Autism Spectrum Disorders in Tanzania: Awareness, Diagnosis, Risk Factors and Endophenotypes

by

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Abstract

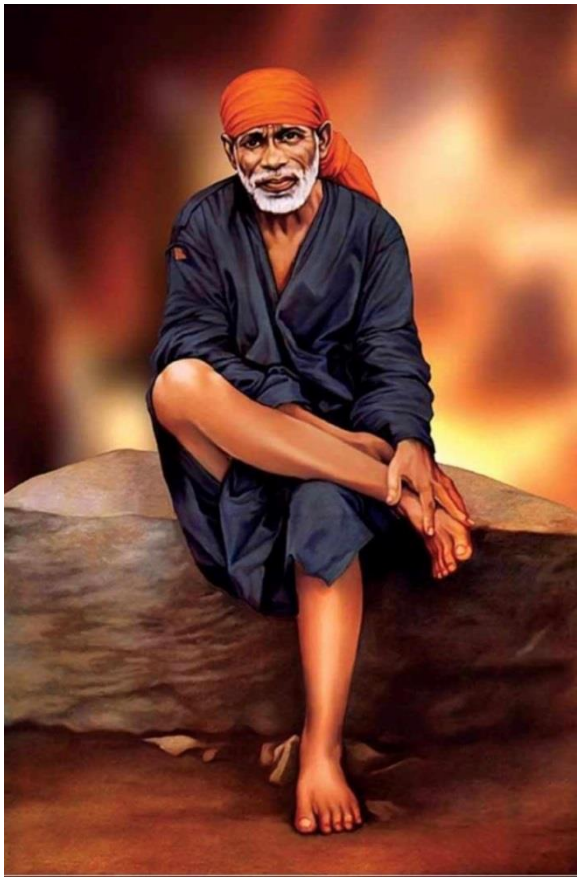
Autism Spectrum Disorder (ASD) is common worldwide, but little is known of the condition in sub-Saharan Africa (SSA). I set out to study the lived experiences, identification, risk factors and phenotypic expressions of ASD in Dar-es-Salaam, Tanzania.

I conducted a systematic review of the Broader Autism Phenotype (BAP) in biological parents of ASD probands. I conducted a qualitative study using 7 focus group discussions and 13 in-depth interviews to investigate the knowledge and lived experiences of 14 caregivers of children with ASD and 37 key community informants. I screened 284 children (108 had ASD, 60 had other neurodevelopmental disorders (NDD) and 116 were typically developing (TD)), and used these groups of children to validate the Social Communication Questionnaire (SCQ), and for determining risk factors for ASD. Psychometric properties were examined, and risk factors determined in multivariable models. I further assessed BAP traits of 267 parents (of 103 children with ASD, 57 children with NDD and 107 TD children) exploring the psychometric properties of the Autism Spectrum Quotient (AQ).

The systematic review identified social/communication deficits, rigid/aloof personality traits, and pragmatic language difficulties as useful socio-behavioural endophenotype traits. The qualitative study identified consistent emerging sub-themes: knowledge/awareness in the identification/presentation of ASD, its' perceived causes, and the challenges experienced by caregivers and community stakeholders. The Kiswahili SCQ showed between acceptable and excellent reliability (Cronbach's (α)=0.65-0.92) and supports a 2-factor model of combined social interaction and communication, and repetitive behaviours, recommended by DSM-5 criteria. Early-life malaria was associated with the greatest independent risk for ASD, being more common among the ASD (31%) than TD group (4%). The Kiswahili AQ had acceptable reliability (Cronbach's α=0.84) for all items. The BAP in parents of children with ASD (53%) was higher than for those with NDD (21%) or TD (16%), suggesting BAP are particularly characteristic of ASD.

Om Shri Sai Nathay Namah

Om Sai Namo Namah, Shri Sai Namo Namah, Jay Jay Sai Namo Namah, Satguru Sai Namo Namah



Dedicated with Humble Pranams at the Divine Lotus Feet of my Dear Guru Sri Shirdi Sai Baba

May Sai and Lord Ganesha lead these army of words

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Table of Contents

List of Publications

Ruparelia, K., Abubakar, A., Badoe, E., Bakare, M., Visser, K., Chugani, D. C., ... & Newton, C. R. (2016). Autism Spectrum Disorders in Africa: Current challenges in identification, assessment, and treatment: A report on the International Child Neurology Association Meeting on ASD in Africa, Ghana, April 3-5, 2014. *Journal of Child Neurology*, *31*(8), 1018–1026. https://doi.org/10.1177/0883073816635748

Ruparelia, K., Manji, K., Abubakar, A., & Newton, C. R. (2017). Investigating the evidence of behavioral, cognitive, and psychiatric endophenotypes in autism: a systematic review. *Autism Research and Treatment, 2017*. https://doi.org/10.1155/2017/6346912

Abubakar, A., **Ruparelia, K**., Gona, J. K., Rimba, K., Mapenzi, R., de Vries, P. J., … & Newton, C. R. (In Press). Potential challenges of importing Autism Spectrum Disorder screening and diagnostic tools from high-income countries to resource-poor settings. In Chawarska & Volkmar (Eds.), *Autism Spectrum Disorders in the first years of life*. New York: Guildford.

List of Tables

List of Figures

Abbreviations

3Di: Developmental, Dimensional and Diagnostic Interview

ABC: Autism Behaviour Checklist

ACT: Auditory Consonant Trigram

ADHD: Attention Deficit Hyperactive Disorder

ADI-R: Autism Diagnostic Interview - Revised

ADOS: Autism Diagnostic Observation Schedule

ADOS-2: Autism Diagnostic Observation Schedule - 2nd Edition

ARC: Autism Research Centre

AS: Asperger Syndrome

ASD: Autism Spectrum Disorder

AQ: Autism Spectrum Quotient

AUC: Area Under the Curve

BAPQ: Broader Autism Phenotype Questionnaire

BDI: Beck Depression Inventory

BPASS: Broader Phenotype Autism Symptom Scale

BPRS: Brief Psychiatric Rating Scale

BVAQ-B: Bermond-Vorst Alexithymia Questionnaire - B

CARS-2: Childhood Autism Rating Scale - 2nd Edition

CCA: Communication Checklist - Adult

CESD: Centre for Epidemiological Studies - Depression Scales

CFA: Confirmatory Factor Analysis

CI: Confidence Interval

CFI: Comparative Fit Index

COSTECH: Tanzania Commission for Science and Technology

CPM: Coloured Progressive Matrices

CTOPP: Comprehensive Test of Phonological Processing

DISCO: Diagnostic Interview for Social and Communication Disorders

DK-EFS: Delis Kaplan Executive Function System

DSM-III: Diagnostic and Statistical Manual for Mental Disorders - 3rd Edition

DSM-IV: Diagnostic and Statistical Manual for Mental Disorders - 4th Edition

DSM-5: Diagnostic and Statistical Manual for Mental Disorders - 5th Edition

EEG: Electroencephalogram/Electroencephalography

EFT: Embedded Figures Test

ELRCD: Early Language Related Cognitive Difficulties

ERT: Edinburgh Reading Test

ES: Effect Size

EQ: Empathy Quotient

ER40: Penn Emotion Recognition Test

EVT: Expressive Vocabulary Test

FAQ: French Autism Spectrum Quotient

FGD: Focus Group Discussion

FHI: Family History Interview

FHS: Family History Schedule

FI: Friendship Interview

FSIQ: Full Scale IQ

GFI: Goodness of Fit Index

GORT: Gray Oral Reading Test

HFA: High Functioning Autism

HIC: High-income Countries

ICC: Intraclass Correlation Coefficient

ID: Intellectual Disability

IDED: Intradimensional / Extradimensional Set-Shifting

IDI: In-Depth Interviews

IQ: Intelligence Quotient

IQR: Interquartile Range

KDEF: Karolinska Directed Emotional Faces

KEMRI: Kenya Medical Research Institute

KWTRP: KEMRI-Wellcome Trust Research Programme

LAMIC: Low and Middle Income Countries

LRT: Likelihood Ratio Tests

MAP: Medium Autism Phenotype

M-CHAT: Modified Checklist for Autism in Toddlers

MNH: Muhimbili National Hospital

MPAS: Modified Personality Assessment Schedule

MPAS-R: Modified Personality Assessment Schedule - Revised

MPX: Multiple Incidence Autism Families

MUHAS: Muhimbili University of Health and Allied Sciences

NAP: Narrow Autism Phenotype

NAPA-T: National Association for People with Autism - Tanzania

NART: National Adult Reading Test

NDD: Neurodevelopmental Disorders

NEO-PI: NEO Personality Inventory

NEPSY: A Developmental Neuropsychological Assessment

NIMR: National Institute for Medical Research

NVIQ: Nonverbal IQ

OR: Odds Ratio

PAS: Physical Anhedonia Scale

PCA: Principal Component Analysis

PDD: Pervasive Developmental Disorders

PDD-NOS: Pervasive Developmental Disorders - Not Otherwise Specified

PIQ: Performance IQ

PPVT: Peabody Picture Vocabulary Test

PPVT-III: Peabody Picture Vocabulary Test - 3rd Edition

PRS: Pragmatic Rating Scale

PRS-M: Pragmatic Rating Scale - Modified

PSSI: Personality Style and Disorder Inventory

RAN: Rapid Automized Naming

RHQ: Reading History Questionnaire

RIL: Response to Inhibition and Load

RMSEA: Root Mean Square Error of Approximation

ROC: Receiver Operating Characteristic

RPM: Raven's Progressive Matrices

SADS-L: Schedule for Affective Disorders and Schizophrenia - Lifetime Version

SADS-LA-R: Schedule for Affective Disorders and Schizophrenia - Lifetime Version - Modified for the Study of Anxiety Disorders - Revised

SAS: Social Anhedonia Scale

SCL-90-R: Symptom Checklist - 90 Revised

SCQ: Social Communications Questionnaire

SD: Standard Deviation

SPX: Single Incidence Autism Families

SRS: Social Responsiveness Scale

SSA: Sub-Saharan Africa

SST: Schonell Spelling Test

STAI-Y: State-Trait Anxiety Inventory Form Y

TAS-20: Toronto Alexithymia Scale

TD: Typically developing

TLI: Tucker Lewis Index

TMT: Trail Making Test

ToH: Tower of Hanoi

ToL: Tower of London

TOLC-E: Test of Language Competence - Expanded Edition

TQQ: Ten Questions Questionnaire

TROG-2: Test for Reception of Grammar - 2

UOT: Unexpected Outcomes Test

VIQ: Verbal IQ

WCST: Wisconsin Card Sorting Test

WJ-R: Woodcock-Johnson Psycho-Educational Battery - Revised

WPS: Western Psychological Services

Chapter 1

Introduction

1.1. Definition, prevalence and burden of Autism Spectrum Disorders (ASD)

Neurodevelopmental disorders (NDD) are a group of conditions with onset in the early developmental period and are characterized by deficits that produce impairments of personal, social, academic, or occupational functioning (DSM-5, APA 2013). NDD include disorders such as attention deficit hyperactivity disorder (ADHD), intellectual disability, motor disorders, language disorders and autism spectrum disorders (ASD), among others. Of these NDDs, ASD are the most complex and are characterised by impairments in social communication and interaction and restricted and repetitive patterns of behaviour, interests or activities. Since the publication of the latest revision of Diagnostic and Statistical Manual of Mental Disorders - Fifth edition (DSM-5; APA 2013), children receive a diagnosis of ASD, rather than previous Fourth edition of the Diagnostic and Statistical Manual (DSM-IV; APA 1994) sub-classifications of the spectrum such as autistic disorder, Asperger syndrome, or pervasive developmental disorder - not otherwise specified (PDD-NOS).

The minimum pooled prevalence for all NDDs in low and middle-income countries (LAMIC), based on available literature, is reported to be 7.6 (95% CI: 7.5 - 7.7) per 1,000 suggesting a considerable underestimate of the burden (Bitta et al., 2017), given that prevalence of some neurological disorders in rural Africa may be as high as 6.1% (Mung'ala-Odera et al., 2006). The prevalence estimates for ASD based on available literature, however, is reported to be 0.6 (95% CI: 0.5 - 0.6) per 1,000 (Bitta et al., 2017). However, these estimates are likely to be a gross underestimation of the true burden due to a paucity of studies, logistical expert challenges in assessment, and methodological biases in LAMIC (Abubakar et al., 2016a). Checklists of mental health problems shows that pervasive developmental disorders (PDD) are fairly common in preschool children from Africa (Kariuki et al., 2017a), suggesting ASD may be common in these settings. In high-income countries (HIC) there is evidence that one in every 132 (0.8%) to one in every 68 (1.5%) individuals suffer from ASD (Baxter et al., 2015; Wingate et al., 2014) and according to the latest report, the global prevalence of ASD was estimated to be at 0.62% (Elsabbagh et al., 2012), although there is little contribution by studies from LAMIC, particularly sub-Saharan Africa (SSA).

This thesis aims to contribute studies on ASD conducted in Dar-es-Salaam, Tanzania, with particular interest and emphasis on the awareness, diagnosis, endophenotypes, and risk factors of ASD in this region.

1.2. Review of current literature on ASD in SSA

ASD was previously perceived to occur only in the well-resourced countries with high technological development. A few decades ago, Sanua (1983) questioned the universality of ASD, however many recent studies have dispelled this idea that ASD may not be universal. There has since been evidence of an increase in the prevalence of ASD and knowledge about the disorder in other parts of the world. Some researchers believe the increase in burden of ASD could reflect the true burden relating to the epidemiological transition of the risk factors such as neurotoxins from urbanization etc. Others believe this is due to the improved and increased awareness of ASD over the years and many of such cases went undetected before. However, it is worth noting that some of the increasing burden may be due to false positives particularly in LAMIC where there are few experts for diagnosing the condition and healthcare systems are weak.

The first literature review of ASD in Africa (Bakare and Munir (2011a)) found 12 relevant articles, 2 of which reported epidemiological data. These were publications of ASD including reports of African immigrants in Sweden (Barnevik-Olsson et al., 2008; Barnevik-Olsson et al., 2010) and of 9 Arabic speaking countries, for example Tunisia and Egypt (Seif Eldin et al., 2008). Children with ASD in Africa were diagnosed relatively late (from 8 years through to adolescence) compared to those in HIC (Bakare and Munir (2011b). Two of these studies revealed that over half of children with ASD in their cohorts did not have any expressive language and/or had severe intellectual disability (Belhadj et al., 2006; Mankoski et al., 2006); it is possible that more impaired cases were identified and that onset of ASD was before the milestones for speech and language were achieved. This delay in diagnosis may delay acquisition or accelerate deterioration of language skills in many of the children with ASD, in part because they did not have access to early interventions. Identifying children with ASD in Africa is problematic because of the lack of appropriate services, expertise and inadequate standard of available educational and medical infrastructure (Ruparelia et al., 2016).

Awareness of ASD was not only wanting in the general population in Africa, but also among the medical community (Bakare et al., 2009a), many regarding ASD to have supernatural causes. They reported that it is a common practice in Africa for children with an NDD to be taken first to a traditional healer, before a parent seeks biomedical assistance. This potential delay in seeking medical assistance may contribute to a late diagnosis and could be a further exacerbating factor in the more severe cognitive and expressive language outcomes reported in children with ASD. These findings highlight a need for earlier recognition and diagnosis of ASD in Africa. Although in HIC there are many ‘‘gold-standard’’ tools available to screen and diagnose ASD, there are no available validated tools from Africa. The perception of abnormal behaviour may be mediated by culture, and screening measures need to take into account these contextual factors. For example, children in some rural parts

of Africa are not allowed to look at elders in the eye, and deficits in eye contact are very common in ASD so these children would score high on the ASD screening process, not because they have ASD but because they are conditioned by their culture to behave in this manner. These cultural factors need to be taken into account when developing or adapting screening measures (de Leeuw et al., 2020).

Although major advances in the genetic basis and developmental aspects of ASD have been made, many aspects of the condition are still poorly understood in LAMIC. More specifically, there is little research to date exploring risk factors per se for ASD in SSA (Abubakar et al., 2016b). There is also no detailed epidemiological research for risk factors of ASD as there is for other NDD like epilepsy (Ngugi et al., 2013). This means that children with ASD are likely to miss out on policy decisions aimed at identification and management.

Prevalence of ASD is reported to be higher in children of Somali origin living in Stockholm (Barnevik-Olsson et al, 2010), maternal birth outside the Nordic countries living in Sweden (Haglund & Källén et al., 2011) and mothers of African origin living in the United Kingdom (Keen et al., 2010). These findings suggest that ASD in Africa may be more common than is recognized and that epidemiological research in Africa is needed to clarify the situation.

A more recent systematic review on ASD in SSA (Abubakar, et al., 2016b) found that 74% of studies meeting their inclusion criteria were conducted in either South Africa or Nigeria, with 83% carried out in the last decade and did not identify a single case-control study examining risk factors associated with ASD for this region. Findings from another recent scoping review of ASD in SSA (Franz et al., 2017), highlight a substantial need for large-scale clinical, training and research programmes to improve the lives of people with ASD in SSA. In a report on the first International Child Neurology Association Meeting on ASD in Africa (Ruparelia et al., 2016), strategies were proposed to improve identification, diagnosis, management and support delivery for individuals with ASD across Africa in these culturally diverse, low-resource settings. Emphasis was put on raising public awareness through community engagement, improving access to information and training in ASD with special considerations for the cultural, linguistic, and socioeconomic factors within Africa.

1.3. Screening for ASD

Currently there are no biomarkers for ASD, thus diagnosis depends largely on behavioural assessment and observation. The diagnostic process is complex and requires collecting information about characteristics of current and lifetime behaviours in early developmental periods using interviews, questionnaires and/or direct observations in standardized administration settings.

Since ASD diagnostic tools such as the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 2000) and the Autism Diagnostic Interview–Revised (ADI-R) (Le Couteur et al., 2003) require formal clinical training and large amounts of resources, screening instruments have been developed to aid in initial screening for ASD. These are administered to the child's primary caregiver, are less costly and time consuming and can provide an efficient method for screening children who may require further evaluation. A number of screening tools have been developed in HIC for ASD. The relative ease of using these tools in HIC largely depends on the high literacy levels of parents. Table 1.1 highlights some examples of ASD specific screening tools that can be easily administered to a parent or caregiver and have been culturally adapted.

Table 1.1 - ASD specific screening tools that can be administered to a parent or caregiver.

Screening tools	Reference	Age range	Brief description	Cultural adaptation and/or validation
Autism Behaviour Checklist (ABC)	Krug et al (2008)	3 – 14 years	57-item questionnaire answered in yes/no format and takes approx. 20 minutes. Results indicate cut-off score ranges based on different diagnoses.	Brazil (Marteleto & Pedromônico, 2005) Iran (Yousefi et al., 2015) Turkey (Özdemir et al., 2013)
Modified Checklist for Autism in Toddlers (M-CHAT)	Robbins et al (2001)	16 – 30 months	23-item questionnaire answered in yes/no format and takes approx. 5-10 minutes. Results indicate need for further evaluation.	China (CHAT-23 - Wong et al., 2005)[a] France (Baduel et al., 2016) Japan (Inada et al., 2011) Mexico (Albores-Gallo et al., 2012) Spain (Canal-Bedia et al., 2010) Turkey (Kndolot et al., 2016)
Social Communication Questionnaire (SCQ)	Rutter et al (2003)	4+ years	40-item questionnaire answered in yes/no format and takes approx. 10-15 minutes The Lifetime Form focuses on the developmental history and behaviour. The Current Form focuses on behaviour during the last 3 months. Results are reported using a total score and defined cut-off points.	Brazil (Sato et al., 2008) Germany (Bolte et al., 2008) Greece (Zarokanellou et al., 2017) Taiwan (Gau et al., 2011) Turkey (Avcil et al., 2015)
Social Responsiveness Scale (SRS)	Constantino & Gruver (2005)	4 – 18 years	65-item questionnaire using a rating scale and takes approx. 10-20 minutes. Results are reported as a quantitative score for autistic social impairment.	China (Gau et al., 2013) France (Stordeur et al., 2019) Germany (Bölte et al., 2008a) Iran (Tehrani-Doost., 2018)

[a]CHAT-23 is a new checklist translated into Chinese, combining the M-CHAT (23 questions) with graded scores and section B (observational section) of the CHAT.

Only few published studies specifically on ASD screening and diagnosis in SSA were identified by recent reviews (Franz et al., 2017; Abubakar et al., 2016b). An Ugandan tool development study (Kakooza-Mwesige et al., 2014), which piloted a 23-question screener (the 23Q), including the Ten Questions Questionnaire (TQQ) (Durkin et al., 1995) and 13 additional questions specifically aimed at ASD detection was modestly successful in identifying children at high risk of ASD, but showed a relatively low positive predictive value of only 8% (Kakooza-Mwesige et al., 2014). Harrison et al. (2014) used the Childhood Autism Rating Scale, Second Edition (CARS-2; Schopler et al., 2010) in Tanzania. They combined this observational diagnostic aid for ASD as part of a larger test battery to diagnose ASD and described the process of cultural adaptation, however, the tool was not formally validated. Additionally, two studies in South Africa have also evaluated the cultural adaptability of ASD screening and diagnostic tools in their setting. The first by Smith et al. (2016) examined the cultural appropriateness of the materials and procedures for administration of the Autism Diagnostic Observation Schedule-2 (ADOS-2) and found that most of the materials and activities were appropriate for use in their setting with only minor modifications. However, potential linguistic and semantic biases were observed and therefore guidelines for using ADOS in their setting were developed. The second by Chambers et al. (2016) adapted several measures for early screening for ASD, providing initial evidence that the measures are feasible for use in their setting.

More recently, Marlow et al. (2019) published a review of screening tools for the identification of ASD in infants and young children in LAMIC and recommended 3 tools for screening and detection of ASD for use in LAMIC. They recommend the M-CHAT R/F (Robbins et al., 2014), the Pictorial Autism Assessment Schedule (PAAS - Perera et al., 2009, 2017) and the Three-Item Direct Observation Screen (TIDOS - Oner et al., 2013), as these are brief, low-cost and can be implemented by paraprofessionals or lay community health workers.

These findings highlight a need for accelerated availability of validated screening tools for earlier recognition and diagnosis of ASD in Africa. Although in HIC there are many tools available to screen and diagnose ASD, there is a dearth of available validated tools for the use of screening and identifying ASD in SSA. There is a need for investment in adapting and validating screening and diagnostic tools for ASD as possible through consortiums of researchers working together across continents or LAMIC regions while continuously engaging with local and international governments to ensure sustainability of the process.

1.4. Risk factors associated with ASD

The heritability of ASD is estimated to be 70%-90% (Bailey et al., 1995; Hallmayer et al., 2011) indicating that it is a strongly genetically determined childhood disorder. Research suggests that siblings of individuals with ASD are at a 20-fold increased risk of developing ASD compared with the

general population (Ritvo et al., 1989; Lauritsen et al., 2005; Constantino et al., 2010; Ozonoff et al., 2011). Despite major advances in understanding the genetic and developmental aspects of ASD in HIC, there are few or no genetic or heritability studies of ASD in LAMIC. Yet the available evidence shows strong genetic basis for these conditions, for instance the clustering of the broader autism phenotypes in family members of autistic probands (Ruparelia et al., 2017).

There is strong evidence of the interplay between genetic and environmental factors (Hallmayer et al., 2011; Sandin et al., 2014; Volk et al., 2014) in the development of ASD. Table 1.2 summarizes common environmental risk factors for ASD in the literature. Recent epidemiologic research has emphasized the prenatal and neonatal period as the most relevant period for environmental risk factors to be associated with ASD. Gardener et al. (2009) published the first quantitative review and meta-analysis of the association between maternal pregnancy-related factors and risk for ASD. They examined over 50 prenatal factors and found advanced parental age, maternal prenatal medication use, bleeding, gestational diabetes and being first born to be associated with a risk for ASD. In a subsequent review and meta-analysis on over 60 perinatal and neonatal factors, Gardener et al. (2011) found abnormal presentation, low birth weight, small for gestational age, congenital malformations, feeding difficulties and meconium aspiration amongst others to be associated with a risk for ASD. However, the authors warned of insufficient evidence to implicate any single prenatal, perinatal and neonatal factor in ASD aetiology since these factors may interact synergistically (e.g. additively or multiplicatively) or even antagonistically to determine the risk for ASD (Gardener et al., 2009; Gardener et al., 2011).

More recently, in a retrospective case-cohort study, Hisle-Gorman et al. (2018) explored 29 prenatal, perinatal and neonatal factors previously associated with ASD, reporting that the greatest risk was associated with neonatal seizures, maternal mental health and epilepsy medications. In one of the few studies examining the prenatal and perinatal factors associated with ASD, using a sibling design and correlating these factors with ASD core symptoms, Chien et al. (2019) reported that probands with ASD and their unaffected siblings from Taiwan had more prenatal and perinatal events than typically developing controls, with higher number of prenatal and perinatal factors in probands than in unaffected siblings. They also found the total number of prenatal and perinatal factors in ASD probands to be associated with overall symptom severity as well as specific symptoms such as social communication deficits.

Table 1.2 - Common risk factors for ASD in the literature.

Risk factor categories	Types of risk factors	Study	Range of odds ratios across studies (95% CI)*
Parental factors	Advanced parental age	Durkin et al (2008)[a]; King et al (2009)[a]; Mamidala et al (2013)[b]; Sandin et al (2016)[a]; Wang et al (2017)[a, b]	Maternal: 0.7 (0.5 – 1.0) – 1.84 (1.37 – 2.47) Paternal: 1.05 (1.02 – 1.08) – 1.71 (1.41 – 2.08)
Prenatal factors *Chemical and toxicant factors*	Air pollution	Becerra et al (2013)[a]; Gong et al (2017)[a]; Raz et al (2018)[a]	0.77 (0.59- 1.00) – 1.40 (1.09 – 1.80)
	Pesticides	Roberts et al (2007)[a]; Shelton et al (2014)[a]	0.6 (0.1 – 4.3) -7.6 (3.1 – 18.6)
Nutritional factors	Maternal obesity	Andersen et al (2018)[a]; Getz et al (2016)[a]	1.39 (1.11 – 1.75) – 1.54(1.262 – 1.89)
	Gestational Vitamin D deficiency	Magnusson et al (2016)[a]; Vinkhuyzen et al (2017)[a]	0.99 (0.52 – 1.87) – 5.08 (2.53- 10.20)
Pregnancy medical complications	Gestational hypertension; gestational diabetes; preeclampsia; maternal bleeding	Chien et al (2018)[a]; Wang et al (2017)[a, b]	1.33 (1.14 – 1.56) – 5.43 (1.76 – 16.77)
Pregnancy infections	Prenatal fever; Respiratory infection	Atladóttir et al (2012)[a]; Gardener et al (2009)[a, b]; Mamidala et al (2013)[b]	1.0 (0.9 – 1.2) - 3.80 (1.18 – 12.29) -
Medication use during pregnancy	Antibiotics; Valproate; Lmotrigine+Valproate; SSRIs	Atladóttir et al (2012)[a]; Rai et al (2013)[a]; Veroniki et al (2017)[a, b]	1.2 (1.0 – 1.4) – 1.32.70 (7.41 to 3851.00)
Gestational term	≤ 36 weeks	Larsson et al (2005)[a]; Mamidala et al (2013)[b]; Wang et al (2017)[a, b];	1.31 (1.16 - 1.48) – 2.45 (1.55 – 3.86)
Perinatal factors *Delivery method*	Caesarean section; Vacuum Forceps; Assisted vaginal	Chien et al (2018)[a]; Wang et al (2017)[a, b]	1.30 (1.15 - 1.48) – 1.40 (1.08 – 1.82)
Labour	Induced labour	Mamidala et al (2013)[b]; Wang et al (2017)[a, b];	1.11 (1.04 – 1.20) – 4.52 (2.27 – 9.01)

complications	Prolonged labour		
Birth complications	Breech presentation; Umbilical cord complications	Larsson et al (2005)[a]; Wang et al (2017)[a, b]	1.47 (1.23 – 1.76) – 1.63 (1.18 – 2.26)
Adverse perinatal events	Fetal distress; Birth asphyxia; Delayed birth cry	Hadjkacem et al (2016)[b]; Mamidala et al (2013)[b]; Wang et al (2017)[a, b]	1.40 (1.11 – 1.76) – 10.63 (3.69 – 30.59)
Neonatal factors	Low birth weight (≤ 2.5 kg)	Chien et al (2018)a; Wang et al (2017)[a, b]	1.26 (1.20 – 1.34) – 3.46 (1.32 – 9.09)
	Neonatal jaundice	Mamidala et al (2013)[b]	2.89 (1.58 – 5.28)
	Neonatal seizures	Hisle-Gorman et al (2018)[a]	7.57 (5.68 – 10.07)
	Seizures disorders (epilepsy)	Sundelin et al (2016)[a]	10.49 (9.55-11.53)

Note. CI = Confidence Interval.

[a]Studies conducted in high-income countries (HIC); [b]Studies conducted in low and middle income countries (LAMIC).

[*]$p < 0.05$

However, most of these studies were not conducted in SSA, where the incidence of these risk factors is high. In recent comprehensive scoping review of ASD in SSA only 3 risk factor studies were identified (Franz et al., 2017; Abubakar et al., 2016b). In a descriptive case series study in Tanzania, Mankoski et al. (2006) reported 3 out of 14 children studied developed ASD upon recovery from malaria, suggesting that severe neurological infections, in the first few years of life, is associated with ASD. Claassen et al. (2008) conducted a retrospective case study of dizygotic twin siblings in South Africa, one of whom had ASD. They suggested that maternal stress contributed to the pathogenesis of ASD as the blood plasma of the ASD probands had elevated glucocorticoids and serotonin in comparison to the unaffected siblings. van Wijngaarden et al. (2013) conducted a longitudinal descriptive study in the Republic of Seychelles and found no association between prenatal methyl mercury exposure and ASD phenotype behaviours as measured by scores on two ASD screening tools. However, key methodological aspects, in particular systematic diagnosis and translation/validation of the tools is not available or questionable in these studies (Franz et al., 2017).

One Swedish report found 3 to 4-fold increase in prevalence of ASD in children of Somali origin living in Stockholm compared to a non-Somali group (Barnevick-Olsson et al., 2008). Furthermore, a study conducted in the UK, found maternal immigration and ethnicity to be associated with an increased risk of ASD; in particular mothers of African and Caribbean ethnicity having increased risk of ASD compared to mothers of white ethnicity (Keen et al., 2010). Another study looking at perinatal factors and migration in Sweden found that maternal birth outside the Nordic countries was associated with ASD (Haglund & Källén, 2011), indicating that children of women who were born in SSA or East Asia had the highest risk for ASD. However, these factors of ethnicity and immigration can have association with ASD due to two hypotheses. The social causation hypothesis asserts that experiencing economic hardship increases the risk of subsequent mental illness. The selection hypothesis asserts that mental illness can inhibit socioeconomic attainment and lead people to drift into the lower social class or never escape poverty. Research suggests there is a reciprocal relationship between socioeconomic status and mental health problems, some of which are in the spectrum of neurodevelopmental disorders such as ASD (Hudson, 2005; Mossakowski et al., 2014).

Many of the risk factors mentioned earlier are common in SSA, suggesting that ASD may be more common than recognized in this region, highlighting the need for more epidemiological studies in this region to reliably determine the burden.

1.5. Endophenotypes of ASD

Despite the significant heritability in ASD (Bailey et al., 1995; Freitag et al., 2010; Hallmayer et al., 2011; Tick et al., 2015), the search for the underlying genes has proved to be challenging, raising questions on the underlying genetic mechanisms of ASD (Abrahams & Geschwind, 2008).

Recent evidence suggests that sub-threshold autistic traits are continuously distributed across the general population (Constantino & Todd, 2003; Plomin et al., 2009; Ruzich et al., 2015). Several researchers have found that first-degree relatives of autistic individuals often display milder forms of autistic traits referred to as the Broader Autism Phenotype (BAP) (Ruparelia et al., 2017; Cruz et al., 2013; Gerdts & Bernier et al., 2011; Sucksmith et al., 2011). This constellation of sub-threshold autistic traits includes a set of behavioural and cognitive characteristics that reflect the phenotypic expression that is qualitatively similar in unaffected relatives of autistic individuals. For instance, mild challenges in social cognition in using facial cues and other features to determine mental states have been noted in parents of children with ASD (e.g. Baron-Cohen & Hammer, 1997). Additional studies report similar differences in emotion processing abilities, particularly emotion identification (e.g. Di Michele et al., 2007; Szatmari et al., 2008) and phonological processing and reading abilities (e.g. Schmidt et al., 2008). Research that includes such quantitative measures of autistic traits and underlying mechanisms responsible for such features in first degree relatives is fundamental in studying the genetic basis of ASD as it can help to identify which characteristics aggregate in family members, and are thus likely to be potential endophenotypes for ASD at the neurocognitive level, and may inform targeted preventative and therapeutic interventions.

Evidence of behavioural, cognitive and psychiatric endophenotypes in parents of children with ASD is reviewed in more details in Chapter 2. Various instruments have been developed to assess the BAP in adults. These include self-report and/or informant questionnaires, semi-structured interviews and interviews combined with direct observation/assessment. Table in 2.1 of Chapter 2 describes the BAP measures specifically developed to assess the BAP. To date, no studies have been conducted in SSA on the BAP.

1.6. Study rationale

Currently, very little is known on the risk factors of ASD in Africa and the clinical profile of this disorder remain unclear in this region (Ruparelia et al., 2016; Abubakar et al., 2016a; Elsabbagh et al., 2012). It is evident that more epidemiological studies are required in order to define the scale of the problem of ASD as well as defining the characteristics in particular the phenotypes of children with ASD in Africa. This may help shed light on the aetiology of ASD and any reasons for possible

differences in prevalence between geographical regions, if any exist, as well as estimates to plan interventions and management.

Good epidemiological studies depend on availability of appropriately adapted and validated tools. Findings from the few studies conducted in Africa not only indicate a need for earlier recognition and diagnosis of ASD in the region, but also highlight the need for culturally appropriate and standardized measures for the diagnosis of ASD. This study aims to identify children with ASD using gold standard screening tools which are adapted to the local language and culture in SSA. Furthermore, this study endeavours to assess whether the profile of ASD is similar to HIC.

There is currently no research exploring risk factors for ASD in Africa. Many of the established risk factors for ASD are common in East Africa, suggesting that ASD may be more common than recognized. This study aims to collect data on family medical history and past and current health conditions of children identified with ASD in Tanzania and their biological parents, enabling us to compare our findings to those of HIC.

More sophisticated research of the endophenotypes of parents of children with ASD may help develop better measures of evaluation of the BAP. To the best of our knowledge, there are no published studies exploring the BAP and endophenotypes of ASD in Africa. This study aims to detect subtle subclinical autistic traits in the parents of children with a confirmed diagnosis of ASD by exploring the psychometric properties of an existing BAP measure. This can target care for both probands and relatives.

1.7. Objectives

General objective

To explore the awareness, screening, endophenotypes and risk factors of ASD in Dar-es-Salaam, Tanzania.

Specific objectives

(1) Systematically review the evidence of behavioural, cognitive and psychiatric endophenotypes in parents of children with ASD.
(2) To explore the knowledge and lived experiences of ASD in Dar-es-Salaam, Tanzania.
(3) To adapt and evaluate the psychometric characteristics of the Social Communication Questionnaire (SCQ).
(4) To determine the risk factors for ASD in Dar-es-Salaam, Tanzania.

(5) To adapt and evaluate the psychometric properties of the Autism Spectrum Quotient (AQ)
(6) To describe the BAP in biological parents of autistic children.

1.8. Structure of the PhD thesis

Chapter 2 provides a comprehensive systematic review on the behavioural, cognitive and psychiatric endophenotypes and the BAP in parents of children with ASD. The content of this systematic review is published in Autism Research and Treatment (Ruparelia et al., 2017 - Appendix 1).

Chapter 3 provides an overview of the methodology of the study, in particular, the study site, population, study design, procedures and statistical analysis in general terms. Specific procedures and statistical analysis will be mentioned in the respective subsequent chapters.

Chapter 4 presents qualitative data on the awareness and lived experiences of families of children with ASD and community stakeholders in Dar-es-Salaam, Tanzania. Data was collected using focus group discussions (FGD) and in-depth interviews (IDI) and results are presented under the following topic guidelines: knowledge and awareness on the identification and presentation of ASD and perceived causes of ASD as well as the challenges encountered. This chapter also includes a thematic model of lived experiences. This chapter is broadly organised into a brief background, brief methodology, main findings and summary or brief discussion of the findings.

Chapter 5 focuses on the validation and adaptation of the screening measure Social Communication Questionnaire (SCQ) among children with a known diagnosis of ASD, other NDD (that are not ASD) and a comparison group of typically developing children in Dares-Salaam. This chapter includes data on psychometric properties, in particular internal consistency, test-retest and inter-informant reliability and discriminant validity. The fit indices for the confirmatory factor analysis (CFA) of SCQ are also provided. This chapter is broadly organised into a brief background, brief methodology, main findings and summary or brief discussion of the findings.

Chapter 6 presents results on the risk factors among children with a known diagnosis of ASD, other NDD (that are not ASD) and typically developing children in Dar-es-Salaam. This chapter is broadly organised into a brief background, brief methods and procedures, main findings and summary or brief discussion of the findings.

Chapter 7 focuses on the validation and adaptation of the BAP measure Autism Spectrum Quotient (AQ) among biological parents of children with a known diagnosis of ASD, parents of children with

other NDD (but no ASD) and parents of typically developing children in Dar-es-Salaam. This chapter includes data on psychometric properties, in particular internal consistency, test-retest and inter-informant reliability and discriminant validity. This chapter is broadly organised into a brief background, brief methodology, main findings and summary or brief discussion of the findings.

The last chapter, Chapter 8, synthesises the content of all chapters, whilst comparing main findings with other published studies. This chapter outlines the contributions of these PhD studies to the literature, provides directions for future research, highlights public health value of the findings and discusses the strengths and limitations of the studies.

Chapter 2

Systematic review on Autism Spectrum Disorders (ASD) and endophenotypes

2.1. Background

The heritability of ASD is estimated to be from 70% to 90% (Bailey et al., 1995; Hallmayer et al., 2011). Research suggests the risk of developing ASD in siblings of individuals with ASD is between 10 to 20%, considerably higher than when compared to about 1% for siblings of typically developing children (Ozonoff et al., 2011; Constantino et al., 2010). These data suggest a strong genetic basis, despite the clinical heterogeneity. Since numerous studies using linkage or candidate gene approaches have not discovered a single genetic locus of major effect, it is thought that the definition of the endophenotypes may provide insights into the biological basis of this condition.

Studies have provided substantial evidence indicating that first degree relatives of autistic individuals often display milder forms of autistic traits referred to as the broader autism phenotype (BAP) (Piven et al., 1997a). This milder expression includes a set of behavioral and cognitive characteristics that reflect the phenotypic expression that is qualitatively similar in unaffected relatives of autistic individuals. For instance, mild challenges in social cognition in using facial cues and other features to determine mental states have been noted in parents of children with ASD (Baron-Cohen & Hammer, 1997). Additional studies report similar differences in emotion processing abilities, particularly emotion identification (Di Michele et al., 2007; Szatmari et al., 2008) and phonological processing (Schmidt et al., 2008). Research that includes such quantitative measures of autistic traits and underlying mechanisms responsible for such features in first degree relatives is fundamental in studying the genetic basis of ASD as it can help to identify which characteristics aggregate in family members, and are thus likely to be potential endophenotypes for ASD at the neurocognitive level.

Endophenotypes are heritable markers associated with a given condition and can provide insight into its etiology. Gottesman & Gould (2003) offered a set of criteria for identification of useful endophenotypes suggesting that deficits must be: a) associated with illness in the population; b) heritable; c) state-independent (manifests in an individual whether or not illness is active); d) co-segregated with the condition within families; and e) also found in unaffected relatives at a higher prevalence than in the general population. The study of endophenotypes is particularly useful in understanding developmental disorders such as ASD that are diagnosed on clinical features, but are of

neurobiological origin, and can aid to better identify and characterize the nature of the genetic contributions to this complex disorder.

Several researchers have reviewed the BAP traits in first degree relatives of autistic probands (Cruz et al., 2013; Gerdts & Bernier, 2011; Sucksmith et al., 2011). Some reviews include studies that have examined the BAP in parents and siblings of autistic probands. Although features of the ASD phenotype have been found in the 'at risk' infant sibling studies, no clear distinction can be made to determine whether they are the characteristics of the BAP or that the infant siblings may later receive an ASD diagnosis. Thus, I limited this review process to parents only by employing a systematic approach to focus on the socio-behavioural, cognitive and psychiatric profiles of the BAP to determine candidate endophenotypic traits for ASD.

I conducted a systematic review of the literature to assess the evidence of behavioral, cognitive and psychiatric endophenotypes of ASD in parents. The aim of this review was to ascertain whether parents of probands with ASD have higher prevalence of various components of the BAP, and more specifically of behavioral, cognitive and other psychiatric conditions. The questions addressed were:

i. What are the behavioral, cognitive and other psychiatric (focusing primarily on depression and anxiety) endophenotypes of ASD as manifested through the BAP in biological parents of autistic probands?
ii. What are the tools used to measure these endophenotypes and the magnitude of effect?
iii. Do patterns evident in endophenotypes of ASD provide insight into cultural and geographical differences?

2.2. Review methods

2.2.1. Data sources and search strategy

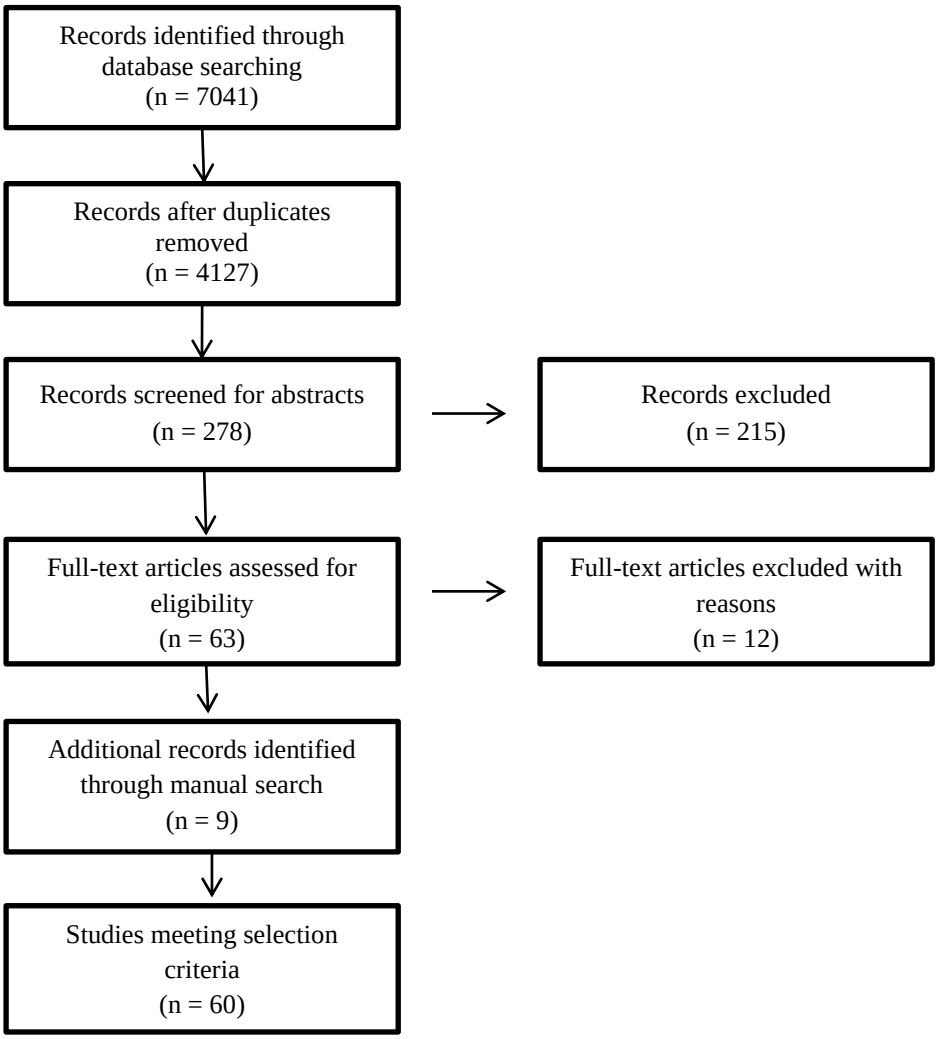
A comprehensive literature search was performed to collate evidence of behavioral, cognitive and psychiatric endophenotypes in ASD. Literature searches for published and grey literature were subsequently carried out using 5 databases: EMBASE, MEDLINE, PsychINFO, PsychEXTRA and Global Health from inception through to August 2014 without language restriction. The strategy was developed by breaking down the review questions into elemental facets according to the recommendations of the National Health Service Centre for Reviews and Disseminations (Khan et al., 2001). These facets included exposure, outcome, population, publication language and keywords (Table 2.1). The initial search strategy used the words 'autis* AND endophenotyp* OR phenotyp*'. These searches were further refined by the addition of the outcome terms and population ('parent* OR

relative OR famil*’). The bibliographies of key references were later hand-searched to identify articles missed in the database search. Figure 2.1 illustrates our literature search strategy.

Table 2.1 - Description of search strategy.

Search Element	**EMBASE**	**MEDLINE**	**PsycINFO**	**PsycEXTRA**	**Global Health**
Exposure	Thesaurus terms exploded: Autis*;				
Keywords	Endophenotyp* OR Phenotyp*				
Outcome	Thesaurus terms exploded behavior language social interaction repetitive restrictive cognitive executive function central coherence theory of mind social cognition visual attention depression anxiety	Thesaurus terms exploded behavior language social interaction repetitive restrictive cognitive executive function central coherence theory of mind social cognition visual attention depression anxiety	Thesaurus terms exploded behavior language social interaction repetitive restrictive cognitive executive function central coherence theory of mind social cognition visual attention depression anxiety	Thesaurus terms exploded behavior language social interaction repetitive restrictive cognitive executive function central coherence theory of mind social cognition visual attention depression anxiety	Thesaurus terms exploded behavior language social interaction repetitive restrictive cognitive executive function central coherence theory of mind social cognition visual attention depression anxiety
Population	Parent* OR Relative* OR Famil*				
Language	Any				

Figure 2.1 - Flow chart of study selection.



2.2.2. Data selection criteria

The titles and abstracts of papers identified were reviewed and the full versions of potential papers were read to decide on final selection. The inclusion criteria were:

i. Original studies that employed a quantitative methodological approach to investigate behavioral, cognitive and psychiatric (depression and anxiety) endophenotypes in biological parents.

ii. The autistic proband (other conditions on the spectrum such as Asperger Syndrome, Pervasive Developmental Disorder and Pervasive Developmental Disorder Not Otherwise Specified were also included) must have a clinically established diagnosis of ASD (minimum DSM-III) and no concomitant medical conditions associated with autistic symptomatology and visual, auditory and motor impairment such as Fragile X or Tuberous Sclerosis.

iii. Studies that carried out a comparison of endophenotypes between parents of individuals diagnosed with ASD and unaffected adults, a normative parental control group and/or a clinical parental control group.

I excluded any studies investigating the BAP in the general population, studies on genetics and ASD and studies examining the neuroanatomical and neurofunctional dimensions of the BAP. All single case, case series, book chapters, theoretical papers, review papers, unpublished dissertations/theses and studies not published in English were excluded.

The final set of papers was restricted to those that quantitatively evaluated behavioral, cognitive and psychiatric endophenotypes in biological parents of autistic probands.

2.2.3. Data extraction

I examined the titles, abstracts, and studies with study selection criteria. Data were organized into broad domains for each of the three categories: Socio-behavioural i.e. direct assessment of BAP expression, other measures of personality and friendships, social interaction, repetitive/restrictive interests and social and narrative language; Cognitive i.e. intellectual functioning, structural language, social cognition, executive function, local visual processing (central coherence) and visual perception; Other psychiatric conditions, specifically depression and anxiety.

2.2.4. Effect sizes

The data extracted was based on heterogeneous measures and outcomes, so pooling the data in a meta-analysis was inappropriate. To compare the robustness of the measures used, for each behavioral, cognitive and psychiatric variable of interest an effect size (ES) was computed from the data reported in each study. Cohen's effect size statistic (*d*) was calculated as the difference between the means of both groups divided by the pooled standard deviation. The following criteria were used to assess the magnitude of effect: $d < 0.2$ (small), $d > 0.5$ (medium), and $d > 0.8$ (large) (Cohen, 1988).

2.3. Results

2.3.1. Search results

The initial electronic search identified 7,041 records, of which 4,127 records remained after duplicates were removed. 278 articles were eligible for full review after examination of titles and abstracts (Figure 2. 1). After full text review, we excluded 12 articles for the following reasons: in 9 studies it was not possible to distinguish parent and sibling data when results were reported for combined first

degree relatives, and in 3 studies, proband diagnosis was established using criteria prior to DSM-III. The search criteria, additional articles identified through manual search and total numbers of articles meeting selection criteria are shown in Figure 1.

2.3.2. Results of literature extraction

Twenty five of the 60 studies that fulfilled the inclusion criteria directly evaluated the BAP expression (including personality, social behavior and pragmatic language features of the BAP). An additional 7 studies assessed other aspects within the socio-behavioural domain. Thirty seven reports assessed the broad domain of cognitive functioning and seven studies investigated other psychiatric conditions. Twenty seven of the studies were conducted in North America, 24 in Western Europe, 4 in the Middle East, 3 in Western Pacific, 1 in South America and 1 used combined samples from North America, Western Europe and Western Pacific. However, no studies were conducted in Asia or Africa. Index families included a total of 4,833 mothers and 3,065 fathers that took part across all studies reviewed (few studies did not specify sex breakdown). Studies varied greatly in their choice of comparison control group, with 26 studies using a non-clinical comparison group, 21 studies using a normative control sample and 13 studies using a combined sample of clinical and non-clinical control groups. Thirteen studies evaluated the gradation of expression across family types using families with multiple incidence autism (MPX) and single incidence autism (SPX).

I summarized the results of the literature search according to different socio-behavioural, cognitive and psychiatric domains. For each domain I present the measures used within that domain and any significant differences found between index parents and parental controls, and so results are described in relation to proband diagnosis. All background measures used to establish BAP status without using a comparison group as well as control tasks are not reported under the specific criteria in this review.

2.3.3. Socio-behavioural domain

This domain includes studies that evaluated the BAP expression using measures designed specifically to assess social abilities, communication skills and personality traits characteristic of the BAP, as well as measures of reciprocal interaction, restrictive and repetitive interest and social and narrative language. Refer to Appendix 2 for the review of socio-behavioural studies of parents of autistic probands.

BAP expression through direct clinical assessment

Studies explored the BAP using a variety of measures and research designs with some studies utilizing conservative selection criteria, dividing parents of autistic probands into ‘BAP present’

(BAP+) and 'BAP absent' (BAP-) groups. As shown in Appendix 1, from eight of the measures specifically designed to assess the BAP, four are more recent Questionnaires aiming to assess the BAP quantitatively, and four use interviews and direct behavioral observations. Of the four questionnaires, one is a self-report measure (Autism Spectrum Quotient - AQ), two are informant-report measures (Communication Checklist - Adult - CCA; and Social Responsiveness Scale - SRS), and one is a self – and informant report questionnaire (Broader Autism Phenotype Questionnaire - BAPQ). Of the four remaining measures, two are semi-structured interviews (Family History Interview – FHI / Family History Schedule - FHS and Modified Personality Assessment Schedule – MPAS / Modified Personality Assessment Schedule - Revised - MPAS-R), and two assess BAP via interviews and direct clinical observation/assessment (Broader Phenotype Autism Symptom Scale - BPASS and Pragmatic Rating Scale - PRS / Pragmatic Rating Scale - Modified - PRS-M).

Autism Spectrum Quotient (AQ)

A total of ten reports measured the BAP using the self-report AQ (ES range 0.01 – 1.34). Three studies used adaptations of the AQ; one in Italian (Ruta et al., 2012), one in Turkish (Köse et al., 2013) and one in French (Robel et al., 2014). Within the 'Social Skills' factor, five studies found significantly higher deficits in social skills compared to parents of typically developing children (Ruta et al., 2012; Köse et al., 2013; Bishop et al., 2004a; Kadak et al., 2014; Wheelwright et al., 2010). Two studies reported significantly higher prevalence of 'Attention Switching' deficits between the index parents and parents of typically developing children (Wheelwright et al., 2010) and parents of children with specific language impairment (Whitehouse et al., 2007). One study evaluating the 'Attention to Detail' subscale, reported mothers of typically developing children scoring significantly higher than index mothers (Schereen & Stauder, 2008). Within the 'Communication' subscale, five out of eight studies report significantly higher communication deficits between index parents and parents of typically developing children (Ruta et al., 2012; Köse et al., 2013; Bishop et al., 2004a; Wheelwright et al., 2010) and parents of children with a specific language impairment (Whitehouse et al., 2007). However, only Wheelwright et al.'s (2010) study reported a significant trend for index parents to have more deficits in 'Imagination' subscale compared to a sample of parents of typically developing children. For the total AQ score, four studies reported higher combined total scores among index parents when compared to parents of typically developing children (Ruta et al., 2012; Köse et al., 2013; Wheelwright et al., 2010) and parents of children with specific language impairment (Whitehouse et al., 2007).

Ingersoll et al. (2011) combined the social skill and communication factors and revealed index mothers to score significantly higher than normative mothers on the AQ. Furthermore, in a more recent study, using a validated French Autism Quotient (FAQ), Robel et al. (2014) distributed AQ

scores between two main factors, F1 corresponding to socialization and communication, and F2 corresponding to imagination and rigidity. They reported index parents to have more symptomatic scores in the F1 domain compared to parents of typically developing children. No significant differences were found for the F2 domain, however, the global score (F1 and F2 combined) remained significant with index parents scoring higher.

Broader Autism Phenotype Questionnaire (BAPQ)

Two studies evaluated the BAP using the BAPQ (ES range 0.26 – 1.49). Hurley et al. (2007) used the method of pre-establishing parents of autistic probands into 'BAP present' (BAP+) and 'BAP absent' (BAP-) groups by direct assessment on MPASR and PRS, reporting consistently higher scores for 'BAP+' group compared to 'BAP-' group and community control parents on all subscales; aloof, rigid, pragmatic language and the total score. More recently, Sasson et al. (2013) reported similar results for all BAPQ subscales and total score, with index fathers scoring significantly higher than normative fathers and the same trend was significant for mothers of both groups.

Broader Phenotype Autism Symptom Scale (BPASS)

Bernier et al (2012) used the BPASS to assess the BAP in MPX parents compared to parents of SPX families, parents of developmentally delayed children and parents of typically developing children (ES range 0.75 – 1.28). Differences among groups were found in the 'Social Motivation' subscale where MPX parents showed significantly more deficits than the SPX parents, parents of developmentally delayed children and parents of typically developing children. In both 'Expressiveness' and 'Restricted Interests' subscales a significant difference was found only between the MPX parents scoring higher than parents of typically developing children. No group differences were found within the 'Communication' subscale and interestingly, SPX parents did not differ from parents of children with developmental delay or typical development.

Communication Checklist – Adult Version (CC-A)

Whitehouse et al (2010) assessed the BAP using the CC-A (ES range 0.04 – 0.43), and found only the 'Social Engagement' subscale had statistically significant differences between the index parents and a normative sample, suggesting a more passive communication style for the index parents. No group differences were found in the 'Language Structure' and 'Pragmatic Language' subscales, however, analysis of the total score of the two groups (1 standard deviation below mean) was found to be significant.

Family History Interview / Family History Schedule (FHI/FHS)

Three studies evaluated the BAP using the FHI/FHS semi-structured interview method (no ES available). Folstein et al (1999) analyzed four items (language delays, reading difficulties, spelling difficulties and articulation) on the 'Communication' subscale. Accordingly, 'Early language-related cognitive difficulties' (ELRCD) were scored and a 'definite' or 'probable' rating was applied. Significantly higher rates of definite and probable ELRCD's were found in index parents compared to parents of children with Down's Syndrome. However, two other studies found index parents to perform equally to comparison groups on the 'Communication' subscale (Piven et al., 1997a; Pickles et al., 2013). Within the 'Social' factor, Piven et al. (1997a) found parents from MPX families had significantly higher prevalence of social deficits than parents of Down's Syndrome children, particularly in index fathers. Similarly, Pickles et al. (2013) reported significantly increased social deficits in index parents compared to parents of children with specific language impairment. Interestingly, no group differences were found between index parents and parents of children with a combined diagnosis of specific language impairment and ASD. Only Piven et al (1997a) assessed the 'Stereotyped Behaviors' subscale and reported MPX parents to have significantly more repetitive stereotyped behaviors compared to parents of Down's Syndrome children.

Modified Personality Assessment Schedule (MPAS/MPAS-R)

One study used the MPAS to evaluate the BAP (Piven et al., 1994) and three subsequent studies have used a modified version (MPAS-R) (Piven et al., 1997b; Losh et al., 2008; Losh et al., 2012) (ES not available). Three out of the four studies assessing the 'Aloof' subscale found significantly higher rates of aloofness in index parents compared to parents of Down's Syndrome children (Piven et al., 1994; Piven et al., 1997b), with one study reporting MPX parents to score significantly higher than SPX parents who in turn scored significantly higher than parents of children with Down's Syndrome (Losh et al., 2012). Similarly, the same trend for the 'Anxious', 'Hypersensitive', 'Rigid' and 'Untactful' personality traits was reported (Losh et al., 2012). Piven et al., (1997b) reported significantly higher rates of anxiousness, hypersensitiveness and rigidity in MPX parents in comparison to parents of Down's Syndrome, however, they found no significant differences between the two groups in the 'Untactful', 'Undemonstrative' and 'Unresponsive' traits. Piven et al., (1994), however, did find significantly higher rates of untactfulness and undemonstrativeness in index parents compared to parents of children with Down's Syndrome. In a more recent study, Losh et al (2012) failed to find a significant difference for the 'Overly Conscientious' subscale, but they did find a significant difference in the 'Rigidity' subscale.

Pragmatic Rating Scale (PRS / PRS-M)

A total of five studies assessed the BAP using the PRS (ES range 0 – 1.14). Landa et al (1992) combined blind and unblind ratings and reported higher total scores for the index parents compared to their control sample of parents of Down's Syndrome and typical development. Losh et al (2012) found in their sample of mothers only, that index mothers had similar pragmatic language violations to mothers of children with Fragile X Syndrome, and both these groups had higher frequency of violations than mothers of typically developing children. Piven et al (1997b) reported higher frequency of pragmatic language violations and speech errors in MPX parents compared to parents of Down's Syndrome children. Additionally, Losh et al (2008), found a linear trend for both pragmatic language violations and speech errors, reporting MPX parents to score significantly higher than SPX parents who in turn scored significantly higher than parents of children with Down's Syndrome. Ruser et al (2007), used a modified version of the PRS (PRS-M) and reported index parents to have significantly higher deficits in subscales of emotional expressiveness and awareness of the other, over-talkativeness and language in comparison to parents of children with Down's Syndrome. Group differences in the communicative factor was not found to be significant, however, index fathers showed significantly increased communication deficits than index mothers. The total PRS-M score revealed significant group differences between index parents and Down's Syndrome parents, with index fathers scoring higher than index mothers.

Social Responsiveness Scale (SRS)

The SRS was used as a measure to assess the BAP by two studies in our review (ES range 0.02 – 0.90). De la Marche (2012) reported all index fathers (MPX and SPX combined) having a significantly higher total score compared to unaffected adult males, however no statistical differences were found between MPX fathers and SPX fathers and SPX fathers and male controls. In contrast, Schwichtenberg et al (2010) found that both the MPX and SPX fathers in their sample scored significantly higher than fathers of typically developing children. No differences between mothers in both groups were found.

Other measures of personality and friendships

Another personality measure used in studies of the BAP is the NEO Personality Inventory (NEO-PI). Two studies show a trend for parents from MPX families scoring significantly higher on the neuroticism subscale in comparison to parents of children from SPX families (Losh et al., 2008) and parents of Down's Syndrome probands (Piven et al., 1997b; Losh et al., 2008) (ES 0.79, n = 1). Furthermore, the same two studies assessed quality of friendships using the Friendship Interview (FI), indicating significantly fewer friendships in parents from MPX families in comparison to parents of

children from SPX families (Losh et al., 2008) and parents of Down's Syndrome children (Piven et al., 1997b; Losh et al., 2008). Interestingly, Losh et al. (2008) also found sex differences in the quality of friendships within ASD parents, with fathers from MPX families and SPX families having significantly fewer friendships than mothers from MPX families and SPX families (ES 1.14, n = 1).

Reciprocal social interaction

Two studies assessed alexithymia (i.e. inability to identify and describe emotions in oneself) as part of the BAP. Szatmari et al (2008) used the Toronto Alexithymia Scale (TAS-20) as a measure of alexithymia and despite its three factors (difficulty identifying feelings, difficulty describing feelings and externally-oriented thinking) not reaching significance, the total score confirmed higher frequency of alexithymia in index parents compared to parents of children with Prader Willi syndrome. Using the same scale, however, Berthoz et al (2013) failed to find a statistically significant difference between index parents and unaffected adults (ES range 0.14 – 0.25). Another measure of alexithymia used by Berthoz et al (2013) was the Bermond-Vorst Alexithymia Questionnaire-B (BVAQ-B), however no significant differences were found between the samples (ES range 0.02 – 0.19).

Berthoz et al (2013) further assessed social anhedonia (i.e. inability to experience pleasure from activities usually found enjoyable), using the Revised version of the Social Anhedonia Scale (SAS) (ES 0.25) and found no significant differences between the index parents and unaffected adults. However, Berthoz et al (2013) found index parents to score significantly higher than unaffected adults on physical anhedonia as measured by the Physical Anhedonia Scale (PAS) (ES 0.33).

Social and narrative language

In addition to the PRS, which was specifically designed to assess the deficits in social language as a BAP expression, two other measures have assessed social and narrative language. Di Michele et al (2007) used the Grice's Conversational Maxims task to assess pragmatic conversations and found the index parents performed significantly worse when compared to parents of typically developing children and parents of children with Down Syndrome (ES not available). Landa et al (1991) used 'spontaneous narrative discourse performance' to assess narrative-discourse deficits. They reported control adults producing significantly more complete episodes and stories with multiple episodes, and the mean overall quality for the index parents was significantly less than for the comparison adults (ES range 0.35 – 0.73).

Repetitive / restrictive behaviors and interests

Repetitive and restrictive behaviors are a core symptom of ASD. The majority of findings in parents of autistic probands corresponding to this domain are covered in the studies that assess the BAP in terms of rigid and perfectionistic personalities. Only one study used an experimental questionnaire designed to examine real-life, non-social skills and preferences such as insistence on routines and circumscribed hobbies. Briskman et al (2001), reported index parents to score significantly higher than parents of boys with dyslexia and typical development (ES range 0.37 – 1.11).

2.3.4. Cognitive domain

Most forms of neuropsychological tests involve multiple cognitive functions suggesting that cognitive domains can be related to each other. I have organized the measures for this broad domain under different categories based on the cognitive function which they predominantly assess, however, an overlap may exist. Refer to Appendix 3 for the review of cognitive studies of parents of autistic probands. References for the different measures can be found in the studies included in this review and in more specialized text book resources (Lezak et al., 2012).

General intellectual functioning

Intelligence Quotient (IQ) was measured with different versions of the Weschler Scales in the studies. Thirteen studies assessed total Verbal IQ (VIQ) (ES range 0.05 – 1.28, n = 12), with scores for index parents similar to comparison groups in all but one study (Fombonne et al., 1997) with higher scores for index parents when compared to parents of Down's Syndrome children. Several VIQ subtests were also independently tested. Three studies used the Digit span subtest (some modified it to assess short term memory) (ES range 0.04 – 0.67), of which two found better performance in index parents compared to parents with children with Down's Syndrome (Fombonne et al., 1997) and parents of children with specific language impairment (Whitehouse et al., 2007). Only one study used the Arithmetic subscale and found no significant differences between index parents compared to parents with children with Down's Syndrome (Fombonne et al., 1997) (ES 0.25). Four studies used the Vocabulary subtest (ES range 0.04 – 0.96) and results were mixed, with one study indicating higher scores for index parents compared to parents of children with Down's Syndrome (Fombonne et al., 1997), another indicating a reverse trend with index parents scoring significantly lower than parents of typically developing children (Smalley & Asarnow, 1990), and two revealing no significant differences between groups. Four studies assessed the Comprehension subtest (ES range 0.31 – 0.74), with only one indicating a significant difference with index parents scoring significantly higher than parents of children with Down's Syndrome (Fombonne et al., 1997). Additionally, two studies used

the Similarities subtest (ES range 0.13 – 0.35) with only one reporting a significant difference (Fombonne et al., 1997).

Thirteen studies also assessed total Performance IQ (PIQ) (ES range 0 – 1.16, n = 12), with three studies reporting a significant difference, with index parents performing poorer than parents of children with Down's Syndrome (Folstein et al., 1999; Piven & Palmer, 1997) and unaffected adults (Schmidt et al., 2008). One study, however, reported an opposite trend with index fathers performing significantly better than fathers with a child with specific language impairment (Lindgren et al., 2009). Several PIQ subtests were also independently tested. Four studies used the Picture Completion subtest (ES range 0.07 – 0.65), however only two reported significant lower scores for index parents compared to parents of children with Down's Syndrome (Folstein et al., 1999; Piven & Palmer, 1997). Moreover, Folstein et al (1999) also reported lower scores on the Picture Arrangement subtest with the same trend of significance (ES range 0.03 – 0.26, n = 2). Two studies assessed the Object Assembly subtest (ES range 0.12 – 0.62), however only one reported a significant difference with MPX parents scoring lower than parents of Down's Syndrome children (Piven & Palmer, 1997). Furthermore, Schmidt et al. (2008), found significantly lower scores on the Matrix Reasoning subtest in index parents compared to unaffected adults (ES 0.67). Interestingly, none of the five studies assessing the Block Design subtest (ES range 0.04 – 0.43) and one study assessing the Digit Symbol subtest found significant differences between groups (ES range 0.17 – 0.19).

Full Scale IQ (FSIQ) (ES range 0.05 – 1.88, n = 13) was assessed in fourteen studies in our review with three studies reporting a significant poorer performance in index parents when compared to parents of children with Down's Syndrome (Folstein et al., 1999; Losh et al., 2008) and a combined clinical group of parents of children with Down's Syndrome and typical development (Losh & Piven, 2007).

Additionally, four studies used the Raven's Progressive Matrices to report Nonverbal IQ (NVIQ), with no significant differences found between groups (Bölte & Poustka, 2003; Bölte and Poustka, 2006; Bölte et al., 2007; Sucksmith et al., 2013) (ES range 0.05 – 0.57).

Structural language abilities

A number of studies assessed structural language abilities using a variety of different measures. Results are divided into specific domains. Receptive language skills were assessed by three studies using two measures. The Peabody Picture Vocabulary Test (PPVT-III) (ES range 0.33 – 1.58) was used by two studies with only one study reporting index mothers as having significantly more deficits

than mothers of children with ASD and language impairment who in turn had more deficits compared to mothers of children with a specific language impairment (Lindgren et al., 2009). Whitehouse et al (2007) used the Test for Reception of Grammar-2 (TROG-2) to evaluate receptive grammar and reported no differences between groups (ES not available). Schmidt et al (2008) assessed expressive language using the Expressive Vocabulary Test (EVT) (ES 0.10) and the Verbal Fluency subtest of the Delis Kaplan Executive Function System (DK-EFS) (ES 0.16 – 0.39) reporting no significant differences between index parents and unaffected adults. Additionally, they assessed figurative language using the Figurative Language subtest from the Test of Language Competence - Expanded Edition (TOLC-E) reporting no significant differences between the two groups (ES 0.28).

Phonological processing was assessed in five reports using five different tests. Lindgren et al (2009) used the Comprehensive Test of Phonological Processing (CTOPP) (ES range 0.02 – 1.42, n = 2), revealing significantly better performance in phonological awareness and the non-word repetition subtests in the index mothers compared to mothers of children with a specific language impairment. In contrast, however, Schmidt et al (2008) found index parents to perform significantly lower than unaffected adults in the same non-word subtest. Bishop et al (2004b) used a different Non-word Memory Test (ES range 0.02 – 0.04) and a Nonsense Passage Reading test (ES range 0.04 – 0.42) to assess phonological processing, none indicating significant differences between index parents and parents of typically developing children. However, Whitehouse et al (2007) did find index parents to perform significantly better than parents of children with specific language impairment in the Nonsense Words subtest of the NEPSY (A Developmental Neuropsychological Assessment Test Battery) (ES range 0.04 – 0.88). In contrast, Plumet et al (1995) found no significant differences in composite verbal scores when comparing index parents to parents of children with Down's Syndrome using a battery of verbal tasks with an emphasis on orthographic and phonological abilities (ES 0.22).

Reading skills were assessed by eight studies using seven different measures. Piven and Palmer (1997) used the Rapid Automized Naming (RAN) task and found no differences in the number and letter categories, however, they found significant differences with MPX parents taking longer to complete the task on the color and object categories (ES range 0.17 – 0.58). Similarly, Losh et al. (2010) combined the color and object categories and reported index parents taking longer to complete the task when compared with parents of typically developing children (ES not available). The Woodcock-Johnson Psycho-Educational Battery – Revised (WJ-R) has several subtests, and no significant differences were found in the broad reading (ES range 0.48 – 2.11) and reading skill composite scores (Lindgren et al., 2009) (ES range 0.40 – 1.84), the word attack subtest (Piven & Palmer, 1997; Lindgren et al., 2009) (ES range 0.09 – 1.35) and letter word subtest (Piven & Palmer,

1997). However, Folstein et al (1999) found a significantly lower reading age and reading grade using the nonsense word reading subtest in index parents compared to parents of children with Down's Syndrome (ES 0.40). Mothers of children with ASD performed better in the dictation (ES range 0.17 – 0.99, n = 2) and passage comprehension subtests (ES range 0.45 – 1.54, n = 2) compared to mothers of children with specific language impairment (Lindgren et al., 2009). In contrast, Piven and Palmer (1997) found MPX parents had more difficulties in the passage comprehension subtest when compared with parents of children with Down's Syndrome. Interestingly, no differences were noted in comprehension (ES range 0.12 – 0.36) and passage reading subtests (ES range 0.21 – 0.36) using the Gray Oral Reading Test (GORT) (Folstein et al., 1999; Fombonne et al., 1997) and the Edinburgh Reading Test (ERT) (Fombonne et al., 1997). Fombonne et al (1997) also used the National Adult Reading Test (NART) (ES range 0.20 – 0.44, n = 2) reporting index parents scoring significantly lower than parents of children with Down's Syndrome. However, Baron-Cohen & Hammer (1997) found no significant differences in error scores between index parents and parents of typically developing children. Whitehouse et al (2007) used the Test of Word Reading Efficiency (ES range 0.03 – 0.62) and found index parents performed better than parents of children with specific language impairment on the phonemic decoding efficiency subtest (nonsense words). Finally, Schmidt et al (2008) found no significant differences in reading difficulties using the Reading History Questionnaire (RHQ) between index parents and unaffected adults (ES 0.34).

Three studies assessed spelling abilities using two different measures. Whitehouse et al (2007) found no group differences using a Speeded Dictation task (ES not available). Furthermore, Fombonne et al (1997) found a superior performance by index parents on the Schonell Spelling Test (SST) (ES range 0.02 – 0.13, n = 2). Only one study assessed oromotor functioning using the oromotor sequencing subtest of the NEPSY Test Battery (ES range 0.43 – 0.54) reporting index families performing better than parents of children with specific language impairment (Whitehouse et al., 2007).

Social cognition

In this domain measures assess the ability to process information relating to other people's mental states. Five reports assessed the 'Theory of Mind' using different versions of Reading the Mind in the Eyes Test (ES range 0.03 – 1.51, n = 4). Three studies reported deficits between index parents and comparison groups (Baron-Cohen & Hammer, 1997; Losh & Piven, 2007; Losh et al., 2009). In contrast, Gocken et al (2009) and Tajmirriyahi et al (2013), found no significant group differences in mental state decoding in the eyes test. Furthermore, Gocken et al (2009) explored mental state decoding using a faces test and reported no significant differences between index parents and a normative sample (ES 0.23). Tajmirriyahi et al (2013), however, used a novel method of Reading the

Mind in the Voice Test to reveal significantly higher deficits in mental state decoding in index parents when compared to parents of children with Down's Syndrome and typical development (ES range 0.63 – 0.98). Additionally, Di Michele et al (2007) used False Belief Tasks (smarties task, Sally-Anne task and unexpected transfer test) and found index parents passed fewer false belief tests in comparison to parents of children with Down's Syndrome and typical development (ES not available). Similarly, Gocken et al (2009) reported poorer performance in index parents compared to a normative sample using the Unexpected Outcomes Test (UOT) (ES 0.58), however, they did not find a significant difference using The Hinting Task (ES 0.36).

Remarkably, only one study assessed empathy using the Empathy Quotient (EQ) reporting significant impairments in empathy in index fathers compared to unaffected males (Sucksmith et al., 2013) (ES 0.11 – 0.40).

Affect perception was assessed in eight studies using twelve different tests of emotion recognition and labeling. Using the 'Bubbles' method with pictures of facial affect, Adolphs et al (2008), showed no difference in accuracy and reaction time, however, the 'BAP+' group used significantly different facial information (eye region and mouth region) in comparison to the 'BAP-' group and parents of typically developing children (ES not available). Using the Penn Emotion Recognition Test (ER40), das Neves (2011) reported significantly longer time for correct responses in index parents compared to unaffected adults (ES range 0.54 – 1.09). They also report less accurate responses, identification of female and male faces as well as mild and extreme emotions. Bölte and Poustka (2003) showed no significant differences in groups using the Facial Affect Recognition Test (pictures by Ekman and Friesen) (ES range 0.32 – 2.06). Similarly, Sucksmith et al (2013) found no significant differences in accuracy and adjusted response time in index parents compared to unaffected adults using the Karolinska Directed Emotional Faces task (KDEF) (ES range 0.08 – 0.30). Kadak et al (2014), used the Emotion Recognition Test (using photos of facial affect from Ekman and Friesen) and found index parents had impaired recognition of happy, surprised and neutral faces compared to parents of typically developing children (ES range 0.05 – 0.50).

Two studies assessed emotional labeling and matching of facial patterns using three different measures. Using Schematic Line Drawings (ES not available), Palermo et al (2006) showed impaired labeling for sad, disgust and overall recognition of facial patterns in index parents compared to parents of typically developing children. In contrast, using the Emotion Matching Task (ES 0.06) and the Emotion Labeling Task (ES 0.19), Smalley and Asarnow (1990) found no significant impairments.

Executive function

Executive function encompasses abilities that underlie goal directed behavior. This broad domain was split into specific subdomains. Cognitive flexibility was assessed by four studies evaluating set-shifting tasks. Two studies using the Intradimensional/Extradimensional set shifting task (IDED) revealed significantly higher rates of learned irrelevance (Wong et al., 2006) (ES 0.52), trials to criterion (Hughes et al., 1997) (ES range 0.69 – 0.83) and errors to criterion (Hughes et al., 1997) (ES range 0.64 – 0.70) in index parents compared to control samples in the Extradimensional Stage only. However, Bölte & Poustka (2006) used the Wisconsin Card Sorting Test (WCST) (ES range 0.06 – 0.18) and the Trail Making Test (TMT – Parts A and B) (ES range 0.13 – 0.38) and found no impaired cognitive control between groups. Similarly, Losh et al (2009) also showed no significant difference in the total time to complete the TMT task between groups.

Five reports assessed planning abilities using two measures. Using the Tower of London (ToL) (ES range 0.07 – 0.93, n = 2), Hughes et al (1997) found index parents requiring a significantly increased number of extra moves to complete the task compared to unaffected adults. In contrast, Wong et al (2006) found no significant group differences in the number of extra moves and rule violations. Three studies used the Tower of Hanoi version (ToH) revealing no significant differences in the total time to complete variable (ES range 0.01 – 0.45n = 1) between index parents and a matched clinical sample (Bölte & Poustka, 2006) and non-clinical sample (Losh et al., 2009), and one study reporting significant differences in planning efficiency between index parents and parents of children with Down's Syndrome (Piven & Palmer, 1997).

One study assessed generativity using the Pattern Meanings test which measures ideational fluency, indicated a significantly impaired overall response generativity in index parents compared to a mixed sample of clinical and non-clinical comparison group (Wong et al., 2006) (ES 0.51).

Spatial working memory was assessed by one study using a Visual Search Test, indicating index parents scoring significantly higher between search errors when compared to unaffected adults (Hughes et al, 1997) (ES range 0.27 – 0.95). In contrast, however, using the Response to Inhibition and Load (RIL) test, Wong et al (2006) tested inhibition and it's interaction with working memory and found unimpaired reaction times and number of errors in index parents (ES range 0.04 – 0.28).

Verbal working memory was assessed using three measures by one study. Using the Stroop Interference Test (ES 0.2) and a Verbal Fluency test (letters KAS in Turkish) (ES 0.26), Gocken et al

(2009) revealed no significant differences between groups. However, they did show impaired accuracy in index parents using the Auditory Consonant Trigrams (ACT) (ES 0.55).

