10.8%-23.5%), significant heterogeneity was found (Q value= 39.1, P value<0.001, I^2 = 87%).

3.2.4 Quantitative Synthesis (Random effect mode)

The overall pooled prevalence of consanguinity among ASD patients based on REM was 24% (95% CI: 17%-32%) (Figure 6). The prevalence reported by Adnan et al, 2014 was higher than this study's overall pooled prevalence, 55% (95% CI: 42.4%-67%). The estimated prevalence in Fouad et al, 2017, Roksana Sasanfar et al, 2012, A.M.AL-Ansari et al, 2012 and Saleh.M.Al-Salehi et al, 2009 were relatively higher than our overall pooled prevalence, 40%(95%CI:33%-48%),32.4% (95% CI: 26%-

39.6%), 29% (95% CI: 21%-38.6%) and 28.6% (95% CI: 17.7%-42.6%) respectively. In Madhu P. Mamidala et al, 2015, the prevalence was slightly less than the pooled prevalence, 20% (95% CI: 16.7%-23.7%), while it were 14% (95% CI: 9.1%-20.9%), 13% (95% CI: 7.7%-21.1%) and 12.8% (95% CI: 7.2%-21.6%) in Dikran et al, 2018, Farida et al, 2011 and Hamadé et al, 2013 respectively. The lowest prevalence was reported in Muhammed Mahajnah et al, 2014, 9% (95% CI: 5.8%-14.7%).

From the cross-sectional studies (Fouad et al, 2017, Saleh.M. Al-Salehi et al, 2009 and Muhammed Mahajnah et al, 2014), the pooled prevalence of consanguinity among ASD patients was 23% (95% CI: 4%-50%) (Figure 7). The highest prevalence was reported in Fouad et al, 2017,40%(95%CI:33%-48%), followed by Saleh.M. Al-Salehi et al, 2009, 28% (95% CI: 17.7%-42.6%), while Muhammed Mahajnah et al, 2014 reported the lowest prevalence, 9% (95% CI: 5.8%-14.7%).

Regarding case-control studies (Dikran et al, 2018, Farida et al,v2011 and Hamadé et al, 2013, Dr. Adnan et al, 2014, Roksana Sasanfar et al, 2012, A.M.AL-Ansari et al, 2012 and Madhu P. Mamidala et al, 2015) the estimated pooled prevalence was 23.3% (95% CI: 15.8%-33%) (Figure 8). The highest prevalence was reported by Dr. Adnan et al, 2014 was higher than the overall pooled prevalence, 55% (95% CI: 42.4%-67%). Followed by Roksana Sasanfar et al, 2012 and A.M.AL-Ansari et al, 2012, 32.4% (95% CI: 26%-39.6%) and 29% (95% CI: 21%-38.6%) respectively. The other 3 studies (Dikran et al,2018, Farida et al,2011 and Hamadé et al,2013) have an estimated prevalence lower than our pooled prevalence (14% (95% CI: 9.1%-20.9%), 13% (95% CI: 7.7%-21.1%) and 12.8% (95% CI: 7.2%-21.6%) respectively).

As in figure 9, the estimated pooled prevalence of consanguinity among ASD patients in GCC countries (Qatar, Bahrain and KSA) reported from 4 studies (Fouad et al, 2017, Saleh.M. Al-Salehi et al, 2009, Dr. Adnan et al, 2014 and A.M.AL-Ansari et al, 2012) was38% (95% CI: 28%-49%). Adnan et al, 2014 reported higher prevalence than the overall pooled prevalence, 55% (95% CI: 42.4%-67%), followed by Fouad et al, 2017, 40% (95% CI: 33%-48%). A.M.AL-Ansari et al, 2012 and Saleh.M. Al-Salehi et al, 2009 reported approximately the same prevalence, 29% (95% CI: 21%-38.6%) and 28.6% (95% CI: 17.7%-42.6%) respectively.

Regarding the other countries (other than GCC countries) the estimated pooled prevalence reported in six studies (Roksana Sasanfar et al, 2012, Madhu P. Mamidala et al, 2015, Dikran et al, 2018, Farida et al, 2011 and Hamadé et al, 2013 and Muhammed Mahajnah et al, 2014), was 16.2% (95% CI: 10.8%-23.5%). The highest prevalence was reported in Roksana Sasanfar et al, 2012, 32.4% (95% CI: 26%-39.6%), while Muhammed Mahajnah et al, 2014 reported the lowest prevalence, 9% (95% CI: 5.8%-14.7%) as it shown in figure 10.

Figure 11. Show the pooled estimated odd ratio for consanguinity among ASD patients and controls in the case-control studies. We excluded A.M.AL-Ansari et al, 2012 from this analysis as it did not mention the prevalence of consanguinity among controls; the other 6 case-control studies were included. The pooled estimated odd ratio was 1.5 (95% CI: 0.896-2.561). Madhu P. Mamidala et al, 2015 showed the highest odd ratio,3.2 (95% CI: 2.15-4.83), while Farida et al, 2011 showed the least, 0.54 (95% CI: 0.28-1.07). In addition to Muhammed Mahajnah et al, 2014, Dikran et al, 2018 and Dr. Adnan et al, 2014 also reported higher than pooled estimated odd ratio, 2.66 (95% CI: 0.98-4.34) and 2.11 (95% CI: 1.2-3.96) respectively. Roksana

Sasanfar et al, 2012 and Hamadé et al, 2013 reported odd ratio was 1.34 (95% CI: 0.59-2.99) and 1.09 (95% CI: 0.80-1.55) respectively.

