Mental Health Comorbidities in Adults with Autism Spectrum Disorder: Prevalence rates and the role of adverse life events and parental mental health and wellbeing

Thesis Portfolio

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Thesis Portfolio Abstract

Introduction: Adults with autism spectrum disorders (ASD) are at heightened risk for several comorbid mental health conditions. However, the prevalence of common co-occurring difficulties such as anxiety and depression and associated risk factors are poorly understood. **Aim:** The aim of this thesis was to both quantify the prevalence of anxiety and depression in adults with ASD and to investigate how internalising (anxiety and depression) and externalising (conduct problems) symptoms in adulthood are related longitudinally to symptoms in childhood, quantifying any additional impact of exposure to adverse life events and poor parental mental health. **Method:** The prevalence of anxiety and depression was estimated by conducting a systematic review and meta-analysis consisting of 36 studies, including 30 studies measuring anxiety (n=26,070) and 29 measuring depression (n=26,117). The empirical study included 115 young adults with ASD who were assessed at three time-points (at 12,15 and 23 years of age) on measures of internalizing and externalizing symptoms. Structural Equation Modelling was used to investigate the impact of adverse life events and parental mental health on internalizing and externalizing symptoms. **Results:** The estimated current and lifetime prevalence for anxiety and depression in adults with ASD was 27% and 42%, and 23% and 37%, respectively. Results of the empirical study indicated that internalizing and externalizing symptoms in young adults with ASD are significantly related to exposure to adverse life events and mental health symptoms in childhood and adolescence. Additionally, poor parental mental health and wellbeing was found to predict a higher frequency of externalising problems but did not moderate the impact of adverse life events. **Discussion:** The results of this thesis suggest that anxiety and depression are highly prevalent in adults with ASD and that symptom severity in childhood and adolescence, exposure to life events and poorer parent mental health are all independent predictors of symptom severity.

Part 1 – Meta Analysis

CHAPTER 1: Anxiety and Depression in Adults with Autism Spectrum Disorder: A Systematic Review and Meta-analysis

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Abstract

Adults with autism spectrum disorder (ASD) are thought to be at disproportionate risk of developing mental health comorbidities, with anxiety and depression being considered most prominent amongst these, yet no systematic review has yet been carried out to examine rates of both anxiety and depression focusing specifically on adults with ASD. This systematic review and meta-analysis examined the rates of anxiety and depression in adults with ASD and the impact of factors such as assessment methods and diagnosis of comorbid intellectual disability (ID) on estimated prevalence rates. Electronic database searches for studies published between January 2000 and September 2017 identified a total of 36 studies, including 27 studies measuring anxiety (n = 26,070, mean age (SD) = 30.9 (6.2) years) and 29 measuring depression (n = 26,117, mean age (SD) = 31.1 (6.8) years). The pooled estimation of current and lifetime prevalence for adults with ASD were 27% and 42% for any anxiety disorder, and 23% and 37% for depressive disorder. Further analysis revealed that use of questionnaire measures and the presence of ID, may significantly influence estimates of prevalence. The current literature suffers from a high degree of heterogeneity in study method and an overreliance on clinical samples. These results highlight the importance of community based studies and, the identification and inclusion of well characterised samples, to reduce heterogeneity and bias in estimates of prevalence for comorbidity both in adults with ASD and other populations with complex psychiatric presentations.

Key words: Affective Disorders; Autism; Comorbidity; Epidemiology; Prevalence.

Introduction

Our understanding of the clinical and social needs of individuals with an autism spectrum disorder (ASD) across the lifespan has increased in recent years (Baxter *et al.* 2015), and there has been increased emphasis on better understanding this in adults (Taylor & Seltzer 2011; Howlin 2013; Moss *et al.* 2015, 2017). Adults with ASD are thought to be at heightened risk for several co-occurring mental health conditions, with anxiety and depressive disorders being the most prominent (Joshi *et al.* 2013). However, estimates of the rates of these co-occurring disorders in adults with ASD vary considerably, with some studies reporting rates of anxiety or depression as high as 70% (Charlot et al. 2008; Mazefsky et al. 2008), and others reporting rates as low as <1% for depression (Buck et al. 2014) and 5% for anxiety (Tsakanikos, et al. 2011).

Given that ASD has so far been primarily considered a diagnosis of childhood, most research to date has focused on the child and adolescent period. van Steensel and colleagues produced a meta-analysis of the prevalence of anxiety in young people with ASD aged <18 years of age (van Steensel *et al.* 2011). Their results indicated that 39.6% of young people with ASD had at least one anxiety disorder diagnosis, with specific phobias, obsessive compulsive disorder (OCD) and social anxiety being most commonly reported. Co-occurring depression in young people with ASD has so far received less attention than anxiety, possibly due to lower prevalence estimates in some studies. For instance, evidence from a population derived sample of children and adolescents with ASD reported a 3-month point prevalence of any depressive disorder to be 1.4% compared to 41.9% for any anxiety disorder (Simonoff *et al.* 2008). In contrast, clinical studies based on treatment seeking adults suggest that

depression may indeed be common in adults with ASD, with reported rates ranging from 20-35% (Gotham et al. 2015; Mazefsky et al. 2008). If this is the case then it would indicate a prevalence much higher than would be expected based on studies in the non-ASD population which suggest current rates of around 7% for depression and between 1 -12% for anxiety, depending on the specific diagnosis (Kessler et al. 2006; 2012).

There are several challenges to the use of meta-analytic methods with studies on the prevalence of anxiety and depression in adults with ASD. Prominent amongst these are the lack of measures available to assess mental health comorbidities in those with ASD, particularly in adulthood, which are validated in autism and non-autism populations. This, along with variability in the assessment of ASD itself and a lack of community-based studies focusing on co-occurring mental health presentations in the adult period, means that there is substantial heterogeneity in both the populations being assessed and the study designs and methods/tools used to measure anxiety and depression. This is a potential caveat in the use of meta-analytic techniques to combine the literature currently available, but nonetheless, this enables us to quantify the degree of heterogeneity in a robust way.

One important issue to consider when reviewing the available literature on mental health comorbidities in those with ASD is the problem of diagnostic over-shadowing (Wood & Gadow 2010). This phenomenon has most often been discussed in relation to the most commonly reported in ASD anxiety disorders, namely social phobia and OCD (Ozsivadjian *et al.* 2012; Kerns *et al.* 2014; Magiati *et al.* 2017). In the case of social phobia, it has been suggested that the reduced social motivation or difficulties in social situations commonly observed in

ASD can appear behaviourally similar to the anxious avoidance of social situations which is characteristic of social phobia. In addition, compulsive behaviours in OCD can appear similar in presentation to restrictive and repetitive behaviours as observed in ASD, and indeed recent evidence has suggested some neurobiological overlap (Carlisi *et al.* 2017). Similarly, social disinterest and atypical social communication may be difficult to distinguish from psychomotor symptoms of depression in those with ASD (Chandrasekhar & Sikich 2015; Stewart et al. 2006).

Another factor that adds to the complexity of determining the rates of anxiety and depressive disorders is the wide range of intellectual, verbal and adaptive functioning in adults with ASD. With regards to intellectual functioning, for example, it has been suggested that in clinical samples approximately one third of people with ASD have intellectual functioning in the impaired range (Kim *et al.* 2011). Therefore, it is important to consider individuals' functioning when considering and interpreting findings from different studies of individuals with ASD with and without intellectual disability (ID).

The aim of the current systematic review and meta-analysis was to examine the rates of anxiety and depression in adults with ASD based on the literature currently available. To our knowledge, previous systematic reviews have focused solely on depression rates, have considered both children and adults together, or have included only a limited range of studies (i.e. Wigham et al. 2017; Stewart et al. 2006). Therefore, a systematic review is now required that focuses on adults, and examines both rates of depression and anxiety. Given our *a-priori* knowledge of a lack of community based prevalence studies in this area, we have opted to be inclusive in our selection criteria. As discussed above, the

current literature has been affected by a high degree of between study heterogeneity, both in terms of the clinical populations assessed, as well as the study methodology and measures used to assess anxiety and depression. Therefore, as well as providing the first, to our knowledge, meta-analysis of rates of anxiety and depression in adults with ASD, we aimed to explore the potential impact of ASD diagnostic measures, measures of comorbidity and the role of intellectual disability on the estimates provided.

Methods

Definition/ operationalization of key constructs

In the current systematic review and meta-analysis, anxiety was defined as either clinically significant/ elevated symptoms of anxiety (defined as scores above clinical cut-offs on questionnaires) or a clinical diagnosis of any specific anxiety disorder (including generalized anxiety disorder; social phobia/social anxiety; specific phobia; separation anxiety; panic/agoraphobia; post-traumatic stress disorder (PTSD); or obsessive-compulsive disorder (OCD)[1]). Most studies present panic disorder and agoraphobia as a single estimate, but in cases where they are presented separately the highest rate of the two was included. This was to reduce the chances of them being double coded due to high comorbidity, given that most articles did not specify levels of multiple comorbidity in their samples (Kessler *et al.* 2006).

[1] We have included PTSD and OCD as they have a strong anxiety component and were previously organized and conceptualized under anxiety disorders in DSM-IV-TR, when many of the included studies took place.

For depression, we only included cases which were above recommended clinical cut-off scores on validated questionnaires were met or where a professional/ clinical diagnosis of major depression was given. As an example, for the most commonly used questionnaire, the Beck Depression Inventory (BDI; Beck 1978), depending on the version, a cut-off score of “20” or “24” or at least depression in the moderate range would be required. For all other questionnaires used, their specific published cut-offs as applied by the original authors were used.

Information Sources & Search approach

We conducted a search of three electronic literature databases (PsycINFO, PubMed, and Web of Science) selected to provide good coverage of both medical and psychology literature. The search included publications from the start of the year 2000 and ran up until 30th of September 2017. The start date was selected based on the publication of the text revision of the DSM-IV, to reduce the challenge of combining definitions from multiple diagnostic systems.

The search terms used were “autis*” OR “Asperger*” OR “Pervasive Developmental Disorder”); AND (“anxi*” OR “anxiety disorder” OR “anxious”) OR (“comorbid* OR “psychiatric disorder” OR “mental health”) OR (“depress*” OR “mood disorder” OR “low mood”) AND (“adults” NOT “animal”).

Two earlier systematic reviews (Stewart et al. 2006; Wigham et al. 2017) and a narrative review (Chandrasekhar & Sikich 2015) on depression in adults with ASD were examined and one additional citation (Crane *et al.* 2013) from that review met our inclusion criteria and was included. We did not identify any reviews focused on the prevalence of anxiety in adults with ASD. One review of comorbid Bipolar disorder was reviewed for depression related literature, but no

additional citations were identified (Vannucchi *et al.* 2014). A Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flowchart (Figure 1) is displayed as a summary of our search and review process. See Table 1 for inclusion and exclusion criteria. This meta-analysis was pre-registered on PROSPERO an international prospective register of systematic reviews (PROSPERO 2016 CRD42016051094).

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flowchart.

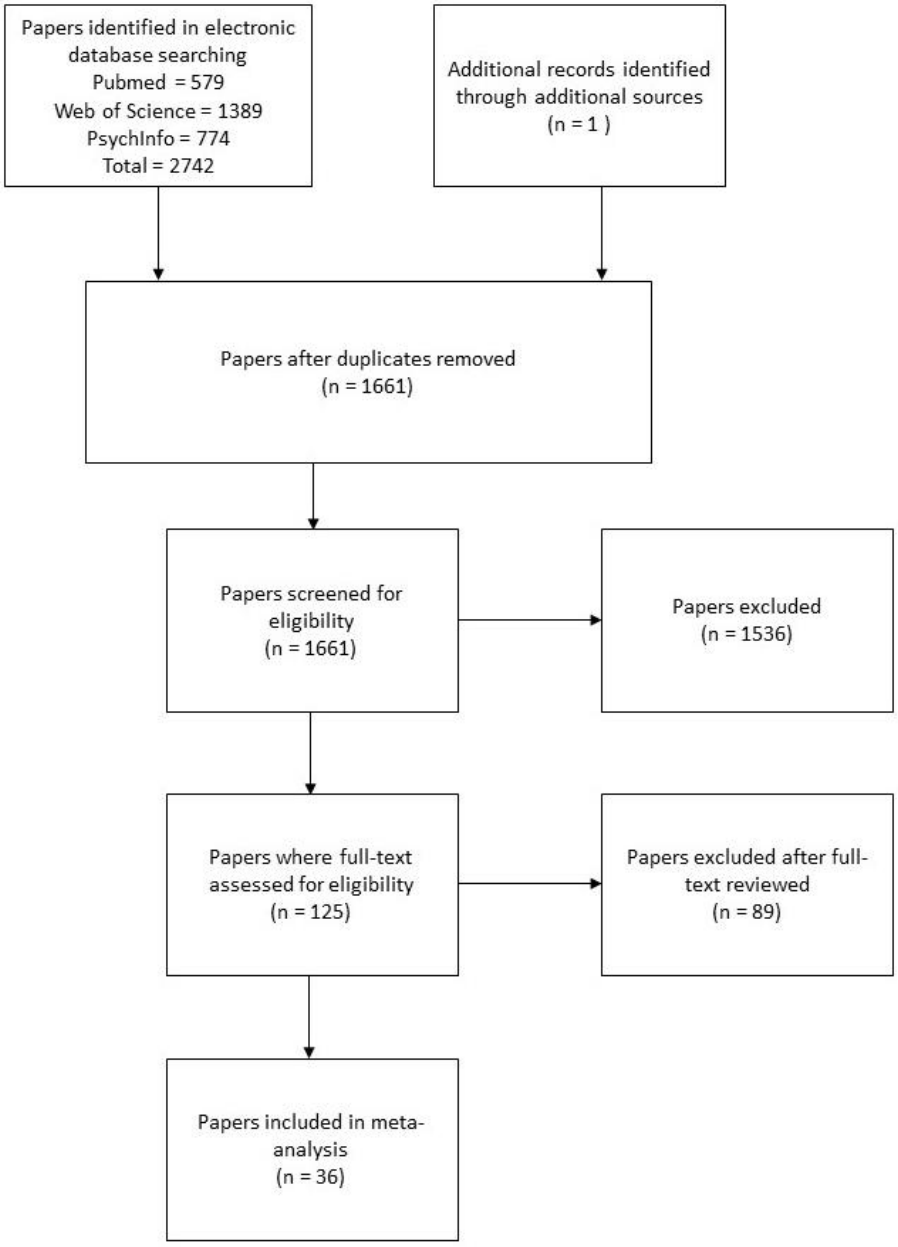

Table 1. Inclusion and exclusion criteria to be eligible for inclusion in the current systematic review

Inclusion criteria	Exclusion criteria
(i) include participants with a diagnosis of ASD based on either DSM or ICD criteria. Where the ASD diagnosis was not carried out using an ADOS or/ an ADI-R, we took an inclusive approach with the aim to explore the impact of ASD diagnostic tools on prevalence estimate in a sensitivity analysis; (ii) study participants, or an identifiable sub-group, with mean group age ≥ 18 years with the youngest participant being no younger than 16; (iii) include an assessment of comorbid anxiety or depression using either a diagnostic interview, or a validated questionnaire measure with cut-off scores for clinical caseness or a clinical diagnosis based on either DSM or ICD criteria; (iv) be published in English or have an English translation available.	(i) Studies which had not undergone peer review. (ii) Other systematic reviews which do not provide new data on rates of anxiety or depression in adults with ASD. (iii) Single case studies or case series methodologies. (iv) Treatment trial studies looking specifically at interventions for co-occurring psychiatric conditions in people with ASD, as these constituted clinical samples; (v) Studies which focused on genetic syndromes associated with ASD (e.g., Fragile X Syndrome, Rett Syndrome). (vi) Studies of dysthymia or bipolar disorder, as we focused on depression.

Selecting studies for inclusion in the review.

One author (MJH) initially screened titles and abstracts for eligibility and excluded those that clearly did not meet criteria; following this, two authors (MJH & J-WL) reviewed all remaining full-texts for eligibility. Disagreements were discussed and resolved on a case-by-case basis (see Reliability).

Data extraction

We extracted the following information from each study: a) sampling strategy; b) descriptive variables (e.g., age, gender); c) tools used to diagnose ASD; d) number of participants with an ID in the sample; e) tools used to assess anxiety/depression; f) whether diagnostic overshadowing/symptom overlap was considered in the study; and g) current and lifetime estimates of anxiety and depression; as the primary interest of this meta-analysis is on current prevalence, all sensitivity analyses were conducted on current estimates only. Three studies included both current and lifetime estimates and both were used in their respective analyses (Joshi et al. 2013; Buck et al. 2014; Gillberg et al. 2016).

Reliability

Selecting studies. There was good inter-rater reliability in study selection for inclusion in the review/meta-analysis (intra-class correlation = 0.72) and all disputes were resolved by referring to inclusion/exclusion criteria. On three occasions, the same dataset was used in data analyses in three different publications, with different subsamples from the same study being analysed (Tsakanikos *et al.*, 2006, 2007, 2011). In this case, we included the most recent citation which had the most participants. Other reasons for the exclusion included no clinical cut-off/diagnostic algorithm applied (*n=28)*, didn't measure

anxiety/depression (*n=25), minimum age <16 years* (*n=11), non-ASD sample* (*n=9), no English translation available* (*n=8), not peer reviewed* (*n=3), intervention study* (*n=1) and being a review article* (*n=1).*

Data extraction. All data was extracted by the first author (MJH) and then a randomly selected sample of 25% of the studies was checked for accuracy (J-WL), resulting in no disagreement.

Study Sample

The final sample included 36 studies across both anxiety and depression, with 27 studies measuring anxiety, 29 measuring depression, and 21 measuring both. Studies measuring anxiety included a total of 26,070 participants (mean age = 30.9 years, SD=6.2), and for depression there were in total of 26,117 participants (mean age = 31.1 years, SD=6.8; see Tables 2 & 3 for study characteristics and summary of main findings).