Local visual processing (Central Coherence)

Central coherence is a specific perceptual-cognitive style leading to a local visual processing bias. Five studies assessed dis-embedding performance using two tests. All five studies used the Embedded Figures Test (EFT) with mixed results. Three out of the five studies found significantly longer response times for index parents (Baron-Cohen & Hammer, 1997; Bölte & Poustka, 2006) and more specifically in index fathers, when compared to control fathers (Happé et al., 2001) (ES range 0.01 – 1.60, n = 5). No significant results were reported within the accuracy variable (Losh et al., 2009; Happé et al., 2001) (ES range 0.11 – 0.77, n = 2), however, de Jonge et al (2006) reported significantly fewer incorrect responses in index parents when compared to parents of children with Down's Syndrome (ES range 0.18 – 0.52). Furthermore, Happé et al (2001) revealed a similar trend with index parents making fewer errors using the Titchener Circles Illusion test (ES not available).

Mental segmentation ability was assessed with an Un/Segmented Block Design task (adaptation from the Weschler subtest) in two studies. Happé et al (2001) found faster response times in index parents in the unsegmented task (ES range 0.24 – 0.84, n = 1), and in contrast, Losh et al (2009) found significantly faster reaction times in the segmented task only (ES range 0.04 – 0.63, n = 1). Furthermore, de Jonge et al (2009) showed no group differences in mean number of errors using a Block Design Reconstruction task (patterns by Akshoomoff and Stiles) (ES range 0.10 – 0.16).

The Sentence Completion task was used by two studies to assess global sentence completions revealing significantly increased number of errors in index parents (Losh et al., 2009; Happé et al., 2001) and longer response times in index parents (Piven & Palmer, 1999).

Visual processing

Interestingly only one study assessed visual processing using four different measures. Contrast sensitivity was measured using the Vistech Contrast Sensitivity Charts and no significant differences were found between index parents and parents of children with Down's Syndrome (de Jonge et al., 2007) (ES 0.55). Similarly, tasks of motion discrimination (Motion Coherence Task (ES 0.25) and Moving Shape Task (ES 0.17)) and form discrimination (Form discrimination (Shape) Task) (ES 0.05) revealed no significant differences between the same groups (de Jonge et al., 2007).

2.3.5. Other psychiatric conditions domain

This domain was assessed in seven reports using nine different measures. Refer to Appendix 4 for the review of other psychiatric conditions of parents of autistic probands. Piven et al (1991) used the Schedule for Affective Disorders and Schizophrenia - Lifetime Version (SADS-L) and found significantly higher scores in the 'Anxiety' factor when compared to parents of children with Down's Syndrome, and no statistical significance was found for the 'Major Depressive Disorder' subscale between the two groups (ES not available). However, using a modified version of the Schedule for Affective Disorders and Schizophrenia - Lifetime Version Modified for the Study of Anxiety Disorders, Revised (SADS-LA-R), Piven and Palmer (1999) did find significantly higher frequency of 'Major Depressive Disorder' in index parents in addition to the 'Social Phobia' factor.

Micali et al (2004) devised a parental questionnaire and validated their results from consented medical records from GPs, found a significant trend towards higher prevalence of 'Depression' and 'Anxiety' in index parents. Using the Symptom Checklist-90-Revised (SCL-90-R), Bölte et al (2007), found significantly increased frequency in index parents in four of the nine subscales (Depression, Hostility, Phobic-anxiety and Paranoid Ideation) (ES range 0 – 1.33). Additionally, Bölte et al (2007) also assessed personality style and disorder using the Personality Style and Disorder Inventory (PSSI), and reported significantly higher rates in index parents in five out of fourteen factors (Reserved/Schizoid, Self-critical/Insecure, Critical/Negativistic, Spontaneous/Borderline and Quiet/Depressive) (ES range 0.02- 1.18).

Gocken et al (2009) assessed Depression and Anxiety factors using the Brief Psychiatric Rating Scale (BPRS) between index parents and a normative comparison group and only found a statistically significant difference in the Depression factor with index parents scoring higher (ES range 0.29 – 0.44). Similarly, Ingersoll et al (2011) assessed depressed mood using the Centre for Epidemiological Studies – Depression Scales (CESD) and showed index mothers as having increased rates of depression when compared to a normative sample of mothers (ES 0.35). Interestingly, Berthoz et al (2013), reported no significant differences in levels of depressive mood using the Beck Depression Inventory (BDI) (ES 0.50) and no significant differences were found in Anxiety levels using the State (ES 0.19) and Trait portions (ES 1.24) of State-Trait Anxiety Inventory Form Y (STAI-Y) (Berthoz et al., 2013).

2.4. Discussion

This systematic review aimed to assess the evidence of behavioral, cognitive and psychiatric profiles of the BAP in unaffected biological parents of autistic probands by synthesizing the evidence from 60

studies meeting *a priori* search criteria. Results are discussed according to the following criteria: i) the number of studies that indicate significant impairments in each domain and subdomain; ii) quantitative criteria using effect sizes; and iii) the possible emerging themes across studies. Table 2.2 represents a summary of all measures used by studies meeting our search criteria.

Table 2.2 - Summary of the frequency of all measures used by studies meeting our search criteria and effect size ranges for each domain.

Socio-Behavioural Category		
BAP Expression (ES range 0.01 – 1.49)		**Frequency**
	Autism Spectrum Quotient (AQ)	10
	Broader Autism Phenotype Questionnaire (BAPQ)	2
	Broader Phenotype Autism Spectrum Scale (BPASS)	1
	Communication Checklist – Adult (CC-A)	1
	Family History Interview / Family History Schedule (FHI/FHS)	3
	Modified Personality Assessment Schedule – Revised (MPAS-R)	4
	Pragmatic Rating Scale (PRS)	4
	Social Responsiveness Scale (SRS)	2
Other Measures of Personality and Friendships (ES range 0.79 – 1.14)		**Frequency**
	The Friendship Interview (FI)	2
	The Neo Personality Interview (NEO-PI)	2
Reciprocal Social Interaction (ES 0.33)		**Frequency**
Alexithymia	Toronto Alexithymia Scale (TAS-20)	2
	Bermond-Vorst Alexithymia Questionnaire – B (BVAQ-B)	1
Anhedonia	Revised Social Anhedonia Scale (SAS)	1
	Physical Anhedonia Scale(PAS)	1
Social & Narrative Language (ES 0.50 – 0.73)		**Frequency**
	Grice's Conversational Maxims Task	1
	Spontaneous Narrative Language	1
Repetitive, Restrictive Behaviors & Interests (ES 0.37 – 1.11)		**Frequency**
Everyday Preferences & Abilities	Real Life Skills & Preferences	1
Cognitive Category		
General Intellectual Functioning (ES range 0.14 – 1.16)		**Frequency**
	Weschler Scales	19
	Raven's Progressive Matrices (RPM)	4

Structural Language Abilities (ES range 0.04 – 1.65)		**Frequency**
Receptive Language	Peabody Picture Vocabulary Test (PPVT-III)	2
	Test for Reception of Grammar - 2 (TROG-2)	1
Expressive Language	Expressive Vocabulary Test (EVT)	1
	Verbal Fluency Subtest - Delis Kaplan Executive Function System (DK-EFS)	1
Figurative Language	Figurative Language Subtest - Test of Language Competence – Expanded (TOLC-E)	1
Phonological Awareness	Comprehensive Test of Phonological Processing (CTOPP)	2
	Nonword Memory Test	1
	Nonsense Passage Reading Test	1
	Nonsense Words Subtest - Nepsy Test Battery	1
	Battery of Verbal Tasks (inc. orthographic & phonological abilities)	1
Reading Abilities	Rapid Automized Naming (RAN)	2
	Woodcock-Johnson Psycho-Educational Battery – Revised (WJ-R)	3
	Gray Oral Reading Test (GORT)	2
	Edinburgh Reading Test (ERT)	1
	National Adult Reading Test (NART)	2
	Test of Word Reading Efficiency	1
	Reading History Questionnaire (RHQ)	1
Spelling Abilities	Schonell Spelling Test (SST)	1
	Speeded Dictation Task	2
Oromotor Functioning	Oromotor Sequencing Subtest - NEPSY Test Battery	1
Social Cognition (ES range 0.05 – 1.51)		**Frequency**
Theory of Mind	Reading the Mind in the Eyes Test (different versions)	5
	The Faces Test	1
	Reading the Mind in the Voice Test	1
	False Belief Tasks (Smarties task; Sally-Anne task; unexpected transfer test)	1
	Unexpected Outcomes Test (UOT)	1
	The Hinting Task	1
Empathy	Empathy Quotient (EQ)	1
Affect Perception / Emotion Recognition	Pictures of Facial Affect – 'Bubbles' Method	1
	Penn Emotion Recognition Test (ER40)	1
	Facial Affect Recognition Test	1
	Emotion Recognition Test	1

	Karolinska Directed Emotional Faces task (KDEF)	1
	Point Light Basic Emotions task	1
	Trustworthiness of Faces task	1
	The Morphed Faces task	1
	The Movie Still task	1
	Schematic Line Drawings task	1
	Emotion Matching Task	1
	Emotion Labeling Task	1
Executive Function (ES range 0.27 – 1.27)		**Frequency**
Set-Shifting	Intradimensional – Extradimensional Set-Shifting task (IDED)	2
	Wisconsin Card Sorting Test (WCST)	1
	Trail Making Test (A & B)	2
Planning	Tower of London (ToL)	2
	Tower of Hanoi (ToH)	3
Generativity / Ideational Fluency	Pattern Meanings	1
Spatial Working Memory / Inhibition	Visual Search Test	1
	The Delayed Oculomotor Task	1
	Response Inhibition & Load (RIL)	1
Verbal Working memory	Auditory Consonant Trigrams (ACT)	1
	Verbal Fluency Test	1
	Stroop Interference Test	1
Central Coherence (Local Visual Processing) (ES range 0.18- 1.60)		**Frequency**
Disembedding Performance	Embedded Figures Test (EFT)	5
	Titchener Circles Illusion	1
Mental Segmentation Ability	Unsegmented Block Design Task (adapted from Weschler Scales)	2
	Segmented Block Design Task (adapted from Weschler Scales)	2
	Block Design task (Weschler scales)	2
	Block Design Reconstruction task	1
Attentional Engagement	Detection Task	1
Global Sentence Completions	Sentence Completion Task	2
Visual Processing (ES not available)		**Frequency**
Contrast	Vistech Contrast Sensitivity Charts	1

Sensitivity		
Motion Discrimination	Motion Coherence Task	1
	Moving Shape Task	1
Form Discrimination	Form Discrimination (Shape) Task	1
Other Psychiatric Conditions Category (Depression and Anxiety) (ES range 0 – 1.33)		**Frequency**
	Brief Psychiatric Rating Scale (BPRS)	1
	Personality Style & Disorder Inventory (PSSI)	1
	Symptom Checklist 90 – Revised (SCL-90-R)	1
	Schedule for Affective Disorders and Schizophrenia – Lifetime Version (SADS-L)	1
	Schedule for Affective Disorders and Schizophrenia – Lifetime Version Modified for the Study of Anxiety Disorders – Revised (SADS-LA-R)	1
	Parental Questionnaire	1
	The Centre for Epidemiological Studies – Depression Scales (CESD)	1
	Beck Depression Inventory (BDI)	1
	State-Trait Anxiety Inventory Form Y (STAI-Y)	1

Note. BAP = Broader Autism Phenotype; ES = Effect Size.

2.4.1. Summary of findings

Findings emerging from this review are discussed according to each domain. Within the socio-behavioural domain, eight measures that directly assess the BAP expression in unaffected parents showed substantial deficits in the domain of social and communication skills (AQ, 7/10 studies; BPASS, 1 study; CC-A, 1 study; FHI/FHS, 2/2 studies; SRS, 2/2 studies), rigid and perfectionistic (BAPQ, 2/2 studies; MPAS-R, 3/3 studies) and aloof (BAPQ, 2/2; MPAS-R, 3/4 studies) personality traits as well as pragmatic language difficulties (BAPQ, 2/2 studies; PRS, 4/4 studies) related to the core deficit in ASD and are reported consistently across most studies. Moreover, additional deficits in social and narrative language have been highlighted using measures of spontaneous narrative discourse (Landa et al., 1992) and the Grice's Conversational Maxims task (Di Michele et al., 2007). Available evidence also points to index parents establishing fewer friendships (FI, 2/2 studies) and an elevated frequency of neuroticism (NEO-PI, 2/2 studies). Despite being a core domain of a clinical diagnosis for ASD, the majority of findings in parents of autistic probands corresponding to restricted and repetitive behaviors and interests are covered in the studies that assess the BAP in terms of rigid and perfectionistic personality styles. Only one study used an experimental questionnaire designed to

examine -real life non-social skills and preferences such as insistence on routines and circumscribed hobbies (Briskman et al., 2001).

Within the socio-behavioural domain, reciprocal social interaction is probably the least studied subdomain in parents of autistic probands. As such, findings from alexithymia (TAS-20, 1/2 studies; BVAQ-B, 1 study with no significance found) and physical (PAS, 1/1 study) and social anhedonia (SAS, 1 study with no significance found) are modest and require further studies to explore these traits. Thus, I agree with previous reviews (Cruz et al., 2013; Gerdts & Bernier, 2011; Sucksmith et al., 2011) indicating that mild social/communication deficits, rigid/aloof personality traits and pragmatic language difficulties may be the most useful social behavioral candidate endophenotype traits as they meet all the established criteria (Gottesman & Gould, 2003), however, effect sizes throughout this domain varied considerably.

At the cognitive level, a remarkable finding is the discrepancies found in intellectual functioning of parents of autistic probands compared to parents of children with and without a clinical diagnosis. One of thirteen studies revealed significantly higher VIQ scores when compared to a clinical sample of parents of a child with Down's Syndrome Fombonne et al., 1997). Three of thirteen studies assessing PIQ reached a similar significant trend when compared to parents with a Down's Syndrome child (Folstein et al., 1999; Piven & Palmer, 1997) and unaffected adults (Schmidt et al., 2008). Total PIQ scores were significantly higher in index parents when compared to parents with a child with specific language impairment (Lindgren et al., 2009). Only two of twelve reports reached a significant deficit in FSIQ when index parents were compared to parents of children with Down's Syndrome (Folstein et al., 1999) and when compared to a combined sample of parents of a child with Down's Syndrome and of typical development. However, it is noteworthy that scores for all parents were well within the average range in all studies. Thus there is limited evidence for the role of intellectual functioning as an endophenotype for ASD with no clear clinical significance.

Several measures were used to assess the structural language abilities within the cognitive domain. Interestingly, no significant differences were found in the expressive language (TROG-2, 1 study with no significance found; EVT, 1 study with no significance found; DK-EFS Verbal Fluency Subtest, 1 study with no significance found) and figurative language categories (TOLCE-E Figurative Language Subtest, 1 study with no significance found). Lindgren et al (2009) found index parents to perform better than parents with a child with a specific language impairment on measures assessing receptive language (PPVT III, 1/2 studies; TROG-2, 1 study with no significance found) refuting the hypothesis

that families with ASD and specific language impairment don't share similar genetic loading for language.

In phonological awareness, findings are mixed with studies only reporting few deficits in nonsense word/passage reading tests (2/3 studies) with index parents performing better than parents with a specific language impairment child (Whitehouse et al., 2007) and parents of children with Down's Syndrome (Folstein et al., 1999). Using the RAN measure for reading skills, two studies reported faster times to complete the colour and object only tasks in index parents when compared to parents of children with Down's Syndrome (piven & Palmer et al., 1997) and parents of typically developing children (Losh et al., 2010). This may have relevance with regards to perceptual load in ASD. However, no significant differences were found in the rapid naming subtest of the CTOPP (Lindgren et al., 2009).

Findings from the social cognition domain including mental state decoding, affect perception, emotion recognition and labeling in the BAP also report mixed and conflicting results. Remarkably only one studied assessed empathy warranting further research in this subdomain.

Evidence from the broad domain of executive function in the BAP is also inconsistent but it is worth noting the few studies that have found impairments did not appropriately match experimental and control groups for IQ (e.g. Hughes et al., 1997).

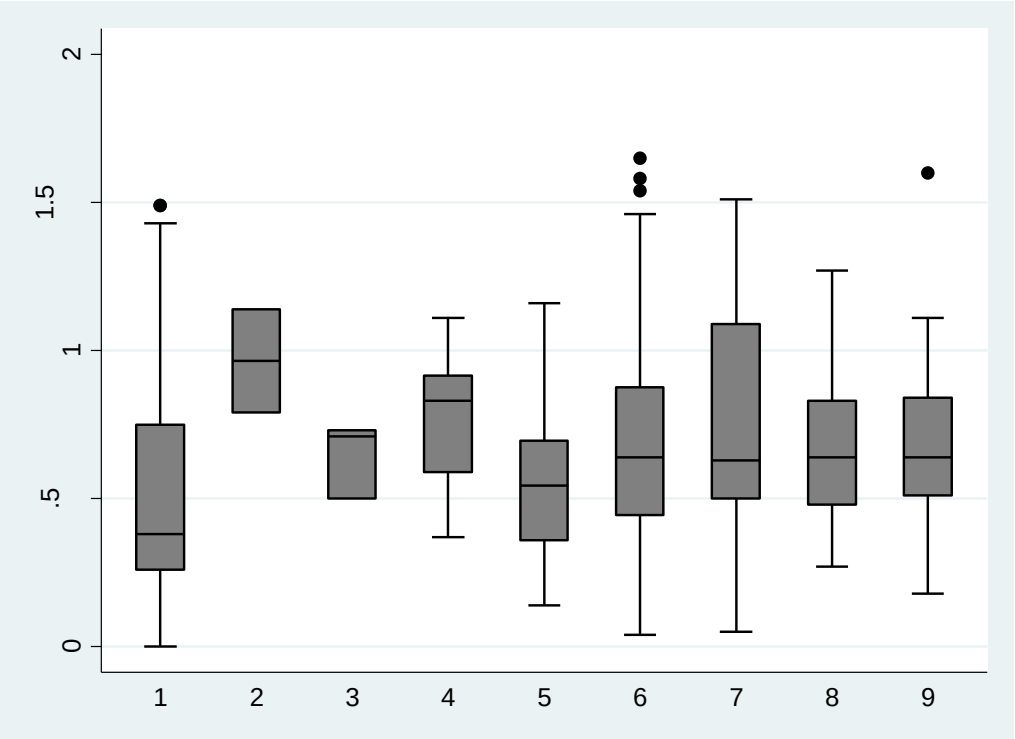
Similarly, findings from studies assessing performance on tests where local visual processing is an advantage (central coherence) were mixed in studies of the BAP. Conflicting results in the disembedding performance was noted (EFT, 4/8 studies; Titchener Circles Illusion, 1 study) as well as mental segmentation abilities (Unsegmented Block Design task, 1/2 studies; Segmented Block Design task, 1/2 studies; Block Design Reconstruction Task, 1 study with no significance found). Two studies, however, indicate higher frequency of errors and response times in index parents during a global sentence completion task (Sentence Completion task, 2/2 studies). Nonetheless, this area of cognition in the BAP also warrants further research.

Lastly, a number of studies have documented higher rates of depression (in 5/7 measures), anxiety (in 2/6 measures) and social phobia/social phobic anxiety (in 4/6 measures) in parents of children with ASD compared to normative samples (e.g. Gocken et al., 2009) and a clinical sample (e.g. Bölte et al., 2007). I also note depression and anxiety to be more prevalent (2/6 studies) in mothers of children with ASD. Ingersoll et al (2011) reported increased depressed mood in index mothers when compared

to mothers of typically developing children, with similar findings from Micali et al (2004). Although one can assume that having a child with a disability can effect mood and anxiety levels, many studies indicate an onset of these conditions before the birth of the child with ASD, suggesting that the stress of caring for a child with a disability did not cause the symptoms. Findings from our review revealed moderate to high magnitude of effect, thus, depression and anxiety may have a genetic link with ASD, supporting findings from a previous meta-analysis of psychiatric disorders in parents of children with ASD (Yirmiya & Shaked, 2005).

Figure 2.2 displays the boxplots reflecting effect size ranges for the socio-behavioural and cognitive domains and subdomains. It was not possible to include effect size ranges for the domain of other psychiatric conditions as depression and anxiety could not be divided into separate subdomains due to the measures used in the studies. The reciprocal social interaction subdomain was omitted as there was only one effect size available for one significant finding. Similarly, the visual processing subdomain was also omitted as findings were not significant.

Figure 2.2 - Boxplot reflecting effect size ranges for the socio-behavioural and cognitive domains.



1 = BAP Expression; 2 = Other Measures of Personality and Friendships; 3 = Social & Narrative Language; 4 = Repetitive, Restrictive Behaviours and Interests; 5 = General Intellectual Functioning; 6 = Structural Language Abilities; 7 = Social Cognition; 8 = Executive Function; 9 = Local Visual Processing (Central Coherence).

2.4.2. Emerging themes

A number of studies reviewed suggest that subclinical autistic traits aggregate in MPX families and occur less frequently in SPX families (Bernier et al., 2012; Losh et al., 2008). For instance a decreased number and intensity of BAP traits observed in parents of SPX in comparison to MPX provide behavioral evidence consistent with findings of increased de novo, non-inherited genetic events in SPX families (e.g. Sebat et al., 2007). Losh et al (2008) suggest that the BAP gradation expression across family types is consistent with increasing genetic liability to ASD.

A male bias is a well-documented feature in ASD (Werling & Geschwind, 2013). Findings from our review also indicate few sex differences, indicating this male bias (Ruser et al., 2007; De la Marche et al., 2012; Schwichtenberg et al., 2010). However, despite this and the clear sex bias in ASD, many studies do not suggest sex differences for most BAP features (e.g. Klusek et al., 2014).

Furthermore, our findings indicate that the majority of the studies reviewed were conducted in Western countries. There were too few studies from non-Western countries to make any meaningful comparisons. Further cross-cultural research is required to understand the endophenotypes of ASD within different cultural and geographical settings in order to tackle this geographical distribution bias.

2.4.3. Measure quality

It is clear from this review that a large number of measures have been utilized to assess the BAP in relation to different domains and the constructs analyzed are heterogeneous. However it should be noted that the current review does not assess in depth whether the BAP measures are valid or reliable in measuring BAP. Domain-wise, in many cases the same measures have been used by other studies. I discuss whether results for each measure in the same domain show the same magnitude and in the same direction.

For instance, Davidson et al (2014) reported that frequency of BAP traits vary significantly depending upon the measure utilized, highlighting the need for a different approach that utilizes multiple informants and relies on the assessment of distinct BAP traits.

2.4.4. Methodological limitations of studies

Any discordant findings in the studies reviewed may be partly explained by methodological differences between studies. Sample size and choice of comparison group play an important role in

the outcome of results. Six studies enrolled 30 or less index parents. Thus, relatively small sample sizes may lead to false negative results and/or limit the power to detect the BAP in the three domains.

Studies vary in their choice of a comparison group with some relying on the convenience of clinic-based samples where selection biases may lead to distorted results and others emphasizing the use of population based samples. For example, parents of children with Down's Syndrome were frequently used, but these parents are likely to be older and possibly different socio-economic status. Few studies matched index parents to control groups on intellectual functioning, age and socio-economic basis, thus making it difficult to assimilate if differences on specific cognitive tasks represent a specific impairment in functioning or are attributable to differences in demographic data.

2.4.5. Limitations and future directions

In addition to the limitation outlined above, there are other limitations. Given that nine additional studies were found through a manual search after the initial search, it is possible that other studies were not ascertained by our search terms. To address this limitation, future research may also consider additional search terms beyond those used here.

This review aimed to identify endophenotypes in behavioral, cognitive and psychiatric domains independently, and as such we did not assess associations between the BAP features across different domains. Losh et al (2009) suggest that it is likely that specific BAP traits co-segregate with performance in other domains. For instance, parents displaying rigid/perfectionistic personality traits could perform differently on tasks requiring cognitive flexibility. Additionally, most studies meeting our search criteria assessed only one or two domains, rendering it difficult to establish whether an endophenotypic overlap, if any, exists.

Future reviews should also include studies that examine neuroanatomical and neurofunctional correlates of the BAP. These are essential in furthering our understanding of the neural correlates of the behavioral, cognitive and psychiatric aspects of ASD.

More sophisticated research of the endophenotypes of parents of children with ASD may help develop better measures of evaluation of the BAP. Future studies should use a more comprehensive and quantitative framework using more robust measures to detect subtle subclinical autistic traits in the BAP in cross-cultural settings. To the best of our knowledge, no study assessing the endophenotypic profile of ASD in Africa has been published yet. Such research by our team is underway.

2.4.6. Conclusions

In summary, the current review increases our understanding of the BAP and extends the findings of previous reviews (Gerdts & Bernier, 2011; Sucksmith et al., 2011). It also supplements a systematic review (Cruz et al., 2013) and a meta-analysis (Yirmiya & Shaked, 2005) with a broader scope. However, findings should be interpreted with caution because of the small number of studies in such heterogeneously broad domains and other methodological limitations.

The assessment of the BAP profile in parents of autistic probands allows us to have a better insight into the varying underlying genetic mechanisms in ASD. The behavioral, cognitive and psychiatric endophenotypes in parents of autistic probands are still not clarified, however, evidence points towards mild social/communication deficits, rigid/aloof personality traits and pragmatic language difficulties as the most useful social behavioral candidate endophenotype traits. The existence of some deficits in the cognitive domain, does suggest familial vulnerability for ASD, however, more research is required to elucidate these findings within this domain. Furthermore, increased depressed mood and anxiety can also be useful markers of vulnerability.

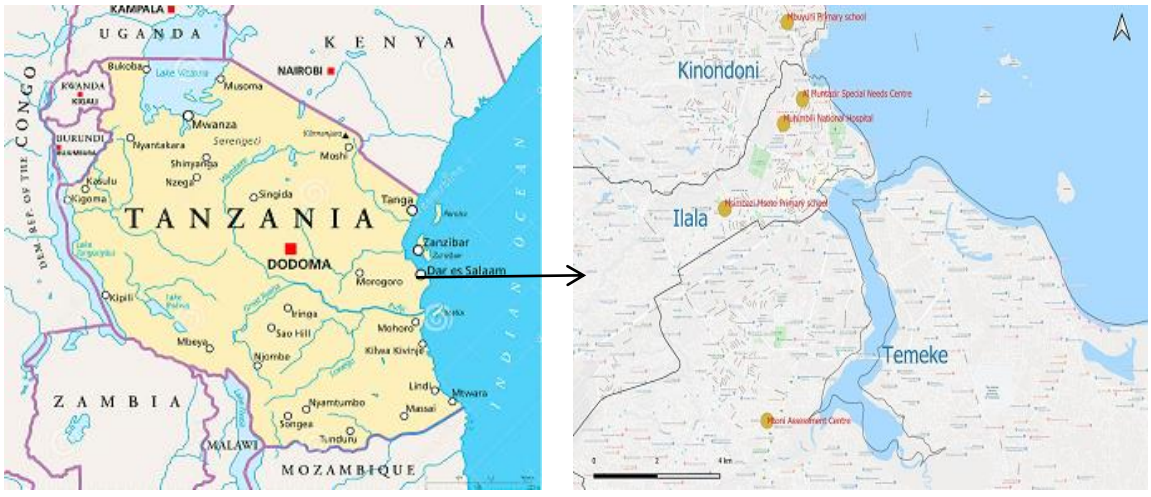
Chapter 3

Study design and general methodology

3.1. Study setting

This study was conducted in Dar-es-Salaam, Tanzania. Dar-es-Salaam is the *de facto* capital of Tanzania, with an ethnically diverse population of approximately 6.7 million in 2020. Kiswahili and English are the official languages in Tanzania. Data from the Directorate of Mental Health at the Ministry of Health, Social Welfare, Gender, Elderly and Children and indicate that childhood mental health is not given much importance and parents rarely seek care for children with developmental disorders. Currently, children are referred for diagnosis of Autism Spectrum Disorders (ASD) to Muhimbili National Hospital (MNH), a tertiary care center in Dar-es-Salaam, where the Diagnostic and Statistical Manual 4th Edition (DSM-IV) is used to diagnose ASD. At present, there are two registered public schools in Dar-es-Salaam, two privately owned faith-based organizations and a few unregistered centers which cater for children with ASD.

Figure 3.1 - Map of Dar-es-Salaam, Tanzania, including ASD registered schools and organizations.



3.2. Study design

This project involved qualitative and quantitative studies. The first phase employed qualitative research methodology to assess local experiences of ASD. The subsequent phase involved the

evaluation of the psychometric properties of the Social Communications Questionnaire (SCQ) and it's utility as a screening measure in my sample, an evaluation of the Autism Spectrum Quotient (AQ) and investigating the broader autism phenotype (BAP) in parents of children with ASD, as well as a case-control study to determine the risk factors for ASD in this region.

3.3. Sample size determination

3.3.1 Validation of the SCQ study

In order to obtain reliable and valid computations, a minimum sample size of 100 participants is required (Kline, 1979; MacCallum et al. 1999). For discriminant validity, I estimated sample sizes based on a validation study conducted in China (Guo et al., 2011) that had a similar design to my proposed study. In the Chinese study, the adapted measure was validated based on data from three groups of children; those with a previous diagnosis of ASD, those with neurodevelopmental disorders and typically developing children. The differences in test scores between children with autistic traits (Mean = 25.3, SD = 9.20) and those with a neurodevelopmental disorder (Mean = 12.2, SD = 10.6) were large. I assumed a Gaussian distribution. Using these mean scores I computed an effect size, Cohen d = 1.36. This effect size indicates that I would be able to detect the differences in performance in a minimum sample size of 40 children. Taking into consideration that I am working in a new region with little or limited expertise compared to China, I computed the sample size based on a more modest effect size of 0.7, an alpha of 0.05 and assuming a power of 95%; which indicates that a total of 100 children are needed to detect differences in performance.

3.3.2 Risk factor study

In order to establish a sample size requirement for the risk factor study, I estimated sample sizes based on a risk factor study conducted in India (Mamidala, 2014) in which they assess pre and perinatal risk factors for ASD. I chose fetal distress as the risk variable of interest for the purpose of sample size determination. Using the percentages of distribution of risk factor in children with ASD (23%) and typically developing children (4.2%), I applied a likelihood ratio test of 2 independent proportions at 90% power and 5% significance level. Using these assumptions, I would need at least 122 children, half of whom are cases and the other half controls to measure the risk factors in my study. The children were matched based on their level of expressive language which is necessary for assessments with the ADOS-2 Modules. Epidemiologically, this may have introduced selection bias, and so regression models of case-control studies of risk factors should be adjusted for chronological age, to circumvent this issue.

3.3.3 Broader Autism Phenotype (BAP) study

In order to establish a sample size requirement for the endophenotype study, I estimate sample sizes based on a recent broader ASD phenotype study conducted in Turkey (Kadak, 2014) in which they use the AQ on parents of children with ASD and parents of typically developing children. This would give an indication of how many parents need to be screened in order to detect broader autism phenotype traits in this study, and thus enables us to establish how many children with ASD need to be identified in the previous study. Using mean scores of parents of children with ASD (Mean= 19.63, SD= 5.42) and parents of typically developing children (Mean= 17.61, SD= 4.57) I computed an effect size, Cohen d= 0.39. With an alpha of 0.05 and assuming a power of 90%, a total of 240 parents, half of whom are cases and the other half controls, are needed to detect differences in performance for discriminant validity.

3.4. Assessment measures

3.4.1. ASD screening measure

Social Communication Questionnaire (SCQ - Rutter et al., 2003): The Lifetime version of the SCQ is a brief 40-item yes/no questionnaire that helps to evaluate communication skills and social functioning in children who may have ASD. This questionnaire is a cost effective way of screening for referral for a complete diagnostic evaluation. It is administered to a parent or other primary caregiver and takes less than 10 minutes. The SCQ is suggested for use in children above 4 years of age and is not appropriate for children with a mental age younger than 2 years. The SCQ has strong discriminating power between those with and without ASD (Chandler et al., 2007) and has been translated and validated cross-culturally in German (Bölte et al., 2008b), Portuguese (Sato et al., 2009), Chinese (Gau et al., 2011), Turkish (Avcil et al., 2015) and Greek (Zarokanellou et al., 2017). In addition to the Total Score, the SCQ can also be used to provide sub-scores that match the Reciprocal Interaction domain, the Communication domain and the Restricted, Repetitive and Stereotyped Patterns of Behaviour domain of the ADI-R.

3.4.2. Additional tools used to aid confirmation of the diagnosis of ASD in probands

Autism Diagnostic Observation Schedule, 2nd Edition (ADOS - Lord et al., 2000; ADOS-2 - Lord et al., 2012): The ADOS is designed to diagnose and assess ASD using a series of structured and semi-structured tasks that involve social interaction between the examiner and the subject. It consists of four modules; each attuned to differing developmental and language levels, ranging from little if any expressive and receptive language, and therefore can be administered to subjects ranging from children as young as 18 months through adolescence and adulthood. Each module takes 30 to 40 minutes to administer, making it a quick and robust instrument. The ADOS has been found to have

exceptional diagnostic sensitivity and specificity (Lord et al., 2000). Other diagnostic tools for ASD are also available including the Autism Diagnostic Interview Revised (ADI-R; Le Couteur et al., 2003), the Diagnostic Interview for Social and Communication Disorders (DISCO; Wing et al., 2002) and the Developmental, Dimensional and Diagnostic Interview (3Di; Skuse et al., 2004), all of which use interview techniques with parents or caretakers as a means of collecting information concerning the developmental history and current behaviour. The ADOS, however, is an observational assessment and can be used to evaluate almost anyone suspected of having ASD, from toddlers to adults, from children with no speech to adults who are verbally fluent.

Diagnostic Statistical Manual of Mental Disorders, 5th Edition (DSM-5 - APA, 2013): A DSM-5 checklist and guidelines were used for clinical assessments of the children in my sample (Appendix 5). The DSM-5 defines ASD within two domains; "persistent difficulties with social communication and social interaction" and "restricted and repetitive patterns of behaviours, activities and interests (this includes sensory behaviour). To diagnose the child with ASD, he/she must display all 3 criteria under the social interaction and social communication domain and at least 2 out of 4 under the restricted interests and repetitive behaviour domain. The symptoms must be present since early childhood and limit and impair everyday functioning. The DSM-5 also requires a severity rating be given for each domain ranging from requiring some support to requiring very substantial support.

3.4.3. Broader Autism Phenotype (BAP) measure

***Autism Spectrum Quotient - Adult (AQ – Baron-Cohen et al., 2001)*:** This is a self-report questionnaire used as a measure of the extent of autistic traits in adults. There are 50-items covering behaviors from 5 domains; communication, social skills, attention switching, imagination and attention to detail. Participants rate to what extent they agree or disagree on statements on a 4-point Likert scale. It is quick and easy to use and produces a near normal distribution in the general population (Baron-Cohen et al., 2001). The AQ has been used extensively and has been shown to have consistent results across culture (e.g. Dutch AQ: Hoekstra et al., 2008; Japanese AQ: Wakabayashi et al., 2006), and the AQ score is a good predictor of clinical diagnosis (Woodbury-Smith et al., 2005). Wheelwright et al (2010) have documented the AQ as providing an efficient method for quantifying where an individual lies along the dimension of autistic traits, and extends the notion of a broader phenotype among first degree relatives of those with ASD.

3.4.4. Socio-demographic questionnaire

A socio-demographic questionnaire was used to collect data for each participant's family and socio-demographic information (Appendix 6). This was designed based on prior used questionnaires from a

similar setting (e.g. Kariuki et al., 2016). Additionally, it included information on past medical history based on the probable risk factors of ASD from existing literature and those likely to be specific and common in this setting. Care was taken to analyse and include the most relevant and specific risk factors. The risk factors analysed were:

Parental factors: Maternal age at delivery, maternal age at first birth, paternal age at delivery, parental marital status, parental religion, parental ethnicity, parental education, parental occupation, parental age gap, birth order, birth weight and number of children ever born.

Prenatal factors: Pregnancy medical complications (gestational hypertension, gestational diabetes, eclampsia, maternal bleeding), pregnancy infections (prenatal fever, malaria during pregnancy), medication use during pregnancy (antibiotics), pre-term birth (≤ 37 weeks).

Perinatal factors: Assisted delivery (vacuum mediated delivery), labour complications (induced labour, prolonged labour), birth complications (breech presentation, umbilical cord complications, meconium aspiration), adverse perinatal events (birth asphyxia, delayed birth cry, difficulties breastfeeding).

Neonatal factors: Low birth weight (< 2.5 kg), neonatal jaundice, neonatal seizures immediately after birth.

Postnatal medical factors: Family history of seizures, seizures disorders, malaria (before the age of 3 years), head injury associated with loss of consciousness (before the age of 3 years).

3.4.5. Neuropsychological testing

For the purpose of this study, I used the adapted version of the Raven's Coloured Progressive Matrices (CPM; Raven et al., 1998; Adapted version; Kitsao-Wekulo et al., 2012) and the adapted version of the Peabody Picture Vocabulary Test (PPVT; Dunn & Dunn, 1981; Adapted version; Holding et al., 2004), both providing sound psychometric properties (internal consistency ≥ .70; test reliability ≥.75) enabling reliable administration by a trained person without previous experience in testing.

The Raven's CPM measures reasoning ability and is designed for young children between 5 to 12 years of age, older adults and mentally and physically impaired persons. The test consists of 36 items in 3 sets (A, Ab, B), with 12 items per set and takes between 15 to 30 minutes to administer. The items are arranged to assess the main cognitive processes which children under 11 years of age are usually capable. The PPVT is designed to assess the verbal intelligence of an individual. It measures receptive language processing from 2 years of age and takes 20 to 30 minutes to administer. All children in this study were asked to complete both these neuropsychological tests as a means to control for IQ and receptive language.

3.5. Training

3.5.1. Phase one: Qualitative study

I received training in Focus Group Discussions (FGD) and In-Depth Interviews (IDI) at KEMRI-Wellcome Trust Research Programme (KWTRP) in Kilifi, Kenya, from an experienced researcher with adequate knowledge and training in qualitative assessments. As Kiswahili is not my first language, a fieldworker was recruited to facilitate the FGD and IDI in Kiswahili. The fieldworker had previous experience in qualitative assessments and was familiar with research protocols. Practice sessions were held with primary school administrative staff where some participants were recruited from the attached autism unit.

3.5.2. Phase two: Main case-control studies

I attended a week-long course on the introduction to clinical training and research reliability training on the revised Autism Diagnostic Observation Schedule (ADOS-2) in Stellenbosch and Cape Town, South Africa. I was trained by Prof. Petrus de Vries specifically on (i) updates on ASD diagnosis (including DSM-5) (ii) an introduction to ADOS-2, demonstrations, role-play, hands on coding, discussion of ADOS assessments and (iii) obtaining research reliability training. I attended a further booster training by Prof. Petrus de Vries in research reliability for the ADOS-2 at KWTRP in Kilifi, Kenya. The focus of this training was on the administration of the tool and subsequent coding. I also received training by the team at the Neuroscience Department at KWTRP in Kilifi, Kenya, in quantitative data synthesis, and the administration of the neuropsychological tests such as Raven's CPM and PPVT.

A local fieldworker with prior research experience was trained on the study design, the process of consenting and administration of the socio-demographic questionnaire, SCQ, AQ and neuropsychological testing (Raven's CPM and PPVT). Additionally, the fieldworker was trained in the ethical principles of research conduct with human participants including respect for study participants and confidentiality. I conducted simulation exercises with the fieldworker on consenting, administration of questionnaires, proper handling and coding of questionnaires, over a one week period prior to data collection.

3.6. Translation of measures

Permission was sought and granted from the Western Psychological Services (WPS) to translate the SCQ. Initial translation of the English version of the SCQ into Kiswahili was done by two independent linguistic specialists at KWTRP in Kilifi, Kenya. A panel meeting of experts was held to harmonize all translated items and subsequent back-translation into English was done by another

independent linguistic specialist. Items 21, 34 and 40 were slightly modified to take into account the local cultural context. For instance, for item 34, social games for children such as the 'Mulberry Bush' and 'London Bridge is falling down' were replaced with local games such as 'Ukuti Ukuti', which involves a group of children holding hands, jumping and singing and going around in a circle. The final Kenyan version of the SCQ was then slightly modified to suit the Tanzanian Kiswahili by the fieldworker recruited for phase two and a linguistic specialist at Muhimbili University of Health and Allied Sciences (MUHAS), and back-translated into English by another linguistic specialist at MUHAS. The back-translated version was reviewed by a clinical psychologist from the Department of Psychiatry, Muhimbili National Hospital (MNH), who recommended minor modifications until thee questions therein retained their original meaning (Appendix 7).

Permission was sought and granted from the Western Psychological Services (WPS) to translate the ADOS-2 manual. The same translation and back-translation method as above was used for the ADOS-2 Manual (all modules).

I sought permission from the Autism Research Centre (ARC) at the University of Cambridge to translate the AQ into Kiswahili. The AQ was then translated in Tanzanian Kiswahili by a linguistic specialist at MUHAS, and back-translated into English by another linguistic specialist at MUHAS. The back-translated version was reviewed by a clinical psychologist from the Department of Psychiatry, Muhimbili National Hospital (MNH), who recommended minor modifications until the questions therein retained their original meaning (Appendix 8). We attempted to adapt the AQ, without significant modifications in terms of item content. We made some attempts to use local terms for item 13 and 24 for instance, which refer to library, party, theatre and museum. However, it is possible that some parents may not have had access to or experiences of these places/activities and would not be able to relate to items about them. Nonetheless, care was taken to ensure semantic equivalence of the translated items. The tool was informally piloted with parents for feedback on whether they understood the questions, wording appropriately in case meanings were ambiguous or unclear.

3.7. Ethical considerations and informed consent

This study was approved by the MUHAS Directorate of Research and Publications (Ref. No.MU/DRP/AEC/Vol.XV111/93), National Institute for Medical Research (NIMR; NIMR/HQ/R.8a/Vol.IX/1811) and registered with the Tanzania Commission for Science and Technology (COSTECH; No. 2014-294-NA-2014-127). Where necessary, approval to access special

needs schools, assessment centers, mainstream schools and day care centers was obtained from Ilala, Kinondoni and Temeke municipal councils.

All participants were informed of the objectives of the study. Verbal and written consent were sought from all parties using the consent forms designed for the studies (Appendix 9 & 10). Parents of participating children received an oral description, with examples, of the types of assessments. Parents and guardians were asked for oral consent and the child for assent to proceed. The family was allowed to withdraw the child from the study at any point, without fear or prejudice.

3.8. Sampling and data collection procedures

I was fully involved with the recruitment of participants and collected all the data for these studies with assistance from the fieldworkers where Kiswahili was required. I directly administered the neuropsychological tests, ADOS, SCQ, AQ and the socio-demographic questionnaire. I trained, supervised and oversaw any assistance from the fieldworkers.

I adapted the tools to be administered in the Tanzanian context and for use in low-literate parents. We did forward translation from English to Kiswahili and backward translation from Kiswahili to English, and independently checked whether the translated version retained the original meaning. Additionally, we conducted cognitive interviews with parents and caregivers to ensure that the translated items were understood. We then piloted the tools on parents to check reliability of the interviewers, to time duration of tool administration and to pick any inconsistencies before using them in the main studies. Furthermore, because of literacy issues, each item on the SCQ, AQ and socio-demographic questionnaire was read out to the parents and filled in together with the parents to ensure each item was thoroughly understood.

Considerations were given to blinding of assessors, however, in most instances I was doing the recruitment and assessments and so was not blinded to the case-comparison status. Additionally, due to the conditions of the children with ASD and NDD blinding was not always possible. Some of the children with ASD and NDD presented with severe and often noticeable symptoms that would be difficult for the assessors not to notice when interacting with the child. This may have introduced bias as assessors were aware of the status of each child which may have influenced the way questions were asked as well as expectations of their responses

3.8.1. Phase one: Qualitative study

Recruitment of study participants was done through a purposive sampling procedure. Two groups of participants were interviewed to capture a diversity of perspectives. First, caregivers of children with ASD were recruited through ASD units at Msimbazi Mseto Primary School (Ilala District) and Mbuyuni Primary School (Kinondoni District). Second, a broad range of key community informants were recruited. Parents of typically developing children were recruited from the mainstream facilities of the same two schools. Special needs educators and mainstream teachers were also recruited from these two schools as well as the Mtoni Assessment Centre (Temeke District). The government stakeholder was recruited from the Ministry of Education, Special Needs Division. Clinicians and social workers were recruited from MNH. Chapter 4 describes the participant groups and composition of FGD and IDI.

All FGD's were conducted in Kiswahili by an experienced fieldworker, with between four and seven participants in each, and each took approximately one and a half hours. I organized and supervised all FGD. I conducted ten IDI in English and the fieldworker conducted three in Kiswahili, and each interview took approximately one hour.

Interview schedules were developed by the research team following discussion and agreement between my supervisors and I, which included the following topic guidelines: description of behaviour manifestations, perceived causes of ASD and challenges encountered. Before commencing the FGD and IDI, informed consent was obtained and after completing the session all travel expenses were reimbursed. All FGDs and IDIs were audio-taped with the permission of participants to enable verbatim transcription.

3.8.2. Phase two: Main case-control studies

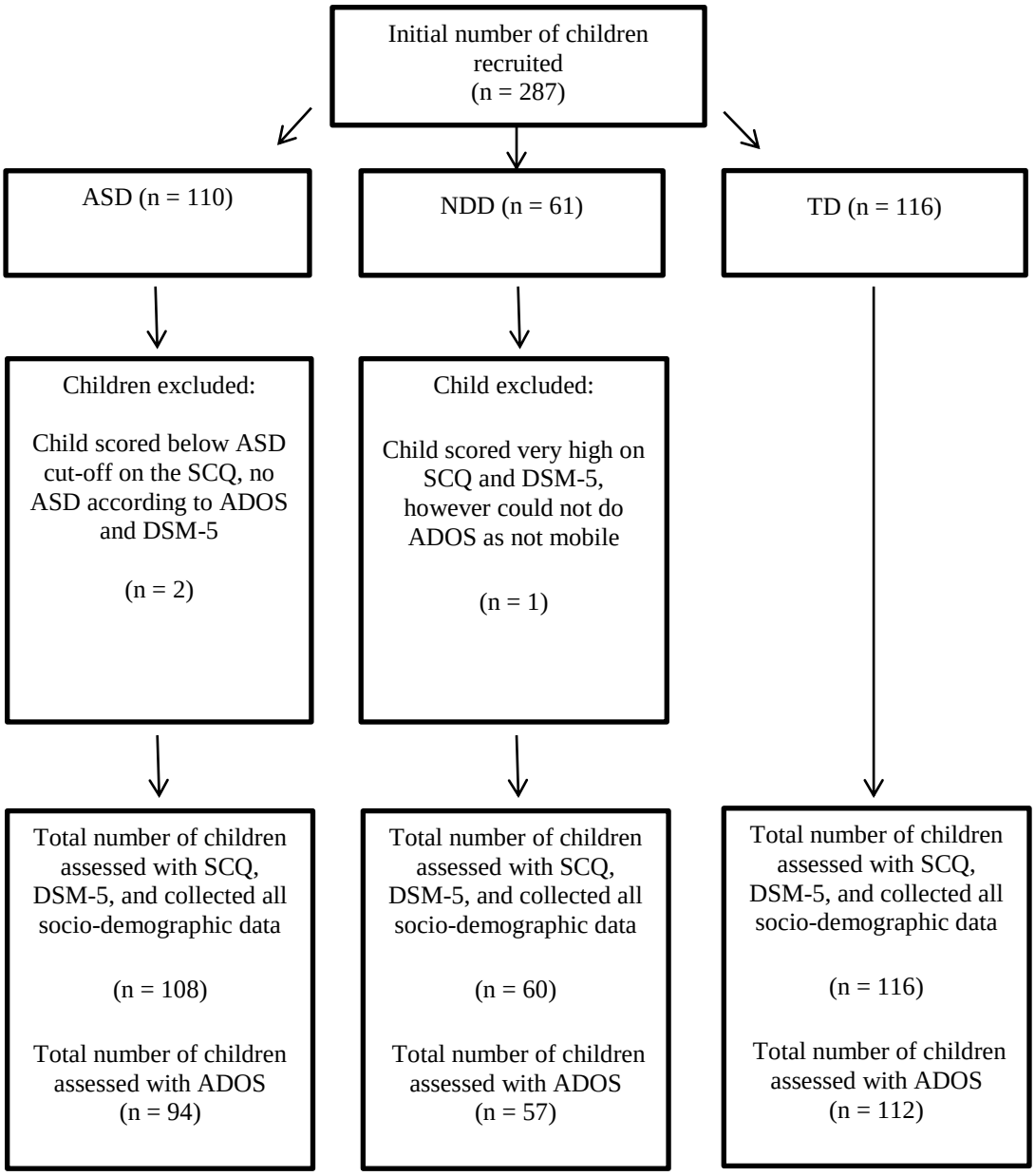
Three groups of children were recruited for the study. Children who had a diagnosis of ASD (n = 110) were recruited from the Child and Adolescent Clinic, Department of Psychiatry, Muhimbili National Hospital (MNH), private clinics and centres, and autism units attached to local primary schools in Dar-es-Salaam Tanzania. These children were aged from 5 to 12 years and had no known genetic disorders, deafness or motor impairment. Previous diagnosis was made by either a psychiatrist at MNH using DSM-IV criteria, or by a paediatrician in a private setting using DSM-IV criteria and the M-CHAT or an education assessment centre using pre-determined assessment criteria. At least one biological parent had to be available for the study (where biological parent was unavailable, data was collected from the caregiver, but excluded from the endophenotype study [AQ data]). Children with neurodevelopmental disorders (NDD n = 61) aged 5 to 12 years were recruited from MNH and special

needs schools in Dar-es-Salaam, Tanzania. The NDD group was matched on chronological age and had a previous diagnosis of a neurodevelopmental disorder which included, Down's Syndrome (n = 10), Learning Disability (n = 33), Seizure Disorders (n = 8) and ADHD (n = 10). The typically developing (TD) children (n = 116) were randomly selected from the community with no known concerns of language and/or behavioral problems and did not have any history of learning or psychiatric disabilities according to our assessments. They were matched with the ASD group on a surrogate marker of IQ i.e. level of expressive language (ADOS-2 Module). This was done as most of the children with ASD in our sample were nonverbal, thus matching on developmental age and verbal ability would allow better comparisons of autistic traits.

Families were invited to the clinic or the schools for assessment. Each visit lasted approximately 2 to 3 hours. After obtaining consent, parents of participating children were asked to complete the Social Demographic Questionnaire and the SCQ. All children were requested to complete the neuropsychological testing (Raven's CPM and the PPVT), followed by an ADOS-2 assessment. Parents were asked to be present in the assessment room and each assessment was videotaped so that later a panel of both local and international experts can categorize these children and this information was used as an extra validity check.

After completing ADOS assessments, two children with a previous diagnosis of ASD were excluded from further analysis as they did not meet the cut-offs for ASD with the ADOS, SCQ and DSM-5 criteria. Additionally one child with Down's syndrome scored very high on the SCQ and DSM-5 criteria, but we were unable to do an ADOS assessment on him as he was not mobile, and as such we excluded him from further analysis. The sample, therefore, consisted of a total of 284 children. It was not possible to do an ADOS assessment on all children for the following reasons; unavailability of the child (n= 6), incomplete assessments due to unmanageable behaviour (n= 15). Additionally, we are missing ADOS video recordings for two children. A number of families with typically developing children did not consent to video record the ADOS assessment (n= 21). Figure 3.2 is a flow chart showing participant enrolment. To ensure quality of assessment, all assessment forms were checked for accuracy and inconsistencies on the day of the assessment.

Figure 3.2 - Flow chart showing participant enrolment.



3.9. Data management and statistical analysis

I was solely involved with the management of the database.

3.9.1. Phase one: Qualitative study

Data collected in Kiswahili was translated and transcribed in English by a trained and experienced bilingual translator, and all data in English was transcribed in full. The transcripts were randomly checked against the recordings and imported into NVivo 10 (QSR International). Data were analyzed

using thematic analysis. The first step was to generate tentative themes representing participants' awareness and experiences in each transcript. For quality control, subsequent analysis involved initial coding of randomly selected transcripts by me and a supervisor. This enabled us to identify patterns across the data set and refine themes which guided the initial coding process. I coded all the data and transcripts were repeatedly re-examined and cross-compared with initial coding by a supervisor to identify common themes and explore participants underlying perceptions. Coherence of themes was discussed during frequent meetings throughout the analytic process, and final themes and subthemes were agreed upon by the research team.

3.9.2. Phase two: Main case-control studies

A database was created on LimeSurvey (https://www.limesurvey.org/), a free and open source on-line survey application written in PHP based on MySQL. I designed the database formats and coding. All ADOS assessment videos were stored in external hard drives.

All analysis were performed between the ASD and TD groups, and then ASD and NDD groups. Additional analysis between NDD and TD groups and between combined NDD+ASD and TD groups were performed for the risk factor analysis. Exploratory analysis on the distribution of continuous variables and univariable analysis were carried out using IBM SPSS Statistics version 20. After checking for normality of continuous variables, transformations (log or square-root) were performed where necessary. Parametric tests such as Student's-t-test were used on the transformed continuous scores if transformation resulted in a normal distribution. Otherwise, non-parametric tests such as the Mann-Whitney U test were used on the raw scores of continuous variables when the transformed scores did not achieve a Gaussian distribution. For categorical variables the Pearson's chi-square test were performed (or Fisher's exact test if frequency was ≤ 5). Multivariate analysis and likelihood ratio tests (LRT) for the risk factor analysis were performed using STATA version 13. Since the outcome variables were binary or dichotomous, logistic regression modelling was applied in computing odds ratios for the univariable and multivariable risk factors. The multivariable model focused on risk factors with plausible biological basis for the risk of ASD in such a way that parental marital status, religion, ethnicity, level of education and occupation were entered into the model as covariates to account for their potential confounding of other risk factors. All variables reaching a significance p-value of ≤ 0.250 in the univariable analysis were entered in the multivariable models, retaining all variables if the model showed acceptable goodness-of-fit statistics (measured using Hosmer-Lemeshow test). LRT was used to test for evidence of departure from linear trend, such that if linear trend was not violated a single odds ratio assuming all categories as linear ordinal levels was

computed, with odds ratios for individual categories computed if there was evidence for departure from linear trend.

For the validation studies, Cronbach's coefficient alphas were used to examine the internal consistency of the instruments using IBM SPSS Statistics version 20. Receiver operating characteristic curve (ROC) analysis was performed using STATA version 15. Further evaluation of the psychometric properties namely confirmatory factor analysis (CFA) and intraclass correlation coefficient (ICC) were performed using R version 3.0.2.

Chapter 4

Awareness and lived experiences of families of children with Autism Spectrum Disorders (ASD) and community stakeholders in Dar-es-Salaam, Tanzania.

4.1. Background

Given the global high prevalence of Autism Spectrum Disorders (ASD), there has been an increased interest to conduct research and provide services for children and families affected by ASD. In Africa, such efforts are constrained by the multitude of challenges. Despite the growing research evidence from the rest of the world there is relatively little known or published research about ASD in sub-Saharan Africa (Ruparelia et al., 2016; Abubakar et al., 2016b; Elsabagh et al., 2012). Poor community awareness, a lack of validated diagnostic tools and scarcity of professional manpower for evaluation and interventions are some of the challenges in conducting research in this this region (Ruparelia et al., 2016; Abubakar et al., 2016a; Bakare et al., 2014; Newton & Chugani, 2013; Bakare & Munir, 2009b).

While there is paucity of research highlighting lived experiences and challenges in raising a child with ASD in other developing countries (e.g. Wang et al., 2011; Divan et al., 2012), there is little research into these experiences and challenges within sub-Saharan Africa (Gona et al., 2016; Tekola et al., 2016). Furthermore, studies in Nigeria report low level of knowledge of ASD not only in the general population, but also among the medical community (Bakare & Munir, 2011a; Eisegbe et al., 2015).

There is currently very limited knowledge on lived experiences of children with ASD throughout Tanzania (Manji & Hogan, 2013); to the best of my knowledge there has been no empirical publications describing these experiences in Tanzania. A National Association for People with Autism - Tanzania (NAPA-T) was formed to bring together efforts of parents and caregivers in caring for and teaching people with ASD. A recent study highlighted a low level of knowledge of ASD amongst mainstream teachers in primary schools in Dar-es-Salaam, (Edward, 2015). Manji and Hogan (2013), however, report limited awareness of ASD at various levels and a lack of facilities for addressing the needs of people with ASD. Ambilike & Outwater (2012) describe the psychological, social, and economic challenges experienced by caregivers of children with neurodevelopmental disorders in Dar-es-Salaam, Tanzania.

Further research exploring the family's experiences of children with ASD in this region is imperative. We carried out a qualitative study to determine the level of knowledge and explore the family's experiences of ASD in Dar-es-Salaam, Tanzania.

4.2. Methodology

This study employed qualitative research methodology to access local experiences of ASD. Both focus group discussions (FGD) and in-depth interviews (IDI) were conducted, since triangulation enhances validity of the collected data. Participation was voluntary and written consent was obtained from all study participants. Ethical approval for the study was obtained from the Directorate of Research and Publications at Muhimbili University of Health and Allied Sciences (MUHAS), the National Institute for Medical Research (NIMR) and the Tanzania Commission for Science and Technology (COSTECH).

4.2.1. Study sample

Recruitment of study participants was done through a purposive sampling procedure. Two groups of participants were interviewed to capture a diversity of perspectives. First, caregivers of children with ASD were recruited through ASD units at Msimbazi Mseto Primary School (Ilala District) and Mbuyuni Primary School (Kinondoni District). Second, a broad range of key community informants were recruited. Parents of typically developing children were recruited from the mainstream facilities of the same two schools. Special needs educators and mainstream teachers were also recruited from these two schools as well as the Mtoni Assessment Centre (Temeke District). The government stakeholder was recruited from the Ministry of Education, Special Needs Division. Clinicians and social workers were recruited from MNH. Table 4.1 describes the participant groups and composition of FGD and IDI. We noted that there were several challenges and barriers to access special needs schools for children with ASD. Firstly, very few special needs schools are available and care given is not comprehensive, not all needs of these children are met, with limited resources and specialist care. It is mostly parents who are educated and economically privileged that are able to send their children to these special facilities, while many children of poor families do not know about these facilities or cannot afford to send their children to them.

Table 4.1 - Description and composition of Focus Group Discussions and In-Depth Interviews.

Participants of Focus Group Discussions ***(n)***	**Age range** ***(years)***	**Sex** ***M/F***	**Education Level** ***(n)***	***Number*** ***(Total = 38)***
Caregivers of children with ASD[a] *(2)*	24 - 60	2/9	P *(6);* S *(4);* N *(1)*	***11***
Special Needs Educators *(2)*	37 - 59	0/9	P (4); S *(4);* H *(1)*	***9***
Parents of typically developing children *(1)*	25 - 43	1/6	P *(5)*; S *(2)*	***7***
Mainstream Teachers *(1)*	29 - 49	1/5	S *(2);* H *(4)*	***6***
Social Workers *(1)*	32 - 57	2/3	H *(5)*	***5***
In-Depth Interviews (IDI)				
Participants interviewed	**Age range** ***(years)***	**Sex** ***M/F***	**Education Level** ***(n)***	***Number*** ***(Total = 13)***
Caregivers of children with ASD*	39 - 43	1 /2	P *(1)*; H *(2)*	***3***
Clinicians[b]	30 – 68	3/1	H *(4)*	***4***
Special Needs Educators	30-53	2/1	S *(1)*; H *(2)*	***3***
Mainstream Teachers	34-52	1/1	S *(1)*; H *(1)*	***2***
Government Official	58	F	H	***1***
Total Number of Participants in FGD and IDI				**51**

Note. M = Male; F = Female; ASD = Autism Spectrum Disorder; P = Primary level education; S = Secondary level education; H = Higher level education; N = None.

[a]Caregivers of children with ASD were mothers, fathers, older brother, grandmothers and maternal aunts; [b]Clinicians were Pediatricians, Clinical Psychologist and General Practitioner.

4.2.2. Procedures

All FGD's were conducted in Kiswahili by an experienced fieldworker, with between four and seven participants in each, and each took approximately one and a half hours. I organized and supervised all FGD. I conducted ten IDI in English and the fieldworker conducted three in Kiswahili, and each interview took approximately one hour.

Interview schedules were developed by the research team following discussion and agreement between the authors and included the following topic guidelines: description of behavior manifestations, perceived causes of ASD and challenges encountered (Table 4.2). Before commencing the FGD and IDI, written consent was obtained (Appendix 9) and after completing the

session any travel expenses were reimbursed. All FGD and IDI were audio-taped to enable verbatim transcription.

Table 4.2 - Interview Schedule for Caregivers.

1. Can you describe the typical behaviors of autistic children that you have seen? In what ways are autistic children different from other children with mental disabilities that you have seen?
2. In your opinion what causes autism?
Parenting issues
3. What challenges do you encounter in your day-to-day caring of your child with autism?
4. How do you cope with these challenges?
5. What kind of assistance or support do you get?
Educational issues
6. Can you tell us your child's experiences within the school system?
7. What are the challenges faced by caregivers of autistic children within the education system?
8. What are the challenges faced by teachers who teach autistic children?
9. Is there anything more you would like to discuss regarding children with autism? Their education? Or any other relevant topic?

Note. Interview schedule was adapted for community stakeholder groups accordingly.

4.2.3. Data management and analysis

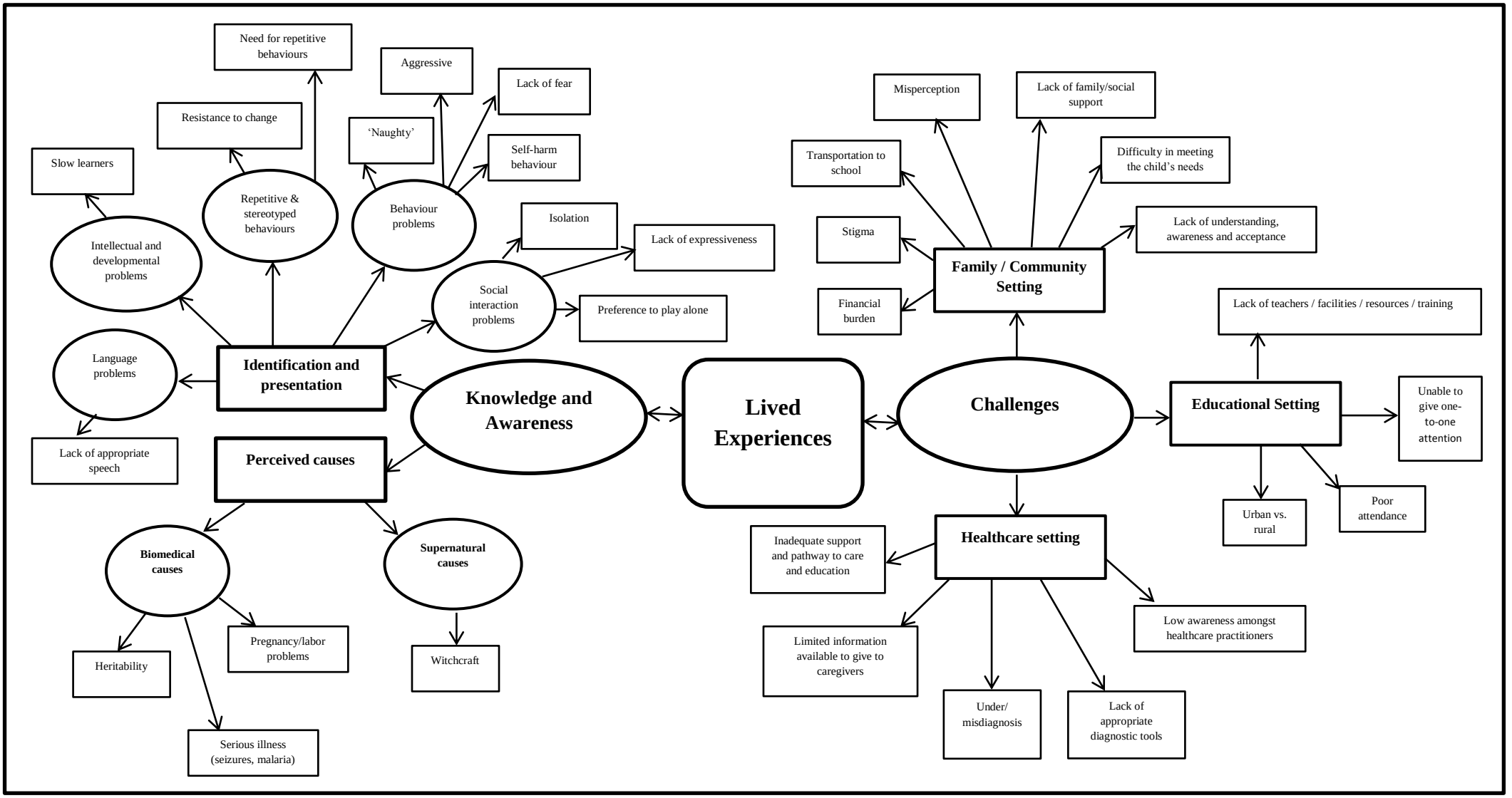
Data collected in Kiswahili was translated and transcribed in English by a trained bilingual translator with experience, and all data in English was transcribed in full. The transcripts were checked against the recordings and imported into NVivo 10 (QSR International). Data were analyzed using thematic analysis. The first step was to generate tentative themes representing participants' awareness and experiences in each transcript. For quality control, subsequent analysis involved initial coding of randomly selected transcripts by two independent people (Prof. Amina Abubakar and myself). This enabled us to identify patterns across the data set and refine themes which guided the initial coding process. I then coded all the data and transcripts were repeatedly re-examined and cross-compared with initial coding by Prof. Amina Abubakar to identify common themes and explore participants underlying perceptions. Coherence of themes was discussed during frequent meetings throughout the analytic process, and final themes and subthemes were agreed upon by the research team.

4.3. Results

The sample included fourteen caregivers of children with ASD (in the context of this study, caregivers include mothers, fathers, siblings, grandmothers and maternal aunts) and a diverse group of 37 key

community informants including special needs educators (*n*=12), mainstream teachers (*n* = 8), parents of typically developing children (*n* = 7), social workers (*n* = 5), clinicians (n = 4) and a government official. Below I present the findings from the main themes which emerged from analysis of the interviews and group discussions. Figure 4.1 illustrates the thematic model emerging from the analysis.

Figure 4.1 - Thematic model of lived experiences.



4.3.1. Knowledge and awareness of ASD: Identification and presentation

This section describes participants' awareness and knowledge of behavioral manifestations seen in children with ASD. Five emerging subthemes were identified as 'social interaction problems', 'repetitive and stereotyped behaviors', 'behavior problems', 'language problems' and 'intellectual and developmental problems'.

Social interaction problems

It was common for all caregivers and most community informants to describe isolation and lack of expressiveness as a core symptom of behavior in children with ASD. Participants often revealed the preference of children with ASD to play alone:

'... they can play alone; they don't like socialization and interaction with others. That is the difference.'

(IDI, Special Needs Educator)

Repetitive and stereotyped behaviors

All participants revealed that a striking characteristic in children with ASD they observed was the need for repetitive and stereotyped behaviors and children often expressed resistance to change:

'... they have repetitive behavior and they want to follow their routines.'

(IDI, Caregiver)

'When there is a visitor coming or a stranger you have to alert them because they resist and react to changes unlike children with intellectual disorder who are easy to follow orders.'

(FGD, Special Needs Educators)

Behavior problems

Generally, most participants perceived children with ASD as 'aggressive'. This term was used frequently during interviews and group discussions. However, perceptions of aggressive behavior were stronger amongst the community informants. Although caregivers perceived their child's behavior as aggressive, at least one parent thought that this was a result of unmet needs of the child, and not just an unprovoked characteristic.

'They are sometimes so quick tempered and aggressive, usually when they feel you do not want to give them what they want.'

(FGD, Caregivers)

Caregivers and special needs educators further expressed their concern for self-harm behaviors and the lack of fear they observed in children with ASD:

' ... they are not afraid of things that can hurt them like fire or crossing the road without keen observation.'

(FGD, Special Needs teachers)

One clinician commented that often children with ASD are perceived as 'naughty' in this setting, primarily due to the lack of awareness of ASD and its' associated behavioral symptoms:

'Some of the people are not aware of autism. Some of them will think this is a naughty child who in Swahili they say 'Mtoto Mtundu'...'

(IDI, Clinician)

Language problems

Both groups consistently revealed that children with ASD lack appropriate speech, or are nonverbal:

'...he is able to understand a lot of things but he is unable to talk.'

(FGD, Caregivers)

'...and they rarely speak.'

(FGD, Mainstream Teachers)

Intellectual and developmental problems

Some participants from both groups perceived children with ASD to be slow learners. However, only parents of typically developing children and mainstream teachers revealed that they were initially unaware that children with ASD could attend school, and believed they could never learn to read or write:

'Autism is an intellectual disorder whereby a child is able to learn and be aware of things but cannot read or write.'

(FGD, Mainstream Teachers)

4.3.2. Knowledge and awareness of ASD: Perceived causes

The attributed causes revealed during the interviews and group discussions were identified as either 'biomedical causes' or 'supernatural causes'.

Biomedical causes

The majority of participants attributed biomedical reasons as the cause of ASD. Participants from both groups attributed heritability as a primary cause for ASD:

'In fact they are trying to tell us that it might be genetic.'

(IDI, Caregiver)

'I think the condition is through inheritance. Sometimes a family can consist of a number of autistic children so I think it's inherited.'

(FGD, Special Needs Educators)

It was also common for participants to reveal pregnancy and labor related problems as another attributed cause:

'What the mother consumes when she is pregnant especially the diet, stress by the mother when still pregnant since the brain of the mother is connected to the child.'

(FGD, Special Needs Educators)

Caregivers, and less commonly amongst other key informants, believed that serious illness, more specifically seizures and malaria were the cause of ASD:

'When my child was three years, she got sick, the doctor said it was nothing. The condition worsened and she experienced seizures. I took her to the witchdoctors and when she started to recover, her developmental stages were affected.'

(IDI, Caregiver)

Supernatural causes

Interestingly, only some parents of typically developing children revealed that they thought supernatural reasons to be a cause of ASD. Witchcraft was the most common within this sub-theme:

'I have no knowledge of the cause of autism but I have heard rumors that parents sacrifice their children to gain wealth and as a result the child becomes disabled.'

(FGD, Parents of typically developing children)

4.3.3. Challenges

This section outlines challenges experienced by caregivers and other key community informants. These challenges are described under three key subthemes; 'family/community setting', 'educational setting' and 'healthcare setting'.

Family/community setting

All participants highlighted the lack of understanding, awareness and acceptance within the community as a core challenge leading to a misperception of ASD and a stigma.

'In my street some of them just come and tell you your kid has been bewitched suggesting you need to go to the priest who can do prayers or to go to the witchdoctors.'

(IDI, Caregiver)

'Other parents are ashamed so they decide to lock their children inside the house and they don't take them to school or the hospital.'

(FGD, Social Workers)

The lack of awareness, acceptance and associated stigma often leads to a financial burden for families caring for a child with ASD in relation to housing and paying for damage.

'There are many challenges, for example, the way one is forced to a hire their own house instead of sharing with other families … when you have other members the child may disturb them or destroy something.'

(IDI, Caregiver)

'… in my case one time my child threw a stone and broke a car window of someone he did not understand, so I had to pay. My prayer is to the society to accept us.'

(FGD, Caregivers)

Another major challenge faced by caregivers is transportation to the school. Many families struggle to send their child to school as the child must be accompanied to school and this can prove to be a challenge in terms of the means and cost of transport and caregivers may also have other duties to attend:

'Using public transport is difficult for these kids, it's not easy taking a 'daladala' (bus), so we pay for the taxi to make sure he goes to school every day. It's very expensive and most parents cannot afford it.'

(IDI, Caregiver)

The lack of family and social support can also be challenging for caregivers, in particular for mothers, who are often left alone to care for their child. Many participants revealed that relationships and marriages were negatively affected as a result of raising a child with ASD:

'... most of the time the mother is blamed for giving birth to such a child. Sometimes they are abandoned and left to take care of the responsibilities. Some fathers think of these children as a misfortune and of no importance.'

(FGD, Special Needs Educators)

Additionally, the difficulty in meeting the child's needs was also revealed, as caregivers often struggle to understand the child's needs and manage their behavior appropriately:

'You feel pain having a child who cannot express himself. You feel like you want to help but don't know how so there is that feeling that you are not doing something right for that child.'

(IDI, Caregiver)

Educational setting

Another important subtheme was the challenges experienced within the educational setting. All participants highlighted the lack of teachers, facilities, resources and training catered specially for ASD:

'I think one is teaching materials, and the other is training because we don't have special programs for teachers, we are just having few visitors who are coming from different countries and helping teachers in Tanzania to handle these children.'

(IDI, Government Official)

Consequently, children with ASD are often put in the same schools or units as other disabilities. Special needs educators further expressed that these challenges hindered their role as teachers as they were not able to give appropriate one to one attention to the children:

'We have few teachers in the school and the number of children is so big. Since every child has to be attended individually it is sometimes impossible to meet all the needs of the children.'

(FGD, Special Needs Educators)

Another common challenge expressed by caregivers and special needs educators was the poor attendance in school:

'... a parent may bring a child twice a week or after three months because of their own personal issues, so it becomes a big challenge for us because every time we have to repeat what we started.'

(FGD, Special Needs Educators)

Interestingly, teachers who taught in mainstream facilities revealed an urban versus rural discrepancy in the initiative caregivers took to seek education for their children with ASD:

'... those who take their children to school are mostly from the town centers and those who are financially stable.'

(FGD, Mainstream Teachers)

'In urban areas parents do take their children to school but you cannot find that in the rural areas. Children are being left at home and neglected. Parents do not see the importance of educating these children.'

(FGD, Mainstream Teachers)

Healthcare setting

A further subtheme which emerged were the challenges experienced within the healthcare setting. All participants emphasized low awareness of ASD amongst the healthcare practitioners and the lack of appropriate diagnostic tools consequently leading to under diagnosing or misdiagnosing ASD:

'In Tanzania, we don't have many psychologists and child and adolescent psychiatrists who have any of the right diagnostic facilities for autism so it is very difficult to first diagnose autism.'

(IDI, Caregivers of children with ASD)

'I don't think there are many of us who know particularly well how to diagnose autism, therefore there is a lot of delay.'

(IDI, Clinician)

Clinicians also expressed their concern that even if a diagnosis was made, they had very limited information and guidance to give to the caregivers in relation to receiving adequate support and an appropriate pathway to care and education:

'... and even if there is a diagnosis made, there are not that many skilled people to intervene like speech therapists, occupational therapists, behavioral therapists ....'

(IDI, Clinician)

4.3.4. Recommendations

Participants had views on what needs have to be met in order to enhance awareness and support for children with ASD in Tanzania, specifically in relation to 'raising awareness' in the hope to increase acceptance and in 'availing more resources'.

Raising awareness

All participants believed there is a clear need to raise awareness in the community in order to increase acceptance of ASD:

'What I would like to say is that most Tanzanians are not aware of autism. There should be programs aired on television to educate people on cases of autistic children. This will help us create and spread more awareness.'

(FGD, Special Needs Educators)

'I would also call upon the government and the society to accept children with these conditions and be able to help them.'

(FGD, Caregivers)

Providing more resources

Increasing more and better facilities and training for ASD was equally important to all participants. Some argued that boarding facilities would help take the burden away from the caregiver, reduce the transport costs incurred by families, and maintain school attendance:

'There should be boarding schools for these children to reduce the cost and the expenses the parents incur.'

(FGD, Mainstream Teachers)

'There should be openings of more units in every district because children are left behind at home.'

(FGD, Special Needs Educators)

Clinicians also highlighted the pressing need for an appropriate diagnostic tool:

'I think it's important to have a diagnostic tool which is acceptable here and for medical professionals and parents to be aware of the problem, how to diagnose and manage the problem.'

(IDI, Clinician)

Interestingly, one parent also raised the provision of social protection as a way forward:

'The government should recognize us and invest in us, there should be financial security for the children in case we are no longer with them.'

(FGD, Caregivers)

4.4. Discussion

This study investigated the knowledge of ASD and lived experiences of caregivers and a diverse group of key community informants in Dar-es-Salaam, Tanzania, using qualitative methodology. The findings indicate consistent sub-themes emerging within the areas of concern: knowledge and awareness in the identification and presentation of ASD and its' perceived causes, and the challenges experienced by caregivers. Additionally, participants provided recommendations for way forward.

Results suggest that despite being a resource limited setting with prevailing poor socio-economic status, caregivers and special needs educators have gained moderate knowledge of ASD, perhaps because they were recruited from schools that catered specifically for children with ASD. In comparison, however, other key community informants such as parents of typically developing children and mainstream teachers had relatively limited knowledge of ASD highlighting the general lack of awareness, understanding and acceptance of ASD within the community. This could be attributed to the high levels of stigma associated with neurodisability in Africa and resonates with previous literature on ASD in Africa (Eisegbe et al., 2015; Igwe et al., 2011; Bakare et al., 2009a; Bakare et al., 2008).