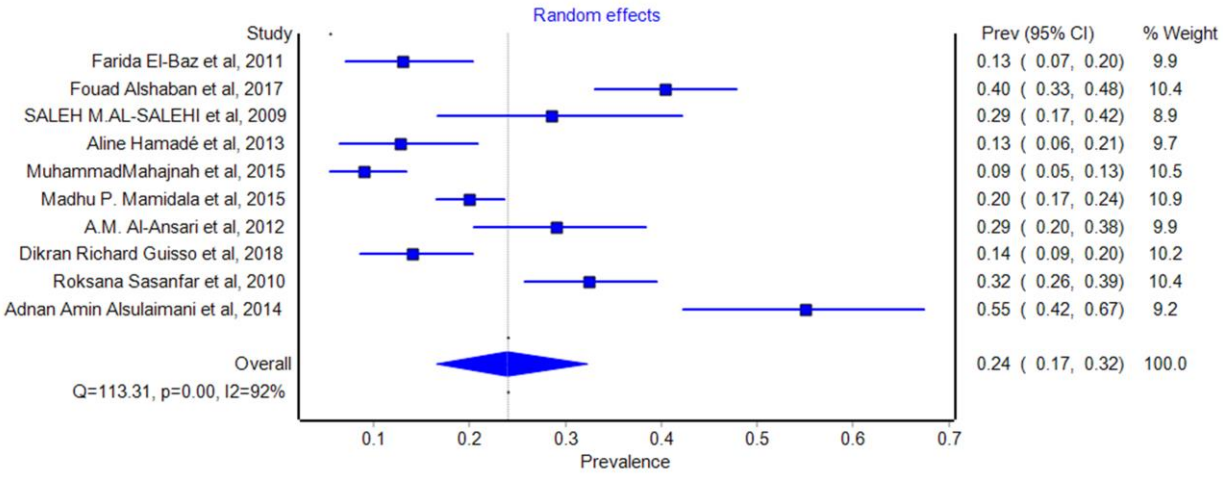


Figure 6. The overall pooled prevalence of consanguinity among ASD patients

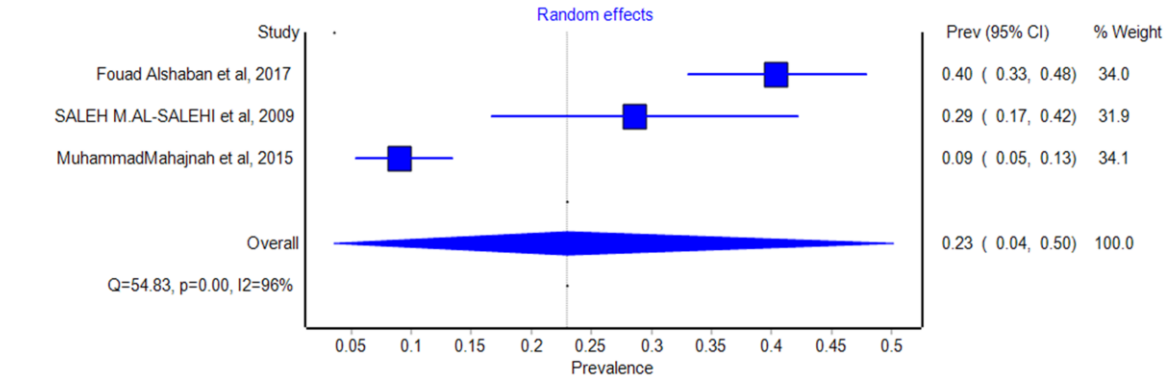


Figure 7. The pooled prevalence of consanguinity among ASD patients in cross-sectional studies

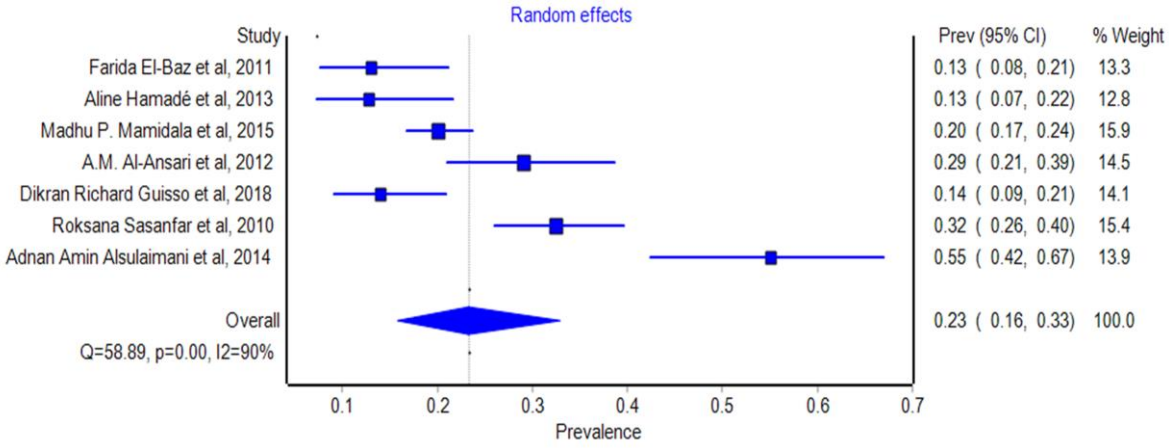


Figure 8. The pooled prevalence of consanguinity among ASD patients in the case-control studies

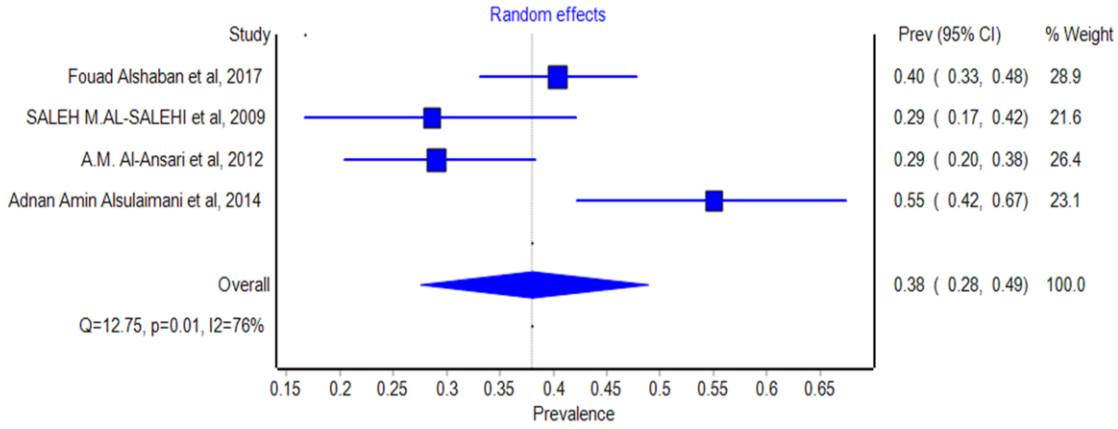


Figure 9. The pooled prevalence of consanguinity among ASD patients in the GCC countries

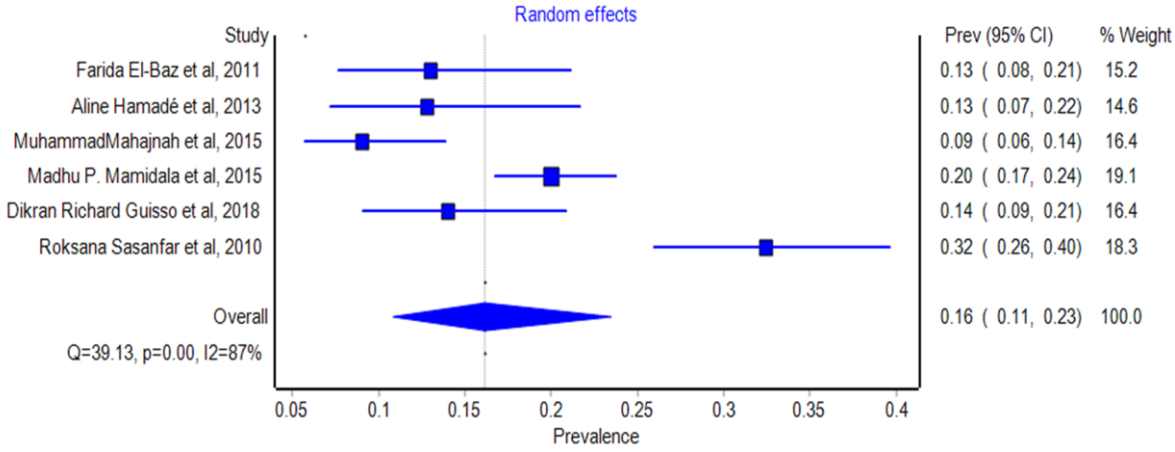


Figure 10. The pooled prevalence of consanguinity among ASD patients in the other than GCC countries