For three studies where the age of the sub-sample of interest was not reported, the mean was estimated based on the age of the overall sample (Morgan *et al.* 2003; Hermans *et al.* 2011; Houghton *et al.* 2017). Seven of the 36 studies included in the meta-analysis included adolescents in the sample (≥16 years old). Nine of the studies included had a sample that included at least 50% of people with an ID and were included in the sub-analysis described below (Buck et al. 2014; Charlot et al. 2008; Helverschou et al. 2009; Hermans et al. 2012; Mazefsky et al. 2008; McDermott et al. 2005; Morgan et al. 2003; Moss et al. 2015; Tsakanikos, et al. 2011).

Table 2. Included studies assessing anxiety, study characteristics and prevalence rates of anxiety

First Author (year)	N	Mean age	Male (%)	ID (%)	Source	Method	Respondent	Current /Lifetime	Rates of Anxiety %							
									ANY ANX	SOC	OCD	GAD	PAN/AGO	SPH	SEP.	PTSD
Ashwood (2016)	260	32	-	0	Clin	I	Self-report	Current	-	18	24	23	16	-	-	-
Bejerot (2014)	50	30	52	0	Clin	I	Self-report	Current	-	28	-	-	-	-	-	-
Buck (2014)	129	36	75	73	Com	I	Self-report	Current / Lifetime	40/53	-	33/36	-	-	-	-	-
Capriola (2016)	18	25	56	0	NT	I	Self-report	Current	-	61	-	-	-	-	-	-
Charlot (2008)	13	39	62	100	Clin	I	Informant	Current	-	-	46	-	-	-	-	-
Croen (2015)	1507	29	73	19	Clin	C	Clinical records	Lifetime	29	-	8	-	-	-	-	-
Ghaziuddin (2008)	28	27	64	7	Clin	I	Self-report	Current	21.4	-	-	-	-	-	-	-
Gillberg (2016)	50	30	100	0	Clin	I	Self-report	Current	22	4	8	10	6	-	-	0
Helverschou (2009)	35	35	74	100	Clin	Q	Informant	Current	17	-	17	-	-	-	-	-
Hermans (2012)	46	-	-	100	Clin	I	Self-report	Current	11	-	-	-	-	-	-	-
Hofvander (2009)	122	27	67	0	Clin	I	Self-report	Lifetime	48	-	24	-	-	-	-	-
Houghton (2017)	22253	-	80	26	Clin	C	Clinical records	Lifetime	25	-	-	-	-	-	-	-
Jones (2014)	120	39	58	0	NT	Q	Self-report	Current	7	-	-	-	-	-	-	-

Joshi (2013)	63	29	65	0	Clin	I	Self/Informant	Current/Lifetime	-	40/56	16/24	29/35	24/35	18/32	3/21	5/11
Ketelaars (2008)	15	22	80	0	Clin	I	Self-report	Current	-	20	7	-	13	-	-	-
Lai (2011)	62	27	53	0	NT	Q	Self-report	Current	44	-	71	-	-	-	-	-
Lever (2016)	138	47	70	0	Clin	I	Self-report	Lifetime	54	15	22	16	s21	12	-	3
Lugnegard (2011)	54	27	48	0	Clin	I	Self-report	Lifetime	56	22	7	22	15	-	-	-
Maddox (2015)	28	24	54	0	NT	I	Self-report	Current	-	50	-	-	-	-	-	-
Mazefsky (2008)	16	25	94	70	Com	I	Informant	Lifetime	77	0	-	41	0	59	-	-
Moss (2015)	21	43	83	0	Clin	Q	Self-report	Current	10	-	-	-	-	-	-	-
Nylander (2013)	270	27	69	12	Clin	C	Clinical records	Current	17	-	-	-	-	-	-	-
Roy (2015)	50	37	68	0	Clin	I	Self-report	Lifetime	-	12	14	-	14	-	-	2
Russell (2016)	474	31	78	0	Clin	I	Self-report	Current	40	12	18	11	4	0.4	-	0.4
Spain (2016)	50	26	100	0	Clin	Q	Self-report	Current	-	26	-	-	-	-	-	-
Sterling (2008)	46	24	91	0	Clin	I	Self-report	Current	17	-	9	-	-	-	-	-
Tsakanikos (2011)	150	29	67	100	Clin	C	Clinical records	Current	5	-	-	-	-	-	-	-

Note. ID= Intellectual Disability; Com= Recruited from a whole community or community sampling strategy was used; Clin= Recruited through a clinical service; NT= Non-treatment seeking and recruited through notices or databases, but not due to clinical contact; I= Structured Interview, Q= Standardised Questionnaire, C= Clinical Records or not reported; ANY ANX= Any Anxiety Disorder; SOC= Social Anxiety Disorder; OCD= Obsessive-compulsive Disorder; GAD= Generalised Anxiety Disorder; PAN/AGO= Panic Disorder/ Agoraphobia; SPH= Specific Phobia; SEP= Separation Anxiety Disorder; PTSD = Post-traumatic Stress Disorder.

Meta-analytic method

A random-effects meta-analysis with arcsine transformation was used to account for issues with study weightings when estimating prevalence (Barendregt *et al.* 2013). Study heterogeneity was assessed using the I^2 statistic, whereby a score of more than 50% indicates moderate, and a score of 75% high levels of heterogeneity, respectively (Higgins & Thompson 2002). Subgroup analyses were conducted to investigate differences based on studies focusing on ID (≥50% of sample had ID); assessment of ASD diagnoses (i.e., using Autism Diagnostic Observation Schedule (ADOS)/Autism Diagnostic Interview (ADI); and measurement of comorbidity (i.e., questionnaire versus structured clinical interview). It was also of interest to investigate the impact of sample type (e.g., clinical versus community sampling). However, as there were few studies that could clearly be defined as non-clinical this was considered under study quality. The significance of differences in pooled estimates between subgroups were assessed via meta-regression analyses. Study quality was assessed on two domains, selection bias and detection bias, which were adapted for this meta-analysis from the Effective Public Health Practice Project Quality Assessment Tool (Armijo-Olivo et al. 2012 ; see Chapter 2). OpenMeta, a tool for running *metafor* package in R (Viechtbauer 2010), was used to conduct the meta-analysis (Wallace *et al.* 2012).

Table 3. Included studies assessing depression, study characteristics and prevalence rates of depression

Author (year)	N	Mean age	Male (%)	ID (%)	Source	Method	Respondent	Current/Lifetime	Rates of Depression (%)
Ashwood (2016)	260	32	-	0	Clin	I	Self-report	Current	22
Berthoz (2013)	38	36	63	0	NT	Q	Self-report	Current	32
Buck (2014)	129	36	75	73	Com	I	Self-report	Current / Lifetime	<1/13
Cederlund (2010)	76	22	100		Clin	Q	Self-report	Current	4
Charlot (2008)	13	36	62	100	Clin	I	Informant	Current	69
Crane (2013)	28	42	50	0	NT	Q	Self-report	Current	36
Croen (2015)	1507	29	73	19	Clin	C	Clinical records	Lifetime	26
Ghaziuddin (2008)	28	27	64	7	Clin	I	Self-report	Current	50
Gillberg (2016)	50	30	100	0	Clin	I	Self-report	Current / Lifetime	28/32
Gotham (2015)	50	21	90	0	Clin	Q	Self-report	Current	20
Hedley (2017)	76	25	91	10	NT	Q	Self-report	Current	25
Helverschou (2009)	35	35	74	100	Clin	Q	Informant	Current	14
Hill (2004)	27	35	56	0	NT	Q	Self-report	Current	22
Hofvander (2009)	122	27	67	0	Clin	I	Self-report	Lifetime	53
Houghton (2017	22253	-	80	25	Clin	C	Clinical records	Lifetime	18
Jones (2014)	120	39	58	0	NT	Q	Self-report	Current	42
Joshi (2013)	63	29	65	0	Clin	I	Self/Informant	Current/Lifetime	31/77
Ketelaars (2008)	15	22	80	NA	Clin	I	Self-report	Current	26
Lai (2011)	62	27	53	0	NT	Q	Self-report	Current	27
Lever (2016)	138	47	70	0	Clin	I	Self-report	Lifetime	54
Lugnegard (2011)	54	27	48	0	Clin	I	Self-report	Lifetime	70

Mazefsky (2008)	16	25	94	70	Com	I	Informant	Lifetime	24
McDermot (2005)	51	27	78	0	Clin	C	Clinical records	Lifetime	6
Morgan (2003)	164	-	56	100	Com	C	Clinical records	Current	20
Moss (2015)	21	43	83	0	Clin	Q	Self-report	Current	10
Roy (2015)	50	37	68	0	Clin	I	Self-report	Lifetime	48
Russell (2016)	474	31	78	0	Clin	I	Self-report	Current	16
Sterling (2008)	46	24	91	0	Clin	I	Self-report	Current	35
Tsakanikos (2011)	150	29	67	100	Clin	C	Clinical records	Current	7

Note. ID= Intellectual Disability; Com= Recruited from a whole community or community sampling strategy was used; Clin= Recruited through a clinical service; NT= Non-treatment seeking and recruited through notices or databases, but not due to clinical contact; I= Structured Interview, Q= Standardised Questionnaire, C= Clinical Records or not reported.

Results

Prevalence of anxiety disorder in adults with ASD

Any anxiety disorder. Meta-analytic pooling of the estimates yielded the prevalence of any *current* anxiety disorder as 27% (95% CI 17% – 37%; *k = 13, n = 431/1444*). Assessment of heterogeneity indicated high levels of variance between studies included in the analysis (I^2 = 96%). A subsequent analysis of the eight studies which were classified as measuring *lifetime* prevalence indicated a prevalence of 42% (95% CI 35% – 50%; *k = 8, n = 6634/25714,* I^2 = 96%; see Table 4).

Social Anxiety. Overall 12 studies reported on rates of social anxiety, together reporting an estimated *current* prevalence of 29% and *lifetime* prevalence of 20% (*current*: 95% CI 18% – 40%, *k = 9*, *n = 200/1009,* I^2 = 91%; *lifetime*: 95% CI 7% – 38%, *k = 5, n = 75/322,* I^2 = 91%).

OCD. Fifteen studies in total measured the rates of OCD with *current* prevalence estimate of 24% and a *lifetime* prevalence of 22% (*current*: 95% CI = 15% – 33%, *k = 10, n = 265/1147,* I^2 = 93%; *lifetime*: 95% CI = 10% – 27%, *n = 247/2063, k = 7,* I^2 = 93%).

GAD. Seven studies reported *current* GAD prevalence of 18% and *lifetime* prevalence of 26% (*current*: 95% CI 10% – 26%, *k* = 4, *n* = 138/847, I^2 = 86%; *lifetime*: 95% CI 15% – 28%, *k* = 4, *n* = 63/272, I^2 = 74%).

Panic/ Agoraphobia. Eight studies in total reported an estimated *current* and *lifetime* prevalence of 15% and 18%, respectively (*current*: 95% CI 8% – 23%, *k = 4, n* = 62/388, I^2 = 62%; *lifetime*: 95% CI 10% - 27%, *k = 4, n* = 66/322, I^2 = 75%).

PTSD. Post-traumatic stress disorder was reported in five studies with a *current* prevalence of 1% and *lifetime* prevalence of 5% was found (current: 95% CI 0% – 5%, *k = 3, n* = 5/587, I^2 = 63%; *lifetime*: 95% C.I. 1% – 10%, *n studies = 3, n* = 12/251, I^2 = 67%).

Specific Phobia. A total of four studies reported on rates of specific phobia yielding an estimated current prevalence of 6% and a *lifetime* prevalence of 31% (*current*: 95% CI 1% – 32%, *k = 2, n* = 13/537, I^2 = 97%; *lifetime*: 95% C.I. 10% – 66%, *k = 3, n* = 46/218, I^2 = 92%).

Separation Anxiety. *Current* separation anxiety was reported by only one study as present in 3% of the sample (*n*=2/62), with a *lifetime* prevalence of 21% (13/62) (Joshi, et al. 2013).

Sub-group analyses: the role of clinical interview versus questionnaire measures, ASD diagnostic tools and intellectual disability on current anxiety prevalence estimates

Use of clinical interview versus questionnaires to measure anxiety. When comparing studies which used a structured clinical interview versus validated questionnaires to assess *current* rate of any anxiety disorder, we again found no significant difference in prevalence estimates (clinical interview: *k* = 7; n = 275/786, estimated prevalence = 28%, 95% CI 19% – 39%, I^2 = 85%; questionnaires: *k* = 4, n = 103/238, estimated prevalence = 31%, 95% CI 12% – 54%, I^2 = 91%).

All but one of the nine of the studies of *current* social anxiety used a structured diagnostic interview, with this one study employing a questionnaire

indicating a prevalence of 51% (Spain *et al.* 2016) versus a pooled prevalence of 26% in the remaining studies (k = 8, n = 174/958, CI 16% – 37%, I^2 = 90%).

Eight studies which assessed *current* OCD used clinical interviews resulting in a significantly lower (β = 0.26, *p = 0.03)* estimated pooled prevalence of 19% versus 43% for questionnaire measures and a reduced level of between study heterogeneity (clinical interview: *k* = 8, n = 215/1050, 95% CI 13% – 23%, I^2 = 79%; questionnaires: *k* = 2, n = 50/97, 95% CI 3% - 92%, I^2 = 97%).

Use of ASD diagnostic tools. Only 4/13 studies of *current* prevalence of any anxiety disorder used the ADOS and/or ADI to confirm ASD diagnosis for inclusion into studies. The use of ADOS/ADI assessment lead to slight, but non-significant, increases in the estimated pooled prevalence (ADOS/ADI studies: *k = 4, n = 223/603,* estimated prevalence = 28%, 95% CI 15% – 43%, I^2 = 86%; non-ADOS/ADI studies: *k = 9, n = 208/841,* estimated prevalence = 25%, 95% CI 13% – 37%, I^2 = 95%).

Similar results were found when looking at the 6/9 studies of *current* social anxiety (ADOS/ADI studies: *k = 6, n = 159/846,* estimated prevalence = 33%, 95% CI 19% – 46%, I^2 = 92%; non-ADOS/ADI studies: *k = 3, n = 41/163,* estimated prevalence = 21%, 95% CI 4% – 48%, I^2 = 93%) and 5/10 studies of *current* OCD (ADOS/ADI: *k = 5, n = 196/857,* estimated prevalence = 24%, 95% CI 12% – 41%, I^2 = 95%; non-ADOS/ADI: *k = 5, n = 69/290,* estimated prevalence = 19%, 95% CI 14% – 31%, I^2 = 65%).

Presence of intellectual disability. Subgroup analysis of studies of *current* prevalence of anxiety disorder or clinically elevated anxiety symptomatology of participants with or without associated ID revealed a reduced, but non-significant, pooled estimate of any anxiety disorder in adults with ASD

and associated ID (*k = 6, n = 79/394,* estimated prevalence = 20%, 95% CI 7% – 39%, I^2 = 93%) compared to samples including only individuals with ASD without ID (*k* =7, n = 352/1050, estimated prevalence = 24%, 95% CI 19% – 43%, I^2 = 93%).

All nine studies of *current* social anxiety included only participants with ASD without an intellectual disability, while only three of ten studies measuring OCD included primarily adults with ASD and ID, resulting in no significant difference on pooled prevalence estimates (ID: *k* = 3, n = 55/177, estimated prevalence = 24%, 95% CI 14% – 36%, I^2 = 49%; non-ID: *k* = 7, n=210/970, estimated prevalence = 20%, 95% CI 10% – 34%, I^2 = 93%).

Prevalence of depression in adults with ASD

Meta-analytic pooling of the estimates yielded a 23% prevalence of *current* co-morbid depression diagnoses or moderate to severe clinically elevated depressive symptoms (k = 22, n = 400/1975; 95% CI 17% – 29%). Assessment of heterogeneity indicated high levels of variance between studies included in the analysis (I^2 = 90%).

A subsequent analysis of the seven studies which were classified as measuring *lifetime* prevalence indicated a prevalence of 37% (k = 10, n = 4603/24384; 95% CI 27% – 47%; I^2 = 98%).

Sub-group analyses: the role of clinical interview versus questionnaire measures, ASD diagnostic tools and intellectual disability on current depression prevalence estimates

Use of clinical interview versus questionnaires to measure depression. When comparing studies which used a structured clinical interview versus validated questionnaires, we found a small, but non-significant, increase

in prevalence estimates for studies using a clinical interview rather than a questionnaire measure (clinical interview: *k* = 11, n = 237/1182, estimated prevalence = 27%, 95% CI 18% – 37%, I^2 = 92%; questionnaire: *k* = 8, n = 106/429, estimated prevalence = 20%, 95% CI 11% – 33%, I^2 = 87%).

Use of ASD diagnostic measures. Only 6/19 studies of current prevalence used the ADOS and/or ADI to assess or confirm ASD. This made little difference to prevalence estimates, but resulted in a considerable drop in heterogeneity between studies (ADOS/ADI studies: *k = 6, n = 170/878,* estimated prevalence = 22%, 95% CI 16% – 28%, I^2 = 66%; non-ADOS/ADI: *k = 15, n = 214/1047,* estimated prevalence = 23%, 95% CI 14% – 34%, I^2 = 93%).

Presence of ID. Subgroup analysis of studies of current prevalence of depression based on whether the sample included participants with or without an ID revealed a significantly reduced pooled estimate of depression (meta-regression: β = .12, $p \leq .05$), compared to samples including only those without ID (ID: *k* = 6, n = 58/512, estimated prevalence = 14%, 95% CI 5% – 28%, I^2 = 92%; non-ID: *k* = 16, n=326/1413, estimated prevalence = 26%, 95% CI 20% – 32%, I^2 = 83%).

Evaluating the quality of included studies

Our analysis of study quality revealed overall poor quality. Most prominent with regards to prevalence is the reliance on clinic samples and little data available on how representative study participants are of adults with ASD more generally. These results can be seen in Chapter 2, and indicate that there are few studies which have clearly taken measures to reduce selection and detection bias.

