KATIE FALL BSc Hons MSc

MEDICATION ADHERENCE IN ADOLESCENTS AND YOUNG ADULTS WITH CHRONIC LIVER DISEASE

Section A: What Variables are Associated with Medication Adherence in Adolescents and Young Adults with Chronic Liver Disease? A Narrative Review

Word Count: 7638 (300)

Section B: What Variables are Associated with and Predictive of Medication Adherence in Adolescents and Young Adults with Chronic Liver Disease? An Empirical Study

Word Count: 7989 (614)

Overall Word Count: 15627 (914)

A thesis submitted in partial fulfilment of the requirements of

Canterbury Christ Church University for the degree of

Doctor of Clinical Psychology

May 2022

SALOMONS INSTITUTE FOR APPLIED PSYCHOLOGY

CANTERBURY CHRIST CHURCH UNIVERSITY

Acknowledgments

Thank you to the service users at this Young Adult Liver Service, without whom this project would not be possible.

Thank you also to my supervisors, Dr Jemma Day (Clinical Psychologist, Young Adult Liver Service) and Dr Fergal Jones (Salomons Centre for Applied Psychology, Canterbury Christ Church University), together with Dr Marianne Samyn (Consultant Hepatologist, Young Adult Liver Service). Your input and support have been invaluable.

Summary

Section A is a review of existing empirical research that has investigated variables associated with medication adherence in adolescents and young adults (9-25 years) with a chronic liver disease. Section B describes an empirical project using cross-sectional and longitudinal archival data from a young adult liver service (16-25 years), which investigated whether demographic and clinical variables, mood and illness perceptions were associated with and/or predictive of medication adherence in adolescents and young adults with a range of chronic liver disease diagnoses.

List of Contents

List of Tables

SECTION A:

SECTION B:

List of Figures

Section A: What Variables are Associated with Medication Adherence in Adolescents and Young Adults with Chronic Liver Disease? A Narrative Review

Word count: 7938

Abstract

Background and Objective: Adolescents and young adults have significantly poorer clinical outcomes than adults and children with chronic liver disease, thought attributable to greater difficulties adhering to medication during this period. The aim of this review was to synthesise literature on variables associated with non-adherence within this population.

Method: Four electronic databases were searched in November 2021 (with no date restriction), identifying ten studies meeting inclusion criteria. Designs and results were appraised, indicating mixed, but generally limited, levels of quality.

Results: This review identified 23 variables that have been investigated in terms of their relationships with adherence. Older age appeared associated with non-adherence, and potential relationships were apparent for other demographic, clinical and mood variables, which warrant further investigation.

Conclusion: Comparison between studies was difficult due to methodological differences and measurement variations. Applying results to health behaviour models was also challenging given limited theoretical references, mixed findings and lack of focus on certain variables. However, important clinical considerations and future research implications were identified that may contribute to improved outcomes in this vulnerable age group.

Keywords: Liver disease, liver transplant, adherence, adolescence, young adult

Introduction

Medication non-adherence significantly contributes to the poorer physical health outcomes experienced by adolescents and young adults (A&YA) compared to children and adults with chronic liver diseases (Dharnidharka et al., 2015; Ebel et al., 2017); it is the leading cause of organ failure and death post-transplant (Lurie et al., 2000). Diagnoses during childhood or adolescence may include autoimmune liver disease (AILD), biliary atresia, Wilson's disease, non-alcoholic fatty liver disease, metabolic conditions, and potential subsequent liver transplant. These conditions differ in both nature and cause to those typically diagnosed in adulthood when diagnoses are more likely associated with lifestyle factors such as alcohol use. Specific causes of many liver diseases in childhood remain unknown but are generally thought to be related to genetics (either inherited or mutations), environmental factors or other conditions including infections (D'Agata & Balistreri, 1999). Management of these lifelong liver conditions involve a multitude of requirements, which A&YAs may understandably find difficult to follow considering other social, physical and psychological competing priorities and challenges this period of life presents (Darcy & Samyn, 2017). Treatment often involves encouragement to modify lifestyle factors (dietary changes, no or minimal alcohol consumption, smoking, substance abuse or unsafe sexual practices) and adhere to medication. It is the latter, particularly to immunosuppressants such as steroids, that is most associated with risk of organ failure, transplant rejection and mortality (Burra et al., 2011) and is thus the topic for this review.

Adherence in the context of a chronic illness refers to the extent a service user follows recommended medical advice, including taking medication as prescribed (World Health Organisation [WHO], 2003). Despite replacing the original term "compliance" following WHO (2003) advice, the now preferred term of "adherence" may still unhelpfully be suggestive of a power imbalance between clinician and service user and blame lying with the latter if they do not follow medical instructions (Bissonnette, 2008). However, it is the selected term within

current literature and thus is used throughout this review to ensure consistency. From here, the term “adherence” refers to medication adherence specifically.

Brown and Bussell (2011) discuss the breadth and severity of difficulties non-adherence poses to both individuals and wider society, also highlighting the myriad of contributing factors at the service user, clinician and broader system level. Age is identified as a significant determining factor, with adolescence the most vulnerable period for non-adherence compared to adult and childhood across multiple chronic diseases (KyngAs et al., 2000).

A variety of psychological theories have been developed or applied to explain this human behaviour, including the Common-Sense Model of Self-Regulation (CSM; Leventhal et al., 1980, 1984) and Health Belief Model (HBM; Becker, 1974). Both models highlight the importance of cognitive representations or perceptions one makes about their illness and treatment, which in turn may impact the likelihood of taking action (in this case adhering to medication). However, they differ in their focus on other elements such as the role demographic, social and structural variables can have on shaping these individual perceptions (HBM) or how emotional factors (such as anxiety and depression) may also contribute to health behaviours (CSM).

Adolescence is the period of transition from childhood to adulthood and is generally accepted to start at puberty and end following the achievement of adult status. Definitions by age therefore vary based on biological (e.g. onset of pubertal development) and social (e.g. cultural expectations for financial and residential independence) factors (Goossens, 2006). More recently, Sawyer et al. (2018) suggested broadening the generally accepted range of 10-19 years into the mid-20s given the demonstration through theoretical and empirical research of the bespoke social, cognitive and psychological challenges and changes experienced within this period (Choudhury et al., 2006). For the purposes of this review, the focus will be on A&YAs

aged 9- 25 years (cf. Sawyer et al., 2018), although it is acknowledged that there is much heterogeneity within this range.

Suris et al. (2004) highlighted the challenges faced during and developmental characteristics associated with adolescence that might conflict with behaviours required for adherence. These include seeking independence from parents, not yet developed abstract thinking abilities, and subsequent difficulty in weighing up risk and long-term consequences. This may be exacerbated in individuals with chronic liver disease who can experience physical puberty later (Hogler et al., 2012), leading to the potential for brain changes associated with maturity to be delayed. This is supported by Kaller et al. (2013) who found children post liver transplant performed significantly poorer than healthy controls across multiple cognitive domains. A liver transplant during adolescence can impact a broad range of areas, including school, work, sports, social activities, relationships, sex and family (Burra, 2012). Furthermore, side effects of certain medications such as weight gain, and requirements such as no/limited alcohol, may be particularly challenging during this period; known to be a time of increased body image awareness, together with greater peer influences (Darcy & Samyn, 2017). It therefore appears understandable that an adolescent faced with lifelong daily medication requirements, may struggle to adhere. The complexities of managing a liver disease during this particularly vulnerable period of physical and psychosocial growth may also contribute to the higher rates of depression and anxiety in this group (Hames et al., 2016).

The role adolescence plays in laying foundations for lifelong health-related behaviours has been recognised (Resnick et al., 2012). Despite this, research into interventions to improve adherence in this population is limited and has not yielded significant improvements (Burra et al., 2011), perhaps attributable to the lack of understanding of variables associated with the behaviour during this period. Furthermore, research into A&YAs with other chronic diseases is

not necessarily transferrable, given some literature suggests the impact of different conditions varies in type and severity (Pinquart & Shen, 2011).

Within hepatology, A&YAs who have undergone a liver transplant appear to have attracted more research attention than those with other liver diseases. This may be due to different treatment centres for transplant recipients in some countries (the US, for example) or the requirement for daily immunosuppressant medication to avoid organ rejection and potential death (Molmenti et al., 1999). Whilst a liver transplant may be a life-saving option for those with acute liver failure or end-stage disease (Sharif & Millar, 2009), it is not a cure in totality and results in chronic life-long dependence on medical care (Shemesh et al., 2004). One-year patient survival post elective transplantation in childhood is approximately 90% whilst longer-term (10-15 years) is 69-83% (Hong et al., 2009). The benefit of further research into those with a broader range of liver conditions or pre-transplant is apparent. For example, AILD generally responds well to immunosuppressants, yet lifelong treatment is typical (Hames et al., 2021) and failure to adhere can result in liver failure and subsequent transplantation (Di Giorgio et al., 2020).

Despite the well-documented poorer adherence rates and associated physical health outcomes in A&YAs with chronic liver disease (non-adherence being four times higher in adolescents than adults following liver transplant, for example; Shemesh, 2004), there have been limited reviews on the underlying associated variables. Literature reviews to date have either, included multiple chronic diseases (Hanghøj & Boisen, 2014; Pai & Ostendorf, 2011), only those with a liver transplant (Burra et al., 2011) or those with other transplant types in addition to liver (Laederach-Hofmann & Bunzel, 2000), with the latter two also looking at both children and adults and not the adolescent period specifically.

Review Aims

The purpose of this paper is therefore to narratively review current empirical literature that addresses the question of what variables are associated with medication adherence in A&YAs with chronic liver disease. A meta-analysis and pooling of effect sizes was not possible considering the breadth of designs, variables and measurement tools. This review will include all liver diseases and those pre- or post-transplant, supported by findings that service users with different liver conditions reported similar levels of difficulties and concern (Hames et al., 2016).

It is hoped an improved understanding of the relationship between adherence and other demographic, psychological, clinical and social factors will support health services in identifying new or refining existing interventions to improve adherence (and subsequent physical health outcomes) for service users and identify target areas for future research.