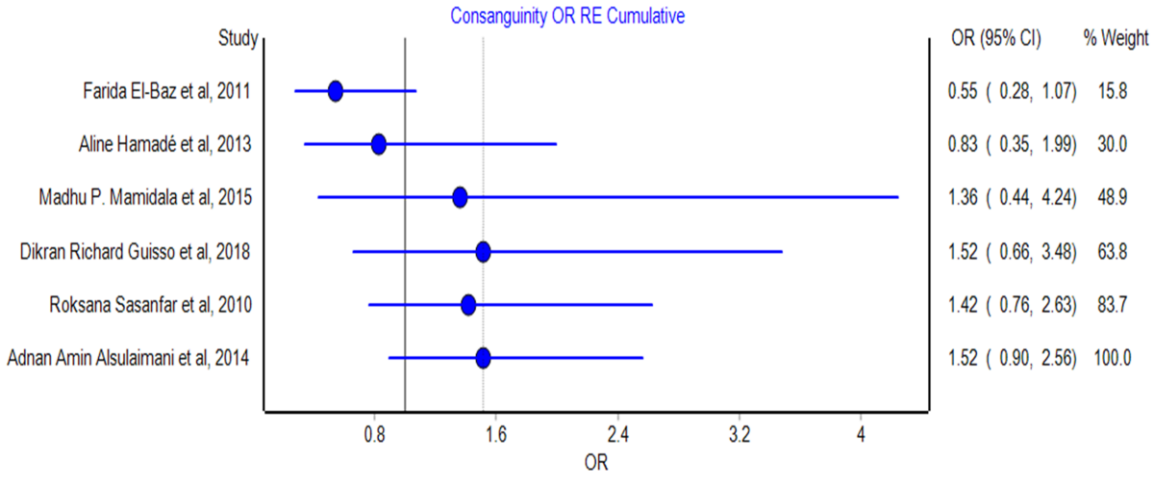


Figure 11. The overall pooled odd ratio of consanguinity among ASD patients and controls

Table 4

Prevalence of consanguinity among ASD individuals

Study Name	Sample size of ASD patients	Consanguinity among ASD patients	Pooled prevalence and 95% confidence interval of consanguinity among ASD patients
Farida El-Baz et al, 2011	100	13	13% (7.7%-21.1%)
Fouad Alshaban et al, 2017	171	16	9.4% (5.8%-14.7%)
Saleh M. Al-Salehi et al, 2009	49	14	28.6% (17.7%-42.6%)
Aline Hamadé et al, 2013	86	11	12.8% (7.2%-21.6%)
MuhammadMahajnah et al, 2015	200	18	9% (5.8%-14.7%).
Madhu P. Mamidala et al, 2015	500	100	20% (16.7%-23.7%),
A.M. Al-Ansari et al, 2012	100	29	29% (21%-38.6%)
Dikran Richard Guisso et al, 2018	136	19	14% (9.1%-20.9%)
Roksana Sasanfar et al, 2010	179	58	32.4% (26%-39.6%)
Adnan Amin Alsulaimani et al, 2014	60	33	55% (42.4%-67%)

3.2.5 Subgroub Analysis

We carried out a subgroub analysis based on study design (cross-sectional and case-control) and geographical location (GCC and Other countries) of the studies.

Table 5

Subgroup analysis of prevalence of consanguinity among ASD patients: study design

Study design	**No of studies (Patients)**	**Pooled prevalence of consanguinity among ASD patients**	**$I^{2\%}$**
Cross-sectional	3 (420)	23% (95% CI: 4%-50%)	96%
Case-control	7 (1161)	23.3% (95% CI: 15.8%-33%)	89%

The estimates were different, but the confidence interval was overlapping, this indicates that there was no statistically significant difference according to the study design used to address the consanguinity among the ASD patients.

Table 6

Subgroup analysis of prevalence of consanguinity among ASD patients: study country

Study country	No of studies (Patients)	Pooled prevalence of consanguinity among ASD patients	I2%
GCC countries	4 (380)	38% (95% CI: 28%-49%)	76%
Other countries	6 (1201)	16.2% (95% CI: 10.8%-23.5%)	87%

On the other hand, regarding consanguinity prevalence among ASD patients the estimate is higher among the GCC countries compared to other countries.

3.2.6 Publication Bias

Publication bias was detected by the funnel plot by plotting the logit of the consanguinity prevalence against the standard error (study size) among ASD patients, studies were scattered around the pooled estimate and the plot was symmetric with no gaps which indicate no evidence of publication bias. Nevertheless, conventional funnel plots that assess publication bias are imprecise for prevalence meta-analysis as proposed by Hunter et al. (2014). Therefore, provided an alternative which are funnel plot of study size against log odds which could be more accurate in studying prevalence studies. They however indicated that funnel plot overestimates the publication bias.