Table 4. Pooled estimates of current and lifetime anxiety and depression in adults with ASD

Diagnosis	Current/ Lifetime	No. of Studies	Participants, *n*	Prevalence, %	95% C.I.	I^2, %
Any anxiety	Current	13	1444	27%	17% - 37%	96%
	Lifetime	8	25714	42%	35% - 50%	96%
Social phobia	Current	9	1009	29%	18% - 40%	91%
	Lifetime	5	322	20%	7% - 38%	91%
OCD	Current	10	1147	24%	15% - 33%	93%
	Lifetime	7	2063	22%	10% - 27%	93%
GAD	Current	4	847	18%	10% - 26%	86%
	Lifetime	4	272	26%	15% - 28%	74%
Panic/agoraphobia	Current	4	388	15%	8% - 23%	62%
	Lifetime	4	322	18%	10% - 27%	75%
Specific phobia	Current	2	537	6%	1% - 32%	97%
	Lifetime	3	218	31%	10% - 66%	92%
PTSD	Current	3	587	1%	0% - 5%	63%
	Lifetime	3	251	5%	1% - 10%	67%
Separation Anxiety	Current	1	63	3%	-	-
	Lifetime	1	63	21%	-	-
Depression	Current	22	1975	23%	17% - 29%	90%
	Lifetime	10	24384	37%	27% - 47%	98%

Discussion

Summary of main findings

While it is widely accepted that adults with a diagnosis of ASD are at higher risk of experiencing comorbid anxiety and depressive disorders, there has yet to be a systematic review and meta-analysis to summarise the range of estimates of prevalence available in the literature (see also Wigham et al., 2017). We found a pooled estimate of *any current* anxiety and depression of 27% and 23% respectively, considerably higher than would be expected based on estimates from the general population (Kessler et al. 2003; 2012). The rate of current depression was consistent with the estimate of >20% reviewed by Wigham et al., 2017, which examined a subset of the studies included in the present meta-analysis. The finding of somewhat higher rates of anxiety compared to depression was also similar for pooled *lifetime* estimates of any anxiety (42%) and depression (37%). Consistent with estimates from childhood (van Steensel et al. 2011), we found that specific anxiety disorders, particularly social phobia and OCD, were more commonly present in adults with ASD. However, our analyses of both heterogeneity and study quality indicated high level of variance between studies, a wide range of study methodology and sample selection, all of which increase the likelihood of bias and reduce our ability to make more firm estimates of prevalence from the studies currently available.

Rates/ prevalence of anxiety and depression in adults with ASD

The findings of the current study are consistent with meta-analyses of the prevalence of anxiety in people with ASD aged 18 years and under (van Steensel *et al.* 2011; van Steensel & Heeman 2017). However, while the 2011 meta-

analytic study suggested a current rate of any anxiety disorder of around 39%, our pooled estimate of anxiety in adulthood appears lower at 27%. This may be explained by lower rates (when measured) of anxiety disorders more typically associated with the childhood period such as separation anxiety (Bögels *et al.* 2013), and a reduction in the estimated prevalence of specific phobias. It is notable, however, that compared to the estimates by van Steensel and colleagues, we found a near 10% higher rate of both social anxiety and OCD in adults. This could in part be accounted for by the fact that these anxiety subtypes were preferentially assessed/reported in the literature included in the current analysis, or these high rates could be at least partially due to diagnostic overshadowing which is a challenge with OCD and social anxiety as discussed above. This may suggest that the process of eliciting a detailed description of the target behaviour, as is often the case when conducting a diagnostic interview and making a clinical judgement on this may minimise the impact of diagnostic overshadowing. Similarly, this may account for the higher heterogeneity of prevalence based on questionnaire measures vs. structured interviews. However, it is important to note that in either case the heterogeneity remains high.

One *a-priori* aim of this systematic review and meta-analysis was to consider the possible impact of diagnostic overshadowing on the estimated reported prevalence of anxiety and depression in adults with ASD. Unfortunately, only four of the total of 36 studies included in this meta-analysis considered diagnostic over-shadowing: two relied on clinical experience or trained research staff who conducted the interviews in differentiating symptoms of anxiety and ASD (Capriola et al. 2016; Maddox & White 2015); one used a measure specifically designed to assess comorbidity in ASD (Helverschou *et al.* 2008),

and one removed all symptoms of OCD which potentially overlapped with those of ASD from their diagnostic coding (Buck et al. 2014). In the latter study, this resulted in the lifetime prevalence dropping from 36% to 22%, suggesting that overlap between ASD and anxiety symptomatology and presentation likely does to some extent impact the estimated reported prevalence and that caution should be exercised when interpreting the results of the other studies and of this meta-analysis. From a clinical perspective this may also suggest that at the current time an overreliance on standardised measures is not recommended. Rather, a detailed assessment and formulation considering a range of factors such developmental history, family wellbeing and the function of the behaviours associated with the presenting comorbidity may be more beneficial.

In contrast to studies in children & adolescents with ASD (Simonoff *et al.* 2008; Salazar *et al.* 2015) which report relatively low rates of depression, our current study found a high estimated pooled prevalence of 22% for depression in adults with ASD. As this study focused on only clinical diagnoses of major depression or clinically elevated symptoms in the moderate to severe range, the rates of depression identified suggest that mood related issues likely pose significant difficulties for many adults with ASD and may also suggest a developmental progression with depression becoming more prominent in the transition to adulthood. In contrast to anxiety, we found reduced (although not a statistically significant difference) prevalence estimates based on questionnaire measures compared to structured interviews. This along with findings that the prevalence of depression was 10% lower in those with ID, suggests that current self-report measures may not be adequately assessing symptoms of depression. This may be because of difficulties with identifying and describing low mood,

which may be further exacerbated by ID or difficulties with the verbal articulation of the physiological, emotional, cognitive and behavioural experiences of depression (Hassiotis & Turk 2012).

Limitations

The results presented here must be considered in the context of several limitations. Due to the high heterogeneity between the studies included, it is difficult to be certain how much our current estimates reflect the true prevalence of anxiety and depression in adults with identified ASD. The high heterogeneity, while making firm conclusions regarding prevalence difficult, is a realistic presentation of the current literature on mental health comorbidities in ASD. Due to several factors, including missing data from studies, we were unable to look at other factors that may influence prevalence rates, such as age and gender ratio. In the future, more focused meta-analyses may benefit from investigating the influence of these factors. There were several studies which we were unable to include due to not being able to extrapolate a prevalence rate which may have influenced the accuracy of our current estimates. In addition, due to the lack of studies which used information from multiple informants we were unable to evaluate the inter-rater reliability of diagnoses. Nevertheless, studies which did used measures from multiple sources suggested a good level of agreement (Gotham et al. 2015; Maddox & White 2015), although degree of agreement did vary between studies (Buck et al. 2014). Furthermore, there were no community studies that included adults whose ASD had not been recognised or who had not been in contact with clinical services, meaning that the samples included in the current analysis may not fully represent ASD in the whole population. Accordingly, our findings should be of value in clinical practice settings but may

be of more limited value to our understanding of the relationship of autism to other forms of mental disorder.

Implications and recommendations for future research

The current analysis has identified several gaps in the literature. Future studies of prevalence can include a focus on using well defined and validated diagnostic assessments to both confirm the diagnosis of ASD and to assess psychiatric comorbidity. We found no studies of non-clinical, i.e. community or general population samples, in which comorbidity is examined. Such studies should be a priority. Further research should ensure that those administering clinical (non-questionnaire) assessments are blinded current diagnoses to reduce bias. In addition, the current literature does not consider difficulties with alexithymia (the ability to label emotions) which are common in ASD (Bird *et al.* 2011). Variability in symptoms of alexithymia may influence the reported levels of emotional symptoms and this should be considered in future studies. The use of standardised and validated ASD diagnostic tools, such as the ADOS and ADI-R, in other prevalence studies may help to reduce heterogeneity and clarify whether the slight increase in current rates of any anxiety disorder, social anxiety disorder and OCD is valid and due to better identification of individuals with typical ASD presentations, but exclusion of individuals with milder or more atypical ASD presentations. Despite the recognition of possible diagnostic overshadowing, there is a dearth of research on validated assessments of depression and anxiety in adults with ASD (Brugha *et al.* 2015).

Conclusion

In conclusion, adults with a diagnosis of ASD experience high rates of comorbid anxiety and depression. The exact prevalence is difficult to estimate

precisely, given high levels of heterogeneity between studies, but our results suggest rates significantly higher than one would expect in the neurotypical population. Although it is possible that depression is underestimated, especially in the context of ASD with ID, both anxiety and depression are prominent and common in adults with ASD.

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CHAPTER 2: Quality assessment of studies included in the meta-analysis

Introduction

This supplementary chapter includes further details regarding the quality analysis conducted as a part of the meta-analysis presented in Chapter 1 and consists of what would typically be included as supplementary material for the submitted manuscript. Therefore, there will be a brief overview of the methods and results but see Chapter 1 for discussion.

Methods

The assessment of study quality was adapted from the Effective Public Health Practice Project Quality Assessment Tool (Armijo-Olivo et al. 2012) and included an assessment of both selection and detection bias, two factors particularly relevant to studies of prevalence. Specific adaptation to the criteria were made to address the specific research questions and target population. There was an emphasis placed on the tools used to assess and diagnose ASD and the target comorbidities. The criteria used to assess quality are outlined below in Table 1.

Table 1. Criteria Quality Analysis Ratings of Study Selection and Detection Bias

	Selection Bias			Detection bias		
Key	Participant selection	Participant Representation	ASD assessment	Researcher blinding	Comorbidity assessment	Participant blinding
	How were participants selected?	What percentage of those approached / population participated?	How was ASD diagnosis assessed/ confirmed?	Were researches blinded to participant clinical history / research aims	What type of measure/assessment was used to assess anxiety or depression?	Were participants aware of research question?
Good	Community Sample	80 – 100%	ADOS/ADI (other structured assessment)	Yes	Structured interview / assessment	No
Satisfactory	Non-treatment seeking	60 – 79%	Clinical diagnosis / judgment	No	Questionnaire	Yes
Poor	Clinical	Less than 60% / cannot tell	Historic diagnosis / cannot tell	Cannot tell	Clinical records/ Cannot tell	Cannot tell

Each paper was reviewed by both myself and one other independent researcher and any disagreement was discussed and reviewed based on the criteria in Table 1. There were four points of contention in total, with all being resolved after discussion.

Results

As can be seen in Table 2 below, studies were rated on six domains as either good (green), satisfactory (yellow) or poor (red). Most of the studies were rated as primarily poor in quality in the different domains assessed. Only ten of the 31 studies used a structured ASD assessment to confirm participants' ASD diagnoses. The domains in which most studies were scored as poor were

participant selection and blinding. While these are important factors when considering estimates of prevalence, it is worth noting that most of the studies included in this meta-analysis were limited by the fact that they were not originally designed as prevalence studies.

Table 2. Results of Quality Analysis of Study Selection and Detection Bias

	Selection Bias			Detection bias		
First author (date)	Participant selection	Participant Represent-tation	ASD assessment	Researcher blinding	Comorbidity assessment	Participant blinding
Ashwood (2016)						
Bejerot (2014)						
Berthoz (2013)						
Buck (2014)						
Capriola (2016)						
Cederlund (2010)						
Charlot (2008)						
Crane (2011)						
Croen (2015)						
Ghaziuddin (2008)						
Gillberg (2016)						
Gotham (2015)						
Hedley (2017)						
Helversc. (2009)						
Hermans (2012)						
Hill (2004)						
Hofvander (2009)						
Houghton (2017)						
Jones (2014)						
Joshi (2013)						
Ketelaars (2008)						
Lai (2011)						
Lever (2016)						
Lugnegard (2011)						
Maddox (2015)						
Mazefsky (2008)						
McDermot (2005)						
Morgan (2003)						
Moss (2015)						
Nylander (2013)						
Roy (2015)						
Russell (2016)						
Spain (2017)						
Sterling (2008)						
Tsakanikos (2011)						

CHAPTER 3: Vulnerability to Mental Health Comorbidities in people with ASD and the role of adverse life events and parental mental health

As discussed in Chapter 1, people with autism spectrum disorder (ASD) experience significant levels of comorbid mental health difficulties, with emotional problems such as anxiety and depression being prominent throughout childhood and into adulthood (Gillberg, Helles, Billstedt, & Gillberg, 2016; Hofvander et al., 2009; Simonoff et al., 2008). In addition to these difficulties, which could be considered under the umbrella of internalizing difficulties, people with ASD often present with significant externalising symptoms. Externalizing symptoms present themselves as a range of conduct problems, antisocial or aggressive behaviours (Achenbach & Edelbrock, 1979; Achenbach, McConaughy, & Howell, 1987), and are linked to diagnostic constructs such as oppositional defiant disorder (ODD) or conduct disorder in childhood (Rowe, Costello, Angold, Copeland, & Maughan, 2010) and a higher risk of a range of mental health difficulties (including depression and anxiety), aggression and contact with the criminal justice system in adulthood (Copeland et al., 2009; Feehan et al., 1995; Moffitt, 1993).

Conduct problems in ASD

While estimates vary between studies, it is thought that around 30% of young people with ASD meet criteria for either ODD or conduct disorder (Salazar et al., 2015; Simonoff et al., 2008). This is considerably higher than the estimated rates in the general population where there is a lifetime prevalence of approximately 12% for ODD and around half that for conduct disorder (Merikangas et al., 2010; Nock, Kazdin, Hiripi, & Kessler, 2007). The Diagnostic and Statistical Manual-5 (DSM-5) has adopted a three-factor model of ODD,

which divides its key symptoms into three domains, namely; 1) angry and irritable symptoms, 2) argumentative and defiant behaviour and 3) vindictiveness. While this approach is based on research in the non-ASD population, the constructs are applicable to those with ASD with the angry and irritable symptoms being strongly related with the high degree of internalizing symptoms reported in those with ASD (Mandy, Roughan, & Skuse, 2014; Mikita et al., 2015). Mental health comorbidities in people with ASD tend to be highly intercorrelated. For example, evidence has suggested that higher levels of social anxiety (a commonly reported anxiety diagnosis in ASD) is related to greater levels of conduct problems, in particular, aggressive behaviours (Pugliese, White, White, & Ollendick, 2013).

Vulnerability to mental health comorbidities and the role of stress

While there is strong evidence in the literature that people with ASD experience high rates of both comorbid internalising and externalising difficulties, to date, it is unclear why this is the case. There is unlikely to be a single factor that can explain the high rates of mental health difficulties experienced by those with ASD and a model in which multiple vulnerability factors combine to increase risk is more likely. A number of specific vulnerability factors have been suggested, including associations between anxiety and sensory sensitivities (Ashburner, Ziviani, & Rodger, 2008; Uljarević, Lane, Kelly, & Leekam, 2016; Wigham, Rodgers, South, McConachie, & Freeston, 2015), differences in neuropsychological processing such as difficulties in executive functioning (Hollocks et al., 2014; Wallace et al., 2016), information processing biases of attention and interpretation (Hollocks, Ozsivadjian, Matthews, Howlin, & Simonoff, 2013; Hollocks, Pickles, Howlin, & Simonoff, 2016), and an inability to

effectively use emotion regulation strategies (Mazefsky & White, 2014; Samson, Huber, & Gross, 2012; Samson, Wells, Phillips, Hardan, & Gross, 2015).

Regardless of the specific pathway it is suggested that people with ASD have an underlying vulnerability to experiencing life events as stressful (Groden et al., 2001). For example, Bishop-Fitzpatrick and colleagues found that adults with ASD experience a greater number of life events than healthy controls, but also found that they perceived these events as more stressful, with both the number and perception of events being significantly related to social disability (Bishop-Fitzpatrick, Minshew, Mazefsky, & Eack, 2017). There is also evidence for differences in the Hypothalamic-Pituitary-Adrenal (HPA) axis in people with ASD, suggesting a biological vulnerability to stress. The HPA-axis is a key endocrine system involved in the body's response to stress which culminates in the release of the hormone cortisol from the adrenal glands (Miller, Chen, & Zhou, 2007). There is consistent evidence that when under conditions of social stress people with ASD show a reduced cortisol response when compared to controls (Corbett, Schupp, & Lanni, 2012; Lanni, Schupp, Simon, & Corbett, 2012; Taylor & Corbett, 2014), a similar pattern to that seen in people without ASD who have experienced chronic stress or trauma (Yehuda & Seckl, 2011). Furthermore, this pattern of responding has been associated with greater symptoms of anxiety in children and adolescents with ASD (Hollocks, Howlin, Papadopoulos, Khondoker, & Simonoff, 2014). Given this apparent vulnerability to stress it is therefore important to consider the evidence linking the exposure to adverse events and mental health difficulties in both people with ASD and general population.

Adverse life events

It is well established that exposure to stress in the form of adverse life events is a risk factor for developing mental health difficulties (Danese & McEwen, 2012; Lovallo, Farag, Sorocco, Cohoon, & Vincent, 2012). In typically developing (non-ASD) populations adverse life events, such as family illness/bereavement, or being a witness of (or exposed to) violent acts, traumatic injury or the death of a family member, can lead to a range of mental health difficulties including conduct problems, depression and anxiety (Dunn et al., 2011; St Clair et al., 2015). Adverse life events also appear to have a cumulative effect with more life events being associated with poorer outcomes and changes in neural reactivity in brain regions important for emotion regulation such as the amygdala (Swartz, Williamson, & Hariri, 2015). Furthermore, recent meta-analytic evidence suggests that exposure to life-events in the adolescent period is significantly related to both internalizing and externalising symptoms in adulthood, but, that this effect may be bidirectional in that poor mental health may mean an individual interprets life events as more stressful (March-Llanes, Marqués-Feixa, Mezquita, Fañanás, & Moya-Higueras, 2017). This finding has also been shown in youths experiencing their first episode of depression with life-events predicting onset, but also being predicted themselves by anxiety and depression in earlier adolescence (Patton, Coffey, Posterino, Carlin, & Bowes, 2003). These studies highlight the importance of the adolescent period and the transition to adulthood where the impact of life events can have a strong contribution to a range of adult mental health difficulties (Casement, Shaw, Sitnick, Musselman, & Forbes, 2013; King & Chassin, 2008; Schilling, Aseltine, & Gore, 2007).