Method

Literature Search

Four electronic databases (Medline, CINAHL, Cochrane and PsychINFO; selected to span the breadth of professions working with this population) were searched in November 2021, systematically combining the search terms detailed in Table 1.

Table 1

Terms Used in Systematic Search

Category	Search Terms (operator)
Adherence	adheren* (OR) nonadheren* (OR) non-adheren* (OR) complian* (OR) noncomplian* (OR) non-complian* (AND)
Adolescence	adolesc* (OR) young people (OR) young adults (OR) children (OR) paediatric (OR) pediatric (AND)
Liver disease	liver disease (OR) liver transplant (OR) AILD (OR) autoimmune liver disease (OR) auto-immune liver disease (OR) biliary atresia (OR) wilson* disease (OR) non-alcohol fatty liver disease

Whilst the selected focus was on medication adherence specifically, a search term to specify "medication" was not included. This was in case relevant literature looked at this as part of a broader examination of adherence, and hence didn't include this term in the title or abstract. No restraint on type of liver disease was applied, to ensure those with or without transplants were included (given the reduced research focused on the latter). Abstracts and full articles were reviewed to identify those not meeting inclusion criteria. Reference lists of identified papers were hand-searched for additional relevant publications.

Inclusion Criteria

Only papers in English from peer-reviewed journals were included. Empirical research investigating factors associated with medication adherence in A&YAs (9-25 years) were included, irrespective of study design. It is acknowledged this is a broad range within which homogeneity of adherence behaviours is not anticipated, thus sample age is considered within

the review. Given the limited literature pool, there was no restriction on publication year or how adherence was assessed, therefore papers were included that:

- statistically investigated associations between (measured) adherence levels with other variables;
- statistically tested whether an intervention was associated with a change in adherence; or
- qualitatively explored individuals' experiences or perceptions of factors associated with adherence.

Studies including a broader range of either participants (e.g. with other disease/transplant types or a wider age range) or aspects of adherence were only included if results regarding medication adherence for those with liver disease within the specified age range were separated.

Assessment of Study Quality

The methodological quality of studies was evaluated, which included an assessment against the best fit Joanna Briggs Critical Appraisal Tool (Joanna Briggs Institute [JBI], 2020). These were favoured over other tools (such as the Critical Appraisal Skills Programme [CASP], 2018) due to inclusion of an option for every design in this review.

Results

Overview of Studies and Their Quality

Figure 1 summarises the search process, which resulted in ten papers identified for inclusion. Details on sample characteristics, methodology and data analyses for each were summarised in Table 2.

Figure 1

Flow-chart to Summarise the Search Process

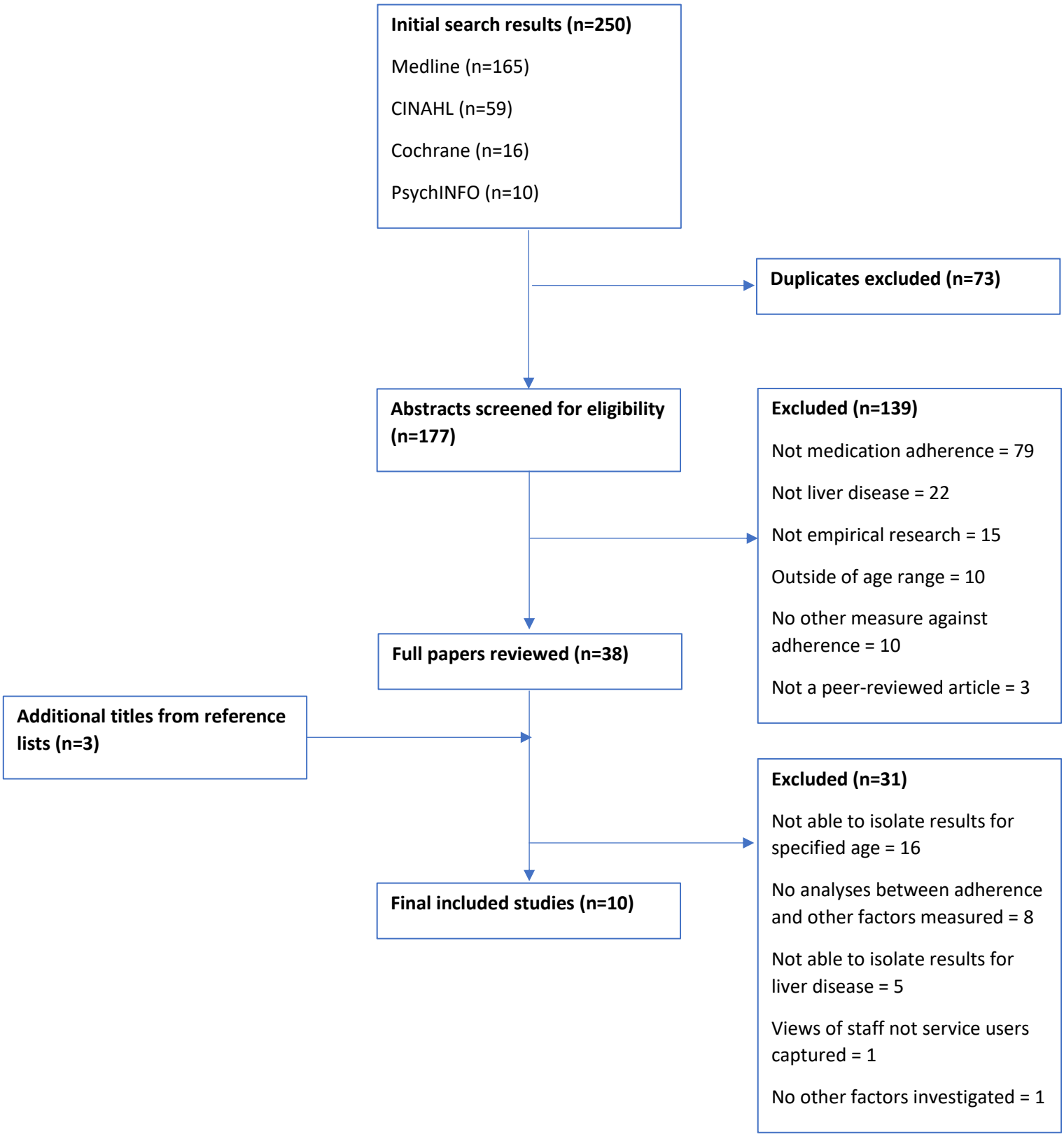


Table 2

Summary of Studies Included in this Review

Authors (date) - Country	Research Design, no. Participants (no. included in this review if different) and Demographic Characteristics, if Provided	Diagnoses (sample age range in years, mean or median if given)	Variables Investigated in Terms of their Relationship with Adherence	Measurement(s) of Medication Adherence and Clinical Outcomes (if included)	Analyses Type (between adherence and other variables only)
Annunziato et al. (2018) - US	Prospective, multi-site, cohort design, n=214 (service user-parent dyads). Sex: Male = 47.4%, female = 52.6%. Race: Missing = 5.2%, Asian = 5.2%, Black or African American = 13.1%, White or Caucasian = 68.1%, Other = 8.5% Service users and parents completed questionnaires upon enrolment, after which medical variables and clinical outcomes were followed over two years.	Liver transplant service users from five paediatric liver transplant centres (9-17 years). Participants were identified from a larger cohort of 400 children aged 1-17 years (the Medication Adherence in Children Who Had a Liver Transplant Study; MALT, Shemesh et al., 2017).	Self-management – Shortened version of the Responsibility and Familiarity with Illness Survey (REFILS, Annunziato et al., 2011) - service user, parent and service user/parent discrepancy scores (at enrolment).	Adherence – Medication Level Variability Index (MLVI); standard deviation (SD) of at least three consecutive tacrolimus blood levels taken quarterly within the two year follow up (SD>2.5 = non-adherent). Clinical outcomes – biopsy-defined rejection (based on two independent pathology readings) within the two year follow up.	Pearson's correlations Chi-squared tests Kruskal Wallis one-way ANOVA
Berquist et al. (2006) - US	Retrospective, dual-site, cohort design, n=97. Chart review over 15 years to extract demographic variables and identify if service users were non-adherent and/or experienced adverse clinical outcomes at any point during this period.	Liver transplant recipients (minimum >1 year post transplant) who were monitored by the team at some point during the ages of 12-21 years.	Demographics - gender, single parent household, socioeconomic status (lower = insured by Medicaid or Comprehensive Community Services [CCS]). Disease variables - immunosuppressive regimen (cyclosporine vs tacrolimus), age at transplant.	Adherence – documentation of reported non-adherence by either the service user, parent or clinician (recorded within medical records) at least once within the review period. (any mention = non-adherent). Clinical outcomes – documentation of biopsy proven rejection (based on laboratory records), re-transplantation or death, within review period.	Chi-square or Fisher exact probability test Unpaired Student's t-test

Authors (date) - Country	Research Design, no. Participants (no. included in this review if different) and Demographic Characteristics, if Provided	Diagnoses (sample age range in years, mean or median if given)	Variables Investigated in Terms of their Relationship with Adherence	Measurement(s) of Medication Adherence and Clinical Outcomes (if included)	Analyses Type (between adherence and other variables only)
Berquist et al. (2008) - US	Retrospective, multi-site (one main plus ten outreach centres), cross-sectional design, n=111. Gender: Male = 47.7%, female = 52.3%, Race: Asian = 16.4%, Black = 4.9%, Caucasian = 50.8%, Hispanic = 1.6%, Pacific Islander = 3.3%. Review of medical records over one year.	Liver transplant recipients (>6 months post-transplant) (12-21 years, mean=15.4).	Demographics - age (categorised into pre-adolescent; 12-13 years, mid-adolescent; 14-17 years, late-adolescent; 18-21 years), gender, socioeconomic status (lower = insured by Medicaid or CCS), single parent status. Disease / clinic variables - clinic site, time since transplant.	Adherence – 1) documentation of service user admission of non-adherence within medical records (any mention = non-adherent), 2) not attending any clinic visit or laboratory test in 2005. Clinical outcomes – biopsy proven rejection (>1 year post transplant), graft loss and death within review period.	Chi-square or Fisher exact probability test Unpaired Student's t-test Univariate and multivariate logistic regression and Wald Chi-square test
Bilhartz et al. (2015) - US	Retrospective, single-site, cross-sectional design, n=48 (plus 37 parents). Gender: Male = 37.5%, Female = 62.5% Review of medical records to extract Assessment of Responsibility (AoR) scores, and demographic and clinical variables from the six months following survey completion. Assessed psychometrics and concurrent validity of the new AoR measure. Investigated relationship between subsequent component scores (after Principal Component Analysis; PCA) with adherence and other variables.	Liver transplant recipients (>1 year post transplant), (11.4-20.1 years, mean=15.8).	AoR – bespoke measure embedded within a Transition Readiness Survey (TRS) completed biannually by service users (and parents/guardians where available) as part of an ongoing quality improvement project to guide transition planning. Demographics - gender, age (when completing AoR). Disease variables - age at transplant, time since transplant.	Adherence – immunosuppressant variability (SD of tacrolimus blood levels) taken from medical records within the six months following TRS/AoR completion. (SD>2 = non-adherent) Clinical outcomes – number of days hospitalised for rejection and episodes of biopsy-proven rejection during the study period.	Mann-Whitney or Chi-square test Spearman's correlations