Most comments about the identification and presentation of ASD fell into the categories of the core symptom domains of ASD with both behavioral and socio-communication deficits being raised. Consistent with earlier reported work (Belhadj et al., 2006; Mankoski et al., 2006; Bakare & Munir, 2011b), nonverbal characteristics of some children with ASD seemed to be overemphasized, perhaps a reflection of late diagnosis and intervention. It was also evident in the findings that some participants, and more frequently parents of typically developing children and mainstream teachers were unable to distinguish ASD symptomatology from other intellectual disorders and behavioral and developmental problems. This finding could be attributed to the lack of awareness of ASD within the community as well as associated neurological comorbidities, more specifically intellectual disability. Kisanji's (1995) study conducted interviews and proverbs surveyed from local literature in Tanzania showed that the characteristics of major disabilities, except mild to moderate intellectual disability were clearly known.

Most of the participants perceived biomedical reasons such as hereditary, brain abnormalities and infectious diseases as the cause of ASD. These etiological explanations support those based on clinical observations by Mankoski et al. (2006), who documented cases of ASD following central nervous system infection or sepsis in a case series of children in Tanzania. Unexpectedly, however, participants may have been well educated or shared socially desirable responses. Surprisingly, only parents with typically developing children attributed ASD etiology to supernatural causes. Stone-MacDonald (2012), however, found cultural beliefs in a rural region of Tanzania centered on God's plan or role in the community, and a mixture of Christian, Muslim, and traditional beliefs. The finding from this study, for instance, is also inconsistent with etiological perceptions of ASD among a significant proportion of healthcare workers in Nigeria who hold beliefs of supernatural causes for ASD (Bakare et al., 2009b). More recently, Gona et al. (2015) compared perceived causes of ASD in families with a child with ASD in urban and rural settings in Kenya, and found supernatural causes as well as biomedical causes were thought to cause ASD across both settings. Although, in this study participants commented that the general perception of the causes of ASD within the community were supernatural causes; these findings however, were different from other research in the region (Bakare et al., 2009b; Gona et al., 2015), in that only parents of typically developing children in this Da-es-Salaam sample within this urban setting perceived ASD to be caused by supernatural beliefs. This highlights the need for public engagement to raise awareness within the community.

In general, there was the belief that there is a significant lack of understanding, awareness and acceptance within the community. These findings indicate that this gap in the community's knowledge often leads to misperception of ASD, negative stigma associated with the symptoms of ASD and a financial burden to families raising a child with ASD. The challenges of transportation to school, lack of family and/or social support and subsequent marital adjustments were also highlighted by participants. It is evident that many of the challenges raised in this study resonate with findings in the existing literature of ASD in other developing countries (e.g. Desai et al., 2012), and in caring for children with ASD (Gona et al., 2016; Tekola et al., 2016). Within the educational setting, challenges reflected the lack of resources, facilities and training as well poor attendance. Participants further emphasized the low level awareness of ASD amongst the healthcare practitioners and the lack of appropriate diagnostic tools consequently leading to under diagnosing or misdiagnosing ASD. This data concurs with previous findings from several studies conducted in Nigeria revealing a low level of knowledge and awareness about ASD in Africa (Eisegbe et al., 2015; Igwe et al., 2011; Bakare et al., 2009a; Bakare et al., 2008).

This study has several limitations. Although a diverse group of participants took part in the study, the sample was limited to key community informants that have had contact with professionals either in the educational setting or healthcare setting. For instance, the mainstream teachers and parents of

typically developing children were recruited from the mainstream primary schools that had ASD units, thus it is not clear whether the views of the participants represent the perceptions and experiences of the larger population. Children living in urban areas have more access to these special schools and facilities and thus parents in rural areas were not included in this study. Furthermore, poorer and less literate parents in urban areas may not bring their children to these schools.

This study provides knowledge, awareness and lived experiences of caregivers and key community informants and contributing to the limited literature on ASD in Tanzania and in Africa. The increased knowledge of these perspectives contributes to better understanding, awareness, acceptance and provision for ASD in Tanzania.

Chapter 5

Evaluation of the psychometric properties of the Lifetime version of the Kiswahili Social Communication Questionnaire (SCQ) in Dar-es-Salaam, Tanzania.

5.1. Background

Despite the growing knowledge of the global prevalence of ASD (Fombonne et al., 2011; Elsabbagh et al., 2012), relatively little is known on the prevalence of ASD in sub-Saharan Africa (SSA) and details of clinical presentations of this disorder remain unclear for this region (Ruparelia et., 2016; Elsabbagh et al., 2012).

A review of cases of ASD in Africa revealed that nearly all of the children were diagnosed relatively late, around the age of 8 years and some into their teenage years (Bakare & Munir, 2011a). Moreover, two of these studies revealed high nonverbal proportion among children with ASD (Belhadj et al., 2006; Mankoski et al., 2006). This delay in diagnosis may also contribute to the lack of appropriate language skills in many of the children with ASD, perhaps because they did not have access to early interventions. One of the major difficulties in identifying children with ASD in Africa lies in the poor standards of available educational and medical infrastructures (Ruparelia et al., 2016). These findings also highlight a need for earlier recognition and diagnosis of ASD in Africa. Although in high income countries (HIC) there are many tools available to screen and diagnose ASD, there is a dearth of available validated tools for the use of screening and identifying ASD in SSA, where the phenotype may be different compared to HIC.

According to a recent scoping review (Franz et al., 2017) and a systematic review on ASD in SSA (Abubakar et al., 2016b) only few published studies specifically on ASD screening and diagnosis in SSA were identified. An Ugandan tool development study (Kakooza-Mwesige et al., 2014), which piloted a 23-question screener (the 23Q), including the Ten Questions Questionnaire (TQQ) (Durkin et al., 1995) and 13 additional questions specifically aimed at ASD detection was modestly successful in identifying children at high risk of ASD, but showed a relatively low positive predictive value of only 8% (Kakooza-Mwesige et al., 2014). Harrison et al. (2014) used the Childhood Autism Rating Scale, Second Edition (CARS-2; Schopler et al., 2010) in Tanzania. They combined this observational diagnostic aid for ASD as part of a larger test battery to diagnose ASD and described the process of cultural adaptation, however, the tool was not validated. Additionally, 2 studies in South Africa have also evaluated the cultural adaptability of ASD screening and diagnostic tools in their setting. Smith et al. (2016) examined the cultural appropriateness of the materials and procedures for administration of

the Autism Diagnostic Observation Schedule-2 (ADOS-2) and found that most of the materials and activities were appropriate for use in their setting with only minor modifications. However, potential linguistic and semantic biases were observed and therefore guidelines for using ADOS in their setting were developed. Chambers et al. (2016) adapted several measures for early screening for ASD, providing initial evidence that the measures are feasible for use in their setting.

Since ASD diagnostic tools such as the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 2000) and the Autism Diagnostic Interview–Revised (ADI-R) (Le Couteur et al., 2003) require formal clinical training and large amounts of resources, screening instruments have been developed to aid in initial screening for ASD. These are administered to the child's primary caregiver, are less costly and time consuming and can provide an efficient method for screening children who may require further evaluation.

One frequently used screening measure is the Social Communication Questionnaire (SCQ) (Berument et al., 1999; Rutter et al., 2003). The SCQ is a brief 40-item caregiver-report screening measure for ASD that focuses on behavioural impairments in the areas of reciprocal social interaction, language and communication, and repetitive and stereotyped patterns of behaviour (Berument et al., 1999). The SCQ is based on the Autism Diagnostic Interview-Revised (ADI-R; Rutter et al., 2003), a semi-structured caregiver interview that covers ASD symptomatology and developmental history. The SCQ manual suggests the SCQ is applicable to subjects of any chronological age above the age of 4.0 years provided that their mental age is at least 2.0 years (Rutter et al., 2003). Since the use of the SCQ under the age of 4.0 years had not been systematically tested and no subjects under the age of 4.0 were included in the sample used in the development of the SCQ, the authors caution against using the SCQ in subjects younger than 4.0 years of age. There are two different versions of the SCQ. The SCQ Lifetime, which measures ASD symptoms that have ever been present, focussing on ages 4-5 years on some questions, or to consider behaviour in the past 12 months if the child is not yet 4 years. The SCQ Current measures behaviours that have been present in the past 3 months.

Berument et al. (1999) published the initial validation study of the SCQ and examined the diagnostic validity, factor structure and convergent validity with the ADI-R in individuals aged 4 to 40 years with pervasive developmental disorders (PDD) including autism and individuals with other psychiatric diagnoses such as language disorders and intellectual disability (ID). They found a sensitivity of 85% and a specificity of 75% for the recommended cut-off score of 15 when differentiating between individuals with and without a diagnosis of ASD, and sensitivity of 96% and specificity of 67% for differentiating ASD from ID.

The SCQ has been adapted and cross-culturally validated for use in other languages and cultural contexts namely; German, Portuguese, Chinese, Turkish and Greek (Table 5.1). Bölte et al. (2008b) published the first cross-cultural validation study using the German version of the SCQ and found acceptable psychometric properties in a child and adolescent psychiatric sample and derived a clinical cut-off that differentiated ASD from other disorders such as anxiety disorders and obsessive-compulsive disorders amongst others (Table 5.1).

Sato et al. (2009) published preliminary analysis of validity of the Portuguese version of the SCQ using a sample that includes children with a diagnosis of PDD, Down's syndrome and other psychiatric disorders. The authors reported acceptable internal consistency and a clinical cut-off that differentiated PDD from the other groups (Table 5.1).

Gau et al. (2011) examined the validity of the Chinese version of the SCQ in children aged 2 to 18 years with a clinical diagnosis of ASD specified according to the DSM-IV diagnostic criteria. They reported acceptable psychometric properties including test–retest reliability, internal consistencies, and concurrent validity when compared with the Chinese version of the ADI-R (Gau et al., 2010). Additionally, they found boys scored significantly higher than girls on the SCQ total score, and children with ID scored significantly higher on the social interaction subscale than children without ID. They also conducted exploratory factor analysis revealing a 3-factor model (social interaction, repetitive behaviours and communication) that had acceptable fits in confirmatory factor analysis (Table 5.1).

Avcil et al. (2015) examined the validity of the Turkish version of the SCQ in children and adolescents aged 4 to 18 years with PDD and others with ID. They reported acceptable test–retest reliability, high internal consistency and recommended the cut-off point of 15 as determined by the receiver operating characteristic (ROC) analysis. After performing factor analysis, the authors report a 4-factor model (reciprocal social interaction, communication, abnormal language and stereotyped repetitive behaviours) (Table 5.1).

Findings from a pilot study investigating the psychometric properties of the Greek version of the SCQ (Zarokanellou et al., 2017) in a sample of children aged 7 to10 years diagnosed with ASD and typically developing children revealed a clinical cut-off point of 15. The authors reported acceptable internal consistencies and fit models for the confirmatory factor analysis (Table 5.1).

Table 5.1 - Review of SCQ cross-cultural validation studies.

Country (Language)	Study	Sample	Factor Analysis			Internal consistency (Cronbach's α)	Test retest Reliability	Cut-off	Sensitivity (95% CI)	Specificity (95% CI)
			No. of items	No. of factors	Fit indices					
Germany (German)	Bölte et al. (2008b)	136 Autism 32 other ASD 174 other PD 22 TD	NA	NA	NA	0.83[ab]	0.76[c]	15	89.0%[*]	91.0%[*]
Brazil (Portuguese)	Sato et al. (2008)	40 PDD 40 DS 40 other PD	NA	NA	NA	0.90[ad] 0.62 - 0.83[de]	0.37 - 0.93[f]	14.5	92.5%[*]	95.5%[*]
Taiwan (Chinese)	Gau et al. (2011)	682 ASD 240 siblings	39	3[g]	0.92[h], 0.98[i], 0.03[j]	0.73 - 0.91[de]	0.77 - 0.78[dk]	NA	NA	NA
Turkey (Turkish)	Avcil et al. (2015)	50 PDD 50 ID	39	4[l]	NA	0.89[ad] 0.77 - 0.83[de]	0.87 - 0.96[dk]	14.5	94.0%[*]	84.0%[*]
Greece (Greek)	Zarokanellou et al. (2017)	53 ASD 77 TD	39	3[g]	0.93 – 0.96[eh] 0.90 – 0.95[ei] 0.06 – 0.08[ej]	0.91[ad] 0.70 - 0.86[de]	NA	15	96.3% (81.0 – 99.9)	98.7% (93.0 – 99.9)

Note. CI = Confidence Interval; ASD = Autism Spectrum Disorder; PD = Psychiatric Disorders; TD = Typically Developing; NA = Not Available; PDD = Pervasive Developmental Disorder; DS = Down's Syndrome; ID = Intellectual Disability.

[*]95% CI not reported.

[a]Total score; [b]ASD sample; [c]Pearson's Correlation Coefficient (*r*); [d]Whole sample; [e]Subscales range; [f]Cohen's Kappa Coefficient for the lowest and highest questions; [g]Confirmatory Factor Analysis (CFA); [h]Goodness of Fit Index (GFI); [i]Comparative Fit Index (CFI); [j]Root Mean Square Error of Approximation (RMSEA); [k]Intraclass Correlation Coefficint (ICC); [l]Principle Components Analysis (PCA) - explained 43.0% of the observed total variance.

Chesnut et al. (2017) examined the utility of the SCQ as a screening measure for ASD by meta-analysing the area under the curve (AUC) using parametric and bootstrapping techniques. Their findings suggest the SCQ is an acceptably accurate screener for ASD. Variations in methodological decisions, however, greatly influenced the accuracy of the SCQ, and the authors caution against using the Current version of the SCQ, using the SCQ in children younger than 4 years and relying upon convenience samples. Similarly, in an analysis of the use of the SCQ as a screening measure for children aged less than 4 years, Marvin et al. (2017) recommend using the Lifetime version, rather than the SCQ Current, due to poor psychometric properties in the under 4 year age group.

In summary, the SCQ is a widely accepted screening measure for ASD with good psychometric properties. There is a need to adapt and validate the SCQ into the Tanzanian population as most Tanzanians are more conversant in Kiswahili than English and have a unique culture that may influence the understanding of some terms in the SCQ. To date, no studies have been conducted in Tanzania on the validity and clinical utility of the SCQ. The purpose of the current study is to adapt the SCQ Lifetime version in Kiswahili and investigate the psychometric properties of the SCQ in a sample of children with a confirmed diagnosis of ASD, children with a known NDD and typically developing children in Dar-es-Salaam, Tanzania.

5.2. Methodology

This case-control study was approved by the Muhimbili University of Health and Allied Sciences (MUHAS) Directorate of Research and Publications, National Institute for Medical Research (NIMR) and registered with the Tanzania Commission for Science and Technology (COSTECH). Parents and guardians gave verbal and written consent.

5.2.1. Study sample

Three groups of children were recruited for the study. Children who had a diagnosis of ASD (n = 108) were recruited from the Child and Adolescent Clinic, Department of Psychiatry, Muhimbili National Hospital (MNH), private clinics and centres, ASD units attached to local primary schools in Dar-es-Salaam, Tanzania. These children were aged from 5 to 12 years and had no deafness or motor impairment, and genetic causes were not determined. Previous diagnosis was made by either a psychiatrist at MNH using DSM-IV criteria, or by a paediatrician in a private setting using DSM-IV criteria and the M-CHAT or an education assessment centre using pre-determined assessment criteria. At least one biological parent had to be available for the study (where biological parent was unavailable, data was collected from the caregiver). Children with other neurodevelopmental disorders (NDD n = 60) aged 5 to 12 years were recruited from MNH and special needs schools in Dar-es-Salaam, Tanzania. The NDD group was matched on chronological age and had a previous diagnosis of a neurodevelopmental disorder which included, Down's Syndrome (n = 9), Learning

Disability (n = 33), Seizure Disorders (n = 8) and ADHD (n = 10). Typically developing (TD) children (n = 116) were randomly selected from the community with no known concerns of language and/or behavioral problems and did not have any history of learning or psychiatric disabilities according to our assessments. They were matched with the ASD group on a surrogate marker of IQ i.e. level of expressive language (ADOS-2 Module).

5.2.2. Assessment measures

ASD screening instrument

Social Communication Questionnaire (SCQ; Rutter et al., 2003): The SCQ Lifetime version was used in this study. This is a brief 40-item Yes/No questionnaire that helps to evaluate communication skills and social functioning suggested for use in children above 4 years of age who may have ASD. This questionnaire is a cost-effective way of screening for referral for a complete diagnostic evaluation. It is administered to a parent or other primary caregiver and takes less than 10 minutes. The SCQ has strong discriminating power between those with and without ASD and has been translated and validated cross-culturally (Table 5.1). In addition to the Total Score, the SCQ can also be used to provide subscores that match the Reciprocal Interaction domain, the Communication domain and the Restricted, Repetitive and Stereotyped Patterns of Behaviour domain of the ADI-R. Although formal scoring of these subdomains is not supported in the SCQ Auto Score materials, the manual is in full support of researchers wanting to investigate these subdomains. It is important to note, according to the SCQ manual, items 17, 18 and 38 do not belong to any of the subdomains and are therefore omitted from domain-wise analysis and factor analysis.

Additional tools used to aid confirmation of the diagnosis of ASD in probands

Autism Diagnostic Observation Scale, 2nd Edition (ADOS; Lord et al., 2000; ADOS-2; Lord et al., 2012): The ADOS is designed to diagnose and assess ASD using a series of structured and semi-structured tasks that involve social interaction between the examiner and the subject. It consists of four modules; each attuned to differing developmental and language levels, ranging from little if any expressive and receptive language, and therefore can be administered to subjects ranging from children as young as 18 months through adolescence and adulthood. Each module takes just 30-40 minutes to administer, making it a quick and robust instrument. ADOS has been found to have exceptional diagnostic sensitivity and specificity (Lord et al., 2000). Other diagnostic tools for ASD are also available including the Autism Diagnostic Interview Revised (ADI-R; Le Couteur et al., 2003), the Diagnostic Interview for Social and Communication Disorders (DISCO; Wing et al., 2002) and the Developmental, Dimensional and Diagnostic Interview (3Di; Skuse et al., 2004), all of which use interview techniques with parents or caretakers as a means of collecting information concerning the developmental history and current behaviour. The ADOS, however, is an observational

assessment and can be used to evaluate almost anyone suspected of having ASD, from toddlers to adults, from children with no speech to adults who are verbally fluent.

Diagnostic Statistical Manual of Mental Disorders, 5th Edition (DSM-5 - APA, 2013): A DSM-5 checklist (Appendix 5), guidelines and criteria exemplars were used for clinical assessments of the children in our sample. DSM-5 defines ASD within two domains; "persistent difficulties with social communication and social interaction" and "restricted and repetitive patterns of behaviours, activities and interests" (this includes sensory behaviour). To diagnose the child with ASD, he/she must display all 3 criteria under the social interaction and social communication domain and at least 2 out of 4 under the restricted interests and repetitive behaviour domain. The symptoms must be present since early childhood and limit and impair everyday functioning. The DSM-5 also requires a severity rating be given for each domain ranging from requiring some support to requiring very substantial support.

Neuropsychological testing

For the purpose of this study, we used the adapted version of the Raven's Coloured Progressive Matrices (CPM; Raven et al., 1998; Kitsao-Wekulo et al., 2012) and the adapted version of the Peabody Picture Vocabulary Test (PPVT; Dunn & Dunn, 1981; Holding et al., 2004), both providing sound psychometric properties (internal consistency $\geq .70$; test reliability $\geq .75$) enabling reliable administration by a trained person without previous experience in testing.

The Raven's CPM measures reasoning ability and is designed for young children between 5 to 12 years of age, older adults and mentally and physically impaired persons. The test consists of 36 items in 3 sets (A, Ab, B), with 12 items per set and takes between 15 to 30 minutes to administer. The items are arranged to assess the main cognitive processes which children under 11 years of age are usually capable. The PPVT is designed to assess the verbal intelligence of an individual. It measures receptive language processing from 2 years of age and takes 20 to 30 minutes to administer. All children in this study were asked to complete both these neuropsychological tests as a means to control for IQ and receptive language.

5.2.3. Translation of measures

Permission was sought and granted from the Western Psychological Services (WPS) to translate the SCQ. Initial translation of the English version of the SCQ into Kiswahili was done by two independent linguistic specialists at KEMRI-Wellcome Trust Research Programme (KWTRP) in Kilifi, Kenya. A panel meeting of experts was held to harmonize all translated items and subsequent back-translation into English was done by another independent linguistic specialist. Items 21, 34 and 40 were slightly modified to take into account the local cultural context. For instance, for item 34, social games for children such as the 'Mulberry Bush' and 'London Bridge is falling down' were replaced with local games such as 'Ukuti Ukuti', which involves a group of children holding hands,

jumping and singing and going around in a circle. The final Kenyan version of the SCQ was then slightly modified to suit the Tanzanian Kiswahili by the fieldworker recruited for phase two and a linguistic specialist at MUHAS, and back-translated into English by another linguistic specialist at MUHAS. The back-translated version was reviewed by a clinical psychologist from the Department of Psychiatry at MNH, who recommended minor modifications until the questions therein retained their original meaning (Appendix 7). Permission was sought and granted from the WPS to translate the ADOS-2 Manual. The same translation and back-translation method as above was used for the ADOS-2 Manual (all modules).

5.2.4. Procedures

Parents and guardians were informed of the objectives of the study. Verbal and written consent were sought from all parties. Families were invited to the clinic or the schools for assessment. Each visit lasted approximately 2 to 3 hours. After obtaining consent, parents of participating children were asked to complete the Social Demographic Questionnaire and the SCQ. All children were requested to complete the neuropsychological testing (RAVEN's CPM and the PPVT), followed by an ADOS-2 assessment. Parents were asked to be present in the assessment room and each assessment was videotaped so that later a panel of experts can categorize these children and this information was used as an extra validity check. Of the 284 respondents, 50 were selected using a fixed interval sample method. Of these, 35 (70%) completed the SCQ after at least 2 weeks to examine the test-retest reliability. I was fully involved with the recruitment of participants and collected all the data for this study with assistance from the fieldworker where Kiswahili was required. I directly administered the neuropsychological tests, ADOS, SCQ and the socio-demographic questionnaire. I trained, supervised and oversaw any assistance from the fieldworker.

5.2.5. Statistical analysis

Data analysis was done using IBM SPSS version 20 and R version 3.0.2. Descriptive statistics were computed and the distribution of scores per group explored. To evaluate discriminant validity, differences in scores between sex and respondent groups were tested using Mann Whitney U tests. A p-value of ≤ 0.05 was considered statistically significant. The internal consistency of the SCQ was calculated using Cronbach's coefficient alpha (α) (Cronbach, 1951). An Intraclass Correlation Coefficient (ICC) and Spearman's correlation coefficient were used to evaluate the test–retest reliability. Confirmatory Factor Analysis (CFA) with diagonally weighted least squares was performed to determine a 2 factor model of the SCQ. The factors were derived from the DSM-5 criteria of ASD; combining social interaction and communication as one factor, and restricted, repetitive behaviour or interests as the second factor. For the purposes of further factor analysis, responses for all nonverbal children were replaced with a score of 1. The cut-off for standardized coefficient loadings was set at 0.30. An acceptable model fit was obtained if the Root Mean Squared

Error of Approximation (RMSEA) was < 0.06 and if the Tucker Lewis Index (TLI) and Comparative Fit Index (CFI) were > 0.9 (Yu, 2002; Browne & Cudeck, 1992). ROC analysis was performed to test the sensitivity and specificity of the SCQ.

5.3. Results

5.3.1. General sample description

SCQ data was collected for 108 children diagnosed with ASD, 116 typically developing (TD) children and 60 children with other neurodevelopmental disorders (NDD). Of these eligible children, males formed 79% of the ASD group, 57% of the TD group and 65% of the NDD group. The median age was significantly different between ASD and TD groups (7.1 vs. 2.8; $p < 0.0001$), because the TD group was matched on expressive language level. There was also a significant difference between the median age between ASD and NDD groups (7.1 vs. 10.0; $p < 0.0001$). Frequency of males was significantly higher in the ASD group than in the TD group (79% vs. 57%; $p = 0.001$). Item 1 on the SCQ documents whether or not the child has phrase speech ("Is she/he now able to talk using short phrases or sentences?"). Only 24% of our ASD sample had phrase speech in comparison to 93% of the TD group ($p < 0.0001$) and 58% of the NDD group ($p = 0.001$). Furthermore, only 6% of the ASD group were able to complete the Raven's CPM in comparison to 30% of the NDD group ($p < 0.0001$) and only 11% of the ASD group were able to complete the PPVT in comparison to the 72% of NDD group ($p < 0.0001$). It was not possible to do the Raven's CPM and PPVT neuropsychological testing on the TD group since they were too young. The 108 respondents in the ASD group comprised of 91 (84%) mothers, 14 (13%) fathers and 3 (3%) other caregivers. Similarly, more mothers were respondents in the TD (87%) and NDD groups (85%). Table 5.2 compares the distribution of participant characteristics between ASD and TD groups and ASD and NDD groups.

Table 5.2 - Distribution of participant characteristics between ASD, NDD and TD groups enrolled in this study.

Participant characteristics	ASD (n = 108)	TD (n = 116)	NDD (n = 60)	ASD vs. TD *p*-value	ASD vs. NDD *p*-value
Age in years: Median (IQR)	7.1 (5.9 – 9.1)	2.8 (2.6 – 3.1)	10.0 (8.2 – 11.0)	$< 0.0001^{*a}$	$< 0.0001^{*a}$
Male sex	85 (79%)	66 (57%)	39 (65%)	0.001^{*b}	0.053^{b}
Phrase speech (SCQ Item 1)	26 (24%)	108 (93%)	35 (58%)	$< 0.0001^{*b}$	0.001^{*b}
Raven's CPM	6 (6%)	NA	18 (30%)	NA	0.001^{*b}
PPVT	12 (11%)	NA	43 (72%)	NA	$< 0.0001^{*b}$

Note. ASD = Autism Spectrum Disorder; TD = Typically Developing; NDD = Neurodevelopmental Disorders; IQR = Interquartile Range; SCQ = Social Communication Questionnaire; CPM = Coloured Progressive Matrices; PPVT – Peabody Picture Vocabulary Test.
[a]Mann Whitney U test; [b]Pearson's chi-squared test (dichotomous and categorical variables). $^{*}p < 0.05$

5.3.2 Distribution of SCQ scores by group

Item positive response frequency

SCQ item positive response frequencies for all three groups are given in Table 5.3. Item 1 on the SCQ simply documents whether or not the child has phrase speech and does not have a scoring value. Of the 39 items, 35 items showed significant differences between ASD and TD groups. Of these 35, 32 items were significantly more frequent in the ASD group than in the TD group, while the remaining 3 were significantly more frequent in the TD group than the ASD group. These 3 items include items 5 (32.8% vs. 12.0%; "Pronoun reversals"; $p < 0.0001$), 6 (19.8% vs. 10.2%; "Neologisms", $p = 0.044$) and 13 (80.2% vs. 66.7%; "Circumscribed interests"; $p = 0.022$). Of the 32 items that were significantly more frequent in the ASD group than the TD group, items with the highest frequencies include items 39 (93.5% vs. 36.2%; "Imaginative play with peers"; $p < 0.0001$) and 40 (78.7% vs. 12.9%; "Group play"; $p < 0.0001$) which belong to the Social Interaction Domain, items 35 (97.2% vs. 35.3%; "Imaginative play"; $p < 0.0001$) and 20 (88% vs. 18.1%; "Social chat"; $p < 0.0001$) which belong to the Communication Domain, and items 8 (83.3% vs. 14.7%; "Compulsions and rituals"; $p < 0.0001$) and 15 (75.9% vs. 0.9%; "Hand and finger mannerisms"; $p < 0.0001$) which belong to the Repetitive Behaviors Domain.

Of the 39 items, 30 items showed significant differences between ASD and NDD groups. Of these 30, 27 items were significantly more frequent in the ASD group than in the NDD group, while the remaining 3 were significantly more frequent in the NDD group than the ASD group. These 3 items include items 3 (16.7% vs. 30.0%; "Stereotyped utterances"; $p = 0.44$), 5 (12.0% vs. 30.0%; "Pronoun reversals"; $p = 0.004$) and 6 (10.2% vs. 28.3%; "Neologisms", $p = 0.002$). Of the 27 items that were significantly more frequent in the ASD group than the NDD group, items with the highest frequencies were similar to the ASD vs. TD comparisons.

Table 5.3 - Item positive response frequency for ASD vs. TD groups and ASD vs. NDD groups.

SCQ Items	ASD (n = 108)	TD (n = 116)	NDD (n = 60)	ASD vs. TD *p*-value	ASD vs. NDD *p*-value
2. Conversation	4 (3.7%)	2 (1.7%)	6 (10.0%)	0.432[b]	0.170[b]
3. Stereotyped utterances	18 (16.7%)	18 (15.5%)	18 (30.0%)	0.815[a]	0.044*[a]
4. Inappropriate questions	7 (6.5%)	10 (8.6%)	9 (15.0%)	0.546[a]	0.071[a]
5. Pronoun reversal	13 (12.0%)	38 (32.8%)	18 (30.0%)	< 0.0001*[a]	0.004*[a]
6. Neologisms	11 (10.2%)	23 (19.8%)	17 (28.3%)	0.044*[a]	0.002*[a]
7. Verbal rituals	20 (18.5%)	27 (23.3%)	11 (18.3%)	0.382[a]	0.976[a]
8. Compulsions and rituals	90 (83.3%)	17 (14.7%)	25 (41.7%)	< 0.0001*[a]	< 0.0001*[a]
9. Inappropriate facial expressions	31 (28.7%)	1 (0.9%)	14 (23.3%)	< 0.0001*[b]	0.451[a]

10. Use of other's body	89 (82.4%)	11 (9.5%)	19(31.7%)	< 0.0001[*a]	< 0.0001[*a]
11. Unusual preoccupations	74 (68.5%)	6 (5.2%)	40 (66.7%)	< 0.0001[*a]	0.805[a]
12. Repetitive use of objects	45 (41.7%)	1(0.9%)	6 (10.0%)	< 0.0001[*b]	< 0.0001[*a]
13. Circumscribed interests	72 (66.7%)	93 (80.2%)	46 (76.7%)	0.022[*a]	0.174[a]
14. Unusual sensory interests	77 (71.3%)	24 (20.7%)	30 (50.0%)	< 0.0001[*a]	0.006[*a]
15. Hand and finger mannerisms	82 (75.9%)	1 (0.9%)	14 (23.3%)	< 0.0001[*a]	< 0.0001[*a]
16. Complex body mannerisms	52 (48.1%)	1 (0.9%)	20 (33.3%)	< 0.0001[*a]	0.063[a]
17. Self-injury	49 (45.4%)	4 (3.4%)	11 (18.3%)	< 0.0001[*a]	< 0.0001[*a]
18. Unusual attachment to objects	59 (54.6%)	15 (12.9%)	27 (45.0%)	< 0.0001[*a]	0.232[a]
19. Friends	84 (77.8%)	4 (3.4%)	4 (6.7%)	< 0.0001[*a]	< 0.0001[*b]
20. Social chat	95 (88.0%)	21 (18.1%)	45 (75.0%)	< 0.0001[*a]	0.031[a]
21. Imitation	65 (60.2%)	15 (12.9%)	25 (41.7%)	< 0.0001[*a]	0.021[a]
22. Pointing to express interest	68 (63.0%)	4 (3.4%)	19 (31.7%)	< 0.0001[*a]	< 0.0001[*a]
23. Gestures	72 (66.7%)	3 (2.6%)	19 (31.7%)	< 0.0001[*a]	< 0.0001[*a]
24. Nodding to say yes	91 (84.3%)	17 (14.7%)	14 (23.3%)	< 0.0001[*a]	< 0.0001[*a]
25. Head shaking to mean no	89 (82.4%)	17 (14.7%)	13 (21.7%)	< 0.0001[*a]	< 0.0001[*a]
26. Eye gaze	73 (67.6%)	3 (2.6%)	4 (6.7%)	< 0.0001[*a]	< 0.0001[*b]
27. Social smiling	40 (37.0%)	1 (0.9%)	6 (10.0%)	< 0.0001[*a]	< 0.0001[*a]
28. Sowing and directing attention	75 (69.4%)	11(9.5%)	12 (20.0%)	< 0.0001[*a]	< 0.0001[*a]
29. Offering to share	62 (57.4%)	2 (1.7%)	20 (33.3%)	< 0.0001[*a]	0.003[*a]
30. Seeking to share enjoyment	74 (68.5%)	20 (17.2%)	13 (21.7%)	< 0.0001[*a]	< 0.0001[*a]
31. Offering comfort	60 (55.6%)	20 (17.2%)	26 (43.3%)	< 0.0001[*a]	0.129[a]
32. Quality of social overtures	65 (60.2%)	0	12(20.0%)	< 0.0001[*a]	< 0.0001[*a]
33. Range official expressions	66 (61.1%)	3 (2.6%)	7 (11.7%)	< 0.0001[*a]	< 0.0001[*a]
34. Imitative social play	84 (74.1%)	3 (2.6%)	24 (40.0%)	< 0.0001[*a]	< 0.0001[*a]
35. Imaginative play	105 (97.2%)	41 (35.3%)	32 (53.3%)	< 0.0001[*a]	< 0.0001[*a]
36. Interest in children	77 (71.3%)	1 (0.9%)	5 (8.3%)	< 0.0001[*a]	< 0.0001[*b]
37. Response to other children	70 (64.8%)	0	8 (13.3%)	< 0.0001[*a]	< 0.0001[*a]
38. Attention to voice	63 (58.3%)	14 (12.1%)	17 (28.3%)	< 0.0001[*a]	< 0.0001[*a]
39. Imaginative play with peers	101 (93.5%)	42 (36.2%)	35 (58.3%)	< 0.0001[*a]	< 0.0001[*a]
40. Group play	85 (78.7%)	15 (12.9%)	25 (41.7%)	< 0.0001[*a]	< 0.0001[*a]

Note. SCQ = Social Communication Questionnaire; ASD = Autism Spectrum Disorder; TD = Typically Developing; NDD = Neurodevelopmental Disorders.

[a]Mann Whitney U test; [b]Pearson's chi-squared test (dichotomous and categorical variables).

[*]$p < 0.05$

Discriminant validity

The SCQ median total scores and median scores on all three domains were compared between ASD and TD groups and ASD and NDD groups (Table 5.4). The median SCQ total score was significantly higher for the ASD group compared to the TD group (23.0 (IQR 19.0 – 25.0) vs. 5.0 (IQR 2.25 – 6.0); p< 0.0001) and significantly higher for the ASD group compared to the NDD group (23.0 (IQR 19.0 – 25.0) vs. 12.0 (IQR 9.0 – 15.0); p< 0.0001). A similar trend was found when comparing ASD to TD groups and ASD to NDD groups on all three domains (p< 0.001). Figure 5.1 illustrates the boxplots for group differences for SCQ total scores and all three domains.

Table 5.4 - Discriminant validity for ASD vs. TD groups and ASD vs. NDD groups.

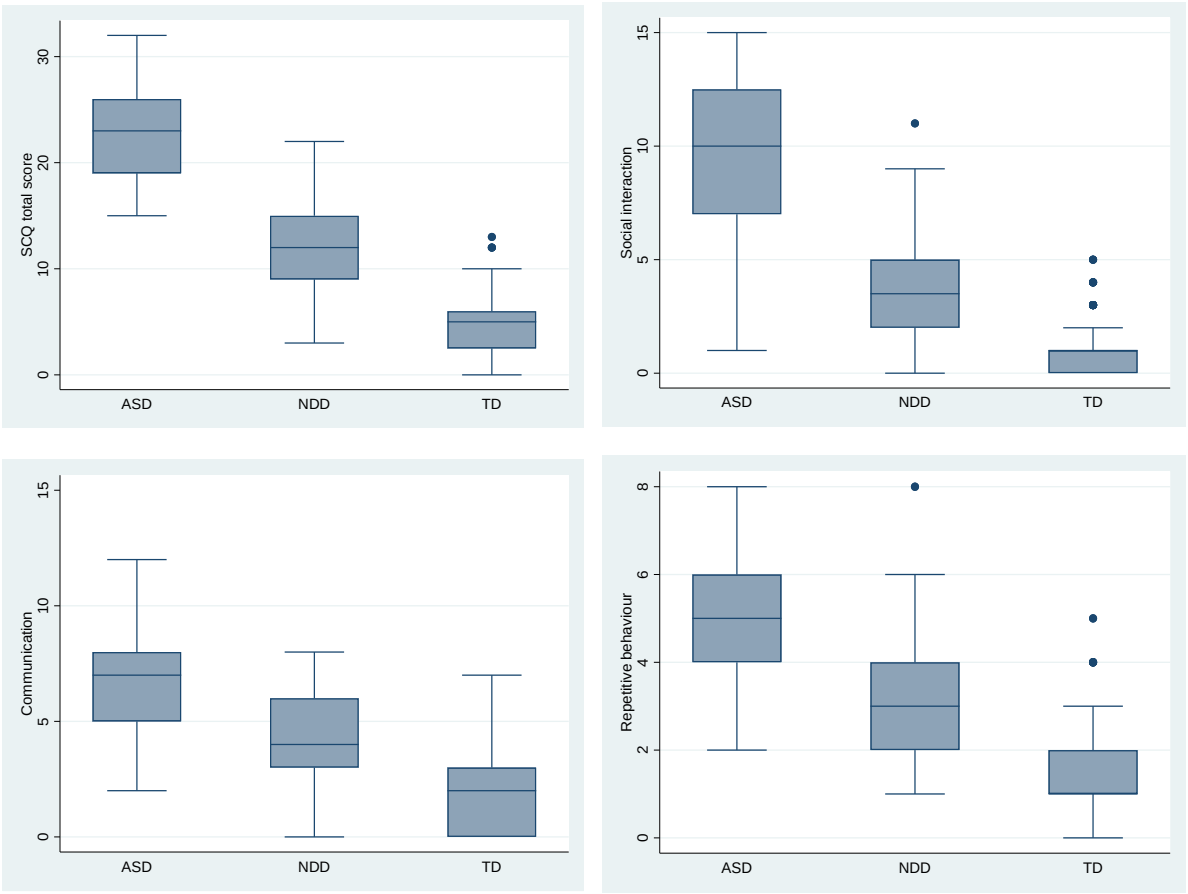
SCQ Scores	ASD (n = 108)	TD (n = 116)	NDD (n = 60)	ASD vs. TD *p*-value[a]	ASD vs. NDD *p*-value[a]
Total Score: Median (IQR)	23.0 (19.0 – 26.0)	5.0 (2.3 – 6.0)	12.0 (9.0 – 15.0)	< 0.0001*	< 0.0001*
Social Interaction Domain: Median (IQR)	10.0 (7.0 -12.5)	1.0 (0 – 1.0)	3.5 (2.0 -5.0)	< 0.001*	< 0.001*
Communication Domain: Median (IQR)	7.0 (5.0 – 8.0)	2.0 (0- 3.0)	4.0 (3.0 – 6.0)	< 0.001*	< 0.001*
Repetitive Behaviours Domain: Median (IQR)	5.0 (4.0 – 6.0)	1.0 (1.0 – 2.0)	3.0 (2.0 – 4.0)	< 0.001*	< 0.001*

Note. SCQ = Social Communication Questionnaire; ASD = Autism Spectrum Disorder; TD = Typically Developing; NDD = Neurodevelopmental Disorders; IQR = Interquartile Range.

[a] Mann Whitney U test as continuous variable and non-parametric despite log-transforming it.

* $p < 0.05$

Figure 5.1 - Group comparison boxplots.



Note. SCQ = Social Communication Questionnaire; ASD = Autism Spectrum Disorder; NDD = Neurodevelopmental Disorders; TD = Typically Developing.

Participant sex and respondent effects

Differences in SCQ total scores and all three domains between male and female participants were compared for each group; ASD, NDD and TD respectively (Table 5.5). Our results found only one significant difference between male participants with NDD and female participants with NDD for the repetitive behaviors domain (3 (IQR 2 – 5) vs. (2 (IQR 2 – 3); p= 0.030).

Table 5.6 demonstrates the differences in SCQ total scores and all three domains between mother and father respondents and mother and caregiver respondents for each group. When comparing respondent differences, no significant differences were found between mothers of children with ASD and fathers of children with ASD, mothers of children with ASD and caregivers of children with ASD, mothers of children with NDD and fathers of children with NDD, mothers of children with NDD and caregivers of children with NDD, mothers of TD children and fathers of TD children, as well as mothers of TD children and caregivers of TD children.

Table 5.5 - Differences in SCQ total scores and the 3 domains between male and female participants for each group.

SCQ	Whole group (n=284)	ASD Male (n = 85)	ASD Female (n=23)	TD Male (n= 66)	TD Female (n = 50)	NDD Male (n = 39)	NDD Female (n=21)	Difference between ASD male and ASD female *p*-value[a]	Difference between NDD male and NDD female *p*-value[a]	Difference between TD male and TD female *p*-value[a]
Total score Median (IQR)	12 (5 – 21)	24 (20 - 26)	22 (18 – 25)	5 (3 – 6)	4 (2 – 6)	12 (9 – 15)	12 (10 – 15)	0.256	0.518	0.259
Social interaction domain Median (IQR)	3 (1 – 9)	10 (7 – 13)	9 (6 – 12)	1 (0 - 2)	1 (0 – 1)	2 (1 – 5)	4 (2 – 5)	0.338	0.132	0.281
Communication domain Median (IQR)	4 (2 – 7)	7 (5 – 8)	7 (5 – 8)	2 (0 – 3)	1 (0 – 2)	3 (2 – 6)	5 (3 – 7)	0.232	0.121	0.062
Repetitive behaviour domain Median (IQR)	3 (1 – 5)	5 (4 – 6)	5 (3 – 6)	1 (1 – 2)	1 (1 – 2)	3 (2 – 5)	2 (2 – 3)	0.786	0.030*	0.180

Note. Social Communication Questionnaire; ASD = Autism Spectrum Disorder; TD = Typically Developing; NDD = Neurodevelopmental Disorders; IQR = Interquartile Range.

[a] Mann Whitney U test.

*$p < 0.05$

Table 5.6 - Differences in SCQ total scores and the 3 domains between mother and father respondents and mother and caregiver respondents for each group.

SCQ	ASD			NDD			TD			ASD		NDD		TD	
	Mo (n = 91)	Fa (n = 14)	Cg (n = 3)	Mo (n =51)	Fa (n = 6)	Cg (n = 3)	Mo (n=101)	Fa (n = 6)	Cg (n = 9)	Mo vs. Fa *p*-value[a]	Mo vs. Cg *p*-value[a]	Mo vs. Fa *p*-value[a]	Mo vs. Cg *p*-value[a]	Mo vs. Fa *p*-value[a]	Mo vs. Cg *p*-value[a]
Total score Median (IQR)	23 (18 – 26)	24.5 (20 – 26)	21 (17 – 21)	12 (9 -15)	10 (10 – 14)	12 (11 – 16)	5 (3 – 6)	4.5 (3 – 6)	3 (1 – 5)	0.688	0.306	0.855	0.622	0.769	0.164
Social interaction domain Median (IQR)	10 (7 – 13)	10 (8 – 12)	10 (3 – 10)	3 (2 – 5)	2 (1 – 4)	4 (4 – 5)	1 (0 -1)	0 (0 – 3)	1 (0 – 1)	0.677	0.369	0.422	0.445	0.670	0.954
Comm. domain Median (IQR)	7 (5 – 8)	7 (6 – 8)	7 (7 – 8)	4 (3 – 6)	6 (1 – 6)	4 (3 – 6)	2 (0 -3)	1.5 (1 – 4)	1 (0 – 2)	0.512	0.542	0.958	0.894	0.846	0.108
Repetitive behaviour domain Median (IQR)	5 (4 – 6)	5 (4 – 6)	4 (3 – 5)	3 (2 – 4)	2.5 (2 – 5)	3 (2 – 5)	1 (1 – 2)	1 (1 – 2)	1 (1 – 2)	0.477	0.381	0.884	0.817	0.769	0.732

Note. ASD = Autism Spectrum Disorder; NDD = Neurodevelopmental Disorders; TD = typically developing; Mo = Mother; Fa = Father; Cg = Caregiver; IQR = Interquartile Range.

[a]Mann Whitney U test.

[*]$p < 0.05$

5.3.3. SCQ reliability

Internal consistency of the SCQ

The internal consistency of the SCQ as measured by Cronbach's coefficient alpha for all items for the whole group was 0.92 (95% CI, 0.91-0.93) and was 0.68 (95% CI, 0.58-0.76) for the ASD group, 0.67 (95% CI, 0.54-0.78) for the NDD group and 0.56 (95% CI, 0.44-0.67) for the TD group (Table 5.7). All three domains of the SCQ had acceptable to excellent Cronbach's coefficient alphas (0.65–0.92) for the whole group. However, when measuring the internal consistency of the individual groups for each domain the Cronbach's coefficient alphas were much lower (0.25-0.75) with higher Cronbach's coefficient alphas for the social interaction domain for the ASD group (0.75) and lowest for the repetitive behaviours domain for the ASD group (0.25). However, when the social interaction and communication domains were combined the Cronbach's coefficient alphas were much higher (Table 5.7).

Table 5.7 - Internal consistency of the SCQ for all items and all 3 domains for individual groups and the whole group.

SCQ	ASD Cronbach's α (95% CI)	NDD Cronbach's α (95% CI)	TD Cronbach's α (95% CI)	Whole Group Cronbach's α (95% CI)
All items	0.68 (0.58 – 0.76)	0.67 (0.54 – 0.78)	0.56 (0.44 – 0.67)	0.92 (0.91 – 0.93)
Social Interaction Domain	0.75 (0.68 – 0.82)	0.61 (0.45 – 0.74)	0.45 (0.29 – 0.59)	0.91 (0.89 – 0.93)
Communication Domain	0.44 (0.28 – 0.59)	0.51 (0.31 – 0.69)	0.47 (0.31 – 0.60)	0.74 (0.69 – 0.78)
Social and Communication Domain[a]	0.74 (0.67 – 0.81)	0.68 (0.55 – 0.71)	0.58 (0.46 – 0.68)	0.92 (0.91 – 0.93)
Repetitive Behaviours Domain	0.25 (0.02 – 0.45)	0.46 (0.22 – 0.64)	0.29 (0.08 – 0.47)	0.65 (0.58 – 0.71)

Note. SCQ = Social Communication Questionnaire; ASD = Autism Spectrum Disorder; NDD = Neurodevelopmental Disorders; TD = Typically Developing; CI = Confidence Interval.

[a] Based on combining the social interaction domain and communication domain.

Test-retest reliability

The SCQ was initially filled out by parents or caregivers of a total of 284 children. Of these 284 children, 35 were screened again after two weeks. Table 5.8 shows the SCQ demonstrated excellent test-retest reliability (ICC = 0.972 [95% CI, 0.945-0.986] – 0.998 [95% CI, 0.996-0.999]). The before and after SCQ total scores were significantly correlated (Spearman correlation coefficient (rho) = 0.995; $p < 0.001$).

Table 5.8 - Test-retest reliability of the SCQ for the total score and all 3 domains.

SCQ	ICC (95% CI)	Spearman's rho
Total score	0.998 (0.996 – 0.999)	0.995 (<0.001)
Social interaction domain	0.994 (0.988 – 0.997)	0.994 (<0.001)
Communication domain	0.972 (0.945 – 0.986)	0.972 (<0.001)
Repetitive behaviours domain	0.968 (0.938 – 0.984)	0.964 (<0.001)

Note. SCQ = Social Communication Questionnaire; ICC = Intraclass Correlation Coefficient; CI = Confidence Interval.

5.3.4. SCQ validity

Confirmatory Factor Analysis (CFA)

We employed a 2 factor model of confirmatory factor analysis and found the model reached adequate fit levels (root mean squared error of approximation (RMSEA) = 0.057 (0.052 – 0.062); Comparative Fit Index (CFI) = 0.976; Tucker-Lewis Index (TLI) = 0.974) (Table 5.9). Five items (items 2, 3, 4, 5 and 6) from the social interaction and communication factor and 2 items (items 2 and 13) from the repetitive behaviours factor did not reach the factor loadings cut-off for standardized coefficients of 0.30 when the responses for all nonverbal children were missing for items 2 to 7. However, when their responses for items 2 to 7 were replaced with a score of 1, all items but one (item 13) loaded above the cut-off of 0.30 and reached adequate fit levels (root mean squared error of approximation (RMSEA) = 0.067 (0.063 – 0.072); Comparative Fit Index (CFI) = 0.977; Tucker-Lewis Index (TLI) = 0.976) (Table 5.9).

Table 5.9 - Factor loadings of the SCQ based on a 2-factor model of confirmatory factor analysis.

SCQ Factors and Items	Factor loadings Score 1[a]	Factor loadings Score 2[b]
Factor 1 Social interaction and communication		
2. Conversation	-0.05	0.778
3. Stereotyped utterances	-0.158	0.68
4. Inappropriate questions	-0.136	0.735
5. Pronoun reversal	-0.288	0.564
6. Neologisms	-0.201	0.653
9. Inappropriate facial expressions	0.363	0.358
10. Use of other's body	0.658	0.66
19. Friends	0.724	0.705
20. Social chat	0.643	0.651
21. Imitation	0.498	0.462
22. Pointing to express interest	0.642	0.616
23. Gestures	0.698	0.682

24. Nodding to say yes	0.815	0.774
25. Head shaking to mean no	0.823	0.78
26. Eye gaze	0.671	0.662
27. Social smiling	0.542	0.525
28. Sowing and directing attention	0.764	0.737
29. Offering to share	0.48	0.489
30. Seeking to share enjoyment	0.716	0.699
31. Offering comfort	0.401	0.392
32. Quality of social overtures	0.675	0.66
33. Range official expressions	0.727	0.699
34. Imitative social play	0.733	0.716
35. Imaginative play	0.647	0.64
36. Interest in children	0.762	0.736
37. Response to other children	0.708	0.696
39. Imaginative play with peers	0.636	0.633
40. Group play	0.673	0.677
Factor 2 Repetitive behaviors		
7. Verbal rituals	-0.165	0.718
8. Compulsions and rituals	0.65	0.655
11. Unusual preoccupations	0.545	0.558
12. Repetitive use of objects	0.533	0.513
13. Circumscribed interests	-0.192	-0.172
14. Unusual sensory interests	0.377	0.414
15. Hand and finger mannerisms	0.762	0.732
16. Complex body mannerisms	0.545	0.527

Note. SCQ = Social Communication Questionnaire.

[a]SCQ scores with responses from nonverbal children missing from items 2 to 7; [b]SCQ scores with responses from nonverbal children replaced with a score of 1 from items 2 to 7.

5.3.5. Diagnostic accuracy of the SCQ

Sensitivity & Specificity

I used a pre-determined total score cut-off of > 15 suggested by the authors (Rutter et al., 2003) as our sample size was not sufficient to explore cut-offs. Previous diagnosis by a clinician and adherence to DSM-5 criteria was used as clinical confirmation. When comparing ASD and TD groups, and using the cut-off point of >15 both sensitivity and specificity were 100% (AUC=1) (Table 5.10). Similarly, sensitivity remained at 100% when comparing ASD and NDD (AUC= 0.85) and for whole group (AUC= 0.95) but specificity decreased to 70.0% and 89.8% respectively. Figures 5.2, 5.3 and 5.4 illustrate the ROC curve analysis.

Table 5.10 - Sensitivity, specificity and ROC analysis (AUC).

	Sensitivity	Specificity	ROC Analysis (AUC)
ASD vs TD	100%	100%	1
ASD vs NDD	100%	70.0%	0.85
GROUP	100%	89.8%	0.95

Note. ASD = Autism Spectrum Disorder; TD = Typically Developing; NDD = Neurodevelopmental Disorders; ROC = Receiver Operating Curve; AUC = Area under the Curve.

Figure 5.2 - Area under the curve (AUC) for all groups.

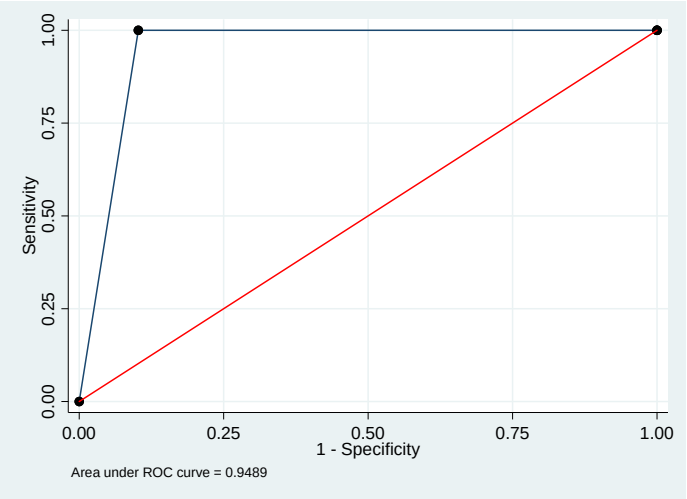


Figure 5.3 - Area under the curve (AUC) for ASD vs. TD.

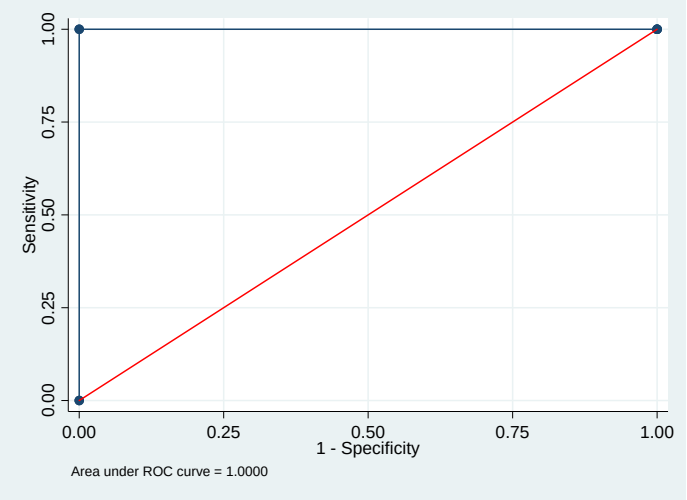
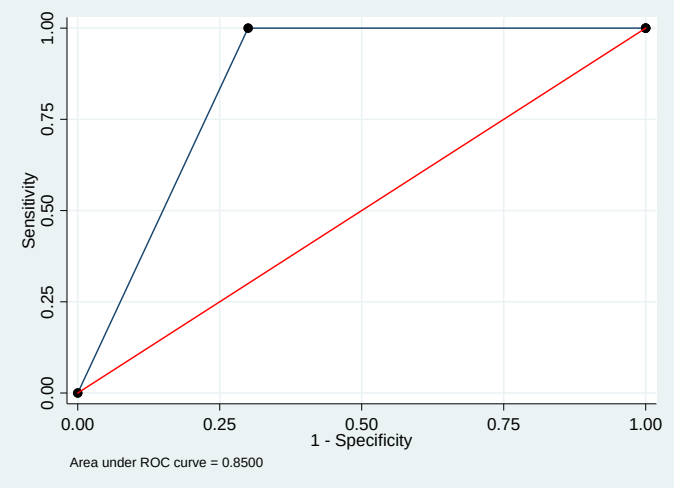


Figure 5.4 - Area under the curve (AUC) for ASD vs. NDD.



5.4. Discussion

There are currently no available validated screening tools for ASD in SSA. Therefore, this study sought to evaluate the psychometric properties of the Kiswahili version of the SCQ in a sample of children with a confirmed diagnosis of ASD, children with a known NDD and typically developing children in Dar-es-Salaam, Tanzania. After careful translation and adaptation of the SCQ, our findings indicate that the SCQ is a reliable and valid screening measure of ASD symptoms in this population.

5.4.1. Discriminant validity

In order to examine the discriminant validity of the SCQ, we compared the median total scores and median scores on all three domains between ASD and TD groups and ASD and NDD groups. Our results indicate that the ASD group scored significantly higher than both TD and NDD groups on the total score and all three domains, implying that the SCQ scores discriminated effectively between children with ASD from children with other NDD and typically developing children demonstrating that the SCQ has good discriminant validity. This is in line with previous research using the original English SCQ comparing ASD and non-ASD samples (Chandler et al., 2007; Charman et al., 2007), the German SCQ comparing ASD and non-ASD samples (Bölte et. al., 2008b), the Portuguese SCQ comparing PDD, Downs Syndrome and other psychiatric disorders, the Chinese SCQ comparing ASD children with their unaffected siblings (Gau et al., 2011), the Turkish SCQ comparing children and adolescents with PDD and ID (Avcil et al., 2015) and the Greek SCQ comparing ASD and non-ASD samples(Zarokanellou et al., 2017).

5.4.2. Participant sex and respondent effects

Our sample for all three groups included more males than females. However, our findings did not reveal any sex differences for any group for the SCQ total score, social interaction domain and

communication domain. Only one significant difference between male participants with NDD and female participants with NDD for the repetitive behaviors domain was found with males scoring higher in this domain than females. These findings conflict with those published by Gau et al. (2011), who found significant higher total scores for ASD males compared to ASD females using the Chinese version of the SCQ. In addition, many studies have reported sex differences in ASD, in particular that females have lower frequency of challenging behaviours (McLennan et al., 1993), exhibit less stereotyped behaviour during play (Lord et al., 1982) and had better language and social skills (Gillberg & Coleman, 2000). One reason for this discrepancy could be that the phenotype maybe different in this population. Our sample included more mothers than fathers and caregivers and similar respondent patterns across the groups (ASD = 84% mothers; TD = 87% mothers; NDD = 85% mothers). When comparing respondent effects, our results revealed that there were no significant differences between mother and father respondents and mother and caregiver respondents for all group comparisons.

5.4.3. Reliability of the SCQ

The reliability coefficient alphas for the whole group for all items (Cronbach's $\alpha = 0.92$) and all three domains (Cronbach's $\alpha = 0.65 – 0.91$) of the SCQ were acceptable to excellent, highlighting the SCQ as a valuable screening measure in this population. Our findings reveal higher reliability coefficient alphas than other cross-cultural validation studies of the SCQ total scores (e.g. Sato et al., 2009; Avcil et al., 2015) and similar for the domain scores (Gau et al., 2011), although the latter used only ASD samples and non-effected siblings. The coefficient alphas for the individual groups for all items and the three domains were much lower, perhaps due to smaller sample sizes. For instance, Bolte et al. (2008) documented a higher correlation coefficient (Cronbach's $\alpha = 0.83$) for their slightly larger ASD sample. Our findings revealed excellent test-retest reliability (ICC = 0.972 – 0.998) for the SCQ total scores and three domains, with the before and after scores significantly correlated ($r = 0.964 – 0.995$; $p < 0.001$) suggesting the stability of the SCQ over time. Our finding was better than that reported from a German version of the SCQ (0.76).

5.4.4. Validity of the SCQ

According to confirmatory factor analysis, our findings support the use of a 2-factor model as recommended by DSM-5 criteria since all fit indices reached acceptable levels. This is clinically important in that use of items for impairments in social interaction may predict problems in communication and vice versa. Previous studies also demonstrate an evident overlap between the social interaction domain and the communication domains (Avcil et al., 2015; Gau et al., 2011). All item loadings were above the cut-off for standardized coefficients of 0.3 except one (item 13) when the responses for items 2 to 7 were replaced with a score of 1. Similar to our study, high standardized

coefficients have been reported in another cross cultural study from Taiwan which used a 3 factor model rather than the 2 model used in our study(Gau et al., 2011).

5.4.5. Sensitivity and specificity of the SCQ

ROC curve analyses suggested excellent predictive ability in our study. At the standard cut-off point of 15 our results yielded sensitivity of 100% and specificity of 100% (AUC = 1) when discriminating ASD with TD samples and sensitivity remained at 100% when discriminating ASD with NDD (AUC= 0.85) and for whole group (AUC= 0.95) but specificity decreased to 70.0% and 89.8% respectively. Our findings are better than that reported in the initial validation study of the SCQ (Berument et al., 1999) when discriminating ASD with non-ASD, as well as when discriminating between ASD and ID, and similar in terms of higher sensitivity estimates than specificity estimates. In contrast, other studies found still adequate but lower sensitivity estimates and higher specificity estimates (Bolte et al., 2008; Sato et al., 2009; Zarokanellou et al., 2017). The use of preselected groups with a known diagnosis may have led to these findings in our study.

5.4.6. Strengths and limitations

The strengths of the present study include the careful translation and adaptation of the SCQ into the local language Kiswahili. The inclusion of NDD and TD samples and using both verbal and nonverbal children to evaluate diagnostic validity lends additional support for the utility of the SCQ as a screening measure in clinical practice. The use of additional tools such as the ADOS and DSM-5 criteria to aid in the confirmation of the diagnosis of the ASD sample and the use of a clinical consensus process corroborated by independent expert rating are also strengths. One limitation of the present study is that the age of the TD sample at the time of screening was much younger (< 4 years of age) than the ASD and NDD samples and younger than would be required for first-level screening of children using the SCQ. Another limitation in our study is that we had to make an assumption that all nonverbal children in our sample had a score of 1 for items 2-7 in the SCQ. A larger sample size would allow for more comprehensive validity analysis with CFA and further explore different cut-off points. Analysis of inter-informant reliability would have also allowed for further reliability tests for the SCQ. Additionally, our method of sampling approach meant that parents of children from rural areas did not participate and their responses may have been different.

5.4.7. Conclusions

We report on the performance of the Kiswahili version of the SCQ in screening for ASD in a sample of children with a diagnosis of ASD, children with a known NDD and typically developing children. Our findings reveal good discriminant validity, acceptable internal consistency properties and excellent test–retest correlation coefficients. Additionally a 2-factor model of social and communication as well as repetitive behaviours reached an adequate fit. ROC curve analyses

suggested excellent discriminant ability in our study as scoring above the recommended cut-off of 15 for ASD was highly indicative that the child had ASD. In sum, the SCQ has suitable psychometric properties confirming the utility of the SCQ as a first level screening measure for ASD among Tanzanian children.

Chapter 6

Risk factors associated with Autism Spectrum Disorders (ASD) in Dar-es-Salaam, Tanzania: a case-control study.

6.1. Background

The underlying aetiology of Autism Spectrum Disorders (ASD) remains unknown, particularly in low and middle-income countries (LAMIC) in sub-Saharan Africa (SSA), where the incidence of risk factors such as pregnancy complications and adverse perinatal events is high. The heritability of ASD is estimated to be 70%-90% (Bailey et al., 1995; Hallmayer et al., 2011) indicating that it is a strongly genetically determined childhood disorder. Research suggests that siblings of individuals with ASD are at a 20-fold increased risk of developing ASD compared with the general population (Ritvo et al., 1989; Lauritsen et al., 2005; Constantino et al., 2010; Ozonoff et al., 2011). Despite major advances in understanding the genetic and developmental aspects of ASD in high-income countries, there are few or no genetic or heritability studies of ASD in LAMIC.

Furthermore, there is strong evidence of the interplay between genetic and environmental factors (Hallmayer et al., 2011; Meek et al, 2013; Sandin et al., 2014; Volk et al., 2014) suggesting that both factors play an important role in the development of ASD. Recent epidemiologic research has emphasized the prenatal and neonatal period as the most relevant period for environmental risk factors to be associated with ASD. Gardener et al. (2009) published the first quantitative review and meta-analysis of the association between maternal pregnancy-related factors and risk for ASD. They examined over 50 prenatal factors and found advanced parental age, maternal prenatal medication use, bleeding, gestational diabetes and being first born to be associated with a risk for ASD. In a subsequent review and meta-analysis on over 60 perinatal and neonatal factors, Gardener et al. (2011) found abnormal presentation, low birth weight, small for gestational age, congenital malformation, feeding difficulties and meconium aspiration amongst others to be associated with a risk for ASD. However, the authors warned of insufficient evidence to implicate any single prenatal, perinatal and neonatal factor in ASD aetiology (Gardener et al., 2009; Gardener et al., 2011).

More recently, in a retrospective case-cohort study, Hisle-Gorman et al. (2018) explored 29 prenatal, perinatal and neonatal factors previously associated with ASD, reporting the greatest increased risk was associated with neonatal seizures, maternal mental health and epilepsy medications. In one of the few studies examining the prenatal and perinatal factors associated with ASD using a sibling design and correlating these factors with ASD core symptoms, Chien et al. (2018) report probands with ASD

and their unaffected siblings had more prenatal and perinatal events than typically developing controls, with higher number of prenatal and perinatal factors in probands than in unaffected siblings. They also found the total number of prenatal and perinatal factors in ASD probands to be associated with overall symptom severity as well as specific symptoms such as social communication deficits.

However, most of these studies were not conducted in SSA, where these risk factors are also common. In a recent comprehensive scoping review of ASD in SSA only 3 risk factor studies were identified (Franz et al., 2017; Abubakar et al., 2016b). In a descriptive case series study in Tanzania, Mankoski et al. (2006) reported 3 out of 14 children studied developed ASD upon recovery from malaria, suggesting that severe neurological infections, when contracted in the first few years of life, can cause ASD. Claassen et al. (2008) conducted a retrospective case study of dizygotic twin siblings in South Africa, one of whom had ASD. They suggested that maternal stress contributed to the pathogenesis of ASD as the blood plasma of the ASD proband had elevated glucocorticoids and serotonin in comparison to the unaffected sibling. van Wijngaarden et al. (2013) conducted a longitudinal descriptive study in the Republic of Seychelles and found no association between prenatal methyl mercury exposure and ASD phenotype behaviours as measured by scores on two ASD screening tools. However, key methodological aspects, in particular systematic diagnosis and translation/validation of the tools is not available or questionable in these studies (Franz et al., 2017).

One Swedish report found increased prevalence of ASD (three to four times) in children of Somali origin living in Stockholm compared to a non-Somali group (Barnevick-Olsson et al., 2008). Furthermore, a study conducted in the UK, found maternal immigration and ethnicity to be associated with an increased risk of ASD; in particular mothers of African and Caribbean ethnicity having increased risk of ASD compared to mothers of white ethnicity (Keen et al., 2010). Another study looking at perinatal factors and migration in Sweden found that maternal birth outside the Nordic countries was associated with ASD (Haglund & Källén, 2011), indicating that children of women who were born in SSA or East Asia had the highest risk for ASD. Additionally, many of the risk factors mentioned earlier are common in SSA, suggesting that ASD may be more common than recognized in this region.

The current study was designed to investigate the prenatal, perinatal, neonatal and postnatal risk factors for ASD in Dar-es-Salaam, Tanzania. As such 3 groups of children were recruited for this study: (i) children with an ASD diagnosis; (ii) children diagnosed with other neurodevelopmental disorders (NDD) that are not ASD; and (iii) typically developing children (TD). The ASD group was compared to the TD group in order to identify the general risk factors for ASD. Additionally, the ASD group was compared to the NDD group to identify factors unique to ASD as neurodevelopmental disorders are a broad category. The NDD group was also compared to the TD group in order to find

the general risk factors for other neurodevelopmental disorders excluding ASD. Lastly, the ASD and NDD groups were combined and compared to the TD group as both groups are related disorders and may have common risk factors and combining them also improves the power to identify the common risk factors.

6.2. Methodology

This case-control study was approved by the Muhimbili University of Health and Allied Sciences (MUHAS) Directorate of Research and Publications, National Institute for Medical Research (NIMR) and registered with the Tanzania Commission for Science and Technology (COSTECH). Parents and guardians gave verbal and written consent.

6.2.1. Study sample

Three groups of children were recruited for the study. Children who had a diagnosis of ASD (n = 108) were recruited from the Child and Adolescent Clinic, Department of Psychiatry, Muhimbili National Hospital (MNH), private clinics and centres, and autism units attached to local primary schools in Dar-es-Salaam, Tanzania. These children were aged from 5 to 12 years and had no known genetic disorders, deafness or motor impairment. Previous diagnosis was made by either a psychiatrist at MNH using DSM-IV criteria, or by a paediatrician in a private setting using DSM-IV criteria and the M-CHAT or an education assessment centre using pre-determined assessment criteria. At least one biological parent had to be available for the study (where biological parent was unavailable, data was collected from the main caregiver). Children with other neurodevelopmental disorders (NDD n = 60) aged 5 to 12 years were recruited from MNH and special needs schools in Dar-es-Salaam, Tanzania. The NDD group was matched on chronological age and had a previous diagnosis of a neurodevelopmental disorder which included, Down's Syndrome (n = 9), Learning Disability (n = 33), Seizure Disorders (n = 8) and ADHD (n = 10). Typically developing (TD) children (n = 116) were randomly selected from the community with no known concerns of language and/or behavioral or emotional problems and did not have any history of learning or psychiatric disabilities according to our further assessments. They were matched with the ASD group on a surrogate marker of IQ i.e. level of expressive language (ADOS-2 Module) but not by age.

6.2.2. Procedures

Families were invited to the clinic or the schools for assessment. Each visit lasted approximately 2 to 3 hours. After obtaining consent, parents of participating children were asked to complete the Social Demographic Questionnaire and the Social Communication Questionnaire (SCQ). Children in the ASD group and the NDD group were requested to complete the neuropsychological testing (RAVEN's Coloured Progressive Matrices and the Peabody Picture Vocabulary Test). It was inappropriate for the children in the TD group to do these neuropsychological tests as they were

younger than 5 years of age. All children were subsequently asked to proceed for an ADOS-2 assessment. Parents were asked to be present in the assessment room. Each assessment was videotaped so that later a panel of both local and international experts can categorize these children and this information will be used as an extra validity check. I was fully involved with the recruitment of participants and collected all the data for this study with assistance from the fieldworker where Kiswahili was required. I directly administered the neuropsychological tests, ADOS, SCQ and the socio-demographic questionnaire. I trained, supervised and oversaw any assistance from the fieldworker.

6.2.3. Definition of investigated risk factors

A socio-demographic questionnaire was designed to collect data for each participant's parental and socio-demographic information such as age at delivery and first birth, employment, education, religion and ethnicity. Additionally, it included information on past medical history based on the possible risk factors of ASD from existing literature and those likely to be specific and common in our setting such as adverse perinatal events. Care was taken to analyse and include the most relevant and specific risk factors. The risk factors analysed are defined in Table 6.1.

Table 6.1 - Definition of investigated risk factors.

Risk factors	Types of risk factors	Categories for analysis
Parental factors	Mother's age (years) at delivery	< 30 30 – 35 ≥ 35
	Father's age (years) at delivery	< 30 30 – 35 35 – 40 ≥ 40
	Mother's age at first birth	
	Mother / Father's marital status	Single Married Separated/ Divorced Widowed
	Mother / Father's religion	Catholic Protestant Islam
	Mother / Father's ethnicity	Northern Southern Eastern Central

		Other
	Mother / Father's education level	None Primary Secondary Tertiary
	Mother / Father's occupation	Formal employment Informal employment None
	Parental age gap	The difference between the father's and mother's age
	Birth order	Order in which a child was born e.g. first born, second born or last born
	Birth weight	As reported by parents
	Number of children ever born	Children ever born in family whether dead or alive
Prenatal factors	Pregnancy medical complications	Gestational hypertension Gestational diabetes Eclampsia Maternal bleeding
	Pregnancy infections	Prenatal fever Malaria during pregnancy
	Medication use during pregnancy	Antibiotics
	Gestational term	≤ 37 weeks
Perinatal factors	Assisted delivery	Vacuum mediated delivery
	Labour complications	Induced labour Prolonged labour
	Birth complications	Breech presentation Umbilical cord complications Meconium aspiration
	Adverse perinatal events	Birth asphyxia Delayed birth cry Difficulties breastfeeding
Neonatal factors	Low birth weight	≤ 2.5 kg
	Neonatal jaundice	Parental reports of yellow colouration of skin and/or eyes at birth of child
	Neonatal seizures immediately after birth	Parental reports of seizures at birth
Postnatal factors	Family history of seizures	Parental reports of seizures in the family (first and second degree relatives)
	Seizures disorders	Parental reports of seizures

	Malaria	Before age 3
	Head injury with loss of consciousness	Before age 3

Note. Eight (7%) mothers of children with Autism Spectrum Disorder (ASD), 1 (1%) mother of a typically developing child (TD) and 5 (8%) mothers from the neurodevelopmental disorders (NDD) group were from other African ethnicities, but have lived in Dar-es-Salaam for more than 15 years. All children enrolled in this study were from a singleton pregnancy, born in hospital and had all their childhood immunizations.

6.2.4. Statistical analysis

Exploratory analysis on the distribution of continuous variables and univariable analysis were carried out using IBM SPSS Statistics version 20. After checking for normality of continuous variables, transformations (log or square-root) were performed where necessary. Parametric tests such as Student's-t-test were used on the transformed continuous scores if transformation resulted in a normal distribution. Otherwise, non-parametric tests such as the Mann-Whitney U test were used on the raw scores of continuous variables when the transformed scores did not achieve a Gaussian distribution. For categorical variables the Pearson's chi-square test were performed (or Fisher's exact test if frequency was ≤ 5). Multivariate analysis and likelihood ratio tests (LRT) for the risk factor analysis were performed using STATA version 13. Since the outcome variables were binary or dichotomous, logistic regression modelling was applied in computing odds ratios for the univariable and multivariable risk factors. The multivariable model focused on risk factors with plausible biological basis for the risk of ASD in such a way that parental marital status, religion, ethnicity, level of education and occupation were entered into the model as covariates to account for their potential confounding of other risk factors. All variables reaching a significance p-value of ≤ 0.250 in the univariable analysis were entered in the multivariable models, retaining all variables if the model showed acceptable goodness-of-fit statistics (measured using Hosmer-Lemeshow test). LRT was used to test for evidence of departure from linear trend, such that if linear trend was not violated a single odds ratio assuming all categories as linear ordinal levels was computed, with odds ratios for individual categories computed if there was evidence for departure from linear trend.

6.3. Results

We collected data on parental and socio-demographic information for 108 children diagnosed with ASD, 116 typically developing (TD) children and 60 children with other neurodevelopmental disorders (NDD) in Dar-es-Salaam, Tanzania. Of these eligible children, males formed 79% of the ASD group, 57% of the TD group and 65% of the NDD group. Table 6.2 compares the distribution of characteristics, socio-demographic and family history data between ASD and TD groups, ASD and NDD groups, NDD and TD groups and lastly combined ASD+NDD and TD groups. Statistically significant differences between the groups were observed for some socio-demographic and medical history factors. Odds ratios (OR) and 95% confidence intervals (CI) for all group comparisons were calculated using logistic regression analyses (Tables 6.3 – 6.10 respectively).

Table 6.2 - Distribution of characteristics, socio-demographic and family history data between ASD, TD, NDD and combined ASD+NDD groups enrolled in this study.