There have been relatively few studies to look directly at the impact of adverse life events on mental health in adults with ASD. However, as eluded to above, there is emerging evidence to suggest that adults with ASD both experience more adverse life events (Berg, Shiu, Acharya, Stolbach, & Msall, 2016), and perceive those events as more stressful, than those without ASD (Bishop-Fitzpatrick, Mazefsky, Minshew, & Eack, 2015; Bishop-Fitzpatrick et al., 2017; Rigles, 2017; Taylor & Gotham, 2016). Studies which have looked directly at the association between the cumulative effect of adverse life events in ASD have shown significant associations with both depression and anxiety (Ghaziuddin, Alessi, & Greden, 1995; Kerns, Newschaffer, Berkowitz, & Lee, 2017; Taylor & Gotham, 2016), but have not evaluated any association with externalising symptoms. The impact of adverse life events on mental health is influenced both by the total number of events and the presence of potentially traumatic events (Kerns, Newschaffer, & Berkowitz, 2015).

Research in non-ASD clinical populations and healthy controls have identified several factors which may act to moderate the relationship between exposure to adverse life events and poorer mental health. This includes a range of areas which people with ASD may have difficulties with, including differences in temperament/emotion regulation ability (Flouri, Tzavidis, & Kallis, 2010; Nakai et al., 2015), and differences in cognitive processing. This may include negative biases in attention and interpretation of events (Flouri & Kallis, 2007; Flouri & Panourgia, 2011; Spence, Sheffield, & Donovan, 2002) or specific styles of thinking such as intolerance of uncertainty (Bardeen, Fergus, & Wu, 2013; Zlomke & Jeter, 2014), a construct which has been shown to be associated with anxiety in ASD (Boulter, Freeston, South, & Rodgers, 2014). The importance of

a range of parenting and family factors as a potential moderating factor has also been reported by several studies investigating the impact of life events on a young person's mental health (Bouma, Riese, Ormel, Verhulst, & Oldehinkel, 2009; Puff & Renk, 2014; Rasmussen, Nielsen, Petersen, Christiansen, & Bilenberg, 2014). There have been few studies which have investigated this directly in ASD, however one study has shown that good parental mental health may act to reduce the impact of bullying on symptoms of anxiety experienced by their child (Weiss, Cappadocia, Tint, & Pepler, 2015).

Parental Stress & Mental Health

There has been a substantial amount of research investigating the impact of stress on parents of those with ASD. A meta-analysis conducted by Hayes and Watson found that parents of a child with ASD reported experiencing greater levels of stress compared to both parents of healthy controls and of children with another (non-ASD) developmental disability (Hayes & Watson, 2013). More recently, it has also been shown that the stress levels associated with caring for an adult with ASD with no co-occurring intellectual difficulties is comparable to that experienced by caregivers of individuals with schizophrenia or major depression (Grootscholten, van Wijngaarden, & Kan, 2018). Furthermore, parents of children with ASD report high rates of emotional difficulties, particularly anxiety and depression (Cohrs and Leslie, 2017; Piven et al., 1991; Su et al., 2017).

There is consistent evidence to suggest a relationship between parental stress and mental health and both internalising and externalising symptoms in both children and adults with ASD (Bauminger, Solomon, & Rogers, 2010; Jellett, Wood, Giallo, & Seymour, 2015; Lecavalier, Leone, & Wiltz, 2006; Maljaars,

Boonen, Lambrechts, Van Leeuwen, & Noens, 2014; Weiss et al., 2015) but the relationship with externalizing symptoms appears to be more consistently demonstrated (Falk, Norris, & Quinn, 2014). However, much of the literature is cross-sectional in design and so cannot establish the directionality of any effect. There have been some studies focusing on externalising symptoms which have used a longitudinal design to establish a bidirectional relationship between parent stress and problem behaviour in children with ASD. These studies have found that problem behaviours are driven by the magnitude of the parent's general distress (stress accounted for by non-parenting factors) and not vice versa (Totsika et al, 2013; Zaidman-Zait et al., 2014). This may suggest that poor mental health & wellbeing could interfere with parents' ability to respond to their child's emotional needs, thereby increasing the likelihood of an externalizing behaviour (Deater-Deckard, 1998). The intergeneration transmission of internalising symptoms in families with a child with ASD has received much less attention than the associations between parental mental health and externalising symptoms and challenging behaviour. However, based on the literature in non-ASD clinical samples, it could be hypothesised that cognitions and behaviours associated with anxiety and depression could be learnt through the child's modelling the parents' behaviours (Burstein & Ginsburg, 2010; Rapee, 2012) or the disruption of early attachment relationships (Warren, Huston, Egeland, & Sroufe, 1997).

Conclusion

While it is now well established that people with ASD experience significant levels of comorbid mental health difficulties, the specific susceptibility factors for this are yet to be identified. There is increasing evidence to suggest

that people with ASD experience life events as more stressful than those without ASD and that this may be related, through its interaction with various individual and/or environmental vulnerabilities, to the propensity to experience both internalizing and externalising difficulties. Despite there being some evidence to suggest a significant association between life events and mental health in people ASD, this relationship has not been considered using longitudinal data to control for mental health symptoms prior to the exposure to life events in the critical transition period between late adolescence and early adulthood. Equally, while parental mental health and wellbeing has been shown to directly relate to the mental health of young people with ASD, the role this has in the context of exposure adverse life events has yet to be investigated.

Part 2 – Empirical Study

CHAPTER 4: Extended Methodology

This chapter provides extra information regarding the research sample and the statistical analysis which will not be included in the empirical paper (Chapter 5). This includes further details of the recruitment of participants, ethical issues and a description of the statistical methods used and the relevant underlying statistical principles. All information necessary to understand the analysis is included in the empirical paper chapter, including details on the measures used and all the descriptive and inferential statistics.

The Special Needs and Autism Project (SNAP)

The Special Needs and Autism Project (SNAP) is a population cohort study which originally included 56,946 children born between July 1, 1990 and December 31, 1991, in 12 districts of the South Thames region of London, United Kingdom. The sample was identified by accessing the special needs register of child health services to identify both known cases of autism spectrum disorder (ASD) and further cases with possible ASD to be screened. All children on the special needs register with what was known as a statement of special education needs were considered as potentially at risk of having an unidentified ASD. Additional cases were identified in collaboration with local clinicians by searching registers of children known to child health services or speech and language therapy for any children reported as having a social communication difficulty or an ASD, with or without a statement of educational needs.

All children identified through the above process were then screened using the Social Communication Questionnaire (Rutter, Bailey, & Lord, 2003), a parent-report measure which assesses behaviours associated with ASD both currently

and when the child was between 4-5 years of age. Following initial screening a random sample of 363 children who completed the SCQ for ASD and opted-in for further assessment was then generated. The sample was weighted to be representative of the whole population by using a two-way stratification based on previous clinical diagnosis and level of SCQ score (low score <8, moderately low score 8–14, moderately high score 15–21, high score ≥22).

Of the 363 children invited to take part in further assessment 66 opted-out, 30 were uncontactable and 12 did not attend; this left a total sample of 255 children (223 boys, 32 girls), with a mean age of 11.5 years who completed an in depth assessment including the Autism Diagnostic Interview–Revised (ADI-R; Lord et al., 1994) and the Autism Diagnostic Observational Schedule-Generic (ADOS-G; Lord et al., 2008) as well as supplementary measures of intellectual functioning, language and adaptive functioning. Information from teachers was gathered about social communication skills and behaviour. Three principle clinical investigators with expertise in paediatrics, child psychiatry and child clinical psychology reviewed all clinical material for every case and made clinical diagnoses of ASD based on the international classification of diseases 10th revision (ICD-10). In total, this resulted in 158 children who met criteria for an ASD. The quadratic weighted agreement between initial and consensus diagnostic categories for childhood autism, ASD, and no ASD was 95% with kappa 0.85 (Baird et al., 2006).

Of the original sample 131 children were approached to take part in wave 2 of the study in adolescence (age range at assessment 14-16 years), 19 declined to take part, 11 could not be contacted and one stated interest but could not take part before the end of the study. This led to a total sample of 100 young

people at 15 years. Finally, families were re-approached when the young people were between 21-23 years of age with a total of 126 people being seen for assessment (age-range at assessment 21-25 years. An analysis of attrition rates across the three time-points indicated that that there were no systematic differences between those who did or did not attend across time points on variables related to the child's cognitive, emotional or behavioural functioning. However, it was noted that the parents of young people who did not return for follow-up were significantly more likely to have one, or both parent, being unemployed ($x^2 = 7.55$; $p \leq 0.01$).

Ethical issues

There are limited ethical considerations for this project due to the work being based on the analysis of existing data. The SNAP project underwent full ethical review for each wave of data collection. The data used for this project was in the form of an anonymised dataset and I had no access to the personal information of the research participants or any data linked to personal identifiers. However, it was still important to consider how the data can be used in an ethical way. This was done by ensuring that the data were treated in a statistically valid and robust way to add meaningfully to the current psychological literature. In this way the contributions of participants to the study can lead to greater understanding of the mental health difficulties experiences by those with ASD.

Data processing and missing data

The current project included data from wave 3 of SNAP comprising of the 126-young people with confirmed ASD diagnoses who were seen for assessment when they were aged between 21-25 years, as well as their corresponding data from wave 1 and wave 2. As the primary variable of interest only data from

participants with a completed parent-reported life events questionnaire were included in the analysis; reducing the final sample size to *n = 115* (mean age 23.1 years; range 21.3 – 25.1).

There was a considerable amount of missing data in the dataset across the waves 1 and 2 of data collection due to the changing demands of the research protocol over time. There was complete data for variables measured at wave 3, but at previous timepoints there was missing data for the Strengths and Difficulties Questionnaire (SDQ, wave1 *n=9*; wave2 *n=39*) and full-scale IQ (FSIQ *n = 16*). Patterns of missing dataset were explored and considered to be missing at random; missingness was accounted for using full-information maximum-likelihood estimation (MLE) as a component of the structural equation model (*see below*). MLE uses the information provided by the actual data to estimate the probability of observing a certain value and uses this to estimate the resulting regression coefficients.

Normality and data quality

Prior to conducting the analysis all key variables went through a procedure of data quality checks including an analysis of outliers, identification of erroneous values and an assessment of normality via the assessment of skew and kurtosis using the "***sktest"*** command in Stata 15, and the visual assessment distributions using boxplots. A skewedness and kurtosis of ±2 was considered as acceptable evidence of normal distribution (George & Mallery, 2010). The total life events score was found to have three outliers with a high number of report life events (15, 16 and 17 individual adverse life events). To account for this the maximum value was truncated at the upper quartile with the three values being converted

to a maximum value of 13 and this value was used in all inferential statistics. This is an appropriate approach given that these values represent true scores in the extreme range and were not considered to be erroneous values. All remaining variables were observed to be normally distributed. Each participant was then assessed for multivariate normality across all key variables and no outliers were found (Billor, Hadi, & Velleman, 2000). The multivariate normal distribution is used to describe the disruption of any combination of random variables that may correlate with each other and is an important assumption for SEM (see below). The independence of variables included in the analysis was assessed by computing variance inflation factors (VIF) which estimates how much regression coefficients between variable are inflated due to collinearity. A cut-off VIF value ≤ 5 has been suggested as an acceptable level (Stine, 1995), with all variables included in the SEM model having a VIF ≤ 2.

Structural Equation Modelling

Here I introduce some basic concepts behind the use of structural equation modelling (SEM) approach to supplement the description in the empirical paper.

SEM is an extension of the standard general linear model which allows the simultaneous estimation of multiple associations (regression coefficients) between variables included in the model. This has the advantage of being able to test the relative contribution of multiple independent predictor variables on the dependant variable while accounting for their inter-relationships. SEM also allows the constraint of specific paths within the model to test for specific hypothesis or to find the best fit for the data. This means that for any set of data one or more models can be fitted to the same covariance matrix. Therefore, it is necessary to establish statistically the goodness of fit of the data to any given

model. The primary index of this is chi-square (χ^2) likelihood ratio test of comparative model fit, whereby the model defined population covariances and the actual observed sample covariances are compared (Barrett, 2007). In a model with good fit the null hypothesis (that the population and observed covariances are equal) is accepted at a *p-value* ≥ 0.05.

There are number of supplementary measures of model-fit which can be used as indices of model-fit, including the root mean square error of approximation (RMSEA), and the comparative fit index (CFI) (Hu & Bentler, 1999). RMSEA is an example of absolute-fit index which looks at how well the model reconstructs the sample data, in contrast, the CFI is an incremental-fit index and is measure of the incremental improvement in fit between nested models (models created by constraining/removing components of an original overall model). An adequate model fit is indicated by the above fit statistics would include a chi-square likelihood ratio test *p*-value ≥ 0.05, CFI ≥ 0.95 and a RMSEA ≤ 0.08 (Hu & Bentler, 1999).

Assumptions of the statistical analysis

As with any parametric statistical test SEM based analyses are assumed to meet certain assumptions. As SEM is a special case of a general linear model the assumptions made are an extension of those associated with other test of this type but with a greater emphasis on the join distributions of the variables. The assumptions also vary depending on the estimation method used, but the following are relevant to a full-information maximum-likelihood estimation:

1. Variables included in the model are univariate normal
2. The joint distribution of the variables are multivariate normal

3. The variables included in the SEM are independent and are unstandardized
4. The variables are measured without error.

As described above the data included in this analysis have been checked for outliers/erroneous data, univariate and multivariate normality, and multicollinearity of variables and it was found that the above assumptions were met.

One important issue to briefly discuss is the assumption of directionality that is made when constructing a SEM. It is typical for SEM to be constructed indicating a direction of effect between variables. The direction of these relationships is generally defined based on a-priori hypothesis based on the current understanding of a given topic. For this assumption to be correct several conditions must be met (Kline, 2012):

1. The presumed causal variable must occur before the presumed effect (temporal precedence).
2. There is covariance between the presumed causal variable and the presumed effect.
3. The distribution of the data is known, and it meets the assumptions of the statistical test being conducted.
4. There are no other plausible explanations of that covariance (or the association holds when controlling for other variables which may affect the outcome.

Assumptions 1-3 can be dealt with in terms of the design of the research and statistical approach taken. As described above and in the empirical paper

the levels of covariance and the distribution of variables is known. As will be discussed in more detail below the use of a cross-lagged longitudinal regression model allows temporal precedence to be assumed (but with caution). Assumption 4 is a challenge in psychological research due to the complexity of the hypotheses being tested. All possible variables which may affect the dependant variable in this analysis are unlikely to have been measured and so this must be considered when interpreting the results.

Latent variables

One advantage of SEM is the ability to create latent variables consisting of multiple observed variables which all load significantly into a single factor. Typically, the variables which are combined into a latent variable are selected due to shared measurement properties or are theoretically associated with one another (Borsboom, Mellenbergh, & Van Heerden, 2003). In the current study a latent variable was constructed using four distinct but highly correlated measures of parental anxiety, depression and stress and coping. This has the advantage practically of including a greater amount of clinical information and statistically by reducing the impact of measurement error. When there is measurement error in the observed variable then variance will be larger than the variance of the latent variable, meaning error has a greater impact when using individual observed variable.

Investigation of longitudinal invariance

The importance of testing for the measurement invariance of a total score or latent variable over time is based on the principle that a psychological measure is designed in such a way that it should measure the same construct if

administered to the same individual or group of individuals multiple times. Therefore, in a longitudinal analysis measurement invariance is defined as a case in which the distributions of the observed values used to make up a scale are unchanging when the construct being measured is also stable overtime (Millsap, 2010). This is relevant when considering the longitudinal stability or change in a scores on a measure because to do this you must first establish if the total scores are being driven at each point by the same items. For example, it is plausible that an individual may have the same total score on a questionnaire measure of depression over-time but that this score at time 1 is driven mostly by loss of interest and pleasure, but at time 2 by physical symptoms.

While there are several types of invariance in longitudinal data the most important in the current study is metric invariance, or the invariance in the factor loadings on the latent variable at each time point. This can be tested by comparing the model fit between the original model with a nested model where equality constraints are imposed to see whether any differences are greater than expected by chance (Horn & McArdle, 1992; Steenkamp & Baumgartner, 1998). If there is no difference in model fit between the constrained and unconstrained models, then the latent construct can be considered invariant. In the current study an initial model is constructed to test the structural invariance (or stability) of emotional and conduct problems overtime. In this model scores overtime is considered stable if there is a strong and significant relationship (autoregression) between the latent variable between timepoints. As in this study the structure of the emotional and conduct problem scales are considered both invariant and stable they are included as observed total scores in the subsequent analyses.

Cross-lagged regression model

The primary analysis of the current study consists of a cross-lagged regression model designed to investigate impact of adverse-life events on scores of emotional and conduct symptoms at age 23, when accounting for emotional and conduct symptoms at ages 12 and 15. The primary goal of a cross-lagged analysis is to use longitudinal data to investigate the causal direction of the relationship between two variables. As emotional and conduct symptoms are measured at multiple time points this enables the directionality of effect between adverse life events and symptoms scores to be tested. The autoregression coefficients that were discussed earlier in terms of the stability of the variable over time are used in the cross-lagged model to control for symptom levels at earlier time points when estimating the effects of adverse life event on emotional and conduct symptoms at 23 years. Therefore, by estimating the partial effect of the earlier time point this approach has a significant advantage over estimating the model using cross-sectional data.

Once this first model has been constructed then additional observed or latent variables (see *latent variable* section above) can be added to the model with the same principle that the effects identified are in the context of the partial effect of the measures at earlier time points. In the case of the current analysis this takes the form of a parent mental health and wellbeing latent variable (see *latent variables* above). The impact of adding or constraining paths in the model are assessed using the model fit statistics described above. Like all analyses based on a general linear model the results can be influenced by measurement error. However, earlier steps such as ensuring metric invariance in the symptom

scores and by using a latent variable, rather than multiple observed variables for parental measures can minimise this effect.

In summary, the analysis conducted in the empirical paper consists of a series of nested cross-lagged regression models in the form of structural question models (SEM). These models are designed to investigate impact of adverse-life events on scores of emotional and conduct symptoms at age 23, when accounting for emotional and conduct symptoms at ages 12 and 16 and finally including parental mental health and wellbeing latent variable to investigate this as a possible risk/resilience factor.