Authors (date) - Country	Research Design, no. Participants (no. included in this review if different) and Demographic Characteristics, if Provided	Diagnoses (sample age range in years, mean or median if given)	Variables Investigated in Terms of their Relationship with Adherence	Measurement(s) of Medication Adherence and Clinical Outcomes (if included)	Analyses Type (between adherence and other variables only)
Fredericks et al. (2008) - US	Prospective (with retrospective collection of demographic/disease data), cross-sectional, single-site design, n= 25 (plus 25 parents/guardians). Gender: Male = 32%, female = 68%. Race: White = 72%, African American = 28% Service users and parents/guardians completed adherence and Health Related Quality of Life (HRQOL) questionnaires. Demographic, medical and adherence data were obtained from a demographic survey and medical records.	Liver transplant recipients (not actively being treated for post-transplant lymphoproliferative disorder or other malignancy) (12-17.9 years, mean = 15.1).	HRQOL – using two questionnaires, 1) The Pediatric Quality of Life Inventory Core Scales (PedsQL4.0, Varni et al., 2001) – completed by service user and parent/guardian, 2) Child Health Questionnaire parent (CHQ-PF50) and child/service user (CHQ-CF87) (Landgraf et al., 1999).	Adherence – 1) clinician-conducted interviews using the Medication Adherence Measure (MAM; Zelikovsky & Schast, 2008) (self-report of missing/taking late >10% medication in previous seven days = non-adherent) 2) immunosuppressant variability (SD of consecutive tacrolimus blood levels taken from year preceding study participation, SD>2 = non-adherent), Clinical outcomes – frequency of hospital admissions, liver biopsies, episodes of rejection (taken from medical records in the year prior to survey completion).	Pearson's correlations Two sample t-tests

Authors (date) - Country	Research Design, no. Participants (no. included in this review if different) and Demographic Characteristics, if Provided	Diagnoses (sample age range in years, mean or median if given)	Variables Investigated in Terms of their Relationship with Adherence	Measurement(s) of Medication Adherence and Clinical Outcomes (if included)	Analyses Type (between adherence and other variables only)
Fredericks et al. (2010) - US	Retrospective, cross-sectional, single-site design, n=71 (plus 58 parents). Gender: Male = 44%, Female = 56%. Ethnicity: 37% belonged to a minority group. Review of medical records identified service users who had completed the TRS since October 2007. Component Factor Analysis (CFA) and PCA conducted on TRS scores prior to analyses between the four domains and demographic variables with adherence and clinical outcomes.	Liver transplant recipients (>6 months post-transplant), (11-20 years).	Demographics - age. Transition readiness – bespoke TRS with service user (A/YA; adolescent/young adult) and P; parent/guardian) versions. Survey covered four domains: self-management skills, regimen knowledge, demonstrated skills, psychosocial adjustment. The self-management domain also included a scale to assess AoR in the two weeks preceding the survey. Medication knowledge – service users asked to verbally list medications, their doses, timing and function.	Adherence – 1) Immunosuppressant variability (SD of consecutive tacrolimus or cyclosporine taken from medical records for the previous year; tacrolimus SD>2 and cyclosporine SD>30 = non-adherent) 2) proportion of immunosuppressant blood levels outside of specified target range (>50% blood levels outside target range = non-adherent) Clinical outcomes – liver blood tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT] and bilirubin), graft function, frequency of hospital admissions, liver biopsies and episodes of rejection taken from medical records for the year prior to study participation.	Pearson's or Spearman's correlations

Authors (date) - Country	Research Design, no. Participants (no. included in this review if different) and Demographic Characteristics, if Provided	Diagnoses (sample age range in years, mean or median if given)	Variables Investigated in Terms of their Relationship with Adherence	Measurement(s) of Medication Adherence and Clinical Outcomes (if included)	Analyses Type (between adherence and other variables only)
Hames et al. (2021) - UK	Retrospective, cross-sectional, single-site design, n=68. Gender: Male = 45.6%, Female = 54.4%. Service users completed an online electronic screening questionnaire during routine clinic appointments as part of the Integrating Mental and Physical Healthcare: Research, Training and Services (IMPARTS). Demographic and clinical variables were captured from medical records from the appointment coinciding with questionnaire completion.	Auto-immune Liver Disease (AILD), (16-25 years, median = 17.9).	Demographics - age, gender, employment status. Disease variables - age at diagnosis, disease duration, number of medications, medication (prednisone) dose. Depression – Patient Health Questionnaire (PHQ2; Gilbody et al., 2007 and PHQ9; Kroenke & Spitzer, 2002). Anxiety – Generalised Anxiety Disorder questionnaire (GAD2; Kroenke et al., 2007 and GAD7; Lowe et al., 2008). Distress – bespoke distress/worry thermometer. Illness perceptions - Brief Illness Perceptions Questionnaire (BIPQ; Broadbent et al., 2006)	Adherence - service user self-report using a bespoke, adherence questionnaire (rating of <80% to the question “In general, what percentage of the time do you take your medication” = non-adherent). Clinical outcomes – liver function tests (AST, ALT, bilirubin, albumin, international normalised ratio; and immunoglobin G levels).	Student t-test or Mann-Whitney *U* test Chi-squared test Spearman’s correlations

Authors (date) - Country	Research Design, no. Participants (no. included in this review if different) and Demographic Characteristics, if Provided	Diagnoses (sample age range in years, mean or median if given)	Variables Investigated in Terms of their Relationship with Adherence	Measurement(s) of Medication Adherence and Clinical Outcomes (if included)	Analyses Type (between adherence and other variables only)
Jerson et al. (2013) - US	Two-group, mixed-method, quasi-experimental design, n=9 (experimental group), n=13 (control group). Experimental group gender: Male = 44.4%, female = 55.5%. Race and ethnicity: Black/African American = 33.3%, Caucasian = 33.3%, Hispanic = 11.1%, Asian American = 11.1%, Other = 11.1%. Participants were assigned to either a "mentor now" (experimental) or "mentor later" (control) group (allocated using sign-up date), to examine whether participation as a peer-mentor improved adherence and psychosocial outcomes (together with the acceptability and feasibility of this intervention).	Diagnosed with liver disease or who had had a liver transplant at least six months prior (16-23 years in experimental group, 16-29 years in control group). *Note that although the inclusion criteria of 16-30 years was outside the specified age range for this review, this study was included as those in the experimental group were within the age range.*	Participation as a peer mentor (including attending a half day workshop and then allocation to a mentee aged 6-16 years, supported by a mentor facilitator).	Adherence – immunosuppressant variability (SD of tacrolimus). *Note that at baseline and three months post intervention additional measures were administered (but not analysed in terms of their relationship with adherence) using the Developmentally Based Healthcare Management Skills Checklist (Annunziato et al., 2011) and Short Form 36 (SF-36) health survey (Ware., 1993), assessing HRQOL.*	Repeated measures ANOVA (between groups) Paired sample t-tests (within groups)
Jakubowska-Winecka and Biernecka (2018) - Poland	Cross-sectional study with four groups, total n=197 (liver transplant group n= 44). Sex in liver transplant group: Male = 43.2%, female = 56.%. Participants completed anonymous psychological tests either during a stay at hospital or visit to an outpatient clinic.	Four groups: 1) liver transplant recipients, 2) kidney transplant recipients, 3) diabetes diagnosis, 4) inflammatory bowel disease diagnosis. (Total group age range = 2-18 years, median = 14.71. Liver group age range = 12-18 years, median = 14.43).	Parental Attitudes scale (PAS; Plopa, 2008; as cited in Jakubowska-Winecka and Biernecka, 2018), identifying five types of parental attitudes (accepting, overly demanding, autonomous, inconsistent, overly protective).	Adherence - Morisky Medication Adherence Scale (MMAS-8; Morisky et al., 2008).	Spearman's correlations

Authors (date) - Country	Research Design, no. Participants (no. included in this review if different) and Demographic Characteristics, if Provided	Diagnoses (sample age range in years, mean or median if given)	Variables Investigated in Terms of their Relationship with Adherence	Measurement(s) of Medication Adherence and Clinical Outcomes (if included)	Analyses Type (between adherence and other variables only)
Wright et al. (2015) - UK	Qualitative, using semi-structured interviews, n=13.	Liver transplant recipients (>5 years post-transplant), post transfer to adult services or due to transfer within 12 months (15.2-25.1 years, mean=20.6).	n/a - interviewee led interviews focusing on the participant's experiences of growing up and living with a liver transplant (with a bespoke interview schedule to guide question topics). Themes identified included triggers of difference, striving to be normal and taking back control.	Subjective description within interviews.	Interpretive phenomenological analysis.

Study Designs

Five studies involved a retrospective (one cohort, four cross-sectional), three a prospective (one cohort, two cross-sectional), one a qualitative and one a quasi-experimental design. A strength of the latter approach used by Jerson et al. (2013) was the ability to control variables more rigorously, whilst a limitation of cross-sectional designs was the lack of causal conclusions that can be drawn.