Participant characteristics and socio-demographic data	ASD (n = 108)	TD (n = 116)	NDD (n = 60)	ASD+NDD (n = 168)	ASD vs. TD *p*-value	ASD vs. NDD *p*-value	NDD vs. TD *p*-value	ASD+NDD vs. TD *p*-value
Child's age in years: Median (IQR)	7.1 (5.9 – 9.1)	2.8 (2.6 – 3.1)	9.95 (8.2 – 11.0)	8.1 (6.3 - 10.2)	< 0.0001[*a]	< 0.0001[*a]	< 0.0001[*a]	< 0.0001[*a]
Child's male sex	85 (79%)	66 (57%)	39 (65%)	124 (74%)	0.001[*b]	0.053[b]	0.299[b]	0.003[*b]
Parental factors								
Mother's age in years: Mean (SD)	36.5 (4.86)	31.5 (7.21)	39.1 (6.74)	37.5 (5.72)	< 0.0001[*c]	0.005[*c]	< 0.0001[*c]	< 0.0001[*c]
Mother's age at delivery in years: Mean (SD)	28.9 (4.53)	28.6 (7.17)	29.7 (6.82)	29.2 (5.45)	0.473[e]	0.473[e]	0.313[e]	0.301[e]
< 30	70 (65%)	70 (60%)	27 (45%)	97 (58%)	0.334[b]	0.035[*b]	0.050[*b]	0.484[b]
30 – 35	26 (24%)	25 (22%)	20 (33%)	46 (27%)				
≥ 35	12 (11%)	21 (18%)	13 (12%)	25 (15%)				
Mother's age at first birth in years: Median (IQR)	26.0 (23.0 – 28.0)	22.0 (19.0 – 25.0)	23.0 (19.0 – 27.8)	26.0 (22.0 – 29.0)	< 0.0001[*f]	0.098[f]	0.019[*f]	< 0.0001[*f]
Mother's marital status					0.115[d]	0.001[*d]	0.159[d]	0.659[d]
Single	3 (3%)	10 (9%)	6 (10%)	9 (5%)				
Married	98 (90%)	92 (79%)	40 (67%)	138 (82%)				
Separated/ Divorced	5 (5%)	10 (9%)	12 (20%)	17 (10%)				
Widowed	2 (2%)	4 (3%)	2 (3%)	4 (2%)				
Mother's religion					< 0.0001[*b]	0.004[*b]	0.086[b*]	<0.0001[b*]

Catholic	42 (39%)	15 (13%)	14 (23%)	56 (33%)				
Protestant	30 (28%)	13 (11%)	10 (17%)	40 (24%)				
Islam	36 (33%)	88 (76%)	36 (60%)	72 (43%)				
Mother's ethnicity					< 0.0001[*d]	0.074[d]	0.005[*d]	<0.0001[*d]
Northern	57 (53%)	27 (23%)	20 (33%)	77 (46%)				
Southern	23 (21%)	42 (36%)	13 (22%)	36 (21%)				
Eastern	14 (13%)	41 (35%)	15 (25%)	29 (17%)				
Central	6 (6%)	5 (4%)	7 (12%)	13 (8%)				
Other	8 (7%)	1 (1%)	5 (8%)	13 (8%)				
Mother's education level					< 0.0001[*d]	< 0.0001[*d]	0.068[d]	<0.0001*[d]
None	1(1%)	2 (1%)	3 (5%)	4 (2%)				
Primary	18 (17%)	74 (64%)	31 (52%)	49 (29%)				
Secondary	26 (24%)	29 (25%)	13 (22%)	39 (23%)				
Tertiary	63 (58.3%)	11 (10%)	13 (22%)	76 (45%)				
Mother's occupation					< 0.0001[*b]	< 0.0001[*b]	0.075[b]	<0.0001*[b]
Formal employment	80 (74%)	19 (16%)	19 (32%)	99(59%)				
Informal employment	19 (18%)	57 (49%)	24 (40%)	43 (26%)				
None	9 (8%)	40 (35%)	17 (28%)	26 (15%)				
Father's age in years:	40.8	33.8	42.8	41.5	< 0.0001[*c]	0.601[c]	<0.0001*[c]	<0.0001*[c]
Mean (SD)	(5.82)	(6.41)	(7.50)	(6.51)				
Father's age at delivery in years:	33.2	31.0	33.4	33.3	0.005[*c]	0.838[c]	0.025*[c]	0.0026*[c]
Mean (SD)	(5.39)	(6.41)	(7.48)	(6.20)				
< 30	31 (29%)	64 (55%)	16 (27%)	47 (28%)	0.001[*b]	0.581[b]	0.002*[b]	<0.0001*[b]
30 – 35	41 (38%)	23 (20%)	20 (33%)	61 (36%)				
35 – 40	23 (21%)	19 (16%)	12 (20%)	35 (21%)				

≥ 40	13 (12%)	10 (9%)	12 (20%)	25 (15%)				
Father's marital status					0.028[*d]	0.008[*d]	0.340*[d]	0.260*[d]
Single	3 (3%)	8 (7%)	6 (10%)	9 (5%)				
Married	100 (93%)	93 (80%)	40 (67%)	140 (83%)				
Separated / Divorced	4 (4%)	14 (12%)	12 (20%)	16 (10%)				
Widowed	1 (1%)	1 (1%)	2 (3%)	3(2%)				
Father's religion					< 0.0001[*b]	0.002[*b]	0.182*	<0.0001*[b]
Catholic	40 (37%)	15 (13%)	14 (23%)	54 (32%)				
Protestant	33 (31%)	18 (15%)	10 (17%)	43 (26 %)				
Islam	35 (32%)	83 (72%)	36 (60%)	71 (42%)				
Father's ethnicity					< 0.0001[*d]	0.013[*d]	0.669*[d]	< 0.0001[*d]
Northern	55 (51%)	26 (22%)	17 (28%)	72 (43%)				
Southern	19 (18%)	44 (38%)	20 (33%)	39 (23|%)				
Eastern	19 (18%)	36 (31%)	17 (28%)	36 (21%)				
Central	6 (5%)	9 (7.8%)	4 (7%)	10 (6%)				
Other	9 (8%)	1 (1%)	2 (3%)	11 (7%)				
Father's education level					< 0.0001[*d]	0.001[*d]	0.252*[d]	< 0.0001[*d]
None	1 (1%)	1 (1%)	3 (5%)	4 (2%)				
Primary	10 (9%)	62 (53%)	31 (52%)	41 (24%)				
Secondary	22 (20%)	34 (29%)	13 (22%)	35 (21%)				
Tertiary	75 (70%)	19 (16%)	13 (22%)	88 (52%)				
Father's occupation					< 0.0001[*d]	< 0.0001[*d]	0.001*[b]	<0.0001*[b]
Formal employment	86 (80%)	37(32%)	33 (55%)	119 (71%)				
Informal employment	19 (18%)	70 (60%)	18 (30%)	37 (22%)				
None	3 (3%)	9 (8%)	9 (15%)	9 (5%)				

Parental age gap in years: Median (IQR)	3.55 (0.10 - 9.26)	1.85 (-1.69 - 9.82)	2.95 (-0.45 - 10.4)	3.50 (-0.01 - 9.26)	0.006*[a]	0.281[a]	0.261[a]	0.012*[a]
Mother is older than Father	10 (9%)	16 (14%)	6 (10%)	16 (10%)	0.290[b]	0.290[b]	0.396[b]	0.036*[b]
Father is older than Mother	97(90%)	90 (78%)	49 (82%)	146 (87%)	0.019*[b]	0.014*[b]	0.471[b]	0.263[b]
Birth order: Median (IQR)	1 (1-2)	2 (1-2)	2 (1-3)	2 (1-2)	0.466[a]	0.042*[a]	0.141[a]	0.853[a]
Birth weight (kg): Median (IQR)	3.2 (3 – 3.6)	3.0 (2.8 - 3.5)	3.0 (2.9 - 3.5)	3.2 (3.0 - 3.6)	0.056[a]	0.188[a]	0.875[a]	0.150[a]
No. of children ever born: Median (IQR)	2.0 (2 - 3)	2.0 (1- 2)	3.0 (2 - 4)	2 (2-3)	< 0.0001*[a]	0.027*[a]	<0.0001[a]	<0.0001[a]
Prenatal factors								
Pregnancy medical complications (gestational hypertension, gestational diabetes, eclampsia and maternal bleeding)	10 (9%)	4 (4%)	3 (5%)	13 (8%)	0.098[d]	0.383[d]	0.691[d]	0.202[d]
Pregnancy infections (prenatal fever and malaria during pregnancy)	21 (19%)	4 (4%)	2 (3%)	23 (14%)	< 0.0001*[d]	0.004*[d]	1.00[d]	0.004*[d]
Medication use during pregnancy	30 (28%)	20 (17%)	18 (30%)	48 (29%)	0.058[b]	0.760[b]	0.051*[b]	0.028*[b]
Gestational term ≤ 37 weeks	8 (7%)	0 (0%)	2 (3%)	10 (6%)	0.003*[d]	0.498[d]	0.268[b]	0.025*[b]
Perinatal factors								
Assisted delivery (vacuum mediated delivery)	5 (5%)	2 (2%)	1 (2%)	6 (4%)	0.266[d]	0.423[d]	0.978[d]	0.335[d]
Labour complications (induced labour and prolonged labour)	18 (17%)	2 (2%)	2 (3%)	20 (12%)	< 0.0001*[d]	0.012*[d]	0.606[d]	0.001*[d]

Birth complications (breech presentation, umbilical cord complications and meconium aspiration)	18 (17%)	2 (2%)	5 (8%)	23 (14%)	< 0.0001*[d]	0.162[d]	0.046*[d]	<0.0001*[d]
Adverse perinatal events (birth asphyxia, delayed birth cry and difficulties breastfeeding)	35 (32%)	2 (2%)	24 (40%)	59 (35%)	< 0.0001*[d]	0.399[b]	<0.0001*[d]	<0.0001*[d]
Neonatal factors								
Low birth weight (≤ 2.5 kg)	12 (11%)	17 (15%)	11 (18%)	23 (14%)	0.430[b]	0.192[b]	0.527[b]	0.818[b]
Neonatal jaundice	9 (8%)	0 (0%)	6 (10%)	15 (9%)	< 0.0001*[d]	0.717[b]	0.007*[d]	0.003*[d]
Neonatal seizures immediately after birth	6 (6%)	0 (0%)	7 (12%)	13 (8%)	0.012*[d]	0.155[b]	0.002*[d]	0.010*[d]
Postnatal factors								
Family history of seizures	11 (10%)	9 (8%)	7 (12%)	18 (11%)	0.525[b]	0.766[b]	0.393[b]	0.404[b]
Seizures disorders	22 (20%)	0 (0%)	8 (13%)	30 (18%)	< 0.0001*[d]	0.254[b]	0.001*[d]	<0.0001*[d]
Malaria (before age 3)	33 (31%)	5 (4%)	3 (5%)	36 (21%)	< 0.0001*[d]	< 0.0001*[d]	1.00[d]	<0.0001*[d]
Head injury with loss of consciousness (before age 3)	9 (8%)	0 (0%)	11 (18%)	20 (12%)	0.001*[d]	0.055[b]	<0.0001*[d]	<0.0001*[d]

Note. ASD = Autism Spectrum Disorder; TD = Typically Developing; NDD = Neurodevelopmental Disorders; IQR = Interquartile Range; SD = Standard Deviation. Non parametric continuous data is reported as median and parametric data is reported as means. No parent in our study was from the Western Region of Tanzania.

[a]Mann Whitney U test; [b]Pearson's chi-squared test (dichotomous and categorical variables); [c]t-test on raw data (continuous variable); [d]Fisher's exact test (if less than 5); [e]t-test on square root transformed; [f]t-test on log transformed.

*$p < 0.05$

6.3.1. ASD vs. TD groups

General description

The median age was significantly different between ASD and TD groups (7.1 vs. 2.8; $p < 0.0001$), because the TD was matched on expressive language level. Frequency of males was significantly higher in the ASD group than in the TD group (79% vs. 57%; $p = 0.001$) (Table 6.2).

Mother's age at assessment ($p < 0.0001$) and mother's age at first birth ($p < 0.0001$) were significantly higher for mothers of children with ASD compared to mothers of TD children. However, mothers of children with ASD were similar to the TD group mothers in terms of age at delivery. Mothers of children with ASD were also more likely to have higher education levels (58% vs. 10%; $p < 0.0001$) and working in formal employment (74% vs. 16%; $p < 0001$) compared to mothers of the TD group. Statistically significant differences were also noted for mother's religion and ethnicity between the two groups ($p < 0.0001$) (Table 6.1).

Father's age at assessment ($p < 0.0001$) and delivery ($p < 0.0001$) were significantly higher for fathers of children with ASD compared to fathers of the TD group. Similarly, fathers of children with ASD were more likely to be married (93% vs. 80%; $p = 0.028$), have higher levels of education (70% vs. 16%; $p < 0.0001$) and working in formal employment (80% vs. 32%; $p < 0.0001$) compared to TD fathers. There was a significant difference between the parental age gap in the ASD and TD groups ($p < 0.006$), and with 90% of fathers older than mothers in the ASD group compared to 78% of fathers in the TD group ($p = 0.019$).

Within the prenatal factors, mothers of children with ASD were significantly more likely to have infections during pregnancy (19% vs. 4%; $p < 0.0001$) and pre-term births (7% vs. 0%; $p = 0.003$) compared to mothers of the TD group. Labour complications (17% vs. 2%; $p < 0.0001$), birth complications (17% vs. 2%; $p < 0.0001$) and adverse perinatal events (32% vs. 2%; $p < 0.0001$) were significantly more common in the ASD group compared to the TD group. The ASD group were also more likely to have neonatal jaundice (8% vs. 0%; $p < 0.0001$) and neonatal seizures immediately after birth (6% vs. 0%; $p = 0.012$) compared to the TD group. Significant differences between the ASD and TD groups in postnatal factors included seizures disorders (20% vs. 0%; $p < 0.0001$), malaria before the age of 3 years (31% vs. 4%; $p < 0.0001$) and head injury with loss of consciousness before the age of 3 years (8% vs. 0%; $p = 0.001$).

Risk factors for ASD, compared to the TD group

Univariable analysis of ASD vs. TD groups

The factors listed in Table 6.3 were evaluated as possible risk factors for ASD. Of all the factors investigated for univariable analysis, 34 factors reached the significant cut-off of 0.05. Of these

significant factors, 23 showed increased risk for ASD, with OR ranging from 1.07 - 29.42, and the remainder showed reduced risk for ASD, with OR ranging from 0.05 - 0.37. The univariable risk factors with the largest OR, among those showing increased risk for ASD, were seizures disorders (OR 29.42 [95%CI: 3.89 – 222.5], $p < 0.0001$), adverse perinatal events (OR 27.33 [95%CI: 6.38 – 117.08], $p < 0.0001$), labour complications (OR 11.40 [95%CI: 2.56 – 50.42], $p = 0.001$) and birth complications (OR 11.40 [95%CI: 2.56 – 50.42], $p = 0.001$). The univariable risk factors with the smallest OR among those showing decreased risk for ASD were mother's being unemployed (OR 0.05 [95%CI: 0.02 – 0.12], $p <0.0001$)), mother's being in informal employment (OR 0.08 [95%CI: 0.03 – 0.16], $p < 0.0001$), and fathers being in informal employment (OR 0.11[95%CI:0.06 – 0.22], $p < 0.0001$). However, when considering the conventional cut-off of $p \leq 0.25$, 44 risk factors qualified for the multivariable analysis reported in the next section. Univariable association according to categories of risk factors are described below.

Table 6.3 - Univariable analysis of relevant parental, perinatal and neonatal factors associated with ASD compared to TD children.

Risk factor variables	**ASD (n = 108)**	**TD (n = 116)**	**Odds ratio (95% CI)**	***p*-value**
Child's age in years: Median (IQR)	7.1 (5.9 – 9.1)	2.8 2.6 – 3.1	NA	NA
Child's male sex	85 (79%)	66 (57%)	2.79 (1.55 – 5.05)	0.0006*
Parental factors				
Mother's age in years	36.5 (SD: 4.8)	31.5 (SD: 7.2)	1.14 (1.09 – 1.20)	< 0.0001*
Mother's age at delivery in years	28.9 (SD: 4.53)	28.6 (SD: 7.17)	1.01(0.96 – 1.05)	0.695
Ordinal categories for Mother's age at delivery[a]	-	-	0.80 (0.56 – 1.15)	0.246
Mother's age at first birth in years	26.0 (23.0 – 28.0)	22.0 (19.0 – 25.0)	1.16 (1.08 – 1.23)	< 0.0001*
Mother's marital status[b]				
Single	3 (3%)	10 (9%)	Ref	Ref
Married	98 (90%)	92 (79%)	3.55 (0.95 – 13.31)	0.060
Separated/ Divorced	5 (5%)	10 (9%)	1.67 (0.31 – 8.92)	0.551
Widowed	2 (2%)	4 (3%)	1.67 (0.20 – 14.05)	0.639
Mother's religion[b]				
Catholic	42 (39%)	15 (13%)	Ref	Ref
Protestant	30 (28%)	13 (11%)	0.82 (0.34 – 1.98)	0.666
Islam	36 (33%)	88 (76%)	0.15 (0.07 – 0.30)	< 0.0001*
Mother's ethnicity[b]				

Northern	57 (53%)	27 (23%)	Ref	Ref
Southern	23 (21%)	42 (36%)	0.26 (0.13 – 0.51)	< 0.0001*
Eastern	14 (13%)	41 (35%)	0.16 (0.08 – 0.35)	< 0.0001*
Central	6 (6%)	5 (4%)	0.57 (0.16 – 2.03)	0.384
Other	8 (7%)	1 (1%)	3.79 (0.45 – 31.85)	0.220
Mother's education level[a]				
Ordinal categories	4 (IQR: 3-4)	2 (IQR: 2-3)	4.46 (3.01 – 6.58)	< 0.0001*
Mother's occupation[b]				
Formal employment	80 (74%)	19 (16%)	Ref	Ref
Informal employment	19 (18%)	57 (49%)	0.08 (0.03- 0.16)	< 0.0001*
None	9 (8%)	40 (35%)	0.05 (0.02 – 0.12)	< 0.0001*
Father's age in years	40.8 (SD: 5.82)	33.8(SD: 6.41)	1.21 (1.41 – 1.27)	< 0.0001*
Father's age at delivery in years	33.2 (SD: 5.39)	31.0 (SD: 6.41)	1.07 (1.02 – 1.12)	0.006*
Categories for Father's age at delivery (years)[b]				
< 30	31 (29%)	64 (55%)	Ref	0.005*
30 – 35	41 (38%)	23 (20%)	3.68 (1.88 – 7.16)	0.001*
35 – 40	23 (21%)	19 (16%)	2.49 (1.18 – 5.25)	0.016*
≥ 40	13 (12%)	10 (9%)	2.68 (1.05 – 6.79)	0.037*
Father's marital status[b]				
Single	3 (3%)	8 (7%)	Ref	Ref
Married	100 (93%)	93 (80%)	2.86(0.73 – 11.13)	0.128
Separated / Divorced	4 (4%)	14 (12%)	0.76 (0.13 – 4.30)	0.758
Widowed	1 (1%)	1 (1%)	2.67 (0.12 – 57.62)	0.532
Father's religion[a]				
Ordinal categories	-	-	0.37 (0.26 – 0.53)	< 0.0001*
Father's ethnicity[b]				
Northern	55 (51%)	26 (22%)	Ref	Ref
Southern	19 (18%)	44 (38%)	0.20 (0.10 – 0.42)	< 0.0001*
Eastern	19 (18%)	36 (31%)	0.25 (0.12 – 0.52)	< 0.0001*
Central	6 (6%)	9 (8%)	0.32 (0.10 (0.97)	0.046*
Other	9 (8%)	1 (1%)	0.43 (0.51 – 35.37)	0.180
Father's education level[a]				
Ordinal categories	-	-	4.63 (3.10 – 6.92)	< 0.0001*
Father's occupation[b]				
Formal employment	86 (80%)	37(32%)	Ref	Ref
Informal employment	19 (18%)	70 (60%)	0.11 (0.06 – 0.22)	< 0.0001*
None	3 (3%)	9 (8%)	0.14 (0.03 – 0.56)	0.005*

Parental age gap in years[c]	3.55 (IQR: 0.10 - 9.26)	1.85 (IQR: -1.69 – 9.82)	1.08 (1.02 – 1.15)	0.006*
Mother is older than father	10 (9%)	16 (14%)	0.64 (0.28 – 1.47)	0.293
Father is older than mother	97(90%)	90 (78%)	2.55 (1.19 – 5.45)	0.016*
Birth order	1 (IQR: 1-2)	2 (IQR: 1-2)	0.87 (0.68 – 1.11)	0.281
Birth weight (kg)	3.2 (IQR: 3.0 – 3.6)	3.0 (IQR: 2.8 – 3.5)	1.48 (0.97 – 2.27)	0.070
No. of children ever born	2 (IQR: 2 – 3)	2.0 (IQR: 1- 2)	1.40 (1.11 – 1.78)	0.005*
Prenatal factors				
Pregnancy medical complications	10 (9%)	4 (4%)	2.86 (0.87 – 9.40)	0.084
Pregnancy infections	21 (19%)	4 (4%)	6.76 (2.24 – 20.41)	< 0.0001*
Medication use during pregnancy	30 (28%)	20 (17%)	1.85 (0.97 – 3.50)	0.060
Gestational term ≤ 37 weeks[d]	8 (7%)	0 (0%)	9.28 (1.20 – 415.177)	0.012*
Perinatal factors				
Assisted delivery	5 (5%)	2 (2%)	2.78 (0.53 – 14.57)	0.2299
Labour complications	18 (17%)	2 (2%)	11.40(2.56 – 50.42)	0.001*
Birth complications	18 (17%)	2 (2%)	11.40(2.56 – 50.42)	0.001*
Adverse perinatal events	35 (32%)	2 (2%)	27.33 (6.38 – 117.08)	< 0.0001*
Neonatal factors				
Low birth weight (≤ 2.5 kg)	12 (11%)	17 (15%)	0.73 (0.33- 1.60)	0.4311
Neonatal jaundice[d]	9 (8%)	0 (0%)	10.54 (1.40 – 466.03)	0.006*
Neonatal seizures immediately after birth[d]	6 (6%)	0 (0%)	6.82 (0.80 – 316.46)	0.042*
Postnatal factors				
Family history of seizures	11 (10%)	9 (8%)	1.35 (0.56 – 3.39)	0.526
Seizures disorders[d]	22 (20%)	0 (0%)	29.42 (3.89 – 222.5)	< 0.0001*
Malaria (before age 3)	33 (31%)	5 (4%)	9.77 (3.65 – 26.16)	< 0.0001*
Head injury with loss of consciousness (before age 3)[d]	9 (8%)	0 (0%)	10.50 (1.41 – 466.03)	0.006*

Note. ASD = Autism Spectrum Disorder; TD = Typically Developing; CI = Confidence Interval; IQR = Interquartile Range; SD = Standard Deviation. Means and standard deviations (SD) are provided for continuous variables with a normal or near normal distribution, while medians and interquartile ranges (IQR) are provided for continuous or count variables without a normal distribution. Age >3.4 predicts ASD data perfectly so cannot run a logistic regression.

[a]There is no departure from trend (likelihood ratio test LRT $p > 0.05$) so the ordered levels rather than the individual categories are reported; [b]There is departure from trend (LRT p value < 0.05) so the individual categories are reported; [c]Generated by subtracting mother's age from the father's age; [d]The zero count is assumed as 1 to allow computation of odds ratios with exact confidence intervals. All other odds ratios were computed with logistic regression.

*$p < 0.05$

According to the statistical analysis there was a significant association between ASD and the child's male sex (OR: 2.79 [95% CI: 1.55, 5.05], $p = 0.0006$). Among the parental variables, the most striking or important risk factors that appeared to increase risk for ASD were mother's education level (OR: 4.46 [95% CI: 3.01, 6.58], $p < 0.0001$), father's education level (OR: 4.63 [95% CI: 3.10, 6.92], $p < 0.0001$) and father's age at delivery as individual age categories (age 30-35: OR: 3.68 [95% CI: 1.88, 7.16], $p = 0.001$; age 35-40: OR: 2.49 [95% CI: 1.18, 5.25], $p = 0.016$; age ≥ 40: OR: 2.68 [95% CI: 1.05, 6.79], $p = 0.037$). Among the parental variables, the most striking or important risk factors that appeared to decrease risk for ASD were mother's being unemployed (OR: 0.05 [95% CI: 0.02, 0.12], $p < 0.0001$), mother's working in informal employment (OR: 0.08 [95% CI: 0.03, 0.16], $p < 0.0001$) and fathers working in informal employment (OR: 0.11 [95% CI: 0.06, 0.22], $p < 0.0001$) . Other parental univariable risk factors are shown in Table 6.1.

When assessing prenatal factors, a univariable association was found between ASD and pregnancy infections (OR: 6.76 [95% CI: 2.24, 20.41], $p < 0.0001$) and gestational term ≤ 37 weeks (OR: 9.28 [95% CI: 1.20, 415.177], $p = 0.012$), but not pregnancy medical complications (OR: 2.86 [95% CI: 0.87, 9.40], $p = 0.084$) and medication use during pregnancy (OR: 1.85 [95% CI: 0.97, 3.50], $p = 0.060$).

From the 4 perinatal factors analysed, a univariable significant association was found between ASD and labour complications (OR: 11.40 [95% CI: 2.56, 50.42], $p = 0.001$), birth complications (OR: 11.40 [95% CI: 2.56, 50.42], $p = 0.001$), and adverse perinatal events (OR: 27.33 [95% CI: 6.38, 117.08], $p < 0.0001$), but not assisted delivery (OR: 2.78 [95% CI: 0.53, 14.57], $p = 0.2299$).

Three neonatal factors were analysed and an univariable association was found between ASD and neonatal jaundice (OR: 10.54 [95% CI: 1.40, 466.03], $p = 0.006$) and neonatal seizures immediately after birth (OR: 6.82 [95% CI: 0.80, 316.46], $p = 0.042$) but not with low birth weight (OR: 0.73 [95% CI: 0.33, 1.60], $p = 0.4311$).

Among postnatal factors, seizures disorders (OR: 29.42 [95% CI: 3.89, 222.5], $p < 0.0001$) malaria before the age of 3 years (OR: 9.77 [95% CI: 3.65, 26.16], $p < 0.0001$) and head injury with loss of consciousness before the age of 3 years (OR: 10.50 [95% CI: 1.41, 466.03], $p = 0.006$) were all found to have strong significant univariable association with ASD.

Multivariable analysis of ASD vs. TD groups

The most significant risk factors reaching a p-value of ≤ 0.25 in the univariable analysis were selected for the multivariable model as specified in table 6.4. After adjusting for parental and socio-demographic data, 20 variables were included in the multivariable model.

A strong significant association with ASD was found for the parental factors of mother's age at first birth (OR: 1.38 [95% CI: 1.12, 1.70], $p = 0.002$) and the number of children ever born (OR: 3.69 [95% CI: 1.68, 8.07], $p = 0.001$). The birth weight variable showed a trend towards significance (OR: 4.30 [95% CI: 0.96, 19.24], $p = 0.056$). None of the prenatal and neonatal factors were significantly associated with ASD. Adverse perinatal events (OR: $7.3x10^2$ [95% CI: 35.52, $1.6x10^4$], $p < 0.0001$) was the only perinatal factor reaching significance and malaria before the age 3 years (OR: 42.31 [95% CI: 3.46, $5.2x10^2$], $p = 0.003$) was the only postnatal factor reaching significance.

Table 6.4 - Multivariable analysis of relevant parental, perinatal and neonatal factors associated with ASD compared to typically developing children adjusted for parental socio-demographic and economic status.

Risk factor variables	ASD (n = 108)	TD (n = 116)	Odds ratio (95% CI)	*p*-value
Child's male sex	85 (79%)	66 (57%)	1.98 (0.37 – 10.70)	0.427
Parental factors				
Mother's age at first birth in years	26.0 (IQR: 23.0 – 28.0)	22.0 (IQR: 19.0 – 25.0)	1.38 (1.12 – 1.70)	0.002*
Father's age at delivery in years[a]	33.2 (SD: 5.4)	31.0 (SD: 6.4)	0.88 (0.74 – 1.04)	0.121
Parental age gap in years	3.55 (IQR: 0.10 - 9.26)	1.85 (IQR: -1.69 – 9.82)	1.16 (0.94 – 1.44)	0.159
Father is older than mother	97(90%)	90 (78%)	7.91 (0.56 – 111.82)	0.126
Birth weight (kg)	3.2 (IQR: 3.0 – 3.6)	3.0 (IQR: 2.8 – 3.5)	4.30 (0.96 - 19.24)	0.056
No. of children	2 (IQR: 2 – 3)	2.0 (IQR: 1- 2)	3.69 (1.68 – 8.07)	0.001*
Prenatal factors				
Pregnancy medical complications	10 (9%)	4 (4%)	0.24 (0.01 – 3.88)	0.312
Pregnancy infections	21 (19%)	4 (4%)	3.05 (0.11 – 81.04)	0.505
Medication use during pregnancy	30 (28%)	20 (17%)	0.64 (0.93 – 4.38)	0.646
Gestational term ≤ 37 weeks	8 (7%)	0 (0%)	0.56 (0.02 – 15.76)	0.734
Perinatal factors				
Assisted delivery	5 (5%)	2 (2%)	7.31 (0.62 – 863.10)	0.414
Labour complications	18 (17%)	2 (2%)	3.43 (0.94 – 24.65)	0.501
Birth complications	18 (17%)	2 (2%)	6.43 (0.51 – 81.59)	0.151

Adverse perinatal events	35 (32%)	2 (2%)	$7.3x10^{2}$ (35.52 - $1.6x10^{4}$)	< 0.0001*
Neonatal factors				
Neonatal jaundice	9 (8%)	0 (0%)	28.08 (0.48 – $1.6x10^{3}$)	0.109
Neonatal seizures immediately after birth	6 (6%)	0 (0%)	$4.4x10^{-3}$ ($0.05x10^{-8}$ – $6.5x10^{2}$)	0.960
Postnatal factors				
Seizures disorders	22 (20%)	0 (0%)	$4.3x10^{3}$ (0.02 – $7.49x10^{8}$)	0.174
Malaria (before age 3)	33 (31%)	5 (4%)	42.31 (3.46 – $5.2x10^{2}$)	0.003*
Head injury with loss of consciousness (before age 3)	9 (8%)	0 (0%)	0.11 ($3.3x10^{-3}$ – 35.80)	0.222

Note. ASD = Autism Spectrum Disorder; TD = Typically Developing; CI = Confidence Interval; SD = Standard Deviation; IQR = Interquartile Range. In the multivariable analysis only variables that reached a p value cut-off of ≤ 0.25in the Univariable analysis and were not in multicollineality with each other were included.

[a]Follows the linear trend assumptions explained in the Univariable analysis table.

*$p < 0.05$

6.3.2. ASD vs. NDD groups

General description

The median age was different between ASD and NDD groups (7.1 vs. 9.95; $p < 0.0001$). Frequency of males was higher in the ASD group than in the NDD group (79% vs. 65%) but did not reach significance (Table 6.2).

Mother's age at assessment ($p = 0.005$) and mother's age at delivery as a categorical variable ($p = 0.035$) were significantly higher for mothers of children with ASD compared to mothers of the NDD group, however, mothers of children with ASD were similar to the NDD group mothers in terms of age at first birth. Mothers of children with ASD were also more likely to be married (90% vs.67%; $p = 0.001$), have higher education levels (58% vs. 22%; $p < 0.0001$) and working in formal employment (74% vs. 32%; $p < 0001$) compared to mothers of the NDD group.

When comparing ASD and NDD groups' father's age at assessment and delivery, no significant differences were noted. However, fathers of children with ASD were more likely to be married (93% vs. 67%; $p = 0.008$), have higher levels of education (70% vs. 22%; $p = 0.001$) and working in formal employment (80% vs. 55%; $p < 0.0001$) than fathers of the NDD group. There was no significant difference between the parental age gap of the two groups, however, with the variable father older than mother, significant difference was found (90% vs. 82%; $p = 0.014$). Parents of children with

NDD were also more likely to have a higher number of children than parents of children with ASD ($p = 0.027$).

Within the prenatal factors, mothers of children with ASD were more likely to have pregnancy infections (19% vs. 3%; $p < 0.004$) compared to mothers of the NDD group. Labour complications (17% vs. 3%; $p < 0.012$) were the only perinatal factor associated with the risk of ASD, and no neonatal factors reached significance. Malaria before the age of 3 years (31% vs. 5%; $p < 0.0001$) was the only postnatal factor associated with increased risk of ASD.

Factors that are specific to ASD compared to NDD group

Univariable analysis of ASD vs. NDD groups

The factors listed in Table 6.5 were evaluated to identify those that are unique to ASD. Of all the factors investigated for univariable analysis, 18 factors reached the significant cut-off of 0.05. Of these significant factors, 6 were unique for ASD with OR ranging from 2.83 – 8.36, and the remainder were not unique to ASD, with OR ranging from 0.29 – 0.92. The unique factors with the largest OR, among those showing strongest association with ASD, were malaria before the age of 3 years (OR 8.36 [95% CI: 2.44 – 28.63], $p = 0.001$), pregnancy infections (OR 7.00 [95% CI: 1.58 – 31.00], $p = 0.010$) and labour complications (OR 5.80 [95% CI: 1.30 – 25.93], $p = 0.021$). The factors with the smallest OR among those not unique to ASD were father's being of Southern ethnicity (OR 0.29 [95% CI: 0.13 – 0.67], $p = 0.004$), mother's occupation (OR 0.31 [95% CI: 0.20 – 0.50], $p < 0.0001$), and fathers being of Eastern ethnicity (OR 0.35 [95% CI: 0.15 – 0.81], $p = 0.014$). However, when considering the conventional cut-off of $p \leq 0.25$, 27 factors to be examined in the multivariable analysis reported in the next section. Univariable association according to categories of risk factors are described below.

Table 6.5 - Univariable analysis of relevant parental, perinatal and neonatal factors associated with ASD compared to children with NDD.

Risk factor variables	ASD (n = 108)	NDD (n = 60)	Odds ratio (95% CI)	*p*-value
Child's age in years: Median (IQR)	7.1 (5.9 – 9.1)	9.95 (8.2 – 11.0)	0.64 (0.54 – 0.76)	< 0.0001*
Child's male sex	85 (79%)	39 (65%)	1.98 (0.99 – 4.01)	0.055
Parental factors				
Mother's age in years	36.5 (SD:4.86)	39.1 (SD:6.74)	0.92 (0.87 – 0.98)	0.006*
Mother's age at delivery in years	28.7 (IQR: 26.1 –	30.5 (IQR: 25.2 –	0.97 (0.92 – 1.03)	0.366

	32.2)	34.0)		
Ordinal categories for Mother's age at delivery[a]	-	-	0.58 (0.38 – 0.88)	0.312
Mother's age at first birth in years	26.0 (IQR:23.0 – 28.0)	23.0 (IQR:19.0 – 27.75)	1.05 (0.98 – 1.12)	0.177
Mother's marital status[b]				
Single	3 (3%)	6 (10%)	Ref	Ref
Married	98 (90%)	40 (67%)	4.90 (1.17 – 20.55)	0.030*
Separated / Divorced	5 (5%)	12 (20%)	0.83 (0.15 – 4.70)	0.837
Widowed	2 (2%)	2 (3%)	2.00 (0.18 – 22.06)	0.571
Mother's religion[b]				
Ordinal categories	-	-	0.56 (0.37 – 0.82)	0.003*
Mother's ethnicity				
Ordinal categories	-	-	0.81 (0.67 – 0.99)	0.038*
Mother's education level[a]				
Ordinal categories	-	-	2.83 (1.90 – 4.20)	< 0.0001*
Mother's occupation[a]				
Ordinal categories	-	-	0.31 (0.20 – 0.50)	< 0.0001*
Father's age in years	40.8 (SD:5.82)	42.8 (SD:7.50)	0.95 (0.91 – 1.00)	0.063
Father's age at delivery in years	33.2 (SD:5.39)	33.4 (SD:7.48)	0.99 (0.95 – 1.05)	0.837
Ordinal categories for Father's age at delivery[a]	-	-	0.85 (0.62 – 1.16)	0.309
Father's marital status[a]				
Ordinal categories	-	-	0.42 (0.20 – 0.89)	0.024*
Father's religion[a]				
Ordinal categories	-	-	0.55 (0.37 – 0.82)	0.003*
Father's ethnicity[b]				
Northern	55 (51%)	17 (28%)	Ref	Ref
Southern	19 (18%)	20 (33%)	0.29 (0.13 – 0.67)	0.004*
Eastern	19 (18%)	17 (28%)	0.35 (0.15 – 0.81)	0.014*
Central	6 (6%)	4 (7%)	0.46 (0.12 – 1.84)	0.274
Other	9 (8%)	2 (3%)	1.39 (0.27 – 7.07)	0.691
Father's education level[a]				
Ordinal categories	-	-	3.36 (2.19 – 5.16)	< 0.0001*
Father's Occupation[a]				
Ordinal categories	-	-	0.38 (0.22 – 0.65)	< 0.0001*

Parental age gap in years[c]	3.55 (IQR: - 0.10 – 9.26)	2.95 (IQR: -0.45 – 10.4)	1.03 (0.96 – 1.11)	0.410
Mother is older than Father	10 (9%)	6 (10%)	0.92 (0.32 – 2.66)	0.875
Father is older than Mother	97(90%)	49 (82%)	1.98 (0.80 – 4.89)	0.139
Birth order	1 (IQR:1-2)	2 (IQR:1-3)	0.71 (0.53 – 0.94)	0.016*
Birth weight (kg)	3.2 (IQR: 3 – 3.6)	3.0 (IQR: 2.9 – 3.5)	1.45 (0.89 – 2.37)	0.1344
No. of children	2 (2 – 3)	3.0 (2- 4)	0.75 (0.59 – 0.96)	0.020*
Prenatal factors				
Pregnancy medical complications	10 (9.3%)	3 (5%)	1.94 (0.51 – 7.34)	0.330
Pregnancy infections	21 (19%)	2 (3%)	7.00 (1.58 – 31.00)	0.010*
Medication use during pregnancy	30 (28%)	18 (30%)	0.90 (0.45 – 1.80)	0.760
Gestational term ≤ 37 weeks	8 (7%)	2 (3%)	2.32 (0.48 – 11.30)	0.297
Perinatal factors				
Assisted delivery	5 (5%)	1 (2%)	2.86 (0.33 – 25.10)	0.342
Labour complications	18 (17%)	2 (3%)	5.80 (1.30 – 25.93)	0.021*
Birth complications	18 (17%)	5 (8%)	2.20 (0.77 – 6.26)	0.140
Adverse perinatal events	35 (32%)	24 (40%)	0.72 (037 – 1.38)	0.324
Neonatal factors				
Low birth weight (≤ 2.5 kg)	12 (11%)	11 (18%)	0.56 (0.23 – 1.35)	0.196
Neonatal jaundice	9 (8%)	6 (10%)	0.82 (0.28 – 2.42)	0.717
Neonatal seizures immediately after birth	6 (6%)	7 (12%)	0.45 (0.14 – 1.39)	0.164
Postnatal factors				
Family history of seizures	11 (10%)	7 (12%)	0.86 (0.31 – 2.35)	0.766
Seizures disorders	22 (20%)	8 (13%)	1.66 (0.69 – 4.01)	0.257
Malaria (before age 3)	33 (31%)	3 (5%)	8.36 (2.44 – 28.63)	0.001*
Head injury with loss of consciousness (before age 3)	9 (8%)	11 (18%)	0.41 (0.16 – 1.04)	0.061

Note. ASD = Autism Spectrum Disorder; NDD = Neurodevelopmental Disorders; CI = confidence interval; IQR = Interquartile Range; SD = Standard Deviation. Means and standard deviations (SD) are provided for continuous variables with a normal or near normal distribution, while medians and interquartile ranges (IQR) are provided for continuous or count variables without a normal distribution.

[a]There is no departure from trend (likelihood ratio test LRT $p > 0.05$) so the ordered levels rather than the individual categories are reported; [b]There is departure from trend (LRT p value < 0.05) so the individual categories are reported; [c]Generated by subtracting mother's age from the father's age.

*$p < 0.05$

According to the statistical analysis, the child's age (OR: 0.64 [95% CI: 0.54, 0.76], $p < 0.0001$) was a factor unique to ASD compared to NDD. Mother's marital status of 'married' (OR: 4.90 [95% CI: 1.17, 20.55], $p = 0.030$), mother's education level as an ordinal category (OR: 2.83 [95% CI: 1.90,

4.20], $p < 0.0001$) and father's education level as an ordinal category (OR: 3.36 [95% I: 2.19, 5.16], $p < 0.0001$) were significant factors unique to ASD when compared to the NDD group. Among the parental variables, the most striking or important factors unique to ASD were father's being of Southern ethnicity (OR 0.29 [95%CI: 0.13 – 0.67], $p = 0.004$), mother's occupation (OR 0.31 [95%CI: 0.20 – 0.50], $p < 0.0001$), and fathers being of Eastern ethnicity (OR 0.35 [95% CI: 0.15 – 0.81], $p = 0.014$). Other parental associations are shown in Table 6.2.

Infections during pregnancy (OR: 7.00 [95% CI: 1.58, 31.00], $p = 0.010$) and labour complications (OR: 5.80 [95% CI: 1.30, 25.93], $p = 0.021$) were unique to ASD, when compared to the NDD group. The strongest univariable association, however, was found between ASD and malaria before the age of 3 (OR: 8.36[95% CI: 2.44, 28.63], $p = 0.001$), when compared to the NDD group.

Multivariable analysis of ASD vs. NDD groups

The most significant factors unique to ASD reaching a p-value of ≤0.25 in the univariable analysis were selected for the multivariable model as specified in table 6.6. After adjusting for parental and socio-demographic data, 14 were included in the multivariable model.

One parental factor 'father older than mother' (OR: 3.68 [95% CI: 1.04, 13.00], $p = 0.043$) was found to show unique significant association with ASD. None of the prenatal, perinatal and neonatal factors included in this multivariable model reached significance. Malaria before the age of 3 years (OR: 8.91 [95% CI: 1.90, 41.73], $p = 0.005$) was the only postnatal factor unique to ASD, compared to NDD.

Table 6.6 - Multivariable analysis of relevant parental, perinatal and neonatal factors associated with ASD compared to children with NDD adjusted for parental socio-demographic and economic status.

Risk factor variables	ASD (n = 108)	NDD (n = 60)	Odds ratio (95% CI)	*p*-value
Child's male sex	85 (79%)	39 (65%)	1.26 (0.49 – 3.24)	0.635
Parental factors				
Mother's age at first birth in years	26.0 (IQR: 23.0 – 28.0)	23.0 (IQR: 19.0 – 27.75)	1.02 (0.92 – 1.12)	0.758
Father's age in years	40.8 (SD:5.82)	42.8 (SD:7.50)	0.95 (0.88 – 1.04)	0.278
Father is older than mother	97(90%)	49 (82%)	3.68 (1.04 – 13.00)	0.043*
Birth order	1 (IQR:1-2)	2 (IQR:1-3)	1.10 (0.66 – 1.84)	0.709
Birth weight (kg)	3.2 (IQR: 3	3.0 (IQR:	0.74 (0.29 – 1.91)	0.546

	– 3.6)	2.9 – 3.5)		
No. of children	2 (2 – 3)	3.0 (2- 4)	0.93 (0.61 – 1.44)	0.756
Prenatal factors				
Pregnancy infections	21 (19%)	2 (3%)	4.41 (0.78 – 24.97)	0.093
Perinatal factors				
Labour complications	18 (17%)	2 (3%)	2.79 (0.47 – 16.49)	0.258
Birth complications	18 (17%)	5 (8%)	1.72 (0.44 – 6.67)	0.434
Neonatal factors				
Low birth weight (≤ 2.5 kg)	12 (11%)	11 (18%)	0.26 (0.05 – 1.49)	0.132
Neonatal seizures immediately after birth	6 (6%)	7 (12%)	0.55 (0.13 – 2.37)	0.423
Postnatal factors				
Malaria (before age 3)	33 (31%)	3 (5%)	8.91 (1.90 – 41.73)	0.005*
Head injury with loss of consciousness (before age 3)	9 (8%)	11 (18%)	0.48 (0.13 – 1.72)	0.258

Note. ASD = Autism Spectrum Disorder; NDD = Neurodevelopmental Disorders; CI = confidence interval; IQR = Interquartile Range; SD = Standard Deviation. In the multivariable analysis only variables that reached a *p* value cut-off of ≤ 0.25in the Univariable analysis and were not in multicollineality with each other were included.

*$p < 0.05$

6.3.3. NDD vs. TD groups

General description

The median age was significantly different between NDD and TD groups (9.95 vs. 2.8; $p < 0.0001$), as mentioned earlier because the TD was matched on expressive language level. There was no significant difference in the frequency of male participants in both the NDD group and in the TD group (65% vs. 57%; $p = 0.299$) (Table 6.2).

Mother's age at assessment ($p < 0.0001$), mother's age at delivery ($p = 0.050$) and mother's age at first birth ($p = 0.019$) were significantly higher for mothers of children with NDD compared to mothers of TD children. There were no significant differences in other maternal socio-demographic factors except for a statistically significant difference in mother's ethnicity between the NDD and TD groups ($p = 0.005$).

Father's age at assessment ($p < 0.0001$) and delivery ($p = 0.002$) were significantly higher for fathers of children with NDD compared to fathers of the TD group. Fathers of children with NDD were more likely to be working in formal employment (55% vs. 32%; $p = 0.001$), however no other significant differences were noted for other paternal socio-demographic factors.

Mothers of children with NDD were significantly more likely to have taken medication during pregnancy (30% vs. 17%; $p = 0.051$) compared to mothers of the TD group. Birth complications (8% vs. 2%; $p = 0.046$) and adverse perinatal events (40% vs. 2%; $p < 0.0001$) were significantly more common in the NDD group compared to the TD group. The NDD group were also more likely to have neonatal jaundice (10% vs. 0%; $p = 0.007$) and neonatal seizures immediately after birth (12% vs. 0%; $p = 0.002$) compared to the TD group. Significant differences between the NDD and TD groups in postnatal factors included seizures disorders (13% vs. 0%; $p = 0.001$) and head injury with loss of consciousness before the age of 3 years (18% vs. 0%; $p < 0.0001$).

Risk factors for NDD, compared to the TD group

Univariable analysis of NDD vs. TD groups

The factors listed in Table 6.7 were evaluated as possible risk factors for other NDD but not ASD. Of all the factors investigated for univariable analysis, 18 factors reached the significant cut-off of 0.05. Of these significant factors, 12 showed increased risk for other NDD, with OR ranging from 1.05 – 38.00, and the remainder showed reduced risk for other NDD, with OR ranging from 0.28 - 0.78. The univariable risk factors with the largest OR, among those showing increased risk for other NDD, were adverse perinatal events (OR 38.00 [95% CI: 8.56 – 168.67], $p < 0.0001$), head injury with loss of consciousness before the age of 3 (OR 25.81 [95% CI: 3.24 – 205.45], $p = 0.002$) and seizures disorders (OR 17.69 [95% CI: 2.15 – 145.13], $p = 0.007$). The univariable risk factors with the smallest OR among those showing decreased risk for other NDD were fathers working in informal employment (OR 0.28 [95% CI: 0.14 – 0.57], $p <0.0001$) and mother's being of Southern ethnicity (OR 0.41 [95% CI: 0.17 – 0.97], $p = 0.044$). However, when considering the conventional cut-off of $p \leq 0.25$, 27 risk factors qualified for the multivariable analysis reported in the next section. Univariable association according to categories of risk factors are described below.

Among the parental variables, the risk factors that appeared to increase risk for other NDD were mother's age at assessment (OR: 1.15 [95% CI: 1.09, 1.21], $p < 0.0001$), mother's age at first birth (OR: 1.07 [95% CI: 1.01, 1.14], $p < 0.0001$), father's age at assessment (OR: 1.29 [95% CI: 1.13, 1.26], $p < 0.0001$), father's age at delivery (OR: 1.05 [95% CI: 1.00, 1.10], $p = 0.027$) and the number of children ever born (OR: 1.59 [95% CI: 1.25, 2.02], $p < 0.0001$). Among the parental variables, the risk factors that appeared to decrease risk for other NDD were mothers being of Islamic religion (OR: 0.43 [95% CI: 0.19, 1.00], $p = 0.050$), mothers being of Southern ethnicity (OR: 0.41 [95% CI: 0.17, 0.97], $p = 0.044$), mothers achieving tertiary level education (OR: 0.78 [95% CI: 0.11, 5.59], $p = 0.012$), mother's being unemployed (OR: 0.42 [95% CI: 0.18, 0.99], $p = 0.049$), mother's working in informal employment (OR: 0.42 [95% CI: 0.19, 0.93, $p = 0.033$) and fathers working in informal employment (OR: 0.28 [95% CI: 0.14, 0.57], $p < 0.0001$) .

When assessing prenatal factors, only one univariable association was found between other NDD and mother's medication use during pregnancy (OR: 2.05 [95% CI: 0.98, 4.28], $p = 0.054$).

From the 4 perinatal factors analysed, a univariable significant association was found between other NDD and birth complications (OR: 5.10 [95% CI: 0.97, 27.55], $p = 0.054$), and adverse perinatal events (OR: 38.00 [95% CI: 8.56, 168.67], $p < 0.0001$).

Three neonatal factors were analysed and an univariable association was found between other NDD and neonatal jaundice (OR: 12.77 [95% CI: 1.50, 108.77], $p = 0.020$) and neonatal seizures immediately after birth (OR: 15.18 [95% CI: 1.82, 126.59], $p = 0.012$) but not with low birth weight (OR: 1.30 [95% CI: 0.56, 3.00], $p = 0.528$).

Among postnatal factors, seizures disorders (OR: 17.69 [95% CI: 2.15, 145.13], $p = 0.007$) and head injury with loss of consciousness before the age of 3 years (OR: 25.81 [95% CI: 3.24, 205.45], $p = 0.002$) were found to have strong significant univariable association with other NDD, but not family history of seizures (OR: 1.57 [95% CI: 0.55, 4.44], $p = 0.396$) and malaria before the age of 3 years (OR: 1.16 [95% CI: 0.26, 5.06], $p = 0.835$).

Table 6.7 - Univariable analysis of relevant parental, perinatal and neonatal factors associated with NDD compared to typically developing children.

Risk factor variables	**NDD (n = 60)**	**TD (n = 116)**	**Odds ratio (95% CI)**	***p*-value**
Child's age in years: Median (IQR)	10.0 (8.2 – 11.0)	2.8 (2.6 – 3.1)	N/A	N/A
Child's male sex	39 (65%)	66 (57%)	1.40 (0.73-2.68)	0.308
Parental factors				
Mother's age in years	39.1 (SD:6.74)	31.5 (SD: 7.2)	1.15 (1.09-1.21)	<0.0001*
Mother's age at delivery in years	30.5 (IQR: 25.2 – 34.0)	28.6 (SD: 7.17)	1.02 (0.97-1.06)	0.323
Ordinal categories for Mother's age at delivery[a]	-	-	-	-
Mother's age at first birth in years	23.0 (IQR: 19.0 – 27.75)	22.0 (19.0 – 25.0)	1.07 (1.01-1.14)	0.020*
Mother's marital status[a]				
Ordinal categories	-	-	-	-

Mother's marital status[b]				
Single	6 (10%)	10 (9%)	Ref	Ref
Married	40 (67%)	92 (79%)	0.72 (0.24-2.12)	0.558
Separated / Divorced	12 (20%)	10 (9%)	2.00 (0.53-7.44)	0.301
Widowed	2 (3%)	4 (3%)	0.83 (0.11-6.01)	0.857
Mother's religion[a]				
Ordinal categories	-	-	-	-
Mother's religion[b]				
Catholic	14 (23%)	15 (13%)	Ref	Ref
Protestant	10 (17%)	13 (11%)	0.82 (0.27-2.47)	0.730
Islam	36 (60%)	88 (76%)	0.43 (0.19-1.00)	0.050*
Mother's ethnicity[a]				
Ordinal categories	-	-		
Mother's ethnicity[b]				
Northern	20 (33%)	27 (23%)	Ref	Ref
Southern	13 (22%)	42 (36%)	0.41 (0.17-0.97)	0.044*
Eastern	15 (25%)	41 (35%)	0.49 (0.21-1.12)	0.095
Central	7 (12%)	5 (4%)	1.89 (0.52-6.83)	0.332
Other	5 (8%)	1 (1%)	6.74 (0.73-62.36)	0.092
Mother's education level[a]				
Ordinal categories	-	-	-	-
Mother's education level[b]				
None	3 (5%)	2 (1%)	Ref	Ref
Primary	31 (52%)	74 (64%)	0.27 (0.04-1.75)	0.174
Secondary	13 (22%)	29 (25%)	0.29 (0.04-2.00)	0.214
Tertiary	13 (22%)	11 (10%)	0.78 (0.11-5.59)	0.012*
Mother's occupation[a]				
Ordinal categories	-	-		
Mother's occupation[b]				
Formal employment	19 (32%)	19 (16%)	Ref	Ref
Informal employment	24 (40%)	57 (49%)	0.42 (0.19-0.93)	0.033*
None	17 (28%)	40 (35%)	0.42 (0.18-0.99)	0.049*
Father's age in years	42.8 (SD:7.50)	33.8 (SD:6.41)	1.29 (1.13-1.26)	<0.0001*
Father's age at delivery in years	33.4 (SD:7.48)	31.0 (SD:6.41)	1.05 (1.00-1.10)	0.027*
Ordinal categories for Father's age at delivery[a]	-	-	-	-
Father's marital status[a]				

Ordinal categories	-	-	-	-
Father's marital status[b]				
Single	6 (10%)	8 (7%)	Ref	Ref
Married	40 (67%)	93 (80%)	1.29 (0.32-5.09)	0.716
Separated / Divorced	12 (20%)	14 (12%)	1.71 (0.35-8.23)	0.501
Widowed	2 (3%)	1 (1%)	7.99 (0.58-110.26)	0.120
Father's religion[a]				
Ordinal categories	-	-	-	-
Father's religion[b]				
Catholic	14 (23%)	15 (13%)	Ref	Ref
Protestant	10 (17%)	18 (15%)	0.59 (0.20-1.72)	0.338
Islam	36 (60%)	83 (72%)	0.46 (0.20-1.06)	0.069
Father's ethnicity[a]				
Ordinal categories	-	-		
Father's ethnicity[b]				
Northern	17 (28%)	26 (22%)	Ref	Ref
Southern	20 (33%)	44 (38%)	0.69 (0.30-1.55)	0.378
Eastern	17 (28%)	36 (31%)	0.72 (0.31-1.67)	0.448
Central	4 (7%)	9 (7.8%)	0.67 (0.18-2.56)	0.569
Other	2 (3%)	1 (1%)	3.05 (0.25-36.41)	0.376
Father's education level[a]				
Ordinal categories	-	-		
Father's education level[b]				
None	3 (5%)	1 (1%)	Ref	Ref
Primary	31 (52%)	62 (53%)	0.20 (0.01-2.41)	0.210
Secondary	13 (22%)	34 (29%)	0.25 (0.02-2.95)	0.271
Tertiary	13 (22%)	19 (16%)	0.39 (0.03-4.78)	0.465
Father's Occupation[a]				
Ordinal categories	-	-	-	-
Father's Occupation[b]				
Formal employment	33 (55%)	37(32%)	Ref	Ref
Informal employment	18 (30%)	70 (60%)	0.28 (0.14-0.57)	<0.0001*
None	9 (15%)	9 (8%)	1.12 (0.39-3.16)	0.829
Parental age gap in years[c]	2.95 (IQR: -0.45 – 10.4)	1.85 (IQR: -1.69 – 9.82)	1.05 (0.98-1.12)	0.103
Mother is older than Father	6 (10%)	16 (14%)	0.69 (0.25-1.87)	0.473
Father is older than Mother	49 (82%)	90 (78%)	1.28 (0.58-2.82)	0.529
Birth order	2 (IQR:1-3)	2 (IQR: 1-2)	1.19 (0.94-1.51)	0.133

Birth weight (kg)	3.0 (IQR: 2.9 – 3.5)	3.0 (IQR: 2.8 – 3.5)	0.98 (0.58-1.67)	0.956
No. of children	3.0 (2- 4)	2.0 (IQR: 1-2)	1.59 (1.25-2.02)	<0.0001*
Prenatal factors				
Pregnancy medical complications	3 (5%)	4 (4%)	1.47 (0.31-6.80)	0.619
Pregnancy infections	2 (3%)	4 (4%)	0.96 (0.17-5.42)	0.968
Medication use during pregnancy	18 (30%)	20 (17%)	2.05 (0.98-4.28)	0.054*
Gestational term ≤ 37 weeks[d]	2 (3%)	0 (0%)	3.96 (0.35-44.64)	0.265
Perinatal factors				
Assisted delivery	1 (2%)	2 (2%)	0.96 (0.08-10.87)	0.978
Labour complications	2 (3%)	2 (2%)	1.96 (0.26-14.31)	0.505
Birth complications	5 (8%)	2 (2%)	5.10 (0.97-27.55)	0.054*
Adverse perinatal events	24 (40%)	2 (2%)	38.00 (8.56-168.67)	<0.0001*
Neonatal factors				
Low birth weight (≤ 2.5 kg)	11 (18%)	17 (15%)	1.30 (0.56-3.00)	0.528
Neonatal jaundice[d]	6 (10%)	0 (0%)	12.77 (1.50-108.77)	0.020*
Neonatal seizures immediately after birth[d]	7 (12%)	0 (0%)	15.18 (1.82-126.59)	0.012*
Postnatal factors				
Family history of seizures	7 (12%)	9 (8%)	1.57 (0.55-4.44)	0.396
Seizures disorders[d]	8 (13%)	0 (0%)	17.69 (2.15-145.13)	0.007*
Malaria (before age 3)	3 (5%)	5 (4%)	1.16 (0.26-5.06)	0.835
Head injury with loss of consciousness (before age 3)[d]	11 (18%)	0 (0%)	25.81 (3.24-205.45)	0.002*

Note. NDD = Neurodevelopmental Disorders; TD = Typically Developing; CI = Confidence Interval; IQR = Interquartile Range; SD = Standard Deviation. Means and standard deviations (SD) are provided for continuous variables with a normal or near normal distribution, while medians and interquartile ranges (IQR) are provided for continuous or count variables without a normal distribution.

[a]There is no departure from trend (likelihood ratio test LRT $p > 0.05$) so the ordered levels rather than the individual categories are reported; [b]There is departure from trend (LRT p value < 0.05) so the individual categories are reported; [c]Generated by subtracting mother's age from the father's age. [d]The zero count is assumed as 1 to allow computation of odds ratios with exact confidence intervals. All other odds ratios were computed with logistic regression.

*$p < 0.05$

Multivariable analysis of NDD vs. TD groups

The most significant risk factors reaching a p-value of ≤ 0.25 in the univariable analysis were selected for the multivariable model as specified in table 6.8. After adjusting for parental and socio-demographic data, 10 variables were included in the multivariable model.

Among the parental variables, a strong significant association with other NDD was found for the number of children ever born (OR: 5.38 [95% CI: 1.60, 18.09], $p = 0.007$). None of the prenatal and neonatal factors were significantly associated with other NDD. Birth complications (OR: 78.06 [95% CI: 1.73, $3.56x10^3$], $p = 0.025$) and adverse perinatal events (OR: 383.31[95% CI: 16.66, $8.82x10^2$], $p < 0.0001$) were the only perinatal factors reaching significance and seizures disorders (OR: 125.01 [95% CI: 1.73, $9.04x10^3$], $p = 0.027$) and head injury with loss of consciousness before the age of 3 years (OR: 925.765 [95% CI: 7.98, $1.07x10^5$], $p = 0.005$) were the only postnatal factors reaching significance.

Table 6.8 - Multivariable analysis of relevant parental, perinatal and neonatal factors associated with NDD compared to typically developing children adjusted for parental socio-demographic and economic status.

Risk factor variables	NDD (n = 60)	TD (n = 116)	Odds ratio (95% CI)	*p*-value
Parental factors				
Parental age gap in years	2.95 (IQR: -0.45 – 10.4)	1.85 (IQR: -1.69 – 9.82)	0.08 (0.00 – $1.144x10^5$)	0.793
Birth order	2.0 (IQR: 1 – 3)	2.0 (IQR: 1 – 2)	0.12 (0.03 – 0.44)	0.001*
No. of children	3.0 (IQR: 2 – 4)	2.0 (IQR: 1- 2)	5.38 (1.60 – 18.09)	0.007*
Prenatal factors				
Medication use during pregnancy	18 (30%)	20 (17%)	1.96 (0.21 – 17.98)	0.55
Perinatal factors				
Birth complications	5 (8%)	2 (2%)	78.06 (1.73 – $3.56x10^3$)	0.025*
Adverse perinatal events	24 (40%)	2 (2%)	383.31 (16.66 – 8.82 $x10^2$)	0.000*
Neonatal factors				
Neonatal jaundice	6 (10%)	0 (0%)	0.82 (0.03 – 19.53)	0.901
Neonatal seizures immediately after birth	7 (12%)	0 (0%)	4.35 (0.09 – 211.41)	0.458
Postnatal factors				
Seizures disorders	8 (13%)	0 (0%)	125.01 (1.73 – $9.04x10^3$)	0.027*
Head injury with loss of	11 (18%)	0 (0%)	925.765 (7.981 –	0.005*

consciousness (before age 3)			$1.07x10^5$)	

Note. NDD = Neurodevelopmental Disorders; TD = typically developing; CI = Confidence Interval; IQR = Interquartile Range. In the multivariable analysis only variables that reached a p value cut-off of ≤ 0.25in the Univariable analysis and were not in multicollineality with each other were included.

$^{*}p < 0.05$

6.3.4 Combined ASD+NDD vs. TD groups

General description

The median age was significantly different between the combined ASD+NDD and TD groups (8.1 vs. 2.8; $p < 0.0001$), as mentioned earlier because the TD was matched on expressive language level. Frequency of males was significantly higher in the combined ASD+NDD group than in the TD group (74% vs. 57%; $p = 0.003$) (Table 6.2).

Mother's age at assessment ($p < 0.0001$) and mother's age at first birth ($p < 0.0001$) were significantly higher for mothers in the combined ASD+NDD group compared to mothers of the TD group. There were significant differences in mother's religion ($p < 0.0001$), ethnicity ($p < 0.0001$), education ($p < 0.0001$) and occupational ($p < 0.0001$) levels between the combined ASD+NDD and TD groups.

Father's age at assessment ($p < 0.0001$) and delivery ($p < 0.0001$) were significantly higher for fathers of children in the combined ASD+NDD group compared to fathers of the TD group. There were significant differences in father's religion ($p < 0.0001$), ethnicity ($p < 0.0001$), education ($p < 0.0001$) and occupational ($p < 0.0001$) levels between the combined ASD+NDD and TD groups. The parental age gap ($p < 0.0001$) and the number of children ever born ($p < 0.0001$) were significantly higher in the combined ASD+NDD group compared to the TD group.

Mothers of children in the combined ASD+NDD group were significantly more likely to have had pregnancy infections (14% vs. 4%; ($p = 0.004$), taken medication during pregnancy (29% vs. 17%; $p = 0.028$) and have had preterm delivery (6% vs. 0%; $p = 0.025$) compared to mothers of the TD group. Labour complications (12% vs. 2%; $p = 0.001$), birth complications (14% vs. 2%; $p < 0.0001$) and adverse perinatal events (35% vs. 2%; $p < 0.0001$) were significantly more common in the combined ASD+NDD group compared to the TD group. The combined ASD+NDD group were also more likely to have neonatal jaundice (19% vs. 0%; $p = 0.003$) and neonatal seizures immediately after birth (8% vs. 0%; $p = 0.010$) compared to the TD group. Significant differences between the combined ASD+NDD and TD groups in postnatal factors included seizures disorders (18% vs. 0%; $p < 0.0001$), malaria before the age of 3 years (21% vs. 4%; $p < 0.0001$) and head injury with loss of consciousness before the age of 3 years (12% vs. 0%; $p < 0.0001$).

Risk factors for combined ASD+NDD, compared to the TD group

Univariable analysis of NDD vs. TD groups

The factors listed in Table 6.9 were evaluated as possible risk factors for NDD including ASD. Of all the factors investigated for univariable analysis, 29 factors reached the significant cut-off of 0.05. Of these significant factors, 18 showed increased risk for ASD+NDD, with OR ranging from 1.06 – 38.85, and the remainder showed reduced risk for ASD+NDD, with OR ranging from 0.12 - 0.41. The univariable risk factors with the largest OR, among those showing increased risk for ASD+NDD, were adverse perinatal events (OR 38.85 [95% CI: 7.35 – 129.37], $p < 0.0001$), head injury with loss of consciousness before the age of 3 (OR 15.54 [95% CI: 2.05 – 117.51], $p < 0.0001$) and seizures disorders (OR 25.00 [95% CI: 3.35 – 186.14], $p = 0.002$) . The univariable risk factors with the smallest OR among those showing decreased risk for ASD+NDD were mothers in unemployment (OR 0.12 [95% CI: 0.06 – 0.25], $p <0.0001$), mothers working in informal employment (OR 0.14 [95% CI: 0.07 – 0.27], $p <0.0001$) and father's working in informal employment (OR 0.16 [95% CI: 0.09 – 0.28], $p < 0.0001$). However, when considering the conventional cut-off of $p \leq 0.25$, 39 risk factors qualified for the multivariable analysis reported in the next section. Univariable association according to categories of risk factors are described below.

Child's male sex was a significant risk factor for ASD+NDD (OR 2.13 [95% CI: 1.29 – 3.53], $p = 0.003$). Among the parental variables, the risk factors that appeared to increase risk for ASD+NDD were mother's age at assessment (OR: 1.15 [95% CI: 1.10, 1.20], $p < 0.0001$), mother's age at first birth (OR: 1.12 [95% CI: 1.06, 1.18], $p < 0.0001$), father's age at assessment (OR: 1.29 [95% CI: 1.13, 1.26], $p < 0.0001$), father's age at delivery (OR: 1.06 [95% CI: 1.02, 1.10], $p = 0.003$), parental age gap (OR 1.07 [95% CI: 1.02 – 1.13], $p = 0.005$) and the number of children ever born (OR: 1.53 [95% CI: 1.23, 1.90], $p < 0.0001$). Among the parental variables, the risk factors that appeared to decrease risk for other NDD were mothers being of Islamic religion (OR: 0.21 [95% CI: 0.11, 0.41], $p < 0.0001$), mothers being of Southern ethnicity (OR: 0.30 [95% CI: 0.16, 0.56], $p < 0.0001$), mothers being of Eastern ethnicity (OR 0.24 [95% CI: 0.12 – 0.47], $p <0.0001$), mother's being unemployed (OR: 0.12 [95% CI: 0.06, 0.25], $p < 0.0001$), mother's working in informal employment (OR: 0.14 [95% CI: 0.07, 0.27, $p < 0.0001$), fathers being of Islamic religion (OR: 0.23 [95% CI: 0.12, 0.45], $p < 0.0001$), fathers being of Southern ethnicity (OR: 0.32 [95% CI: 0.17, 0.59], $p < 0.0001$), fathers being of Eastern ethnicity (OR 0.36 [95% CI: 0.18 – 0.68], $p = 0.002$), father's being unemployed (OR: 0.41 [95% CI: 0.16, 1.06], $p < 0.0001$), father's working in informal employment (OR: 0.16 [95% CI: 0.09, 0.28, $p < 0.0001$).

Among the prenatal factors, a univariable association was found between ASD+NDD and pregnancy medical complications (OR: 9.04 [95% CI: 2.08, 39.14], $p = 0.003$), pregnancy infections (OR: 4.44

[95% CI: 1.49, 13.21], $p = 0.007$) and medication use during pregnancy (OR: 1.92 [95% CI: 1.06, 3.45], $p = 0.029$).

When analysing perinatal factors, a univariable significant association was found between ASD+NDD and labour complications (OR: 7.70 [95% CI: 1.76, 33.63], $p = 0.007$), birth complications (OR: 9.04 [95% CI: 2.08, 39.14], $p = 0.003$) and adverse perinatal events (OR: 38.85 [95% CI: 7.35, 129.37], $p < 0.0001$).

A univariable association was found between ASD+NDD and neonatal jaundice (OR: 11.27 [95% CI: 1.46, 86.59], $p = 0.020$) and neonatal seizures immediately after birth (OR: 9.64 [95% CI: 1.24, 74.28], $p = 0.030$) but not with low birth weight (OR: 0.92 [95% CI: 0.46, 1.81], $p = 0.818$).

Among postnatal factors, seizures disorders (OR: 25.00 [95% CI: 3.35, 186.14], $p = 0.002$), malaria before the age of three years (OR: 6.05 [95% CI: 2.29, 15.95], $p < 0.0001$) and head injury with loss of consciousness before the age of 3 years (OR: 15.54 [95% CI: 2.05, 117.51], p 0.0001) were found to have strong significant univariable association with ASD+NDD, but not family history of seizures (OR: 1.42 [95% CI: 0.61, 3.29], $p = 0.406$).

Table 6.9 - Univariable analysis of relevant parental, perinatal and neonatal factors associated with ASD+NDD compared to typically developing children.

Risk factor variables	**ASD + NDD (n = 168)**	**TD (n = 116)**	**Odds ratio (95% CI)**	***p*-value**
Child's age in years: Median (IQR)	8.1 6.3 – 10.2	2.8 2.6 – 3.1	N/A	N/A
Child's male sex	124 (74%)	66 (57%)	2.13 (1.29-3.53)	0.003*
Parental factors				
Mother's age in years	37.5 (SD: 5.72)	31.5 (SD: 7.2)	1.15 (1.10-1.20)	<0.0001*
Mother's age at delivery in years	29.2 (SD: 5.45)	28.6 (SD: 7.17)	1.01 (0.97-1.05)	0.424
Ordinal categories for Mother's age at delivery[a]	-	-	-	-
Mother's age at delivery in years[b]				
< 30	97 (58%)	70 (60%)	Ref	Ref
30 – 35	46 (27%)	25 (22%)	1.32 (0.74-2.36)	0.335
≥ 35	25 (15%)	21 (18%)	0.85 (0.44-1.65)	0.650

Mother's age at first birth in years	26.0 (22.0 – 29.0)	22.0 (19.0 – 25.0)	1.12 (1.06-1.18)	<0.0001*
Mother's marital status[a]				
Ordinal categories	-	-	-	-
Mother's marital status[b]				
Single	9 (5%)	10 (9%)	Ref	Ref
Married	138 (82%)	92 (79%)	1.66 (0.65-4.25)	0.286
Separated / Divorced	17 (10%)	10 (9%)	1.88 (0.57-6.22)	0.296
Widowed	4 (2%)	4 (3%)	1.11 (0.21-5.80)	0.901
Mother's religion[a]				
Ordinal categories	-	-		
Mother's religion[b]				
Catholic	56 (33%)	15 (13%)	Ref	ref
Protestant	40 (24%)	13 (11%)	0.82 (0.35-1.92)	0.654
Islam	72 (43%)	88 (76%)	0.21 (0.11-0.41)	<0.0001*
Mother's ethnicity[a]				
Ordinal categories	-	-		
Mother's ethnicity[b]				
Northern	77 (46%)	27 (23%)	Ref	ref
Southern	36 (21%)	42 (36%)	0.30 (0.16-0.56)	<0.0001*
Eastern	29 (17%)	41 (35%)	0.24 (0.12-0.47)	<0.0001*
Central	13 (8%)	5 (4%)	0.91 (0.29-2.79)	0.872
Other	13 (8%)	1 (1%)	4.55 (0.56-36.51)	0.153
Mother's education level[a]				
Ordinal categories	-	-		
Mother's education level[b]				
None	4 (2%)	2 (1%)	Ref	Ref
Primary	49 (29%)	74 (64%)	0.33 (0.05-1.87)	0.212
Secondary	39 (23%)	29 (25%)	0.67 (0.11-3.92)	0.659
Tertiary	76 (45%)	11 (10%)	3.45 (0.56-21.13)	0.180
Mother's occupation[a]				
Ordinal categories	-	-		
Mother's occupation[b]				
Formal employment	99(59%)	19 (16%)	Ref	ref
Informal employment	43 (26%)	57 (49%)	0.14 (0.07-0.27)	<0.0001*
None	26 (15%)	40 (35%)	0.12 (0.06-0.25)	<0.0001*
Father's age in years	41.5 (SD: 6.51)	33.8 (SD:6.41)	1.20 (1.14-1.26)	<0.0001*
Father's age at delivery in years	33.3	31.0	1.06 (1.02-1.10-)	0.003*

	(SD: 6.20)	(SD:6.41)		
Ordinal categories for Father's age at delivery[a]	-	-	-	-
Father's marital status[a]				
Ordinal categories	-	-		
Father's marital status[b]				
Single	9 (5%)	8 (7%)	Ref	Ref
Married	140 (83%)	93 (80%)	2.07 (0.69-6.18)	0.188
Separated / Divorced	16 (10%)	14 (12%)	1.23 (0.33-4.54)	0.747
Widowed	3(2%)	1 (1%)	5.33 (0.46-60.79)	0.178
Father's religion[a]				
Ordinal categories	-	-		
Father's religion[b]				
Catholic	54 (32%)	15 (13%)	Ref	Ref
Protestant	43 (26 %)	18 (15%)	0.66 (0.30-1.46)	0.311
Islam	71 (42%)	83 (72%)	0.23 (0.12-0.45)	<0.0001*
Father's ethnicity[a]				
Ordinal categories	-	-		
Father's ethnicity[b]				
Northern	72 (43%)	26 (22%)	Ref	Ref
Southern	39 (23|%)	44 (38%)	0.32 (0.17-0.59)	<0.0001*
Eastern	36 (21%)	36 (31%)	0.36 (0.18-0.68)	0.002*
Central	10 (6%)	9 (7.8%)	0.40 (0.14-1.09)	0.075
Other	11 (7%)	1 (1%)	3.97 (0.48-32.29)	0.197
Father's education level[a]				
Ordinal categories	-	-		
Father's education level[b]				
None	4 (2%)	1 (1%)	Ref	Ref
Primary	41 (24%)	62 (53%)	0.19 (0.01-1.93)	0.162
Secondary	35 (21%)	34 (29%)	0.38 (0.03-3.84)	0.415
Tertiary	88 (52%)	19 (16%)	1.57 (0.15-16.01)	0.699
Father's Occupation[a]				
Ordinal categories	-	-	-	-
Father's Occupation[b]				
Formal employment	119 (71%)	37(32%)	Ref	Ref
Informal employment	37 (22%)	70 (60%)	0.16 (0.09-0.28)	<0.0001*
None	9 (5%)	9 (8%)	0.41 (0.16-1.06)	<0.0001*
Parental age gap in years[c]		1.85 (IQR: -1.69	1.07 (1.02-1.13)	0.005*

		– 9.82)		
Mother is older than Father	16 (10%)	16 (14%)	0.65 (0.31-1.37)	0.266
Father is older than Mother	146 (87%)	90 (78%)	1.91 (1.02-3.58)	0.041*
Birth order	2 (IQR: 1 – 2)	2 (IQR: 1-2)	1.00 (0.82-1.23)	0.942
Birth weight (kg)	3.2 (IQR: 3.0 – 3.5)	3.0 (IQR: 2.8 – 3.5)	1.28 (0.87-1.87)	0.200
No. of children	2 (2 – 3)	2.0 (IQR: 1-2)	1.53 (1.23-1.90)	<0.0001*
Prenatal factors				
Pregnancy medical complications	13 (8%)	4 (4%)	9.04 (2.08-39.14)	0.003*
Pregnancy infections	23 (14%)	4 (4%)	4.44 (1.49-13.21)	0.007*
Medication use during pregnancy	48 (29%)	20 (17%)	1.92 (1.06-3.45)	0.029*
Gestational term ≤ 37 weeks[d]	10 (6%)	0 (0%)	7.27 (0.91-57.65)	0.060
Perinatal factors				
Assisted delivery	6 (4%)	2 (2%)	2.11 (0.41-10.64)	0.365
Labour complications	20 (12%)	2 (2%)	7.70 (1.76-33.63)	0.007*
Birth complications	23 (14%)	2 (2%)	9.04 (2.08-39.14)	0.003*
Adverse perinatal events	59 (35%)	2 (2%)	30.85 (7.35-129.37)	<0.0001*
Neonatal factors				
Low birth weight (≤ 2.5 kg)	23 (14%)	17 (15%)	0.92 (0.46-1.81)	0.818
Neonatal jaundice[d]	15 (9%)	0 (0%)	11.27 (1.46-86.59)	0.020*
Neonatal seizures immediately after birth[d]	13 (8%)	0 (0%)	9.64 (1.24-74.28)	0.030*
Postnatal factors				
Family history of seizures	18 (11%)	9 (8%)	1.42 (0.61-3.29)	0.406
Seizures disorders[d]	30 (18%)	0 (0%)	25.00 (3.35-186.14)	0.002*
Malaria (before age 3)	36 (21%)	5 (4%)	6.05 (2.29-15.95)	<0.0001*
Head injury with loss of consciousness (before age 3)[d]	20 (12%)	0 (0%)	15.54 (2.05-117.51)	<0.0001*

Note.ASD = Autism Spectrum Disorder (ASD); NDD = Neurodevelopmental Disorders; TD = Typically Developing; CI = Confidence Interval; IQR = Interquartile Range; SD = Standard Deviation. Means and standard deviations (SD) are provided for continuous variables with a normal or near normal distribution, while medians and interquartile ranges (IQR) are provided for continuous or count variables without a normal distribution.

[a]There is no departure from trend (likelihood ratio test LRT $p > 0.05$) so the ordered levels rather than the individual categories are reported; [b]There is departure from trend (LRT p value < 0.05) so the individual categories are reported; [c]Generated by subtracting mother's age from the father's age. [d]The zero count is assumed as 1 to allow computation of odds ratios with exact confidence intervals. All other odds ratios were computed with logistic regression.

*$p < 0.05$

Multivariable analysis of ASD+NDD vs. TD groups

The most significant risk factors reaching a p-value of ≤ 0.25 in the univariable analysis were selected for the multivariable model as specified in table 6.10. After adjusting for parental and socio-demographic data, 17 variables were included in the multivariable model.

Child's male sex had a significant association with ASD+NDD (OR: 6.87 [95% CI: 1.31, 36.15], p = 0.023). None of the parental, prenatal and neonatal factors were significantly associated with ASD+NDD. Birth complications (OR: 22.87 [95% CI: 1.14, 457.86], p = 0.041) and adverse perinatal events (OR: 206.96 [95% CI: 20.47, $2.10x10^3$], $p < 0.0001$) were the only perinatal factors reaching significance. Seizures disorders (OR: 64.94 [95% CI: 2.29, $1.84x10^3$], p = 0.014), malaria before the age of 3 years (OR: 12.94 [95% CI: 1.74, 96.44], p = 0.013) and head injury with loss of consciousness before the age of 3 years (OR: 78.06 [95% CI: 3.75, $1.62x10^3$], p = 0.005) were the postnatal factors reaching significance.

Table 6.10 - Multivariable analysis of relevant parental, perinatal and neonatal factors associated with ASD compared to typically developing children adjusted for parental socio-demographic and economic status.