CHAPTER 5: Adverse Life Events and Mental Health in Young Adults with Autism Spectrum Disorders when Accounting for Childhood Symptoms and the Role of Parental Mental Health and Wellbeing

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Abstract

People with ASD are known to be at risk of developing co-occurring mental health difficulties across the lifespan. There are number of environmental and family factors which may act as vulnerability factors leading to those with ASD to experience life events as particularly stressful and thus contribute to the development of further mental health difficulties. This study included 115 young adults with ASD who were assessed at three time-points (at 12, 15, and 23 years of age) on measures of internalizing and externalizing symptoms. Exposure to adverse life events and parent mental health and wellbeing were also measured at age 23. Using structural equation modelling the impact of adverse life events on emotional and conduct problems at 23 years when controlling for earlier symptoms was investigated. Parent mental health and wellbeing was also investigated as potential moderator of the relationship between adverse life events and mental health outcomes. Results indicated that internalizing and externalizing symptoms in young adults with ASD are significantly related to exposure to adverse life events and mental health symptoms in childhood and adolescence. Additionally, poor parental mental health and wellbeing was found to predict a higher frequency of externalising problems but did not moderate the impact of adverse life events. This suggests that child and adolescent symptom severity, exposure to life events and poorer parent mental health are all independent predictors of co-occurring mental health difficulties in people with ASD. **Lay summary:** This study used statistical techniques to show the significant impact of both exposure to adverse life events and poor parental mental health on emotional and behavioural symptoms in young adults with ASD when controlling for childhood symptoms.

Introduction

Young adults with autism spectrum disorder (ASD) are at disproportionate risk of developing co-occurring mental health difficulties compared to those without the diagnosis (Lugnegård *et al.* 2011; van Steensel *et al.* 2011; Joshi *et al.* 2013). Evidence suggests that prominent amongst these are significant internalising difficulties, with a higher than expected prevalence rate of anxiety and depression compared with the general population (Mazefsky *et al.* 2008; Hofvander *et al.* 2009). People with ASD also report significant levels of externalising behaviour; with prevalence rates of conduct disorder in children with ASD being estimated to be around 30% (Simonoff *et al.* 2008; Salazar *et al.* 2015).

In typically developing young people the presence of internalising and/or externalising symptoms strongly predicts adult outcomes and the presence of a range of mental health diagnoses (Jaffee *et al.* 2002; Rutter *et al.* 2006). Similarly, for young people with ASD scores on measures of internalising and externalising symptoms predict rates of employment, social engagement and the continuation of mental health difficulties into adulthood (Howlin *et al.* 2004; Chiang & Gau 2015; Taylor *et al.* 2015). Indeed, internalising and externalising symptoms in people with ASD appear to remain relatively stable throughout childhood and into early adulthood (Simonoff et al., 2013; Woodman et al., 2016).

In young people without ASD exposure to adverse life events is associated with higher rates of both internalising and externalising symptoms and a number of different mental health difficulties (Tiet *et al.* 2001; St Clair *et al.* 2015), particularly diagnoses such as depression and anxiety (Clark *et al.* 2012; Hassanzadeh *et al.* 2017; Sheerin *et al.* 2017). There is evidence to suggest that

adults with ASD both experience more adverse life events (Berg *et al.* 2016), and perceive those events as more stressful, than those without ASD (Bishop-Fitzpatrick *et al.* 2015, 2017; Taylor & Gotham 2016; Rigles 2017) and this one pathway by which this population is vulnerable to developing high rates of co-occurring mental health difficulties.

To date, there have been few studies that have looked specifically at the impact of adverse life events and trauma on mental health outcomes in those with ASD. Those studies that have investigated this relationship have tended to focus on children or adolescents rather than young adults and suggest varying degrees of association between the overall number of events and depression and anxiety, with the association being stronger when exposed to a potentially traumatic event (Ghaziuddin *et al.* 1995; Taylor & Gotham 2016; Kerns *et al.* 2017). Overall, the limited literature suggests that those with ASD are both at an increased risk of experiencing traumatic or adverse life events and more likely to experience detrimental effects as a result (Kerns et al 2015).

These issues may be of particular relevance when considering the transition period between adolescence and early adulthood, which has been reported to be a particularly stressful time for people with ASD (Pozo & Sarria 2015). Interestingly, evidence from non-ASD populations suggests that environmental factors such as parental support and coping (Tiet *et al.* 2001) may moderate the impact of adverse life events on mental health outcomes.

There have been several studies that have shown a relationship between parental stress and mental health and internalising and/or externalising symptoms in both children and adults with ASD (Lecavalier *et al.* 2006;

Bauminger *et al.* 2010; Maljaars *et al.* 2014; Jellett *et al.* 2015; Weiss *et al.* 2015). For example, higher levels of expressed emotion by parents of both children and adults with ASD are related to a greater number of externalising symptoms and challenging behaviour (Greenberg *et al.* 2006; Bader & Barry 2014; Bader *et al.* 2015). A study by Bauminger and colleagues demonstrated that parental stress was significantly associated with both internalizing and externalizing symptoms, while other parenting factors such as attachment quality and mother-child relationship quality were not significantly related to symptom scores (Bauminger *et al.* 2010). Furthermore, it has also been suggested that parental mental health may act to mediate the relationship between adverse events and mental health, for example, reducing the effects of bullying on severity of anxiety symptoms (Weiss *et al.* 2015).

The strong relationship between parental stress and mental health outcomes is particularly relevant for this population, as there is evidence to suggest that parents of those with ASD suffer from more stress than parents of typically developing children or even parents of those with other developmental difficulties (Hayes & Watson 2013), and that the consequences of caring for an adult with ASD and no intellectual difficulties is comparable to that experienced by caregivers of individual with schizophrenia or major depression (Grootscholten *et al.* 2018).

A major issue when considering the significant relationship between parental stress/mental health and internalizing/externalizing symptoms in people with ASD is the difficultly of delineating the directionality of the effect. Based on research focusing on challenging behaviour, a transactional model has been proposed which suggests that a child's behaviour increases parental stress,

which then serves to escalate the problem behaviours further (Hastings 2002). However, studies that have examined the bi-directional relationships between parent stress and externalising behaviour in children with ASD have found that problem behaviour was driven by the magnitude of the parent's general distress (stress accounted for by non-parenting factors) and not vice versa (Totsika *et al.* 2013; Zaidman-Zait *et al.* 2014). One hypothesis, supported by literature in the typically developing population, is that poor parental wellbeing could interfere with the ability to respond sensitively to their child's emotional needs, impeding their ability to promote self-regulation, thereby increasing the likelihood of an externalizing behaviour (Deater-Deckard 1998).

The aim of this current analysis is to investigate the impact of adverse life events experienced in the first years of adulthood on internalizing and externalizing symptoms in people with ASD. Given that these symptom domains are reported to be stable from adolescence into adulthood (Woodman et al., 2016), the effect of life events on adult symptoms will be considered while controlling for the effect of symptoms across childhood and adolescence. Given the known relationship between parental wellbeing and internalizing and externalizing symptoms in both young people with and without ASD (Bauminger *et al.* 2010), and the suggestion that this may act as risk/resilience factor when exposed to adverse life events (Tiet *et al.* 2001), the pathways by which parental mental health may impact on mental health in the young adults with ASD will be explored.

Methods

Participants

This study included 115 participants recruited as a part of the larger Special Needs and Autism Project (SNAP). SNAP includes data from 158 young people with ASD and their parents, who have been followed up from childhood and into early adulthood. The study consists of three time-points at 12 years, 15 years and 23 years of age. This analysis included only participants who had a completed parent-reported life events scale at 23 years. Full details of sample selection and characteristics in SNAP can be found in Baird et al. 2006 (Baird et al., 2006; *see Extended Methodology section*). ASD diagnoses were confirmed according to the ICD-10 criteria based on a full clinical assessment, including the Autism Diagnostic Interview-Revised (Lord *et al.* 1994), the Autism Diagnostic Observation Schedule-Generic (Lord *et al.* 2000), and the Social Communication Questionnaire (Rutter *et al.* 2003). This study was reviewed and approved by the South East London Research Ethics Committee (05/MRE01/67).

Measure of Life Events

*Adverse Life Events Questionnaire***.** Adverse life events were measured by a questionnaire developed specifically for SNAP. The questions included in this measure were combined from several different sources and were designed to cover a wide range of possible life events. Broadly, the 27 items included in the questionnaire covered the following categories: 1) Illness or death of a close relative or significant other; 2) witnessing or experiencing the injury and death of another or interpersonal trauma (e.g., being deliberately harmed by another); 3) being arrested or convicted of a crime 4) employment or financial issues; and 5) problems with relationships. Except for category one, which records events that

have occurred "*ever*", the time frame for the questions was the previous five years. Each question can be answered "yes" or "no" indicating the events occurrence or absence in the respective time frame. For the current analysis a total adverse life events score was created to represent to total number of reported life events which occurred in the last five years (not including items coded as occurring "ever") minus those related to being arrested or convicted of a crime. These were removed to prevent any artificial relationships between the total life events score and conduct problems (see statistical analysis section).

Mental health measures

Strength and Difficulties Questionnaire (SDQ). The *SDQ* (Goodman 1997) is an emotional and behavioral screening questionnaire consisting of 25 questions, which measures five domains of functioning: 1) emotional problems; 2) conduct problems; 3) hyperactivity/inattention; 4) peer relationship problems; and 5) prosocial behavior. The SDQ includes child-report, parent-report and teacher-report versions. The current analysis focuses on parent-report, which was collected at 12, 15 and 23 years and includes only the emotional problems and conduct problems subscales.

Parental Stress and Coping.

Family Stress and Coping Interview (FSCI). The FSCI is a parent-reported measure of stress and coping in families of people with developmental disabilities (Nachshen *et al.* 2003). The FSCI consists of twenty-three life-span issues (see Appendix C) that are rated on a five-point Likert scale between "0" (not stressful) and "4" (extremely stressful), which can be summed to create a total score. We

found that the items on the FSCI demonstrated excellent internal consistency when completed by parents of young adults with ASD (Cronbach's α = 0.95).

Beck Anxiety Inventory. Validated questionnaire used to measure parent reported symptoms of anxiety (Beck *et al.* 1988a). We found that the scale showed good internal consistency when used in this sample (Cronbach's α = 0.90)

Beck Depression Inventory. Validated questionnaire used to measure parent reported symptoms of depression (Beck *et al.* 1988b). When used in this sample we found that the BDI showed excellent internal consistency (Cronbach's α = 0.94)

General Health Questionaire-12. The GHQ-12 is a 12-item questionnaire developed to screen for non-specific psychiatric morbidity (Goldberg & Blackwell 1970). The GHQ-12 was developed from longer versions of the GHQ by removing items related to physical health difficulties and individual items scores can be combined to give an overall total score. While the GHQ-12 is designed to be a screen for non-specific mental health concerns and has been shown to have adequate psychometric properties the questions included means the measure is most sensitive to symptoms of depression (Romppel *et al.* 2013). We found that the GHQ-12 showed good internal consistency when used in this sample (Cronbach's α = 0.88).

Statistical analysis

Statistical analysis consisted of a series of nested cross-lagged regression models in the form of structural equation models (SEM). An SEM is an extension of the standard general linear model which allows the simultaneous estimation of

multiple associations between independent, dependant and latent variables. This allows the estimation of the relationship between independent and dependant variables while accounting for the relative contingencies between them. These individual relationships can be constrained to establish the best fit of the data to the model. Models were fitted to raw data using full information maximum-likelihood to account for missing data and alternative models were compared using chi-square likelihood ratio test of comparative model fit, comparative fit index (CFI), and root mean square error of approximation (RMSEA). There is no definitive guidance of the sample size requirements of SEM but it is suggested that approximately 10 participants are required for every observed variable included in the model (Bentler & Chou 1987). Wolf and colleagues propose several factors, such as the level of missing data and the number of paths included in the model, which can increase the required sample size (Wolf et al. 2015). However, they also suggested that the use latent variables and items with high factor loading act to reduce the necessary sample size. SEM was performed in the statistical modelling software MPLUS version 5 (Muthén & Muthén 2012).

The cross-lagged regression models were designed to investigate the impact of adverse-life events on scores of emotional and conduct symptoms at age 23, when accounting for emotional and conduct symptoms at ages 12 and 15 and including parental stress as a possible risk/resilience factor. The final models were constructed in two parts with the aim to address the above questions. The overall goal of a cross-lagged model is to examine the causal relations of two variables across time. First, an initial model was constructed to test the structural invariance (or stability) of the two symptom domains overtime. Building on this, a second model was then constructed looking at the impact of

adverse life events on emotional problems and conduct problems at 23 years. This enabled the effect of adverse life events in young adults on mental health to be modelled while also accounting for childhood symptoms. Secondly, this enabled the evaluation of any relationships between childhood symptoms and the occurrence of life events. Finally, a latent variable representing parental mental health and wellbeing was added as a covariate to investigate whether this acts a risk/resilience factor to the experience of emotional or conduct symptoms in young adulthood. The parental stress and coping latent variable is made up of four observed variables: i) parental depression (BDI), ii) parental anxiety (BAI), iii) the Family Stress and Coping Interview and iv) the GHQ-12. To explore whether parental mental health and wellbeing act as a mediating factor between adverse events and mental health symptoms both direct and indirect (via parental measures) associations with symptom scores were explored.

Results

Descriptive statistics

The final sample included 115 young people with ASD, with a mean age of 23.1 years (range 21.3 – 25.1) and mean full-scale IQ of 84.5 (range 40 -124). At 23 years, 38% of participants had SDQ emotional problems scores in the abnormal range (emotional problems subscale score ≥ 5), compared to 50% and 53% at 12 and 15 years, respectively. In contrast, only 17% of participants reached the suggested cut-off for abnormal levels of conduct problems at 23 years (conduct problems subscale score ≥ 4), compared to 47% and 44% at 12 and 15 years of age. However, it should be noted that these cut-off scores are not validated for use in adults and should be interpreted with caution. The relationship between symptom scores over-time are considered in the analyses

below. See Table 1 for full descriptive statistics. Seventeen percent of parents of young adults with ASD scored in the moderate or severe range on the BDI and 13% in the moderate or severe range on the BAI. The scores on parental measures of mental health and wellbeing are displayed in Table 2.

Table 1. Descriptive Statistics

Variable	Mean	SD	Range
Age (years)	23.1	0.80	21.3 – 25.1
Full-scale-IQ	84.5	24.2	40 - 124
Gender (Male:Female)	104:11	-	-
SDQ Emotional Problems 12 years (% above cut-off*)	4.4 (50%)	2.6	0 - 10
SDQ Emotional Problems 15 years (% above cut-off*)	3.4 (53%)	2.3	0 - 9
SDQ Emotional Problems 23 years (% above cut-off*)	3.9 (38%)	2.4	0 - 9
SDQ Conduct Problems 12 years (% above cut-off*)	3.2 (47%)	2.1	0 – 9
SDQ Conduct Problems 15 years (% above cut-off*)	1.9 (44%)	1.7	0 – 8
SDQ Conduct Problems 23 years (% above cut-off*)	2.2 (17%)	1.7	0 - 8

SDQ = Strengths and Difficulties Questionnaire

Table 2. Mean and Clinical Cut-off Scores on Measures of parent Mental Health and Wellbeing

Variable	Mean (% above cut-off)	SD	Range
BAI - Mean	7.6	8.2	0-39
% minimal	57%		
% mild	30%		
% moderate	9%		
% severe	4%		
BDI - Mean	9.4	10.6	0-46
% minimal	74%		
% mild	9%		
% moderate	10%		
% severe	7%		
GHQ-12	12.6	5.5	3-35
Family stress (FSCI)	27.9	16.6	0-67

BDI = Beck Depression Inventory, BAI = Beck Anxiety Inventory, GHQ-12 = General Health Questionnaire – 12, FSCI = Family Stress & Coping Inventory.

The occurrence and nature of adverse life events experienced by young adults with ASD

The number of participants who experienced each of the 18 adverse life events included in the life events total score can be seen in Table 3. Of note was the high proportion of parents that reported their child had moved residence (45%), been unemployed or seeking work (41%) or been in contact with a government agency regarding welfare (33%) in the last 5 years. Reports of problems with being bullied (27%), serious problems with a close friend, neighbour or relative (21%), or a breakdown of a relationship with a parent or partner (10% and 13%, respectively) were also common. Potentially traumatic events, like being involved in a serious accident, being deliberately harmed by another adult, or being hospitalised, each occurred in around 10% of the sample.