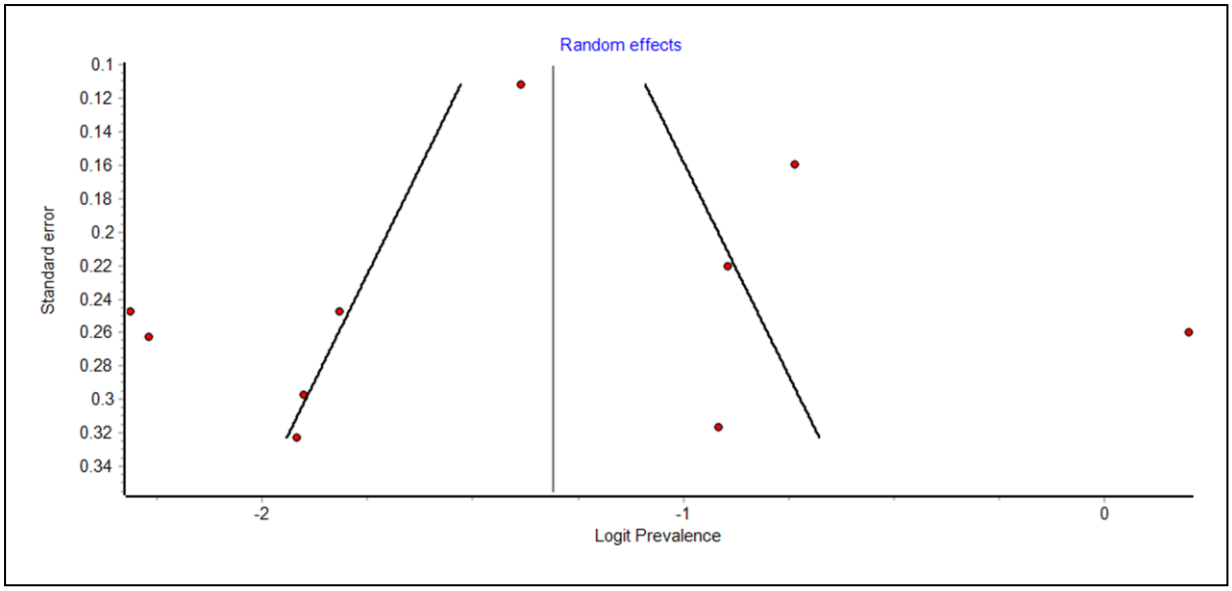


Figure 12. Funnel plot for consanguinity prevalence among all ASD patients

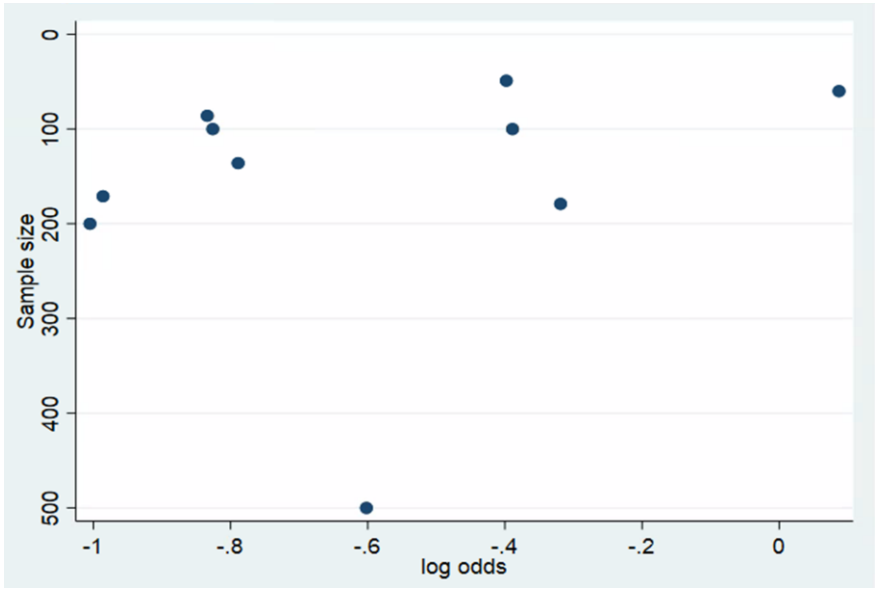


Figure 13. Hunter plot for consanguinity prevalence among all ASD patient

Chapter 4: Cross-sectional study

4.1 Methods

This is a cross-sectional study using secondary data from the Autism spectrum disorder in Qatar: Profiles and correlates of a large clinical sample short report data.

4.1.1 Study Population and data sources

Participation in the current study was based on participation in a previous research study titled "Autism spectrum disorder in Qatar: Profiles and correlates of a large clinical sample" (Alshaban et al., 2017). Recruiting of the participants took place between the years 2011 and 2015 at Shafallah Center for Individuals with Special Needs. The center was established in 1999 to provide services for both citizens and expatriates with disabilities, mainly ASD, between the ages of 3 and 18 years of age.

4.1.3 Data collection:

Data collection took place between the years 2011 and 2015 at Shafallah Center for Individuals with Special Needs through a comprehensive record review which contained diagnostic, medical, and developmental history. This enabled access to information regarding comorbid conditions, intellectual ability, family history of ASD and consanguinity, prenatal and postnatal history, and other relevant information.

4.1.4 Sample Size:

A total of 171 cases of ASD were identified from Shafallah Center for Individuals with Special Needs in Doha, Qatar.

4.1.5 Study variables

To achieve our aim in this study; the association of consanguinity with ASD comorbidities (epilepsy and ID) we included the variables mentioned below:

4.1.5.1 Outcome variables

- Intellectual Disability: mild, moderate and severe.
- Epilepsy: Yes, no.

4.1.5.2 Main exposure variable

- Consanguinity: Yes, no.

4.1.5.3 Other potential variables

- Socio-Demographic factors: age and gender, nationality number of proband and monthly income.
- Environmental and genetic risk factors: Method of labor, feeding practices and prenatal and postnatal factors (hypoxia, jaundice and head trauma).
- Syndromic ASD: Fragile X, Rett's syndrome and Tuberous sclerosis.

4.1.6 Data management and analysis plan:

Anonymous secondary data was properly cleaned and checked for range and consistency. Univariable, and multivariable analyses were conducted to estimate the prevalence of consanguinity and assess associations between consanguinity and both epilepsy and ID among ASD children. The multivariable analysis included consanguinity and both epilepsy and ID control of other potential confounding determinants. Descriptive analysis summarized all potential determinant and

consanguinity using proportions. Univariable and multivariable logistic regression models were used to model the likelihood of consanguinity association with both epilepsy and ID. Goodness of fit was done using H and L goodness of fit test, and the model was found to be fit (P-value >0.05).

Associations were quantified using unadjusted and adjusted Odds Ratios and their 95% confidence intervals. Purposive selection method was used to develop the best parsimonious multivariable logistic regression models. Also, clinically significant variables were included in both multivariable models.

4.1.8 Ethical considerations

De-identified and anonymous data used in this project were previously collected electronically and were stored in password protected in an accredited USB flash.

Data were primarily extracted by Dr. F. Alshaban from Shafallah center records. As for the procedure, it included acquisition of consent forms signed by patients voluntarily. Patients were given the complete right to withdraw at any moment without exception. Hence data were confidential, and privacy was maintained throughout the research process. Ethical approval was obtained from both Institutional Review Board of Hamad Medical Corporation and Qatar University.

4.2 Results

Participation in the current study was based on participation in a previous research study titled “Autism spectrum disorder in Qatar: Profiles and correlates of a large clinical sample” (Alshaban et al., 2017). Recruiting of the participants took place between the years 2011 and 2015 at Shafallah Center for Individuals with Special Needs.

4.2.1 Descriptive analysis

This study included a total of 171 cases. The mean age of the study population was 13.5 years (SD=5.9years) (Table 7). About 47% of the study population were Qatari nationals and majority were males (80%) translating into a male-to-female ratio 4:1. The largest age group was between 10 and 14 years of age (53%) while the smallest was between 0 and 4 years (2.3%). Seventy percent of the cases were outcome of normal vaginal delivery, 22% were delivered by caesarian section and 8% were delivered by assisted vaginal delivery. Hypoxia was reported in 13% of the cases and jaundice and head trauma were reported in 11% and 5% of the cases respectively. Results showed that 47.5% of families were in the highest income group (>20,000 QR per month), whereas 40.9% had a monthly income between 10,000–20,000 QR, and only 21.5% had a monthly income less than 10,000 QR. Consanguinity was reported by 40% of the cases families. However, ASD affected one sibling in 83% of the cases families, two siblings in only 9.9% of cases families and only 7.1% of families had more than two siblings affected. In terms of language,76.6% of the cases were nonverbal or delayed. Eighty three percent of the cases were in ID range with approximately half of the patients having moderate ID (48.5%) based on Stanford-Binet test (Gale, 2003). Epilepsy was found in 19% within this sample, while 8 cases had syndromic ASD (4.7%) (Table 7).

Table 7

Distribution of sociodemographic variables of the study population

Variables	Frequency	Percentage
Age Category		
0 – 4	4	2.3
5 – 9	44	25.7
10 – 14	53	30.9
15 – 19	49	28.6
>20	21	12.2
Gender		
Male	136	79.5
Female	35	20.5
Nationality		
Qatari	80	47.0
Non-Qatari	91	53.0
Consanguinity		
Consanguineous	69	40.3
Nonconsanguineous	102	59.7

Variables	Frequency	Percentage
Number of proband		
Single family(1proband)	142	83.0
Extended family (2 probands)	17	9.9
Extended family (>2 probands)	12	7.1
Monthly family income (QR)		
<10,000	37	21.5
10–20,000	70	40.9
<20,000	64	47.5
Method of labor		
Normal unassisted delivery	120	70.0
C-section	38	22.0
Forceps/or suction	10	6.0
Protracted/induced	3	2.0
Prenatal and postnatal factors		
Hypoxia		
Yes	23	13.5
No	148	86.5

Variables	Frequency	Percentage
Jaundice		
Yes	19	11.0
No	152	89.0
Head trauma		
Yes	8	4.7
No	163	95.3
Syndromic ASD and other comorbidities		
Fragile X		
Full mutation	3	1.8
Pre-mutation	2	1.2
Rett's syndrome		
MECP2 +ve	3	1.8
Tuberous sclerosis	1	0.5
None	162	94.7
Epilepsy		
Yes	32	18.7
No	139	81.3

Variables	Frequency	Percentage
Intellectual Disability (ID)		
Normal	29	17.0
Mild	37	21.6
Moderate	83	48.5
Sever	22	12.9
Communication (Language)		
Verbal	40	23.4
Nonverbal	82	48.0
Delayed	49	28.6

4.2.2 Descriptive analysis: Epilepsy

Table 8. presents the distribution of the potential risk factors among ASD cases with and without epilepsy. Thirty-two cases had a comorbid diagnosis of epilepsy; 18.7% of the total sample. 24 cases were in male (17.7%), 13 cases in Qatari (16.3%) and 27 cases in families with a single proband (19%). Regarding consanguinity, 16 out of the 32 epileptic patients were product of consanguineous marriage (23.2%). Moreover, around 21 cases were outcome of normal vaginal delivery (17.5%), 12 were nonverbal (14.6%). Most of the epileptic patients do not have history of prenatal and post-natal

risk factors (hypoxia, jaundice, head trauma: 26 cases (17.6%), 27 cases (17.8%) and 30 cases (18.4%) respectively).