Participants, Recruitment and Data Collection

Whilst using retrospective routine clinical data has the advantages of being less time-consuming and the potential for a larger data set, the design may introduce bias and confounding variables, including clinician or environmental variability. Only Bilhartz et al. (2015) identified these potential confounding variables as an explicit limitation. Use of retrospective data also resulted in variation in time between appointments (for example, Berquist et al., 2006) together with reliance on staff to extract information consistently.

As per Table 2, there appears to have been a reasonable representation of sex and gender, and race and ethnicity, where this was reported. However, the latter was not detailed in full for five studies and so generalisability cannot be assumed. This appears a particular limitation considering wider evidence for systemic health outcome variations for different racial groups (Nazroo, 2003).

A common limitation was recruitment from only one site (Bilhartz et al., 2015; Fredericks et al., 2008; 2010; Hames et al., 2021), which may also have limited generalisability. This was a strength of Annunziato et al. (2018), likely possible due to the use of cohort data from five paediatric transplant centres. However, unlike Berquist et al. (2008) they did not assess whether site difference was associated with adherence.

Geographical generalisability was also limited given all but three studies recruited from the US. Across these, it was not possible to rule out use of data from the same participants. Specifically, one of the five medical centres Annunziato et al. (2018) used for recruitment was the same as Jerson et al. (2013). Berquist et al's (2006, 2008) studies also recruited from the same medical centre, as did Bilhartz et al. (2015) with Fredericks et al. (2008, 2010). Whilst dates specified for chart reviews or data collection were generally distinct, they may still plausibly have included some of the same participants, considering their inclusion criteria. Independence between studies can therefore not be assumed.

A general issue across all studies was the lack of power calculations. Whilst sample sizes varied, they were comparatively small for Bilhartz et al. (2015), Fredericks et al. (2008) and Jerson et al. (2013) raising the possibility of Type II errors. Only the latter recognised themselves this may have limited the power to identify significant yet small effects. However, Fredericks et al. (2008) and Jerson et al. (2013) did recognise other implications, such as the latter suggesting a larger sample would have allowed methodological improvements. The large sample in Annunziato et al's (2018) study will have provided greater power, although they suggested this may explain why some of their significant correlations were for relatively small effects.

Not all studies included potential reasons for non-participation and some rates appeared high. This may have introduced potential bias to the sample by excluding those not currently attending clinic (and potentially therefore not taking medication), for example. Fredericks et al. (2008) stated only 66.7% of eligible service users approached agreed to participate, although they did detail reasons for this (time or transport constraints, lack of interest and other children present), which was a strength. Similarly, Bilhartz et al. (2015) assessed demographic differences between participants vs non-participants (none of which were statistically significant) and looked into reasons for non-participation.

Hames et al. (2021) and Jerson et al. (2013) were the only two studies who did not limit their sample to transplant recipients. This highlights the need to include participants with a broader range of chronic liver diagnoses and/or those pre-transplant. Inclusion criteria for studies involving liver transplant recipients varied from >6 months to >5 years post-transplant, with three papers (Annunziato et al., 2018; Fredericks et al., 2008; Jakubowska-Winecka & Biernecka, 2018) not specifying, so it is difficult to establish how comparable the samples were.

Statistical Analyses

Type of analyses varied with quantitative studies typically using one or a combination of correlations, chi-square tests, t-tests and ANOVAs as appropriate, with only one (Berquist et al., 2008) using logistic regression.

Most studies did not control for multiple comparisons, which may have resulted in spurious results and increased likelihood of Type I errors. Bilhartz et al. (2015) did, however, justify their lack of correction application given their exploratory focus and prioritisation of identifying areas for future research over the potential for false positives.

Measurement of Adherence

Standard deviation (SD) of immunosuppressant levels (usually tacrolimus, with the addition of cyclosporine by Fredericks et al., 2010) in blood tests was used to measure medication adherence in five papers (Annunziato et al., 2018; Bilhartz et al., 2015; Fredericks et al., 2008; Fredericks et al., 2010; Jerson et al., 2013). All justified their approach by the stronger relationship this has with transplant rejection compared to service user, parent or clinician reports, as demonstrated by Shemesh (2004), for example. A further benefit highlighted by Bilhartz et al. (2015) was that this measure can be calculated using blood tests taken routinely in clinic. However, there are limitations, such as the lack of consideration for

individual drug metabolism and potential variations in confounding factors such as timing of blood tests and other medication.

The threshold for non-adherence (in categorical analyses) varied from either a tacrolimus SD >2 (Bilhartz et al., 2015; Fredericks et al., 2008; Fredericks et al., 2010) to >2.5 (Annunziato et al., 2018; Jerson et al., 2013). All quoted literature to justify their thresholds, such as the recommendation of two by Venkat et al. (2008). It should also be noted that both the intervals and range from which blood tests were taken and subsequently used to calculate SD differed. A strength of Bilhartz et al's (2015) and Fredericks et al's (2010) designs was the additional adherence measure of percentage of blood levels outside the service user's individual target range.

Fredericks et al. (2008) also used an (unvalidated) tool as part of a semi-structured interview to capture self-report data, with missing/taking late >10% medications indicative of non-adherence. Two papers used only self-report data for their measure of medication adherence. Hames et al. (2021) used a non-validated measure developed by clinicians, which also included questions on punctuality and routine. Jakubowska-Winecka and Biernecka (2018) provided little information on the validity and reliability of their tool. Whilst self-report measures are common and comparatively cheap, it is thought service users may under-report non-adherence (Vik et al., 2004).

Two further papers did not use an objective measure of adherence. Berquist et al. (2006; 2008) relied on documentation (by service user, and in 2006 also by parent/guardian or clinician) of non-adherence within patient records over a specified period. The authors recognised this introduced potential bias, either due to non-adherence not being identified and/or recorded in the first instance or through a reviewer missing a record. They also recognised this categorical measure reduced the possibility of assessing the degree of non-

adherence, although they suggested this would have a limited impact on the accuracy of results considering previous findings that even small deviations from prescribed medication regimens result in poorer clinical outcomes in other populations (De Geest et al., 1998). A strength of most other studies was their inclusion of both categorical and continuous measures of adherence (e.g. Hames et al., 2021).

Where papers quantified prevalence of adherence within their sample, these are detailed in Table 3 to provide context to subsequent findings and demonstrate the difficulty variation in measurement methods and thresholds pose when comparing results. This is supported by the finding from Fredericks et al's (2008) multi-method approach that none of their adherence measures were associated with each other, suggesting they evaluated different constructs within adherence behaviour.

Table 3

Percentage of Participants Found to be Non-adherent, by Study

Authors (date)	Percentage of Participants Classified as Non-adherent
Annunziato et al. (2018)	Not included
Berquist et al. (2006)	38.1% (56.8% of whom were identified by self-report and 43.2% by parent or clinician report)
Berquist et al. (2008)	45% (48% of whom were identified by self-report)
Bilhartz et al. (2015)	33.3%
Fredericks et al. (2008)	40% from self-reports during clinician conducted interview, 32% from tacrolimus standard deviation (SD)
Fredericks et al. (2010)	31% from tacrolimus or cyclosporine SD, 26.8% from immunosuppressant blood tests outside of target range
Hames et al. (2021)	17%. In addition, 44% reported taking medications more frequently in the weeks preceding a clinic appointment, 31% had no routine for medication taking, 63% reported sometimes forgetting medication, 7% stated they choose not to take medication.
Jerson et al. (2013)	Not included
Jakubowska-Winecka and Biernecka (2018)	30-50% (note that overall adherence prevalence was not separated so this figure was for an age and disease range broader than this review's specified criteria). However, 11.4% of liver transplant recipients reported taking medication irregularly, compared to 5.8% in the kidney transplant, 15.7% in the diabetes and 16% in the inflammatory bowel disease groups).
Wright et al. (2015)	Not measured (qualitative interviews)

Assessment against Joanna Briggs Criteria (JBI, 2020)

Tables 4-7 summarise JBI assessment findings, with full justification included in Appendix A. Note that where designs were mixed, the best fit checklist was selected.

Table 4

Assessment Against Joanna Briggs Criteria (2020) for Analytical Cross-Sectional Designs

Question	Berquist et al. (2008)	Bilhartz et al. (2015)	Fredericks et al. (2008)	Fredericks et al. (2010)	Hames et al. (2021)	Jakubowska-Winecka & Biernecka (2018)
Were the criteria for inclusion in the sample clearly defined?	Yes	Yes	Yes	Yes	Yes	Yes
Were the study subjects and the setting described in detail?	Yes	Partly	Yes	No	Yes	No
Was the exposure measured in a valid and reliable way?	Yes	Partly	Yes	Partly	Yes	Partly
Were objective, standard criteria used for measurement of the condition?	No	Yes	Yes	Yes	Partly	No
Were confounding factors identified?	No	Yes	No	No	No	No
Were strategies to deal with confounding factors stated?	No	No	No	No	No	No
Were the outcomes measured in a valid and reliable way?	No	Yes	Yes	Yes	Partly	No
Was appropriate statistical analysis used?	Yes	Yes	Partly	Yes	Yes	Partly

Table 5

Assessment Against Joanna Briggs Criteria (2020) for Cohort Designs

Question	Annunziato et al. (2018)	Berquist et al. (2006)
Were the two groups similar and recruited from the same population?	n/a	n/a
Were the exposures measured similarly to assign people to both exposed and unexposed groups?	n/a	n/a
Was the exposure measured in a valid and reliable way?	Yes	Yes
Were confounding factors identified?	No	No
Were strategies to deal with confounding factors stated?	No	No
Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	n/a	n/a
Were the outcomes measured in a valid and reliable way?	Yes	Partly
Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Partly	Yes
Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Partly	Partly
Were strategies to address incomplete follow up utilized?	No	n/a
Was appropriate statistical analysis used?	Yes	Yes

Table 6

Assessment Against Joanna Briggs Criteria (2020) for Quasi-experimental Designs

Question	Jerson et al. (2013)
Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	Yes
Were the participants included in any comparisons similar?	Yes
Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Partly
Was there a control group?	Yes
Were there multiple measurements of the outcome both pre and post the intervention/exposure?	Yes
Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	No
Were the outcomes of participants included in any comparisons measured in the same way?	Yes
Were outcomes measured in a reliable way?	Partly
Was appropriate statistical analysis used?	Partly

Table 7

Assessment Against Joanna Briggs Criteria (2020) for Qualitative Designs

Question	Wright et al. (2015)
Is there congruity between the stated philosophical perspective and the research methodology?	Partly
Is there congruity between the research methodology and the research question or objectives?	Yes
Is there congruity between the research methodology and the methods used to collect data?	Yes
Is there congruity between the research methodology and the representation and analysis of data?	Yes
Is there congruity between the research methodology and the interpretation of results?	Yes
Is there a statement locating the researcher culturally or theoretically?	No
Is the influence of the researcher on the research, and vice-versa, addressed?	Yes
Are participants, and their voices, adequately represented?	Yes
Is the research ethical according to current criteria or, for recent studies, and is there evidence of ethical approval by an appropriate body?	Yes
Do the conclusions drawn in the research report flow from the analysis, or interpretation, of the data?	Yes

Reviews indicated mixed quality, although the qualitative and quasi-experimental studies appeared more robust overall in terms of their designs. Discussion on quality of designs is embedded throughout the subsequent sections, to provide context to interpretation of results.