Risk factor variables	**ASD+NDD (n = 168)**	**TD (n = 116)**	**Odds ratio (95% CI)**	***p*-value**
Child's male sex	85 (79%)	66 (57%)	6.87 (1.31 – 36.15)	0.023*
Parental factors				
Parental age gap in years	3.50 (IQR: -0.01 – 9.26)	1.85 (IQR: -1.69 – 9.82)	1.67 (0.00 – $1.38x10^5$)	0.929
Father is older than Mother	146 (87%)	90 (78%)	1.67 (0.21 – 13.41)	0.632
Birth weight (kg)	3.2 (IQR: 3.0 – 3.6)	3.0 (IQR: 2.8 – 3.5)	1.04 (0.36 – 2.97)	0.946
No. of children	2.0 (IQR: 2 – 3)	2.0 (IQR: 1- 2)	1.15 (0.62 – 2.16)	0.656
Prenatal factors				
Pregnancy medical complications	13 (8%)	4 (4%)	0.10 (0.01 – 1.90)	0.125
Pregnancy infections	23(14%)	4 (4%)	1.63 (0.05 – 54.18)	0.785
Medication use during pregnancy	48 (29%)	20 (17%)	0.94 (0.18 – 5.03)	0.943
Gestational term ≤ 37 weeks	10 (6%)	0 (0%)	0.42 (0.01 – 12.42)	0.616
Perinatal factors				
Labour complications	20 (12%)	2 (2%)	13.73 (0.23 – 818.58)	0.209
Birth complications	23 (14%)	2 (2%)	22.87 (1.14 – 457.86)	0.041*

Adverse perinatal events	59 (35%)	2 (2%)	206.96 (20.47 – $2.10x10^3$)	0.000*
Neonatal factors				
Neonatal jaundice	15 (9%)	0 (0%)	15.68 (0.85 – 288.94)	0.064
Neonatal seizures immediately after birth	13 (8%)	0 (0%)	12.67 (0.29 – 548.27)	0.186
Postnatal factors				
Seizures disorders	30 (18%)	0 (0%)	64.94 (2.29 – $1.84x10^3$)	0.014*
Malaria (before age 3 years)	36 (21%)	5 (4%)	12.94 (1.74 – 96.44)	0.013*
Head injury with loss of consciousness (before age 3 years)	20 (12%)	0 (0%)	78.06 ($3.75 – 1.62x10^3$)	0.005*

Note. ASD = Autism Spectrum Disorder; NDD = Neurodevelopmental Disorders; TD = Typically Developing; CI = Confidence Interval; IQR = Interquartile Range. In the multivariable analysis only variables that reached a p value cut-off of ≤ 0.25in the Univariable analysis and were not in multicollineality with each other were included.

*$p < 0.05$

6.4. Discussion

To our knowledge, this is the first case-control study to comprehensively investigate risk factors for ASD in Tanzania, comparing ASD with TD and NDD groups. Our findings show that a number of risk factors are associated with ASD, in particular, socio-demographic, prenatal, perinatal, neonatal and postnatal factors. These factors are different to those associated with other NDDs. These findings indicate that some risk factors are unique to ASD, but many are shared between these disorders. The findings from the current study are summarized below according to ASD vs. TD and ASD vs. NDD. These comparisons are also discussed in the context of other additional comparisons with NDD vs. TD and combined ASD+NDD vs. TD analysis.

6.4.1. ASD vs. TD summary of findings

In the present study, socio-demographic factors such as the child's male sex were positively associated with an increased risk of ASD when compared to TD groups. Our results are consistent with the theory that ASD affects males four times more than females (Fombonne, 2005) as several theories have suggested the involvement of the sex chromosome in the aetiology of ASD, and the role of hormonal influences in utero (Baron-Cohen et al., 2011). These sex differences in the risk of ASD are also dependent on phenotypic diversity in brain structure, whereby risk for ASD is greatest with relatively thinner cerebral cortex, the typical neuroanatomical brain phenotype for males compared to females (Ecker et al., 2017). Given that children with ASD were recruited from care centres, it may be helpful to rule out admission bias for male children, through future qualitative studies, since this trend

was also observed in previous studies of neurological disorders in rural parts of Africa (Kariuki et al., 2015).

This study showed that advanced parental age at delivery was associated with an increased risk of ASD. There is an inconsistent association of advanced parental age with ASD reported from several studies. However, in a recent meta-analysis of 27 studies, Wu et al (2017) found that every 10-year increase in maternal and paternal age increases the risk of ASD in the offspring by 18 and 21% respectively. Furthermore, the oldest age category (in both mothers and fathers) was associated with a small but significant increase in risk of ASD in the offspring. However, I found an association of ASD with mother's age at first birth but not father's age at delivery, in the multivariable model. This could mean mother's age at birth has more impact on development of ASD than father's age at delivery in this setting. This hypothesis can be examined by examining the risk of ASD at different age quartiles for the fathers, but this sample was too small to run this sensitivity analysis. Additionally, these findings of a significant increase in ASD risk with increasing parental age gap, albeit the association did not reach multivariable statistical significance, is consistent with a recent population-based cohort study suggesting an association with increasing difference in age between parents and ASD risk (Sandin et al., 2016). Genetic factors are thought to determine the association between parental age and risk for ASD, in particular *de novo* mutation for advanced father's age and chromosomal changes and/or epigenetic modifications for mother's advanced age (Sandin et al., 2016).

The findings indicate an increased risk of ASD associated with adverse perinatal events. The evidence of the association perinatal factors and risk of ASD in the literature is mixed and warrants more research (Ng et al, 2017). Among the perinatal factors investigated in this study, labor complications, birth complications and adverse perinatal events were found to be strongly associated with ASD than the TD group, even in the multivariable analysis. Previous studies have reported significant associations of prenatal risk factors such as gestational hypertension and maternal bleeding with ASD (e.g. Gardener et al., 2009; Gardener et al, 2011). Perinatal factors have also been highlighted in a recent review of neurodevelopmental disorders, including ASD (Bitta et al., 2017). Given that this risk factors has been consistently identified in epidemiological studies of neurological disorders such as epilepsy (Ngugi et al., 2013) and mental health problems (Kariuki et al., 2017a) underlines its importance in neurodevelopment.

Obstetric complications are plausibly associated with an increased risk for ASD as the prenatal period is found to be critical for fetal brain development. The most common type of perinatal damage is hypoxic-ischaemic encephalopathy, which can be detected early on electroencephalography and neuroimaging (Hagberg eta l., 2016) although these investigative resources are very limited in LAMIC. Infection during the pregnancy can have a detrimental effect on the development of the

foetal immune system, but infections during pregnancy did not reach multivariable significance in this study probably because this information could not be recalled reliably by the mothers. Pre-term birth (< 37 weeks) was another prenatal factor strongly associated with an increased risk for ASD in the univariable but not multivariable analysis. Pre-term births are common in LAMIC and may increase risk for ASD according to a recent scoping review (Ng, 2017). The lack of independent association of preterm birth with ASD in our study may be due to challenges of reporting of conception dates by the mothers, most of who do not attend antenatal clinics.

Postnatal factors such as seizures disorders, malaria before the age of 3 years and head injury with loss of consciousness before the age of 3 years were all found to be significantly associated with ASD. Of the risk factors investigated in this study, malaria before the age of three was associated with the highest independent risk of ASD in the multivariable analysis, being frequently more common among the ASD group (31%) than the TD group (4%). A recent study in Nigeria observed that children between the ages of 2 - 5 years had the highest prevalence of *Plasmodium* infections compared with the other age groups (Nmadu et al., 2015). Malaria especially when presenting with impaired consciousness and seizures is known to cause brain damage. Malaria can sequester into the brain capillaries causing diffuse brain damage, but electroencephalogram (EEG) recordings showed that the damage is more prominent in the posterior-temporal regions of the brain that are supplied by middle and posterior cerebral arteries (Kariuki et al., 2017b). Features similar to those of impaired communication in ASD, in particular speech and language impairment, were documented in Kenyan children previously treated for severe malaria in hospital (Carter et al., 2006). The strong significant association of ASD with malaria may have attenuated the independent association of seizures with ASD in the multivariable analysis, since most seizures in parasitaemic children are attributable to malaria (Kariuki et al., 2011). There, however, have been no single cohort studies examining all endophenotypes of ASD following severe malaria in Africa. Only a previous case series study conducted in Dar-es-Salaam, Tanzania where authors were able to confirm 3 out of 14 children diagnosed with ASD developed ASD following severe infections including malaria (Mankoski et al., 2006) , but these numbers were small and there were no comparison controls. Given the enormous burden of severe malaria with neurological involvement in many rural parts of Africa (Idro et al., 2007), studies on ASD following severe are urgently needed to inform preventative strategies.

Other neonatal factors such as neonatal jaundice were identified in the univariate analysis, but not in the multivariate analysis. Elevated serum bilirubin levels can be toxic to the developing central nervous system (Maimburg & Vaeth, 2006; Zhang et al., 2010). It is possible that the impact of neonatal factors on neurodevelopmental disorders, including ASD, is only apparent on long-term follow-ups (Mwaniki et al., 2012), and this should be examined in prospective cohort studies.

6.4.2. ASD vs. NDD summary of findings

Comparing children with ASD with those with other NDD enabled us to examine if there are unique risk factors for ASD. Although several factors reached significance in the univariable analysis, only fathers being older than mother and malaria under 3 years remained significant in the multivariable analysis. This is important in targeted control for unique factors for ASD in these poor settings in Africa. The finding that a father being older than mother is a risk factor for ASD is not surprising as it has consistently been documented in the literature. It is thought the consistency is due to long-term potential for fathering children even in advanced age, especially in settings where polygamy is allowed. Therefore, the role of a father's age on ASD may be mediated through spontaneous mutations. Perhaps fathers can be educated about the importance of having children early as a way of preventing ASD in their offspring, although the success of such interventions in largely patriarchal societies remains to be seen.

Malaria before the age of 3 years and father being older than mother were independent risk factors unique to ASD when comparing ASD and NDD groups, suggesting that control of these postnatal risk factor may specifically reduce the burden of ASD. As suggested above, follow-up studies of malaria as a risk factor for ASD should be urgently set-up in endemic area, to quantify the burden of ASD attributable to severe malaria. These studies should follow-up different phenotypes of severe malaria (e.g. impaired consciousness, malarial seizures, malarial prostration and malarial anemia) to understand the underlying mechanisms for development of ASD.

It is important to note that the lack of significance in the ASD vs. NDD analysis for factors that were significant in the ASD vs. TD analysis e.g. adverse perinatal events is of public health importance as it may suggest that these risk factors are shared between ASD and other NDD. This hypothesis was supported by identification of adverse perinatal events as independent risk factors for NDD when compared to TD; similar risk factors were found for ASD when compared to TD. Epidemiological studies have so far shown that this supposition is true when adverse perinatal events are associated with both neurological disorders and mental health problems. Hypothetically, control of such risk factors would not only reduce the burden of ASD but also that for other NDD. The later analysis of NDD vs. TD also helped identify risk factors such as seizure disorders, head injury and number of children that may be more important to other NDD than to ASD, although few observations may explain the differences in associations. These factors identified in NDD vs. TD but not in ASD vs. TD (e.g. seizures and head injury) cause direct brain damage, suggesting that symptomatic causes are more important causes of other NDD than they are for ASD, which are highly determined by genetic factors. Combining other NDD with ASD and comparing with TD improved the power for detecting risk factors such as seizure disorders and head injury which may have role in ASD, but did not reach significance in the ASD vs. TD comparison because of small observation for each group. It is

important to note that the large confidence intervals (CI) in our results may mean that there were few observations in some groups.

6.4.3. Strengths and limitations

Strengths

Our study has several strengths. Firstly, to the best of my knowledge, this is the first study to attempt to study the biologically plausible risk factors for ASD in SSA. The ASD screening (Social Communication Questionnaire – SCQ) tool was standardized and underwent adaptation and validation to the local population before its application in this study. Furthermore, all children were directly observed for their behaviour and language using the Autism Diagnostic Observation Schedule (ADOS) which aided in the clinical confirmation of the child's diagnosis. The inclusion of the NDD group made the study more robust, allowing us to identify risk factors unique to ASD. A large number of risk factors were investigated which were pragmatically selected by a thorough search of the literature, and included risk factors that have biological plausibility with regard to the association with ASD and NDD. A robust statistical analysis approach was used (including testing for departure from linear trend for ordinal variables and examining goodness of fit of the models) and we accounted for potential confounders in the multivariable model. Findings from this analysis may not be representative of other areas in Tanzania, especially rural areas, where participants were not drawn.

Limitations

There are several potential limitations in our study. Recall and reporting bias of retrospective self-reporting answers by parents/caregivers might have occurred, resulting in insignificant associations for some factors. This was not a community based study and therefore children with ASD and NDD recruited from care centres may not be representative of the general population. It is possible that we may have missed out on some children who may not have attended the facilities we approached in our method of identification of the study participants. Children living in urban areas have more access to these special schools and facilities and thus parents in rural areas were not included in this study. Furthermore, poorer and less literate parents in urban areas may not bring their children to these schools. Our sample size was relatively small; a larger sample size might have yielded more power to detect more significant associations. The TD group were matched by level of expressive language and this may have caused age selection bias. These differences were inevitable because delayed diagnosis and lack of expressive language is common in ASD, which would result in older children seeking care. However, the inclusion of the NDD comparison may have helped to deal with this limitation since the NDD children were slightly older than the ASD children. It is, however, important to note that the NDD group comprised of heterogeneous conditions. This is especially relevant since conditions such as Down's syndrome has a distinct genetic aetiology that is not shared with the parents, while ADHD and learning disability are often idiopathic and likely influenced by common

genetic factors and by a range of possible environmental factors. Residual confounding due to other unmeasured characteristics cannot be ruled out. It is important to note, that the majority of ASD children in this study had comorbidity with intellectual disability, and it may be that ASD with and without intellectual disability may have different risk factors, but the small sample size could not allow this sensitivity analysis. Neurobiological factors that might explain the heterogeneity of ASD such as differences in risk between males and females, differences between subtypes, and relation of symptom severity to risk factors were not investigated. Biomarkers of ASD, in particular electrophysiology (e.g. Bosl et al., 2017) and neuroimaging (e.g. Ecker et al., 2015), were not investigated.

6.4.4. Conclusions

In conclusion, this study identified postnatal malaria (before age 3 years) and father being older than mother as a significant independent risk factor unique to ASD. Other factors such as seizures disorders and head injury were more important to other NDD that were not ASD. Our results underscore the importance of ASD research and its association with malaria in SSA populations since in this region infectious diseases like malaria which are associated with central nervous system complications (Carter et al., 2003) continue to be a major public health concern. Further studies are needed to understand the mechanisms for associations between communicable and non-communicable diseases such as malaria and NDD, and between genetic and environmental factors specifically associated with ASD. Furthermore, future studies need to examine if advanced age in fathers is associated with spontaneous mutations for ASD in the offspring. The study also shows that some risk factors in particular adverse perinatal events are shared between ASD and other NDD. Interventions to control such risk factors would not only reduce the burden of ASD, but also that for other NDD.

Chapter 7

Assessing the Broader Autism Phenotype (BAP): Cross-cultural validation of the Kiswahili Autism Spectrum Quotient (AQ) in a Tanzanian parent sample.

7.1. Background

Despite ASD's significant heritability (Bailey et al., 1995; Freitag et al., 2010; Hallmayer et al., 2011; Tick et al., 2015), the search for the underlying genes has proved to be challenging, raising questions on the underlying genetic mechanisms of ASD (Abrahams & Geschwind, 2008). Recent evidence suggests that sub-threshold autistic traits are continuously distributed across the general population (Constantino & Todd, 2003; Plomin et al., 2009; Ruzich et al., 2015). Several researchers have reviewed substantial evidence indicating that first-degree relatives of autistic individuals often display milder forms of autistic traits referred to as the Broader Autism Phenotype (BAP) (Ruparelia et al., 2017; Cruz et al., 2013; Gerdts & Bernier et al., 2011; Sucksmith et al., 2011). This constellation of sub-threshold autistic traits includes a set of behavioural and cognitive characteristics that reflect the phenotypic expression that is qualitatively similar in unaffected relatives of autistic individuals.

Various instruments have been developed to assess the BAP in adults. These include self-report and/or informant questionnaires, semi-structured interviews and interviews combined with direct observation/assessment. One of the most widely used quantitative measures of autistic traits is the Autism Spectrum Quotient (AQ) developed by Baron-Cohen et al (2001), and its scoring follows a continuous quantitative approach. The AQ is a brief self-administered, forced-choice questionnaire that has been used extensively to measure autistic traits in adults (≥16 years) with normal intelligence in the general population, as well as in clinical samples. It is also used in relatives of individuals with a diagnosis of ASD to measure the BAP.

The AQ consists of 50 items about ability and preference. It has five subscales of 10 items each: *Social Skills, Communication, Attention Switching, Attention to Details and Imagination*. Individuals are instructed to respond to each item using a 'definitely agree', 'slightly agree', 'slightly disagree' and 'definitely disagree' scale. Using a binary system, responses for items endorsing an autistic trait are scored as +1, while the opposite responses are scored as a 0, summing to a maximum score of 50. Some researchers have used an alternative scoring system using a 4-point Likert scale (Hoekstra et al., 2008; Austin, 2005), whereby the highest score is 200 and lowest 50. To avoid a response bias, all items on the AQ are counterbalanced so that half of the 'agree' responses and half of the 'disagree' responses are scored as an autistic trait.

In the first validation study of the AQ using (i) adult males and females with Asperger Syndrome (AS) and high functioning autism (HFA); (ii) scientists versus non-scientists in Cambridge University students; (iii) winners of the UK Mathematics Olympiad and (iv) control adults, Baron-Cohen et al. (2001) found that the total AQ score and its five subscale scores are normally distributed and have demonstrated good test-retest reliability, good internal consistency and high sensitivity and specificity. Additionally, they report sex differences in the mean total AQ score with males scoring higher than females.

The AQ has since been adapted and validated in other languages and cultural contexts using clinical and non-clinical samples (Japan - Wakabayashi et al., 2006; Austria - Voracek & Dressler, 2006; Netherlands - Hoekstra et al., 2008; Scotland - Stewart & Austin, 2009; French-Canadian sample - Lepage et al., 2009; Australia - Broadbent et al., 2013; Poland - Pisula et al., 2013). Freeth et al. (2013) conducted a cross-cultural comparison of the expression of autistic traits in Western and Eastern cultures. They used the original English AQ in the UK, India and Malaysia and found behaviours associated with autistic traits were reported to a greater extent in the Eastern cultures than the Western culture. Additionally, some researchers have sought to conduct cross-cultural validation of the AQ to identify the BAP in parents of children with ASD (e.g. French - Rousselot-Pailley et al. 2011; Italian - Ruta et al., 2012; Persian - Mohammadi et al., 2012). However, these studies initially assessed the psychometric properties of the AQ using a general population sample, before the application of the tool in parents of children with ASD. To date, only two studies have investigated the psychometric properties of AQ using parent samples of children with ASD, to derive a standardized quantitative measure to define the BAP. Table 7.1 illustrates a review of the two AQ cross-cultural validation studies using parent samples.

Lau et al. (2013) examined the psychometric properties of the Chinese version of the AQ using a large sample of parents of children with ASD and parents of typically developing children in Taiwan. After performing factor analysis, the authors reported a 35 item 5-factor model (*Socialness, Mindreading, Patterns, Attention to Details and Attention Switching*) with acceptable fit indices. They reported fair internal consistency and test-retest reliability (Table 7.1). Findings from a large study investigating the psychometric properties of the Mandarin version of the AQ for Mainland China (Zhang et al., 2016) in a sample of parents of children with ASD and parents of typically developing children revealed acceptable test-retest reliability and internal consistency (Table 7.1).

Parental BAP tools may be useful in analysing or understanding sources of variability in ASD etiology and for informing the development of parent-mediated ASD interventions such as those aimed at improving a child's disruptive behaviours and communication. A recent systematic review of

BAP in parents of children with ASD reported a prevalence of BAP that ranged from 2.6% to 80% (using different measures), being more prevalent in fathers than mothers (Rubenstein & Chawla, 2018).

In summary, the AQ is a widely accepted and reliable measure of BAP in parents of children with ASD. Furthermore, cross-cultural findings indicate that patterns are stable and possibly independent of cultural influences. To date, no studies have been conducted in SSA on the validity of the AQ. This study aims to build on existing cross-cultural research assessing the validity of the Kiswahili version of the AQ and examining the distribution of scores in a sample of parents of children with a confirmed diagnosis of ASD, parents of children with a known NDD and parents of typically developing children in the Tanzanian population.

Table 7.1 - Review of AQ cross-cultural validation studies using parent samples.

Country (Language)	Study	Sample	Factor Analysis			Internal consistency (Cronbach's α)	Test retest Reliability
			No. of items	No. of factors	Fit indices		
Taiwan (Chinese)	Lau et al. (2013)	1208 ASD 2984 TD	35	5 [a]	0.54 [b] 0.969 [c]	0.84 [de] 0.54 - 0.88 [df]	0.65 [deg] 0.40 - 0.72 [def]
China (Mandarin)	Zhang et al. (2016)	1037 ASD (522Mo / 515Fa) 1040 TD (515Mo / 525Fa) 32 ASD* (6F / 26M) 37 SCH* (7F / 30M) 38 OCD* (7F / 31M) 38 HC* (8F / 30M)	NA	NA	NA	0.817 [eh] 0.622 - 0.765 [fh] 0.806 [ei] 0.619 - 0.760 [fi]	0.79 [ehj] 0.42 - 0.75 [fhj] 0.89 [eij] 0.62 - 0.85 [fij]

Note: ASD = Autism Spectrum Disorder; TD = Typically Developing; HC = Healthy Controls; SCH = Schizophrenia; OCD = Obsessive Compulsive Disorder; Mo = Mother; Fa = Father; F = Female; M = Male; NA = Not Available.

*Not a parent sample.

[a]Confirmatory Factor Analysis (CFA) – modification of original subscales as per their 5 factor Principal Component Analysis (PCA); [b]Root Mean Square Error of Approximation (RMSEA); [c]Comparative Fit Index (CFI); [d]Whole sample; [e]Total score; [f]Subscale range; [g]Intraclass Correlation Coefficient (ICC); [h]ASD parent group; [I]TD parent group; [j]Pearson's Correlation Coefficient (*r*).

7.2. Methodology

This case-control study was approved by Muhimbili University of Health and Allied Sciences (MUHAS) Directorate of Research and Publications, National Institute for Medical Research (NIMR) and registered with the Tanzania Commission for Science and Technology (COSTECH). All parents gave verbal and written consent.

7.2.1. Study sample

Three groups of parents were recruited for this study. Parents of children who had a diagnosis of ASD (n = 103) were recruited from the Child and Adolescent Clinic, Department of Psychiatry, Muhimbili National Hospital (MNH), private clinics and centres, ASD units attached to local primary schools in Dar-es-Salaam Tanzania. At least one biological parent had to be available for the study. Parents of children with other neurodevelopmental disorders which included, Down's Syndrome (n = 9), Learning Disability (n = 32), Seizure Disorders (n = 6) and ADHD (n = 10) (NDD n = 57) were recruited from MNH and special needs schools in Dar-es-Salaam, Tanzania. Parents of typically developing (TD) children (n = 107) were randomly selected from the community. I was fully involved with the recruitment of participants and collected all the data for this study with assistance from the fieldworker where Kiswahili was required. I directly administered the AQ. I trained, supervised and oversaw any assistance from the fieldworker.

7.2.2. BAP measure

***Autism Spectrum Quotient - Adult (AQ – Baron-Cohen et al., 2001)*:** This is a self-report questionnaire used as a measure of the extent of autistic traits in adults. Participants rate to what extent they agree or disagree on statements on a 4-point Likert scale. In its initial validation with English speaking samples in the UK, it was observed to be relatively quick and easy to use and produces a near normal distribution in the general population (Baron-Cohen et al., 2001). The AQ has been used extensively and has been shown to have consistent results across cultures (Dutch AQ: Hoekstra et al., 2008; Japanese AQ: Wakabayashi et al., 2006), and the AQ score has been reported to be a good predictor of clinical diagnosis (Woodbury-Smith et al., 2005). Wheelwright et al (2010) used the AQ to define the broader, medium and narrow autism phenotype (subsequently abbreviated as BAP, MAP and NAP, respectively).

As in previous AQ studies (Lau et al., 2013; Hoekstra et al., 2008; Austin, 2005), this study also employed a scoring method with an ordinal scale (4-point Likert scale ranging from 1 to 4 for items portraying autistic features, and inverted for the reversed items) instead of the original dichotomous scale. This was done in order to obtain a better approximate of continuous distribution and to provide more information for procedures such as factor analysis (Swygert et al., 2001; Gorsuch, 1983). The

same scoring protocol was subsequently applied when performing group comparisons (except item positive response frequency distribution, where the original scoring protocol was used).

7.2.3. Translation of the AQ

Permission was sought from the Autism Research Centre (ARC) at the University of Cambridge to translate the AQ into Kiswahili. The AQ was then translated in Tanzanian Kiswahili by a linguistic specialist at MUHAS, and back-translated into English by another linguistic specialist at MUHAS. The back-translated version was reviewed by a clinical psychologist from the Department of Psychiatry, Muhimbili National Hospital (MNH), who recommended minor modifications. This iterative process continued until the team was satisfied that the Kiswahili version retained the original meaning (Appendix 8). We attempted to adapt the AQ, without significant modifications in terms of item content. We made some attempts to use local terms for item 13 and 24 for instance, which refer to library, party, theatre and museum. However, it is possible that some parents may not have had access to or experiences of these places/activities and would not be able to relate to items about them. Nonetheless, care was taken to ensure semantic equivalence of the translated items. The tool was informally piloted with parents for feedback on whether they understood the questions, wording appropriately in case meanings were ambiguous or unclear.

7.2.4. Procedures

Parents were informed of the objectives of the study. After obtaining consent, parents of participating children in our other study were asked to complete the AQ. Of the 267 respondents, 50 were selected using a fixed interval sample method. Of these, 35 (70%) completed the AQ after at least 2 weeks to examine the test-retest reliability.

7.2.5. Statistical analysis

Data analysis was done using IBM SPSS version 20 and R version 3.0.2. Descriptive statistics were computed and the distribution of scores per group explored. To evaluate discriminant validity, differences in scores between all parents, mothers and fathers for each group were tested using Mann Whitney U-tests. Between and within group differences across the 3 groups (ASD, TD and NDD) were tested using the non-parametric Kruskal Wallis test since the data was not normally distributed. A p-value of ≤ 0.05 was considered statistically significant. The internal consistency of the SCQ was calculated using Cronbach's coefficient alpha (α) (Cronbach, 1951). An interclass correlation coefficient (ICC) and Spearman's correlation coefficient were used to evaluate the test–retest reliability. Confirmatory factor analysis (CFA) with diagonally weighted least squares was performed to determine a 5 factor model of the AQ. If the items did not follow specified factorial structures in the literature an exploratory Principle Components Analysis (PCA) was performed using varimax rotation. The cut-off for standardized coefficient loadings was set at 0.30. Wheelwright et al.'s (2010)

proposed definition of the BAP (AQ total scores of ≥1SDs above the mean), MAP (AQ total scores of ≥2 SDs above the mean) and NAP (AQ total scores ≥ 3 SDs above the mean) was used in order to determine the proportion of parents with each phenotype.

7.3. Results

7.3.1. General sample description

AQ data was collected from 103 parents of children diagnosed with ASD, 107 parents of typically developing children and 57 parents of children with other neurodevelopmental disorders (NDD). Mothers formed 70% of the ASD group, 77% of the TD group and 79% of the NDD group with no significant differences between the ASD and TD parent groups ($p = 0.270$) and the ASD and NDD parent groups ($p = 0.217$) . The median age of the child was significantly different between ASD and TD groups (7.0 vs. 2.8; $p < 0.0001$), because the TD group was matched on expressive language level. There was also a significant difference between the child's median age between ASD and NDD groups (7.0 vs. 9.9; $p < 0.0001$). Child's male sex was significantly higher in the ASD group than in the TD group (78% vs. 58%; $p = 0.001$). The median age of the mother was significantly different between ASD and TD parents groups (36.5 vs. 31.0; $p < 0.0001$) as well as ASD and NDD parent groups (36.5 vs. 38.9; $p < 0.0001$). However, in the father's age there was only a significant difference between the ASD and TD parent groups (40.8 vs. 33.8; $p < 0.0001$). Table 7.2 compares the distribution of participant characteristics between ASD and TD parent groups and ASD and NDD parent groups.

Table 7.2 - Distribution of participant baseline characteristics between ASD, NDD and TD groups enrolled in this study.

Participant characteristics	ASD (n = 103)	TD (n = 107)	NDD (n = 57)	ASD vs. TD *p*-value	ASD vs. NDD *p*-value
Child age in years: Median (IQR)	7.0 (5.8 – 9.0)	2.8 (2.6 – 3.1)	9.9 (8.1 – 10.8)	< 0.0001[*a]	< 0.0001[*a]
Child male sex	80 (78%)	62 (58%)	37 (65%)	0.001[*b]	0.061[b]
Mother's age in years: Mean (SD)	36.5 (4.80)	31.0 (7.07)	38.9 (6.85)	< 0.0001[*c]	0.007[*c]
Father's age in years: Mean (SD)	40.8 (5.86)	33.8 (6.55)	42.5 (7.51)	< 0.0001[*c]	0.491[c]
Gender of parents				0.270[b]	0.217[b]
Mothers	72 (70%)	82 (77%)	45 (79%)		
Fathers	31 (30%)	25 (23%)	12 (21%)		

Note. ASD = Autism Spectrum Disorder; TD = Typically Developing; NDD = Neurodevelopmental Disorders; IQR = Interquartile Range; SD = Standard Deviation.

[a]Mann Whitney U test; [b]Pearson's chi-squared test (dichotomous and categorical variables); [c]t-test on raw data (continuous variable).

[*] $p < 0.05$

7.3.2. Distribution of AQ scores by group

Item positive response frequency

AQ item positive response frequencies for all three groups are given in Table 7.3. The original scoring protocol was applied for the purpose of reporting item positive response frequencies in this section. Of the 50 items, 20 items showed significant differences between ASD and TD groups. Of these 20, 19 items were significantly more frequent in the ASD group than in the TD group, while the remaining one was significantly more frequent in the TD group than the ASD group (item 30: 95.3% vs. 71.8%; "I don't usually notice small changes in a situation, or a person's appearance"; $p < 0.0001$). Of the 20 items that were significantly more frequent in the ASD group than the TD group, items with the highest frequencies include item 12 (78.6% vs. 36.2%; "I tend to notice details that others do not"; $p = 0.005$) which belongs to the Attention Switching subscale, item 25 (74.8% vs. 57.9%; "It does not upset me if my daily routine is disturbed"; $p = 0.010$) which belongs to the Attention to Detail subscale and item 7 (64.1% vs. 43.9%; "Other people frequently tell me that what I've said is impolite, even though I think it is polite"; $p = 0.003$) which belongs to the Communication subscale.

Of the 50 items, 24 items showed significant differences between ASD and NDD groups. Of these 24, 17 items were significantly more frequent in the ASD group than in the NDD group, while the remaining 7 were significantly more frequent in the NDD group than the ASD group. These 6 items

include items 6 (91.2% vs. 69.9%; "I usually notice car number plates or similar strings of information"; p = 0.002), 9 (77.2% vs. 56.3%; "I am fascinated by dates"; p = 0.009), 16 (96.5% vs. 76.7%; "I tend to have very strong interests which I get upset about if I can't pursue", p = 0.001), 20 (42.1% vs. 27.2%; "When I'm reading a story, I find it difficult to work out the characters' intentions"; p = 0.054), 24 (89.5% vs. 76.7%; "I would rather go to the theatre than a museum"; p = 0.0047), 30 (87.7% vs. 71.8%; "I don't usually notice small changes in a situation, or a person's appearance"; p = 0.021) and 46 (89.5% vs. 72.8%; "New situations make me anxious", p = 0.014). Of the 17 items that were significantly more frequent in the ASD group than the NDD group, items with the highest frequencies include item 43 (97.1 % vs. 86%; "I like to plan any activities I participate in carefully"; p = 0.011) which belongs to the Attention Switching subscale, and items 12 (78.6% vs. 56.1%; "I tend to notice details that others do not"; p = 0.003) and 49 (56.3% vs. 33.3%; "I am not very good at remembering people's date of birth"; p = 0.005) which belong to the Attention to Detail subscale.

Table 7.3 – Item positive response frequency for ASD vs. TD groups and ASD vs. NDD groups.

AQ	ASD (n = 108)	TD (n = 116)	NDD (n = 60)	ASD vs. TD *p* – value	ASD vs. NDD *p* – value
1. I prefer to do things with others rather than on my own.	30 (29.1%)	4 (3.7%)	0	< 0.000[*b]	< 0.000[*b]
2. I prefer to do things the same way over and over again.	31 (30.1%)	24 (22.4%)	8 (14.0%)	0.206[a]	0.0023[*a]
3. If I try to imagine something, I find it very easy to create a picture in my mind.	16 (15.5%)	1 (0.9%)	2 (3.5%)	< 0.000[*b]	0.0020[*a]
4. I frequently get so strongly absorbed in one thing that I lose sight of other things.	43 (41.7%)	29 (27.1 %)	21 (36.8%)	0.025[*a]	0.544[a]
5. I often notice small sounds when others do not.	59 (57.3%)	58 (54.2%)	33 (57.9%)	0.654[a]	0.940[a]
6. I usually notice car number plates or similar strings of information.	72 (69.9%)	83 (77.6%)	52 (91.2%)	0.206[a]	0.002[*a]
7. Other people frequently tell me that what I've said is impolite, even though I think it is polite.	66 (64.1%)	47 (43.9%)	39 (68.4%)	0.003[*a]	0.580[a]
8. When I'm reading a story, I	20	13	4	0.148[a]	0.039[*b]

can easily imagine what the characters might look like.	(19.4%)	(12.1%)	(7.0%)		
9. I am fascinated by dates.	58 (56.3%)	63 (58.9%)	44 (77.2%)	0.707[a]	0.009[*a]
10. In a social group, I can easily keep track of several different people's conversations.	29 (28.2%)	20 (18.7%)	4 (7.0%)	0.105[a]	0.002[*b]
11. I find social situations easy.	25 (24.3%)	35 (32.7%)	7 (12.3%)	0.176[a]	0.069[a]
12. I tend to notice details that others do not.	81 (78.6%)	65 (60.7%)	32 (56.1%)	0.005*a	0.003[*a]
13. I would rather go to a library than a party.	55 (53.4%)	22 (20.6%)	29 (50.9%)	< 0.0001[*a]	0.760[a]
14. I find making up stories easy.	43 (41.7%)	31 (29.0%)	21 (36.8%)	0.053[a]	0.544[a]
15. I find myself drawn more strongly to people than to things.	51 (49.5%)	27 (25.2%)	18 (31.6%)	< 0.0001[*a]	0.028[*a]
16. I tend to have very strong interests which I get upset about if I can't pursue.	79 (76.7%)	93 (86.9%)	55 (96.5%)	0.055[a]	0.001[*a]
17. I enjoy social chit-chat.	26 (25.2%)	13 (12.1%)	3 (5.3%)	0.015[*a]	0.002[*a]
18. When I talk, it isn't always easy for others to get a word in edgeways.	27 (26.2%)	9 (8.4%)	2 (3.5%)	0.001[*a]	< 0.0001[*b]
19. I am fascinated by numbers.	46 (44.7%)	59 (55.1%)	24 (42.1%)	0.129[a]	0.755[a]
20. When I'm reading a story, I find it difficult to work out the characters' intentions.	28 (27.2%)	27 (25.2%)	24 (42.1%)	0.748[a]	0.054[*a]
21. I don't particularly enjoy reading fiction.	38 (36.9%)	29 (27.1%)	18 (31.6%)	0.128[a]	0.500[a]
22. I find it hard to make new friends.	50 (48.5%)	12 (11.2%)	18 (31.6%)	< 0.0001[*a]	0.038[*a]
23. I notice patterns in things all the time.	79 (76.7%)	91 (85%)	45 (78.9%)	0.124[a]	0.744[a]
24. I would rather go to the	79	71	51	0.097[a]	0.047*[a]

theatre than a museum.	(76.7%)	(66.4%)	(89.5%)		
25. It does not upset me if my daily routine is disturbed.	77 (74.8%)	62 (57.9%)	38 (66.7%)	0.010*a	0.276[a]
26. I frequently find that I don't know how to keep a conversation going.	39 (37.9%)	16 (15.0%)	15 (26.3%)	< 0.0001[*a]	0.139[a]
27. I find it easy to "read between the lines" when someone is talking to me.	24 (23.3%)	16 (15.0%)	16 (28.1%)	0.124[a]	0.505[a]
28. I usually concentrate more on the whole picture, rather than the small details.	23 (22.3%)	4 (3.7%)	0	< 0.0001[*b]	< 0.000[*b]
29. I am not very good at remembering phone numbers.	66 (64.1%)	76 (71.0%)	32 (56.1%)	0.282[a]	0.324[a]
30. I don't usually notice small changes in a situation, or a person's appearance.	74 (71.8%)	102 (95.3%)	50 (87.7%)	< 0.0001[*a]	0.021[*a]
31. I know how to tell if someone listening to me is getting bored.	8 (7.8%)	1 (0.9%)	0	0.017[*b]	0.051[b]
32. I find it easy to do more than one thing at once.	29 (28.2%)	19 (17.8%)	2 (3.5%)	0.073[a]	< 0.0001[*b]
33. When I talk on the phone, I'm not sure when it's my turn to speak.	13 (12.6%)	2 (1.9%)	2 (3.5%)	0.002[*a]	0.087[b]
34. I enjoy doing things spontaneously.	75 (72.8%)	67 (62.6%)	34 (59.6%)	0.114[a]	0.087[a]
35. I am often the last to understand the point of a joke.	12 (11.7%)	0	0	< 0.0001[*b]	0.005[*b]
36. I find it easy to work out what someone is thinking or feeling just by looking at their face.	18 (17.5%)	4 (3.7%)	9 (15.8%)	0.001[*b]	0.830[a]
37. If there is an interruption, I can switch back to what I was doing very quickly.	13 (12.6%)	15 (14.0%)	1 (1.8%)	0.766[a]	0.020[*b]
38. I am good at social chit-chat.	9 (8.7%)	0	2 (3.5%)	0.001[*b]	0.330[b]
39. People often tell me that I	28	21	13	0.195[a]	0.544[a]

keep going on and on about the same thing.	(27.2%)	(19.6%)	(22.8%)		
40. When I was young, I used to enjoy playing games involving pretending with other children.	10 (9.7%)	0	1 (1.8%)	0.001[*b]	0.099[b]
41. I like to collect information about categories of things (e.g. types of car, types of bird, types of train, types of plant, etc.).	67 (65.0%)	82 (76.6%)	31 (54.4%)	0.064[a]	0.185[a]
42. I find it difficult to imagine what it would be like to be someone else.	69 (67.0%)	63 (58.9%)	31 (54.4%)	0.224[a]	0.115[a]
43. I like to plan any activities I participate in carefully.	100 (97.1%)	106 (99.1%)	49 (86.0%)	0.294[a]	0.011[*a]
44. I enjoy social occasions.	19 (18.4%)	7 (6.5%)	8 (14.0%)	0.009[*a]	0.476[a]
45. I find it difficult to work out people's intentions.	69 (67.0%)	62 (57.9%)	38 (66.7%)	0.176[a]	0.967[a]
46. New situations make me anxious.	75 (72.8%)	73 (68.2%)	51 (89.5%)	0.466[a]	0.014[*a]
47. I enjoy meeting new people.	8 (7.8%)	0	0	0.003[*b]	0.051[b]
48. I am a good diplomat.	7 (6.8%)	3 (2.8%)	0	0.208[b]	0.051[b]
49. I am not very good at remembering people's date of birth.	58 (56.3%)	29 (27.1%)	19 (33.3%)	< 0.000[*a]	0.005[*a]
50. I find it very easy to play games with children that involve pretending.	28 (27.2%)	17 (15.9%)	6 (10.5%)	0.046[*a]	0.014[*a]

Note. AQ = Autism Spectrum Quotient; ASD = Autism Spectrum Disorder; TD = Typically Developing; NDD = Neurodevelopmental Disorders.

[a]Mann Whitney U test; [b]Pearson's chi-squared test (dichotomous and categorical variables).

[*]$p < 0.05$

Discriminant validity

The AQ median total scores and median scores for all five subscales for all parent groups (combined parents, mothers and fathers) were compared between ASD and TD parent groups and ASD and NDD parent groups (Table 7.4). The median AQ total score was significantly higher for all parents from the

ASD group compared to the all parents from the TD group (88 (IQR 79 – 99) vs. 77 (IQR 66 – 83); $p< 0.0001$) and significantly higher for all parents from the ASD group compared to all parents from the NDD group (88 (IQR 79 – 99) vs. 76 (IQR 66 – 84); $p< 0.0001$). A similar trend was found when comparing all parents and mothers only from the ASD to TD groups and ASD to NDD groups on total score and all five subscales of the AQ ($p< 0.0001$). In the ASD versus TD comparisons, the only significant difference for fathers was for the attention to detail subscale. In the ASD versus NDD comparisons, there was a significant difference for fathers on the total score and all subscales except for the imagination subscale. Furthermore, all AQ total scores and subscales differed across the 3 groups (ASD, TD and NDD) for all parents and mothers only. For fathers, significant differences across the 3 groups were only observed for total score and attention to detail (Table 7.5).

Table 7.4 - Discriminant validity for AQ for all parents, mothers and fathers in ASD vs. TD groups and ASD vs. NDD groups for AQ total score and sub-subscales.

AQ Scores	ASD (n = 103)			TD (n = 107)			NDD (n = 57)			ASD vs. TD[a] *p*-value			ASD vs. NDD[a] *p*-value		
	All parents	Mothers (n = 72)	Fathers (n = 31)	All parents	Mothers (n = 82)	Fathers (n = 25)	All parents	Mothers (n = 45)	Fathers (n = 12)	All parents	Mothers	Fathers	All parents	Mothers	Fathers
Total Score: Median (IQR)	88 (79 - 99)	89 (83 - 100)	81 (72 - 99)	77 (66 - 83)	76 (67 - 82)	80 (66 - 84)	76 (66 - 84)	78 (66 - 84)	70 (65 - 77)	< 0.0001*	< 0.0001*	0.1335	< 0.0001*	< 0.0001*	0.0122*
Social Skills: Median (IQR)	17 (15 - 20)	17 (16 – 20)	15 (13 - 20)	15 (13 - 18)	15 (13 – 18)	15 (12 - 18)	14 (12 - 18)	15 (12-18)	13 (11 - 15)	< 0.0001*	< 0.0001*	0.5794	< 0.0001*	0.0003*	0.0165*
Attention switching: Median (IQR)	18 (15 - 20)	18 (15 – 20)	17 (14 - 19)	15 (13 - 16)	15 (13 – 16)	14 (13 - 17)	15 (13- 17)	15 (12 – 18)	16 (13 - 17)	< 0.0001*	< 0.0001*	0.0632	< 0.0001*	0.0003*	0.0465*
Attention to detail: Median (IQR)	17 (14 - 20)	18 (14- 21)	17 (14 - 20)	15 (12 - 17)	15 (12 – 17)	14 (12 - 16)	14 (12 - 17)	15 (13 – 17)	14 (12- 16)	< 0.0001*	< 0.0001*	0.0300*	< 0.0001*	0.0008*	0.0486*
Communication: Median (IQR)	18 (15 - 21)	18 (17- 22)	16 (14 - 20)	15 (13 - 17)	14 (13 – 16)	15 (13 - 18)	15 (13 - 17)	15 (13 – 17)	14 (13 - 16)	< 0.0001*	< 0.0001*	0.172	< 0.0001*	< 0.0001*	0.0336*
Imagination: Median (IQR)	18 (15 - 21)	18 (16 – 21)	16 (15 - 19)	15 (13 - 18)	15 (13 – 18)	16 (15 - 17)	15 (13 - 18)	15 (13 – 18)	15 (13 - 18)	< 0.0001*	< 0.0001*	0.3237	< 0.0001*	< 0.0001*	0.1781

Note. AQ = Autism Spectrum Quotient; ASD = Autism Spectrum Disorder; TD = Typically Developing; NDD = Neurodevelopmental Disorders; IQR = Interquartile Range.

[a]Mann Whitney U test as continuous variable and non-parametric despite log-transforming it.

*$p < 0.05$

Table 7.5 - Discriminant validity for AQ for all parents, mothers and fathers across all groups (ASD, TD and NDD) for AQ total score and sub-subscales.

AQ Scores	ASD (n = 103)			TD (n = 107)			NDD (n = 57)			Group differences (ASD, TD & NDD)[a] *p*-value		
	All parents	Mothers (n = 72)	Fathers (n = 31)	All parents	Mothers (n = 82)	Fathers (n = 25)	All parents	Mothers (n = 45)	Fathers (n = 12)	All parents	Mothers	Fathers
Total Score: Median (IQR)	88 (79 - 99)	89 (83 - 100)	81 (72 - 99)	77 (66 - 83)	76 (67 - 82)	80 (66 - 84)	76 (66 - 84)	78 (66 - 84)	70 (65 - 77)	< 0.0001*	< 0.0001*	0.032*
Social Skills: Median (IQR)	17 (15 - 20)	17 (16 – 20)	15 (13 - 20)	15 (13 - 18)	15 (13 – 18)	15 (12 - 18)	14 (12 - 18)	15 (12-18)	13 (11 - 15)	< 0.0001*	< 0.0001*	0.076
Attention switching: Median (IQR)	18 (15 - 20)	18 (15 – 20)	17 (14 - 19)	15 (13 - 16)	15 (13 – 16)	14 (13 - 17)	15 (13- 17)	15 (12 – 18)	16 (13 - 17)	< 0.0001*	< 0.0001*	0.062
Attention to detail: Median (IQR)	17 (14 - 20)	18 (14- 21)	17 (14 - 20)	15 (12 - 17)	15 (12 – 17)	14 (12 - 16)	14 (12 - 17)	15 (13 – 17)	14 (12- 16)	< 0.0001*	< 0.0001*	0.040*
Communication: Median (IQR)	18 (15 - 21)	18 (17- 22)	16 (14 - 20)	15 (13 - 17)	14 (13 – 16)	15 (13 - 18)	15 (13 - 17)	15 (13 – 17)	14 (13 - 16)	< 0.0001*	< 0.0001*	0.083
Imagination: Median (IQR)	18 (15 - 21)	18 (16 – 21)	16 (15 - 19)	15 (13 - 18)	15 (13 – 18)	16 (15 - 17)	15 (13 - 18)	15 (13 – 18)	15 (13 - 18)	< 0.0001*	< 0.0001*	0.324

Note. AQ = Autism Spectrum Quotient; ASD = Autism Spectrum Disorder; TD = Typically Developing; NDD = Neurodevelopmental Disorders; IQR = Interquartile Range.

[a]Kruskal Wallis test.

*$p < 0.05$

7.3.3. AQ reliability

Internal consistency of the AQ

The internal consistency of the AQ as measured by Cronbach's coefficient alpha for all items for the whole group was 0.84 (95 % CI, 0.80-0.88) and was 0.84 (95 % CI, 0.77-0.90) for the ASD group, 0.86 (95 % CI, 0.82-0.89) for the TD group and 0.80 (95 % CI, 0.77–0.85) for the NDD group (Table 7.6). However, for most subscales the Cronbach's coefficient alphas were much lower (0.45–0.57) for the whole group. When measuring the internal consistency of the individual groups for each subscale the Cronbach's coefficient alphas were varied (0.41-0.70) with higher Cronbach's coefficient alphas for the social skills subscale for the TD group (0.70) and lowest for the attention switching subscale for the NDD group (0.41) (Table 7.6).

Table 7.6 - Internal consistency of the AQ for all items and all 5 sub-subscales for individual groups and the whole group.

AQ	ASD Cronbach's α (95% CI)	TD Cronbach's α (95% CI)	NDD Cronbach's α (95% CI)	Whole Group Cronbach's α (95% CI)
All items	0.84 (0.77 – 0.90)	0.86 (0.82 – 0.89)	0.80 (0.77 – 0.85)	0.84 (0.80 – 0.88)
Social skills	0.60 (0.50 – 0.70)	0.70 (0.58 – 0.89)	0.53 (0.39 – 0.67)	0.54 (0.44 – 0.64)
Attention switching	0.48 (0.33 – 0.62)	0.49 (0.37 – 0.62)	0.41 (0.27 – 0.55)	0.45 (0.34 – 0.57)
Attention to detail	0.63 (0.48 – 0.78)	0.56 (0.41 – 0.71)	0.60 (0.49 – 0.72)	0.57 (0.43 – 0.71)
Communication	0.53 (0.40 – 0.68)	0.60 (0.51 – 0.69)	0.54 (0.41 – 0.63)	0.55 (0.44 – 0.65)
Imagination	0.46 (0.31 – 0.62)	0.65 (0.57 – 0.73)	0.67 (0.57 – 0.77)	0.56 (0.46 – 0.65)

Note. AQ = Autism Spectrum Quotient; ASD = Autism Spectrum Disorder; TD = Typically Developing; NDD = Neurodevelopmental Disorders; CI = Confidence Interval.

Test-retest reliability

The AQ was initially administered to a total of 267 parents. Of these 267 parents, 35 were asked to fill in the AQ again after two weeks. Table 7.7 shows the AQ demonstrated excellent test-retest reliability (ICC = 0.90 [95 % CI, 0.83-0.94] – 0.98 [95 % CI, 0.92-1.00]). The before and after AQ total scores were significantly correlated (Spearman correlation coefficient (rho) = 0.892-0.949.; $p < 0.001$).

Table 7.7 - Test-retest reliability of the AQ for the total score and all 5 sub-subscales.

AQ	ICC (95% CI)	Spearman's rho
Total score	0.98 (0.92 – 1.00)	0.947 (<0.0001)
Social skills	0.96 (0.93 – 0.97)	0.949 (<0.0001)
Attention switching	0.94 (0.90 – 0.96)	0.880 (<0.0001)
Attention to detail	0.97 (0.94 – 0.98)	0.942 (<0.0001)
Communication	0.90 (0.83 – 0.94)	0.928 (<0.0001)
Imagination	0.94 (0.89 – 0.96)	0.892 (<0.0001)

Note. AQ = Autism Spectrum Quotient; ICC = Intraclass Correlation Coefficient; CI = Confidence Interval.

7.3.4. AQ factorial structure

We employed a 5 factor model of confirmatory factor analysis and found that the fit indices were poor and most of the standardized coefficients did not reach the cutoff of 0.30 (Appendix 11). We further performed principle components analysis and found that items that reached a cutoff of 0.30 in a specific component could not be categorized into a conceptual or meaningful subscale (Appendix 12).

7.3.5. Proportion of parents with BAP, MAP and NAP

I computed the mean scores for parents of TD children. The mean scores for parents of TD children in the dataset were 75.80, with a corresponding 1 SD of 11.49, 2 SD of 22.99 and 3 SD of 34.49. Using these measures of central tendency, the cut-off for BAP was set at scores equal to or greater than the mean scores plus 1 SD, which equaled 87.30; that for MAP was set at scores equal to or greater than mean plus 2 SD, which equaled 98.80; and that for NAP was set at scores equal to or greater than mean plus 3 SD, which equaled 110.29. Using these set cut-offs the prevalence for BAP, MAP and NAP for parents of children with ASD, parents of children with NDD and parents of TD children are shown in Table 7.8.

Table 7.8 - Proportion of parents with BAP, MAP and NAP in each group.

Autism Phenotype	ASD (95% CI)	NDD (95% CI)	TD (95% CI)
BAP	53.4% (43.3%-63.3%)	21.1% (11.4%-33.8%)	15.8% (9.5%-24.2%)
MAP	26.2% (18.0%-35.8%)	1.7% (0.04%-9.4%)	5.6% (2.0%-11.8%)
NAP	5.8% (2.2%-12.2%)	0%	0%

Note. ASD = Autism Spectrum Disorder; NDD = Neurodevelopmental Disorders; TD = Typically Developing; CI = Confidence Interval; BAP = Broader Autism Phenotype; MAP = Medium Autism Phenotype; NAP = Narrow Autism Phenotype.

The BAP prevalence for the ASD group (53.4% [95% CI: 43.3%-63.3%]) was higher than the other groups, and so was that for MAP (26.2% [95% CI: 18.0%-35.8%]) and NAP prevalence (5.8% [95% CI: 2.2%-12.2%]).

7.4. Discussion

To date, no studies have been conducted in SSA on the validity of the AQ. This study examined the psychometric properties of the Kiswahili version of the AQ as well as the distribution of scores in a sample of parents of children with a confirmed diagnosis of ASD, parents of children with a known NDD and parents of typically developing children in Dar-es-Salaam, Tanzania. After careful translation of the AQ, the full scale indicates strong internal consistency although caution has to be applied when interpreting subscale scores due to low reliability in several instances.
The prevalence of BAP, MAP and NAP was greater in children with ASD than in those with NDD and TD.

7.4.1. Discriminant validity of the AQ

In order to examine the discriminant validity of the AQ, we compared the median total scores and median scores on all five subscales between ASD and TD groups and ASD and NDD groups as well as across all groups. Our results indicate that the ASD group scored significantly higher than both TD and NDD groups on the total score and all five subscales, implying that the AQ scores discriminated effectively between parents of children with ASD from parents of children with other NDD and parents of children of typically developing children demonstrating that the AQ has good discriminant validity. This is in line with previous research comparing AQ scores of parents with children with ASD and parents of typically developing children (Zhang et al., 2016; Kose et al., 2013; Ruta et al., 2012; Mohammadi et al., 2012; Wheelwright et al., 2010; Bishop et al., 2004a). To date, there is only one study that did not find any significant difference between the parents of children with ASD and control parents (Scheeren & Stauder, 2008), perhaps because their sample size was relatively small.

Although previous studies using the AQ have found sex differences in healthy adults (Hoekstra et. al, 2008; Baron-Cohen et al., 2001; Wakabayashi et al., 2006) it is necessary to determine whether the sex differences play a part in the expression of the BAP phenotype in parents. In this study, we found mothers from the ASD group scored significantly higher than mothers in the TD and NDD groups on the total score and all five subscales of the AQ. When comparing scores for the fathers in the ASD versus TD comparisons, the only significant difference was for the attention to detail subscale. In the ASD versus NDD comparisons, there was a significant difference for fathers on the total score and all subscales except for the imagination subscale. These findings are somewhat atypical from the AQ literature reporting either no difference or significantly lower scores for mothers of children with ASD compared to mothers of typically developing children (e.g. Lau et al., 2013; Scheeren & Stauder,

2008) and significantly higher scores for fathers of children with ASD compared to fathers of typically developing children in particular in the social skills and communication subscales (e.g. Bishop et al., 2004a). This could be attributed to the notion that fathers of children with ASD in our sample may have been more knowledgeable about the heritability and behaviour patterns of ASD, avoiding the label of being autistic due to the stigma attached and therefore under-reporting autistic features of themselves. This could also be because few fathers participated in this study.

7.4.2. Reliability of the AQ

The reliability coefficient alpha for the whole group for all items (Cronbach's $\alpha = 0.84$) was good and comparable to the Chinese cross-cultural validation for use in Taiwan (Lau et. al, 2013), however, their sample did not include a third group of parents of children with a known NDD. However, our findings for all five subscales (Cronbach's $\alpha = 0.45 – 0.57$) reveal much lower coefficient alphas than that reported by Lau et al. (Cronbach's $\alpha = 0.54 – 0.88$), perhaps because the sample size in this study was much smaller even though we included three groups of parents. The coefficient alphas for the individual groups for all items and the five subscales were much lower, perhaps also due to smaller sample sizes. For instance, Zhang et al. (2008) documented higher correlation coefficient (Cronbach's $\alpha = 0.817$) for all items in their larger ASD sample.

7.4.3. Factorial analysis of the AQ

The factorial analysis of the AQ in this setting needs further evaluation in future studies as many items didn't reach the cut-off of a standardized coefficient of 0.30 nor could they be categorized into a conceptual or meaningful subscale. This could suggest that the information gained about the interdependencies between observed items cannot be used to reduce the set of variables into independent latent factors. Therefore, it is possible to argue that the items possess more unique variance (that is specific to individual items) than common variance that is usually shared across highly correlated items. This could be a result of the small sample size in our study and perhaps the structure of the AQ is less defined in our context, and so a unidimensional structure can be used. For instance, Lau et al. (2013) examined the psychometric properties of the Chinese version of the AQ using a much larger sample of parents of children with ASD and parents of TD children in Taiwan, found a 35 item 5-factor model with acceptable fit indices.

7.4.4. Proportion of BAP, MAP and NAP

The prevalence of BAP in parents of children with ASD (53.4%) was higher than for parents with either children with NDD (21.1%) or developing typically (15.8%), suggesting these BAP phenotypes are particularly characteristic of ASD in our settings. Similar to BAP, there was a preponderance of MAP and NAP in parents of children with ASD than those with NDD or TD, supporting that this is not a chance, but biological/clinically meaningful occurrence. These prevalence estimates for ASD

are comparable to previous studies from HIC (ASD, 13.8% - 43.5%; TD, 8.2% - 22.0%) (Bishop et al., 2004a; Bishop et al., 2004b; Wheelwright et al., 2010; Ruta et al., 2012; Berthoz et al., 2013) and to a few others in LAMIC (ASD, 25.2% - 50.0%; TD, 8.1% - 11.8%) (Mohammadi et al., 2012; Bora et al., 2017). The prevalence was lowest in parents of TD children as expected, and could suggest a lowered familial clustering of genetic or environmental risk factors in these families compared to those of ASD families.

7.4.5. Strengths and limitations

To the best of my knowledge, this is the first study to validate a BAP measure in SSA. The AQ was carefully translated into the local language Kiswahili. The inclusion of parents of children with a known NDD made the study more robust. It is, however, important to note that the NDD group comprised of heterogeneous conditions. This is especially relevant since conditions such as Down's syndrome has a distinct genetic aetiology that is not shared with the parents, while ADHD and learning disability are often idiopathic and likely influenced by common genetic factors and by a range of possible environmental factors. However, our sample size was relatively small; a larger sample size would allow for more comprehensive validity analysis with CFA and PCA and address some weaknesses in the internal consistencies. Other factors other than small sample sizes could also contribute to poor internal consistencies and poor factorial structure. For instance parents may have found it difficult to interpret some items (which reflects error variance that is a subset of unique variance) and maybe the structure of the AQ is less defined in our context (may represent specific variance that is a subset of unique variance). It is also important to note that the AQ was not adapted in terms of item content, and this could have introduced possible issues with cultural relevance of some of the AQ items. Children living in urban areas have more access to these special schools and facilities and thus parents in rural areas were not included in this study. Furthermore, poorer and less literate parents in urban areas may not bring their children to these schools.

7.4.6. Conclusions

The findings from this study suggest the Kiswahili version of the AQ has average to acceptable psychometric properties highlighting reasonable cross-cultural stability of autistic traits in this population. Further studies of BAP can include the concepts of the MAP and NAP and could be more specific in explaining variance for genetic studies since they are based on a more stringent cut-off threshold. Future studies are warranted to further investigate the BAP in other close relatives and to relate AQ scores to molecular genetic differences. These BAP estimates should be replicated in studies from other settings in Africa.

Chapter 8

Synthesized discussion

8.1. Background

The aim of this thesis was to explore the situation, features and presentation of Autism Spectrum Disorders (ASD) in Dar-es-Salaam, Tanzania, comparing children with ASD with other neurodevelopmental disorders (NDD) that are not ASD, as well as typically developing children (TD). In particular, describing the knowledge and lived experiences of caregivers of children with ASD and community stakeholders, developing and adapting tools for the identification of children with ASD, identifying the risk factors for ASD and characterizing the Broader Autism Phenotype (BAP) in parents of children with ASD in this population.

There are relatively little data on the prevalence of ASD in sub-Saharan Africa (SSA) and the clinical presentation of ASD in this region is not fully understood (Ruparelia et. al, 2016; Elsabbagh et al., 2012). There is limited knowledge on lived experiences and challenges of children with ASD throughout Tanzania (Manji & Hogan, 2013). Additionally, recent epidemiologic research has highlighted the prenatal and neonatal period as the most vulnerable period when most environmental risk factors are associated with ASD (Gardener et al., 2009; Gardener et al., 2011). However, there are very few epidemiological studies of ASD conducted in SSA where there is a high incidence of risk factors such as pregnancy complications, adverse perinatal events, and infections with a propensity for the central nervous system. Furthermore, cross-cultural findings from BAP studies indicate that patterns are stable and independent of cultural influences, pointing to some biological basis for manifestations of these phenotypes.

This chapter is a synthesized discussion of the results of this PhD thesis. Initially, I conducted a systematic review to synthesize available evidence of behavioral, cognitive and psychiatric profiles of the BAP in unaffected biological parents of ASD probands, as well as NDD and TD probands. I assimilated the evidence from 60 studies that met *a priori* search criteria from scientific databases. Thereafter, I conducted a qualitative study to investigate the knowledge and lived experiences of caregivers of children with ASD (n = 14) and key community informants (n = 37). Additionally, I conducted a case-control study in 284 children living in Dar-es-Salaam, Tanzania including children with ASD (n = 108), children with other neurodevelopmental disorders (NDD) that are not ASD (n = 60) and typically developing children (TD) (n = 116), to clinically validate ASD screening tools (e.g. the Social Communication Questionnaire (SCQ)) and to identify potential risk factors for ASD in this

population, comparing between those unique to ASD and those other NDD that are not ASD. This followed a final case-control study assessing the BAP traits of parents of children in my case-control studies mentioned above (n = 267) which included parents of children with ASD (n = 103), parents of children with other NDD (n = 57) and parents of TD children (n = 107).

8.2. Overview and interpretation of findings

8.2.1. Systematic review

The findings from the Systematic Review identify mild social/communication deficits, rigid/aloof personality traits, and pragmatic language difficulties as the most important socio-behavioural endophenotype traits. The existence of deficits in the cognitive domains and depressed mood / anxiety can also be useful markers for familial vulnerability clustering of ASD.

Findings from the socio-behavioural domain are in concordance with previous reviews (Cruz et al., 2013; Gerdts & Bernier, 2011; Sucksmith et al., 2011) indicating that mild social/communication deficits, rigid/aloof personality traits, and pragmatic language difficulties may be the most useful socio-behavioural candidate endophenotype traits as they meet all the established criteria for the identification of useful endophenotypes (Gottesman & Gould, 2003). Cruz et al (2013) for instance, also found parents of ASD probands to have more difficulties in interpersonal relationships and in pragmatic language use as well as more rigidity traits.

Findings from the cognitive domain reveal limited evidence for the role of intellectual functioning as an endophenotype for ASD with no clear significance. Although several measures assessed structural language abilities, phonological awareness, social cognition, executive functioning and visual processing, findings were variable suggesting these areas of cognition warrant further research because their assessments require standardised tools and requires specialized training. A number of studies documented higher frequency of depression, anxiety and social phobia/social phobic anxiety in parents of children with ASD compared to normative and clinical samples, with depression and anxiety being more prevalent in mothers of children with ASD, relative to a normative comparison group. Although it can be argued that having a child with a disability can affect mood and anxiety levels, many studies indicate an onset of these conditions before the birth of the child with ASD, suggesting these BAP symptoms were not directly related to caring for a child with a disability. Findings from our review revealed moderate to high magnitude of effect of BAP symptoms; thus, depression and anxiety may have a genetic link with ASD, supporting constellation of psychiatric disorders in parents of children with ASD (Yirmiya & Shaked, 2005).

Subclinical autistic traits aggregate in families with multiple incidence of ASD (MPX) and occur less frequently in families with single incidence of ASD (SPX) (Bernier et al., 2012; Losh et al., 2008),

which is consistent with findings of increased de novo, non-inherited and spontaneous genetic events in SPX families (e.g., Sebat et al 2007). Findings from my review also indicate few sex differences, indicating a male bias (Ruser et al., 2007; Schwichtenberg et al., 2010; De la Marche et al., 2012), perhaps related to their heightened sensitivity for being associated with raising children with neurobehavioural disorders. However, despite this and the clear sex bias in ASD, many studies do not suggest sex differences for most BAP features (e.g. Klusek et al., 2014). Furthermore, my findings indicate that the majority of the studies reviewed were conducted in Western countries, which are not representative of many settings in SSA.

However, findings from my review should be interpreted with caution because of the small number of studies in such heterogeneously broad domains and several methodological limitations. For instance, different tools were used to determine BAP and cut-offs scores were arbitrary. This complicated the pooling of overall prevalence of BAP across the eligible studies, because of the aforementioned sources of heterogeneity.

8.2.2. Awareness and lived experiences of ASD

Findings from the qualitative study indicate consistent sub-themes emerging within the areas of concern. These emerging sub-themes were useful in underlining knowledge and awareness in the identification and presentation of ASD and its' perceived causes, and the challenges experienced by caregivers. The results show that caregivers and special needs educators have gained moderate knowledge of ASD, perhaps because they were recruited from schools that catered specifically for children with ASD. In comparison, however, other key community informants such as parents and mainstream teachers had relatively limited knowledge of ASD consistent with general lack of awareness, understanding and acceptance of ASD within the communities in Africa. This could be attributed to the high levels of stigma associated with many neurobehavioural impairments in Africa previously recognized (Eisegbe et al., 2015; Igwe et al., 2011; Bakare et al., 2009a; Bakare et al., 2008).

As in earlier work (Belhadj et al., 2006; Mankoski et al., 2006; Bakare & Munir, 2011b), nonverbal characteristics of children with ASD seemed to be overemphasized, perhaps an indicator of poor diagnostic approaches which contributed to only the severe cases being known. Many parents of typically developing children and mainstream teachers were unable to distinguish ASD symptomatology from other intellectual disorders and behavioral/developmental problems. This could reflect the lack of awareness of ASD within the community.

Most of the participants perceived biomedical reasons such as hereditary, brain abnormalities and infectious diseases as the cause of ASD, which is similar to clinical observations in Tanzania (2006).

Only parents with TD children in our study attributed ASD etiology to supernatural causes, which is inconsistent with community perceptions from other research in the region (Bakare et al., 2009b; Gona et al., 2015), highlighting the need for public engagement to raise awareness within the community.

My findings reveal that many of the challenges raised in this study resonate with findings in the existing literature of ASD from other developing countries (e.g. Desai et al., 2012; Gona et al., 2016; Tekola et al., 2016). Participants emphasized and acknowledged the low level awareness of ASD amongst the healthcare practitioners and the lack of appropriate diagnostic tools. These Tanzanian data concur with previous findings from several studies conducted in Nigeria revealing a low- level of knowledge and awareness about ASD in Africa (Eisegbe et al., 2015; Igwe et al., 2011; Bakare et al., 2009a; Bakare et al., 2008).

8.2.3. Psychometric properties of the SCQ

My findings reveal good discriminant validity since the ASD group scored significantly higher than both TD and NDD groups on the total score and all three domains, similar to previous studies of English SCQ (Chandler et al., 2007; Charman et al., 2007), and other languages (German SCQ - Bölte et. al., 2008b; Portuguese SCQ – Sato et al., 2009; Chinese SCQ - Gau et al., 2011; Turkish SCQ - Avcil et al., 2015; Greek SCQ - Zarokanellou et al., 2017). I did not find any sex differences for any group for the SCQ total score, social interaction domain and communication domain, although some studies from elsewhere did report particularly higher scores for females (McLennan et al., 1993; Lord et al., 1982; Gillberg & Coleman, 2000). These findings also revealed that there were no significant differences between mother and father respondents and mother and caregiver respondents for all group comparisons.

The results indicate acceptable to excellent reliability coefficients (Cronbach's $\alpha = 0.65\text{-}0.93$) which are higher than other cross-cultural validation studies of the SCQ total scores (e.g. Sato et al., 2009; Avcil et al., 2015) and similar for the domain scores (Gau et al., 2011). Additionally, our findings reveal excellent test-retest reliability (ICC = 0.972 – 0.998) for the SCQ total scores and its three domains, with the before and after scores significantly correlated ($r = 0.964 – 0.995$; $p < 0.001$). Furthermore, the results support the use of a 2-factor model of combined social interaction and communication and repetitive behaviours as recommended by DSM-5 criteria since all fit indices reached acceptable levels. All item loadings were above the cut-off for standardized coefficients of 0.3 except one (item 13) when the responses for items 2 to 7 were replaced with a score of 1 in order to include all nonverbal children.

The ROC curve analyses suggested excellent predictive ability as scoring above the recommended cut-off of 15 for ASD was highly indicative that the child had ASD. Results yielded sensitivity of 100% and specificity of 100% (AUC = 1) when discriminating ASD with TD samples and sensitivity remained at 100% when discriminating ASD with NDD (AUC= 0.85) and for whole group (AUC= 0.95) but specificity decreased to 70.0% and 89.8% respectively. Our findings are better than that reported in the initial validation study of the SCQ (Berument et al., 1999) when discriminating ASD with non-ASD, as well as when discriminating between ASD and ID, and similar in terms of higher sensitivity estimates than specificity estimates.

8.2.4. Risk factors associated with ASD

A number of risk factors were assessed for their association with ASD, in particular, socio-demographic, prenatal, perinatal, neonatal and postnatal factors. Some risk factors were unique to ASD, but many are shared with other NDD disorders.

ASD vs. TD summary of findings

Socio-demographic factors such as the child's male sex were positively associated with an increased risk of ASD when compared to TD groups. Our results are consistent with the theory that ASD affects males four times more than females (Fombonne, 2005) as several theories have suggested the involvement of the sex chromosome in the aetiology of ASD, the role of hormonal influences *in utero* (Baron-Cohen et al., 2011) and phenotypic diversity in brain structure (Ecker et al., 2017). This trend was also observed in neurological disorders in rural parts of Africa (Kariuki et al., 2015).
Advanced parental age at delivery was associated with an increased risk of ASD, but there is an inconsistent association of advanced parental age with ASD reported from several studies. Wu et al (2017) found that maternal and paternal age increases the risk of ASD in the offspring by up to 21%. I found that mother's age at birth has more impact on development of ASD than father's age at delivery in this setting. An association of ASD with increasing difference in age between parents is reported (Sandin et al., 2016), but did not reach multivariable statistical significance in my study. Genetic factors are thought to determine the association between parental age and risk for ASD (Sandin et al., 2016).

The findings indicate an increased risk of ASD associated with adverse perinatal events. Previous studies have reported significant associations of prenatal risk factors such as gestational hypertension and maternal bleeding with ASD (e.g. Gardener et al., 2009; Gardener et al, 2011). Perinatal factors have also been highlighted in a recent review of neurodevelopmental disorders, including ASD (Bitta et al., 2017). The lack of independent association of preterm birth and infections during pregnancy with ASD in our study may be due to poor health records.

Of the postnatal factors risk factors investigated in this study, malaria before the age of three was associated with the highest independent risk of ASD in the multivariable analysis, being frequently more common among the ASD group (31%) than the TD group (4%). This is in line with a case-series study from Tanzania reporting encephalitis as a potential cause for ASD (Mankoski et al., 2006). Malaria can cause diffuse brain damage, but the damage is more prominent in the posterior-temporal regions of the brain that are supplied by middle and posterior cerebral arteries, subsequently causing features similar to those of impaired communication in ASD, in particular speech and language (Carter et al., 2006). The strong significant association of ASD with malaria may have attenuated the independent association of seizures with ASD in the multivariable analysis, since most seizures in parasitaemic children are attributable to malaria (Kariuki et al., 2011). This could support the double hit hypothesis in which the vulnerability of ASD may start during embryogenesis, but will not manifest phenotypically until another adverse event / risk factor happens sometime later, for instance, exposure to brain infections (Wiśniowiecka-Kowalnik & Nowakowska, 2019). It is plausible that exposure to malaria before age 3 years, activates non-heritable gene mutations, that adds to pre-existing heritable gene mutations, in a dose dependent manner, enhancing penetrance of ASD phenotype (e.g. Girrirajan & Eichler, 2010). Late onset of ASD would be due to either delayed onset of the second non-heritable mutation or onset of both non-heritable mutations that are required for expression of ASD phenotype. Given the enormous burden of severe malaria with neurological involvement in many rural parts of Africa (Idro et al., 2007), studies on ASD following severe malaria are urgently needed to inform preventative strategies. It is possible that the impact of neonatal factors such as jaundice (which did not reach multivariate significance) on neurodevelopmental disorders, including ASD, is important on long-term follow-ups (Mwaniki et al., 2012), which should be examined in prospective cohort studies.

ASD vs. NDD summary of findings

Although several factors reached significance in the univariable analysis, only fathers being older than mother and malaria under 3 years remained significant in the multivariable analysis. As suggested above, follow-up studies of malaria as a risk factor for ASD should be urgently set-up in endemic area, to quantify the burden of ASD attributable to severe malaria. Cultural ways e.g. polygamy may explain fathering children in advanced age, and the role of a father's age on ASD may be mediated through spontaneous mutations.

The lack of significance in the ASD vs. NDD analysis may suggest that these risk factors are shared between ASD and other NDD. This hypothesis was supported by identification of adverse perinatal events as independent risk factors for NDD when compared to TD; similar risk factors were found for ASD when compared to TD. Hypothetically, interventions to control of such risk factors would not only reduce the burden of ASD but also that for other NDD. These factors identified in NDD vs. TD

but not in ASD vs. TD (e.g. seizures and head injury) cause direct brain damage, suggesting NDD have a symptomatic basis that may have a poorer prognosis as shown recently (Abuga et al., 2019). It is important to note that the large confidence intervals (CI) in our results may mean that there were few observations in some groups.

8.2.5. Psychometric properties of the AQ

The findings indicate that the AQ has good discriminant validity as the AQ scores discriminated effectively between parents of children with ASD from parents of children with other NDD and parents of children of typically developing children. This is in line with previous research comparing AQ scores of parents with children with ASD and parents of typically developing children (Zhang et al., 2016; Köse et al., 2013; Ruta et al., 2012; Mohammadi et al., 2012; Wheelwright et al., 2010; Bishop et al., 2004a).

Mothers from the ASD group scored significantly higher than mothers in the TD and NDD groups on the total score and all five subscales of the AQ. When comparing scores for the fathers in the ASD versus TD comparisons, the only significant difference was for the attention to detail subscale. In the ASD versus NDD comparisons, there was a significant difference for fathers on the total score and all subscales except for the imagination subscale. These findings are somewhat atypical from the AQ literature reporting either no difference or significantly lower scores for mothers of children with ASD compared to mothers of typically developing children (e.g. Lau et al., 2013; Scheeren & Stauder, 2008) and significantly higher scores for fathers of children with ASD compared to fathers of typically developing children in particular in the social skills and communication subscales (e.g. Bishop et al., 2004a). It is possible that fathers of children with ASD in our sample may have been more aware about the problematic behaviours patterns of ASD, avoiding the label of being autistic due to the stigma attached and therefore under-reporting autistic features of themselves.

The whole group Cronbach's coefficient alpha was acceptable (Cronbach's $\alpha = 0.84$) and comparable to the Chinese cross-cultural validation for use in Taiwan (Lau et. al, 2013), however, their sample did not include a third group of parents of children with a known NDD, which may share genetic, clinical and social profiles with ASD. These findings show that the items are homogeneously assessing ASD constructs. Lower coefficient alphas were found for all five subscales than that reported by Lau et al. (2013), perhaps because the sample size in this study was much smaller even though we included three groups of parents. The coefficient alphas for the individual groups for all items and the five subscales were much lower, as would be expected with smaller sample sizes.

This study also found higher prevalence of BAP in parents of children with ASD (53%) than those with either NDD (21%) or developing typically (16%), implying familiar clustering of these

neurodevelopmental disorders, and that there should be targeted interventions for all family members. These BAP estimates for ASD are comparable to previous studies from HIC (Bishop et al., 2004a; Bishop et al., 2004b; Wheelwright et al., 2010; Ruta et al., 2012; Taylor et al., 2013; Berthoz et al., 2013) and few in LAMIC (Mohammadi et al., 2012; Bora et al., 2017). The prevalence was lowest in parents of TD children as expected, and could suggest a lowered familial clustering in these families compared to ASD families. More research is warranted to determine the prevalence of BAP and its utility in guiding interventions in other LAMIC and in particular SSA.

8.3. Public health significance of the findings

The findings from this study have several important implications. There is need to describe the endophenotypes of parents of children with ASD to help develop better measures to detect subtle subclinical autistic traits in the BAP in African settings. These BAP findings would justify tailored interventions to the entire family of children with ASD and possibly other NDD, as well as support the basis for inclusion of trios (mother, father and child triad) in genetic studies of ASD and related NDD. This study identifies the gap in knowledge in the general community highlighting the need for sustained awareness and sensitization programs to improve understanding, acceptance and management of ASD in African settings. The adaptation and validation of the SCQ lends support for the clinical utility of the SCQ as a first level screening measure for ASD among Tanzanian children and can inform specialized care and initiation/evaluation of intervention thereby reducing the diagnostic and treatment gaps. This study also identifies postnatal malaria (before age 3 years) as a significant independent risk factor unique to ASD. This findings can inform policy on preventative and therapeutic measures such as improving coverage and utilization of treated bed nets, development of new and effective vaccines for malaria (as only RTS,S/AS01 has reached implementation) and acceleration of discovery of new anti-malarial medicines. Some risk factors in particular adverse perinatal events are shared between ASD and other NDD, and therefore interventions to control such risk factors would not only reduce the burden of ASD, but also that for other related NDD. The higher BAP prevalence in ASD than other NDDs and TD justifies the need to invest in the investigation of the genetic basis of ASD, and supports intervention programs to extend and include caregivers and families of children with ASD. Parental BAP may be an important tool for analysing sources of heterogeneity in ASD etiology (estimating variability explained by either genetic or environmental conditions) and for informing the development of parent-mediated ASD interventions such as those aimed at improving a child's disruptive behaviours and communication.