Table 3. Frequency of adverse life events as reported by parents of young adult with ASD

Adverse life event	***n***	**%of ASD sample**
Witnessed Injury or death	19	17%
Been hospitalised for a physical condition	14	12%
Diagnosed with a severe disease	6	5%
Experienced a serious accident (e.g. house fire, car crash.)	11	10%
Been seriously injured	3	3%
Been bullied by someone	31	27%
Deliberately harmed by another adult	12	10%
Harmed in the course of being disciplined for bad behaviour	6	5%
Contact with any agency about welfare (e.g., social services, police, health visitor)	38	33%
Serious problems with a close friend, neighbour or relative	24	21%
Moved away from parents or change of carer	9	8%
Breakdown of relationships with partner	15	13%
Breakdown of relationships with parent	11	10%
Laid off/sacked from work	9	8%

Structural invariance and stability of symptoms over time

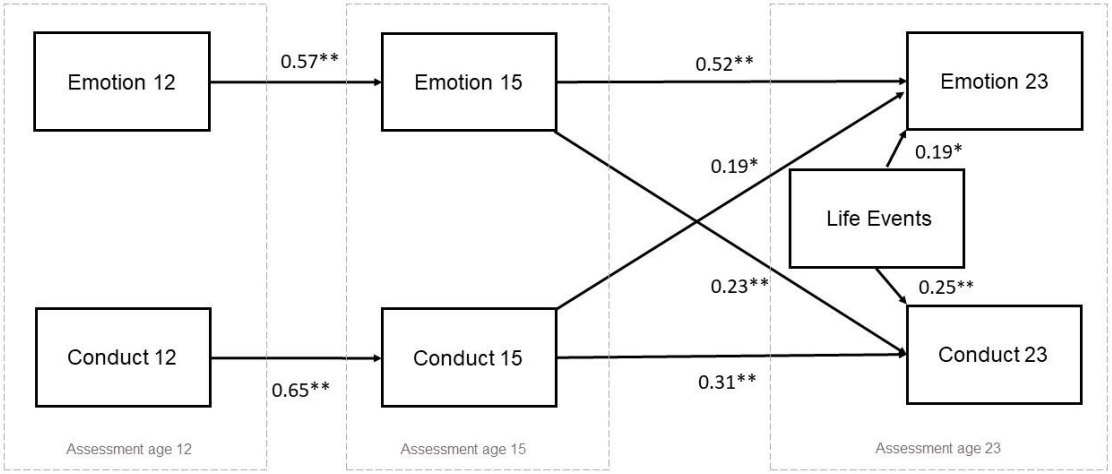
To investigate the relative contributions of factor loadings over-time for the SDQ, emotional symptoms and conduct problems scales, basic models were compared both with and without equality constraints between timepoints. There was no difference in model parameters between the unconstrained (χ^2 (DF) = 144 (78), CFI = 0.85, RMSEA 0.086) and constrained models (χ^2 (DF) = 153 (86), CFI = 0.85, RMSEA 0.083) for the emotional symptoms scale, indicating invariance in factor loadings across timepoints. Emotional symptoms at 12 years were significantly associated to emotional symptoms at 15 years (β = 0.61, $p \leq 0.01$), and symptoms scores at 15 years were significantly associated with scores at 23 years (β = 0.72, $p \leq 0.01$), indicating stability in emotional symptoms over time. Similarly, for the conduct problems scale there was no difference in model parameters between the unconstrained (χ^2 (DF) = 134 (78), CFI = 0.80, RMSEA 0.079) and constrained models (χ^2 (DF) = 140 (86), CFI = 0.80, RMSEA 0.074), indicating invariance in factor loading across timepoints. Conduct problems at 12 years were significantly associated to conduct problems at 15 years (β = 0.56, $p \leq 0.01$), and symptoms scores at 15 years were significantly associated with scores at 23 years (β = 0.56, $p \leq 0.01$), indicating stability in conduct difficulties across timepoints. As longitudinal invariance in factor loading has been demonstrated both scales were included as observed variables in the main analysis (see below).

The relationship between adverse life events and emotional symptoms and conduct problems at 23 years when accounting for childhood symptoms.

Our initial model with adverse life events predicting both emotional and conduct problems at 23 years with additional pathways between emotional and conduct problems at 15 years and frequency of adverse life events had a relatively poor fit to the data (χ^2 (DF) = 26.6 (13), $p = 0.01$; CFI = 0.89, RMSEA 0.095). The model indicated that adverse life events were significantly associated with both emotional (β = 0.19, SE = 0.08; $p = 0.02$) and conduct problems at 23 years (β = 0.22, SE = 0.08; $p \leq 0.01$). There was no significant association between either emotional problems or conduct problems at 15 years and frequency of life events. Full-scale IQ was regressed onto the model and was significantly negatively associated with conduct problems at 23 years (β = -0.25, SE = 0.09; $p \leq 0.01$), but not emotional problems.

To test for better model-fit and to account for possible direct associations with emotional symptoms and conduct problems at 15 with those at 23 years, the model was repeated constraining non-significant paths and regressing emotional problems at 15 years onto conduct problems at 23 years; and conduct problems at 15 years onto emotional problems at 23 years. This resulted in good model-fit (χ^2 (DF) = 18.1 (12), $p = 0.15$; CFI = 0.96, RMSEA 0.06; see Figure 1), confirming the significant relationship between adverse life events and both emotional and conduct problems at 23 years. This analysis also indicates significant direct associations between emotional problems at 15 years and conduct problems at 23 years (β = 0.23, SE = 0.10; $p \leq 0.01$); and conduct problems at 15 years and emotional problems at 23 years (β = 0.19, SE = 0.09; $p = 0.03$).

Figure 1. Model showing the relationship between adverse life events and emotion and conduct problems at 23 years when accounting for symptoms in childhood and adolescents



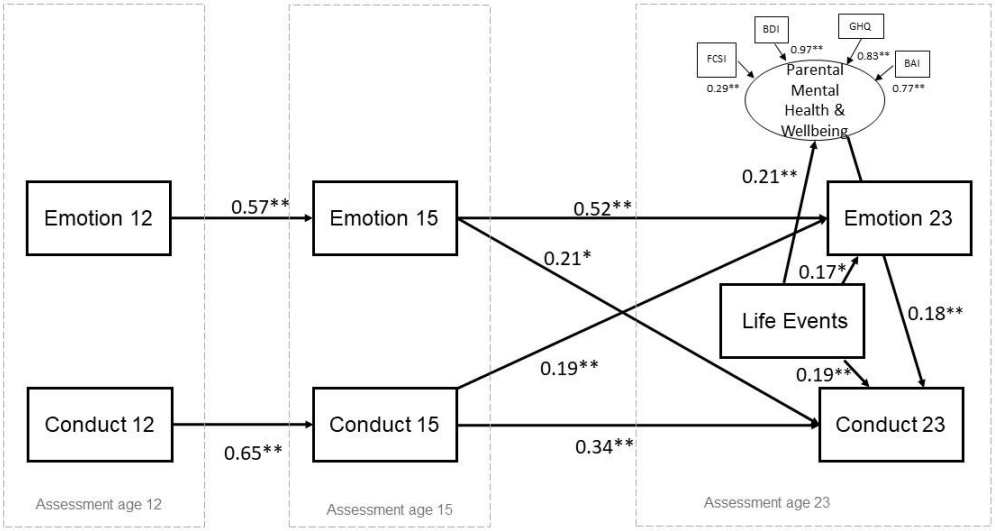
χ^2 (DF) = 18.1 (12), CFI = 0.96, RMSEA 0.06; ** significance at $p \leq 0.01$, * significance at $p \leq 0.05$

The impact of parental mental health and wellbeing on emotional symptoms and conduct problems and relationships with adverse life events.

Building on the model described above, the parental mental health & wellbeing latent variable was regressed onto both emotional and conduct problems at 23 years, while life events were regressed onto the latent variable (see Methods section). This analysis indicated good model-fit (χ^2 (DF) = 45.3 (41), p = 0.29; CFI = 0.99, RMSEA 0.030; see Figure 2) and revealed that a greater frequency of adverse life events was significantly associated with worse parental mental health & wellbeing (β = 0.21, SE = 0.09; p = 0.02), while at the same time a poorer parental mental health & wellbeing was significantly associated with conduct (β = 0.18, SE = 0.08; p = 0.03), but not emotional problems at 23 years (β = 0.11, SE = 0.08; p = 0.20). The direct associations between life events and

both conduct (β = 0.19, SE = 0.08; *p* = 0.02) and emotional problems (β = 0.17, SE = 0.08; *p* = 0.03) remained significant, but with a slight reduction in the standardised β coefficient. To test whether the frequency of adverse life events may impact on conduct problems via the relationship with parental mental health and wellbeing, indirect effects were tested. There was no significant indirect effect between adverse life event and conduct problems via parental mental health and wellbeing (β = 0.03, SE = 0.02; *p* = 0.11), suggesting that they can both be considered independent predictors of conduct problems at 23 years.

Figure 2. Model showing the relationship between parental mental health & wellbeing, adverse life events and emotion and conduct problems at 23 years when accounting for symptoms in childhood and adolescents



χ^2 (DF) = 45.3 (41), CFI = 0.99, RMSEA 0.03; ** significance at $p \leq 0.01$, * significance at $p \leq 0.05$

Discussion

In this study, the stability of emotional and conduct problems in young people with ASD was established, before then demonstrating the significant impact of exposure to adverse life events on emotional and conduct symptoms in adulthood, while controlling for the effect of symptoms in adolescence. Finally, parental mental health and wellbeing was found to be significantly, and negatively, impacted by their child's exposure to adverse life events. In turn, poorer parental mental health and wellbeing was related to more conduct, but not emotional problems.

The finding that both internalizing and externalizing symptoms in people with ASD are stable across childhood and into early adulthood is consistent with the previous literature (Woodman et al., 2016), including previous analyses of the current data set focusing on childhood and adolescence (Simonoff *et al.* 2013). However, it is important to note that despite the overall stability of the constructs over time, the proportion of people meeting the clinical cut-off for both emotional and conduct problems did reduce in early adulthood, with this reduction being most prominent for conduct problems. This is consistent with evidence to suggest that the prevalence of some mental health difficulties experienced in childhood and adolescence may reduce overtime, while others may increase (Lenze & Wetherell 2011; Costello & Maughan 2015). However, based on the data available we were unable to estimate whether the overall rates of comorbidity had reduced (i.e., when considering the wider range of possible mental health difficulties).

The finding of a significant association between exposure to adverse life events and emotional symptoms is consistent with the few studies that have

looked specifically at the impact of adverse life events and trauma on mental health outcomes in young people with ASD (Ghaziuddin *et al.* 1995; Taylor & Gotham 2016; Kerns *et al.* 2017). However, previous studies did not focus on young adults and have not used longitudinal data to demonstrate that this relationship is still present, even when controlling for symptoms in childhood and adolescence. However, while taking this approach has demonstrated the important impact of adverse life events on emotional symptoms, it has also shown that the strongest single predictor of mental health in early adulthood is symptom severity in adolescence. There is a lack of research looking at the association between adverse life events and conduct problems in ASD, however, our current findings are consistent with previous literature showing a significant association between adverse life events and conduct problems in non-ASD clinical populations (Tiet *et al.* 2001).

In addition to the impact of adverse life events, we also found that parental mental health and wellbeing was significantly related to increased conduct, but not emotional problems. While some previous research conducted with non-ASD participants has shown a relationship between parental measures and internalizing symptoms (Bauminger *et al.* 2010), it is the relationship with externalising symptoms which is shown to be more consistent in the literature (Lecavalier *et al.* 2006; Zaidman-Zait *et al.* 2014). While we also found that a greater number of adverse life events was significantly related to poorer parent mental health and wellbeing, this was not found to be a mediating factor, but rather an independent predictor of conduct problems in young adults. This is particularly interesting, given that our measures of parental mental health are strongly weighted towards internalizing symptoms and supports the hypothesis

that externalising behaviour may arise due to the inability of the parent to be available to the child's emotional needs as a consequence their own emotional difficulties. This was particularly the case in this sample, where 17% and 13% of parents report clinical levels of depression and anxiety, respectively. However, it is also important to recognise that this hypothesis which is based on research in the typically developing (non-ASD) population may not necessarily apply for people with ASD who have a range of differences in their cognitive processing and interpersonal relationships. There are several different factors associated with emotional difficulties in ASD which may have accounted for the current results such as difficulties with emotional regulation (Mazefsky & White, 2014). However, due to the limitations of the current analysis we cannot test this hypothesis directly, but future research may be able to do this by including repeated measurements of both parental wellbeing and parent-child interaction, as well as measures of internalizing symptoms, to investigate their interactions over time.

Limitations

While this study has several strengths, including a relatively large sample of well-characterised participants with ASD followed over a 11-year period, the current results should be interpreted in the context of several limitations. Firstly, although this study included a relatively large sample the number of paths included in the model and the presence of missing data means that the study may have been underpowered to pick-up some important effects, such as any significant mediating effect of parental meant health and exposure to adverse life events, therefore increasing the risk of a type-2 error. In addition, as this study included participants with a wide range of intellectual and verbal ability, we relied

entirely on parental report. While this can be considered an advantage, as it enabled us to include those with intellectual disability in the analysis, it may also have introduced some bias. This may also be the case considering that some of the parents included are known to have clinical levels of depression and anxiety and so may have been more likely to endorse negative items on questionnaire measures. However, it should be noted that previous research has shown that there is good parent-child agreement on measures of emotional symptoms for youth ASD samples (Blakeley-Smith *et al.* 2012; Ozsivadjian *et al.* 2013). In addition, the wide range of intellectual functioning has been accounted for by the inclusion of FSIQ as a covariate in the analysis. Nevertheless, future research could focus on replicating and extending these findings in a more homogenous sample, using both parent and child report.

Another limitation is the use of a checklist approach to measuring life events. While this is approach is consistently used in the literature, (Berden, Althaus, & Verhulst, 1990) it makes assumptions that all life events are equal and that the total number of events if the most important indicator of poor outcomes. Due to the binary nature (yes/no response) it was not possible to extrapolate statistically and useful subscale to address this. Future research could focus on using qualitative approaches to assess what types of life event are most important for individuals and subsequently these may impact on their mental health.

A related point refers to the lack of clinical measures that have been validated for use in the ASD population. While the SDQ is widely used with children and adolescence and has been shown to have utility when used with young people with ASD (Findon *et al.* 2016), there has yet to be a large-scale study of its validity in this clinical population. While for the purposes of this study

we have primarily used the SDQ as a continuous measure, which poses less of a concern, the interpretation of the clinical cut-offs used should be made with caution. More recently, efforts have been made to validate measures specifically for people with ASD and future research would benefit from use of both validated measures (Magiati *et al.* 2017), and measures adapted for those with intellectual disability.

Clinical implications

Given that people with ASD are at both an increased risk of experiencing traumatic or adverse life events (Kerns et al 2015), and our finding that such events can have a sustained negative impact on mental health in early adulthood, it is important to consider how the current result may be able to guide clinical practice. The results described in this study suggest three important and independent predictors of internalising and externalising problems occurring in young adults with ASD. The first of these related to the strong predictive value of both the presence of emotional or conduct problems in childhood and adolescence. This emphasises the importance of early intervention focused not only on what may be considered the core characteristics of ASD (i.e., social communication difficulties), but also on providing strategies to manage co-occurring mental health deficits. The second is related to the vulnerability of this population to experiencing adverse life events and the additional impact that this has on mental health. One way that young people with ASD could be supported is through extra support during key periods of stress such as the transition from children's to adult services and increased input from both mental health services and social care. Finally, evidence that parent mental health and wellbeing may directly drive externalizing behaviours throughout childhood and into adulthood

(Totsika *et al.* 2013; Zaidman-Zait *et al.* 2014), suggests that increased support for parents throughout childhood and adolescence may have a beneficial effect for both parents and their children across the lifespan. Brief interventions with parents based on the principles of Cognitive Behaviour Therapy immediately after diagnosis has shown some promise (Feinberg *et al.* 2014)

Conclusion

Internalizing and externalizing symptoms in young adults with ASD are significantly related to exposure to adverse life events and mental health symptoms in childhood and adolescence. Additionally, poor parental mental health and wellbeing are significantly related to a higher frequency of externalising problems. Symptoms in childhood and adolescence, exposure to adverse life events and parent mental health and wellbeing all represent independent predictors of mental health in adults with ASD and are good targets for the implementation and/or development of current and novel treatment approaches.

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CHAPTER 6: Exploratory Structural Equation Models Investigating the Impact of Low- and High-Frequency Life Events on Mental Health Symptoms at 23 years

Introduction

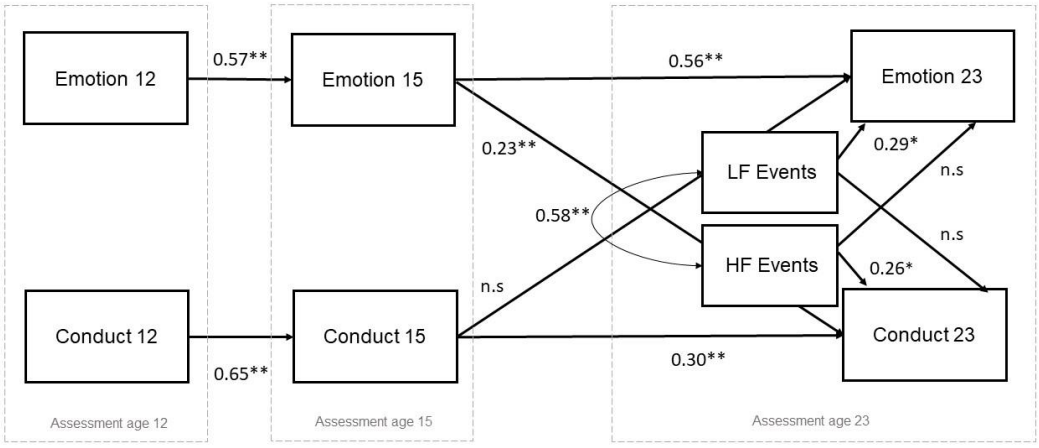
This chapter presents some additional post-hoc exploratory analyses to supplement those presented in the empirical paper. In the following analyses the cross-lagged regression models presented in the empirical paper are repeated but with the total life events score divided into low-frequency and high-frequency events. Low-frequency events refer to those which have occurred in less than 10% of the sample over the last five-years (see Chapter 4; Table 3). The rationale for dividing the events in this way was to crudely define those events that may be potentially traumatic (low-frequency; e.g., being seriously injured by an adult) versus those which are regular occurrences and may be things that a lot of young adults with ASD experience or may related to the environment (high-frequency e.g., being bullied or moving to a new house/residence). These results were not included in the empirical paper as this way of dividing the data is not empirically driven. Nevertheless, these additional analyses may be useful to differentiate the effects potential traumatic versus day-to-day adverse events on internalising and externalising symptoms.

Results

In the first model both low-frequency and high-frequency adverse life events were added predicting emotional and conduct problems at 23 years while controlling for emotional and conduct problems at 12 and 15 years (see Figure 1). This model had adequate fit (χ^2 (df) = 14.6 (12), $p = 0.26$; CFI = 0.98, RMSEA

0.044). The model indicated that low-frequency life events were significantly associated with emotional (β = 0.29, SE = 0.10; $p \leq 0.01$), but not conduct problems at 23 years (β = 0.06, SE = 0.10; $p = 0.59$). In contrast, high-frequency life events were significantly associated with conduct (β = 0.26, SE = 0.09; $p = 0.02$), but not emotional problems (β = -0.07, SE = 0.09; $p = 0.45$). Low-frequency and high-frequency life events were significantly associated with each other (β = 0.58, SE = 0.06; $p \leq 0.01$). Full-scale IQ (not shown in Figure 1) was regressed onto the model and was significantly negatively associated with conduct problems at 23 years (β = -0.26, SE = 0.08; $p \leq 0.01$), but not emotional problems.