Table 8

Characteristics of ASD patients with and without Epilepsy (N=171)

Characteristics	With Epilepsy (N=32)	Without Epilepsy (N=139)
Age categories		
0 - 4	1 (25.0)	3 (75.0)
5 - 9	5 (11.4)	39 (88.6)
10 - 14	10 (18.9)	43 (81.1)
15 - 19	10 (20.4)	39 (79.6)
>20	6 (28.6)	15 (71.4)
Gender		
Female	8 (22.9)	27 (77.1)
Male	24 (17.7)	112 (82.3)
Nationality		
Qatari	13 (16.3)	67 (83.7)
Non-Qatari	19 (20.9)	72 (79.1)

Characteristics	With Epilepsy (N=32)	Without Epilepsy (N=139)
Consanguinity		
Yes	16 (23.2)	53 (76.8)
No	16 (15.7)	86 (84.3)
No. of proband		
Single	27 (19.0)	115 (81.0)
Extended (2 proband)	4 (23.5)	13 (76.5)
Extended (>2 proband)	1 (8.3)	11 (91.7)
Monthly family income (QR)		
<10,000	6 (16.2)	31 (83.8)
10–20,000	15 (21.4)	55 (78.6)
>20,000	11 (17.2)	53 (82.8)
Mode of delivery		
NVD	21 (17.5)	99 (82.5)
C-Section	9 (23.7)	29 (76.3)
Forceps/Suction	2 (20.0)	8 (80.0)
Protracted/Induced	0	3 (100)

Characteristics	With Epilepsy (N=32)	Without Epilepsy (N=139)
Prenatal and postnatal factors		
Hypoxia		
Yes	6 (26.0)	17 (74.0)
No	26 (17.6)	122 (82.4)
Head trauma		
Yes	2 (25.0)	6 (75.0)
No	30(18.4)	133 (81.6)
Neonatal jaundice		
Yes	5 (26.3)	14 (73.7)
No	27 (17.8)	125 (82.2)
Language		
Verbal	10 (25.0)	30 (75.0)
Delayed	10 (20.4)	39 (79.6)
Non-verbal	12 (14.6)	70 (85.4)

4.2.3 Univariable analysis: Epilepsy

Univariable logistic regression analysis was done to select potential candidate variables for the multivariable logistic regression analysis. Based on the pre-set p-value criteria cut off point ≤0.25, age, gender, nationality, number of the family probands, monthly income, mode of delivery, feeding practice, language and the postnatal and prenatal factors not significant and therefore were not included in the adjusted model.

The univariable logistic regression showed that only consanguinity was significantly associated with epilepsy (P-value=0.220) (Table 9). Although not significant in the univariable model, age, gender, prenatal and postnatal factors (hypoxia and neonatal jaundice) were included in the adjusted model based on clinical significance. Despite that history of head trauma is considered an important risk factor for epilepsy, this variable was not included in the adjusted model as only 6% of epileptic patient experienced it.

Table 9

Crude Association between Epilepsy and potential risk factors (Univariable logistic regression analysis)

Variable	OR	95% CI	P value
Age categories			0.53
0 - 4	0.80	0.071 – 9.68	0.88
5 - 9	0.30	0.08 – 1.20	0.09
10 - 14	0.60	0.18 – 1.87	0.36
15 – 19	0.60	0.19 – 2.07	0.46
>20	Ref		
Gender			
Male	0.70	0.29 – 1.78	0.48
Female	Ref		
Nationality			
Qatari	0.70	0.34 – 1.60	0.44
Non-Qatari	Ref		

Variable	Variable	Variable	Variable	Variable
Consanguinity				
Yes	1.60	0.74 – 3.51		0.22
No	Ref			
No. of family proband				0.52
Single	2.60	0.32 – 20.87		0.37
Extended (2 proband)	3.40	0.33 – 34.91		0.30
Extended (>2 proband)	Ref			
Monthly income (QR)				0.74
10.000 – 20.000	1.40	0.49 – 4.00		0.52
>20.000	1.10	0.36 – 3.18		0.90
<10.000	Ref			
Mode of delivery				0.71
C-Section	1.50	0.60 – 3.54		0.40
Forceps/Suction	1.20	0.23 – 5.95		0.84
Protracted/Induced	1	empty		0.37
NVD	Ref			

Variable	Variable	Variable	Variable	Variable
Language				
Delayed	0.77	0.28 – 2.08		0.61
Non-verbal	0.51	0.20 – 1.31		0.17
Verbal	Ref			
Neonatal jaundice				
Yes	1.70	0.55 – 4.98		0.37
No	Ref			
Hypoxia				
Yes	1.70	0.59 – 4.60		0.33
No	Ref			
Head Trauma				
Yes	1.50	0.28 – 7.68		0.642
No	Ref			

4.2.4 Multivariable analysis: Epilepsy

In the final adjusted multivariable logistics regression model, none of the variables were statistically significant associated with epilepsy (Table 10). The odds of having epilepsy increased by 90% among those whose parents were consanguineous (OR = 1.90; 95% CI: 0.83 –4.23). History of hypoxia was associated with 50% higher odds of having epilepsy (OR = 1.50; 95% CI: 0.54 –4.40). Also, history of neonatal jaundice was associated with 70% higher odds of having epilepsy (OR = 1.70; 95% CI: 0.54 –5.54). However male gender showed to decrease the odds having epilepsy by 30% (OR 0.70; 95% CI: 0.25-1.73). Cases aged 5-9 years old have the lowest odds of having epilepsy (OR= 0.20; 95% CI: 0.06-0.98) compared to the others age categories, which was statistically significant. All other variables were not statistically significant, so will report the univariable analysis.

For confounding assessment, we entered variables that were not included in the full model separately (nationality, number of family proband, monthly income, mode of delivery and language). the coefficients of these variables did not change by 15-20%, indicating that these variables did not confound the relationship between consanguinity and epilepsy. Hosmer and Lemeshow showed that model fit well (P value > 0.05).