8.4. Study strengths and limitations

This study has some strengths. The ASD screening tool (SCQ) was standardized and underwent adaptation and validation to the local population before its application in this study. Furthermore, all children were directly observed for their behaviour and language using the internationally recognised

Autism Diagnostic Observation Schedule (ADOS-2) and complemented by the DSM-5 criteria which aided in the clinical confirmation of the diagnosis of the ASD sample. Another strength is that this clinical consensus process was iteratively corroborated by independent expert rating. The inclusion of the NDD and TD comparison groups and using both verbal and nonverbal children made the study more robust, lending additional support for the utility (in terms of reliability and validity) of the SCQ as a screening measure in clinical practice. The inclusion of the NDD group also allowed us to identify risk factors unique to ASD as well those shared by these disorders. Additionally, a large number of risk factors were investigated, which were pragmatically selected by a thorough search of the literature, and included risk factors that have biological plausibility in the pathophysiological and pathogenetic processes of ASD and NDD. A robust statistical analysis approach was used (including testing for departure from linear trend for ordinal variables and examining goodness of fit of the models) and we accounted for potential confounders in the multivariable models. Lastly, the BAP questionnaire (AQ) was carefully translated and adapted into the local language Kiswahili, and the inclusion of parents of children with a known NDD aided in the development of cut-offs for the BAP scores.

There are several potential limitations in this study. This was not a community-based study and therefore children with ASD and NDD recruited from care centres may not be representative of the general population due to Berkson's bias, but this will only be important in follow-up studies of children with these disorders. It is possible that some children may be missed because they did not attend the facilities we approached for identification of study participants. Children living in urban areas have more access to these special schools and facilities and thus parents in rural areas were not included in this study. Furthermore, poorer and less literate parents in urban areas may not bring their children to these schools. Furthermore, blinding of assessors was not fully possible, and this may have introduced bias as assessors were aware of the status of each child which may have influenced the way questions were asked as well as expectations of their responses. Although our sample size was sufficient to allow for comprehensive reliability and validity analysis, slightly larger samples might have yielded more power to detect more significant associations in the multivariable analysis of risk factors. The TD group were matched by level of expressive language and this may have caused age selection bias in the identification of risk factors that are time dependent. These differences were inevitable because delayed diagnosis and lack of expressive language is common in ASD, which would result in older children seeking care. However, the inclusion of the NDD comparison group may have helped to deal with this limitation since the age of NDD children were similar to or slightly older than that of ASD children. It is, however, important to note that the NDD group comprised of heterogeneous conditions. This is especially relevant since conditions such as Down's syndrome has a distinct genetic aetiology that is not shared with the parents, while ADHD and learning disability are often idiopathic and likely influenced by common genetic factors and by a range of possible

environmental factors. Cultural beliefs in this region may be associated with stigma and therefore the inevitable under-reporting of ASD or BAP symptoms. Recall and reporting bias of retrospective self-reporting answers by parents/caregivers might have occurred, resulting in insignificant associations for some factors.

8.5. Directions for future research

There is a strong need for lobbying for funding and investment in the development of assessment tools, and guidelines for preventative and management interventions for children with ASD and possibly other related NDD in Africa. Further studies are needed to understand the pathogenesis of ASD, for instance genomics studies, identification of biological and neurophysiological biomarkers and prospective follow up studies of children with ASD, to examine long-term consequences. Further studies in this population can focus on refining and characterizing the phenotype of ASD in Africa, comparing with other settings worldwide. There is need to further investigate the BAP in other close relatives and to relate to molecular genetic differences as well as examining the neuroanatomical and neurofunctional correlates of the BAP, comparing with that of children with ASD. Further studies are also needed to understand the mechanisms for associations between communicable diseases such as malaria and ASD or other NDD, and on the interaction between genetic and environmental factors specifically associated with these disorders. Furthermore, future studies need to examine the mechanisms through which advanced age in fathers is associated with spontaneous mutations for ASD in the offspring, but it is possible advanced age increases the probability of transmitting more ASD-penetrant mutations to the offspring. Finally, there is an urgent need for raising public awareness about the causes, risk factors and nature of ASD in SSA to improve understanding, acceptance and provision of care for children with ASD in Tanzania and other similar settings in SSA.

8.6. Conclusions

In summary, the systematic review increases our understanding of the BAP profile in parents of probands with ASD, allowing appreciation of potential varying underlying genetic mechanisms in ASD, and need for tailored interventions for both children with ASD and their close relatives. Evidence from the systematic review pointed towards mild social/communication deficits, rigid/aloof personality traits, and pragmatic language difficulties as the most useful social behavioural candidate endophenotype traits, but more research is required to clarify the cognitive domains of BAP since deficits in this domain, like socio-behavioural ones, does suggest familial vulnerability for ASD. Furthermore, increased depressed mood and anxiety can also be useful markers of vulnerability for ASD. The Kiswahili adaptation of the AQ provides preliminary evidence that the prevalence of BAP is relatively high particularly in parents of probands with ASD in SSA, and warrants further investigations in future studies.

Our findings also indicate consistent emerging sub-themes with regards to knowledge of the identification and presentation of ASD and its' perceived causes, and the challenges experienced by caregivers, that should be addressed through future sensitization programs. These awareness programs should take into consideration the recommendations that were raised by the study participants such as increasing investment in facilities and appropriate diagnostic tools. After careful translation and adaptation of the SCQ and AQ, our findings indicate that the SCQ is a reliable and valid screening measure of ASD symptoms in this population and the AQ has fairly acceptable psychometric properties which may highlight reasonable cross-cultural stability of autistic traits in this population. Nonetheless, validation and adaptation of other ASD assessment and BAP tools should be encouraged through collaborative efforts between researchers, stakeholders and policy makers.

Additionally, this study identified postnatal malaria (before age 3 years) and father being older than mother as a significant independent risk factor unique to ASD, both of which render credibility to the double hit hypothesis. Other factors such as seizures disorders and head injury were more important to other NDD that were not ASD, implying symptomatic pathology is more important in the former disorders. Our results highlight the importance of ASD research and its association with malaria in SSA populations since in this region infectious disease like malaria (Mankoski et al., 2006) which are associated with central nervous system complications (Carter et al., 2003) continue to be a major public health concern. Further research is warranted to understand the pathophysiological and pathogenetic mechanisms for development of ASD and other related NDD in this and other settings of SSA.

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Appendix 1: Published Systematic Review

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Review Article

Investigating the Evidence of Behavioral, Cognitive, and Psychiatric Endophenotypes in Autism: A Systematic Review

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Substantial evidence indicates that parents of autistic individuals often display milder forms of autistic traits referred to as the broader autism phenotype (BAP). To determine if discrete endophenotypes of autism can be identified, we reviewed the literature to assess the evidence of behavioral, cognitive, and psychiatric profiles of the BAP. A systematic review was conducted using EMBASE, MEDLINE, PsycINFO, PsycEXTRA, and Global Health. Sixty papers met our inclusion criteria and results are discussed according to the proportion of studies that yield significant deficits per domain. The behavioral, cognitive, and psychiatric endophenotypes in parents of autistic probands are still not clarified; however, evidence suggests mild social/communication deficits, rigid/aloof personality traits, and pragmatic language difficulties as the most useful sociobehavioral candidate endophenotype traits. The existence of deficits in the cognitive domain does suggest familial vulnerability for autism. Furthermore, increased depressed mood and anxiety can also be useful markers; however, findings should be interpreted with caution because of the small number of studies in such heterogeneously broad domains and several methodological limitations.

1. Introduction

Autism is a life-long complex neurodevelopmental disorder which has heterogeneous clinical manifestations and multifactorial aetiology. It is characterized by impairments in social interaction and communication and restricted patterns of behavior, interests, and activities, occurring within the first 3 years of life [1].

The heritability of autism is estimated to be from 70% to 90% [2, 3]. Research suggests the risk of developing autism in siblings of individuals with autism is between 10 and 20%, considerably higher than when compared to about 1% for siblings of typically developing children [4, 5]. These data suggest a strong genetic basis, despite the clinical heterogeneity. Since numerous studies using linkage or candidate gene approaches have not discovered a single genetic locus of major effect, it is thought that the definition of the endophenotypes may provide insights into the biological basis of this condition.

Studies have provided substantial evidence indicating that first-degree relatives of autistic individuals often display milder forms of autistic traits referred to as the broader autism phenotype (BAP) [6]. This milder expression includes a set of behavioral and cognitive characteristics that reflect the phenotypic expression that is qualitatively similar in unaffected relatives of autistic individuals. For instance, mild challenges in social cognition in using facial cues and other features to determine mental states have been noted in parents of children with autism [7]. Additional studies report similar differences in emotion processing abilities, particularly emotion identification [8, 9] and phonological processing [10]. Research that includes such quantitative measures of autistic traits and underlying mechanisms responsible for such features in first-degree relatives is fundamental in studying the genetic basis of autism as it can help to identify which characteristics aggregate in family members and are thus likely to be potential endophenotypes for autism at the neurocognitive level.

Endophenotypes are heritable markers associated with a given condition and can provide insight into its etiology. Gottesman and Gould [11] offered a set of criteria for

identification of useful endophenotypes suggesting that deficits must be (a) associated with illness in the population; (b) heritable;
(c) state-independent (manifesting in an individual whether or not illness is active); (d) cosegregated with the condition within families; and (e) also found in unaffected relatives at a higher prevalence than in the general population. The study of endophenotypes is particularly useful in understanding developmental disorders such as autism that are diagnosed on clinical features but are of neurobiological origin and can aid to better identify and characterize the nature of the genetic contributions to this complex disorder.

Several researchers have reviewed the BAP traits in first-degree relatives of autistic probands [12–14]. Some reviews include studies that have examined the BAP in parents and siblings of autistic probands. Although features of the autism phenotype have been found in the "at risk" infant sibling studies, no clear distinction can be made to determine whether they are the characteristics of the BAP or whether the infant siblings may later receive an autism diagnosis. Thus, we limited this review process to parents only by employing a systematic approach to focus on the sociobehavioral, cognitive and psychiatric profiles of the broader autism phenotype to determine candidate endophenotypic traits for autism.

We conducted a systematic review of the literature to assess the evidence of behavioral, cognitive, and psychiatric endophenotypes of autism in parents. The aim of this review was to ascertain whether parents of probands with autism have higher prevalence of various components of the BAP and more specifically of behavioral, cognitive, and other psychiatric conditions. The questions addressed were as follows:

(1) What are the behavioral, cognitive, and other psychiatric (focusing primarily on depression and anxiety) endophenotypes of autism as manifested through the broader autism phenotype in biological parents of autistic probands?

(2) What are the tools used to measure these endophenotypes and the magnitude of effect?

(3) Do patterns evident in endophenotypes of autism provide insight into cultural and geographical differences?

2. Review Methods

2.1. Data Sources and Search Strategy. A comprehensive literature search was performed to collate evidence of behavioral, cognitive, and psychiatric endophenotypes in autism. Literature searches for published and grey literature were subsequently carried out using 5 databases, EMBASE, MEDLINE, PsycINFO, PsycEXTRA, and Global Health, from inception to August 2014 without language restriction. The strategy was developed by breaking down the review questions into elemental facets according to the recommendations of the National Health Service Centre for Reviews and Disseminations [15]. These facets included exposure, outcome, population, publication language, and keywords (Table 1). The initial search strategy used the words "autis* AND endophenotyp* OR phenotyp*". These searches were further refined by the addition of the outcome terms and population ("parent* OR relative OR famil*"). The bibliographies of key references were later hand-searched to identify articles missed in the database search. Figure 1 illustrates our literature search strategy.

2.2. Data Selection Criteria. The titles and abstracts of papers identified were reviewed and the full versions of potential papers were read to decide on final selection. The inclusion criteria were

(1) original studies that employed a quantitative methodological approach to investigate behavioral, cognitive, and psychiatric (depression and anxiety) endophenotypes in biological parents,

(2) the fact that autistic proband (other conditions on the spectrum such as Asperger Syndrome, Pervasive Developmental Disorder, and Pervasive Developmental Disorder Not Otherwise Specified were also included) must have a clinically established diagnosis of autism (minimum DSM-III) and no concomitant medical conditions associated with autistic symptomatology and visual, auditory, and motor impairment such as Fragile X or Tuberous Sclerosis.

(3) Studies that carried out a comparison of endophenotypes between parents of individuals diagnosed with autism and unaffected adults, a normative parental control group, and/or a clinical parental control group.

We excluded any studies investigating the BAP in the general population, studies on genetics and autism, and studies examining the neuroanatomical and neurofunctional dimensions of the BAP. All single case studies, case series, book chapters, theoretical papers, review papers, unpublished dissertations/theses, and studies not published in English were excluded.

The final set of papers was restricted to those that quantitatively evaluated behavioral, cognitive, and psychiatric endophenotypes in biological parents of autistic probands.

2.3. Data Extraction. The author (KR) examined the titles, abstracts, and studies with study selection criteria. Data were organized into broad domains for each of the three categories: sociobehavioral, that is, direct assessment of BAP expression, other measures of personality and friendships, social interaction, repetitive/restrictive interests, and social and narrative language; cognitive, that is, intellectual functioning, structural language, social cognition, executive function, local visual processing (central coherence), and visual perception; other psychiatric conditions, specifically depression and anxiety.

Table 1: Description of search strategy.

Search element	EMBASE	MEDLINE	PsycINFO	PsycEXTRA	Global Health
Exposure	Thesaurus terms explored: Autis*				
Keywords	Endophenotyp* OR Phenotyp*				
Outcome	*Thesaurus terms explored* Behavior Language Social interaction Repetitive Restrictive Cognitive Executive function Central coherence Theory of mind Social cognition Visual Attention Depression anxiety	*Thesaurus terms explored* Behavior Language Social interaction Repetitive Restrictive Cognitive Executive function Central coherence Theory of mind Social cognition Visual Attention Depression anxiety	*Thesaurus terms explored* Behavior Language Social interaction Repetitive Restrictive Cognitive Executive function Central coherence Theory of mind Social cognition Visual Attention Depression anxiety	*Thesaurus terms explored* Behavior Language Social interaction Repetitive Restrictive Cognitive Executive function Central coherence Theory of mind Social cognition Visual Attention Depression anxiety	*Thesaurus terms explored* Behavior Language Social interaction Repetitive Restrictive Cognitive Executive function Central coherence Theory of mind Social cognition Visual Attention Depression anxiety
Population	Parent* OR Relative* OR Famil*				
Language	Any				

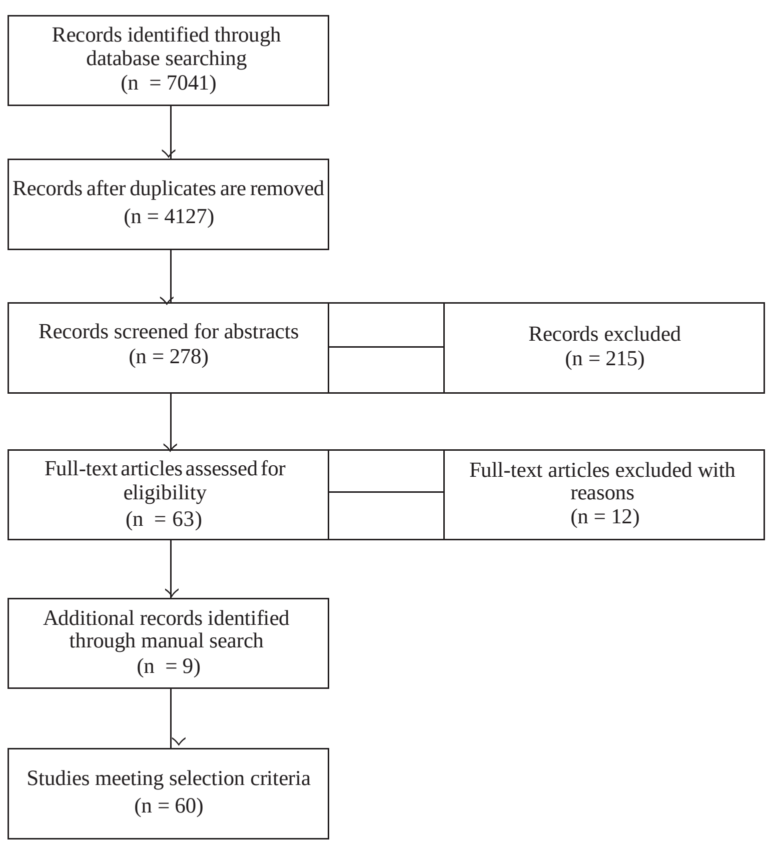

Figure 1: Flow chart of study selection.

2.4. Effect Sizes. The data extracted was based on heterogeneous measures and outcomes, so pooling the data in a meta- analysis was inappropriate. To compare the robustness of the measures used, for each behavioral, cognitive, and psychiatric variable of interest an effect size (ES) was computed from the data reported in each study. Cohen's effect size statistic (d) was calculated as the difference between the means of both groups divided by the pooled standard deviation. The following criteria were used to assess the magnitude of effect:
$d < 0.2$ (small), $d > 0.5$ (medium), and $d > 0.8$ (large) [16].

3. Results

3.1. Search Results. The initial electronic search identified 7,041 records, of which 4,127 records remained after duplicates were removed. 278 articles were eligible for full review after examination of titles and abstracts (Figure 1). After full text review, we excluded 12 articles for the following reasons: in 9 studies it was not possible to distinguish parent and sibling data when results were reported for combined first-degree relatives, and, in 3 studies, proband diagnosis was established using criteria prior to DSM-III. The search criteria, additional articles identified through manual search, and total numbers of articles meeting selection criteria are shown in Figure 1.

3.2. Results of Literature Extraction. Twenty-five of the 60 studies that fulfilled the inclusion criteria directly evaluated the BAP expression (including personality, social behavior, and pragmatic language features of the BAP). An additional 7 studies assessed other aspects within the sociobehavioral domain. Thirty-seven reports assessed the broad domain of cognitive functioning and seven studies investigated other psychiatric conditions. Twenty-seven of the studies were conducted in North America, 24 in Western Europe, 4 in the Middle East, and 3 in Western Pacific and 1 was conducted in South America and 1 used combined samples from North America, Western Europe, and Western Pacific. However, no studies were conducted in Asia or Africa. Index families included a total of 4,833 mothers and 3,065 fathers that took part across all studies reviewed (few studies did not specify sex breakdown). Studies varied greatly in their choice of comparison control group, with 26 studies using a nonclinical comparison group, 21 studies using a normative control sample, and 13 studies using a combined sample of clinical and nonclinical control groups. Thirteen studies evaluated the gradation of expression across family types using families with multiple incidence autism (MPX) and single incidence autism (SPX).

We summarized the results of the literature search according to different sociobehavioral, cognitive and psychiatric domains. For each domain we present the measures used within that domain and any significant differences found between index parents and parental controls, and so results are described in relation to proband diagnosis. All background measures used to establish BAP status without using a comparison group as well as control tasks are not reported under the specific criteria in this review.

3.3. Sociobehavioral Domain (Supplementary Table 1). This domain includes studies that evaluated the BAP expression using measures designed specifically to assess social abilities, communication skills, and personality traits characteristic of the BAP, as well as measures of reciprocal interaction, restrictive, and repetitive interest and social and narrative language.

3.3.1. BAP Expression through Direct Clinical Assessment. Studies explored the BAP using a variety of measures and research designs with some studies utilizing conservative selection criteria, dividing parents of autistic probands into "BAP present" (BAP+) and "BAP absent" (BAP−) groups. As shown in Supplementary Table 1 in Supplementary Material available online at https://doi.org/10.1155/2017/6346912, from eight of the measures specifically designed to assess the BAP, four are more recent questionnaires aiming to assess the BAP quantitatively, and four use interviews and direct behavioral observations. Of the four questionnaires, one is a self-report measure (Autism Spectrum Quotient (AQ)), two are informant report measures (Communication Checklist-Adult (CCA); and Social Responsiveness Scale (SRS)), and one is a self-report and informant report questionnaire (Broader Autism Phenotype Questionnaire (BAPQ)). Of the four remaining measures, two are semistructured interviews (Family History Interview (FHI)/Family History Schedule (FHS) and Modified Personality Assessment Schedule (MPAS)/Modified Personality Assessment Schedule-Revised (MPAS-R)) and two assess BAP via interviews and direct clinical observation/assessment (Broader Phenotype Autism Symptom Scale (BPASS) and Pragmatic Rating Scale (PRS)).

Autism Spectrum Quotient (AQ). A total of ten reports measured the BAP using the self-report AQ (ES range: 0.01–1.34). Three studies used adaptations of the AQ: one in Italian [17], one in Turkish [18], and one in French [19]. Within the "social skills" factor, five studies found significantly higher deficits in social skills compared to parents of typically developing children [17, 18, 20–22]. Two studies reported significantly higher prevalence of "Attention Switching" deficits between the index parents and parents of typically developing children [22] and parents of children with specific language impairment [23]. One study evaluating the "Attention to Detail" subscale reported mothers of typically developing children scoring significantly higher than index mothers [24]. Within the "Communication" subscale, five out of eight studies reported significantly higher communication deficits between index parents and parents of typically developing children [17, 18, 20, 22] and parents of children with a specific language impairment [23]. However, only Wheelwright et al.'s (2010) [22] study reported a significant trend for index parents to have more deficits in "Imagination" subscale compared to a sample of parents of typically developing children. For the total AQ score, four studies reported higher combined total scores among index parents when compared to parents of typically developing children [17, 18, 22] and parents of children with specific language impairment [23].

Ingersoll et al. (2011) [25] combined the social skill and communication factors and revealed index mothers to score significantly higher than normative mothers on the AQ.

Furthermore, in a more recent study, using a validated French Autism Quotient (FAQ), Robel et al. (2014) [19] distributed AQ scores between two main factors, F1 corresponding to socialization and communication and F2 corresponding to imagination and rigidity. They reported index parents to have more symptomatic scores in the F1 domain compared to parents of typically developing children. No significant differences were found for the F2 domain; however, the global score (F1 and F2 combined) remained significant with index parents scoring higher.

Broader Autism Phenotype Questionnaire (BAPQ). Two studies evaluated the BAP using the BAPQ (ES range: 0.26–1.49). Hurley et al. (2007) [26] used the method of preestablishing parents of autistic probands into "BAP present" (BAP+) and "BAP absent" (BAP−) groups by direct assessment on MPAS- R and PRS, reporting consistently higher scores for "BAP+" group compared to "BAP−" group and community control parents on all subscales: aloof, rigid, pragmatic language, and the total score. More recently, Sasson et al. (2013) [27] reported similar results for all BAPQ subscales and total score, with index fathers scoring significantly higher than normative fathers, and the same trend was significant for mothers of both groups.

Broader Phenotype Autism Symptom Scale (BPASS). Bernier et al. (2012) [28] used the BPASS to assess the BAP in MPX parents compared to parents of SPX families, parents of developmentally delayed children, and parents of typically developing children (ES range 0.75–1.28). Differences among groups were found in the "Social Motivation" subscale where MPX parents showed significantly more deficits than the SPX parents, parents of developmentally delayed children, and parents of typically developing children. In both "Expressiveness" and "Restricted Interests" subscales a significant difference was found only between the MPX parents scoring higher than parents of typically developing children. No group differences were found within the "Communication" subscale and, interestingly, SPX parents did not differ from parents of children with developmental delay or typical development.

Communication Checklist-Adult Version (CC-A). Whitehouse et al. (2010) [29] assessed the BAP using the CC-A (ES range: 0.04–0.43), and found only the "Social Engagement" subscale had statistically significant differences between the index parents and a normative sample, suggesting a more passive communication style for the index parents. No group differences were found in the "Language Structure" and "Pragmatic Language" subscales; however, analysis of the total score of the two groups (1 standard deviation below mean) was found to be significant.

Family History Interview/Family History Schedule (FHI/FHS). Three studies evaluated the BAP using the FHI/FHS semistructured interview method (no ES available). Folstein et al. (1999) [30] analyzed four items (language delays, reading difficulties, spelling difficulties, and articulation) on the "Communication" subscale. Accordingly, "early language- related cognitive difficulties" (ELRCD) were scored and a "definite" or "probable" rating was applied. Significantly higher rates of definite and probable ELRCD were found in index parents compared to parents of children with Down's Syndrome. However, two other studies found index parents to perform equally to comparison groups on the "Communication" subscale [6, 31]. Within the "social" factor, Piven et al. (1997) [6] found parents from MPX families had significantly higher prevalence of social deficits than parents of Down's Syndrome children, particularly in index fathers. Similarly, Pickles et al. (2013) [31] reported significantly increased social deficits in index parents compared to parents of children with a specific language impairment. Interestingly, no group differences were found between index parents and parents of children with a combined diagnosis of specific language impairment and autism. Only Piven et al. (1997) [6] assessed the "Stereotyped Behaviors" subscale and reported MPX parents to have significantly more repetitive stereotyped behaviors compared to parents of Down's Syndrome children.

Modified Personality Assessment Schedule (MPAS/MPAS-R). One study used the MPAS to evaluate the BAP (Piven et al., 1994) [32] and three subsequent studies have used a modified version (MPAS-R) [33–35] (ES not available). Three out of the four studies assessing the "Aloof" subscale found significantly higher rates of aloofness in index parents compared to parents of Down's Syndrome children [32, 33], with one study reporting MPX parents to score significantly higher than SPX parents who in turn scored significantly higher than parents of children with Down's Syndrome [35]. Similarly, the same trend for the "Anxious," "Hypersensitive," "Rigid," and "Untactful" personality traits was reported [35]. Piven et al. (1997) [33] reported significantly higher rates of anxiousness, hypersensitiveness, and rigidity in MPX parents in comparison to parents of Down's Syndrome; however, they found no significant differences between the two groups in the "Untactful," "Undemonstrative," and "Unresponsive" traits. Piven et al. (1994) [32], however, did find significantly higher rates of untactfulness and undemonstrativeness in index parents compared to parents of children with Down's Syndrome. In a more recent study, Losh et al. (2012) [35] failed to find a significant difference for the "Overly Conscientious" subscale, but they did find a significant difference in the "Rigidity" subscale.

Pragmatic Rating Scale (PRS/PRS-M). A total of five studies assessed the BAP using the PRS (ES range: 0–1.14). Landa et al. (1992) [36] combined blind and nonblind ratings and reported higher total scores for the index parents compared to their control sample of parents of Down's Syndrome and typical development. Losh et al. (2012) [35] found in their sample of mothers only that index mothers had similar pragmatic language violations to mothers of children with Fragile X Syndrome, and both these groups had higher frequency of violations than mothers of typically developing children. Piven et al. (1997) [33] reported higher frequency of pragmatic language violations and speech errors in MPX parents compared to parents of Down's Syndrome children. Additionally, Losh et al. (2008) [34] found a linear trend for both pragmatic language violations and speech errors,

reporting MPX parents to score significantly higher than SPX parents who in turn scored significantly higher than parents of children with Down's Syndrome. Ruser et al. (2007) [37] used a modified version of the PRS (PRS-M) and reported index parents to have significantly higher deficits in subscales of emotional expressiveness and awareness of the other, overtalkativeness, and language in comparison to parents of children with Down's Syndrome. Group differences in the communicative factor were not found to be significant; however, index fathers showed significantly increased communication deficits than index mothers. The total PRS- M score revealed significant group differences between index parents and Down's Syndrome parents, with index fathers scoring higher than index mothers.

Social Responsiveness Scale (SRS). The SRS was used as a measure to assess the BAP by two studies in our review (ES range: 0.02–0.90). De la Marche et al. (2012) [38] reported all index fathers (MPX and SPX combined) having a significantly higher total score compared to unaffected adult males; however no statistical differences were found between MPX fathers and SPX fathers and SPX fathers and male controls. In contrast, Schwichtenberg et al. (2010) [39] found that both the MPX and SPX fathers in their sample scored significantly higher than fathers of typically developing children. No differences between mothers in both groups were found.

3.3.2. Other Measures of Personality and Friendships. Another personality measure used in studies of the BAP is the NEO Personality Inventory (NEO-PI). Two studies show a trend for parents from MPX families scoring significantly higher on the neuroticism subscale in comparison to parents of children from SPX families [34] and parents of DS probands [33, 34] (ES 0.79, n = 1). Furthermore, the same two studies assessed quality of friendships using the Friendship Interview (FI), indicating significantly fewer friendships in parents from MPX families in comparison to parents of children from SPX families [34] and parents of Down's Syndrome children [33, 34]. Interestingly, Losh et al. (2008) [34] also found sex differences in the quality of friendships within ASD parents, with fathers from MPX families and SPX families having significantly fewer friendships than mothers from MPX families and SPX families (ES 1.14, n = 1).

3.3.3. Reciprocal Social Interaction. Two studies assessed alexithymia (i.e., inability to identify and describe emotions in oneself) as part of the BAP. Szatmari et al. (2008) [9] used the Toronto Alexithymia Scale (TAS-20) as a measure of alexithymia and, despite its three factors (difficulty identifying feelings, difficulty describing feelings, and externally oriented thinking) not reaching significance, the total score confirmed higher frequency of alexithymia in index parents compared to parents of children with Prader Willi syndrome. Using the same scale, however, Berthoz et al. (2013) [40] failed to find a statistically significant difference between index parents and unaffected adults (ES range: 0.14–0.25). Another measure of alexithymia used by Berthoz et al. (2013) [40] was the Bermond-Vorst Alexithymia Questionnaire-B (BVAQ-B); however no significant differences were found between the samples (ES range: 0.02–0.19).

Berthoz et al. (2013) [40] further assessed social anhedonia (i.e., inability to experience pleasure from activities usually found enjoyable), using the revised version of the Social Anhedonia Scale (SAS) (ES 0.25) and found no significant differences between the index parents and unaffected adults. However, Berthoz et al. (2013) [40] found index parents to score significantly higher than unaffected adults on physical anhedonia as measured by the Physical Anhedonia Scale (PAS) (ES 0.33).

3.3.4. Social and Narrative Language. In addition to the PRS, which was specifically designed to assess the deficits in social language as a BAP expression, two other measures have assessed social and narrative language. Di Michele et al. (2007) [8] used Grice's Conversational Maxims task to assess pragmatic conversations and found the index parents performed significantly worse when compared to parents of typically developing children and parents of children with Down Syndrome (ES not available). Landa et al. (1991) [41] used "spontaneous narrative discourse performance" to assess narrative discourse deficits. They reported control adults producing significantly more complete episodes and stories with multiple episodes, and the mean overall quality for the index parents was significantly less than that for the comparison adults (ES range: 0.35–0.73).

3.3.5. Repetitive/Restrictive Behaviors and Interests. Repetitive and restrictive behaviors are a core symptom of autism. The majority of findings in parents of autistic probands corresponding to this domain are covered in the studies that assess the BAP in terms of rigid and perfectionistic personalities. Only one study used an experimental questionnaire designed to examine real-life, nonsocial skills and preferences such as insistence on routines and circumscribed hobbies. Briskman et al. (2001) [42] reported index parents to score significantly higher than parents of boys with dyslexia and typical development (ES range: 0.37–1.11).

3.4. Cognitive Domain (Supplementary Table 2). Most forms of neuropsychological tests involve multiple cognitive functions suggesting that cognitive domains can be related to each other. We have organized the measures for this broad domain under different categories based on the cognitive function which they predominantly assess; however, an overlap may exist. References for the different measures can be found in the studies included in this review and in more specialized text book resources [43].

3.4.1. Intellectual Functioning. Intelligence Quotient (IQ) was measured with different versions of the Wechsler Scales in the studies. Thirteen studies assessed total Verbal IQ (VIQ) (ES range: 0.05–1.28, n = 12), with scores for index parents similar to comparison groups in all but one study [44] with higher scores for index parents when compared to parents of Down's Syndrome children. Several VIQ subtests were also independently tested. Three studies used the digit span subtest (some modified it to assess short term memory)

(ES range: 0.04–0.67), of which two found better performance in index parents compared to parents with children with Down's Syndrome [44] and parents of children with specific language impairment [23]. Only one study used the Arithmetic subscale and found no significant differences between index parents compared to parents with children with Down's Syndrome [44] (ES: 0.25). Four studies used the vocabulary subtest (ES range: 0.04–0.96) and results were mixed, with one study indicating higher scores for index parents compared to parents of children with Down's Syndrome [44], another indicating a reverse trend with index parents scoring significantly lower than parents of typically developing children [45], and two revealing no significant differences between groups. Four studies assessed the comprehension subtest (ES range: 0.31–0.74), with only one indicating a significant difference with index parents scoring significantly higher than parents of children with Down's Syndrome [44]. Additionally, two studies used the similarities subtest (ES range: 0.13–0.35) with only one reporting a significant difference [44].

Thirteen studies also assessed total Performance IQ (PIQ) (ES range: 0–1.16, n = 12), with three studies reporting a significant difference, with index parents performing poorer than parents of children with Down's Syndrome [30, 46] and unaffected adults [10]. One study, however, reported an opposite trend with index fathers performing significantly better than fathers with a child with specific language impairment [47]. Several PIQ subtests were also independently tested. Four studies used the picture completion subtest (ES range: 0.07–0.65); however only two reported significant lower scores for index parents compared to parents of children with Down's Syndrome [30, 46]. Moreover, Folstein et al. (1999) [30] also reported lower scores on the picture arrangement subtest with the same trend of significance (ES range: 0.03–0.26, n = 2). Two studies assessed the object assembly subtest (ES range: 0.12–0.62); however only one reported a significant difference with MPX parents scoring lower than parents of Down's Syndrome children [46]. Furthermore, Schmidt et al. (2008) [10] found significantly lower scores on the matrix reasoning subtest in index parents compared to unaffected adults (ES 0.67). Interestingly, none of the five studies assessing the block design subtest (ES range: 0.04–0.43) and one study assessing the digit symbol subtest found significant differences between groups (ES range: 0.17–0.19).

Full Scale IQ (FSIQ) (ES range: 0.05–1.88, n = 13) was assessed in fourteen studies in our review with three studies reporting a significant poorer performance in index parents when compared to parents of children with Down's Syndrome [30, 34] and a combined clinical group of parents of children with Down's Syndrome and typical development [48].

Additionally, four studies used Raven's Progressive Matrices to report Nonverbal IQ (NVIQ), with no significant differences found between groups [49–52] (ES range: 0.05–0.57).

3.4.2. Structural Language Abilities. A number of studies assessed structural language abilities using a variety of different measures. Results are divided into specific domains. Receptive language skills were assessed by three studies using two measures. The Peabody Picture Vocabulary Test (PPVT-III) (ES range: 0.33–1.58) was used by two studies with only one study reporting index mothers as having significantly more deficits than mothers of children with autism and language impairment who in turn had more deficits compared to mothers of children with a specific language impairment [47]. Whitehouse et al. (2007) [23] used the Test for Reception of Grammar-2 (TROG-2) to evaluate receptive grammar and reported no differences between groups (ES not available). Schmidt et al. (2008) [10] assessed expressive language using the Expressive Vocabulary Test (EVT) (ES 0.10) and the verbal fluency subtest of the Delis Kaplan Executive Function System (DK-EFS) (ES: 0.16–0.39) reporting no significant differences between index parents and unaffected adults. Additionally, they assessed figurative language using the figurative language subtest from the Test of Language Competence-Expanded Edition (TOLC-E) reporting no significant differences between the two groups (ES: 0.28).

Phonological processing was assessed in five reports using five different tests. Lindgren et al. (2009) [47] used the Comprehensive Test of Phonological Processing (CTOPP) (ES range: 0.02–1.42, n = 2), revealing significantly better performance in phonological awareness and the nonword repetition subtests in the index mothers compared to mothers of children with a specific language impairment. In contrast, however, Schmidt et al. (2008) [10] found index parents to perform significantly lower than unaffected adults in the same nonword subtest. Bishop et al. (2004) [53] used a different Nonword Memory Test (ES range: 0.02–0.04) and a Nonsense Passage Reading test (ES range: 0.04–0.42) to assess phonological processing, none indicating significant differences between index parents and parents of typically developing children. However, Whitehouse et al. (2007) [23] did find index parents to perform significantly better than parents of children with specific language impairment in the nonsense words subtest of the NEPSY (a Developmental Neuropsychological Assessment Test Battery) (ES range: 0.04–0.88). In contrast, Plumet et al. (1995) [54] found no significant differences in composite verbal scores when comparing index parents to parents of children with Down's Syndrome using a battery of verbal tasks with an emphasis on orthographic and phonological abilities (ES: 0.22).

Reading skills were assessed by eight studies using seven different measures. Piven and Palmer (1997) [46] used the Rapid Automized Naming (RAN) task and found no differences in the number and letter categories; however, they found significant differences with MPX parents taking longer to complete the task on the color and object categories (ES range: 0.17–0.58). Similarly, Losh et al. (2010) [55] combined the color and object categories and reported index parents taking longer to complete the task when compared with parents of typically developing children (ES not available). The Woodcock-Johnson Psychoeducational Battery-Revised (WJ-R) has several subtests, and no significant differences were found in the broad reading (ES range: 0.48–2.11) and reading skill composite scores [47] (ES range: 0.40–1.84), the word attack subtest [46, 47] (ES range: 0.09–1.35), and letter word subtest [46]. However, Folstein et al. (1999) [30]

found a significantly lower reading age and reading grade using the nonsense word reading subtest in index parents compared to parents of children with Down's Syndrome (ES: 0.40). Mothers of children with autism performed better in the dictation (ES range: 0.17–0.99, n = 2) and passage comprehension subtests (ES range: 0.45–1.54, n = 2) compared to mothers of children with specific language impairment [47]. In contrast, Piven and Palmer (1997) [46] found MPX parents had more difficulties in the passage comprehension subtest when compared with parents of children with Down's Syndrome. Interestingly, no differences were noted in comprehension (ES range: 0.12–0.36) and passage reading subtests (ES range: 0.21–0.36) using the Gray Oral Reading Test (GORT) [30, 44] and the Edinburgh Reading Test (ERT) [44]. Fombonne et al. (1997) [44] also used the National Adult Reading Test (NART) (ES range: 0.20–0.44, n = 2) reporting index parents scoring significantly lower than parents of children with Down's Syndrome. However, Baron-Cohen and Hammer (1997) [7] found no significant differences in error scores between index parents and parents of typically developing children. Whitehouse et al. (2007) [23] used the Test of Word Reading Efficiency (ES range: 0.03–0.62) and found index parents performed better than parents of children with specific language impairment on the phonemic decoding efficiency subtest (nonsense words). Finally, Schmidt et al. (2008) [10] found no significant differences in reading difficulties using the Reading History Questionnaire (RHQ) between index parents and unaffected adults (ES: 0.34).

Three studies assessed spelling abilities using two different measures. Whitehouse et al. (2007) [23] found no group differences using a Speeded Dictation task (ES not available). Furthermore, Fombonne et al. (1997) [44] found a superior performance by index parents on the Schonell Spelling Test (SST) (ES range: 0.02–0.13, n = 2). Only one study assessed oromotor functioning using the oromotor sequencing subtest of the NEPSY Test Battery (ES range: 0.43–0.54) reporting index families performing better than parents of children with specific language impairment [23].

3.4.3. Social Cognition. In this domain measures assess the ability to process information relating to other people's mental states. Five reports assessed the "Theory of Mind" using different versions of Reading the Mind in the Eyes Test (ES range: 0.03–1.51, n = 4). Three studies reported deficits between index parents and comparison groups [7, 48, 56]. In contrast, Gocken et al. (2009) [57] and Tajmirriyahi et al. (2013) [58] found no significant group differences in mental state decoding in the eyes test. Furthermore, Gocken et al. (2009) [57] explored mental state decoding using a faces test and reported no significant differences between index parents and a normative sample (ES: 0.23). Tajmirriyahi et al. (2013) [58], however, used a novel method of Reading the Mind in the Voice Test to reveal significantly higher deficits in mental state decoding in index parents when compared to parents of children with Down's Syndrome and typical development (ES range: 0.63–0.98). Additionally, Di Michele et al. (2007) [8] used False Belief tasks (smarties task, Sally-Anne task, and unexpected transfer test) and found index parents passed fewer false belief tests in comparison to parents of children with Down's Syndrome and typical development (ES not available). Similarly, Gocken et al. (2009) [57] reported poorer performance in index parents compared to a normative sample using the Unexpected Outcomes Test (UOT) (ES: 0.58); however, they did not find a significant difference using the Hinting task (ES: 0.36).

Remarkably, only one study assessed empathy using the Empathy Quotient (EQ) reporting significant impairments in empathy in index fathers compared to unaffected males [52] (ES: 0.11–0.40).

Affect perception was assessed in eight studies using twelve different tests of emotion recognition and labeling. Using the "Bubbles" method with pictures of facial affect, Adolphs et al. (2008) [59] showed no difference in accuracy and reaction time; however, the "BAP+" group used significantly different facial information (eye region and mouth region) in comparison to the "BAP−" group and parents of typically developing children (ES not available). Using the Penn Emotion Recognition Test (ER40), das Neves et al. (2011) [60] reported significantly longer time for correct responses in index parents compared to unaffected adults (ES range: 0.54–1.09). They also reported less accurate responses, identification of female and male faces, and mild and extreme emotions. Bölte and Poustka (2003) [49] showed no significant differences in groups using the Facial Affect Recognition Test (pictures by Ekman and Friesen) (ES range: 0.32–2.06). Similarly, Sucksmith et al. (2013) [52] found no significant differences in accuracy and adjusted response time in index parents compared to unaffected adults using the Karolinska Directed Emotional Faces task (KDEF) (ES range: 0.08–0.30). Kadak et al. (2014) [21] used the Emotion Recognition Test (using photos of facial affect from Ekman and Friesen) and found index parents had impaired recognition of happy, surprised, and neutral faces compared to parents of typically developing children (ES range: 0.05–0.50).

Two studies assessed emotional labeling and matching of facial patterns using three different measures. Using Schematic Line Drawings (ES not available), Palermo et al. (2006) [61] showed impaired labeling for sad, disgust, and overall recognition of facial patterns in index parents compared to parents of typically developing children. In contrast, using the Emotion Matching task (ES: 0.06) and the Emotion Labeling task (ES: 0.19), Smalley and Asarnow (1990) [45] found no significant impairments.

3.4.4. Executive Function. Executive function encompasses abilities that underlie goal directed behavior. This broad domain was split into specific subdomains. Cognitive flexibility was assessed by four studies evaluating set-shifting tasks. Two studies using the intradimensional/extradimensional set-shifting task (IDED) revealed significantly higher rates of learned irrelevance [62] (ES: 0.52), trials to criterion [63] (ES range: 0.69–0.83), and errors to criterion [63] (ES range: 0.64–0.70) in index parents compared to control samples in the extradimensional stage only. However, Bölte and Poustka (2006) [50] used the Wisconsin Card Sorting Test (WCST) (ES range: 0.06–0.18) and the Trail Making Test (TMT, Parts A and B) (ES range: 0.13–0.38) and found no impaired

cognitive control between groups. Similarly, Losh et al. (2009) [56] also showed no significant difference in the total time to complete the TMT task between groups.

Five reports assessed planning abilities using two measures. Using the Tower of London (ToL) (ES range: 0.07–0.93, n = 2), Hughes et al. (1997) [63] found index parents requiring a significantly increased number of extra moves to complete the task compared to unaffected adults. In contrast, Wong et al. (2006) [62] found no significant group differences in the number of extra moves and rule violations. Three studies used the Tower of Hanoi version (ToH) revealing no significant differences in the total time to complete variable (ES range: 0.01–0.45 n = 1) between index parents and a matched clinical sample [50] and nonclinical sample [56], and one study reported significant differences in planning efficiency between index parents and parents of children with Down's Syndrome [46].

One study assessed generativity using the Pattern Meanings test which measures ideational fluency, indicating a significantly impaired overall response generativity in index parents compared to a mixed sample of clinical and nonclinical comparison group [62] (ES: 0.51).

Spatial working memory was assessed by one study using a Visual Search Test, indicating index parents scoring significantly higher between search errors when compared to unaffected adults [63] (ES range: 0.27–0.95). In contrast, however, using the Response to Inhibition and Load (RIL) test, Wong et al. (2006) [62] tested inhibition and its interaction with working memory and found unimpaired reaction times and number of errors in index parents (ES range: 0.04–0.28). Verbal working memory was assessed using three measures by one study. Using the Stroop Interference Test (ES: 0.2) and a Verbal Fluency Test (letters KAS in Turkish) (ES: 0.26), Gocken et al. (2009) [57] revealed no significant differences between groups. However, they did show impaired accuracy in index parents using the Auditory Consonant Trigrams (ACT) (ES: 0.55).

3.4.5. Local Visual Processing (Central Coherence). Central coherence is a specific perceptual-cognitive style leading to a local visual processing bias. Five studies assessed disembedding performance using two tests. All five studies used the Embedded Figures Test (EFT) with mixed results. Three out of the five studies found significantly longer response times for index parents [7, 50] and more specifically in index fathers, when compared to control fathers [64] (ES range: 0.01–1.60, n = 5). No significant results were reported within the accuracy variable [56, 64] (ES range: 0.11–0.77, n = 2); however, De Jonge et al. (2006) [65] reported significantly fewer incorrect responses in index parents when compared to parents of children with Down's Syndrome (ES range: 0.18–0.52). Furthermore, Happé et al. (2001) [64] revealed a similar trend with index parents making fewer errors using the Titchener Circles Illusion test (ES not available).

Mental segmentation ability was assessed with an Unsegmented/Segmented Block Design task (adaptation from the Weschler subtest) in two studies. Happé et al. (2001) [64] found faster response times in index parents in the unsegmented task (ES range: 0.24–0.84, n = 1), and, in contrast,Losh et al. (2009) [56] found significantly faster reaction times in the segmented task only (ES range: 0.04–0.63, n = 1). Furthermore, De Jonge et al. (2009) [66] showed no group differences in mean number of errors using a Block Design Reconstruction task (patterns by Akshoomoff and Stiles) (ES range: 0.10–0.16).

The sentence completion task was used by two studies to assess global sentence completions revealing significantly increased number of errors in index parents [56, 64] and longer response times in index parents [56].

3.4.6. Visual Processing. Interestingly only one study assessed visual processing using four different measures. Contrast sensitivity was measured using the Vistech Contrast Sensitivity Charts and no significant differences were found between index parents and parents of children with Down's Syndrome [67] (ES: 0.55). Similarly, tasks of motion discrimination (Motion Coherence task (ES: 0.25) and Moving Shape task (ES: 0.17)) and form discrimination (Form Discrimination (Shape) task) (ES: 0.05) revealed no significant differences between the same groups [67].

3.5. Other Psychiatric Conditions Domain (Supplementary Table 3). This domain was assessed in seven reports using nine different measures. Piven et al. (1991) [68] used the Schedule for Affective Disorders and Schizophrenia-Lifetime Version (SADS-L) and found significantly higher scores in the "anxiety" factor when compared to parents of children with Down's Syndrome, and no statistical significance was found for the "major depressive disorder" subscale between the two groups (ES not available). However, using a modified version of the Schedule for Affective Disorders and Schizophrenia-Lifetime Version Modified for the Study of Anxiety Disorders, Revised (SADS-LA-R), Piven and Palmer (1999) [69] did find significantly higher frequency of "major depressive disorder" in index parents in addition to the "social phobia" factor.

Micali et al. (2004) [70] devised a parental questionnaire and validated their results from consented medical records from GPs and found a significant trend towards higher prevalence of "depression" and "anxiety" in index parents. Using the Symptom Checklist-90-Revised (SCL-90-R), Bölte et al. (2007) [51] found significantly increased frequency in index parents in four of the nine subscales (depression, hostility, phobic anxiety, and paranoid ideation) (ES range: 0–1.33). Additionally, Bölte et al. (2007) [51] also assessed personality style and disorder using the Personality Style and Disorder Inventory (PSSI) and reported significantly higher rates in index parents in five out of fourteen factors (reserved/schizoid, self-critical/insecure, critical/negativistic, spontaneous/borderline, and quiet/depressive) (ES range: 0.02–1.18).

Gocken et al. (2009) [57] assessed depression and anxiety factors using the Brief Psychiatric Rating Scale (BPRS) between index parents and a normative comparison group and only found a statistically significant difference in the depression factor with index parents scoring higher (ES range: 0.29–0.44). Similarly, Ingersoll et al. (2011) [25] assessed depressed mood using the Centre for Epidemiological

Studies-Depression Scales (CESD) and showed index mothers as having increased rates of depression when compared to a normative sample of mothers (ES: 0.35). Interestingly, Berthoz et al. (2013) [40] reported no significant differences in levels of depressive mood using the Beck Depression Inventory (BDI) (ES: 0.50) and no significant differences were found in anxiety levels using the state (ES: 0.19) and trait portions (ES: 1.24) of State-Trait Anxiety Inventory Form Y (STAI-Y) [40].

4. Discussion

This systematic review aimed to assess the evidence of behavioral, cognitive, and psychiatric profiles of the BAP in unaffected biological parents of autistic probands by synthesizing the evidence from 60 studies meeting a priori search criteria. Results are discussed according to the following criteria: (i) the number of studies that indicate significant impairments in each domain and subdomain; (ii) quantitative criteria using effect sizes; and (iii) the possible emerging themes across studies. Table 2 represents a summary of all measures used by studies meeting our search criteria.

4.1. Summary of Findings. Findings emerging from this review are discussed according to each domain. Within the sociobehavioral domain, eight measures that directly assess the BAP expression in unaffected parents showed substantial deficits in the domain of social and communication skills (AQ, 7/10 studies; BPASS, 1 study; CC-A, 1 study; FHI/FHS, 2/2 studies; SRS, 2/2 studies), rigid and perfectionistic (BAPQ, 2/2 studies; MPAS-R, 3/3 studies) and aloof (BAPQ, 2/2; MPAS-R, 3/4 studies) personality traits, and pragmatic language difficulties (BAPQ, 2/2 studies; PRS, 4/4 studies) related to the core deficit in autism and are reported consistently across most studies. Moreover, additional deficits in social and narrative language have been highlighted using measures of spontaneous narrative discourse [36] and Grice's Conversational Maxims task [8]. Available evidence also points to index parents establishing fewer friendships (FI, 2/2 studies) and an elevated frequency of neuroticism (NEO-PI, 2/2 studies). Despite being a core domain of a clinical diagnosis for autism, the majority of findings in parents of autistic probands corresponding to restricted and repetitive behaviors and interests are covered in the studies that assess the BAP in terms of rigid and perfectionistic personality styles. Only one study used an experimental questionnaire designed to examine real-life nonsocial skills and preferences such as insistence on routines and circumscribed hobbies [42].

Within the sociobehavioral domain, reciprocal social interaction is probably the least studied subdomain in parents of autistic probands. As such, findings from alexithymia (TAS-20, 1/2 studies; BVAQ-B, 1 study with no significance found) and physical (PAS, 1/1 study) and social anhedonia (SAS, 1 study with no significance found) are modest and require further studies to explore these traits. Thus, we agree with previous reviews [12–14] indicating that mild social/communication deficits, rigid/aloof personality traits, and pragmatic language difficulties may be the most useful social behavioral candidate endophenotype traits as they meet all the established criteria [11]; however, effect sizes throughout this domain varied considerably.

At the cognitive level, a remarkable finding is the discrepancies found in intellectual functioning of parents of autistic probands compared to parents of children with and without a clinical diagnosis. One of thirteen studies revealed significantly higher VIQ scores when compared to a clinical sample of parents of a child with Down's Syndrome [44]. Three of thirteen studies assessing PIQ reached a similar significant trend when compared to parents with a Down's Syndrome child [30, 46] and unaffected adults [10]. Total PIQ scores were significantly higher in index parents when compared to parents with a child with specific language impairment [47]. Only two of twelve reports reached a significant deficit in FSIQ when index parents were compared to parents of children with Down's Syndrome [30] and when compared to a combined sample of parents of a child with Down's Syndrome and of typical development. However, it is noteworthy that scores for all parents were well within the average range in all studies. Thus there is limited evidence for the role of intellectual functioning as an endophenotype for autism with no clear clinical significance.

Several measures were used to assess the structural language abilities within the cognitive domain. Interestingly, no significant differences were found in the expressive language (TROG-2, 1 study with no significance found; EVT, 1 study with no significance found; DK-EFS verbal fluency subtest, 1 study with no significance found) and figurative language categories (TOLCE-E figurative language subtest, 1 study with no significance found). Lindgren et al. (2009) [47] found index parents to perform better than parents with a child with a specific language impairment on measures assessing receptive language (PPVT-III, 1/2 studies; TROG-2, 1 study with no significance found) refuting the hypothesis that families with autism and specific language impairment do not share similar genetic loading for language.

In phonological awareness, findings are mixed with studies only reporting few deficits in nonsense word/passage reading tests (2/3 studies) with index parents performing better than parents with a specific language impairment child [23] and parents of children with Down's Syndrome [30]. Using the RAN measure for reading skills, two studies reported faster times to complete the color and object only tasks in index parents when compared to parents of children with Down's Syndrome [46] and parents of typically developing children [55]. This may have relevance with regard to perceptual load in autism. However, no significant differences were found in the rapid naming subtest of the CTOPP [47].

Findings from the social cognition domain including mental state decoding, affect perception, emotion recognition, and labeling in the BAP also report mixed and conflicting results. Remarkably only one studied assessed empathy warranting further research in this subdomain.

Evidence from the broad domain of executive function in the BAP is also inconsistent but the few studies that have found impairments did not appropriately match experimental and control groups for IQ are worth noting (e.g., [63]).

TABLE 2: Summary of the frequency of all measures used by studies meeting our search criteria and effect size ranges for each domain.

	Frequency
Sociobehavioral category	
BAP expression (ES range: 0.01–1.49)	
Autism Spectrum Quotient (AQ)	10
Broader Autism Phenotype Questionnaire (BAPQ)	2
Broader Phenotype Autism Spectrum Scale (BPASS)	1
Communication Checklist-Adult (CC-A)	1
Family History Interview/Family History Schedule (FHI/FHS)	3
Modified Personality Assessment Schedule-Revised (MPAS-R)	4
Pragmatic Rating Scale (PRS)	4
Social Responsiveness Scale (SRS)	2
Other measures of personality and friendships (ES range: 0.79–1.14)	
The Friendship Interview (FI)	2
The Neo Personality Interview (NEO-PI)	2
Reciprocal social interaction (ES: 0.33)	
Alexithymia	
Toronto Alexithymia Scale (TAS-20)	2
Bermond-Vorst Alexithymia Questionnaire-B (BVAQ-B)	1
Anhedonia	
Revised Social Anhedonia Scale (SAS)	1
Physical Anhedonia Scale (PAS)	1
Social and narrative language (ES: 0.50–0.73)	
Grice's Conversational Maxims task	1
Spontaneous Narrative Language	1
Repetitive, restrictive behaviors & interests (ES: 0.37–1.11)	
Everyday Preferences & Abilities	
Real Life Skills & Preferences	1
Cognitive category	
General intellectual functioning (ES range: 0.14–1.16)	
Wechsler Scales	19
Raven's Progressive Matrices (RPM)	4
Structural language abilities (ES range: 0.04–1.65)	
Receptive language	
Peabody Picture Vocabulary Test (PPVT-III)	2
Test for Reception of Grammar-2 (TROG-2)	1
Expressive language	
Expressive Vocabulary Test (EVT)	1
Verbal Fluency Subtest-Delis Kaplan Executive Function System (DK-EFS)	1
Figurative language	
Figurative Language Subtest-Test of Language Competence-Expanded (TOLC-E)	1
Phonological awareness	
Comprehensive Test of Phonological Processing (CTOPP)	2
Nonword Memory Test	1
Nonsense Passage Reading Test	1
Nonsense Words Subtest-NEPSY Test Battery	1
Battery of Verbal tasks (including orthographic & phonological abilities)	1

TABLE 2: Continued.

	Frequency
Reading abilities	
Rapid Automized Naming (RAN)	2
Woodcock-Johnson Psychoeducational Battery-Revised (WJ-R)	3
Gray Oral Reading Test (GORT)	2
Edinburgh Reading Test (ERT)	1
National Adult Reading Test (NART)	2
Test of Word Reading Efficiency	1
Reading History Questionnaire (RHQ)	1
Spelling abilities	
Schonell Spelling Test (SST)	1
Speeded Dictation task	2
Oromotor functioning	
Oromotor Sequencing Subtest-NEPSY Test Battery	1
Social cognition (ES range: 0.05–1.51)	
Theory of Mind	
Reading the Mind in the Eyes Test (different versions)	5
The Faces Test	1
Reading the Mind in the Voice Test	1
False Belief tasks (Smarties task; Sally-Anne task; unexpected transfer test)	1
Unexpected Outcomes Test (UOT)	1
The Hinting task	1
Empathy	
Empathy Quotient (EQ)	1
Affect perception/emotion recognition	
Pictures of facial affect, "Bubbles" method	1
Penn Emotion Recognition Test (ER40)	1
Facial Affect Recognition Test	1
Emotion Recognition Test	1
Karolinska Directed Emotional Faces task (KDEF)	1
Point Light Basic Emotions task	1
Trustworthiness of Faces task	1
The Morphed Faces task	1
The Movie Still task	1
Schematic Line Drawings task	1
Emotion Matching task	1
Emotion Labeling task	1
Executive function (ES range: 0.27–1.27)	
Set-shifting	
intradimensional-extradimensional Set-Shifting task (IDED)	2
Wisconsin Card Sorting Test (WCST)	1
Trail Making Test (A & B)	2
Planning	
Tower of London (ToL)	2
Tower of Hanoi (ToH)	3
Generativity/ideational fluency	
Pattern Meanings	1

TABLE 2: Continued.

	Frequency
Spatialworking memory/inhibition	
Visual Search Test	1
The Delayed Oculomotor task	1
Response Inhibition & Load (RIL)	1
Verbal working memory	
Auditory Consonant Trigrams (ACT)	1
Verbal Fluency Test	1
Stroop Interference Test	1
Central coherence (local visual processing) (ES range: 0.18–1.60)	
Disembedding performance	
Embedded Figures Test (EFT)	5
Titchener Circles Illusion	1
Mental segmentation ability	
Unsegmented Block Design task (adapted from Wechsler Scales)	2
Segmented Block Design task (adapted from Wechsler Scales)	2
Block Design task (Wechsler scales)	2
Block Design Reconstruction task	1
Attentional engagement	
Detection task	1
Global sentence completions	
Sentence completion task	2
Visual processing (ES not available)	
Contrast sensitivity	
Vistech Contrast Sensitivity Charts	1
Motion discrimination	
Motion Coherence task	1
Moving Shape task	1
Form discrimination	
Form Discrimination (Shape) task	1
Other psychiatric conditions category (depression and anxiety) (ES range: 0–1.33)	
Brief Psychiatric Rating Scale (BPRS)	1
Personality Style & Disorder Inventory (PSSI)	1
Symptom Checklist 90-Revised (SCL-90-R)	1
Schedule for Affective Disorders and Schizophrenia-Lifetime Version (SADS-L)	1
Schedule for Affective Disorders and Schizophrenia-Lifetime Version Modified for the Study of Anxiety Disorders-Revised (SADS-LA-R)	1
Parental questionnaire	1
The Centre for Epidemiological Studies-Depression Scales (CESD)	1
Beck Depression Inventory	1
State-Trait Anxiety Inventory Form Y (STAI-Y)	1

Similarly, findings from studies assessing performance on tests where local visual processing is an advantage (centralcoherence) were mixed in studies of the BAP. Conflicting results in the disembedding performance were noted (EFT, 4/8 studies; Titchener Circles Illusion, 1 study) as well as mental segmentation abilities (Unsegmented Block Design task, 1/2 studies; Segmented Block Design task, 1/2 studies; Block Design Reconstruction task, 1 study with no significance found). Two studies, however, indicate higher frequency of errors and response times in index parents during a global

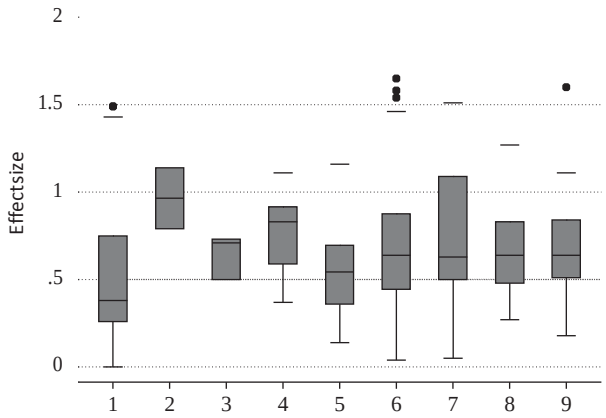

FIGURE 2: Boxplot reflecting effect size ranges for the sociobehavioral and cognitive domains. 1 = BAP expression. 2 = other measures of personality and friendships. 3 = social and narrative language. 4 = repetitive, restrictive behaviors, and interests. 5 = general intellectual functioning. 6 = structural language abilities. 7 = social cognition. 8 = executive function. 9 = local visual processing (central coherence).

sentence completion task (sentence completion task, 2/2 studies). Nonetheless, this area of cognition in the BAP also warrants further research.

Lastly, a number of studies have documented higher rates of depression (in 5/7 measures), anxiety (in 2/6 measures), and social phobia/social phobic anxiety (in 4/6 measures) in parents of children with autism compared to normative samples (e.g., [57]) and a clinical sample (e.g., [51]). We also note depression and anxiety to be more prevalent (2/6 studies) in mothers of children with autism. Ingersoll et al. (2011) [25] reported increased depressed mood in index mothers when compared to mothers of typically developing children, with similar findings from Micali et al. (2004) [70]. Although one can assume that having a child with a disability can affect mood and anxiety levels, many studies indicate an onset of these conditions before the birth of the child with autism, suggesting that the stress of caring for a child with a disability did not cause the symptoms. Findings from our review revealed moderate to high magnitude of effect; thus, depression and anxiety may have a genetic link with autism, supporting findings from a previous meta-analysis of psychiatric disorders in parents of children with autism [71].

Figure 2 displays the boxplots reflecting effect size ranges for the sociobehavioral and cognitive domains and subdomains. It was not possible to include effect size ranges for the domain of other psychiatric conditions as depression and anxiety could not be divided into separate subdomains due to the measures used in the studies. The reciprocal social interaction subdomain was omitted as there was only one effect size available for one significant finding. Similarly, the visual processing subdomain was also omitted as findings were not significant.

4.2. Emerging Themes. A number of studies reviewed suggest that subclinical autistic traits aggregate in MPX families and occur less frequently in SPX families [28, 34]. For instance decreased number and intensity of BAP traits observed in parents of SPX in comparison to MPX provide behavioral evidence consistent with findings of increased de novo, noninherited genetic events in SPX families (e.g., [72]). Losh et al. (2008) [34] suggest that the BAP gradation expression across family types is consistent with increasing genetic liability to autism.

A male bias is a well-documented feature in autism [73]. Findings from our review also indicate few sex differences, indicating this male bias [37–39]. However, despite this and the clear sex bias in autism, many studies do not suggest sex differences for most BAP features (e.g., [74]).

Furthermore, our findings indicate that the majority of the studies reviewed were conducted in Western countries. There were too few studies from non-Western countries to make any meaningful comparisons. Further cross-cultural research is required to understand the endophenotypes of autism within different cultural and geographical settings in order to tackle this geographical distribution bias.

4.3. Measure Quality. It is clear from this review that a large number of measures have been utilized to assess the BAP in relation to different domains and the constructs analyzed are heterogeneous. However it should be noted that the current review does not assess in depth whether the BAP measures are valid or reliable in measuring BAP. Domain wise, in many cases the same measures have been used by other studies. We discuss whether results for each measure in the same domain show the same magnitude and are in the same direction.

For instance, Davidson et al. (2014) [75] reported that frequency of BAP traits varies significantly depending upon the measure utilized, highlighting the need for a different approach that utilizes multiple informants and relies on the assessment of distinct BAP traits.

4.4. Methodological Limitations of Studies. Any discordant findings in the studies reviewed may be partly explained by methodological differences between studies. Sample size and choice of comparison group play an important role in the outcome of results. Six studies enrolled 30 or less index parents. Thus, relatively small sample sizes may lead to false negative results and/or limit the power to detect the BAP in the three domains.

Studies vary in their choice of a comparison group with some relying on the convenience of clinic-based samples where selection biases may lead to distorted results and others emphasizing the use of population based samples. For example, parents of children with Down Syndrome were frequently used, but these parents are likely to be older and possibly of different socioeconomic status. Few studies matched index parents to control groups on intellectual functioning, age, and socioeconomic basis, thus making it difficult to assimilate if differences on specific cognitive tasks represent a specific impairment in functioning or are attributable to differences in demographic data.

4.5. Limitations and Future Directions. In addition to the limitation outlined above, there are other limitations. Given that nine additional studies were found through a manual

search after the initial search, it is possible that other studies were not ascertained by our search terms. To address this limitation, future research may also consider additional search terms beyond those used here.

This review aimed to identify endophenotypes in behavioral, cognitive, and psychiatric domains independently, and as such we did not assess associations between the BAP features across different domains. Losh et al. (2009) [56] suggest that it is likely that specific BAP traits cosegregate with performance in other domains. For instance, parents displaying rigid/perfectionistic personality traits could per- form differently on tasks requiring cognitive flexibility. Additionally, most studies meeting our search criteria assessed only one or two domains, rendering it difficult to establish whether an endophenotypic overlap, if any, exists.

Future reviews should also include studies that examine neuroanatomical and neurofunctional correlates of the BAP. These are essential in furthering our understanding of the neural correlates of the behavioral, cognitive, and psychiatric aspects of autism.

More sophisticated research of the endophenotypes of parents of children with autism may help develop better measures of evaluation of the BAP. Future studies should use a more comprehensive and quantitative framework using more robust measures to detect subtle subclinical autistic traits in the BAP in cross-cultural settings. To the best of our knowledge, no study assessing the endophenotypic profile of autism in Africa has been published yet. Such research by our team is underway.

4.6. Conclusions. In summary, the current review increases our understanding of the BAP and extends the findings of previous reviews [13, 14]. It also supplements a systematic review [12] and a meta-analysis [71] with a broader scope. However, findings should be interpreted with caution because of the small number of studies in such heterogeneously broad domains and methodological limitations.

The assessment of the BAP profile in parents of autistic probands allows us to have a better insight into the varying underlying genetic mechanisms in autism. The behavioral, cognitive, and psychiatric endophenotypes in parents of autistic probands are still not clarified; however, evidence points towards mild social/communication deficits, rigid/aloof personality traits, and pragmatic language difficulties as the most useful social behavioral candidate endophenotype traits. The existence of some deficits in the cognitive domain does suggest familial vulnerability for autism; however, more research is required to elucidate these findings within this domain. Furthermore, increased depressed mood and anxiety can also be useful markers of vulnerability.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Appendix 2: Socio-Behavioral Endophenotype Matrix – Review of studies of parents of autistic probands.