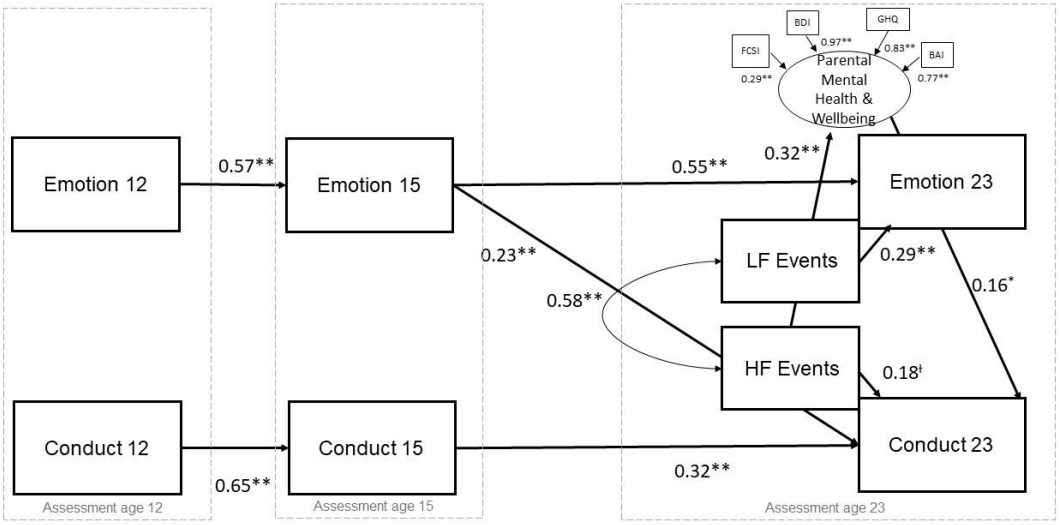
Figure 1. Model showing the relationship between high- and low-frequency adverse life events and emotion and conduct problems at 23 years when accounting for symptoms in childhood and adolescents



X^2 (DF) = 14.6 (12), CFI = 0.98, RMSEA 0.04; ** significance at $p \leq 0.01$, * significance at $p \leq 0.05$

Building on the model described above, the parental mental health & wellbeing latent variable was regressed onto both emotional and conduct problems at 23 years, while each of the adverse life events variables were regressed onto the latent variable. This analysis indicated adequate model-fit (χ^2 (DF) = 60.5 (46), p = 0.08; CFI = 0.96, RMSEA 0.052; see Figure 2). The results suggest that there was a significant association between high-frequency life events and parental wellbeing and mental health (β = 0.32, SE = 0.11; $p \leq 0.01$), while there was no significant association with low-frequency life events (β = -0.05, SE = 0.11; p = 0.62). Furthermore, there was a significant association between the parental mental health and wellbeing latent variable and conduct problems (β = 0.16, SE = 0.08; p = 0.05), but not emotional problems at 23 years (β = 0.16, SE = 0.08; p = 0.13). As with the analysis presented in the empirical paper, the indirect effects of HF life events on conduct problems via parental mental health were investigated but were not found to be significant.

Figure 2. Model showing the relationship between high- and low-frequency adverse life events and parental mental health and wellbeing on emotion and conduct problems at 23



Non-significant paths not displayed; χ^2 (DF) = 60.5(46), CFI = 0.96, RMSEA 0.05; ** significance at $p \leq 0.01$, * significance at $p \leq 0.05$, ł significant at $p \leq 0.07$

Summary & Brief Discussion

This supplementary post-hoc analysis has divided the total life events measure from the primary analysis into two subscales to represent low-frequency (potentially traumatic) and high-frequency life events (common life-events). The results suggest that these subscales are differentially related with internalising and externalising symptoms. Specifically, that the low-frequency potentially traumatic events are associated with higher levels of emotional symptoms but not conduct problems. Conversely, there appears to be a specific relationship between the high-frequency life-events that may relate more to day-to-day or environmental stressors and a greater severity of conduct problems.

As was shown in the primary analysis, poorer parental mental health and wellbeing was significantly associated with conduct, but not, emotional problems. Interestingly, this analysis has shown that like conduct problems, parental mental health and wellbeing is specifically associated with the high-frequency life events sub-scale. Together this may suggest that exposure to a high number of common life events could create a stressful environment having a negative impact on parental wellbeing and subsequently leading to increased externalising behaviours by the young adult with ASD. In contrast, while exposure to low-frequency but potentially high impact events is associated with poorer emotional outcomes for the individual with ASD it was not significantly associated with parental mental health and wellbeing.

The interpretation of this exploratory analysis should be made with caution as the selection of what constitutes a low- or high-frequency life event in this analysis has been made by selecting an arbitrary cut-off of 10%. While it is intuitive that events which occur less often are more likely to be high impact

events, this does not necessarily follow. For example, bullying which is common in people with ASD and coded as a high-frequency life event can be high-impact and this will likely vary significantly between individuals.

CHAPTER 7: Discussion and Critical Evaluation

Overview of results

The first section of this thesis consisted of a systematic review and meta-analysis of 36 studies which examined the current and lifetime prevalence of anxiety and/or depression in adults with autism spectrum disorder (ASD). To my knowledge this was the first meta-analysis to take a comprehensive view of co-occurring anxiety and depression in adults with ASD. The results were consistent with previous meta-analytic studies focused on childhood and adolescence (van Steensel, Bögels, & de Bruin, 2013), and indicated that adults with ASD experience high rates of anxiety and depression. The pooled estimation of current and lifetime prevalence was 27% and 42% for any anxiety disorder, and 23% and 37% for depressive disorder. Again, consistent with the literature in young people with ASD, anxiety disorders such as social phobia, obsessive-compulsive disorder (OCD) and generalised anxiety disorder were found to be most commonly reported. While this is consistent with much of the literature, it does also suggest that from childhood to adulthood there may be an increase in the prevalence of depression and a slight reduction in anxiety. These findings indicate that both anxiety and depression are more common in adults with ASD than you would expect based on estimates from the general population (Kessler et al., 2005; Weich et al., 2011).

Another key finding was high levels of heterogeneity in the current literature on co-occurring anxiety and depression in adults with ASD. The high variability of reported prevalence rates between studies means that reaching a

definitive estimate of prevalence is not currently possible. Results suggested that the use of standardised measures and validated tools, such as the ADOS and ADI-R, as inclusion criteria seemed to go some way to reduce heterogeneity. Furthermore, an analysis of study quality, which included an assessment of both selection and detection bias, indicated the current literature is over-reliant on clinical samples and provides little information on how representative the samples are of the whole ASD population. The lack of community-based studies of co-occurring mental health difficulties in adults with ASD mean that results of the meta-analysis may only inform our understanding of clinical samples, rather than people with ASD more broadly.

The second section on this thesis included an empirical study which investigated the role of exposure to adverse life events and parental mental health as predictors of mental health symptoms in young adults with ASD. This study looked at internalising symptoms such as anxiety and depression, but also externalising symptoms which are also known to be common in people with ASD (Simonoff et al., 2008). Longitudinal data was used to demonstrate that when controlling for symptoms in childhood and adolescence, exposure to adverse life events over a five-year period was a significant predictor of internalising and externalising problems at age 23. An exploratory analysis breaking life events down into low-frequency (potentially traumatic) and high-frequency (common life-events) showed a differential effect on internalising and externalising symptoms. Specifically, that potentially traumatic events are associated with internalising symptoms while exposure to a greater frequency of common life events was associated with externalising symptoms.

A second aim of the empirical study was to investigate the role parental mental health and wellbeing has on their children's level of internalising and externalising problems as young adults. It was of particular interest to establish whether, as had been previously suggested (Tiet et al., 2001; Weiss, Cappadocia, Tint, & Pepler, 2015), parental factors act to moderate the impact of adverse life events on mental health symptoms experienced by the young adults. The results indicated that poorer parental mental health was significantly associated with a greater number of externalising but not internalising systems. While the number of adverse life events experienced was also associated with parental mental health, there was no indirect effect, nor was there any reduction in the significance of the direct relationship between life events and externalising symptoms, meaning that parental factors neither mediate or moderate the relationship between adverse life events and mental health symptoms in the young adults. This suggests that both exposure to life events and a poorer parent mental health and wellbeing are independent risk factors. However, it is also worth highlighting that the strongest predictor of internalising and externalising problems as young adults was the degree of the corresponding symptoms in adolescence.

Theoretical implications

Mental health comorbidity in adults with ASD. The findings of this thesis indicate that the mental health difficulties commonly reported in ASD in childhood and adolescence continue to be a prominent feature in adulthood (Salazar et al., 2015; van Steensel, Bögels, & Perrin, 2011). In addition to the results of the meta-analysis indicating a high prevalence of anxiety and depression, a high rate of conduct problems in adulthood was also shown in the empirical paper. However,

this later finding was based solely on a questionnaire subscale cut-off score, and therefore this should be interpreted with caution.

The results presented in this thesis may also provide some insight into how the rates of prevalence may change across the lifetime of a person with ASD. For example, the most recent meta-analytic studies of anxiety in childhood estimate a prevalence of around 39% (van Steensel et al., 2013, 2011) compared to the estimate presented in chapter 1, of around 27%. This constitutes a substantial reduction in adults and may be related to lower rates of anxiety disorders more typically associated with the childhood period such as separation anxiety (Bögels, Knappe, & Clark, 2013). However, it is worth noting that as the studies included were focused on adult mental health anxiety diagnoses more commonly associated with childhood were rarely assessed.

It is also interesting to note that the only population-based study of comorbidities in children with ASD reports a current prevalence rate of less than 1% for depression (Simonoff et al., 2008), compared to the estimate of 23% suggested here. This difference is likely driven in part by the fact the current meta-analysis lacks any good quality community studies of prevalence to make direct comparisons and so reflects the prevalence of depression in treatment-seeking clinical samples. However, in the current meta-analysis the three studies which were classified as having community based sampling (Buck et al., 2014; Mazefsky et al., 2008; Morgan et al., 2003) provided prevalence rates that were similar to the estimated prevalence rates for anxiety and depression. The exception being a <1% prevalence rate for depression in the study by Buck et al, which may have been influenced by a high proportion of participants with intellectual disability. Nonetheless, it is plausible that the rates of depression in

ASD increase significantly overtime in line with what one may expect based on studies in non-ASD populations and, as demonstrated in empirical paper, that the presence of depression in adolescence strongly predicts the continuity of symptoms into adulthood (Copeland, Shanahan, Costello, & Angold, 2009; Costello, Copeland, & Angold, 2011). It is also important to note that the prevalence rate reported by Simonoff and colleagues was a 3-month point prevalence when children were aged around 12 years of age and therefore represents a significantly different developmental and environmental context than that of the participants included in the meta-analysis, where the mean age was approximately 31 years.

Another important consideration is that the estimated prevalence of both anxiety and depression was lower in studies where all or, a majority of, participants had an intellectual disability. This is important given that depending on the estimate, one third of people with ASD have intellectual functioning in the impaired range (Kim et al., 2011). This goes against the notion, often suggested clinically, and presented in some literature that having an intellectual disability increases the risk of developing a co-occurring mental health difficulty when it occurs in addition to an ASD (Bradley, Summers, Wood, & Bryson, 2004; Morgan, Roy, & Chance, 2003). However, it is also important to consider whether these findings relate to issues of measurement. For instance, it is possible that self-report measures currently available may not be adequately assessing symptoms of anxiety and depression because of the difficulties that people with ASD often have with identifying and describing emotions, which may be further exacerbated by having a poorer verbal ability or intellectual disability (Hassiotis & Turk, 2012).

Measurement issues. One a-priori focus of the meta-analysis was to investigate the impact of diagnostic overshadowing and measurement issues more generally on the estimation of mental health difficulties in adults with ASD. Diagnostic overshadowing refers for the tendency of ASD related behaviours and mental health symptoms to present as behaviourally similar. Clinically this can lead either to mental health difficulties being dismissed as "a part of the ASD" or the rigid thinking that often occurs as a part of clinical anxiety or depression being interpreted as an indicator of an ASD (Wood & Gadow, 2010).

This has a significant impact when measuring co-occurring mental health difficulties in ASD using either questionnaire measures or semi-structured clinical interviews with a pre-defined diagnostic algorithm. This is because the behavioural similarities create an effective phenocopy, resulting in the scores for the co-occurring difficulty to be inflated. One study in the meta-analysis compared prevalence rates for OCD both before and after accounting for this in their diagnostic algorithm, resulting in a drop in prevalence from 36% to 22% (Buck et al. 2014). While it may be assumed that the biggest impact would occur for questionnaire measures when compared to clinical interviews, this was generally not found to be the case when comparing the two assessment measures as a part of the meta-analysis. One exception is the estimate of OCD, in which a significant reduction in the prevalence estimate from 43% to 19% was found when measured by either clinical interview or questionnaire measures, respectively. This suggests that diagnostic overshadowing may be a particular issue in the case of co-occurring OCD due to the behavioural similarities between restrictive and repetitive behaviours in ASD and compulsions and ritualised behaviour in people with OCD (Cadman et al., 2015; Paula-Perez, 2013). This

suggests that OCD may be overestimated in both children and adults with ASD and that clinically the assessment should not be overly reliant on the use of standardized measures.

Pathways to internalizing and externalising difficulties. The aim of the empirical study was to build upon evidence that people with ASD are both psychologically (Bishop-Fitzpatrick, Minshew, Mazefsky, & Eack, 2017; Groden et al., 2001) and biologically (Hollocks, Howlin, Papadopoulos, Khondoker, & Simonoff, 2014; Taylor & Corbett, 2014) vulnerable to the experience of stress and to test the direct impact of exposure to adverse life events on mental health symptoms as young adults. Unlike other studies which have looked at the impact of adverse life events on mental health in people with ASD, this study took advantage of longitudinal data to control for mental health difficulties present earlier in life.

The finding of this study that exposure to life events in early adulthood is significantly associated with both internalizing and externalising symptoms supports the suggestion that there is a cumulative effect of adverse life events on the mental health of people with ASD (Ghaziuddin, Alessi, & Greden, 1995; Kerns, Newschaffer, Berkowitz, & Lee, 2017; Taylor & Gotham, 2016). By using longitudinal data to show this effect remains when accounting for symptoms earlier in life, this study suggests that environmental factors continue to impact on mental health beyond childhood and highlights the transition to adulthood as an important and potential stressful period.

There is some tentative evidence to suggest that there may be differential relationships between low-frequency potentially traumatic events and high-

frequency everyday life events and the type of mental health symptoms experienced by the young adult with ASD. The finding that exposure to potentially traumatic events is related to greater emotional difficulties such as symptoms of anxiety and depression is consistent with the literature on childhood post-traumatic stress (Copeland, Keeler, Angold, & Costello, 2007; Heim & Nemeroff, 2001), and the limited literature investigating the impact of adverse life events in ASD (Kerns, Newschaffer, & Berkowitz, 2015). The finding that a greater number of high-frequency life events which may be related more strongly to environmental factors is consistent with literature in the general population to suggest that greater adversity in the environment is related to eight-fold increase in the chance of developing an externalizing condition such as conduct disorder (Dunn et al., 2011; St Clair et al., 2015).

The role of parental mental health and wellbeing. The results of the current study are consistent with the literature suggesting that parental stress and mental health is associated with mental health outcomes in people with ASD (Jellett et al., 2015; Lecavalier et al., 2006; Maljaars et al., 2014; Weiss et al., 2015). However, the current results suggest that this relationship is specifically with externalising, but not internalising symptoms. This is also consistent with the previous literature as the relationship between parental measures and externalising symptoms has been demonstrated more consistently (Falk, Norris, & Quinn, 2014). Unlike some previous studies, the findings in chapter 5 did not show a relationship between parental mental health and internalizing problems (Bauminger et al., 2010). This may be explained by the inclusion of both internalising and externalising symptoms in a single model, meaning any effect

of parental mental health on internalising symptoms was not significant when accounting for the relationship with externalising.

Previous studies have used longitudinal analyses to investigate the bidirectional relationship between parent stress and externalising behaviours in ASD, finding that the young persons' behaviour is predominantly driven by the parent's levels of stress and not vice versa (Totsika et al., 2013; Zaidman-Zait et al., 2014). In this study, significant relationships between parental mental health and wellbeing and externalising symptoms in young adults were shown to remain even when controlling for the severity of symptoms in childhood. However, the direction of the relationships between parental mental health and wellbeing and externalising symptoms in young adults was not explicitly tested. While this may have been possible using the current dataset the aim of this study was to investigate the role of parental measures as a possible mediating factor between exposure to adverse life events and the severity of mental health symptoms in early adulthood. Future research could build on the current study by testing whether the degree of change in externalising symptoms from adolescence to early adulthood is moderated by parental factors. The finding that both parental mental health and externalising symptoms are related with high-frequency life events is consistent with literature that suggests a strong environmental influence on the expression of conduct problems in childhood (Maughan, Taylor, Caspi, & Moffitt, 2004; O'Connor, Deater-Deckard, Fulker, Rutter, & Plomin, 1998; Shelton et al., 2008).

Strengths and limitations

The work presented in this thesis has several strengths and weaknesses which need to be considered when interpreting the results of both the meta-analysis and empirical study.

Meta-analysis of comorbid anxiety and depression. The meta-analysis conducted in this thesis was the first to take an inclusive view of all published studies which have measured co-occurring anxiety and depression in adults with ASD. Unlike previous studies this included individuals with intellectual disability (Wigham, Barton, Parr, & Rodgers, 2017) a group within the ASD population who are often neglected in research (Jack and Pelphrey, 2017). There were several notable strengths of this piece of work including a detailed evaluation of study quality by two independent researchers and a series of sub-group analyses which aimed to elucidate the impact of measurement and clinical factors on estimates of prevalence.

However, there were also limitations which means that the results should be interpreted with caution. Firstly, as noted above, the high heterogeneity between the studies included in the meta-analysis makes it difficult to be certain on how much our current estimates reflect the true prevalence of anxiety and depression in adults with identified ASD. This however, is a realistic presentation of the current literature on mental health comorbidities in ASD and is in its self an interesting result. In a related point, there were no community studies that included adults whose ASD had not been recognised or who had not been in contact with clinical services, meaning that the samples included in the current analysis may not be fully representative of ASD in the whole population.