Table 10

Adjusted association between Epilepsy and potential risk factors (Multivariate logistic regression analysis)

Variable	OR	95% CI	P value
Age categories			
0 - 4	0.60	0.05 – 7.89	0.71
5 - 9	0.20	0.06 – 0.98	0.05
10 - 14	0.60	0.17 – 1.90	0.36
15 – 19	0.60	0.18– 2.01	0.41
>20	Ref		
Gender			
Male	0.70	0.25 – 1.73	0.40
Female	Ref		
Consanguinity			
Yes	1.90	0.83 – 4.23	0.13
No	Ref		

Variable	OR	95% CI	P value
Neonatal jaundice			
Yes	1.70	0.54 – 5.54	0.35
No	Ref		
Hypoxia			
Yes	1.50	0.54 – 4.40	0.42
No	Ref		

4.2.5 Descriptive analysis: Intellectual Disability

Table 11. presents the distribution of potential risk factors among autistic patients who had ID. These cases constitute 83% of our sample (n=142). 110 cases with ID were male (80.9%), 65 cases were Qatari (81.3%). 3 cases aged (0-4) (75%), 34 cases aged (5-9) (77.3%), 49 cases aged (10-14) (92.5%), 40 cases aged (15-19) (81.6%) and 16 cases aged > 20 years (76.2%). 117 cases were from families with single family proband (82.4%). In regard to consanguinity, 60 cases had consanguineous parents (87%). Furthermore, 98 of the cases were vaginally delivered (81.7%), 72 cases were nonverbal (87.8%). Most of the ID patients do not have history of prenatal and post-natal risk factors (hypoxia, jaundice, head trauma: 121 cases (81.8%), 125 cases (82.2%) and 135 cases (82.8%) respectively). Hosmer and Lemeshow showed that model fit well (P value > 0.05).

Table 11

Characteristics of ASD patients with and without Intellectual disability (ID) (N=171)

Characteristic	With ID (N=142)	Without ID (N=29)
Age categories		
0 - 4	3 (75.0)	1 (25.0)
5 - 9	34 (77.3)	10 (22.7)
10 - 14	49 (92.5)	4 (7.5)
15 – 19	40 (81.6)	9 (18.4)
>20	16 (76.2)	5 (23.5)
Gender		
Female	32 (91.4)	3 (8.6)
Male	110 (80.9)	26 (19.1)
Nationality		
Qatari	65 (81.3)	15 (18.7)
Non-Qatari	77 (84.6)	14 (15.4)
Consanguinity		
Yes	60 (87.0)	9 (13.0)
No	82 (80.4)	20 (19.6)

Characteristic	With ID (N=142)	Without ID (N=29)
No. of family proband		
Single	117 (82.4)	25 (17.6)
Extended (2 proband)	14 (82.4)	3 (17.6)
Extended (>2 proband)	11 (91.7)	1 (8.3)
Monthly Income		
<10.000	32 (86.5)	5 (13.5)
10.000-20.000	55 (78.6)	15 (21.4)
>20.000	55 (85.9)	9 (14.1)
Mode of delivery		
NVD	98 (81.7)	22 (18.3)
C-Section	31 (81.6)	7 (18.4)
Forceps/Suction	10 (100)	0
Protracted/Induced	3 (100)	0
Hypoxia		
Yes	21(91.3)	2 (8.7)
No	121(81.8)	27(18.2)

Characteristic	With ID (N=142)	Without ID (N=29)
Head Trauma		
Yes	7 (87.5)	1 (12.5)
No	135 (82.8)	28 (17.2)
Neonatal jaundice		
Yes	17(89.5)	2 (10.5)
No	125(82.2)	27 (17.8)
Language		
Verbal	32 (80.0)	8 (20.0)
Delayed	38 (77.6)	11(22.4)
Non-verbal	72 (87.8)	10 (12.2)

4.2.6 Univariable analysis: Intellectual Disability

Data was analyzed using univariable logistic regression analysis to select potential candidate variables to include in the multivariable logistic regression analysis. Based on the pre-set p-value criteria cut off point ≤0.25, age, nationality, number of the family probands, monthly income, mode of delivery, feeding practice, language and the postnatal and prenatal factors don't enter the adjusted model. The univariable

logistic regression showed that gender was significantly associated with ID (p-value= 0.150) (Table 12).

Consanguinity was entered in the model because it is our main exposure.

Additionally, based on clinical significance we included neonatal jaundice, although it was not significant in the univariable model. Despite that history of head trauma is a known risk factor for ID, we did not include it in the adjusted model because less than 5% of ID patient had it. Hosmer and Lemeshow showed that model fit well (P value > 0.05).

Table 12

Crude association between ID and potential risk factors (Univariable logistic regression analysis)

Variable	OR	95% CI	P value
Age categories			
0 - 4	0.93	0.08 – 11.14	0.96
5 - 9	1.10	0.31 – 3.62	0.92
10 - 14	3.80	0.92 – 16.01	0.07
15 – 19	1.40	0.40 – 4.78	0.60
>20	Ref		

Variable	OR	95% CI	P value
Gender			
Male	0.40	0.11 – 1.39	0.15
Female	Ref		
Nationality			
Qatari	0.79	0.35 – 1.78	0.56
Non-Qatari	Ref		
Consanguinity			
Yes	1.60	0.69 – 3.82	0.26
No	Ref		
No. of family proband			
Single	0.40	0.04 – 4.66	0.48
Extended (2 proband)	0.40	0.05 – 3.44	0.42
Extended (>2 proband)	Ref		
Monthly income (QR)			
<10.000	Ref		
10.000 – 20.000	0.60	0.19 – 1.72	0.32
>20.000	0.90	0.29 – 3.09	0.94

Variable	OR	95% CI	P value
Mode of delivery			
C-Section	0.90	0.39 – 2.54	0.99
Forceps/Suction	1		
Protracted/Induced	1		
NVD	Ref		
Language			
Delayed	0.80	0.31 – 2.40	0.26
Non-verbal	1.80	0.65 – 4.98	0.78
Verbal	Ref		
Neonatal jaundice			
Yes	1.80	0.40 – 8.42	0.43
No	Ref		
Hypoxia			
Yes	2.30	0.52 – 10.59	0.27
No	Ref		

Variable	OR	95% CI	P value
Head Trauma			
Yes	1.50	0.17 – 12.30	0.73
No	Ref		

4.2.7 Multivariable analysis: Intellectual Disability

In the multivariable logistics regression model (adjusted model) none of the variables were statistically significantly associated with ID (Table 13). The odds of having ID increased by 50% among those whose parents were consanguineous (OR = 1.5; 95% CI: 0.62 – 3.52). History of neonatal jaundice was associated with 2 times odds of having ID (OR = 2; 95% CI: 0.43 –9.30). However male gender showed to decrease the odds having ID by 61% (OR 0.39; 95% CI: 0.11-1.40). As none of the variables were statistically significantly, we will report the univariable analysis.

For confounding assessment, we enter the variables that we removed from the full model separately (gender, nationality, number of family proband, monthly income, mode of delivery and language and hypoxia) we found that the coefficient did not change by 15-20%, so we conclude that they were not confounders. Hosmer and Lemeshow showed that model fit well (P value > 0.05).

Table 13

Adjusted association between ID and potential risk factors (multivariable logistic regression analysis)

Variable	OR	95% CI	P value
Gender			
Male	0.39	0.11-1.40	0.15
Female	Ref		
Consanguinity			
Yes	1.50	0.62-3.52	0.37
No	Ref		
Neonatal jaundice			
Yes	2.0	0.43 – 9.30	0.37
No	Ref		

Chapter 5: Discussion

5.1 The Meta-analysis

To our knowledge, this is the first meta-analysis that studied the prevalence of consanguinity worldwide. Consanguinity has been reported to have severe effects on fetal growth and development, increasing the risk of congenital malformations (Kulkarni & Kurian, 1990). In addition, children born to consanguineous parents have been reported to have lower social behavior (Md Afzal & Sinha, 1983) and cognitive ability (Mohammad Afzal, 1988), which are the main problems with ASD children. Our study qualitatively reviewed the prevalence of consanguinity among ASD patients throughout the world and 10 eligible studies from eight countries were identified. We quantitatively synthesized the results and the key findings of this study showed a 24% overall pooled estimate of consanguinity among ASD patients. GCC countries showed a high estimated pooled prevalence of consanguinity among ASD patients as 38% compared to countries other than GCC 16%, which was higher than our overall pooled prevalence. This high estimate among GCC countries can be related to the high rates of consanguineous marriage in the GCC countries compared to the worldwide rates (20%) (Tadmouri et al., 2009). In Qatar the rate of consanguineous marriage reported as 54% (Bener & Hussain, 2006), while it was 50.5% in United Arabs Emirates (al-Gazali et al., 1997), 56.3% in Oman and 39-45 % in Bahrain (Tadmouri et al., 2009). This high rates may be due to factors like rooted cultural beliefs, social life and customs in addition to, economic benefits of keeping wealth within the families, as reported by (Bener & Hussain, 2006).