Domain	Method / Measure	Factors / Subscales	Country	Study	ASD Parent Group Characteristics	Control Group Characteristics	Key Findings in relation to Proband Diagnosis	
							***P* value**	**Effect Size (*d*)**
BAP Expression *(Measures designed specifically to assess BAP)*	**Autism Spectrum Quotient (AQ)** *Self-report Questionnaire*	Social Skills	UK	Berthoz et al (2013)	ASD-P n = 87 (28%Fa)	UA n = 47 (62%M)	**n.s.**	**ASD-P vs. UA 0.36**
			Australia	Bishop et al (2004a)	ASD-P n = 111 (65Mo/46Fa)	N-P n = 85 (48Mo/37Fa)	**ASD-P > N-P****	**ASD-Mo vs. N-Mo 0.22 ASD-Fa vs. N-Fa 0.60**
			Turkey	Kadak et al (2014)	ASD-P n=72 (36Mo/36Fa)	TD-P n=38 (19Mo/19Fa)	**ASD-P > TD-P****	**ASD-P vs. TD-P 0.5**
			Turkey	Kose et al (2013)	ASD-P n = 100 (53Mo/47Fa)	TD-P n = 100 (52Mo/48Fa)	**ASD-P > TD-P****	**ASD-Fa vs. TD-Fa 0.43 ASD-Mo vs. TD-Mo 0.30**
			Italy	Ruta et al (2012)	ASD-P n= 245 (130Mo/115Fa)	TD-P n = 300 (150Mo/150Fa)	**ASD-P > TD-P****	**ASD-Fa vs. TD-Fa 0.25 ASD-Mo vs. TD-Mo 0.24**
			Netherlands	Scheeren & Stauder (2008)	ASD-P n= 25 (12Mo/13Fa)	TD-P n= 25 (12Mo/13Fa)	**n.s**	
			UK	Wheelwright et al (2010)	ASD-P n= 2000 (1429Mo/571Fa)	TD-P n= 1007 (658Mo/349Fa)	**ASD-P > TD-P*****	**ASD-Fa vs. TD-Fa 0.33 ASD-Mo vs. TD-Mo 0.46**
			UK	Whitehouse et al (2007)	ASD-P n = 30 (20Mo/10Fa)	SLI-P n= 25	**n.s.**	**ASD-P vs. SLI-P 0.67**
		Attention Switching	UK	Berthoz et al (2013)	ASD-P n = 87 (28%Fa)	UA n = 47 (62%M)	**n.s.**	**ASD-P vs. UA 0.14**

			Australia	Bishop et al (2004a)	ASD-P n = 111 (65Mo/46Fa)	N-P n = 85 (48Mo/37Fa)	**n.s.**	**ASD-Mo vs. N-Mo 0.13** **ASD-Fa vs. N-Fa 0.19**
			Turkey	Kadak et al (2014)	ASD-P n=72 (36Mo/36Fa)	TD-P n=38 (19Mo/19Fa)	**n.s.**	**ASD-P vs. TD-P 0.09**
			Turkey	Kose et al (2013)	ASD-P n = 100 (53Mo/47Fa)	TD-P n = 100 (52Mo/48Fa)	**n.s.**	**ASD-Fa vs. TD-Fa 0.33** **ASD-Mo vs. TD-Mo 0.15**
			Italy	Ruta et al (2012)	ASD-P n= 245 (130Mo/115Fa)	TD-P n = 300 (150Mo/150Fa)	**n.s.**	**ASD-Fa vs. TD-Fa 0.13** **ASD-Mo vs. TD-Mo 0.03**
			Netherlands	Scheeren & Stauder (2008)	ASD-P n= 25 (12Mo/13Fa)	TD-P n= 25 (12Mo/13Fa)	**n.s**	
			UK	Wheelwright et al (2010)	ASD-P n= 2000 (1429Mo/571Fa)	TD-P n= 1007 (658Mo/349Fa)	**ASD-P > TD-P*****	**ASD-Fa vs. TD-Fa 0.12** **ASD-Mo vs. TD-Mo 0.38**
			UK	Whitehouse et al (2007)	ASD-P n = 30 (20Mo/10Fa)	SLI-P n= 25	**ASD-P > SLI-P***	**ASD-P vs. SLI-P 0.67**
		Attention to Detail	UK	Berthoz et al (2013)	ASD-P n = 87 (28%Fa)	UA n = 47 (62%M)	**n.s.**	**ASD-P vs. UA 0.37**
			Australia	Bishop et al (2004a)	ASD-P n = 111 (65Mo/46Fa)	N-P n = 85 (48Mo/37Fa)	**n.s.**	**ASD-Mo vs. N-Mo 0.29** **ASD-Fa vs. N-Fa 0.12**
			Turkey	Kadak et al (2014)	ASD-P n=72 (36Mo/36Fa)	TD-P n=38 (19Mo/19Fa)	**n.s.**	**ASD-P vs. TD-P 0.22**

			Turkey	Kose et al (2013)	ASD-P n = 100 (53Mo/47Fa)	TD-P n = 100 (52Mo/48Fa)	**n.s.**	**ASD-Fa vs. TD-Fa 0.04** **ASD-Mo vs. TD-Mo 0.14**
			Italy	Ruta et al (2012)	ASD-P n= 245 (130Mo/115Fa)	TD-P n = 300 (150Mo/150Fa)	**n.s.**	**ASD-Fa vs. TD-Fa 0.04** **ASD-Mo vs. TD-Mo 0.03**
			Netherlands	Scheeren & Stauder (2008)	ASD-P n= 25 (12Mo/13Fa)	TD-P n= 25 (12Mo/13Fa)	**TD-Mo > ASD-Mo***	
			UK	Wheelwright et al (2010)	ASD-P n= 2000 (1429Mo/571Fa)	TD-P n= 1007 (658Mo/349Fa)	**n.s.**	**ASD-Fa vs. TD-Fa 0.13** **ASD-Mo vs. TD-Mo 0.13**
			UK	Whitehouse et al (2007)	ASD-P n = 30 (20Mo/10Fa)	SLI-P n= 25	**n.s.**	**ASD-P vs. SLI-P 0.13**
		Communication	UK	Berthoz et al (2013)	ASD-P n = 87 (28%Fa)	UA n = 47 (62%M)	**n.s.**	**ASD-P vs. UA 0.13**
			Australia	Bishop et al (2004a)	ASD-P n = 111 (65Mo/46Fa)	N-P n = 85 (48Mo/37Fa)	**ASD-P > N-P****	**ASD-Mo vs. N-Mo 0.19** **ASD-Fa vs. N-Fa 0.52**
			Turkey	Kadak et al (2014)	ASD-P n=72 (36Mo/36Fa)	TD-P n=38 (19Mo/19Fa)	**n.s.**	**ASD-P vs. TD-P 0.32**
			Turkey	Kose et al (2013)	ASD-P n = 100 (53Mo/47Fa)	TD-P n = 100 (52Mo/48Fa)	**ASD-P > TD-P****	**ASD-Fa vs. TD-Fa 0.20** **ASD-Mo vs. TD-Mo 0.62**
			Italy	Ruta et al (2012)	ASD-P n= 245 (130Mo/115Fa)	TD-P n = 300 (150Mo/150Fa)	**ASD-P > TD-P****	**ASD-Fa vs. TD-Fa 0.02** **ASD-Mo vs. TD-Mo 0.01**

			Netherlands	Scheeren & Stauder (2008)	ASD-P n= 25 (12Mo/13Fa)	TD-P n= 25 (12Mo/13Fa)	**n.s**	
			UK	Wheelwright et al (2010)	ASD-P n= 2000 (1429Mo/571Fa)	TD-P n= 1007 (658Mo/349Fa)	**ASD-P > TD-P*** **	**ASD-Fa vs. TD-Fa 0.22** **ASD-Mo vs. TD-Mo 0.41**
			UK	Whitehouse et al (2007)	ASD-P n = 30 (20Mo/10Fa)	SLI-P n= 25	**ASD-P > SLI-P***	**ASD-P vs. SLI-P 0.63**
		Imagination	UK	Berthoz et al (2013)	ASD-P n = 87 (28%Fa)	UA n = 47 (62%M)	**n.s.**	**ASD-P vs. UA 0.10**
			Australia	Bishop et al (2004a)	ASD-P n = 111 (65Mo/46Fa)	N-P n = 85 (48Mo/37Fa)	**n.s.**	**ASD-Mo vs. N-Mo 0.07** **ASD-Fa vs. N-Fa 0.19**
			Turkey	Kadak et al (2014)	ASD-P n=72 (36Mo/36Fa)	TD-P n=38 (19Mo/19Fa)	**n.s.**	**ASD-P vs. TD-P 0.02**
			Turkey	Kose et al (2013)	ASD-P n = 100 (53Mo/47Fa)	TD-P n = 100 (52Mo/48Fa)	**n.s.**	**ASD-Fa vs. TD-Fa 0.03** **ASD-Mo vs. TD-Mo 0.07**
			Italy	Ruta et al (2012)	ASD-P n= 245 (130Mo/115Fa)	TD-P n = 300 (150Mo/150Fa)	**n.s.**	**ASD-Fa vs. TD-Fa 0.06** **ASD-Mo vs. TD-Mo 0.57**
			Netherlands	Scheeren & Stauder (2008)	ASD-P n= 25 (12Mo/13Fa)	TD-P n= 25 (12Mo/13Fa)	**n.s**	
			UK	Wheelwright et al (2010)	ASD-P n= 2000 (1429Mo/571Fa)	TD-P n= 1007 (658Mo/349Fa)	**ASD-P > TD-P*** **	**ASD-Fa vs. TD-Fa 0.04** **ASD-Mo vs. TD-Mo 0.29**
			UK	Whitehouse et al	ASD-P n = 30	SLI-P n= 25	**n.s.**	**ASD-P vs. SLI-P**

				(2007)	(20Mo/10Fa)			**0.41**
		AQ Total Score	UK	Berthoz et al (2013)	ASD-P n = 87 (28%Fa)	UA n = 47 (62%M)	**n.s.**	**ASD-P vs. UA 0.06**
			Turkey	Kadak et al (2014)	ASD-P n=72 (36Mo/36Fa)	TD-P n=38 (19Mo/19Fa)	**n.s.**	**ASD-P vs. TD-P 0.39**
			Turkey	Kose et al (2013)	ASD-P n = 100 (53Mo/47Fa)	TD-P n = 100 (52Mo/48Fa)	**ASD-P > TD-P***	**ASD-Fa vs. TD-Fa 0.34 ASD-Mo vs. TD-Mo 0.27**
			Italy	Ruta et al (2012)	ASD-P n= 245 (130Mo/115Fa)	TD-P n = 300 (150Mo/150Fa)	**ASD-P > TD-P****	**ASD-Fa vs. TD-Fa 0.30 ASD-Mo vs. TD-Mo 0.29**
			Netherlands	Scheeren & Stauder (2008)	ASD-P n= 25 (12Mo/13Fa)	TD-P n= 25 (12Mo/13Fa)	**n.s**	**ASD-Fa vs. TD-Fa 0.30 ASD-Mo vs. TD-Mo 0.73**
			UK	Wheelwright et al (2010)	ASD-P n= 2000 (1429Mo/571Fa)	TD-P n= 1007 (658Mo/349Fa)	**ASD-P > TD-P*****	**ASD-Fa vs. TD-Fa 0.17 ASD-Mo vs. TD-Mo 0.38**
			UK	Whitehouse et al (2007)	ASD-P n = 30 (20Mo/10Fa)	SLI-P n= 25	**ASD-P > SLI-P***	**ASD-P vs. SLI-P 0.63**
		AQ Social/Communication score combined	USA	Ingersoll et al (2011)	ASD-Mo n = 71 (Only Mo)	N-Mo n = 94 (Only Mo)	**ASD-Mo > N-Mo***	**ASD-Mo vs. N-Mo 0.33**
		F1 (communication & socialization)	France	Robel et al (2014)	ASD-P n = 66 (35Mo/31Fa)	TD-P n = 127 (67Mo/60Fa)	**ASD-P > TD-P***	**ASD-P vs. TD-P 1.34**
		F2 (imagination &	France	Robel et al	ASD-P n = 66	TD-P n = 127	**n.s.**	**ASD-P vs. TD-P**

		rigidity)		(2014)	(35Mo/31Fa)	(67Mo/60Fa)		**0.24**
		Global score (F1 & F2 combined)	France	Robel et al (2014)	ASD-P n = 66 (35Mo/31Fa)	TD-P n = 127 (67Mo/60Fa)	**ASD-P > TD-P***	**ASD-P vs. TD-P 0.76**
	Broader Autism Phenotype Questionnaire (BAPQ) *Self & Informant Report Questionnaire*	Aloof	USA	Hurley et al (2007)	ASD-P = 86 (40Mo/46Fa) *BAP(+) n = 27* *BAP(-) n = 59*	N-P = 64 (32Mo/32Fa)	**BAP(+) > BAP(-), N-P*****	**BAP(+) vs. BAP(-) 1.49** **BAP(+) vs. N-P 1.30**
			USA	Sasson et al (2013)	ASD-P n=711 (50.5% Fa)	N-P n = 981 (49.9% Fa)	**ASD-Fa > N-Fa**** **ASD-Mo > N-Mo*****	**ASD-Fa vs. N-Fa 0.26** **ASD-Mo vs. N-Mo 0.34**
		Rigid	USA	Hurley et al (2007)	ASD-P = 86 (40Mo/46Fa) *BAP(+) n = 27* *BAP(-) n = 59*	N-P = 64 (32Mo/32Fa)	**BAP(+) > BAP(-), N-P*****	**BAP(+) vs. BAP(-) 0.77** **BAP(+) vs. N-P 0.73**
			USA	Sasson et al (2013)	ASD-P n=711 (50.5% Fa)	N-P n = 981 (49.9% Fa)	**ASD-Fa > N-Fa***** **ASD-Mo > N-Mo*****	**ASD-Fa vs. N-Fa 0.35** **ASD-Mo vs. N-Mo 0.29**
		Pragmatic Language	USA	Hurley et al (2007)	ASD-P = 86 (40Mo/46Fa) *BAP(+) n = 27* *BAP(-) n = 59*	N-P = 64 (32Mo/32Fa)	**BAP(+) > BAP(-)** , N-P***	**BAP(+) vs. BAP(-) 0.94** **BAP(+) vs. N-P 1.13**
			USA	Sasson et al (2013)	ASD-P n=711 (50.5% Fa)	N-P n = 981 (49.9% Fa)	**ASD-Fa > N-Fa**** **ASD-Mo > N-Mo*****	**ASD-Fa vs. N-Fa 0.28** **ASD-Mo vs. N-Mo 0.44**
		Total score	USA	Hurley et al (2007)	ASD-P = 86 (40Mo/46Fa)	N-P = 64 (32Mo/32Fa)	**BAP(+) > BAP(-), N-P*****	**BAP(+) vs. BAP(-) 1.49**

					BAP(+) n = 27 *BAP(-) n = 59*			**BAP(+) vs. N-P 1.43**
			USA	Sasson et al (2013)	ASD-P n=711 (50.5% Fa)	N-P n = 981 (49.9% Fa)	**ASD-Fa > N-Fa***** **ASD-Mo > N-Mo*****	**ASD-Fa vs. N-Fa 0.37** **ASD-Mo vs. N-Mo 0.45**
	Broader Phenotype Autism Symptom Scale (BPASS) *Interview & Direct Behavioral Observation*	Social	USA	Bernier et al (2012)	MPX-P n=39 SPX-P n=22	DD-P n = 20 TD-P n = 20	**MPX-P > SPX-P* > DD-P** > TD-P***	**MPX-P vs. DD-P 0.84** **MPX-P vs. TD-P 0.77** **MPX-P vs. SPX-P 0.75**
		Expressiveness	USA	Bernier et al (2012)	MPX-P n=39 SPX-P n=22	DD-P n = 20 TD-P n = 20	**MPX-P > TD-P***** 	**MPX-P vs. TD-P 1.28**
		Conversation	USA	Bernier et al (2012)	MPX-P n=39 SPX-P n=22	DD-P n = 20 TD-P n = 20	**n.s.**	
		Restricted Interests	USA	Bernier et al (2012)	MPX-P n=39 SPX-P n=22	DD-P n = 20 TD-P n = 20	**MPX-P > TD-P***	**MPX-P vs. TD-P 0.93**
	Communication Checklist - Adult Version (CC-A) *Informant Report Questionnaire*	Language Structure	UK / Ireland / USA / Canada / Australia	Whitehouse et al (2010)	ASD-P n= 238 (115Mo/123Fa)	UA n= 187 (90M/97F)	**n.s.**	**ASD-P vs. UA 0.04**
		Pragmatic Skills	UK / Ireland / USA / Canada / Australia	Whitehouse et al (2010)	ASD-P n= 238 (115Mo/123Fa)	UA n= 187 (90M/97F)	**n.s.**	**ASD-P vs. UA 0.18**
		Social Engagement	UK / Ireland / USA / Canada / Australia	Whitehouse et al (2010)	ASD-P n= 238 (115Mo/123Fa)	UA n= 187 (90M/97F)	**ASD-P < UA***	**ASD-P vs. UA 0.43**
		Total Score (1 SD below mean)	UK / Ireland / USA / Canada / Australia	Whitehouse et al (2010)	ASD-P n= 238 (115Mo/123Fa)	UA n= 187 (90M/97F)	**ASD-P < UA***	

	Family History Interview / Schedule (FHI/FHS) *Interview*	Social	USA	(FHS) Piven et al (1997a)	MPX-P n= 48 (25Mo/23Fa)	DS-P n = 60 (30Mo/30Fa)	**MPX-P > DS-P**** **MPX-Fa > DS-Fa***** **MPX-Mo > DS-Mo***	
			UK	Pickles et al (2013) *Modified version*	ASD-P n = 193 (97Mo/96Fa)	SLI-P n = 103 (54Mo/49Fa) SLI+ASD-P n = 43 (23Mo/20Fa) DS-P n = 70 (35Mo/35Fa)	**ASD-P >SLI-P***	
		Communication	USA	(FHS) Piven et al (1997a)	MPX-P n= 48 (25Mo/23Fa)	DS-P n = 60 (30Mo/30Fa)	**n.s.**	
			UK	Pickles et al (2013) *Modified version*	ASD-P n = 193 (97Mo/96Fa)	SLI-P n = 103 (54Mo/49Fa) SLI+ASD-P n = 43 (23Mo/20Fa) DS-P n = 70 (35Mo/35Fa)	**n.s.**	
		Definite & Probable ELRCD	USA	Folstein et al (1999)	ASD-P n = 166	DS-P n = 75	**ASD-P > DS-P****	
		Definite only ELRCD	USA	Folstein et al (1999)	ASD-P n = 166	DS-P n = 75	**ASD-P > DS-P***	
		Stereotyped behaviours	USA	(FHS) Piven et al (1997a)	MPX-P n= 48 (25Mo/23Fa)	DS-P n = 60 (30Mo/30Fa)	**MPX-P > DS-P***	
	The Modified Personality Assessment Schedule – Revised (MPAS-R) *Interview*	Aloof	USA	Losh et al (2008)	MPX n=48 (25Mo/23Fa) SPX n=78	DS-P n=60	**MPX-P > DS-P**** **SPX-P > DS-P**** **MPX-P > SPX-P***	
			USA	Losh et al (2012)	ASD-Mo n = 89 (All Mo)	FXS-Mo n = 49 (All Mo) TD-Mo n = 23 (All Mo)	**n.s.**	

			USA	(MPAS) Piven et al (1994)	ASD-P n = 87 (45Mo/42Fa)	DS-P n = 38 (19Mo/19Fa)	**ASD-P > DS-P****	
			USA	Piven et al (1997b)	MPX-P n= 39	DS-P n = 58	**MPX-P > DS-P****	
		Anxious	USA	Losh et al (2008)	MPX-P n=48 (25Mo/23Fa) SPX-P n=78	DS-P n=60	**MPX-P > DS-P**** **SPX-P > DS-P*** **MPX-P > SPX-P****	
			USA	Piven et al (1997b)	MPX-P n= 39	DS-P n = 58	**MPX-P > DS-P**** **MPX-Fa > DS-Fa****	
		Hypersensitive	USA	Losh et al (2008)	MPX-P n=48 (25Mo/23Fa) SPX-P n=78	DS-P n=60	**MPX-P > DS-P***** **SPX-P > DS-P*** **MPX-P > SPX-P***	
			USA	Piven et al (1997b)	MPX-P n= 39	DS-P n = 58	**MPX-P > DS-P****	
		Overly conscientious	USA	Losh et al (2008)	MPX n=48 (25Mo/23Fa) SPX n=78	DS-P n=60	**MPX-P > DS-P*** **SPX-P > DS-P***	
			USA	Losh et al (2012)	ASD-Mo n = 89 (All Mo)	FXS-Mo n = 49 (All Mo) TD-Mo n = 23 (All Mo)	**n.s.**	
			USA	Piven et al (1997b)	MPX-P n= 39	DS-P n = 58	**n.s.**	
		Rigid	USA	Losh et al (2008)	MPX-P n=48 (25Mo/23Fa) SPX-P n=78	DS-P n=60	**MPX-P > DS-P***** **SPX-P > DS-P***	

							MPX-P > SPX-P**	
			USA	Losh et al (2012)	ASD-Mo n = 89 (All Mo)	FXS-Mo n = 49 (All Mo) TD-Mo n = 23 (All Mo)	**ASD-P, FXS-P > TD-P***	
			USA	Piven et al (1997b)	MPX-P n= 39	DS-P n = 58	**MPX-P > DS-P****	
		Untactful	USA	Losh et al (2008)	MPX-P n=48 (25Mo/23Fa) SPX-P n=78	DS-P n=60	**MPX-P > DS-P*** **MPX-P > SPX-P***	
			USA	(MPAS) Piven et al (1994)	ASD-P n = 87 (45Mo/42Fa)	DS-P n = 38 (19Mo/19Fa)	**ASD-P > DS-P***	
			USA	Piven et al (1997b)	MPX-P n= 39	DS-P n = 58	**n.s.**	
		Undemonstrative	USA	(MPAS) Piven et al (1994)	ASD-P n = 87 (45Mo/42Fa)	DS-P n = 38 (19Mo/19Fa)	**ASD-P > DS-P***	
			USA	Piven et al (1997b)	MPX-P n= 39	DS-P n = 58	**n.s.**	
		Unresponsive	USA	Piven et al (1997b)	MPX-P n= 39	DS-P n = 58	**n.s.**	
	Pragmatic Rating Scale (PRS) *Interview & Direct Behavioral*	Pragmatic language violations	USA	Losh et al (2008)	MPX-P n=48 (25Mo/23Fa) SPX-P n=78	DS-P n=60	**SPX-P > DS-P****	
			USA	Losh et al (2012)	ASD-Mo n = 89 (All Mo)	FXS-Mo n = 49 (All Mo) TD-Mo n = 23 (All Mo)	**ASD-Mo/FXS-Mo >TD-Mo***	

	Observation							
			USA	Piven et al (1997b)	MPX-P n= 38	DS-P n = 58	**MPX-P > DS-P****	**MPX-P vs. DS-P 0.80**
		Speech errors	USA	Losh et al (2008)	MPX-P n=48 (25Mo/23Fa) SPX-P n=78	DS-P n=60	**SPX-P > DS-P****	
			USA	Piven et al (1997b)	MPX-P n= 38	DS-P n = 58	**MPX-P > DS-P****	**MPX-P vs. DS-P 0.93**
		Total score (blind ratings)	USA	Landa et al (1992)	ASD-P n = 21	TD/DS n = 19	**ASD-P > TD/DS-P***	**ASD-P vs. TD/DS-P 0.71**
		Total score (blind & unblind ratings combined)	USA	Landa et al (1992)	ASD-P n = 43	TD/DS n = 21 TD n = 11 DS n = 10	**ASD-P > TD/DS-P*****	**ASD-P vs. TD/DS-P 0.87**
	Pragmatic Rating Scale - Modified (PRS-M) *Interview & Direct Behavioral Observation*	Emotional expressiveness and awareness of the other	USA	Ruser et al (2007)	ASD-P n= 47 (49% Fa)	SLI-P n= 47 (45% Fa) DS-P n = 21 (48% Fa)	**ASD-P > DS-P***	**ASD-P vs. SLI-P 0.25 ASD-P vs. DS-P 0.58**
		Communicative performance	USA	Ruser et al (2007)	ASD-P n= 47 (49% Fa)	SLI-P n= 47 (45% Fa) DS-P n = 21 (48% Fa)	**n.s.**	**ASD-P vs. SLI-P 0.06 ASD-P vs. DS-P 0.40**
		Over-talkativeness	USA	Ruser et al (2007)	ASD-P n= 47 (49% Fa)	SLI-P n= 47 (45% Fa) DS-P n = 21 (48% Fa)	**ASD-P > DS-P***	**ASD-P vs. SLI-P 0 ASD-P vs. DS-P 0.53**
		Language	USA	Ruser et al (2007)	ASD-P n= 47 (49% Fa)	SLI-P n= 47 (45% Fa) DS-P n = 21 (48% Fa)	**ASD-P > DS-P****	**ASD-P vs. SLI-P 0.14 ASD-P vs. DS-P 0.92**
		Total score	USA	Ruser et al (2007)	ASD-P n= 47 (49% Fa)	SLI-P n= 47 (45% Fa) DS-P n = 21	**ASD-P > DS-P****	**ASD-P vs. SLI-P 0.09 ASD-P vs. DS-P**

						(48% Fa)		**1.14**
	Social Responsiveness Scale (SRS) *Self & Informant Report Questionnaire*		Belgium / Netherlands	De la Marche et al (2012)	ASD-P n = 275 (143Mo/132Fa) MPX-P n = 93 (48Mo/45Fa) SPX-P n = 129 (68Mo/61Fa)	UA n = 595 (295F/300M)	**ASD-Fa > UA-M**** **MPX-Fa > UA-M***	**ASD-Fa vs. UA-M 0.30** **ASD-Mo vs. UA-F 0.28** **MPX-Fa vs. UA-M 0.44** **SPX-Fa vs. UA-M 0.19** **MPX-Fa vs. SPX-Fa 0.23**
			USA	Schwichtenberg et al (2010)	MPX-P n = 21 (10Mo/11Fa) SPX-P n = 239 (115Mo/124Fa)	TD-P n = 163 (81Mo/82Fa)	**MPX-Fa > TD-Fa*** **SPX-Fa > TD-Fa***	**MPX-Fa vs. TD-Fa 0.90** **SPX-Fa vs. TD-Fa 0.35** **MPX-Fa vs. SPX-Fa 0.38** **MPX-Mo vs. TD-Mo 0.27** **SPX-Mo vs. TD-Mo 0.02** **MPX-Mo vs. SPX-Mo 0.18**
Other measures of Personality and Friendships	**The Friendship Interview**	Quality of friendships (higher scores indicate fewer friendships)	USA	Losh et al (2008)	MPX-P n=48 (25Mo/23Fa) SPX-P n=78	DS-P n=60	**SPX-P > DS-P**** **MPX-P > SPX-P***	
			USA	Piven et al (1997b)	MPX-P n= 38	DS-P n = 58	**MPX-P > DS-P*****	**MPX-P vs. DS-P 1.14**
	The NEO Personality Inventory (NEO-PI)	Neuroticism	USA	Losh et al (2008)	MPX-P n=48 (25Mo/23Fa) SPX-P n=78	DS-P n=60	**SPX-P > DS-P***** **MPX-P > SPX-P***	
			USA	Piven et al (1997b)	MPX-P n= 38	DS-P n = 58	**MPX-P > DS-P*****	**MPX-P vs. DS-P 0.79**

Reciprocal Social Interaction ***Alexithymia***	**Toronto Alexithymia Scale (TAS-20)**	Difficulty Identifying Feelings (DIF)	Canada	Szatmari et al (2008)	ASD-P n = 439 (237Mo/202Fa)	PW-P n = 45 (28Mo/17Fa)	**n.s.**	
			UK	Berthoz et al (2013)	ASD-P n = 87 (28%Fa)	UA n = 47 (62%M)	**n.s.**	**ASD-P vs. UA 0.25**
		Difficulty Describing Feelings (DDF)	Canada	Szatmari et al (2008)	ASD-P n = 439 (237Mo/202Fa)	PW-P n = 45 (28Mo/17Fa)	**n.s.**	
			UK	Berthoz et al (2013)	ASD-P n = 87 (28%Fa)	UA n = 47 (62%M)	**n.s.**	**ASD-P vs. UA 0.14**
		Externally-Oriented Thinking (EOT)	Canada	Szatmari et al (2008)	ASD-P n = 439 (237Mo/202Fa)	PW-P n = 45 (28Mo/17Fa)	**n.s.**	
			UK	Berthoz et al (2013)	ASD-P n = 87 (28%Fa)	UA n = 47 (62%M)	**n.s.**	**ASD-P vs. UA 0.16**
		Total score	Canada	Szatmari et al (2008)	ASD-P n = 439 (237Mo/202Fa)	PW-P n = 45 (28Mo/17Fa)	**ASD-P > PW-P***	
			UK	Berthoz et al (2013)	ASD-P n = 87 (28%Fa)	UA n = 47 (62%M)	**n.s.**	**ASD-P vs. UA 0.23**
Anhedonia								
	Bermond-Vorst Alexithymia Questionnaire-B (BVAQ-B)	Total score	UK	Berthoz et al (2013)	ASD-P n = 87 (28%Fa)	UA n = 47 (62%M)	**n.s.**	**ASD-P vs. UA 0.15**
		Cognitive score	UK	Berthoz et al (2013)	ASD-P n = 87 (28%Fa)	UA n = 47 (62%M)	**n.s.**	**ASD-P vs. UA 0.19**
		Affective score	UK	Berthoz et al (2013)	ASD-P n = 87 (28%Fa)	UA n = 47 (62%M)	**n.s.**	**ASD-P vs. UA 0.02**
	Revised Social Anhedonia Scale (SAS)	Total score	UK	Berthoz et al (2013)	ASD-P n = 87 (28%Fa)	UA n = 47 (62%M)	**n.s.**	**ASD-P vs. UA 0.25**

	Physical Anhedonia Scale (PAS)	Total score	UK	Berthoz et al (2013)	ASD-P n = 87 (28%Fa)	UA n = 47 (62%M)	**ASD-P > UA****	**ASD-P vs. UA 0.33**
Social and Narrative Language	**Grice's Conversational Maxims Task**	No. of errors	Italy	Di Michele et al (2007)	ASD n = 46	DS n=14 TD n=12	**ASD-P > TD-P***** **ASD-P > DS-P***	
	Spontaneous Narrative Discourse	Story length (mean o. of clauses)	USA	Landa et al (1991)	ASD-P n = 41	TD/DS-P n = 23 total TD-P n = 10 DS-P n = 13	**n.s.**	**ASD-P vs. TD/DS-P 0.35**
		Stories w/ complete episodes	USA	Landa et al (1991)	ASD-P n = 41	TD/DS-P n = 23 total TD-P n = 10 DS-P n = 13	**ASD-P < TD/DS-P****	**ASD-P vs. TD/DS-P 0.71**
		Stories w/ multiple episodes	USA	Landa et al (1991)	ASD-P n = 41	TD/DS-P n = 23 total TD-P n = 10 DS-P n = 13	**ASD-P < TD/DS-P****	
		Stories w/ incomplete episodes	USA	Landa et al (1991)	ASD-P n = 41	TD/DS-P n = 23 total TD-P n = 10 DS-P n = 13	**ASD-P > TD/DS-P***	**ASD-P vs. TD/DS-P 0.50**
		Mean overall quality	USA	Landa et al (1991)	ASD-P n = 41	TD/DS-P n = 23 total TD-P n = 10 DS-P n = 13	**ASD-P < TD/DS-P****	**ASD-P vs. TD/DS-P 0.73**
Repetitive, restrictive	**Real-life Skills and Preferences**	Social items	UK	Briskman et al (2001)	ASD-P n = 42 (21Mo/21Fa)	DLX-P n = 27 (14Mo/13Fa)	**ASD-P > DLX-P > TD-P***	**ASD-P vs. DLX-P 0.92**

behaviors and interests ***(Everyday Preferences and abilities)***						TD-P n = 28 (14Mo/14Fa)	**ASD-Fa > DLX-Fa**** **ASD-Fa > TD-Fa**** **ASD-Mo > DLX-Mo**** **ASD-Mo > TD-Mo****	**ASD-P vs. TD-P 0.91** **ASD-Fa vs. DLX-Fa 1.03** **ASD-Fa vs. TD-Fa 1.11** **ASD-Mo vs. DLX-Mo 0.89** **ASD-Mo vs. TD-Mo 0.77**
		Non-social items	UK	Briskman et al (2001) [42]	ASD-P n = 42 (21Mo/21Fa)	DLX-P n = 27 (14Mo/13Fa) TD-P n = 28 (14Mo/14Fa)	**ASD-P > TD-P**** **ASD-Fa > TD-Fa***	**ASD-P vs. DLX-P 0.44** **ASD-P vs. TD-P 0.76** **ASD-Fa vs. DLX-Fa 0.37** **ASD-Fa vs. TD-Fa 0.9** **ASD-Mo vs. DLX-Mo 0.54** **ASD-Mo vs. TD-Mo 0.64**

Note. ASD = Autism Spectrum Disorder; BAP = Broad Autism Phenotype; BAP(+) = BAP present; BAP (-) = BAP absent; P = Parent; Mo = Mother; Fa = Father; M = Male; F = Female; MPX = Multiple incidence autism families; SPX = Single incidence autism families; DD = Developmental delay without autism; DLX = Dyslexia; DS = Down Syndrome; FXS = Fragile X Syndrome; N = Normative sample; PWD = Prader Willie; SLI = Specific Language Impairment; TD = typically developing; UA = Unaffected adult.

*p<0.05; **p<0.01; ***p<0.001

Appendix 3: Cognitive Endophenotype Matrix – Review of studies of parents of autistic probands.

Domain	Method / Measure	Factors / Subscales	Country	Study	ASD Parent Group Characteristics	Control Group Characteristics	Key Findings in relation to Proband Diagnosis	
							***P* value**	**Effect Size (*d*)**
General Intellectual Functioning	***Weschler Scales*** Verbal IQ (VIQ)	Total Score or Estimate	Australia	Bishop et al (2004a)	ASD-P n = 121 (69Mo/52Fa)	N-P n = 89 (52Mo/37Fa)	**n.s.**	**ASD-Mo vs. N-Mo 0.20** **ASD-Fa vs. N-Fa 0.21**
			Australia	Bishop et al (2004b)	ASD-P = 142 (77Mo/65Fa)	N-P n = 96 (57Mo/39Fa)	**n.s.**	**ASD-Mo vs. N-Mo 0.19** **ASD-Fa vs. N-Fa 0.07**
			Netherlands	de Jonge et al (2006)	MPX-P n = 51 (26Mo/25Fa)	DS-P n = 54 (28Fa/26Mo)	**n.s.**	**MPX-P vs. DS-P 0.11**
			Netherlands	de Jonge et al (2007)	MPX-P n = 51 (26Mo/25Fa)	DS-P n = 52 (25Fa/27Mo)	**n.s.**	**MPX-P vs. DS-P 0.17**
			Netherlands	de Jonge et al (2009)	MPX-P n = 51 (26Mo/25Fa)	DS-P n = 57 (28Mo/29Fa)	**n.s.**	**MPX-P vs. DS-P 0.09**
			USA	Folstein et al (1999)	ASD-P n = 166	DS-P n = 75	**n.s.**	**ASD-P vs. DS-P 0.19**
			UK	Fombonne et al (1997)	ASD-P n = 160 (86Mo/74Fa)	DS-P n = 42 (23Mo/19Fa)	**ASD-P > DS-P****	**ASD-P vs. DS-P 0.51**
			UK	Happé et al (2001)	ASD-P n = 43 (21Mo/22Fa)	DLX-P n = 30 (15Mo/15Fa) TD-P n = 20 (10Mo/10Fa)	**n.s.**	**ASD-Mo vs. DLX-Mo 0.05** **ASD-Mo vs. TD-Mo 0.17** **ASD-Fa vs. DLX-Fa 0.26** **ASD-Fa vs. TD-Fa 0.19**
			USA	Lindgren et al (2009)	ALN-P n = 39 (20Mo/19Fa) ALI-P n = 62 (31Mo/31Fa)	SLI-P n = 70 (35Mo/35Fa)	**n.s.**	**ALN-Fa vs. ALI-Fa 0.95** **ALN-Fa vs. SLI-Fa 2.10** **ALI-Fa vs. SLI-Fa 0.95** **ALN-Mo vs. ALI-Mo 0.80** **ALN-Mo vs. SLI-Mo 2.10** **ALI-Mo vs. SLI-Mo 1.28**
			USA	Piven & Palmer (1997)	MPX-P n= 48 (25Mo/23Fa)	DS-P n = 60 (30Mo/30Fa)	**n.s.**	**MPX-P vs. DS-P 0.16**
			USA	Ruser et al (2007)	ASD-P n= 47 (49% Fa)	SLI-P n= 47 (45% Fa) DS-P n = 21	**n.s.**	**ASD-P vs. SLI-P 0.09** **ASD-P vs. DS-P 0.26**

						(48% Fa)		
			USA	Schmidt et al (2008)	ASD-P n = 22 (14Mo/8Fa)	UA n = 22 (14F/8M)	**n.s.**	**ASD-P vs. UA 0.07**
			Australia	Wong et al (2006)	ASD-P n = 145 (80Mo/65Fa)	TD-P n = 96 (57Mo/39Fa)	**n.s.**	
		Digit Span	UK	Fombonne et al (1997)	ASD-P n = 160 (86Mo/74Fa)	DS-P n = 42 (23Mo/19Fa)	**ASD-P > DS-P****	**ASD-P vs. DS-P 0.48**
			UK	Whitehouse et al (2007) (modified version to assess short-term memory)	ASD-P n = 30 (20Mo/10Fa)	SLI-P n= 30 (22Mo/8Fa) TD-P n = 30 (23Mo/7Fa)	**ASD-P > SLI-P****	**ASD-P vs. SLI-P 0.67** **ASD-P vs. TD-P 0.14**
			Canada	Szatmari et al (1993)	ASD-P n = 97 (51Mo/46Fa)	DS/LBW-P n = 54 (30Mo/24Fa)	**n.s.**	**ASD-Fa vs. DS/LBW-P 0.40** **ASD-M0 vs. DS/LBW-P 0.04**
		Arithmetic	UK	Fombonne et al (1997)	ASD-P n = 160 (86Mo/74Fa)	DS-P n = 42 (23Mo/19Fa)	**n.s.**	**ASD-P vs. DS-P 0.25**
		Vocabulary	UK	Fombonne et al (1997)	ASD-P n = 160 (86Mo/74Fa)	DS-P n = 42 (23Mo/19Fa)	**ASD-P > DS-P*****	**ASD-P vs. DS-P 0.58**
			USA	Schmidt et al (2008)	ASD-P n = 22 (14Mo/8Fa)	UA n = 22 (14F/8M)	**n.s.**	**ASD-P vs. UA 0.24**
			USA	Smalley & Asarnow (1990)	ASD-P n = 15	TD-P n = 12	**ASD-P < TD-P***	**ASD-P vs. TD-P 0.96**
			Canada	Szatmari et al (1993)	ASD-P n = 97 (51Mo/46Fa)	DS/LBW-P n = 54 (30Mo/24Fa)	**n.s.**	**ASD-Fa vs. DS/LBW-P 0.40** **ASD-M0 vs. DS/LBW-P 0.04**
		Comprehension	UK	Fombonne et al (1997)	ASD-P n = 160 (86Mo/74Fa)	DS-P n = 42 (23Mo/19Fa)	**ASD-P > DS-P***	**ASD-P vs. DS-P 0.35**
			USA	Smalley & Asarnow (1990)	ASD-P n = 15	TD-P n = 12	**n.s.**	**ASD-P vs. TD-P 0.74**
			Canada	Szatmari et al	ASD-P n = 97	DS/LBW-P n = 54	**n.s.**	**ASD-Fa vs. DS/LBW-P 0.36**

				(1993)	(51Mo/46Fa)	(30Mo/24Fa)		**ASD-M0 vs. DS/LBW-P 0.31**
			Iran	Tajmirriyahi et al (2013)	ASD-P n = 48 (38Mo/10Fa)	DS-P n = 31 (25Mo/6Fa) TD-P n = 30 (23Mo/7Fa)	**n.s.**	**ASD-P vs. DS-P 0.42** **ASD-P vs. TD-P 0.39**
		Similarities	UK	Fombonne et al (1997)	ASD-P n = 160 (86Mo/74Fa)	DS-P n = 42 (23Mo/19Fa)	**ASD-P > DS-P***	**ASD-P vs. DS-P 0.35**
			USA	Schmidt et al (2008)	ASD-P n = 22 (14Mo/8Fa)	UA n = 22 (14F/8M)	**n.s.**	**ASD-P vs. UA 0.13**
	Performance IQ (PIQ)	Total Score or Estimate	Australia	Bishop et al (2004a)	ASD-P n = 121 (69Mo/52Fa)	N-P n = 89 (52Mo/37Fa)	**n.s.**	**ASD-Mo vs. N-Mo 0.10** **ASD-Fa vs. N-Fa 0.17**
			Australia	Bishop et al (2004b)	ASD-P = 142 (77Mo/65Fa)	N-P n = 96 (57Mo/39Fa)	**n.s.**	**ASD-Mo vs. N-Mo 0.03** **ASD-Fa vs. N-Fa 0.38**
			Netherlands	de Jonge et al (2006)	MPX-P n=51 (26Mo/25Fa)	DS-P n = 54 (28Fa/26Mo)	**n.s.**	**MPX-P vs. DS-P 0.03**
			Netherlands	de Jonge et al (2007)	MPX-P n = 51 (26Mo/25Fa)	DS-P n = 52 (25Fa/27Mo)	**n.s.**	**MPX-P vs. DS-P 0.11**
			Netherlands	de Jonge et al (2009)	MPX-P n = 51 (26Mo/25Fa)	DS-P n = 57 (28Mo/29Fa)	**n.s.**	**MPX-P vs. DS-P 0.05**
			USA	Folstein et al (1999)	ASD-P n = 166	DS-P n = 75	**ASD-P < DS-P**** **ASD-Fa < DS-Fa***	**ASD-P vs. DS-P 0.35**
			UK	Fombonne et al (1997)	ASD-P n = 160 (86Mo/74Fa)	DS-P n = 42 (23Mo/19Fa)	**n.s.**	**ASD-P vs. DS-P 0.13**
			UK	Happé et al (2001)	ASD-P n = 43 (21Mo/22Fa)	DLX-P n = 30 (15Mo/15Fa) TD-P n = 20 (10Mo/10Fa)	**n.s.**	**ASD-Mo vs. DLX-Mo 0.09** **ASD-Mo vs. TD-Mo 0.26** **ASD-Fa vs. DLX-Fa 0.14** **ASD-Fa vs. TD-Fa 0**

			USA	Lindgren et al (2009)	ALN-P n = 39 (20Mo/19Fa) ALI-P n = 62 (31Mo/31Fa)	SLI-P n = 70 (35Mo/35Fa)	**ALN-Fa > ALI-Fa > SLI-Fa****	**ALN-Fa vs. ALI-Fa 0.44** **ALN-Fa vs. SLI-Fa 1.16** **ALI-Fa vs. SLI-Fa 0.72** **ALN-Mo vs. ALI-Mo 0.37** **ALN-Mo vs. SLI-Mo 0.77** **ALI-Mo vs. SLI-Mo 0.40**
			USA	Piven & Palmer (1997)	MPX-P n= 48 (25Mo/23Fa)	DS-P n = 60 (30Mo/30Fa)	**MPX-P < DS-P***	**MPX-P vs. DS-P 0.74**
			USA	Ruser et al (2007)	ASD-P n= 47 (49% Fa)	SLI-P n= 47 (45% Fa) DS-P n = 21 (48% Fa)	**n.s.**	**ASD-P vs. SLI-P 0.14** **ASD-P vs. DS-P 0.48**
			USA	Schmidt et al (2008)	ASD-P n = 22 (14Mo/8Fa)	UA n = 22 (14F/8M)	**ASD-P< UA***	**ASD-P vs. UA 0.62**
			Australia	Wong et al (2006)	ASD n = 145 (80Mo/65Fa)	TD-P n = 96 (57Mo/39Fa)	**n.s.**	
		Picture Completion	USA	Folstein et al (1999)	ASD-P n = 166	DS-P n = 75	**ASD-P < DS-P****	**ASD-P vs. DS-P 0.42**
			UK	Fombonne et al (1997)	ASD-P n = 160 (86Mo/74Fa)	DS-P n = 42 (23Mo/19Fa)	**n.s.**	**ASD-P vs. DS-P 0.07**
			USA	Piven & Palmer (1997)	MPX-P n= 48 (25Mo/23Fa)	DS-P n = 60 (30Mo/30Fa)	**MPX-P < DS-P***	**MPX-P vs. DS-P 0.65**
			Iran	Tajmirriyahi et al (2013)	ASD-P n = 48 (38Mo/10Fa)	DS-P n = 31 (25Mo/6Fa) TD-P n = 30 (23Mo/7Fa)	**n.s.**	**ASD-P vs. DS-P 0.12** **ASD-P vs. TD-P 0.46**
		Picture Arrangement	USA	Folstein et al (1999)	ASD-P n = 166	DS-P n = 75	**ASD-P < DS-P***	**ASD-P vs. DS-P 0.26**
			UK	Fombonne et al (1997)	ASD-P n = 160 (86Mo/74Fa)	DS-P n = 42 (23Mo/19Fa)	**n.s.**	**ASD-P vs. DS-P 0.03**
		Block Design	UK	Fombonne et al (1997)	ASD-P n = 160 (86Mo/74Fa)	DS-P n = 42 (23Mo/19Fa)	**n.s.**	**ASD-P vs. DS-P 0.21**

			USA	Piven & Palmer (1997)	MPX-P n= 48 (25Mo/23Fa)	DS-P n = 60 (30Mo/30Fa)	**n.s.**	**MPX-P vs. DS-P 0.34**
			USA	Schmidt et al (2008)	ASD-P n = 22 (14Mo/8Fa)	UA n = 22 (14F/8M)	**n.s.**	**ASD-P vs. UA 0.43**
			USA	Smalley & Asarnow (1990)	ASD-P n = 15	TD-P n = 12	**n.s.**	**ASD-P vs. TD-P 0.36**
			Canada	Szatmari et al (1993)	ASD-P n = 97 (51Mo/46Fa)	DS/LBW-P n = 54 (30Mo/24Fa)	**n.s.**	**ASD-Fa vs. DS/LBW-P 0.38** **ASD-M0 vs. DS/LBW-P 0.04**
		Object Assembly	UK	Fombonne et al (1997)	ASD-P n = 160 (86Mo/74Fa)	DS-P n = 42 (23Mo/19Fa)	**n.s.**	**ASD-P vs. DS-P 0.12**
			USA	Piven & Palmer (1997)	MPX-P n= 48 (25Mo/23Fa)	DS-P n = 60 (30Mo/30Fa)	**MPX-P < DS-P***	**MPX-P vs. DS-P 0.62**
		Matrix Reasoning	USA	Schmidt et al (2008)	ASD-P n = 22 (14Mo/8Fa)	UA n = 22 (14F/8M)	**ASD-P < UA***	**ASD-P vs. UA 0.67**
		Digit Symbol	Canada	Szatmari et al (1993)	ASD-P n = 97 (51Mo/46Fa)	DS/LBW-P n = 54 (30Mo/24Fa)	**n.s.**	**ASD-Fa vs. DS/LBW-P 0.19** **ASD-M0 vs. DS/LBW-P 0.17**
	Full Scale IQ (FSIQ)	Total Score or Estimate	USA	Adolphs et al (2008)	AD-P n = 42 total BAP(+) Aloof n = 15 (3Mo/12Fa) BAP(-) n = 27 (20Mo/7Fa)	TD-P n = 20 (8Mo/12Fa)	**n.s.**	**BAP (+) Aloof vs. TD-P 0.47** **BAP(-) vs. TD-P 0.37**
			Netherlands	de Jonge et al (2006)	MPX-P n=51 (26Mo/25Fa)	DS-P n = 54 (28Fa/26Mo)	**n.s.**	**MPX-P vs. DS-P 0.09**
			Netherlands	de Jonge et al (2007)	MPX-P n = 51 (26Mo/25Fa)	DS-P n = 52 (25Fa/27Mo)	**n.s.**	**MPX-P vs. DS-P 0.10**
			Netherlands	de Jonge et al (2009)	MPX-P n = 51 (26Mo/25Fa)	DS-P n = 57 (28Mo/29Fa)	**n.s.**	**MPX-P vs. DS-P 0.06**
			USA	Folstein et al (1999)	ASD-P n = 166	DS-P n = 75	**ASD-P < DS-P**** **ASD-Fa < DS-Fa***	**ASD-P vs. DS-P 0.30**

			UK	Fombonne et al (1997)	ASD-P n = 160 (86Mo/74Fa)	DS-P n = 42 (23Mo/19Fa)	**n.s.**	**ASD-P vs. DS-P 0.25**
			Turkey	Gocken et al (2009)	ASD-P n = 76 (38Mo/38Fa)	N-P n = 41 (21Mo/20Fa)	**n.s.**	**ASD-P vs. N-P 0.09**
			UK	Happé et al (2001)	ASD-P n = 43 (21Mo/22)	DLX-P n = 30 (15Mo/15Fa) TD-P n = 20 (10Mo/10Fa)	**n.s.**	**ASD-Mo vs. DLX-Mo 0.05** **ASD-Mo vs. TD-Mo 0.21** **ASD-Fa vs. DLX-Fa 0.28** **ASD-Fa vs. TD-Fa 0.11**
			USA	Lindgren et al (2009)	ALN-P n = 39 (20Mo/19Fa) ALI-P n = 62 (31Mo/31Fa)	SLI-P n = 70 (35Mo/35Fa)	**n.s.**	**ALN-Fa vs. ALI-Fa 0.81** **ALN-Fa vs. SLI-Fa 1.88** **ALI-Fa vs. SLI-Fa 0.97** **ALN-Mo vs. ALI-Mo 0.66** **ALN-Mo vs. SLI-Mo 1.61** **ALI-Mo vs. SLI-Mo 0.94**
			USA	Losh & Piven (2007)	ASD-P n = 48 (25Mo/23Fa) BAP(+) A*loof* n = 13 BAP(+) R*igid* n = 11 BAP(-) n = 24	TD/DS-P n = 22 TD-P n = 16 DS-P n = 6	**ASD-P < TD/DS-P****	**ASD-P vs. TD/DS-P 0.83**
			USA	Losh et al (2008)	MPX n=48 (25Mo/23Fa) SPX n=78	DS-P n=60	**MPX-P < DS-P*** **SPX-P < DS-P***	
			USA	Losh et al (2009)	ASD-P n= 83 BAP(+) *Social* n = 22 BAP(+) *Rigid/Perfectionistic* n = 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40	TD-P n = 32 (19Mo/13Fa)	**n.s.**	**ASD-P vs.TD-P 0.33**
			USA	Piven et al (1991)	ASD-P n = 81 (42Mo/39Fa)	DS-P n = 34 (18Mo/16Fa)	**n.s**	**ASD-P vs. DS-P 0.21**
			USA	Schmidt et al (2008)	ASD-P n = 22 (14Mo/8Fa)	UA n = 22 (14F/8M)	**n.s.**	**ASD-P vs. UA 0.41**
	Nonverbal Reasoning	Block Design & Matrix Reasoning	UK	Whitehouse et al (2007)	ASD-P n = 30 (20Mo/10Fa)	SLI-P n= 30 (22Mo/8Fa) TD-P n = 30	**n.s.**	**ASD-Fa vs. SLI-Fa 0.30** **ASD-Mo vs. SLI-Mo 0.43** **ASD-Fa vs. TD-Fa 0.01**

						(23Mo/7Fa)		**ASD-Mo vs. TD-Mo 0.53**
	Raven's Progressive Matrices Nonverbal IQ (NVIQ)	Total Score	Germany / Austria / Switzerland	Bölte & Poustka (2003)	ASD SPX-P n = 54 (26Mo/ 28Fa) ASD MPX-P n = 28 (16Mo/12Fa)	Sch SPX-P n = 31 (18Mo/ 13Fa) Sch MPX-P n = 4 (2Mo/2Fa) UA n = 22 (11F/11M)	**n.s.**	**ASD MPX-P vs. Sch MPX-P 0.29** **ASD MPX vs. Sch SPX-P 0.07** **ASD MPX-P vs. UA 0.08** **ASD SPX-P vs. Sch MPX-P 0.28** **ASD SPX-P vs. Sch SPX-P 0.05** **ASD SPX-P vs. UA 0.07**
			Germany	Bölte & Poustka (2006)	ASD n=62 (33Mo/29Fa)	EOS-P n = 36 (20Mo/16Fa) MR-P n = 30 (16Mo/14Fa)	**n.s.**	**ASD-P vs. EOS-P 0.54** **ASD-P vs. MR-P 0.45**
			Germany	Bölte et al (2007)	ASD SPX-P n = 87 (48Mo/39Fa) ASD MPX-P n = 38 (21Mo/17Fa)	OCD-P n = 37 (19Mo/18Fa) EOS-P n = 34 (20Mo/14Fa) MR-P n = 27 (15Mo/12Fa)	**n.s.**	**MPX-P vs. OCD-P 0.13** **MPX-P vs. EOS-P 0.52** **MPX-P vs. MR-P 0.56** **SPX-P vs. OCD-p 0.06** **SPX-P vs. EOS-P 0.48** **SPX-P vs. MR-P 0.57**
			UK	Sucksmith et al (2013)	ASD-P n = 310 (272Mo/38Fa)	UA n = 187 (93M/94F)	**n.s.**	**ASD-P vs. UA 0.17**
Structural Language Abilities ***Receptive Language***	Peabody Picture Vocabulary Test (PPVT-III)	Receptive language	USA	Lindgren et al (2009)	ALN-P n = 39 (20Mo/19Fa) ALI-P n = 62 (31Mo/31Fa)	SLI-P n = 70 (35Mo/35Fa)	**ALN-Mo > ALI-Mo > SLI-Mo*****	**ALN-Fa vs. ALI-Fa 0.77** **ALN-Fa vs. SLI-Fa 1.58** **ALI-Fa vs. SLI-Fa 0.74** **ALN-Mo vs. ALI-Mo 0.42** **ALN-Mo vs. SLI-Mo 1.33** **ALI-Mo vs. SLI-Mo 0.87**
			USA	Schmidt et al (2008)	ASD-P n = 22 (14Mo/8Fa)	UA n = 22 (14F/8M)	**n.s.**	**ASD-P vs. UA 0.33**
	Test for Reception of Grammar-2 (TROG-2)	Receptive Grammar	UK	Whitehouse et al (2007)	ASD-P n = 30 (20Mo/10Fa)	SLI-P n= 30 (22Mo/8Fa) TD-P n = 30 (23Mo/7Fa)	**n.s.**	

Expressive Language	Expressive Vocabulary Test (EVT)	Expressive language	USA	Schmidt et al (2008)	ASD-P n = 22 (14Mo/8Fa)	UA n = 22 (14F/8M)	**n.s.**	**ASD-P vs. UA 0.10**
	Verbal Fluency Subtest - Delis Kaplan Executive Function System (DK-EFS)	Letter fluency	USA	Schmidt et al (2008)	ASD-P n = 22 (14Mo/8Fa)	UA n = 22 (14F/8M)	**n.s.**	**ASD-P vs. UA 0.39**
		Category fluency	USA	Schmidt et al (2008)	ASD-P n = 22 (14Mo/8Fa)	UA n = 22 (14F/8M)	**n.s.**	**ASD-P vs. UA 0.35**
		Category switching	USA	Schmidt et al (2008)	ASD-P n = 22 (14Mo/8Fa)	UA n = 22 (14F/8M)	**n.s.**	**ASD-P vs. UA 0.16**
		Switching Accuracy	USA	Schmidt et al (2008)	ASD-P n = 22 (14Mo/8Fa)	UA n = 22 (14F/8M)	**n.s.**	**ASD-P vs. UA 0.22**
Figurative Language	Figurative Language Subtest - Test of Language Competence-Expanded Edition (TOLC-E)	Figurative Language	USA	Schmidt et al (2008)	ASD-P n = 22 (14Mo/8Fa)	UA n = 22 (14F/8M)	**n.s.**	**ASD-P vs. UA 0.28**
Phonological awareness	Comprehensive Test of Phonological Processing (CTOPP)	Phonological Awareness	USA	Lindgren et al (2009)	ALN-P n = 39 (20Mo/19Fa) ALI-P n = 62 (31Mo/31Fa)	SLI-P n = 70 (35Mo/35Fa)	**ALN-Mo > ALI-Mo > SLI-Mo*****	**ALN-Fa vs. ALI-Fa 0.42 ALN-Fa vs. SLI-Fa 0.86 ALI-Fa vs. SLI-Fa 0.38 ALN-Mo vs. ALI-Mo 0.38 ALN-Mo vs. SLI-Mo 0.78 ALI-Mo vs. SLI-Mo 0.48**
		Phonological memory	USA	Lindgren et al (2009)	ALN-P n = 39 (20Mo/19Fa) ALI-P n = 62 (31Mo/31Fa)	SLI-P n = 70 (35Mo/35Fa)	**n.s.**	**ALN-Fa vs. ALI-Fa 0.08 ALN-Fa vs. SLI-Fa 0.96 ALI-Fa vs. SLI-Fa 0.86 ALN-Mo vs. ALI-Mo 0.74 ALN-Mo vs. SLI-Mo 1.42 ALI-Mo vs. SLI-Mo 0.70**
		Rapid naming	USA	Lindgren et al (2009)	ALN-P n = 39 (20Mo/19Fa)	SLI-P n = 70 (35Mo/35Fa)	**n.s.**	**ALN-Fa vs. ALI-Fa 0.02 ALN-Fa vs. SLI-Fa 0.34**

					ALI-P n = 62 (31Mo/31Fa)			**ALI-Fa vs. SLI-Fa 0.36** **ALN-Mo vs. ALI-Mo 0.09** **ALN-Mo vs. SLI-Mo 0.47** **ALI-Mo vs. SLI-Mo 0.41**
		Non-word repetition	USA	Lindgren et al (2009)	ALN-P n = 39 (20Mo/19Fa) ALI-P n = 62 (31Mo/31Fa)	SLI-P n = 70 (35Mo/35Fa)	**ALN-Mo > ALI-Mo > SLI-Mo*****	**ALN-Fa vs. ALI-Fa 0.28** **ALN-Fa vs. SLI-Fa 1.04** **ALI-Fa vs. SLI-Fa 0.59** **ALN-Mo vs. ALI-Mo 0.51** **ALN-Mo vs. SLI-Mo 1.28** **ALI-Mo vs. SLI-Mo 0.83**
			USA	Schmidt et al (2008)	ASD-P n = 22 (14Mo/8Fa)	UA n = 22 (14F/8M)	**ASD-P < UA****	**ASD-P vs. UA 0.87**
	Nonword Memory Test	Raw score	Australia	Bishop et al (2004b)	ASD-P = 142 (77Mo/65Fa)	N-P n = 96 (57Mo/39Fa)	**n.s.**	**ASD-Fa vs. N-Fa 0.04** **ASD-Mo vs. N-Mo 0.02**
	Nonsense Passage Reading Test	Total score	Australia	Bishop et al (2004b)	ASD-P = 145 (80Mo/65Fa)	N-P n = 96 (57Mo/39Fa)	**n.s.**	**ASD-Fa vs. N-Fa 0.04** **ASD-Mo vs. N-Mo 0.42**
	Nepsy Test Battery - Repetition of Nonsense Words Subtest	Raw score	UK	Whitehouse et al (2007)	ASD-P n = 30 (20Mo/10Fa)	SLI-P n= 30 (22Mo/8Fa) TD-P n = 30 (23Mo/7Fa)	**ASD-P > SLI-P****	**ASD-P vs. SLI-P 0.88** **ASD-P vs. TD-P 0.04**
	Battery of verbal tasks (emphasis on orthographic and phonological abilities)	Composite Verbal Score	France	Plumet et al (1995)	ASD-P n = 47 (25Mo/22Fa)	DS-P n = 44 (23Mo/21Fa)	**n.s.**	**ASD-P vs. DS-P 0.22**
Reading Skills	Rapid Automized Naming (RAN)							
	Number	Time to complete	USA	Piven & Palmer (1997)	MPX-P n= 48 (25Mo/23Fa)	DS-P n = 60 (30Mo/30Fa)	**n.s.**	**MPX-P vs. DS-P 0.19**
	Letter	Time to complete	USA	Piven & Palmer (1997)	MPX-P n= 48 (25Mo/23Fa)	DS-P n = 60 (30Mo/30Fa)	**n.s.**	**MPX-P vs. DS-P 0.17**

	Colour	Time to complete	USA	Piven & Palmer (1997)	MPX-P n= 48 (25Mo/23Fa)	DS-P n = 60 (30Mo/30Fa)	**MPX-P > DS-P***	**MPX-P vs. DS-P 0.72**
	Object	Time to complete	USA	Piven & Palmer (1997)	MPX-P n= 48 (25Mo/23Fa)	DS-P n = 60 (30Mo/30Fa)	**MPX-P > DS-P***	**MPX-P vs. DS-P 0.58**
	Color/Object combined	Time to complete	USA	Losh et al (2010)	ASD-P n = 301	TD-P/DS-P n = 87	**ASD-P > TD-P/DS-P****	
	Woodcock-Johnson Psycho-Educational Battery - Revised (WJ-R)	Broad reading composite	USA	Lindgren et al (2009)	ALN-P n = 39 (20Mo/19Fa) ALI-P n = 62 (31Mo/31Fa)	SLI-P n = 70 (35Mo/35Fa)	**n.s.**	**ALN-Fa vs. ALI-Fa 0.78** **ALN-Fa vs. SLI-Fa 2.11** **ALI-Fa vs. SLI-Fa 1.06** **ALN-Mo vs. ALI-Mo 0.48** **ALN-Mo vs. SLI-Mo 1.69** **ALI-Mo vs. SLI-Mo 1.26**
		Reading skill composite	USA	Lindgren et al (2009)	ALN-P n = 39 (20Mo/19Fa) ALI-P n = 62 (31Mo/31Fa)	SLI-P n = 70 (35Mo/35Fa)	**n.s.**	**ALN-Fa vs. ALI-Fa 0.69** **ALN-Fa vs. SLI-Fa 1.84** **ALI-Fa vs. SLI-Fa 1.00** **ALN-Mo vs. ALI-Mo 0.40** **ALN-Mo vs. SLI-Mo 1.67** **ALI-Mo vs. SLI-Mo 1.24**
		Nonsense Word Reading – Reading age	USA	Folstein et al (1999)	ASD-P n = 166	DS-P n = 75	**ASD-P < DS-P***	**ASD-P vs. DS-P 0.48**
		Nonsense Word Reading – Reading grade	USA	Folstein et al (1999)	ASD-P n = 166	DS-P n = 75	**ASD-P < DS-P***	**ASD-P vs. DS-P 0.40**
		Dictation	USA	Lindgren et al (2009)	ALN-P n = 39 (20Mo/19Fa) ALI-P n = 62 (31Mo/31Fa)	SLI-P n = 70 (35Mo/35Fa)	**ALN-Mo > ALI-Mo > SLI-Mo*****	**ALN-Fa vs. ALI-Fa 0.66** **ALN-Fa vs. SLI-Fa 1.65** **ALI-Fa vs. SLI-Fa 0.87** **ALN-Mo vs. ALI-Mo 0.36** **ALN-Mo vs. SLI-Mo 1.26** **ALI-Mo vs. SLI-Mo 0.99**
			USA	Piven & Palmer (1997)	MPX-P n= 48 (25Mo/23Fa)	DS-P n = 60 (30Mo/30Fa)	**n.s.**	**MPX-P vs. DS-P 0.17**
		Passage comprehension	USA	Lindgren et al (2009)	ALN-P n = 39 (20Mo/19Fa) ALI-P n = 62	SLI-P n = 70 (35Mo/35Fa)	**ALN-Mo > ALI-Mo > SLI-Mo***	**ALN-Fa vs. ALI-Fa 0.59** **ALN-Fa vs. SLI-Fa 1.54** **ALI-Fa vs. SLI-Fa 0.79**

					(31Mo/31Fa)			**ALN-Mo vs. ALI-Mo 0.50** **ALN-Mo vs. SLI-Mo 1.46** **ALI-Mo vs. SLI-Mo 1.01**
			USA	Piven & Palmer (1997)	MPX-P n= 48 (25Mo/23Fa)	DS-P n = 60 (30Mo/30Fa)	**MPX-P < DS-P***	**MPX-P vs. DS-P 0.45**
		Word Attack	USA	Lindgren et al (2009)	ALN-P n = 39 (20Mo/19Fa) ALI-P n = 62 (31Mo/31Fa)	SLI-P n = 70 (35Mo/35Fa)	**n.s.**	**ALN-Fa vs. ALI-Fa 0.48** **ALN-Fa vs. SLI-Fa 1.30** **ALI-Fa vs. SLI-Fa 0.75** **ALN-Mo vs. ALI-Mo 0.31** **ALN-Mo vs. SLI-Mo 1.35** **ALI-Mo vs. SLI-Mo 1.06**
			USA	Piven & Palmer (1997)	MPX-P n= 48 (25Mo/23Fa)	DS –P n = 60 (30Mo/30Fa)	**n.s.**	**MPX-P vs. DS-P 0.09**
		Letter Word	USA	Piven & Palmer (1997)	MPX-P n= 48 (25Mo/23Fa)	DS n = 60 (30Mo/30Fa)	**n.s.**	**MPX-P vs. DS-P 0.24**
	Gray Oral Reading Test (GORT)	Comprehension	USA	Folstein et al (1999)	ASD-P n = 166	DS-P n = 75	**n.s.**	**ASD-P vs. DS-P 0.12**
		Passage	USA	Folstein et al (1999)	ASD-P n = 166	DS-P n = 75	**n.s.**	**ASD-P vs. DS-P 0.21**
		Reading age	UK	Fombonne et al (1997)	ASD-P n = 160 (86Mo/74Fa)	DS-P n = 42 (23Mo/19Fa)	**n.s.**	**ASD-P vs. DS-P 0.36**
	Edinburgh Reading Test (ERT)	Reading age	UK	Fombonne et al (1997)	ASD-P n = 160 (86Mo/74Fa)	DS-P n = 42 (23Mo/19Fa)	**n.s.**	**ASD-P vs. DS-P 0**
	National Adult Reading Test (NART)	Error score	UK	Baron-Cohen & Hammer (1997)	AS-P n = 30 (15Mo/15Fa)	TD-P n = 30 (15Mo/15Fa)	**n.s.**	**ASD-P vs, N-P 0.20**
			UK	Fombonne et al (1997)	ASD-P n = 160 (86Mo/74Fa)	DS-P n = 42 (23Mo/19Fa)	**ASD-P < DS-P***	**ASD-P vs. DS-P 0.44**

	Test of Word Reading Efficiency Sight Word Efficiency Subtest (real words)	Standard score	UK	Whitehouse et al (2007)	ASD-P n = 30 (20Mo/10Fa)	SLI-P n= 30 (22Mo/8Fa) TD-P n = 30 (23Mo/7Fa)	**n.s.**	**ASD-P vs. SLI-P 0.18** **ASD-P vs. TD-P 0.03**
	Phonemic Decoding Efficiency Subtest (nonsense words)	Standard score	UK	Whitehouse et al (2007)	ASD-P n = 30 (20Mo/10Fa)	SLI-P n= 30 (22Mo/8Fa) TD-P n = 30 (23Mo/7Fa)	**ASD-P > SLI-P***	**ASD-P vs. SLI-P 0.62** **ASD-P vs. TD-P 0.24**
	Reading History Questionnaire (RHQ)	Reading difficulties	USA	Schmidt et al (2008)	ASD-P n = 22 (14Mo/8Fa)	UA n = 22 (14F/8M)	**n.s.**	**ASD-P vs. UA 0.34**
Spelling abilities	Schonell Spelling Test (SST)	Total words correct	USA	Folstein et al (1999)	ASD-P n = 166	DS-P n = 75	**n.s.**	**ASD-P vs. DS-P 0.13**
			UK	Fombonne et al (1997)	ASD-P n = 160 (86Mo/74Fa)	DS-P n = 42 (23Mo/19Fa)	**ASD-P > DS-P****	**ASD-P vs. DS-P 0.62**
		Spelling age	USA	Folstein et al (1999)	ASD-P n = 166	DS-P n = 75	**n.s.**	**ASD-P vs. DS-P 0.02**
	Speeded Dictation task	Raw Score	UK	Whitehouse et al (2007)	ASD-P n = 30 (20Mo/10Fa)	SLI-P n= 30 (22Mo/8Fa) TD-P n = 30 (23Mo/7Fa)	**n.s.**	
Oromotor Functioning	Oromotor Sequencing Subtest - NEPSY Test Battery	Raw score	UK	Whitehouse et al (2007)	ASD-P n = 30 (20Mo/10Fa)	SLI-P n= 30 (22Mo/8Fa) TD-P n = 30 (23Mo/7Fa)	**ASD-P > SLI-P****	**ASD-P vs. SLI-P 0.54** **ASD-P vs. TD-P 0.43**
Social	Reading the Mind in Eyes Test	Accuracy	UK	Baron-Cohen & Hammer	AS-P n = 30 (15Mo/15Fa)	TD-P n = 30 (15Mo/15Fa)	**ASD-Fa < N-Fa**** **ASD-Mo < N-Mo*****	**ASD-Fa vs. N-Fa 0.99** **ASD-Mo vs. N-Mo 1.51**

Cognition ***Theory of Mind***				(1997)				
			USA	Losh & Piven (2007)	ASD-P n = 48 (25Mo/23Fa) BAP(+) A*loof* n = 13 BAP(+) R*igid* n = 11 BAP(-) n = 24	TD/DS-P n = 22 TD-P n = 16 DS-P n = 6	**BAP(+) A*loof* < TD/DS-P**** **BAP(+) Aloof < BAP(-)****	**BAP (+) Aloof vs. TD/DS-P 1.51** **BAP (+) Aloof vs. BAP(-) 1.49** **BAP (+) Aloof vs. BAP (+) Rigid 1.48**
			USA	Losh et al (2009)	ASD-P n= 83 BAP(+) *Social* n = 22 BAP(+) *Rigid/Perfectionistic* n = 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40	TD-P n = 32 (19Mo/13Fa)	**ASD-P < TD-P*** **BAP(+) Social< BAP(-)***** **BAP(+) Social < TD-P*****	
			Turkey	Gocken et al (2009)	ASD-P n = 76 (38Mo/38Fa)	N-P n = 41 (21Mo/20Fa)	**n.s.**	**ASD-P vs. N-P 0.43**
			Iran	Tajmirriyahi et al (2013)	ASD-P n = 48 (38Mo/10Fa)	DS-P n = 31 (25Mo/6Fa) TD-P n = 30 (23Mo/7Fa)	**n.s.**	**ASD-P vs. DS-P 0.33** **ASD-P vs. TD-P 0.03**
	The Faces Test (mental state decoding)	Accuracy	Iran	Gocken et al (2009)	ASD-P n = 76 (38Mo/38Fa)	N-P n = 41 (21Mo/20Fa)	**n.s.**	**ASD-P vs. N-P 0.23**
	Reading the Mind in the Voice Test	Accuracy	Iran	Tajmirriyahi et al (2013)	ASD-P n = 48 (38Mo/10Fa)	DS-P n = 31 (25Mo/6Fa) TD-P n = 30 (23Mo/7Fa)	**ASD-P < DS-P**, TD-P*****	**ASD-P vs. DS-P 0.63** **ASD-P vs. TD-P 0.98**
	False belief tasks: ***'Smarties task'; Sally-Anne task; Unexpected transfer test***	No. of tasks passed	Italy	Di Michele et al (2007)	ASD n = 46	DS-P n=14 TD-P n=12	**ASD-P < TD-P***** **ASD-P < DS-P*****	

	Unexpected Outcomes Test (UOT)	Total score	Turkey	Gocken et al (2009)	ASD-P n = 76 (38Mo/38Fa)	N-P n = 41 (21Mo/20Fa)	**ASD-P < N-P****	**ASD-P vs. N-P 0.58**
	The Hinting Task	Accuracy	Turkey	Gocken et al (2009)	ASD-P n = 76 (38Mo/38Fa)	N-P n = 41 (21Mo/20Fa)	**n.s.**	**ASD-P vs. N-P 0.36**
Empathy	**Empathy Quotient (EQ)**	Mean score	UK	Sucksmith et al (2013)	ASD-P n = 310 (272Mo/38Fa)	UA n = 187 (93M/94F)	**ASD-Fa < UA-M***	**ASD-Fa vs. US-M 0.40** **ASD-Mo vs. UA-F 0.11**
Affect Perception / Emotion Recognition	**Pictures of Facial affect - 'Bubbles' method**	Accuracy	USA	Adolphs et al (2008)	AD-P n = 42 total BAP(+) *Aloof* n = 15 (3Mo/12Fa) BAP(-) n = 27 (20Mo/7Fa)	TD-P n = 20 (8Mo/12Fa)	**n.s.**	
		Reaction Time	USA	Adolphs et al (2008)	AD-P n = 42 total BAP(+) *Aloof* n = 15 (3Mo/12Fa) BAP(-) n = 27 (20Mo/7Fa)	TD-P n = 20 (8Mo/12Fa)	**n.s.**	
		Use of Facial Information *Eyes region* *Mouth region*	USA	Adolphs et al (2008)	AD-P n = 42 total BAP(+) *Aloof* n = 15 (3Mo/12Fa) BAP(-) n = 27 (20Mo/7Fa)	TD-P n = 20 (8Mo/12Fa)	**BAP(+) <BAP(-) <TD-P***** **BAP(+) >BAP(-) >TD-P*****	
	Penn Emotion Recognition Test (ER40)	Time for correct answers	Brazil	das Neves et al (2011)	ASD-P n = 40 (30Mo/10Fa)	UA n = 41 (28F/13M)	**ASD-P > UA*****	**ASD-P vs. UA 1.09**
		Accuracy	Brazil	das Neves et al (2011)	ASD-P n = 40 (30Mo/10Fa)	UA n = 41 (28F/13M)	**ASD-P < UA*****	**ASD-P vs. UA 0.76**
		Female faces	Brazil	das Neves et al (2011)	ASD-P n = 40 (30Mo/10Fa)	UA n = 41 (28F/13M)	**ASD-P < UA*****	**ASD-P vs. UA 0.66**
		Male faces	Brazil	das Neves et al (2011)	ASD-P n = 40 (30Mo/10Fa)	UA n = 41 (28F/13M)	**ASD-P < UA***	**ASD-P vs. UA 0.63**

		Mild emotions	Brazil	das Neves et al (2011)	ASD-P n = 40 (30Mo/10Fa)	UA n = 41 (28F/13M)	**ASD-P < UA***	**ASD-P vs. UA 0.61**
		Extreme emotions	Brazil	das Neves et al (2011)	ASD-P n = 40 (30Mo/10Fa)	UA n = 41 (28F/13M)	**ASD-P < UA***	**ASD-P vs. UA 0.54**
	Facial Affect Recognition Test (pictures by Ekman & Friesen)	Expected answers	Germany / Austria / Switzerland	Bölte & Poustka (2003)	ASD SPX-P n = 54 (26Mo/ 28Fa) ASD MPX-P n = 28 (16Mo/12Fa)	Sch SPX-P n = 31 (18Mo/ 13Fa) Sch MPX-P n = 4 (2Mo/2Fa) UA n = 22 (11F/11M)	**n.s.**	**ASD MPX-P vs. Sch MPX-P 0.54** **ASD MPX vs. Sch SPX-P 0.36** **ASD MPX-P vs. UA 2.06** **ASD SPX-P vs. Sch MPX-P 1.39** **ASD SPX-P vs. Sch SPX-P 0.57** **ASD SPX-P vs. UA 0.32**
	Emotion Recognition Test - using set of photographs from Ekman & Friesen's (1976) 'Photos of Facial Affect'	Happiness	Turkey	Kadak et al (2014)	ASD-P n=72 (36Mo/36Fa)	TD-P n=38 (19Mo/19Fa)	**ASD-P < TD-P***	**ASD-P vs. TD-P 0.05**
		Sadness	Turkey	Kadak et al (2014)	ASD-P n=72 (36Mo/36Fa)	TD-P n=38 (19Mo/19Fa)	**n.s.**	**ASD-P vs. TD-P 0.07**
		Fearful	Turkey	Kadak et al (2014)	ASD-P n=72 (36Mo/36Fa)	TD-P n=38 (19Mo/19Fa)	**n.s.**	**ASD-P vs. TD-P 0.19**
		Disgusted	Turkey	Kadak et al (2014)	ASD-P n=72 (36Mo/36Fa)	TD-P n=38 (19Mo/19Fa)	**n.s.**	**ASD-P vs. TD-P 0.28**
		Angry	Turkey	Kadak et al (2014)	ASD-P n=72 (36Mo/36Fa)	TD-P n=38 (19Mo/19Fa)	**n.s.**	**ASD-P vs. TD-P 0.09**
		Surprised	Turkey	Kadak et al (2014)	ASD-P n=72 (36Mo/36Fa)	TD-P n=38 (19Mo/19Fa)	**ASD-P < TD-P***	**ASD-P vs. TD-P 0.40**
		Neutral	Turkey	Kadak et al (2014)	ASD-P n=72 (36Mo/36Fa)	TD-P n=38 (19Mo/19Fa)	**ASD-P < TD-P***	**ASD-P vs. TD-P 0.50**
	Karolinska Directed Emotional Faces task (KDEF)	Mean accuracy p/emotion	UK	Sucksmith et al (2013)	ASD-P n = 297 (261Mo/36Fa)	UA n = 184 (92M/92F)	**n.s.**	**ASD-Fa vs. UA-M 0.12** **ASD-Mo vs. UA-F 0.08**
		Overall mean accuracy adjusted	UK	Sucksmith et al (2013)	ASD-P n = 297 (261Mo/36Fa)	UA n = 184 (92M/92F)	**n.s.**	**ASD-Fa vs. UA-M 0.30** **ASD-Mo vs. UA-F 0.20**

		response time p/emotion						
	Point light basic emotions ***Positive emotions***	Accuracy	USA	Losh et al (2009)	ASD-P n= 83 BAP(+) *Social* n = 22 BAP(+) *Rigid/Perfectionistic* n = 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40	TD-P n = 32 (19Mo/13Fa)	**ASD-P < TD-P****	
	Negative emotions	Accuracy	USA	Losh et al (2009)	ASD-P n= 83 BAP(+) *Social* n = 22 BAP(+) *Rigid/Perfectionistic* n = 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40	TD-P n = 32 (19Mo/13Fa)	**n.s.**	
	Point light trustworthiness ***Positive stimuli***	Accuracy	USA	Losh et al (2009)	ASD-P n= 83 BAP(+) *Social* n = 22 BAP(+) *Rigid/Perfectionistic* n = 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40	TD-P n = 32 (19Mo/13Fa)	**ASD-P <TD-P**** **BAP(+) Social < BAP (-)****	
	Negative stimuli	Accuracy	USA	Losh et al (2009)	ASD-P n= 83 BAP(+) *Social* n = 22 BAP(+) *Rigid/Perfectionistic* n = 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40	TD-P n = 32 (19Mo/13Fa)	**BAP(+) Social > BAP(-)***	

	Trustworthiness of faces ***Positive faces***	Judgment of trustworthiness	USA	Losh et al (2009)	ASD-P n= 83 BAP(+) *Social* n = 22 BAP(+) *Rigid/Perfectionistic* n = 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40	TD-P n = 32 (19Mo/13Fa)	**ASD-P > TD-P*****	
	Negative faces	Judgment of trustworthiness	USA	Losh et al (2009)	ASD-P n= 83 BAP(+) *Social* n = 22 BAP(+) *Rigid/Perfectionistic* n = 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40	TD-P n = 32 (19Mo/13Fa)	**BAP(+) Social < BAP(-), TD-P*****	
	The Morphed faces task **Happy**	Accuracy	USA	Losh et al (2009)	ASD-P n= 83 BAP(+) *Social* n = 22 BAP(+) *Rigid/Perfectionistic* n = 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40	TD-P n = 32 (19Mo/13Fa)	**n.s.**	
	Low morphedness	Accuracy	USA	Losh et al (2009)	ASD-P n= 83 BAP(+) *Social* n = 22 BAP(+) *Rigid/Perfectionistic* n = 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40	TD-P n = 32 (19Mo/13Fa)	**n.s.**	
	High	Accuracy	USA	Losh et al	ASD-P n= 83	TD-P n = 32	**n.s.**	

	morphedness			(2009)	BAP(+) *Social* n = 22 BAP(+) *Rigid/Perfectionistic* n = 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40	(19Mo/13Fa)		
	Sad	Accuracy	USA	Losh et al (2009)	ASD-P n= 83 BAP(+) *Social* n = 22 BAP(+) *Rigid/Perfectionistic* n = 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40	TD-P n = 32 (19Mo/13Fa)	**n.s.**	
	Low morphedness	Accuracy	USA	Losh et al (2009)	ASD-P n= 83 BAP(+) *Social* n = 22 BAP(+) *Rigid/Perfectionistic* n = 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40	TD-P n = 32 (19Mo/13Fa)	**n.s.**	
	High morphedness	Accuracy	USA	Losh et al (2009)	ASD-P n= 83 BAP(+) *Social* n = 22 BAP(+) *Rigid/Perfectionistic* n = 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40	TD-P n = 32 (19Mo/13Fa)	**n.s.**	
	Afraid	Accuracy	USA	Losh et al (2009)	ASD-P n= 83 BAP(+) *Social* n = 22 BAP(+) *Rigid/Perfectionistic* n = 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40	TD-P n = 32 (19Mo/13Fa)	**ASD-P < TD-P****	

	Low morphedness	Accuracy	USA	Losh et al (2009)	ASD-P n= 83 BAP(+) *Social* n = 22 BAP(+) *Rigid/Perfectionistic* n = 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40	TD-P n = 32 (19Mo/13Fa)	**BAP(+) Social < TD-P***	
	High morphedness	Accuracy	USA	Losh et al (2009)	ASD-P n= 83 BAP(+) *Social* n = 22 BAP(+) *Rigid/Perfectionistic* n = 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40	TD-P n = 32 (19Mo/13Fa)	**n.s.**	
	The Movie Stills task ***Without faces***	Accuracy	USA	Losh et al (2009)	ASD-P n= 83 BAP(+) *Social* n = 22 BAP(+) *Rigid/Perfectionistic* n = 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40	TD-P n = 32 (19Mo/13Fa)	**n.s.**	
	Sad	Accuracy	USA	Losh et al (2009)	ASD-P n= 83 BAP(+) *Social* n = 22 BAP(+) *Rigid/Perfectionistic* n = 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40	TD-P n = 32 (19Mo/13Fa)	**ASD-P < TD-P****	
	Angry	Accuracy	USA	Losh et al (2009)	ASD-P n= 83 BAP(+) *Social* n = 22 BAP(+) *Rigid/Perfectionistic* n	TD-P n = 32 (19Mo/13Fa)	**ASD-P < TD-P***	

					= 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40			
	Afraid	Accuracy	USA	Losh et al (2009)	ASD-P n= 83 BAP(+) *Social* n = 22 BAP(+) *Rigid/Perfectionistic* n = 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40	TD-P n = 32 (19Mo/13Fa)	**ASD-P > TD-P*** **	
	With faces	Accuracy	USA	Losh et al (2009)	ASD-P n= 83 BAP(+) *Social* n = 22 BAP(+) *Rigid/Perfectionistic* n = 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40	TD-P n = 32 (19Mo/13Fa)	**BAP(+) Social < BAP(-), TD-P***	
	Sad	Accuracy	USA	Losh et al (2009)	ASD-P n= 83 BAP(+) *Social* n = 22 BAP(+) *Rigid/Perfectionistic* n = 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40	TD-P n = 32 (19Mo/13Fa)	**n.s.**	
	Angry	Accuracy	USA	Losh et al (2009)	ASD-P n= 83 BAP(+) *Social* n = 22 BAP(+) *Rigid/Perfectionistic* n = 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40	TD-P n = 32 (19Mo/13Fa)	**ASD-P < TD-P****	
	Afraid	Accuracy	USA	Losh et al (2009)	ASD-P n= 83 BAP(+) *Social* n = 22 BAP(+)	TD-P n = 32 (19Mo/13Fa)	**n.s.**	

					Rigid/Perfectionistic n = 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40			
	Schematic Line Drawings (emotional labeling of facial patterns)							
	Anger		Italy	Palermo et al (2006)	ASD-P n= 40 (20Mo/20Fa)	TD-P n= 40 (20Mo/20Fa)	**n.s**	
	Happiness		Italy	Palermo et al (2006)	ASD-P n= 40 (20Mo/20Fa)	TD-P n= 40 (20Mo/20Fa)	**n.s.**	
	Sadness		Italy	Palermo et al (2006)	ASD-P n= 40 (20Mo/20Fa)	TD-P n= 40 (20Mo/20Fa)	**ASD-P < TD-P****	
	Surprise		Italy	Palermo et al (2006)	ASD-P n= 40 (20Mo/20Fa)	TD-P n= 40 (20Mo/20Fa)	**n.s.**	
	Disgust		Italy	Palermo et al (2006)	ASD-P n= 40 (20Mo/20Fa)	TD-P n= 40 (20Mo/20Fa)	**ASD-P < TD-P****	
	Overall recognition		Italy	Palermo et al (2006)	ASD-P n= 40 (20Mo/20Fa)	TD-P n= 40 (20Mo/20Fa)	**ASD-P < TD-P****	
	Emotion Matching Task		USA	Smalley & Asarnow (1990)	ASD-P n = 15	TD-P n = 12	**n.s.**	**ASD-P vs. TD-P 0.06**
	Emotion Labeling Task		USA	Smalley & Asarnow (1990)	ASD-P n = 15	TD-P n = 12	**n.s.**	**ASD-P vs. TD-P 0.19**
Executive Function ***Set-Shifting***	**Intradimensional - Extradimensional set-shifting task (IDED)**	Perseveration (EDS Stage)	Australia	Wong et al (2006)	ASD-P n = 145 (80Mo/65Fa)	TD-P n = 96 (57Mo/39Fa)	**n.s.**	
		Learned irrelevance (EDS	Australia	Wong et al (2006)	ASD-P n = 145 (80Mo/65Fa)	TD-P n = 96 (57Mo/39Fa)	**ASD-P > TD-P*** **ASD-Fa > TD-Fa***	**ASD-Fa vs. TD-Fa 0.52**

		Stage)						
		Trials to criterion (EDS Stage)	France	Hughes et al (1997)	ASD-P n=40 (20Mo/20Fa)	LD-P n=40 (22Mo/18Fa) UA n=36 (18M, 15F)	**ASD-P > LD-P**** **ASD-P > UA*****	**ASD-P vs. LD-P 0.69** **ASD-P vs. UA 0.83**
		Errors to criterion (EDS Stage)	France	Hughes et al (1997)	ASD-P n=40 (20Mo/20Fa)	LD-P n=40 (22Mo/18Fa) UA n=36 (18M, 15F)	**ASD-P > LD-P*** **ASD-P > UA****	**ASD-P vs. LD-P 0.64** **ASD-P vs. UA 0.70**
	Wisconsin Card Sorting Test (WCST)	Preservative errors	Germany	Bölte & Poustka (2006)	ASD-P n=62 (33Mo/29Fa)	EOS-P n = 36 (20Mo/16Fa) MR-P n = 30 (16Mo/14Fa)	**n.s.**	**ASD-P vs. EOS-P 0.06** **ASD-P vs. MR-P 0.18**
	Trail Making Test (A & B)	Total time to complete	Germany	Bölte & Poustka (2006)	ASD-P n=62 (33Mo/29Fa)	EOS-P n = 36 (20Mo/16Fa) MR-P n = 30 (16Mo/14Fa)	**n.s.**	**ASD-P vs. EOS-P 0.38** **ASD-P vs. MR-P 0.13**
			USA	Losh et al (2009)	ASD-P n= 83 BAP(+) *Social* n = 22 BAP(+) *Rigid/Perfectionistic* n = 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40	TD-P n = 32 (19Mo/13Fa)	**n.s.**	
Planning	**Tower of London (ToL)**	Number of extra moves	France	Hughes et al (1997)	ASD-P n=40 (20Mo/20Fa)	LD-P n=40 (22Mo/18Fa) UA n=36 (18M, 15F)	**ASD-P > UA***	**ASD-P vs. LD-P 0.41** **ASD-P vs. UA 0.93**
		Adjusted extra moves score	Australia	Wong et al (2006)	ASD-P n = 145 (80Mo/65Fa)	TD-P n = 96 (57Mo/39Fa)	**n.s.**	**ASD-P vs. TD-P 0.07**
		Rule violations	Australia	Wong et al (2006) [62]	ASD-P n = 145 (80Mo/65Fa)	TD-P n = 96 (57Mo/39Fa)	**n.s.**	
		Solutions correct	France	Hughes et al (1997) [63]	ASD-P n=40 (20Mo/20Fa)	LD-P n=40 (22Mo/18Fa) UA n=36	**ASD-P < UA*****	**ASD-P vs. LD-P 0.34** **ASD-P vs. UA 0.93**