Detailed Results by Theme

This review identified 23 variables that were investigated in terms of their relationship with adherence using quantitative or qualitative analyses. These were grouped into five themes (Demographics, Disease and Other Clinical Variables, Personal and Parental Factors, Mental Health and Illness Perceptions, and Social Factors), discussed in separate sections below. A table at the start of each theme indicates whether relationships were identified. Where statistical tests were carried out, only those with significant results were included in the table, with full details in subsequent text. Methodological considerations that support interpretation or the ability to compare findings across studies are incorporated into each theme discussion.

Demographics

Table 8 summarises findings for the six variables grouped under the Demographics theme.

Table 8

Summary of Demographic Variables Found to be/not be Associated with Medication Non-Adherence

Authors (date) n = Sample Size	Race	Sex and Gender	Age	Socio-economic Status	Single-parent or Complex Psychosocial Circumstance	Employment Status
Annunziato et al. (2018) n=214	-	-	Older*	-	-	-
Berquist et al. (2006) n=97	-	NS	Older	Lower*	NS	-
Berquist et al. (2008) n=111	-	NS	Older*	NS	Single parent*	-
Bilhartz et al. (2015) n=48	-	NS	Older*	-	-	-
Fredericks et al. (2008) n=25	NS	NS	NS	-	-	-
Fredericks et al. (2010) n=71	-	-	Older*	-	-	-
Hames et al. (2021) n=68	-	Male* (intentional only)	Older*	-	Complex psychosocial circumstance*	NS
Jerson et al. (2013) n=9	-	-	-	-	-	-
Jakubowska-Winecka and Biernecka (2018) n=44	-	-	-	-	-	-
Wright et al. (2015) n=13	-	-	-	-	-	-

Note. * = Statistically significant finding (typically $p<.05$), category in brackets is associated with higher levels of non-adherence. NS = Non-significant result. - = Not assessed in this study.

Race. Only Fredericks et al. (2008) investigated the association between race (reported by service users) and adherence, finding no statistically significant relationship. It may have been the small sample size and limited diversity (n=25, from only one transplant

site) that meant they lacked sufficient power to detect an effect. A limitation of other studies was their lack of consideration of race or ethnicity; whilst Annunziato et al. (2018) did include ethnicity as a variable, they investigated its association with self-management and not adherence (finding no significant relationship). The lack of clarity surrounding the potential contribution race, ethnicity and/or culture may play in adherence behaviours creates an opportunity for future research, with the need for caution in the meantime if attempting to generalise existing findings to broader populations.

Sex and Gender. Whilst Berquist et al. (2006) found a greater proportion of female service users in their non-adherent group (representing 62.2%), this was not statistically significant. Furthermore, in Berquist et al's (2008) study, female service users represented only 54% of the non-adherent group (again non-significant) and logistic regression analyses demonstrated gender was not predictive of adherence. Bilhartz et al. (2015), Fredericks et al. (2008) and Hames et al. (2021) also found no significant relationship between gender or sex and overall adherence, although the latter identified intentional non-adherence was more prevalent in male service users (who also reported less worry, anxiety and emotional impact of their diagnosis).

Overall, there is no compelling evidence from this review for a gender or sex difference in adherence within this population.

Age. Despite different measures of adherence used, older service users were statistically less likely to be adherent in five of the six studies who investigated this variable (Annunziato et al., 2018; Berquist et al., 2008; Bilhartz et al., 2015; Fredericks et al., 2010; Hames et al., 2021), with the sixth (Berquist et al., 2006) finding most of their non-adherent group were greater than 18 years (approx. 55%), but not specifying if this was statistically significant. Fredericks et al. (2010) found these correlations were significant with most but

not all (SD of tacrolimus) of their adherence measures. However, their categorical analyses did find significant differences between those aged < and >16 years on all measures. Berquist et al. (2008) was the only study to include regression analyses; a strength that crucially highlighted how the risk of non-adherence increased at a rate of 26% for every additional year of age.

Reasons behind the significance of age are explored in most studies; it seems likely to be a complex relationship and multi-faceted interaction given the significant associations also found between age and other variables. For example, age was positively correlated with greater perceived responsibility and self-management (Bilhartz et al., 2015, Fredericks et al., 2010) and Hames et al. (2021) found older service users were more worried, anxious and rated a greater level of concern and emotional impact of their condition.

Socioeconomic Status, Family Circumstances and Employment. Berquist et al. (2006; 2008) found service users with a lower socioeconomic status were less likely to be adherent, although this was only statistically significant in their 2006 study. They also found those from single-parent households less likely to adhere, although only statistically significantly so in 2008; 40% of their non-adherent group were from single-parent homes compared to 18% in the adherent group. Despite this, single-parent homes were not predictive of non-adherence using logistic regression (Berquist et al., 2008). The difference between their study findings may be attributable to the reliance on reports from only service user in 2008, but also by parent/guardian or clinician in 2006.

Hames et al's (2021) clinical team identified eight service users requiring additional professional support because of complex psychosocial circumstances (including domestic abuse and strained family relationships). This group, albeit small, were statistically significantly less likely to be adherent than the rest of the sample. They also identified no

difference in employment status between adherent vs non-adherent groups, although no other study investigated this variable to validate the finding.

Whilst comparison across studies is difficult considering different measures used, there may be elements of an A&YA's home environment that are associated with adherence, which would benefit from future research.

Disease and Other Clinical Variables

Table 9 summarises findings for the four variables grouped under the Disease and Other Clinical Variables theme.

Table 9

Summary of Disease and Other Clinical Variables Found to be/not be Associated with Medication Non-Adherence

Authors (date) n = Sample Size	Clinic Type/Site	Age at Transplant or Diagnosis	Time Since Transplantation or Diagnosis	Immunosuppressive Regimen
Annunziato et al. (2018) n=214	-	-	-	-
Berquist et al. (2006) n=97	-	Older (at transplant)*	-	NS (cyclosporine vs tacrolimus)
Berquist et al. (2008) n=111	NS		Longer (since transplant)*	-
Bilhartz et al. (2015) n=48	-	NS (at transplant)	NS (since transplant)	-
Fredericks et al. (2008) n=25	-	-	-	-
Fredericks et al. (2010) n=71	-	-	-	-
Hames et al. (2021) n=68	-	NS (at diagnosis)	NS (disease duration)	NS (number of medications and dose of prednisone)
Jerson et al. (2013) n=9	-	-	-	-
Jakubowska-Winecka and Biernecka (2018) n=44	-	-	-	-
Wright et al. (2015) n=13	-	-	-	-

Note. * = Statistically significant finding (typically $p<.05$), category in brackets is associated with higher levels of non-adherence. NS = Non-significant result. - = Not assessed in this study.

Clinic Type or Site. Only Berquist et al. (2008) investigated whether clinic type (main vs outreach) was associated with adherence, finding no statistically significant

relationships. It would have been beneficial for the other two studies using data from multiple sites (Annunziato et al., 2018 and Berquist et al., 2006) to explore this and provide validation that medical or other clinical factors do not appear associated with adherence.

Age at or Time Since Transplant or Diagnosis. Hames et al. (2021) found no significant relationship with age at diagnosis as did Bilhartz et al. (2015) for age at transplant. However, Berquist et al. (2006) found a significant difference for age at transplant, with mean ages of 9.12 years and 5.66 years for the non-adherent and adherent group respectively. Furthermore, Berquist et al. (2008) found greater time since transplantation was one of only two factors that predicted non-adherence using logistic regression.

Hames et al. (2021) used a different construct and population (diagnosis of AILD) as opposed to date of transplant within other studies, and also had an older sample range. Furthermore, Bilhartz et al. (2015) had a smaller sample size (n=48) in their cross-sectional design, perhaps leaving them with insufficient timeframes or power to detect an effect compared to Berquist et al's (2006) larger (n=97) cohort study. It is therefore difficult to draw definitive conclusions given the mixed results, although there does appear to be sufficient justification to continue to investigate age at and/or time since transplant or diagnosis in future research.

Immunosuppressive Regimen. Neither medication type (cyclosporine vs tacrolimus) nor number of medications were found to be statistically significantly associated with adherence by Berquist et al. (2006) or Hames et al. (2021), respectively. Although only researched in two studies, the breadth of their samples in terms of age range and diagnosis type suggests little evidence for an association.

Personal Factors

Table 10 summarises findings for the five variables grouped under the Personal and Parental Factors Theme.

Table 10

Summary of Personal and Parental Factors Found to be/not be Associated with Medication Non-Adherence

Authors (date) n = Sample Size	Self-Management / Allocation of Responsibility (AoR)	Health Related Quality of Life (HRQOL)	Perceived Treatment /Regimen Knowledge	Demonstrated Treatment Skills / Knowledge	Parental Attitude
Annunziato et al. (2018) n=214	* (service user responses)	-	-	-	-
Berquist et al. (2006) n=97	-	-	-	-	-
Berquist et al. (2008) n=111	-	-	-	-	-
Bilhartz et al. (2015) n=48	* (parent responses)	-	-	-	-
Fredericks et al. (2008) n=25	-	* (service user and parent responses)	-	-	-
Fredericks et al. (2010) n=71	* (service user responses)	-	NS (service user) *(parent responses)	NS (service user and parent responses)	-
Hames et al. (2021) n=68	-	-	-	-	-
Jerson et al. (2013) n=9	-	-	-	-	-
Jakubowska-Winecka and Biernecka (2018) n=44	-	-	-	-	Accepting and overly protective (adherence), overly demanding (non-adherence)*
Wright et al. (2015) n=13	-	-	-	-	-

Note. * = Statistically significant finding (typically $p<.05$), category in brackets is associated with higher levels of non-adherence. NS = Non-significant result. - = Not assessed in this study.