The overall odd ratio calculated from the case-control studies included in our meta-analysis was 1.5 indicating a 50% increase in odds of having ASD among those

whose parents are related. We calculated the odd ratio from Adnan et al, 2014 which was the only study from the GCC to report the consanguinity prevalence among ASD cases and controls. The estimated odd ratio was 2.6 which was the highest odd ratio after that reported by Madhu P. Mamidala et al, 2015 (3.2).

5.2 Cross-sectional study

Consanguinity is high in the GCC and Middle East communities. In Qatar, the overall prevalence of consanguineous marriages is 55%. Al - Salehi and colleagues found in a Saudi Arabia study that nearly one - third of a cohort of children with autism had a history of consanguinity among their parents. Another study in Saudi Arabia reported that 55% of their subjects were outcome of consanguineous marriage. In India, Madhu P. Mamidala et al, 2015 demonstrate consanguinity prevalence as 20% of their ASD cases. Consanguinity among our sample was reported by 40% of the ASD cases families. Despite that this high prevalence did not provide proof of a direct relation between consanguinity and autism in Qatar. The high prevalence of consanguinity in Qatar, in addition to the rate of family history of autistic disorder among siblings supports the role of genetic factors in certain Qatari families, which other studies have suggested.

Male predominance (79.5%) among subjects was observed. Similar to other research findings; gender ratios showing higher male predominance over female is the most constant joint finding in autism spectrum conditions studies (approximately 4:1). This could be due to genetic gender differences or based on the characteristics of male behavior; the criteria used to diagnose autism.

Earlier studies showed a higher risk of having autistic siblings for children with autism. Ozonoff et al., 2011, reported family rates of more than one person with ASD ranging from 3% to 18%. In our cohort, 17% of the families have 2 probands and 12% have more than two. Similar findings were reported by Farida El-Baz et al, 2011 with 16% of their cohort have a family history of autism.

Autistic children range from 0 to 60 in the IQ spectrum. In our cohort, 83% of the patients were in ID range with approximately half of the patients (48.5%) had moderate ID (IQ 36-51). This high percentage of ID among this cohort may be due to that most high-performance ASD cases in Qatar attend mainstream schools. About 48% of families were in the highest income group (>20,000 QR per month), which was similar to that reported by Farida El-Baz et al, 2011 (48%). Regarding language development, most of the cases were nonverbal (48%), 28.6 % were delayed and 23.4% were verbal.

Epilepsy has been reported to be one of the negative cognitive, adaptive and behavioral factors for people with autism. The rate of epilepsy among ASD cases reported in most developed - country autism studies was 30-40% (Muhle, Trentacoste & Rapin, 2004). Bolton et al, 2011 studied epilepsy's features and correlates in 150 ASD individuals. 22% of participants developed epilepsy. Gender (female), intellectual disability and poorer verbal abilities were associated with epilepsy. Although the occurrence of epilepsy in probands in their families was not associated with a high risk of epilepsy, it was linked with the occurrence of the broader phenotype of autism in relatives. This proposes that family liability for autism was linked to the risk of epilepsy Our results showed a rate of epilepsy of 19%, which was close to that reported by in Saudi Arabia (22.4%).

No other studies looked at association between consanguinity and both epilepsy and ID Despite that, the univariable logistic regression analysis revealed that the odd ratio of having epilepsy and ID increased by consanguinity (OR 1.6 both), the association between epilepsy and ID among ASD patients and consanguinity was not statistically significant (P value >0.05) controlling for other potential risk factors. This may be due to the small number of subjects enrolled in this study and the fact that all the study subjects were recruited from one special needs center. These high odd ratios of having epilepsy and ID among consanguineous ASD patients might have a clinical significance, thus further research with large and more representative sample is needed to investigate this association.

5.3 Limitation:

5.3.1 Meta-analysis

Our study has some limitations, there was no enough reported studies worldwide we only found 10 studies on consanguinity prevalence among the ASD children from eight countries from Middle East and Asia regions. There were no studies reporting consanguinity prevalence among ASD individuals from other world regions as consanguineous marriages in these regions is very low as cited by Bittles AH, Black ML. Moreover, despite higher prevalence of consanguinity in the GCC countries only 4 studies reported the consanguinity prevalence among the ASD. Despite that male predominance in ASD was stated by many studies, we couldn't assess the relation between consanguinity and gender as consanguinity prevalence reported in the included studies as the overall prevalence and was not reported by gender.

After assessing the quality of the studies most of the studies have low to moderate risk of bias, but with higher risk to the external validity because 50% of studies rated

poorly for having a random assignment of the sample population. There was considerable significant heterogeneity among the articles, it present major threat to the pooled estimate as indicated by large confidence interval in our estimates. However, this is the first study that attempt to pool the prevalence of consanguinity among ASD individuals worldwide and this study should be updated after more and high-quality studies are published.

5.3.2 Cross sectional

Some limitations of this study were the lack of comparable data and unavailability of some data such as rates of obstetric complications. The small sample size included in this study as well as the nationality distribution in our study indicated that almost half of them are Qatari which is not reflective of the estimated 2.6 million live in Qatar. This is expected as more Qataris get enrolled to these schools.

Additionally, the nature of the study as analysis of cross-sectional data Ideally, we cannot guarantee the data to be representative.

Furthermore, the models that were developed were multivariable logistic regression purposive selection favoring clinical consideration, but we stop at the preliminary main effect model due to all the predictors were statistically insignificant. Finally, residual confounding is possible due to unmeasured variables.

5.4 Recommendations

More and highly quality epidemiological studies worldwide especially at the GCC countries are required to estimate the prevalence of consanguinity among ASD individuals and identify the high prevalence countries. These studies should pay attention to external validity because most of them rarely randomized their samples. Larger randomly selected patients would give rise to much more precise and accurate estimates that will reflect in smaller confidence intervals in the meta analytical estimates.

Regarding the association between consanguinity with epilepsy and intellectual disability among ASD individuals, additional studies with more sample size, variability and representativeness are necessary to confirm our results.

Conclusion

To our knowledge, this is the first meta-analysis that studied the prevalence of consanguinity worldwide. The globally estimated pooled consanguinity prevalence among ASD patients was 24%, GCC countries showed a higher pooled prevalence (38%). No studies looked at association between consanguinity and both epilepsy and ID. The clinical sample used did not provide any evidence on association between both epilepsy and ID and consanguinity among ASD patients in Qatar. These high odd ratios of having epilepsy and ID among consanguineous ASD patients might have a clinical significance, thus further research with large and more representative sample is needed to investigate this association.