Secondly, although the meta-analysis included a series of sub-analyses, there are several other clinically relevant factors which were not addressed within these. For example, it may have been interesting to investigate the impact of age, gender ratio, or ASD subtype on prevalence estimates. Analysis including age and gender were not included in the current study, in part due to incomplete data, and specifically for age, because there was also relatively low variance in the mean age of participants in individual studies. The meta-analysis also followed the current nomenclature outlined in the DSM-5 of collapsing participants who would previously have been divided into the diagnostic subgroups of childhood autism, Asperger's syndrome and pervasive developmental disorder together under the umbrella of ASD. While this helps bring the result in line with current practice it may be more useful from a clinical standpoint for future studies to undertake a more detailed analysis of participant characteristics on estimates of prevalence, perhaps by looking at subgroups defined by important clinical characteristics such as degree of difficulty on measures of language and communication.

Finally, it is important to note that while a thorough analysis of selection and detection bias was undertaken, publication bias was not explicitly evaluated as a part of this meta-analysis. One reason for this is that the typical method for assessing publication bias, by using a funnel plot, is inaccurate when conducting a meta-analysis for proportions as was the case in the current study (Hunter et al., 2014). However, it is also worth noting that there was a wide spread of prevalence estimates from 1% up to 77% across anxiety and depression which suggests that the non-reporting of low prevalence is not a major concern. In some instances this was likely helped by the fact that many studies were not set

out specifically to measure prevalence. However, this in turn had a negative effect on study quality as it meant fewer studies considered issues such as selection and detection bias when designing their studies. On a related point, the current meta-analysis only includes studies which had been through peer review. While this is a common approach to take to ensure the quality of articles included, it does increase the risk of introducing bias (Lipsey & Wilson, 2001).

Empirical paper. The empirical study in Chapter 5 has several strengths, including the use of data from a large community-based sample of young adults with ASD who had been followed up at three separate time points. The sample was also well characterised from a clinical perspective, having confirmed ASD diagnoses (using ADOS/ADI) and being assessed on a range of clinical measures. The longitudinal nature of this study was a real strength as it enabled me to show that the relationships shown in the adult period are not accounted for solely by metal health difficulties earlier in life. This is of importance given that ASD is a lifelong condition associated with significant co-occurring mental health difficulties throughout childhood.

Despite these strengths there are several limitations to be considered. Firstly, a major limitation is the use of a checklist approach to measuring life events. While this approach is consistently used in the literature, (Berden, Althaus, & Verhulst, 1990; Brugha & Cragg, 1990; Zimmermann et al., 2011) it makes assumptions that all life events are equal and that the total number of events if the most important indicator of poor outcomes. One approach to counteract this would be to weight specific items based on the potential impact to the person. However, this still requires assumptions to be made about what life events impact people the most. In this study this issue was somewhat addressed

by taking a quantitative approach and looking at high- and low-frequency life events. However, this approach suffers from many of the same limitations as the total life events scale. Future research should focus on using qualitative or mixed quantitative-qualitative approaches to try to tease apart which types of life events have the biggest impact on people with ASD and this may be similar or different to those in the typically developing population.

There are also some limitations in the interpretations that can be made from the measures of parental mental health and wellbeing used in the empirical study. Firstly, these measures are heavily weighted towards symptoms of anxiety and depression and therefore do not measure other types of mental health difficulties that could negatively impact on their ability to offer support to their child. Another limitation is that while we have achieved the primary goal of examining the effect of parental mental health, this does not explain the mechanism through which poorer parental mental health and wellbeing impacts on the severity externalising behaviour. For example, it would have been interesting to have additional measures of the specific parenting behaviours or parent-child interactions over time to look at the quality of attachment relationship, which have been shown to be more difficult in families where a child has ASD (Rutgers, Bakermans-Kranenburg, van IJzendoorn, & van Berckelaer-Onnes, 2004). It is also worth noting that because the SNAP study was not explicitly set-up to investigate parental wellbeing there was limited descriptive and clinical information regarding parents. For instance, given evidence of the broader autism phenotype (Baron-Cohen & Hammer, 1997; Piven, Palmer, Jacobi, Childress, & Arndt, 1997) in relatives of those with ASD it would have been interesting to see whether controlling for ASD traits displayed by parents in the

analysis may have influenced the current results or they may have been strong predictors of the parents' own mental health difficulties.

Finally, it is worth considering that this analysis was based purely on parental report. While there is evidence to suggest reasonable parent-child agreement in the ASD population when reporting mental health difficulties (Blakeley-Smith, Reaven, Ridge, & Hepburn, 2012; Ozsivadjian, Hibberd, & Hollocks, 2014), this could have inflated the relationship reported in this study. Parent report was given preference in this study so that data from young people with a broad range of intellectual ability could be collected using consistent measures. Future studies could build on this by replicating these findings separately in people with and without intellectual disability using adapted measures in the former group, or by developing tools specifically for the ASD population which are scalable in terms of their language and intellectual demands.

Future research directions

The results discussed in this chapter have several implications for future research, some of which have already been highlighted above. While the current meta-analysis shows that adults with ASD who are accessing clinical services are at disproportionate risk for developing co-occurring emotional difficulties, the lack of good quality community-based studies of mental health comorbidities in adults with ASD means that our understanding of this issue for the whole population of people with ASD is still incomplete. One approach for future studies would be to undertake a detailed assessment of metal health comorbidity in sample that was truly representative of the ASD population in terms of variability in severity of ASD symptoms, intellectual and verbal ability. Alternatively, more

detailed assessments in subsamples of the population defined in a clinically useful manner may help to both reduce heterogeneity and have a greater potential to inform clinical practice.

Further research focused on either the prevalence or nature of co-occurring mental health difficulties in clinical samples should ensure that clinical (non-questionnaire) assessments are blinded to reduce bias and that issues, such as diagnostic overshadowing, are considered during assessment. There are a lack of clinical measures that have been validated for use in ASD populations (Brugha, Doos, Tempier, Einfeld, & Howlin, 2015) and there is considerable scope for research in this area. It may be that further research focused on measurement issues is needed before a great deal of effort and expenditure is committed to a large-scale community-based study of adult comorbidity in ASD.

While this study has found a significant association between measures of parental mental health and mental health in their adult children, further research is needed to investigate the mechanisms of how this occurs over time. Factors such as the attachment quality or the modelling by parents of unhelpful behaviours or cognition may play an important role in the development of co-occurring mental health difficulties. These factors may call for smaller, more detailed or experimental studies investigating the quality of parent-child interactions across the lifespan in ASD. This more detailed approach may also help to further understand why parental mental health appears to have a specific relationship with externalising difficulties.

Clinical Implications

The result of the meta-analytic study has clear clinical implication in terms of the service provision required to meet the additional need of adults with ASD who present with one or more co-occurring mental health difficulties. Many regions of United Kingdom lack dedicated services to provide psychological support to adults with ASD. Therefore, if the estimated prevalence rates identified in Chapter 1 are anywhere near reflected in clinical services this will be placing a great demand on the resources of community mental health teams. While CBT has been suggested to be moderately helpful with adults with ASD (Spain, Sin, Chalder, Murphy, & Happe, 2015), clinicians in community teams could lack the training or understanding of ASD required to make necessary adaptations to their interventions. This problem can be compounded by the issue of diagnostic overshadowing, which can make accurate formulation a challenge for clinicians trained in adult mental health but with a more limited understanding of neurodevelopmental conditions. While arguments can be made for or against the idea of having dedicated adult services for ASD, enhanced training in both the assessment and treatment of co-occurring mental health difficulties should be promoted.

The lack of well validated clinical measures for the assessment of co-occurring mental health difficulties also presents a challenge. The results of the meta-analysis suggest that using tools designed for use in adults without ASD may lead to inaccurate outcomes. While there have been efforts to validate some existing questionnaires (Magiati et al., 2017; Uljarevic et al., 2017; Zainal et al., 2014), and to develop population specific tools (Bearss et al., 2016; Rodgers et al., 2016), an overreliance on standardised measures is not recommended.

Rather, a detailed assessment and formulation considering a range of factors such developmental history, family wellbeing and the function of the behaviours associated with the presenting comorbidity may be more beneficial.

The results described in the empirical study suggest three important and independent predictors of mental health problems occurring in young adults with ASD. The first of these related to the strong predictive value of both the presence of emotional or conduct problems in childhood and adolescence. This, along with the stability of symptoms from 12 years through to early adulthood, highlights the importance of early intervention focused on mental health difficulties, not only on what may be considered the core characteristics of ASD. Indeed, a recent study has shown longitudinally that early anxiety problems in fact drive future symptoms of ASD and not vice versa (Duvekot, van der Ende, Verhulst, & Greaves-Lord, 2018). The second is related to the vulnerability of this population to experiencing adverse life events and the additional impact that this has on mental health (Kerns et al., 2015). While it is unclear which specific factors may make this population vulnerable to stress, clinical interventions than can build resilience and coping strategies seem all the more important for those with ASD compared to the typically developing population. Interventions in this domain should be focused on early intervention and sit within the remit of schools working closely with clinical psychologists and other professionals involved in the early assessment of ASD at child development centres or within community paediatrics. As with all mental health difficulties, early intervention is preferable to an often increasingly complex intervention later in life. Finally, evidence that parent mental health and wellbeing may directly drive externalizing behaviours throughout childhood and into adulthood (Totsika et al., 2013; Zaidman-Zait et al., 2014) suggests that

increased support for parents throughout childhood and adolescence may have a beneficial effect for both parents and their children across the lifespan. Brief interventions with parents based on the principles of Cognitive Behaviour Therapy immediately after diagnosis has shown some promise (Feinberg et al., 2014). In addition, parent mediated interventions focused on the child may indirectly benefit the parent and empower them to both support their child and in turn reduce stress and risk of developing mental health difficulties (McConachie & Diggle, 2007; Pickles et al., 2016). These interventions would again be most helpfully implemented soon after initial diagnoses to reduce the chances of the propagation of mental health difficulties within the family.

Conclusion

The results presented in this thesis suggest that adults with ASD are at increased risk of experiencing significant co-occurring mental health difficulties, including anxiety, depression and externalising problems compared to the typically developing population (Kessler et al., 2005; Weich et al., 2011). However, the quality of studies investigating the prevalence of mental health comorbidities in ASD is poor and further research using community-based samples is required. While internalising and externalising symptom in ASD are shown to be stable throughout childhood, adolescence and young adulthood, the severity of symptoms at the latter time point can be predicted by exposure to both adverse life events, and in the case of externalising problems, by their parent's mental health and wellbeing. In addition to the direct treatment of co-occurring mental health difficulties with the young person, this research suggests that interventions focused on increasing the resilience to adverse life events and

support for parent of those with ASD, even when their child is an adult, should be prioritised.

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Appendices

Appendix A: Formatting Instructions for Psychological Medicine

CAMBRIDGE | Instructions for Contributors

Psychological Medicine

Editorial Policy

Psychological Medicine is a journal aimed primarily for the publication of original research in clinical psychiatry and the basic sciences related to it. These include relevant fields of biological, psychological and social sciences. Review articles, editorials and letters to the Editor discussing published papers are also published. Contributions must be in English.

Please see the below table for the types of papers accepted:

Article Type	Usual Max Word count*	Abstract	References	Tables/figures**	Supplementary material online only
Original article	4500	250 words, structured, using subheadings Background, Methods, Results, Conclusions	Harvard style – see elsewhere in this document for full details	Usually up to 5 total	Yes
Review article	4500	250 words, not structured	Harvard style	Usually up to 5 total	Yes
Editorial	3500	No	Harvard style	Usually up to 5 total	Yes
Correspondence	1500	No	max 20 Harvard style	Max 1	No
Commentary	2000 By invitation of editor	No	max 20 Harvard style	Not usually	Yes

*** Editors may request shortening or permit additional length at their discretion in individual cases**
**** May be adjusted in individual cases at Editors' discretion**

Generally papers should not have text more than 4500 words in length (excluding abstract, tables/figures and references) and should not have more than a combined total of 5 tables and/or figures. Papers shorter than these limits are encouraged. For papers of unusual importance the editors may waive these requirements. Articles require a structured abstract of no more than 250 words including the headings: Background; Methods; Results; Conclusions. Review Articles require an unstructured abstract of no more than 250 words. The name of an author to whom correspondence should be sent must be indicated and a full postal address given in the footnote. Any acknowledgements should be placed at the end of the text (before the References section).

References

(1) The Harvard (author-date) system should be used in the text and a complete list of References cited given at the end of the article. In a text citation of a work by more than two authors cite the first author's name followed by *et al*. (but the names of all of the authors should be given in the References section). Where several references are cited together they should be listed in rising date order.

(2) The References section should be in alphabetical order. Examples follow:

Brown GW (1974). Meaning, measurement and stress of life events. In *Stressful Life Events: Their Nature and Effects* (ed. B. S. Dohrenwend and B. P. Dohrenwend), pp. 217-244. John Wiley: New York.

Brown J. (1970). *Psychiatric Research*. Smith: Glasgow.

Brown J, Williams E, Wright H (1970). Treatment of heroin addiction. *Psychological Medicine* **1**, 134-136.

Note: authors' names should be in **bold** font; journal titles should always be given in full.

(3) References to material published online should follow a similar style, with the URL included at the end of the reference, with the accession date, if known. Authors are requested to print out and keep a copy of any online-only information, in case the URL changes or is no longer maintained. Examples follow:

Acute Health Care, Rehabilitation and Disability Prevention Research - National Center for Injury Prevention and Control. (http://www.cdc.gov/ncipc/profiles/acutecare/default.htm). Accessed 7 June 2004.

British Psychological Society Research Digest, Issue 12. (http://lists.bps.org.uk/read/messages?id=1423). Accessed 17 February 2004.

Appendix B: Formatting Instructions for Autism Research

AIMS AND SCOPE

Autism Research is owned and supported by **The International Society for Autism Research (INSAR)**, a scientific and professional organization devoted to advancing knowledge about Autism Spectrum Disorder (ASD). For more information, please visit the Society Information section of the journal homepage.

Autism Research covers research relevant to ASD and closely related neurodevelopmental disorders. The journal focuses on genetic, neurobiological, immunological, epidemiological and psychological mechanisms and how these influence developmental processes in ASD. The journal encourages the submission of original research papers (Research Articles and Short Reports) that take a developmental approach to the biology and psychology of autism, with a particular emphasis on identifying underlying mechanisms and integrating across different levels of analysis. Contributions are typically empirical, but the journal also publishes theoretical papers if they significantly advance thinking. The journal encourages papers reporting work on animals or cell or other model systems that are directly relevant to a better understanding of ASD. The journal also publishes reports of carefully conducted clinical trials of treatments for the core symptoms or one of the common co-morbid symptoms of ASD. Papers presenting clinical trials will be judged, in part, on whether there is an empirical justification for the reported treatment. Individuals included in research studies can span the full spectrum of ASD, including the broader phenotype, and there are no restrictions on study participants in terms of age or intellectual ability.

MANUSCRIPT CATEGORIES AND REQUIREMENTS

Research Articles

The text of these articles should include a scientific Abstract (150–250 words), a Lay Summary (see details elsewhere), and they should follow the IMRaD guidelines (***I***ntroduction, ***M***ethods, ***R***esults, ***a***nd ***D***iscussion), which are recommended by the International Committee of Medical Journal Editors (ICMJE) (*J. Pharmacol. Pharmacother.* 2010, *1*, 42–58). Manuscripts should be a maximum of 5,000 words in length (excluding Abstracts and References). If there are extenuating circumstances that require an increased length, authors should contact the Editorial Office with specific details and rationale for the Editor-in-Chief's consideration.

References

Reference should be made only to articles that are published or in press. Unpublished results and personal communications should be cited parenthetically in the text, not in the reference list. Authors are responsible for the accuracy of the references.

References in the text should be made by author's name followed by the year of publication, arranged chronologically, then alphabetically. When there are more than two authors, use the first author's name and et al.

When references are made to more than one paper by the same author, published in the same year, designate them as a, b, c, etc. In the final list, arrange references

alphabetically listing the first six authors, followed by et. al. where applicable, then year of publication. Spell out journal names in roman style, following these examples:

For Journals: Pinter, R., Hogge, W.A., & McPherson, E. (2004). Infant with severe penicillamine embryopathy born to a woman with Wilson disease. American Journal of Medical Genetics, Part A, 128A, 294–298.

Books: Reece, R.J. (2004). Analysis of genes and genomes. New York: Wiley-Liss. 469 p.

Chapter in Book: Hunter, A.G.W. (2005). Down syndrome. In: Cassidy, S.B., Allanson, J.E., editors. Management of genetic syndromes, 2e. New York: Wiley-Liss, pp 191–210.

Web Citation: U.S. Census Bureau. (2004). America's families and living arrangements: 2003 (Table C3). Retrieved November 24, 2004, from www.census.gov/population/www/socdemo/hh-fam/cps2003.html.

Appendix C: Issues on the Family Stress and Coping Interview

1. The diagnosis of _____ as having a developmental disability.
2. Explaining to others about _____'s developmental disability.
3. Your feelings about the cause of _____'s developmental disability.

4. Dealing with friends/family/people in the neighbourhood on a day-to-day basis.

5. Dealing with doctors and other allied health professionals.

6. Dealing with legal professionals.

7.Dealing with _____'s teachers and the educational system.

8. Creating and/or finding opportunities for _____ to make friends and participate in activities.

9. Deciding on the best level of integration for _____.
10. Making the decision concerning accommodation in the home or in the community.
11. Meeting the needs of your (other) children.
12. Meeting your own personal needs.
13. Meeting the needs of your spouse.
14. Maintaining satisfying friendships for yourself.
15. Dealing with _____'s sexuality.
16. Work placements or employment for _____.
17. Long-term planning for accommodation for_____.
18. Planning for wills, trusts and guardianships.
19. Planning for emotional and social support for.
20. Transportation.
21. Day-to-day assistance with care of _____.
22. Time apart from _____.
23. Dealing with financial and insurance issues.