Initial Notes. Fredericks et al. (2010) developed a Transition Readiness Survey (TRS), that included items on self-management, allocation of responsibility (AoR), perceived regimen knowledge, demonstrated skills and psychosocial adjustment (service user and parent versions). These have been separated for the discussion below into their specified domains, which is supported by their Principal Component (PCA) and Cronbach alpha analyses demonstrating internal consistency (although it should be noted that construct and content validity were not established prior to the study).

Self-management and Allocation of Responsibility. Three papers explored the relationship between self-management and/or AoR with adherence, which are discussed collectively here due to their significant overlap. Table 11 summarises measures used, which provides context to interpreting results.

Table 11

Summary of Measures Used to Assess Self-Management and Allocation of Responsibility

Author (date)	Tool Used	Authors' Approach / Further Details
Annunziato et al. (2018)	Service user and parent/guardian versions of the Responsibility and Familiarity with Illness Survey (REFILS; Annunziato et al., 2011), which includes questions for two domains: 1) perceived knowledge or understanding, 2) management of their illness. Note only relationships between adherence and total scores were given.	Authors used factor analyses to reduce the service user burden from the full version (22-item; Annunziato et al., 2013) to 13 items. Respondents selected one of three options; "Never", "Sometimes" or "Always" (scored 1-3 respectively) to indicate how regularly the service user engaged in the specified behaviour, thus higher scores were indicative of greater self-management by the service user. Reliability was determined using Cronbach alpha for internal consistency in addition to Kappa coefficient, and validity through factor analysis.
Bilhartz et al. (2015)	A separate Allocation of Responsibility (AoR) measure added to their Transition Readiness Survey (TRS), administered routinely post-transplant biannually, developed by the clinical team.	It included 13 questions whereby service users (and parent/guardian where relevant) selected whether the parent/guardian assumes responsibility, responsibility is shared, or the service user assumes responsibility (scored at one, two and three points respectively; thus higher scores indicated greater responsibility by the service user). Principal Component analysis (PCA) extracted two components (self-management tasks and communication in the service user survey and communication with healthcare system and self-management or awareness, in the parent survey), all with stable loadings and Cronbach alpha scores indicative of good internal consistency.
Fredericks et al. (2010)	TRS survey, developed by the clinical team.	Their survey (TRS:A/YA; adolescent/young people) consisted of 38 items using a likert scale, with higher scores indicating increased skills acquisition or perceived presence of skills. Questions were grouped into four domains: Self-Management, Regimen Knowledge, Demonstrated Skills and Psychosocial Adjustment. The self-management domain assessed AoR (distribution of meditation-taking responsibility between the A&YA and parent/guardian).

The self-management and AoR measures used aimed to assess the service user's (and parent/guardian's where relevant) perception of the A&YA's management of, and level of

responsibility taken for, their condition. Bilhartz et al. (2015) found that parent/guardian AoR responses had more significant correlations with adherence compared to service user responses, indicating parental/guardian perception of their child's responsibility was more closely aligned with adherence behaviour than the service user's own perception or report. The authors found these relationships with adherence differed depending on the domain and stage of transition, with the largest effect sizes in the 'mid-transition' stage (13–15 years).

Contrary to their hypothesis, Fredericks et al. (2010) found greater service user perceived self-management and higher scores on the AoR subscales within their TRS were associated with non-adherence (specifically proportion of immunosuppressant levels below the target range and cyclosporine SD). However, they expressed caution in the interpretation of the latter, considering the relatively small number of participants receiving this medication as opposed to tacrolimus. They found no significant correlations between parental/guardian responses and any measure of adherence.

Similarly, Annunziato et al. (2018) found A&YAs with greater perceived level of responsibility (those who rated themselves "in charge") were less likely to adhere to medication and more likely to experience organ rejection. They proposed these unexpected findings suggest A&YAs' self-reports may not be an accurate reflection of reality. This was further supported by Annuziato et al's (2018) finding that discrepancy self-management scores (where a service user endorsed greater self-management than their parent) was also associated with both later non-adherence and transplant rejection, but parent scores alone were not.

One limitation of the REFILS used by Annunziato et al. (2018) compared to the AoR questionnaire used by Bilhartz et al. (2015) is that lower scores meant it was unclear whether

greater responsibility lay with the parent or simply that no one was overseeing responsibility. However, Annunziato et al. (2018) did benefit from a greater sample size.

These findings suggest there is some association between adherence and self-management/AoR, yet the discrepancy between results raise questions about the reliability of service user vs. parental/guardian reports at different ages.

Health Related Quality of Life. Only Fredericks et al. (2008) explored HRQOL in relation to adherence, for which they used two measures due to variability in existing literature and lack of evidence demonstrating predictive validity of available tools. They found both service user and parent reported overall HRQOL scores were lower than normative data for healthy children. They also identified that both service user and parent/guardian poorer scores across eight domains and poorer service user scores from a further nine domains across their questionnaires were statistically significantly associated with greater variability in tacrolimus SD (indicative of non-adherence).

Regimen and/or Treatment Perceived Knowledge and Demonstrated Treatment Skills / Knowledge. Fredericks et al. (2010) used their TRS to assess both perceived and actual ("demonstrated") knowledge. They found that whilst most A&YAs (90%) knew their medication names, 73% could not state their correct doses, 51% could not state correct timings and 41% were unable to describe the function of their prescribed immunosuppressants. They also identified that whilst perceived knowledge increased with age, demonstrated knowledge did not. However, neither service user nor parent perceived nor demonstrated knowledge were statistically significantly associated with any measure of medication adherence. One limitation of this study was the lack of investigation into service user vs parent discrepancy score associations with adherence, as Annunziato et al. (2018) had done with the REFILS.

Parental Attitude. Jakubowska-Winecka and Biernecka (2018) found, within the liver transplant group, two parental attitudes had a positive association with adherence; Accepting and Overly Protective; whilst the Overly Demanding attitude had a negative association. Interestingly, these patterns were not consistent across all disease types. Whilst it is possible some of their statistically significant findings were Type I errors (multiple comparisons were not controlled for), it may also provide evidence of a variation in the needs and care requirements dependent on diagnosis.

Mental Health and Illness Perceptions

Table 12 summarises the five variables grouped under the Mental Health and Illness Perception Theme.

Table 12

Summary of Mental Health and Illness Perceptions Found to be/not be Associated with Medication Non-Adherence

Authors (date) n = sample size	Depression	Anxiety	Illness perceptions	Distress	Psychosocial adjustment
Annunziato et al. (2018) n=214	-	-	-	-	-
Berquist et al. (2006) n=97	-	-	-	-	-
Berquist et al. (2008) n=111	-	-	-	-	-
Bilhartz et al. (2015) n=48	-	-	-	-	-
Fredericks et al. (2008) n=25	-	-	-	-	-
Fredericks et al. (2010) n=71	-	-	-	-	NS
Hames et al. (2021) n=68	NS (overall adherence) *(punctuality)	NS	*"treatment control" NS (other illness perceptions)	NS	-
Jerson et al. (2013) n=9	-	-	-	-	-
Jakubowska-Winecka and Biernecka (2018) n=44	-	-	-	-	-
Wright et al. (2015) n=13	-	-	-	-	-

Note. * = Statistically significant finding (typically $p<.05$), category in brackets is associated with higher levels of non-adherence. NS = Non-significant result. - = Not assessed in this study.

Depression, Anxiety, Distress and Psychosocial Adjustment. Depression was statistically significantly associated with one question within Hames et al's (2021) adherence questionnaire; that is, those with higher depression scores were less likely to be punctual in taking medications. However, there was no significant difference between other individual nor overall depression, anxiety or distress scores between the adherent and non-adherent groups. Similarly, Fredericks et al. (2010) found no significant association between any measure of adherence with psychosocial adjustment (a domain within their TRS). It is therefore difficult to say whether Hames et al's (2021) isolated statistically significant finding is valid or instead reflective of a Type I error, particularly given multiple comparisons were not controlled for. It is also possible their comparatively low non-adherence prevalence was indicative of under-reporting or that their cut-off applied for non-adherence (<80%) limited their ability to identify other associations (Type II errors). However, they did identify associations between mood and clinical outcomes, specifically that those not in remission were more likely to be depressed and express greater concern and worry about their condition.

Illness Perceptions. Hames et al. (2021) found no difference in illness perception scores (thoughts and feelings about how someone makes sense of their illness and treatment) between adherent and non-adherent groups, although a greater belief in the helpfulness of prescribed treatment was significantly correlated with better adherence. Significant correlations were also identified between blood tests (indicative of liver function and thus potentially medication adherence) and other illness perceptions. Specifically, greater reported level of understanding with higher (worse) AST (aspartate aminotransferase), and ALT (alanine aminotransferase) results, and greater reported symptoms and emotional impact of their condition with higher (worse) levels of bilirubin. Type I errors appear unlikely here given stronger associations between illness perceptions and adherence found in other

populations, including adult liver transplant recipients (O'Carroll et al., 2006) and adults with asthma (Kaptein et al., 2008). The lack of significance between other illness perceptions with adherence scores and blood tests results may instead be attributable to the comparatively low adherence prevalence within this study, as described above.

Social Factors

Table 13 summarises the three variables grouped under the Social Factors theme.