						(18M, 15F)		
	Tower of Hanoi (ToH)	Total time to complete	Germany	Bölte & Poustka (2006) *4 ring version*	ASD-P n=62 (33Mo/29Fa)	EOS-P n = 36 (20Mo/16Fa) MR-P n = 30 (16Mo/14Fa)	**n.s.**	**ASD-P vs. EOS-P 0.45** **ASD-P vs. MR-P 0.01**
			USA	Losh et al (2009)	ASD-P n= 83 BAP(+) *Social* n = 22 BAP(+) *Rigid/Perfectionistic* n = 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40	TD-P n = 32 (19Mo/13Fa)	**n.s.**	
		Planning efficiency score	USA	Piven & Palmer (1997)	MPX-P n= 48 (25Mo/23Fa)	DS-P n = 60 (30Mo/30Fa)	*3 ring version* **MPX-P < DS-P*** *4 ring version* **MPX-P < DS-P***	*3 ring version* **MPX-P vs. DS-P 0.40** *4 ring version* **MPX-P vs. DS-P 0.48**
			USA	Losh et al (2009)	ASD-P n= 83 BAP(+) *Social* n = 22 BAP(+) *Rigid/Perfectionistic* n = 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40	TD-P n = 32 (19Mo/13Fa)	**n.s.**	
Generativity / Ideational Fluency	**Pattern Meanings**	Overall response generativity	Australia	Wong et al (2006)	ASD-P n = 145 (80Mo/65Fa)	TD-P n = 96 (57Mo/39Fa)	**ASD-P < TD-P*****	**ASD-P vs. TD-P 0.51**
Spatial Working Memory / Inhibition	**Visual Search Test**	Between search errors	France	Hughes et al (1997)	ASD-P n=40 (20Mo/20Fa)	LD-P n=40 (22Mo/18Fa) UA n=36 (18M, 15F)	**ASD-P > UA*** **ASD-Fa > UA-M***	**ASD-P vs. LD-P 0.27** **ASD-P vs. UA 0.95**
		Within search errors	France	Hughes et al (1997)	ASD-P n=40 (20Mo/20Fa)	LD-P n=40 (22Mo/18Fa) UA n=36 (18M, 15F)	**n.s.**	

	The Delayed Oculomotor Task **(Eye movement abnormality)**	Percent premature saccades 1s delay 3s delay	USA	Koczat et al (2002)	ASD-P n = 11 (7Mo/4Fa)	UA n = 17 (8F/9M)	**n.s.**	**ASD-P vs. UA 0.18** **ASD-P vs. UA 0.55**
		Latency remembered saccades 1s delay 3s delay	USA	Koczat et al (2002)	ASD-P n = 11 (7Mo/4Fa)	UA n = 17 (8F/9M)	**n.s.**	**ASD-P vs. UA 0.41** **ASD-P vs. UA 0.04**
		Spatial error of remembered saccades (accuracy) 1s delay 3s delay	USA	Koczat et al (2002)	ASD-P n = 11 (7Mo/4Fa)	UA n = 17 (8F/9M)	**ASD-P < UA****	**ASD-P vs. UA 1.27** **ASD-P vs. UA 0.68**
	Response Inhibition and Load (RIL)	No. of errors	Australia	Wong et al (2006)	ASD-P n = 141	TD-P n = 94	**n.s.**	**ASD-P vs. TD-P 0.28**
		Reaction time for correct responses	Australia	Wong et al (2006)	ASD-P n = 141	TD-P n = 94	**n.s.**	**ASD-P vs. TD-P 0.04**
		Working memory measure	Australia	Wong et al (2006)	ASD-P n = 141	TD-P n = 94	**n.s.**	**ASD-P vs. TD-P 0.08**
Verbal Working Memory	**Auditory Consonant Trigrams (ACT)**	Accuracy	Turkey	Gocken et al (2009)	ASD-P n = 76 (38Mo/38Fa)	N-P n = 41 (21Mo/20Fa)	**ASD-P < N-P****	**ASD-P vs. N-P 0.55**
	Verbal Fluency (letters KAS in Turkish)	Accuracy	Turkey	Gocken et al (2009)	ASD-P n = 76 (38Mo/38Fa)	N-P n = 41 (21Mo/20Fa)	**n.s.**	**ASD-P vs. N-P 0.26**
	Stroop Interference Test	Interference score	Turkey	Gocken et al (2009)	ASD-P n = 76 (38Mo/38Fa)	N-P n = 41 (21Mo/20Fa)	**n.s.**	**ASD-P vs. N-P 0.2**

Central Coherence (Local visual processing) ***Disembedding Performance***	**Embedded Figures Test (EFT)**	Reaction Time	UK	Baron-Cohen & Hammer (1997)	AS-P n = 30 (15Mo/15Fa)	TD-P n = 30 (15Mo/15Fa)	**ASD-Fa > N-Fa**** **ASD-Mo > N-Mo****	**ASD-Fa vs. N-Fa 0.51** **ASD-Mo vs. N-Fa 0.68**
			Germany	Bölte & Poustka (2006)	ASD-P n=62 (33Mo/29Fa)	EOS-P n = 36 (20Mo/16Fa) MR-P n = 30 (16Mo/14Fa)	**ASD-P > EOS-P***** **ASD-P > MR-P***	**ASD-P vs. EOS-P 1.60** **ASD-P vs. MR-P 0.79**
			Netherlands	de Jonge et al (2006)	MPX-P n=51 (26Mo/25Fa)	DS-P n = 54 (28Fa/26Mo)	**n.s.**	**MPX-P vs. DS-P 0.01** **MPX-Fa vs. DS-Fa 0.04** **MPX-Mo vs. DS-Mo 0.09**
			UK	Happé et al (2001)	ASD-P n = 43 (21Mo/22Fa)	DLX-P n = 30 (15Mo/15Fa) TD-P n = 20 (10Mo/10Fa)	**ASD-Fa > DLX-Fa**** **ASD-Fa > TD-Fa****	**ASD-Mo vs. DLX-Mo 0.54** **ASD-Mo vs. TD-Mo 0.64** **ASD-Fa vs. DLX-Fa 1.11** **ASD-Fa vs. TD-Fa 1.09**
			USA	Losh et al (2009)	ASD-P n= 83 BAP(+) *Social* n = 22 BAP(+) *Rigid/Perfectionistic* n = 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40	TD-P n = 32 (19Mo/13Fa)	**n.s.**	
		Accuracy	Netherlands	de Jonge et al (2006)	MPX-P n=51 (26Mo/25Fa)	DS-P n = 54 (28Fa/26Mo)	**n.s.**	**MPX-P vs. DS-P 0.16** **MPX-Fa vs. DS-Fa 0.21** **MPX-Mo vs. DS-Mo 0.11**
			UK	Happé et al (2001)	ASD-P n = 43 (21Mo/22Fa)	DLX-P n = 30 (15Mo/15Fa) TD-P n = 20 (10Mo/10Fa)	**n.s.**	**ASD-Mo vs. DLX-Mo 0.26** **ASD-Mo vs. TD-Mo 0.77** **ASD-Fa vs. DLX-Fa 0.17** **ASD-Fa vs. TD-Fa 0.31**
			USA	Losh et al (2009)	ASD-P n= 83 BAP(+) *Social* n = 22 BAP(+) *Rigid/Perfectionistic* n = 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40	TD-P n = 32 (19Mo/13Fa)	**n.s.**	
		No. of incorrect responses	Netherlands	de Jonge et al (2006)	MPX-P n=51 (26Mo/25Fa)	DS-P n = 54 (28Fa/26Mo)	**ASD-Fa < DS-Fa***	**MPX-P vs. DS-P 0.32** **MPX-Fa vs. DS-Fa 0.52** **MPX-Mo vs. DS-Mo 0.18**

Mental Segmentation Ability								
	Titchener Circles Illusion	No. of errors	UK	Happé et al (2001)	ASD-P n = 43 (21Mo/22Fa)	DLX-P n = 30 (15Mo/15Fa) TD-P n = 20 (10Mo/10Fa)	**ASD-Fa < DLX-Fa***	
	Unsegmented Block Design task (adaptation from Weschler subtest)	Reaction time	UK	Happé et al (2001)	ASD-P n = 43 (21Mo/22Fa)	DLX-P n = 30 (15Mo/15Fa) TD-P n = 20 (10Mo/10Fa)	**ASD-Fa > TD-Fa***	**ASD-Mo vs. DLX-Mo 0.54** **ASD-Mo vs. TD-Mo 0.24** **ASD-Fa vs. DLX-Fa 0.64** **ASD-Fa vs. TD-Fa 0.84**
			USA	Losh et al (2009)	ASD-P n= 83 BAP(+) *Social* n = 22 BAP(+) *Rigid/Perfectionistic* n = 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40	TD-P n = 32 (19Mo/13Fa)	**n.s.**	
	Segmented Block Design task (adaptation from Weschler subtest)	Reaction time	UK	Happé et al (2001)	ASD-P n = 43 (21Mo/22Fa)	DLX-P n = 30 (15Mo/15Fa) TD-P n = 20 (10Mo/10Fa)	**n.s.**	**ASD-Mo vs. DLX-Mo 0.04** **ASD-Mo vs. TD-Mo 0.63** **ASD-Fa vs. DLX-Fa 0.10** **ASD-Fa vs. TD-Fa 0.17**
			USA	Losh et al (2009)	ASD-P n= 83 BAP(+) *Social* n = 22 BAP(+) *Rigid/Perfectionistic* n = 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40	TD-P n = 32 (19Mo/13Fa)	**n.s.**	
	Block Design task (Weschler subtest)	Reaction time	Netherlands	Scheeren & Stauder (2008)	ASD-P n= 25 (12Mo/13Fa)	TD-P n= 25 (12Mo/13Fa)	**n.s**	**ASD-Fa vs. TD-Fa 0.19** **ASD-Mo vs. TD-Mo 0.11**
			Germany	Bölte & Poustka (2006)	ASD n=62 (33Mo/29Fa)	EOS-P n = 36 (20Mo/16Fa) MR-P n = 30 (16Mo/14Fa)	**n.s.**	**ASD-P vs. EOS-P 0.33** **ASD-P vs. MR-P 0.52**

	Block design reconstruction task (patterns by Akshoomoff & Stiles)	Accuracy	Netherlands	de Jonge et al (2009)	MPX-P n = 51 (26Mo/25Fa)	DS-P n = 57 (28Mo/29Fa)	**n.s.**	**MPX-P vs. DS-P 0.16**
		Reconstruction time	Netherlands	de Jonge et al (2009)	MPX-P n = 51 (26Mo/25Fa)	DS-P n = 57 (28Mo/29Fa)	**n.s.**	
		Mean no. of errors	Netherlands	de Jonge et al (2009)	MPX-P n = 51 (26Mo/25Fa)	DS-P n = 57 (28Mo/29Fa)	**n.s.**	**MPX-P vs. DS-P 0.10**
Attentional Engagement	**Detection Task (Reaction time task)**	Eyes task (social)	Netherlands	Scheeren & Stauder (2008)	ASD-P n= 25 (12Mo/13Fa)	TD-P n= 25 (12Mo/13Fa)	**ASD-Fa > TD-Fa***	
		Arrows task (non-social)	Netherlands	Scheeren & Stauder (2008)	ASD-P n= 25 (12Mo/13Fa)	TD-P n= 25 (12Mo/13Fa)	**n.s**	
Global Sentence Completions	**Sentence Completion task**	Errors (local completions) and long delays	UK	Happé et al (2001)	ASD-P n = 43 (21Mo/22Fa)	DLX-P n = 30 (15Mo/15Fa) TD-P n = 20 (10Mo/10Fa)	**ASD-P > DLX-P > TD-P*** ASD-Fa > DLX – Fa*** ASD-Fa > TD-Fa*** ASD-Mo > DLX-Mo** ASD-Mo >TD-Mo****	
		Frequency of errors (no. of global responses)	USA	Losh et al (2009)	ASD-P n= 83 BAP(+) *Social* n = 22 BAP(+) *Rigid/Perfectionistic* n = 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40	TD-P n = 32 (19Mo/13Fa)	**ASD-P > TD-P****	
		Response time	USA	Losh et al (2009)	ASD-P n= 83 BAP(+) *Social* n = 22 BAP(+) *Rigid/Perfectionistic* n = 34 BAP(+) *Social & Rigid* n = 13 (5Mo/8Fa) BAP(-) n = 40	TD-P n = 32 (19Mo/13Fa)	**ASD-P > TD-P* BAP(+) Rigid/Perfectionistic < TD-P** BAP(-) < TD-P***	
Visual	**Vistech contrast sensitivity charts**	Mean contrast sensitivity	Netherlands	de Jonge et al (2007)	MPX-P n = 51 (26Mo/25Fa)	DS-P n = 52 (25Fa/27Mo)	**n.s.**	**MPX-P vs. DS-P 0.55**

Processing ***Contrast Sensitivity***		threshold						
Motion Discrimination	**Motion Coherence Task**	Mean motion coherence threshold	Netherlands	de Jonge et al (2007)	MPX-P n = 51 (26Mo/25Fa)	DS-P n = 52 (25Fa/27Mo)	**n.s.**	**MPX-P vs. DS-P 0.25**
	Moving Shape Task	Reaction time	Netherlands	de Jonge et al (2007)	MPX-P n = 51 (26Mo/25Fa)	DS-P n = 52 (25Fa/27Mo)	**n.s.**	**MPX-P vs. DS-P 0.17**
Form Discrimination	**Form Discrimination (Shape) Task**	Reaction Time	Netherlands	de Jonge et al (2007)	MPX-P n = 51 (26Mo/25Fa)	DS-P n = 52 (25Fa/27Mo)	**n.s.**	**MPX-P vs. DS-P 0.05**

Note. ASD = Autism Spectrum Disorder; BAP = Broad Autism Phenotype; BAP(+) = BAP present; BAP (-) = BAP absent; P = Parent; Mo = Mother; Fa = Father; M = Male; F = Female; MPX = Multiple incidence autism families; SPX = Single incidence autism families; ALN = Autism without language impairment; ALI =Autism with language impairment; DLX = Dyslexia; DS = Down Syndrome; EOS = Early onset Schizophrenia; LBW = low birth weight; LD = learning difficulties; N = Normative sample; MR = Mental Retardation; Sch SPX = single incidence Schizophrenia families; Sch MPX = multiple incidence Schizophrenia families; SLI = Specific Language Impairment; TD = typically developing; UA = Unaffected adult.

*p<0.05; **p<0.01; ***p<0.001

Appendix 4: Other Psychiatric Conditions Endophenotype Matrix – Review of studies of parents of autistic probands.

Domain	Method / Measure	Factors / Subscales	Country	Study	ASD Parent Group Characteristics	Control Group Characteristics	Key Findings in relation to Proband Diagnosis	
							P value	Effect Size (*d*)
Other Psychiatric Conditions	**Brief Psychiatric Rating Scale (BPRS)**	Anxiety	Iran	Gocken et al (2009)	ASD-P n = 76 (38Mo/38Fa)	N-P n = 41 (21Mo/20Fa)	**n.s.**	**ASD-P vs. N-P 0.29**
		Depression	Iran	Gocken et al (2009)	ASD-P n = 76 (38Mo/38Fa)	N-P n = 41 (21Mo/20Fa)	**ASD-P > N-P***	**ASD-P vs. N-P 0.44**
	Personality Style and Disorder Inventory (PSSI)	Reserved/schizoid	Germany	Bölte et al (2007)	ASD SPX-P n = 87 (48Mo/39Fa) ASD MPX-P n = 38 (21Mo/17Fa)	OCD-P n = 37 (19Mo/18Fa) EOS-P n = 34 (20Mo/14Fa) MR-P n = 27 (15Mo/12Fa)	**SPX-P / MPX-P > OCD-P, EOS-P****	**MPX-P vs. OCD-P 1.07 MPX-P vs. EOS-P 1.09 MPX-P vs. MR-P 0.14 SPX-P vs. OCD-p 1.06 SPX-P vs. EOS-P 1.18 SPX-P vs. MR-P 0.15**
		Self-critical/insecure	Germany	Bölte et al (2007)	ASD SPX-P n = 87 (48Mo/39Fa) ASD MPX-P n = 38 (21Mo/17Fa)	OCD-P n = 37 (19Mo/18Fa) EOS-P n = 34 (20Mo/14Fa) MR-P n = 27 (15Mo/12Fa)	**ASD SPX-P /ASD MPX-P > EOS-P****	**MPX-P vs. OCD-P 0.31 MPX-P vs. EOS-P 1.15 MPX-P vs. MR-P 0.32 SPX-P vs. OCD-p 0.02 SPX-P vs. EOS-P 0.86 SPX-P vs. MR-P 0.02**
		Critical/negativistic	Germany	Bölte et al (2007)	ASD SPX-P n = 87 (48Mo/39Fa) ASD MPX-P n = 38 (21Mo/17Fa)	OCD-P n = 37 (19Mo/18Fa) EOS-P n = 34 (20Mo/14Fa) MR-P n = 27 (15Mo/12Fa)	**SPX-P /MPX-P > EOS-P****	**MPX-P vs. OCD-P 0.29 MPX-P vs. EOS-P 0.92 MPX-P vs. MR-P 0.03 SPX-P vs. OCD-p 0.17 SPX-P vs. EOS-P 0.74 SPX-P vs. MR-P 0.06**
		Spontaneous/borderline	Germany	Bölte et al (2007)	ASD SPX-P n = 87 (48Mo/39Fa) ASD MPX-P n = 38 (21Mo/17Fa)	OCD-P n = 37 (19Mo/18Fa) EOS-P n = 34 (20Mo/14Fa) MR-P n = 27	**MPX-P > EOS-P****	**MPX-P vs. OCD-P 0.18 MPX-P vs. EOS-P 0.25 MPX-P vs. MR-P 0.09**

						(15Mo/12Fa)		**SPX-P vs. OCD-p 0.39** **SPX-P vs. EOS-P 0.72** **SPX-P vs. MR-P 0.04**
		Quiet/depressive	Germany	Bölte et al (2007)	ASD SPX-P n = 87 (48Mo/39Fa) ASD MPX-P n = 38 (21Mo/17Fa)	OCD-P n = 37 (19Mo/18Fa) EOS-P n = 34 (20Mo/14Fa) MR-P n = 27 (15Mo/12Fa)	**SPX-P /MPX-P > EOS-P****	**MPX-P vs. OCD-P 0.53** **MPX-P vs. EOS-P 1.03** **MPX-P vs. MR-P 0.31** **SPX-P vs. OCD-p 0.35** **SPX-P vs. EOS-P 0.87** **SPX-P vs. MR-P 0.16**
	Symptom Checklist-90-Revised (SCL-90-R)	Depression	Germany	Bölte et al (2007)	ASD SPX-P n = 87 (48Mo/39Fa) ASD MPX-P n = 38 (21Mo/17Fa)	OCD-P n = 37 (19Mo/18Fa) EOS-P n = 34 (20Mo/14Fa) MR-P n = 27 (15Mo/12Fa)	**MPX-P > OCD-P, EOS-P****	**MPX-P vs. OCD-P 0.89** **MPX-P vs. EOS-P 1.06** **MPX-P vs. MR-P 0.66** **SPX-P vs. OCD-p 0.42** **SPX-P vs. EOS-P 0.57** **SPX-P vs. MR-P 0.15**
		Anxiety	Germany	Bölte et al (2007)	ASD SPX-P n = 87 (48Mo/39Fa) ASD MPX-P n = 38 (21Mo/17Fa)	OCD-P n = 37 (19Mo/18Fa) EOS-P n = 34 (20Mo/14Fa) MR-P n = 27 (15Mo/12Fa)	**n.s.**	**MPX-P vs. OCD-P 0.17** **MPX-P vs. EOS-P 0.92** **MPX-P vs. MR-P 0.29** **SPX-P vs. OCD-p 0.01** **SPX-P vs. EOS-P 0.66** **SPX-P vs. MR-P 0.10**
		Phobic-anxiety	Germany	Bölte et al (2007)	ASD SPX-P n = 87 (48Mo/39Fa) ASD MPX-P n = 38 (21Mo/17Fa)	OCD-P n = 37 (19Mo/18Fa) EOS-P n = 34 (20Mo/14Fa) MR-P n = 27 (15Mo/12Fa)	**SPX-P / MPX-P > OCD-P, EOS-P****	**MPX-P vs. OCD-P 0.25** **MPX-P vs. EOS-P 1.33** **MPX-P vs. MR-P 0.45** **SPX-P vs. OCD-p 0** **SPX-P vs. EOS-P 0.91** **SPX-P vs. MR-P 0.19**
		Paranoid ideation	Germany	Bölte et al (2007)	ASD SPX-P n = 87 (48Mo/39Fa) ASD MPX-P n = 38 (21Mo/17Fa)	OCD-P n = 37 (19Mo/18Fa) EOS-P n = 34 (20Mo/14Fa) MR-P n = 27 (15Mo/12Fa)	**MPX-P > EOS-P****	**MPX-P vs. OCD-P 0.44** **MPX-P vs. EOS-P 0.93** **MPX-P vs. MR-P 0.57** **SPX-P vs. OCD-p 0.19** **SPX-P vs. EOS-P 0.65**

								SPX-P vs. MR-P 0.29
	Schedule for Affective Disorders and Schizophrenia - Lifetime Version (SADS-L)	Anxiety	USA	Piven et al (1991)	ASD-P n = 81 (42Mo/39Fa)	DS-P n = 34 (18Mo/16Fa)	**ASD-P > DS-P***	
		Major Depressive Disorder	USA	Piven et al (1991)	ASD-P n = 81 (42Mo/39Fa)	DS-P n = 34 (18Mo/16Fa)	**n.s**	
	Schedule for Affective Disorders and Schizophrenia - Lifetime Version Modified for the Study of Anxiety Disorders, Revised (SADS-LA-R)	Major Depressive Disorder	USA	Piven & Palmer (1999)	MPX-P n= 48 (25Mo/23Fa)	DS-P n = 60 (30Mo/30Fa)	**ASD-P > DS-P****	
		Social phobia	USA	Piven & Palmer (1999)	MPX-P n= 48 (25Mo/23Fa)	DS-P n = 60 (30Mo/30Fa)	**ASD-P > DS-P***	
	Parental Questionnaire (Devised by Author and results validated by consented medical records from GP)	Depression	UK	Micali et al (2004)	ASD-P n = 152 (79Mo/73Fa)	ODP-P n = 114 (59Mo/55Fa)	**ASD-Mo > ODP-Mo***	
		Anxiety	UK	Micali et al (2004)	ASD-P n = 152 (79Mo/73Fa)	ODP-P n = 114 (59Mo/55Fa)	**ASD-Mo > ODP-Mo*****	
	The Centre for Epidemiological Studies – Depression Scales (CESD)	Depressed Mood	USA	Ingersoll et al (2011)	ASD-Mo n = 71 (Only Mo)	N-Mo n = 94 (Only Mo)	**ASD-Mo > N-Mo***	**ASD-Mo vs. N-Mo 0.35**
	Beck Depression Inventory (BDI)	Depression	UK	Berthoz et al (2013)	ASD-P n = 87 (28%Fa)	UA n = 47 (62%M)	**n.s.**	**ASD-P vs. UA 0.50**

	State-Trait Anxiety Inventory Form Y (STAI-Y)							
	State scale (STAI-S)	Anxiety (State portion)	UK	Berthoz et al (2013)	ASD-P n = 87 (28%Fa)	UA n = 47 (62%M)	**n.s.**	**ASD-P vs. UA 0.19**
	Trait scale (STAI-T)	Anxiety (Trait portion)	UK	Berthoz et al (2013)	ASD-P n = 87 (28%Fa)	UA n = 47 (62%M)	**n.s.**	**ASD-P vs. UA 1.24**

Note. ASD = Autism Spectrum Disorder; BAP = Broad Autism Phenotype; BAP(+) = BAP present; BAP (-) = BAP absent; P = Parent; Mo = Mother; Fa = Father; M = Male; F = Female; MPX = Multiple incidence autism families; SPX = Single incidence autism families; DS = Down Syndrome; EOS = Early onset Schizophrenia; MR = Mental Retardation; N = Normative sample; OCD = Obsessive Compulsive Disorder; ODP = Other developmental problems without autism; UA = Unaffected adult.

*p<0.05; **p<0.01; ***p<0.001

Appendix 5 - DSM-5 Checklist for ASD

DSM V Checklist for Autism Spectrum Disorder

☐ Yes
☐ No

A. Deficits in use or understanding of social communication and social interaction in multiple contexts, not accounted for by general developmental delays, and manifest by all 3 of the following:

☐ Yes
☐ No

1. Deficits in nonverbal communicative behaviors used for social interaction; ranging from poorly integrated verbal and nonverbal communication, through abnormalities in eye contact and body-language, or deficits in understanding and use of nonverbal communication, to total lack of facial expression or gestures.

☐ Yes
☐ No

2. Deficits in social-emotional reciprocity; ranging from abnormal social approach and failure of normal back and forth conversation through reduced sharing of interests, emotions, and affect and response to total lack of initiation of social interaction.

☐ Yes
☐ No

3. Deficits in developing and maintaining relationships appropriate to developmental level (beyond those with caregivers); ranging from difficulties adjusting behavior to suit different social contexts through difficulties in sharing imaginative play and in making friends to an apparent absence of interest in people

☐ Yes
☐ No

B. Restricted, repetitive patterns of behavior, interests, or activities as manifested by 2 of the following:

☐ Yes
☐ No

1. Stereotyped or repetitive speech, motor movements, or use of objects; (such as simple motor stereotypies, echolalia, repetitive use of objects, or idiosyncratic phrases)

☐ Yes
☐ No

2. Excessive adherence to routines, ritualized patterns of verbal or nonverbal behavior, or excessive resistance to change; (such as motoric rituals, insistence on same route or food, repetitive questioning, or extreme distress at small changes)

☐ Yes
☐ No

3. Highly restricted, fixated interests that are abnormal in intensity or focus; (such as strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests)

☐ Yes
☐ No

4. Hyper-or hypo-reactivity to sensory input or unusual interest in sensory aspects of environment; (such as apparent indifference to pain/heat/cold, adverse response to specific sounds or textures, excessive smelling or touching of objects, fascination with lights or spinning objects).

Appendix 6: Socio-demographic Questionnaire

MUHIMBILI AUTISM 2016

SOCIO-DEMOGRAPHY, BIRTH AND MEDICAL HISTORY

FOR UNDER 18 YEARS

Personal Details

Today's Date: (dd/mm/yyyy) [__]__]/[__]__]/[__]__]__]__](**TDATE)**

AS Number: [_A_]_S_]__]__]__ [__](**AS NO)**

PID NO: [ ][ ][ ][ ][ ][ ][ ][ ]**(PID)**

Name: _____

RESID: [__[__]__]__]__]__](**RESID)**

DOB: [__]__]/[__]__]/[__]__]__]__]**(DOB)**

Age: [__][__]**(AGE)**

Sex: [__]**(SEX)**

Does s/he attend school: [__]**(SCH)**

Mother/ Guardian's Name: _____
(**GDNAME**)

Who will answer questions about the index? [__]**(RESP**)

1. Self
2. Self and other
3. The Index's mother
4. The Index's father
5. Index's grandmother
6. Index's sibling
7. Another relative
8. Other.

Is the informant one who mainly takes care of the Index? (Y/N) [__](**INFCT)**

Interviewer:
Has the communication sheet been read to the respondent? (Y/N) ……. [__](**COM_SHT**)
Has the respondent consented to participate in the study? (Y/N)…… [__](**CONSENT**)
If NO consent is given, what reasons are given for the decline?
1……
(**REAS_NOC1**)
2……
(**REAS_NOC2**)
3……
(**REAS_NOC3**)

4……
(**REAS_NOC4**)
5……
(**REAS_NOC5**)

Interviewer Code: [__][__](**FWC)**

Mother's Socio-demographic Information

Q1. Mother's date of Birth [__]__][__]__][__]__]__]__]**(MDOB)**

Q2. Age in completed in years [__]__]**(MOMAGE)**

Q3. Mother's country of Birth [__]__][__]__][__]__]__]__]**(MCOB)**

Q4. Mother's religious affiliation [__]**(MOMREL)**

1.Catholic 2. Protestant 3. Islam 4. Traditional 5. None 6. Other (Specify)

Q5. Marital Status [__]**(MOMMST)**

1. Never married 2. Married 3. Separated 4. Divorced 5. Widowed

Q6. Ethnic Group [__]**(MOMEG)**

1.Wazaramo 2. Wakwele 3. Wandengeleko 4. Makonde 5. Wachaga 6. Other (Specify)

Q7. Has the mother ever attended school [__]**(MOMSCH)**

1.Yes 2. No 3. Do not know

Q8. If Yes, what is the mother's highest level of education? [__]**(MOMLEDU)**

1. Primary 2. Secondary 3. High school/A-level 4. Post secondary

5. Primary incomplete 6. Secondary incomplete 7. Other (specify)

Q9. Has the Mother's Partner ever attended school [__]**(PATSCH)**

1.Yes 2. No 3. Do not know

Q10. Partner's Level of education [__]**(PATLEDU)**

(Use codes in Q7)

Q11. Does the mother do anything to earn cash [__]**(MOMECAC)**

1.Yes 2. No 3. Do not know

Q12. If Yes, What is the mother's occupation? [__]**(MOMOCC)**

1. Prof /Technical 2. Adm/Mngt 3. Clerical 4. Agric 5. Production

6. Services 7. Crafts 8. Others (specify)_____

Q13. Does her partner do anything to earn cash [__]**(PATECAC)**

1.Yes 2. No 3. Do not know

Q14. If Yes, What is his occupation? [__]**(PATOCC)**

(Use codes in Q11)

Q15. Mother's age at first birth [__]__](**AGEBIRTH1)**

Q16. Number of children ever born [__]__]**(CEB)**

Q17. Number of children living with mother [__]__]**(CLWM)**

Q18. Number of children living elsewhere [__]__]**(CLELSE)**

Q19. Number of children dead [__]__](**CDEAD)**

Father's Socio-demographic Information

Q20. Father's date of Birth [__]__][__]__][__]__]__]__](**FDOB)**

Q21. Father's Age in completed in years [__]__](**FATAGE)**

Q22. Father's country of Birth [__]__][__]__][__]__]__]__](**FCOB)**

Q23. Father's religious affiliation [__](**FATREL)**

1.Catholic 2. Protestant 3. Islam 4. Traditional 5. None 6. Other(Specify)

Q24. Marital Status [__](**FATMST)**

1.Never married 2. Married 3. Separated 4. Divorced 5. Widowed

Q25. Ethnic Group [__](**FATEG)**

1.Wazaramo 2. Wakwele 3. Wandengeleko 4. Makonde 5. Wachaga 6. Other (Specify)

Q26. Has the father ever attended school [__](**FATSCH)**

1.Yes 2. No 3. Do not know

Q27. If Yes, what is the father's highest level of education? [__](**FATLEDU)**

1.Primary 2. Secondary 3. High school/A-level 4. Post secondary

5. Primary incomplete 6. Secondary incomplete 7. Other (specify)

Q28. Does the father do anything to earn cash [__](**FATECAC)**

1.Yes 2. No 3. Do not know

Q29. If Yes, What is the father's occupation? [__](**FATOCC)**

1. Prof /Technical 2. Adm/Mngt 3. Clerical 4. Agric 5. Production

6. Services 7. Crafts 8. Others (specify)_____

PAST MEDICAL HISTORY

Family seizure history:

Q30. Does anyone have seizures (fits) in the family (Y/N) [__](**SF)**

Q31. If so who?_____ (**WHOSD**)

Q32. Has anyone in the family ever had seizures (fits) in the past (Y/N) [__](**SFP)**

Q33. If so who?_____ (**WHOSFP**)

Q34. Do any of the brothers or sisters have seizures? (Y/N) [__](**BSS)**

Q35. Has your Mother had seizures? (Y/N) [__](**MS)**

Q36. Has your Father had seizures? (Y/N) [__](**FS)**

Q37. Does anyone of your family have seizures associated with fevers? (Y/N) [__](**SAF)**

Please describe

Prenatal History

Q38. Pregnancy: Normal / Abnormal [__](**NP)**

Q39. If abnormal what was the problem: _____ (**NPP**)

Q40. Pregnancy: Single / Multiple [__](**SMP)**

Q41. Medication: Did the Mother take any medication during pregnancy? [__](**MP)**

Q42. If Yes, describe which medications: _____ (**MPP**)

Perinatal / Neonatal history

Q43. Delivery at Home; Hospital; Clinic; Don't know [__](**DL**)

Q44. Delivery: Was the baby born before 37 weeks (pre-term) [__](**PTD**)

Q45. If born pre-term, at how many weeks did the Mother deliver? _____ [__](**PTDM**)

Q46. Delivery: Normal / Abnormal [__](**NAD**)

Q47. If abnormal what was the problem: [__](**NADP**)

2. Prolonged labour 2. Breech presentation 3. Umbilical cord complications

4. Birth injury or trauma 5. Other (Specify)_____

Q48. Did the baby have a low birth weight? (Y/N) [__](**LBW)**

Q49. Were there any problems after delivery? (Y/N) [__](**PAD)**

Q50. If so what: _____

Q51. Did the baby have difficulties in breathing after delivery? (Y/N) [__](**DBR**)

Q52. Did the baby have difficulties in crying after delivery? (Y/N) [__](**DCRY**)

Q53. Did the baby have difficulties in breast-feeding after delivery? (Y/N) [__](**DFEED**)

Q54. Has s/he been admitted to hospital previously? (Y/N) [__](**HAP)**

Q55. For what_____ [__](**DGS1)**

Q56. If so when_____ [__]__]/[__]__]__]__]**(DOA1)**

Q57. For what_____ [__](**DGS2**)

Q58. If so when_____ [__]__]/[__]__]__]__]**(DOA2)**

Q59. For what_____ [__](**DGS3**)

Q60. If so when_____ [__]__]/[__]__]__]__]**(DOA3)**

Q61. Has s/he ever had a head injury? (Y/N/Dk) [__](**HI)**

Q62. If **Yes** did s/he lose consciousness? (Y/N/Dk) [__](**HIC**)

Q63. Was s/he admitted to hospital? (Y/N/Dk) [__](**HIA)**

Q64. Other relevant history? (Y/N) [__](**ORH)**

Please describe

Q65. Birth weight [__|__].[__](**BW**)

Q66. Birth weight at first visit to Clinic [__|__].[__](**BWC**)

Q67. Completed immunization(Y/N) [__](**CIM**)

Q68. How long have you lived in Dar es Salaam? (Years) _____ (**KDURY**)

Sign if you have checked that the form is complete_____

Appendix 7: Kiswahili version of the Social Communication Questionnaire (SCQ)

MUHIMBILI AUTISM 2016

SOCIAL COMMUNICATION QUESTIONNAIRE (SCQ)

Personal Details

Today's Date: (dd/mm/yyyy) [__]__]/[__]__]/[__]__]__]__](**TDATE)**

AS Number: [_A_]_S_]__]__]__[__](**AS NO)**

PID NO: [ ][ ][ ][ ][ ][ ][ ]**(PID)**

Name: _____

RESID: [__]__]__]__]__](**RESID)**

DOB: [__]__]/[__]__]/[__]__]__]__]**(DOB)**

Age: [__][__]**(AGE)**

Sex: [__]**(SEX)**

Interviewer Code: [__][__](**FWC)**

Section A:

1. Kwa maoni yako ni magumu gani mwanao anayo? (Ni muhimu umsisitize mama kuwa tunataka zaidi kuelewa magumu ya kukua na kuendelea kwa mtoto)

2. Sasa nataka tuongee juu ya mwanao alipokuwa na umri wa miaka 4 hadi 5. Kwa maoni yako ni magumu gani mwanao alikuwa nayo wakati huo? (Ni muhimu umsisitize mama kuwa tunataka zaidi kuelewa magumu ya kukua na kuendelea kwa mtoto

1.	Je kwa sasa anaweza kuongea akitumia maneno au sentensi fupi? K.m Nipe maji Ikiwa hapana ruka mpaka swali la 8	Y	N
2.	**Je unaweza kuwa na mazungumzo ya kueleweka kati yako na yeye?**	**0**	**1**
3.	Je amewahi kutumia maneno yasiyo ya kawaida au kusema kitu hicho hicho tena na tena kwa namna hiyohiyo (au kwa maneno ambayo ameyasikia kwa watu wengine wakiyatumia au ametunga)?	1	0
4.	Je amewahi kuuliza maswali ambayo ni ya aibu au ambayo hayafai kijamii? Kwa mfano wewe umekojoa kitandani leo ?	1	0

5.	Je amewahi kuchanganya maneno k.m kusema yeye au wewe akimaanisha mimi?	1	0
6.	**Je amewahi kutumia maneno aliyotunga mwenyewe au kuongea kimafumbo k.m. kusema tochi ya Mungu kumaanisha mwezi?**	**1**	**0**
7.	Je amewahi kusema kitu kimoja kwa kurudia rudia au kukuhimiza/kukusisitiza useme hivyo tena na tena k.m Nenda nenda, njoo njoo?	1	0
	a) Kuna swali lolote ambalo hukulielewa b) Kuna swali lolote ambalo ungeliuliza kwa njia nyingine c) For every question with a YES please ask the mother to explain and give examples d) For the bolded questions please ask the mother to explain in her own word ' alilielewaje swali hili'		
8.	Je amewahi kuwa na vitu ambavyo anaonekana akivifanya katika mpangilio Fulani au njia fulani au mazoea Fulani alilosisitiza ulipitie? K.m mazoea ya kupitia mahali Fulani kwenye nyumba au kuzoea kuketi katika kiti hicho hicho kila wakati?	1	0
9.	**Je hali yake ya uso huonyesha hali vile ilivyo? K.m huzuni, kama ana huzuni?**	**0**	**1**
10.	Je amewahi kutumia mkono wako kama kifaa/ chombo au kama ni sehemu ya mwili wake (kwa mfano kuota akitumia kidole chako, au kuweka mkono wako ili ufungue mlango)?	1	0
11.	Je amewahi kupenda sana kitu ambacho huchukua muda wake mwingi na ambacho ni kinyume kwa watu wengine(kwa mfano kuangalia mti, mbuzi kwa muda mrefu)?	1	0
12.	Je amewahi kupenda sana sehemu Fulani ya kitu cha kuchezea badala ya kitu chochote (k.m kuzungusha gurudumu la gari la kuchezea), badala ya kusukuma gari hilo?	1	0
	a) Kuna swali lolote ambalo hukulielewa b) Kuna swali lolote ambalo ungeliuliza kwa njia nyingine c) For every question with a YES please ask the mother to explain and give examples d) For the bolded questions please ask the mother to explain in her own word ' alilielewaje swali hili'		
13.	**Je amewahi kupenda kusiko kwa kawaida ambako kwa upande mwingine ni sawa kwa umri wake na marika yake (k.m kucheza na magari kwa muda mrefu)?**	**1**	**0**
14.	Je amewahi kuonekana kupenda kusiko kwa kawaida katika kuona, hisi, sauti, ladha ama harufu ya vitu au watu? K.m kupenda sana sauti ya pikipiki au gari?	1	0
15.	Je amewahi kuwa na tabia Fulani, au njia zisizo za kawaida za kurusha mikono au vidole vyake, kama vile kuinua makwapa juu na chini au kupitisha vidole vyake mbele ya macho yake?	1	0
16.	Je amewahi kuwa na kutikisika kwa mwili kusiko kwa kawaida k.m kujizungusha au kujirusha juu na chini?	1	0
17.	Je amewahi kujiumiza kwa makusudi, kama vile kujiuma mkono au kujigonga kichwa chake?	1	0
18.	Je amewahi kuwa na kitu chochote ambacho alikuwa anakibeba popote aendapo?	1	0

19.	**Je ana marafiki maalum au rafiki mmoja bora/wa karibu?**	**0**	**1**

a) Kuna swali lolote ambalo hukulielewa

b) Kuna swali lolote ambalo ungependa kuliuliza kwa njia nyingine?

c) For every question with a YES please ask the mother to explain and give examples

d) For the bolded questions please ask the mother to explain in her own word ' alilielewaje swali hili'

For the following behaviours please focus on the time period between the child's fourth and fifth birthdays. You may find it easier to remember how things were at that time by focusing on key events, such as starting school, moving house, Christmas time, or other specific events that are particularly memorable for you as a family. If your child is not yet 4 years old, please consider her or his behaviour in the past twelve months.

		Y	N
20.	Alipofika umri wa miaka 4 hadi 5, aliwahi kuongea/kuzungumza nawe kwa uzuri/ukarimu bila nia ya kupata chochote?	0	1
21.	Alipofika umri wa miaka 4 hadi 5, aliwahi kukuigiza kwa kazi uliyokuwa ukifanya (kama kutoa vumbi, kulima, au kurekebisha vitu)?	0	1
22.	Alipofika umri wa miaka 4 hadi 5, aliwahi kuokota vitu vilivyopo karibu naye, kwa makusudi ya kukuonyesha tu (sio sababu alivitaka)?	0	1
23.	Alipofika umri wa miaka 4 hadi 5, aliwahi kutumia ishara, mbali na kuota au kukuvuta mkono kukujulisha anachotaka?	0	1
24.	Alipofika umri wa miaka 4 hadi 5, aliweza kuitikia kwa kichwa akimaanisha ndio?	0	1

a) Kuna swali lolote ambalo hukulielewa

b) Kuna swali lolote ambalo ungeliuliza kwa njia nyingine

c) For every question with a YES please ask the mother to explain and give examples

d) For the bolded questions please ask the mother to explain in her own word ' alilielewaje swali hili'

25.	Alipofika umri wa miaka 4 hadi 5, aliweza kutikisa kichwa akimaanisha la?	0	1
26.	Alipofika umri wa miaka 4 hadi 5, aliweza kukuangalia usoni alipokuwa akifanya vitu pamoja nawe au akiongea nawe?	0	1
27.	Alipofika umri wa miaka 4 hadi 5, je alitabasamu na mtu alipotabasamu kwake?	0	1
28.	Alipofika umri wa miaka 4 hadi 5, aliwahi kukuonyesha vitu vilivyomfurahisha kwa Kutaka umsikilize?	0	1
29.	Alipofika umri wa miaka 4 hadi 5, aliwahi kukubali kugawana nawe vitu mbali na chakula?	0	1

a) Kuna swali lolote ambalo hukulielewa

b) Kuna swali lolote ambalo ungeliuliza kwa njia nyingine

c) For every question with a YES please ask the mother to explain and give examples

d) For the bolded questions please ask the mother to explain in her own word ' alilielewaje swali hili'

30.	Alipofika umri wa miaka 4 hadi 5, aliwahi kuonekana kutaka ujiunge naye	0	1

	katika kufurahia kitu fulani?		
31.	Alipofika umri wa miaka 4 hadi 5, aliwahi kujaribu kukuliwaza/ kukufariji ulipokuwa huna raha au umekasirishwa?	0	1
32.	Alipofika umri wa miaka 4hadi 5, alipokuwa anataka kitu, au anataka msaada alikuangalia na kutumia ishara , na sauti ama maneno ili umsikilize?	0	1
33.	Alipofika umri wa miaka 4 hadi 5, alionyesha hali ya kawaida ya kuwasiliana kwa uso?	0	1
34.	Alipofika umri wa miaka 4 hadi 5, aliwahi kujiunga na kujaribu Kuigiza vitendo katika michezo ya pamoja, kama vile katotokatoto/ukuti?	0	1
a) Kuna swali lolote ambalo hukulielewa b) Kuna swali lolote ambalo ungeliuliza kwa njia nyingine c) For every question with a YES please ask the mother to explain and give examples d) For the bolded questions please ask the mother to explain in her own word ' alilielewaje swali hili'			
35.	Alipofika umri wa miaka 4 hadi 5, aliwahi kucheza michezo ya kuiga k.m wa baba na mama?	0	1
36.	Alipofika umri wa miaka 4 hadi 5, alionekana kupenda watoto wengine wa rika lake ambao hakuwajua?	0	1
37.	Alipofika umri wa miaka 4 hadi 5, je aliweza kumkubali mtoto mwingine alipomkaribia?	0	1
38.	Alipofika umri wa miaka 4 hadi 5, ulipoingia chumbani, na kuanza kuongea naye bila kuita jina lake, je alikuangalia na kukusikiliza?	0	1
39.	Alipofika umri wa miaka 4 hadi 5, alicheza michezo ya kufikiria na mtoto mwingine kwa njia ambayo ungeeleza kuwa kila mmoja alielewa yule mwingine alikuwa anajifanya kuwa nani? K.m mwalimu na mwanafunzi/dereva na conductor.	0	1
40.	Alipofika umri wa miaka 4 hadi 5, je alicheza kwa kushirikiana katika michezo ambayo ilihitaji Kujiunga na kikundi kingine cha watoto wengine, kama vile mchezo wa bao au mchezo Wa mpira?	0	1
a) Kuna swali lolote ambalo hukulielewa b) Kuna swali lolote ambalo ungeliuliza kwa njia nyingine c) For every question with a YES please ask the mother to explain and give examples d) For the bolded questions please ask the mother to explain in her own word ' alilielewaje swali hili'			
TOTAL SCORE			
Comments:			

Sign if you have checked that the form is complete_____

Appendix 8: Kiswahili version of the Autism Spectrum Quotient (AQ)

MUHIMBILI AUTISM 2016

THE ADULT AUTISM SPECTRUM QUOTIENT (AQ)

AGES 16+

Name:..... Sex:.....

Jina:…….. Jinsia yake:……

Date of birth: Today's Date.....

Tarehe ya kuzaliwa:…… Tarehe ya leo:……

How to fill out the questionnaire

Jinsi ya kujaza form ya maswali

Below is a list of statements. Please read each statement very carefully and rate how strongly you agree or disagree with it by circling your answer.

(Hapa chini ni orodha ya maelezo . tafadhali soma kwa makini na ulinganishe kwa kiasi gani unakubali au unakataa kwa kuzungushia jibu lako.

DO NOT MISS ANY STATEMENT OUT. Usiache swali lolote

1. I prefer to do things with others rather than on my own. Napendelea kufanya vitu pamoja na wenzangu kuliko kufanya mwenyewe.	definitely agree nakubali kabisa	slightly agree nakubali kiasi	slightly disagree sikubali kiasi	definitely disagree sikubali kabisa
2. I prefer to do things the same way over and over again. Napendelea kufanya vitu kwa njia ile ile mara zote	definitely agree nakubali kabisa	slightly agree nakubali kiasi	slightly disagree sikubali kiasi	definitely disagree sikubali kabisa

3. If I try to imagine something, I find it very easy to create a picture in my mind. Kama najaribu kufikiria kitu ,huwa inakuwa nirahisi sana kutengeneza picha kwenye akili yangu.	definitely agree nakubali kabisa	slightly agree nakubali kiasi	slightly disagree sikubali kiasi	definitely disagree sikubali kabisa
4. I frequently get so strongly absorbed in one thing that I lose sight of other things. Mara nyingi natumia nguvu nyingi kwa kitu kimoja ambapo sioni vitu vingine kirahisi.	definitely agree nakubali kabisa	slightly agree nakubali kiasi	slightly disagree sikubali kiasi	definitely disagree sikubali kabisa
5. I often notice small sounds when others do not. Mara kwa mara huwa nasikia sauti ndogo ambayo wengine hawaisikii.	definitely agree nakubali kabisa	slightly agree nakubali kiasi	slightly disagree sikubali kiasi	definitely disagree sikubali kabisa
6. I usually notice car number plates or similar strings of information. Kwa kawaida huwa na tambua namba za gari au kitu kinachofanana na taarifa hizo.	definitely agree nakubali kabisa	slightly agree nakubali kiasi	slightly disagree sikubali kiasi	definitely disagree sikubali kabisa
7. Other people frequently tell me that what I've said is impolite, even though I think it is polite. Mara kwa mara watu wengine waniambia nilichosema nimeongea kwa ukali ,japo kuwa mimi nafikiri nimeongea kwa upole.	definitely agree nakubali kabisa	slightly agree nakubali kiasi	slightly disagree sikubali kiasi	definitely disagree sikubali kabisa
8. When I'm reading a story, I can easily imagine what the characters might look like. Ninaposoma hadithi, ninaweza kufikiri kirahisi muhusika anafanaje.	definitely agree nakubali kabisa	slightly agree nakubali kiasi	slightly disagree sikubali kiasi	definitely disagree sikubali kabisa
9. I am fascinated by dates. Huwa Ninavutiwa sana na tarehe.	definitely agree nakubali kabisa	slightly agree nakubali kiasi	slightly disagree sikubali kiasi	definitely disagree sikubali kabisa
10. In a social group, I can easily keep track of several different people's conversations. Ninaweza kufuatilia mazungumzo mengi ya watu mbalimbali kwenye makundi ya kijamii kwa urahisi.	definitely agree nakubali kabisa	slightly agree nakubali kiasi	slightly disagree sikubali kiasi	definitely disagree sikubali kabisa

11. I find social situations easy. Mazingira ya kijamii ni rahisi kwangu.	definitely agree nakubali kabisa	slightly agree nakubali kiasi	slightly disagree sikubali kiasi	definitely disagree sikubali kabisa
12. I tend to notice details that others do not. Najaribu kugundua taarifa ambazo wengine hawawezi kujua.	definitely agree Nakubali kabisa	slightly agree nakubali kiasi	slightly disagree sikubali kiasi	definitely disagree sikubali kabisa
13. I would rather go to a library than a party. Napendelea kwenda maktaba kuliko kwenye sherehe.	definitely agree Nakubali kabisa	slightly agree nakubali kiasi	slightly disagree sikubali kiasi	definitely disagree sikubali kabisa
14. I find making up stories easy. Naweza kutengeneza kirahisi hadithi	definitely agree Nakubali kabisa	slightly agree nakubali kiasi	slightly disagree sikubali kiasi	definitely disagree sikubali kabisa
15. I find myself drawn more strongly to people than to things. Naweza kuchora picha za watu zaidi kuliko za vitu vingine.	definitely agree nakubali kabisa	slightly agree nakubali kiasi	slightly disagree sikubali kiasi	definitely disagree sikubali kabisa
16. I tend to have very strong interests which I get upset about if I can't pursue. Ninapenda sana kufanya jambo fulani lakini ninagadhabika ninaposhindwa kutimiza malengo yangu.	definitely agree nakubali kabisa	slightly agree nakubali kiasi	slightly disagree sikubali kiasi	definitely disagree sikubali kabisa
17. I enjoy social chit-chat. Nafurahia utani wa kijamii.	definitely agree nakubali kabisa	slightly agree nakubali kiasi	slightly disagree sikubali kiasi	definitely disagree sikubali kabisa
18. When I talk, it isn't always easy for others to get a word in edgeways. Ninapo ongea sio rahisi kwa watu wengine kuelewa .	definitely agree nakubali kabisa	slightly agree nakubali kiasi	slightly disagree sikubali kiasi	definitely disagree sikubali kabisa
19. I am fascinated by numbers.	definitely agree	slightly agree	slightly disagree	definitely disagree

Ninavutiwa sana na namba	nakubali kabisa	nakubali kiasi	sikubali kiasi	sikubali kabisa
20. When I'm reading a story, I find it difficult to work out the characters' intentions.	definitely agree	slightly agree	slightly disagree	definitely disagree
Ninaposoma hadithi ninapata ugumu wa kumgundua mhusika wa hadithi hiyo.	nakubali kabisa	nakubali kiasi	sikubali kiasi	sikubali kabisa
21. I don't particularly enjoy reading fiction.	definitely agree	slightly agree	slightly disagree	definitely disagree
Kwa ujumla Sifurahii kusoma hadithi fupi	nakubali kabisa	nakubali kiasi	sikubali kiasi	sikubali kabisa
22. I find it hard to make new friends.	definitely agree	slightly agree	slightly disagree	definitely disagree
Napata ugumu wa kuwa na marafiki wapya	nakubali kabisa	nakubali kiasi	sikubali kiasi	sikubali kabisa
23. I notice patterns in things all the time.	definitely agree	slightly agree	slightly disagree	definitely disagree
Huwa ninagundua mfululizo wa vitu kwa wakati wote.	nakubali kabisa	nakubali kiasi	sikubali kiasi	sikubali kabisa
24. I would rather go to the theatre than a museum.	definitely agree	slightly agree	slightly disagree	definitely disagree
Napenda kwenda kwenye nyumba za starehe kuliko za makumbusho.	nakubali kabisa	nakubali kiasi	sikubali kiasi	sikubali kabisa
25. It does not upset me if my daily routine is disturbed.	definitely agree	slightly agree	slightly disagree	definitely disagree
Mimi sijali hata kama nikipata usumbufu kwenye shughuli zangu za kila siku.	nakubali kabisa	nakubali kiasi	sikubali kiasi	sikubali kabisa
26. I frequently find that I don't know how to keep a conversation going.	definitely agree	slightly agree	slightly disagree	definitely disagree
Mara kwa mara nashindwa kujua jinsi ya kufanya mazungumzo ya endelee	nakubali kabisa	nakubali kiasi	sikubali kiasi	sikubali kabisa
27. I find it easy to "read between the lines" when someone is talking to me.	definitely agree	slightly agree	slightly disagree	definitely disagree
Napata urahisi wa kusoma mstari kwa mstari japokuwa kuna mtu anaongea na mimi .	nakubali kabisa	nakubali kiasi	sikubali kiasi	sikubali kabisa
28. I usually concentrate more on the whole picture, rather than the small details.	definitely agree	slightly agree	slightly disagree	definitely disagree
Mara nyingi nafikiria juu ya picha nzima kuliko kwenye taarifa fupi.	nakubali kabisa	nakubali kiasi	sikubali kiasi	sikubali kabisa

29. I am not very good at remembering phone numbers. Mimi siwezi kukumbuka vizuri namba za simu.	definitely agree nakubali kiasi	slightly agree nakubali kiasi	slightly disagree sikubali kiasi	definitely disagree sikubali kabisa
30. I don't usually notice small changes in a situation, or a person's appearance. Kwa kawaida sigundui hali ya mabadiliko madogo au muonekano wa mtu kwa ujumla.	definitely agree nakubali kabisa	slightly agree nakubali kiasi	slightly disagree sikubali kiasi	definitely disagree sikubali kabisa
31. I know how to tell if someone listening to me is getting bored. Natambua endapo namweleza mtu jambo fulani halafu hafurahii .	definitely agree nakubali kabisa	slightly agree nakubali kiasi	slightly disagree sikubali kiasi	definitely disagree sikubali kabisa
32. I find it easy to do more than one thing at once. Naona ni rahisi kufanya zaidi ya kitu kimoja kwa wakati mmoja.	definitely agree nakubali kabisa	slightly agree nakubali kiasi	slightly disagree sikubali kiasi	definitely disagree sikubali kabisa
33. When I talk on the phone, I'm not sure when it's my turn to speak. Ninapo ongea na simu sinauhakika kama ni zamu yangu kuongea.	definitely agree nakubali kabisa	slightly agree nakubali kiasi	slightly disagree sikubali kiasi	definitely disagree sikubali kabisa
34. I enjoy doing things spontaneously. Nafurahia kufanya vitu kwa ghafla	definitely agree nakubali kabisa	slightly agree nakubali kiasi	slightly disagree sikubali kiasi	definitely disagree sikubali kabisa
35. I am often the last to understand the point of a joke. Mara nyingi nakuwa wa mwisho kuelewa nafasi ya utani.	definitely agree nakubali kabisa	slightly agree nakubali kiasi	slightly disagree sikubali kiasi	definitely disagree sikubali kabisa
36. I find it easy to work out what someone is thinking or feeling just by looking at their face. Ni rahisi kwa kumwangalia mtu kujua ni wakati gani anafikiria au anahisi	definitely agree nakubali kabisa	slightly agree nakubali kiasi	slightly disagree sikubali kiasi	definitely disagree sikubali kabisa
37. If there is an interruption, I can switch back to what I was doing very quickly. Ninapokuwa na mwingiliano,ghafla naweza kurudi kwenye kitu nilichokuwa nakifanya mara moja.	definitely agree nakubali kabisa	slightly agree nakubali kiasi	slightly disagree sikubali kiasi	definitely disagree sikubali kabisa

38. I am good at social chit-chat.	definitely agree	slightly agree	slightly disagree	definitely disagree
Niko vizuri kwa mazungumzo ya kijamii.	nakubali kabisa	nakubali kiasi	sikubali kiasi	sikubali kabisa
39. People often tell me that I keep going on and on about the same thing.	definitely agree	slightly agree	slightly disagree	definitely disagree
Mara nginyi watu huwa wananiambia kuwa naendelea na vitu hivyohivyo.	nakubali kabisa	nakubali kiasi	sikubali kiasi	sikubali kabisa
40. When I was young, I used to enjoy playing games involving pretending with other children.	definitely agree	slightly agree	slightly disagree	definitely disagree
Nilipokuwa mtoto nilifurahi kucheza michezo inayowahusisha na wengine.	nakubali kabisa	nakubali kiasi	sikubali kiasi	sikubali kabisa
41. I like to collect information about categories of things (e.g. types of car, types of bird, types of train, types of plant, etc.).	definitely agree	slightly agree	slightly disagree	definitely disagree
Napenda kukusanya taarifa kuhusu makundi ya vitu (kwa mfano aina za gari, aina za ndege, aina za gari moshi , aina ya mimea)	nakubali kabisa	nakubali kiasi	sikubali kiasi	sikubali kabisa
42. I find it difficult to imagine what it would be like to be someone else.	definitely agree	slightly agree	slightly disagree	definitely disagree
Inaniwia vigumu kufikiria kujifanya kama mtu mwingine.	nakubali kabisa	nakubali kiasi	sikubali kiasi	sikubali kabisa
43. I like to plan any activities I participate in carefully.	definitely agree	slightly agree	slightly disagree	definitely disagree
Ninapenda kupanga shughuli yoyote na kuishiriki kikamilifu	nakubali kabisa	nakubali kiasi	sikubali kiasi	sikubali kabisa
44. I enjoy social occasions.	definitely agree	slightly agree	slightly disagree	definitely disagree
Nafurahia matukio ya kijamii mara chache.	nakubali kabisa	nakubali kiasi	sikubali kiasi	sikubali kabisa
45. I find it difficult to work out people's intentions.	definitely agree	slightly agree	slightly disagree	definitely disagree
Inakuwa nivigumu kwangu kufanyia kazi mitazamo ya watu.	nakubali kabisa	nakubali kiasi	sikubali kiasi	sikubali kabisa
46. New situations make me anxious.	definitely agree	slightly agree	slightly disagree	definitely disagree
Ninakuwa mwoga kwenye mazingira mapya	nakubali	nakubali	sikubali	sikubali

Mabadoliko mapya yanifanya niwe na wasiwasi.	kabisa	kiasi	kiasi	kabisa
47. I enjoy meeting new people. Nafurahia kukutana na wageni.	definitely agree nakubali kabisa	slightly agree nakubali kiasi	slightly disagree sikubali kiasi	definitely disagree sikubali kabisa
48. I am a good diplomat. Mimi ni kiongozi mzuri.	definitely agree nakubali kabisa	slightly agree nakubali kiasi	slightly disagree sikubali kiasi	definitely disagree sikubali kabisa
49. I am not very good at remembering people's date of birth. Mimi si mzuri wa kukumbuka tarehe za watu za kuzaliwa	definitely agree nakubali kabisa	slightly agree nakubali kiasi	slightly disagree sikubali kiasi	definitely disagree sikubali kabisa
50. I find it very easy to play games with children that involve pretending. Naona ni rahisi kucheza na watoto ambao wanajihusisha na michezo ya kuigiza.	definitely agree nakubali kabisa	slightly agree nakubali kiasi	slightly disagree sikubali kiasi	definitely disagree sikubali kabisa

Appendix 9: Consent form for qualitative study (English)

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES

P. O. BOX 65001 □ DAR ES SALAAM □ TANZANIA

A: Informed consent for participants that will take part in the Focus Group Discussions and In-depth Interviews.

Study Title: Evaluating the knowledge, awareness and lived experiences of Autism in Tanzania.
Lay title: Understanding the awareness and experiences of Autism in Tanzania.

Institution	
MUHAS / MNH / KEMRI	Kavita Ruparelia, Karim Manji, Amina Abubakar, Charles Newton

What is MUHAS/MNH /KEMRI and what is this study about?

- MUHAS is the National Public University for Health Sciences, where the scientific aspects of the proposal and supervision will take place. The research committee within MUHAS must agree that the research is important, relevant to Tanzania and follows nationally and internationally agreed research guidelines. This includes ensuring that all participants' safety and rights are respected.
- MNH is the teaching hospital, a public health facility, a tertiary referral hospital. All the research done shall be approved by the host institution/s
- KEMRI is a government organization in Kenya that carries out medical research to find better ways of preventing and treating illness in the future for everybody's benefit. All research at KEMRI has to be approved before it begins by several national committees who look carefully at planned work.

In this study we want to learn more about the knowledge, awareness and experiences of Autism in this community. This is important because Autism is known to be a big problem for families, and to develop appropriate interventions for the families of children with Autism, we first need to identify the level of knowledge, experiences and challenges of Autism in this community.

Why do you want to talk to me and what does it involve?

We have chosen you because we feel that your experience as a parent, teacher, clinician or community representative can contribute much to our understanding and knowledge of Autism. We are requesting you to join us for a discussion on community's perceptions, beliefs, and descriptions of Autism and its symptoms. This discussion will take approximately 1 hour. We would like you to take

part in a discussion with [5-6] other persons with similar experiences or have a one-to-one interview. We would also like to request you to allow us to audio tape the discussions. Recording everything you are saying is important because in case the person who is writing notes misses some information s/he will listen to the tapes. The discussion will be recorded to assist later in fully writing up the information. No-one will be identified by name in the recording.

Are there any risks or disadvantages to me/my child of taking part?

A part from the time it takes to complete the test, there are no disadvantages at all for participating in this research**.**

Benefits of the Study

There will be no direct benefits of the study to you. However, this study is intended to provide a better understanding of the problem of Autism in this community and Tanzania in general. We hope that the findings shall enable better service provision for all children with Autism in the future.

What will happen if I do not agree to participate?

Your participation in this project is voluntary. You are free to withdraw from the study at any time.

Who will see the information from this study?

We will not share individual information about you or other participants with anyone beyond a few people who are closely concerned with the research. Only the principal investigator will listen to the tapes being recorded. All of our documents/ recordings are stored securely in locked cabinets and on password protected computers. We will ask everybody in the discussion to keep what is said in the group confidential, but it is important to recognize that we cannot stop participants sharing what they have heard.

What if I have any questions?

You are free to ask any question about this research. If you have any further questions about the study, you are free to contact the research team using the contact below:

Contacts person

Prof. Karim Manji
MUHAS, P.O. Box 65001, Dar-es-Salam, Tanzania
Telephone: 0754350630

If you want to ask someone independent anything about this research please contact:

Prof. Mainen Moshi, Director of Research and Publication, MUHAS, P.O. Box 65001, Dar-es-Salaam

Or

Ms. Joyce Ikingura, National Health Research Ethics Committee (NatHREC), National Institute for Medical Research (NIMR), P.O. Box 9653, Dar-es-Salaam

I _____, have been told about this study. I have had the study explained to me. I have understood all that has been read/explained and had my questions answered satisfactorily.

Yes *please tick* **I agree to be interviewed**

Yes *please tick* **I agree for the interview to be recorded**

I understand that I can change my mind at any stage and it will not affect me/my child in any way.

Signature:		**Date:**	
Participant		**Time:**	
	(please print name)		

I certify that I have followed the study SOP to obtain consent from the [participant]. S/he apparently understood the nature and the purpose of the study and consents to the participation [of the child] in the study. S/he has been given opportunity to ask questions which have been answered satisfactorily.

Signature:		**Date:**	
Designee/ Investigator's Name:		**Time:**	
	(please print name)		

Thumb print of the parent as named above if they cannot write: _____

Where parent/guardian cannot read, a witness* may observe consent process and sign below if needed:

I attest that the information concerning this research was accurately explained and apparently understood by the subject/parent/guardian and that informed consent was freely given by the subject/parent/guardian.

Witness' signature: _____ Date _____

Witness' name: **_____ Time _____**

**A witness is a person who is independent from the trial or a member of staff who was not involved in gaining the consent.*

Appendix 10: Consent form for main case-control studies (English)

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES

P. O. BOX 65001 □ DAR ES SALAAM □ TANZANIA

B: Informed consent for participants in the families that will take part in the validation studies.

Study Title: Adapting culturally appropriate measures for screening Autism in Tanzania.
Lay title: Developing measures for screening Autism in Tanzania.

Institution	
MUHAS / MNH / KEMRI	Kavita Ruparelia, Karim Manji, Amina Abubakar, Charles Newton

What is MUHAS/MNH /KEMRI and what is this study about?

- MUHAS is the National Public University for Health Sciences, where the scientific aspects of the proposal and supervision will take place. The research committee within MUHAS must agree that the research is important, relevant to Tanzania and follows nationally and internationally agreed research guidelines. This includes ensuring that all participants' safety and rights are respected.
- MNH is the teaching hospital, a public health facility, a tertiary referral hospital. All the research done shall be approved by the host institution/s
- KEMRI is a government organization in Kenya that carries out medical research to find better ways of preventing and treating illness in the future for everybody's benefit. All research at KEMRI has to be approved before it begins by several national committees who look carefully at planned work.

In this study we want to learn more about the causes, distribution and effects of Autism among children. This is important because Autism is known to be a big problem for families, and to develop appropriate interventions for the families of children with Autism, we first need to identify children who have Autism, understand their behavior, know how many children suffer from Autism and why. In order to do this, we need to develop an appropriate tool for identifying children who are Autistic in our communities.

Why do you want to talk to me and what does it involve?

We want to talk to you because you have a child who is attending a special school and the child is aged 6-12 years old. We want to request you and your child to come to MNH, any relevant schools or

clinics, to take part in various activities that will help us develop tools that can be used to recognize children with Autism. During that visit:

- You will answer several questionnaires about your child's behavior and health and also some questions about yourself and your family
- Your child will be requested to take part in various activities and we will request for your child to be video-taped while doing these activities
- Children suspected of Autism will be referred to relevant facilities for necessary assistance

The visit will take approximately 3 hours.

Are there any risks or disadvantages to me/my child of taking part?

A part from the time it takes to complete the test, there are no disadvantages at all for participating in this research**.**

Benefits of the Study

There will be no direct benefits of the study to you. However, this study is intended to provide a better understanding of the problem of Autism in this community and Tanzania in general. We hope that the findings shall enable better service provision for all children with Autism in the future.

What will happen if I do not agree to participate?

Your participation in this project is voluntary. If you do not want to take part, your refusal will not affect your relationship with MNH or MUHAS. You will be able to receive all services as usual. If you agree to participate now you are free to withdraw or withdraw your child from the study at any time without any problem.

Who will see the information from this study?

We will not share individual information about you or other participants with anyone beyond a few people who are closely concerned with the research. All of our documents/ recordings are stored securely in locked cabinets and on password protected computers. The knowledge gained from this research will be shared in summary form, without revealing individuals' identities, with parents, teachers, doctors and nurses.

What if I have any questions?

You are free to ask any question about this research. If you have any further questions about the study, you are free to contact the research team using the contact below:

Contacts person

Prof. Karim Manji

MUHAS, P.O. Box 65001, Dar-es-Salam, Tanzania

Telephone: 0754350630

If you want to ask someone independent anything about this research please contact:

Prof. Mainen Moshi, Director of Research and Publication, MUHAS, P.O. Box 65001, Dar-es-Salaam

Or

Ms. Joyce Ikingura, National Health Research Ethics Committee (NatHREC), National Institute for Medical Research (NIMR), P.O. Box 9653, Dar-es-Salaam

I [being the parent of_____(name of child)], have been told about this study. I have had the study explained to me. I have understood all that has been read/explained and had my questions answered satisfactorily.

Yes *please tick* **I agree to be interviewed**

Yes *please tick* **I agree for the interview to be recorded**

I understand that I can change my mind at any stage and it will not affect me/my child in any way.

Signature:		**Date:**	
Participant / Guardian Name:		**Time:**	
	(please print name)		

I certify that I have followed the study SOP to obtain consent from the [participant/guardian]. S/he apparently understood the nature and the purpose of the study and consents to the participation [of the child] in the study. S/he has been given opportunity to ask questions which have been answered satisfactorily.

Signature:		**Date:**	
Designee/ Investigator's Name:		**Time:**	
	(please print name)		

Thumb print of the parent as named above if they cannot write: _____

Where parent/guardian cannot read, a witness* may observe consent process and sign below if needed:

I attest that the information concerning this research was accurately explained and apparently understood by the subject/parent/guardian and that informed consent was freely given by the subject/parent/guardian.

Witness' signature: _____ Date _____

Witness' name: **_____ Time _____**

**A witness is a person who is independent from the trial or a member of staff who was not involved in gaining the consent.*

Appendix 11: Kiswahili version of the Autism Spectrum Quotient 5-Factor Model using Confirmatory Factor Analysis (CFA).

Factors and Items		Factor Loadings
Factor 1: Social Skills		
1	I prefer to do things with others rather than on my own.	0.019
11	I find social situations easy.	0.162
13	I would rather go to a library than a party.	0.131
15	I find myself drawn more strongly to people than to things.	0.118
22	I find it hard to make new friends.	-0.035
36	I find it easy to work out what someone is thinking or feeling just by looking at their face.	0.031
44	I enjoy social occasions.	0.556
45	I find it difficult to work out people's intentions.	0.604
47	I enjoy meeting new people.	0.775
48	I am a good diplomat.	0.653
Factor 2: Attention Switching		
2	I prefer to do things the same way over and over again.	0.671
4	I frequently get so strongly absorbed in one thing that I lose sight of other things.	0.532
10	In a social group, I can easily keep track of several different people's conversations.	0.129
16	I tend to have very strong interests which I get upset about if I can't pursue.	0.227
25	It does not upset me if my daily routine is disturbed.	0.188
32	I find it easy to do more than one thing at once.	0.223
34	I enjoy doing things spontaneously.	0.164
37	If there is an interruption, I can switch back to what I was doing very quickly.	0.14
43	I like to plan any activities I participate in carefully.	0.062
46	46. New situations make me anxious.	0.099
Factor 3: Attention to Detail		
5	I often notice small sounds when others do not.	0.568
6	I usually notice car number plates or similar strings of information.	0.575
9	I am fascinated by dates.	0.319
12	I tend to notice details that others do not.	0.315
19	I am fascinated by numbers.	0.264
23	I notice patterns in things all the time.	0.25
28	I usually concentrate more on the whole picture, rather than the small details.	0.145
29	I am not very good at remembering phone numbers.	0.168
30	I don't usually notice small changes in a situation, or a person's appearance.	0.31

49	49. I am not very good at remembering people's date of birth.	0.064
Factor 4: Communication		
7	Other people frequently tell me that what I've said is impolite, even though I think it is polite.	0.14
17	I enjoy social chit-chat.	0.055
18	When I talk, it isn't always easy for others to get a word in edgeways.	-0.034
26	I frequently find that I don't know how to keep a conversation going.	0.145
27	I find it easy to "read between the lines" when someone is talking to me.	0.042
31	I know how to tell if someone listening to me is getting bored.	0.289
33	When I talk on the phone, I'm not sure when it's my turn to speak.	0.497
35	I am often the last to understand the point of a joke.	0.526
38	I am good at social chit-chat.	0.637
39	People often tell me that I keep going on and on about the same thing.	0.518
Factor 4: Imagination		
3	If I try to imagine something, I find it very easy to create a picture in my mind.	0.05
8	When I'm reading a story, I can easily imagine what the characters might look like.	0.01
14	I find making up stories easy.	-0.207
20	When I'm reading a story, I find it difficult to work out the characters' intentions.	-0.233
21	I don't particularly enjoy reading fiction.	-0.207
24	I would rather go to the theatre than a museum.	-0.204
40	When I was young, I used to enjoy playing games involving pretending with other children.	0.701
41	I like to collect information about categories of things (e.g. types of car, types of bird, types of train, types of plant, etc.).	0.687
42	I find it difficult to imagine what it would be like to be someone else.	0.729
50	50. I find it very easy to play games with children that involve pretending.	0.203

Fit indices: Root Mean Square Error of Approximation (RMSEA), 0.13 (95% CI 0.127 – 0.133); Comparative Fit Index (CFI), 0.117; Tucker Lewis Index (TLI), 0.08.

Appendix 12: Principle Components Analysis (PCA) for the Kiswahili version of the Autism Spectrum Quotient (AQ) using Varimax rotation.

Original Subscale	Item		Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
CO	38	I am good at social chit-chat.	0.710				
AS	37	If there is an interruption, I can switch back to what I was doing very quickly.	0.678				
IM	41	I like to collect information about categories of things (e.g. types of car, types of bird, types of train, types of plant, etc.).	0.666				
SS	36	I find it easy to work out what someone is thinking or feeling just by looking at their face.	0.654				
IM	40	When I was young, I used to enjoy playing games involving pretending with other children.	0.650				
CO	35	I am often the last to understand the point of a joke.	0.643				
CO	39	People often tell me that I keep going on and on about the same thing.	0.639				
IM	42	I find it difficult to imagine what it would be like to be someone else.	0.573				
AS	34	I enjoy doing things spontaneously.	0.451				
AS	43	I like to plan any activities I participate in carefully.	0.424				
IM	8	When I'm reading a story, I can easily imagine what the characters might look like.		0.666			
CO	7	Other people frequently tell me that what I've said is impolite, even though I think it is polite.		0.660			
SS	11	I find social situations easy.		0.639			
AD	9	I am fascinated by dates.		0.631			
AD	5	I often notice small sounds when others do not.		0.575			
AD	6	I usually notice car number plates or		0.566			

		similar strings of information.					
AS	10	In a social group, I can easily keep track of several different people's conversations.		0.549			
AS	4	I frequently get so strongly absorbed in one thing that I lose sight of other things.		0.492			
IM	3	If I try to imagine something, I find it very easy to create a picture in my mind.		0.478			
SS	13	I would rather go to a library than a party.		0.430			
AD	12	I tend to notice details that others do not.		0.427			
CO	27	I find it easy to "read between the lines" when someone is talking to me.			0.630		
AD	30	I don't usually notice small changes in a situation, or a person's appearance.			0.628		
CO	31	I know how to tell if someone listening to me is getting bored.			0.627		
AD	28	I usually concentrate more on the whole picture, rather than the small details.			0.618		
AD	29	I am not very good at remembering phone numbers.			0.609		
CO	26	I frequently find that I don't know how to keep a conversation going.			0.593		
AS	25	It does not upset me if my daily routine is disturbed.			0.543		
AS	32	I find it easy to do more than one thing at once.			0.506		
AD	23	I notice patterns in things all the time.			0.465		
CO	33	When I talk on the phone, I'm not sure when it's my turn to speak.			0.449		
IM	24	I would rather go to the theatre than a museum.			0.422		
SS	1	I prefer to do things with others			0.349		

		rather than on my own.					
AS	2	I prefer to do things the same way over and over again.			0.345		
SS	48	I am a good diplomat.				0.786	
SS	47	I enjoy meeting new people.				0.783	
AS	46	New situations make me anxious.				0.752	
AD	49	I am not very good at remembering people's date of birth.				0.733	
SS	45	I find it difficult to work out people's intentions.				0.696	
SS	44	I enjoy social occasions.				0.583	
IM	50	I find it very easy to play games with children that involve pretending.				0.507	
IM	21	I don't particularly enjoy reading fiction.					0.665
CO	18	When I talk, it isn't always easy for others to get a word in edgeways.					0.664
IM	20	When I'm reading a story, I find it difficult to work out the characters' intentions.					0.662
AD	19	I am fascinated by numbers.					0.605
SS	22	I find it hard to make new friends.					0.539
AS	16	I tend to have very strong interests which I get upset about if I can't pursue.					0.533
IM	14	I find making up stories easy.					0.485
SS	15	I find myself drawn more strongly to people than to things.					0.479
CO	17	I enjoy social chit-chat.					0.464

Note. CO = Communication; AS = Attention switching; IM = Imagination; SS = Social skills; AD = Attention to detail.