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Appendix

Stata do file commands

```
*****Thesis Data Do file*****

**Descriptive Analysis**

describe

tabstat age , statistics( mean sd count )

//Epilepsy (outcome 1)

tab epi

tabstat age, statistics( mean sd count ) by( epi )

tab age epi ,chi2 row

tab gender epi ,chi2 row

tab fpro epi ,chi2 row

tab nation epi ,chi2 row

tab mi epi ,chi2 row

tab consang epi ,chi2 row

tab mod epi ,chi2 row

tab lang epi ,chi2 row

tab nj epi ,chi2 row

tab hypoxia epi ,chi2 row
```

```
tab htr epi ,chi2 row

*************************************************************************
*

 *//Univariate Analysis

logit epilepsy i.age ,nolog or

logit epilepsy i.sex ,nolog or

logit epilepsy i.nationality ,nolog or

logit epilepsy i.familyprobands ,nolog or

logit epilepsy i.monthlyincome ,nolog or

logit epilepsy i.consanguinty ,nolog or // include 0.220

logit epilepsy i.modeofdelivery ,nolog or

logit epilepsy i.verbal ,nolog or

test 1.verbal 2.verbal

logit epilepsy i.hypoxia ,nolog or

logit epilepsy i.headtrauma ,nolog or

logit epilepsy i.neonataljaundice ,nolog or


*************************************************************************
*

//Multi variable analysis for the epilepsy
```

```
logit epilepsy i.age i.sex i.consanguinty i.hypoxia i.neonataljaundice,nolog or

//Based on the sig 0.25 only consaguinity enter the model,and based on clinical

//sig we enter age, gender,and abnormal perinatal history(jaundice and hypoxia)


**********************************************************************
*

 // Descriptive Analysis (intellectual disability)

tab id

recode id 2=1 3=1

tab age id ,chi2 row

tab sex id ,chi2 row

tab nationality id ,chi2 row

tab familyprobands id ,chi2 row

tab monthlyincome id ,chi2 row

tab consanguinty id ,chi2 row

tab modeofdelivery id ,chi2 row

tab verbal id ,chi2 row

tab hypoxia id ,chi2 row

tab neonataljaundice id ,chi2 row
```

```
tab headtrauma id ,chi2 row

**********************************************************************

*//Univariate Analysis

logit id i.age ,nolog or

logit id i.sex ,nolog or // Pvalue=0.150

logit id i.nationality ,nolog or

logit id i.consanguinty ,nolog or

logit id i.familyprobands ,nolog or

logit id i.monthlyincome ,nolog or

logit id i.modeofdelivery ,nolog or

logit id i.verbal ,nolog or

logit id i.neonataljaundice ,nolog or

logit id i.hypoxia ,nolog or

**********************************************************************

*

//Multi variablr model of the ID

//Based on p value 2 var enter the full model (sex, consanguinity)

//based on clinical sig 2 var enter the model(neonatal jaundice)

logit id i.sex i.consanguinty i.neonataljaundice,nolog or
```

Ethical approvals

جامعة قطر
QATAR UNIVERSITY

Qatar University Institutional Review Board
QU-IRB

January 16, 2019

Dr. Manar Elhassan
Graduate Student Supervisor
College of Health Sciences
Qatar University
Tel.: 4403-7506
Email: melhassan@qu.edu.qa

Dear Dr. Manar Elhassan,

Sub.: **Research Ethics Review Exemption / CHS Graduate Student Project**
Ref.: **Student, Saba F.E. Elhag / Email:** se1700065@student.qu.edu.qa
Project Title, "Consanguinity among Autistic children: Prevalence and Associations with Intellectual Disability and Epilepsy: A Meta-analysis and Cross-sectional Study"

We would like to inform you that your application along with the supporting documents provided for the above student project, is reviewed and having met all the requirements, has been exempted from the full ethics review.

Please note that the exempt projects do not require renewals however, any changes/modification or additions to the original submitted documents during the work and until the completion of the project, should be reported to the committee to seek approval prior to continuation. Also, kindly submit a closure report to the QU-IRB upon completion of the project.

Your Research Ethics Approval No. is: **QU-IRB 1016-E/19**
Kindly refer to this number in all your future correspondence pertaining to this project.

Best wishes,

Dr. Mashael Al-Shafai
Chairperson, QU-IRB

جامعة قطر
Institutional Review Board
(IRB)
Office Of Academic Research

مؤسسة حمد الطبية
Hamad Medical Corporation
HEALTH · EDUCATION · RESEARCH صحة · تعليم · بحوث
مركز البحوث الطبية
Medical Research Center

Hamad Medical Corporation

Institutional Review Board

Email: irb@hamad.qa Tel: 00974-44390614
HMC-IRB Registration: SCH-HMC-020-2015
IRB-MoPH Assurance: MOPH-A-HMC-020

Continuing Review Approval Notice:

Protocol Title: Prevalence of Autism Spectrum Disorder in Qatar
Study Number: 13266/13
JIRB Number: 14-00139
QNRF Number: NPRP 6-093-3-024
HMC Principal Investigator: Lobna Hassan Mohd. Osman Dekair
Date of Letter Issued: 26 October 2017
Review Type: Expedited
Decision: Approved for Renewal
Approved HMC Enrollment: 500 (Prospective) + Existing Data (2013 -2017)

The IRB has reviewed the submitted documents of the above titled research and approval to continue the study has been granted. The list of approved document(s) is attached.

IRB oversight expires 12 months from the date of the current expiry date – as indicated in the stamp at the bottom of the approved documents.

It is the responsibility of the Investigator to ensure timely renewal of study oversight. Progress reports for continuing review must be approved prior to expiration date; therefore submissions must be received by the IRB 60 to 90 days prior to the expiration date.

Requested Resolutions: **None**

Any resolutions submitted must include a letter indicating that the submission is a follow up request by the IRB; this will ensure that resolutions are processed appropriately and in a timely manner.

Please note; this approval only covers HMC, you may also need approvals from other institutions involved in your study. You should not continue your study until all of these have been obtained

If you have any questions or need additional information, Please contact IRB at the above mentioned email address or telephone number.

As part of PI's responsibilities, all research activities must be recorded in Cerner's medical records per visit for each subject involved in the study.

Important Note: The list of your responsibilities as Principal Investigator is attached to this letter.

Sincerely,

Dr. Mohammed Hammoudeh
Sr. Consultant, Rheumatology
Medicine - HMC
001545

Dr. Mohammed Hammoudeh
Chairman Institutional Review Board
Hamad Medical Corporation

Cc: MRC Project File
NPRP Grant Holder: Mohammad Al Dosari, Shafallah Center – Qatar

HMC-IRB, 13266/13, 26Oct17

مؤسسة حمد الطبية
Hamad Medical Corporation
HEALTH · EDUCATION · RESEARCH صحة · تعليم · بحوث
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List of Approved Documents:

1) 13266_Assent_Eng-Ara_16Oct16_02Pages
2) 13266_DataCollectionForm_Eng_02Pages
3) 13266_IdeateApplication_Eng_28Sept14_28Pages
4) 13266_InformedConsent_Eng-Ara_16Oct16_06Pages
5) 13266_ProgressReport_Eng_15Oct17_06Pages
6) 13266_Protocol_Eng_29Aug17_17Pages
7) 13266_QNRFApplication_Eng_RevisedV.Jul11_12Pages
8) 13266_SCQ_Ara_Coyright©2003_byWesternPsychologicalServices_02Pages
9) 13266_SCQ_Eng_Coyright©2003_byWesternPsychologicalServices_02Pages
10) 13266_SignedDelegationLog_Eng_02Pages