Table 13

Summary of Social Factors Found to be/not be Associated with Medication Non-Adherence

Authors (date) n = Sample Size	Being a Peer Mentor	Feeling "different" / Striving to be Normal	Impact of Medication on Other Priorities
Annunziato et al. (2018) n=214	-	-	-
Berquist et al. (2006) n=97	-	-	-
Berquist et al. (2008) n=111	-	-	-
Bilhartz et al. (2015) n=48	-	-	-
Fredericks et al. (2008) n=25	-	-	-
Fredericks et al. (2010) n=71	-	-	-
Hames et al. (2021) n=68	-	-	-
Jerson et al. (2013) n=9	NS	-	-
Jakubowska-Winecka and Biernecka (2018) n=44	-	-	-
Wright et al. (2015) n=13	-	++	++

Note. NS = Non-significant result. - = Not assessed in this study. ++ = identified through qualitative analyses.

Being a Peer Mentor. Jerson et al's (2013) peer mentor programme involved attending a half-day training workshop facilitated by a clinical psychologist, before being assigned a mentee who participants undertook recreational or education activities with. Analyses found a reduction in the baseline mean tacrolimus SD, moving from above their specified non-adherence threshold to an average within normal limits following participation. However, this was not statistically significant. When the waitlist control group later participated in the programme, they experienced a similar improvement (although this age range was outside this review's criteria, and results were also non-significant).

A strength in Jerson et al's (2013) study was the experimental design. Whilst this was limited by lack of randomisation, chi-square analyses demonstrated control and experimental groups were not significantly different in baseline characteristics. It is possible the lack of significance in their findings is attributable to the small sample size, and it may therefore have been helpful to conduct individual analyses on score changes, such as the Reliable Change Index (Jacobson & Truax, 1992).

Feeling "Different" / Striving to be Normal. Wright et al's (2015) qualitative analyses identified a theme of "triggers of difference". Service users described a sense of distance between them and healthy peers because of illness symptoms, a visible scar, lifestyle requirements (such as advice not to drink excessive alcohol) and medication. An ongoing struggle to fit in was also described, including a reluctance to disclose details of their liver transplant to be viewed as "normal" by peers. Given taking daily medication was viewed as a marker of being "different", deliberate non-adherence was seen by some as a way of taking back control. This appeared strong enough to outweigh existing knowledge or understanding about the benefits of taking medication. Only one quantitative study (Hames et al., 2021) had a specific measure of intentional adherence, suggesting further investigation into this would be beneficial.

Impact of Medication on Other Priorities. Participants in Wright et al.'s (2015) study also described the interference taking daily medication had on participation in social activities, such as attending sleepovers and consuming alcohol. This included practical challenges such as not being home when due to take medication. Others talked about prioritising important social activities over medication, which appeared easier when they were feeling well.

A benefit of Wright et al's (2015) qualitative design was the ability to explore individual experiences regarding liver disease. However, they recognised a limitation was the relatively short interviews (30-45 minutes) that, because of being undertaken when attending routine appointments, were sometimes cut short.

Discussion

This review provides a unique insight into the existing, albeit limited, literature within this population and identified 23 variables across five themes that were investigated in terms of their relationship with medication adherence. Inconsistency in the way adherence was measured, what constituted "non-adherence" and the associated broad prevalence range introduced complexity when comparing results. This was likely due to the variability in importance of aspects such as correct timings and dosage depending on the condition and individual (Shemesh, 2004), together with the lack of an accepted and consistently used validated measurement tool (De Geest & Vanhaecke, 1999).

Being older appeared most strongly associated with non-adherence. However, the fact older A&YAs rated themselves as more responsible indicates perception at this age is not necessarily a reliable indicator of subsequent adherence behaviour. Similarly, whilst perception of disease and treatment understanding increased with age, "demonstrated knowledge" did not (although the latter was only researched in one study). This risk is

exacerbated by the demonstration through self-management and AoR measures that A&YAs received less input and monitoring from parents at this age. This pattern appears consistent with literature from other transplant types (Danziger-Isakov et al., 2016). Developmental literature may also provide an explanation; for example, the tendency to take greater risks (Dahl, 2004) and be more socially influenced in decision-making (Weigard et al., 2014) in later adolescence.

Results from this review also suggest social and family/parental factors and poorer HRQOL may be associated with lower reported adherence. It is understandable that families living in complex circumstances may find it difficult to provide an adolescent with the level of support found to be associated with positive adherence behaviours in other populations (adolescents with epilepsy, Gabr & Shams, 2015, for example). Hanghøj and Boisen (2014) identified from their review across multiple chronic disease types that family stress, conflict between parent and adolescent and a reported lack of support and/or understanding from parents, were associated with non-adherence. Existing literature in other populations also supports the findings regarding HRQOL (e.g. La Greca & Bearman, 2003).

There were no significant relationships found between overall reported adherence and mental health, which contradicts literature from similar populations. For example, Sockalingham et al. (2012) found adults with AILD experiencing anxiety or depression were less likely to be adherent and similarly Burra et al. (2011) found psychological distress was a risk factor for non-adherence in adolescent liver transplant recipients. There was only one significant association between illness perceptions and adherence. This contradicts literature in other populations such as adults with a chronic skin condition (Pavon Blanco et al., 2019) and adult outpatients (Wu et al. 2014), together with the underlying theoretical premise of the CSM that illness perceptions are fundamental to shaping behaviour such as adherence. It may be that these relationships do not exist within this population, perhaps due to the

interaction developmental differences in A&YAs may have with illness perceptions. However, these variables were not researched extensively across the papers in this review and methodological or design constraints may have limited the ability to detect effects. The contradiction with other literature justifies their inclusion in further research, ideally with a broader range of liver disease diagnoses and greater sample size.

There were also other demographic factors not significantly associated with adherence in this review that contradicts literature from other populations. For example, with regards to race and ethnicity, which was only investigated in terms of its relationship with adherence by Fredericks et al. (2008). Their non-significant finding contrasts with Tucker et al. (2002), who identified African Americans post renal transplant were less likely to be adherent than White adolescents. Given evidence for systemic differences in health outcomes for different racial groups (Nazroo, 2003), this appears an important topic for future research.

It has been suggested possible gender differences in adherence may be due to side effects of immunosuppressant medication on physical appearance (such as weight gain and swollen face) being more difficult for girls to manage given gender differences in body image and associated self-esteem (Furnham et al., 2002). This appears plausible given female service users were significantly more likely to be worried, anxious and emotionally impacted by their diagnosis (Hames et al., 2021). However, no study found a significant overall relationship between gender and adherence in this review, suggesting no association in this specific population. However, it would be beneficial to explore this in future research, given the association between gender and other variables and relationship identified in other populations.

A consistent limitation throughout the papers in this review was their lack of explicit reference to health behaviour theory. This, together with contradictory results and/or limited

focus on certain variables makes it difficult to draw firm theoretical conclusions. For example, limited significant findings by Hames et al. (2021) and lack of focus on illness perceptions in other studies mean conclusions about the application of CSM is restricted. Similarly, mixed results with regards to demographic factors, mood and limited attention on variables such as disease and medication knowledge, provide similarly poor evidence for the relevance of the HBM. However, the differences identified above between this review's findings and literature from adult populations do justify the need to better consider developmental factors (many of which are not incorporated within these theoretical models and may in part explain the lack of explicit reference to them) as patterns of variables associated with adherence appear different in these age groups.

A range of methodological constraints were identified. Most notable was the lack of validated tool use, small sample sizes and limitations that certain design and/or analysis approaches introduced; specifically, the reliance on retrospective data and lack of predictive statistics, meaning only associations and not causations were generally identified. However, the breadth of designs included in this review are beneficial in making interpretations. For example, the qualitative findings by Wright et al. (2015) provide helpful context to quantitative results from the other nine papers. A&YAs' descriptions of their experiences help highlight the understandable challenges experienced at this age and explain certain behaviours (such as needing to "take back control" perhaps leading to intentional non-adherence, identified by Hames et al., 2021). Furthermore, Jakubowska-Winecka and Biernecka's (2018) study (a unique strength of which was their comparison of liver transplant recipients with groups diagnosed with other disease types), demonstrated the variation in challenges faced by and subsequent clinical needs in different populations.

Clinical Implications

This review identified characteristics that may be associated with greater vulnerability to non-adherence, including demographic variables easily discernible within routine clinics. This may help clinicians identify service users and families who might benefit from more support, particularly given the suggestion that certain parental attitudes, socioeconomic factors and other family setup/situations may be associated with non-adherence. This also highlights the importance of involving and supporting family members as part of routine clinical care, together with a more individualised assessment given the range of potentially interacting factors.

There also remain questions over the reliability of service user vs. parent/guardian reports, particularly when assessing self-management skills and responsibility for self-care. It would therefore be beneficial, where possible, to obtain (and compare) measures from both parties if the service user consented, although the feasibility of this may be reduced where A&YA over 18 years are seen in adult clinics. Comparison of medication adherence prevalence also indicates how varied estimations can be when using different tools, suggesting a multi-method approach is most beneficial within routine clinics, if possible. Clinicians should also be aware of the novel finding by Hames et al. (2021) that A&YAs are more likely to take medication in the lead up to appointments. This raises concerns about the reliance on liver function tests as an indication of adherence and the likelihood of increased non-adherent behaviour outside of these times.

There appears significant potential for self-management skills to be a target within young adult services to address the discrepancy between A&YA perceived and actual skills in this area. Finally, this review has highlighted how unhelpful it may be to rely simply on age as an indicator for transition readiness, given older A&YAs are less likely to adhere.

Research Implications

Jakubowska-Winecka and Biernecka's (2018) finding of variation in results by diagnosis demonstrate the importance of conducting research into A&YAs with different chronic conditions separately. However, this review has also highlighted that, within hepatology, the focus to date has predominantly been on transplant recipients, yet there are many other A&YAs living with chronic liver disease and/or awaiting transplant who would benefit from comparable research attention. The small literature pool is perhaps also associated with the lack of validated tools for assessing both adherence and other measures, leaving a significant area of scope for future research.

The development and evaluation (through experimental studies) of programmes designed to improve adherence would also be beneficial and help complement the promising findings by Jerson et al. (2013). These studies would benefit from a larger sample and randomised controls, together with a focus on identifying what underlies any improvement in adherence found. Wright et al.'s (2015) identification of a theme around feeling "different" appears to help unpick the nature of the relationship identified by Jerson et al. (2013), demonstrating the importance of also conducting further qualitative research (ideally with a larger sample, broader inclusion criteria and less restrictive environment for interviews). There also appears to be a gap in co-produced research, particularly given the combination of difficulties described by A&YA within Wright et al's (2015) study, known potential connotations associated with terminology such as "adherence" and developmental challenges faced by this age group. Helping A&YA clarify for themselves what their goals and values are in relation to disease management and working more collaboratively to design interventions that support them in achieving this might therefore be beneficial.

A large, prospective and multi-site cohort study would likely be of most benefit in future quantitative research, although it is recognised that cost and time constraints may be prohibitive. This would help address limitations of the retrospective studies within this review (such as variability between data collection times and inability to control for confounding variables) and provide greater scope to use validated measures. This could also explore findings that remain unclear, such as the association certain demographic and clinical factors have with adherence behaviours, together with including variables that have received less attention, such as race and ethnicity, mental health and illness perceptions. It would allow for multivariate regression analyses to identify predictors of adherence, together with exploring the distinction between intentional versus non-intentional and patterns of adherence over time. Berquist et al. (2006) recognise the benefit future research could have if used to create and test a model to predict non-adherence within this population. A larger sample using participants with various liver disease diagnoses would be helpful, given the heavy focus to date on liver transplant recipients only.

Conclusion

This review identified two variables (current age and time since transplant/diagnosis) associated with, in addition to others potentially associated with, non-adherence. This has resulted in significant considerations for clinicians that may help reduce risk within this vulnerable age group, together with opportunities for future research to address methodological constraints and gaps within the existing limited literature pool. Further research would help clarify inconsistencies and help unpick what appears to be a complex interaction between adherence and multitude of demographic, disease and other personal variables.

References

Annunziato, R. A., Baisley, M. C., Arrato, N., Barton, C., Henderling, F., Arnon, R., & Kerkar, N. (2013). Strangers headed to a strange land? A pilot study of using a transition coordinator to improve transfer from pediatric to adult services. T*he Journal of Pediatrics, 163*(6), 1628-1633. https://doi.org/10.1016/j.jpeds.2013.07.031

Annunziato, R. A., Bucuvalas, J. C., Yin, W., Arnand, R., Alonso, E. M., Mazariegos, G. V., Venick, R. S., Stuber, M. L., Schneider, B.L., & Shemesh, E. (2018). Self-management measurement and prediction of clinical outcomes in pediatric transplant. *The Journal of Pediatrics, 193,* 128-133. https://doi.org/10.1016/j.jpeds.2017.09.069

Annunziato, R. A., Parkar, S., Dugan, C. A., Barsade, S., Arnon, R., Miloh, T., Iyer, I., Kerkar, N., & Shemesh, E. (2011). Brief report: deficits in health care management skills among adolescent and young adult liver transplant recipients transitioning to adult care settings. *Journal of Pediatric Ppsychology*, *36*(2), 155-159. https://doi.org/10.1093/jpepsy/jsp110

Becker, M. H. (1974). The health belief model and sick role behavior. *Health Education Monographs, 2*(4), 409-419. https://doi.org/10.1177%2F109019817400200407

Berquist, R., Berquist, W. E., Esquivel, C. O., Cox, K. L., Wayman, K. I., & Litt, I. F. (2006). Adolescent non-adherence: prevalence and consequences in liver transplant recipients. *Pediatric Transplantation, 10*(3), 304-310. https://doi.org/10.1111/j.1399-3046.2005.00451.x

Berquist, R. K., Berquist, W. E., Esquivel, C. O., Cox, K. L., Wayman, K. I., & Litt, I. F. (2008). Non-adherence to post-transplant care: prevalence, risk factors and outcomes in adolescent liver transplant recipients. *Pediatric Transplantation, 12*(2), 194-200. https://doi.org/10.1111/j.1399-3046.2007.00809.x

Bilhartz, J. L., Lopez, M. J., Magee, J. C., Shieck, V. L., Eder, S. J., & Fredericks, E. M. (2015). Assessing allocation of responsibility for health management in pediatric liver transplant recipients. *Pediatric Transplantation*, *19*(5), 538-546. https://doi.org/10.1111/petr.12466

Bissonnette, J. M. (2008). Adherence: a concept analysis. *Journal of Advanced Nursing*, *63*(6), 634-643. https://doi.org/10.1111/j.1365-2648.2008.04745.x

Pavon Blanco, A., Turner, M. A., Petrof, G., & Weinman, J. (2019). To what extent do disease severity and illness perceptions explain depression, anxiety and quality of life in hidradenitis suppurativa?. *British Journal of Dermatology*, *180*(2), 338-345. https://doi.org/10.1111/bjd.17123

Broadbent, E., Petrie, K. J., Main, J., & Weinman, J. (2006). The brief illness perception questionnaire. *Journal of Psychosomatic Research*, *60*(6), 631-637. https://doi.org/10.1016/j.jpsychores.2005.10.020

Brown, M. T., & Bussell, J. K. (2011). Medication adherence: WHO cares?. In *Mayo clinic proceedings* (Vol. 86, No. 4, pp. 304-314). Elsevier. https://doi.org/10.4065/mcp.2010.0575

Burra, P., Germani, G., Gnoato, F., Lazzaro, S., Russo, F. P., Cillo, U., & Senzolo, M. (2011). Adherence in liver transplant recipients. *Liver Transplantation*, *17*(7), 760-770. https://doi.org/10.1002/lt.22294

Burra, P. (2012). The adolescent and liver transplantation. *Journal of Hepatology*, *56*(3), 714-722. https://doi.org/10.1016/j.jhep.2011.07.032

Choudhury, S., Blakemore, S. J., & Charman, T. (2006). Social cognitive development during adolescence. *Social Cognitive and Affective Neuroscience, 1,* 165–174. https://doi.org/10.1093/scan/nsl024

Critical Appraisal Skills Programme (2018). CASP (Randomised Controlled Trials) Checklist(s). Retrieved from: https://casp-uk.net/casp-tools-checklists/

D'Agata, I. D., & Balistreri, W. F. (1999). Evaluation of liver disease in the pediatric patient. *Pediatrics in Review*, 20(11), 376-390. http://ftp.columbia.edu/itc/hs/nursing/m6638/2003_2/session03/liver_disease.pdfhttp://ftp.columbia.edu/itc/hs/nursing/m6638/2003_2/session03/liver_disease.pdf

Darcy, A., & Samyn, M. (2017). Looking after young people with liver conditions: understanding chronic illness management in the context of adolescent development. *Clinical Liver Disease*, *9*(5), 103. https://dx.doi.org/10.1002%2Fcld.637

Dahl, R. E. (2004). Adolescent brain development: a period of vulnerabilities and opportunities. Keynote address. *Annals of the New York Academy of Sciences*, *1021*(1), 1-22. https://doi.org/10.1196/annals.1308.001

Danziger-Isakov, L., Frazier, T. W., Worley, S., Williams, N., Shellmer, D., Dharnidharka, V. R., Gupta, N., Ikle. D., Sweet. S. C., & CTOTC-05 Consortium. (2016). Perceived barriers to medication adherence in pediatric and adolescent solid organ transplantation. *Pediatric Transplantation*, *20*(2), 307-315. https://doi.org/10.1111/petr.12648

De Geest, S., Abraham, I., Moons, P., Vandeputte, M., Van Cleemput, J., Evers, G., & Vanhaecke, J. (1998). Late acute rejection and subclinical noncompliance with cyclosporine therapy in heart transplant recipients. *The Journal of heart and lung transplantation: the official publication of the International Society for Heart Transplantation*, *17*(9), 854-863. https://europepmc.org/article/med/9773856

De Geest, S., & Vanhaecke, J. (1999, June). Methodological issues in transplant compliance research. In *Transplantation Proceedings* (Vol. 31, No. 4A, pp. 81S-83S). https://doi.org/10.1016/s0041-1345(99)00137-2

Dharnidharka, V. R., Lamb, K. E., Zheng, J., Schechtman, K. B., & Meier-Kriesche, H. U. (2015). Across all solid organs, adolescent age recipients have worse transplant organ survival than younger age children: a US national registry analysis. *Pediatric Transplantation*, *19*(5), 471-476. https://doi.org/10.1111/petr.12464

Di Giorgio, A., Hadzic, N., Dhawan, A., Deheragoda, M., Heneghan, M. A., Vergani, D., Mielo-Vergani. G., & Samyn, M. (2020). Seamless management of juvenile autoimmune liver disease: long-term medical and social outcome. *The Journal of Pediatrics*, *218,* 121-129. https://doi.org/10.1016/j.jpeds.2019.11.028

Ebel, N. H., Hsu, E. K., Berry, K., Horslen, S. P., & Ioannou, G. N. (2017). Disparities in waitlist and posttransplantation outcomes in liver transplant registrants and recipients 18–24 years old: analysis of the UNOS database. *Transplantation*, *101*(7), 1616. https://dx.doi.org/10.1097%2FTP.0000000000001689

Fredericks, E. M., Magee, J. C., Opipari-Arrigan, L., Shieck, V., Well, A., & Lopez, M. J. (2008). Adherence and health-related quality of life in adolescent liver transplant recipients. *Pediatric Transplantation*, *12*(3), 289-299. https://doi.org/10.1111/j.1399-3046.2008.00901.x

Fredericks, E. M., Dore-Stites, D., Well, A., Magee, J. C., Freed, G. L., Shieck, V., & James Lopez, M. (2010). Assessment of transition readiness skills and adherence in pediatric liver transplant recipients. *Pediatric Transplantation*, *14*(8), 944-953. https://doi.org/10.1111/j.1399-3046.2010.01349.x

Furnham, A., Badmin, N., & Sneade, I. (2002). Body image dissatisfaction: Gender differences in eating attitudes, self-esteem, and reasons for exercise. *The Journal of Psychology*, *136*(6), 581-596. https://doi.org/10.1080/00223980209604820

Gabr, W. M., & Shams, M. E. (2015). Adherence to medication among outpatient adolescents with epilepsy. *Saudi Pharmaceutical Journal*, *23*(1), 33-40. https://doi.org/10.1016/j.jsps.2014.05.003

Gilbody, S., Richards, D., Brealey, S., & Hewitt, C. (2007). Screening for depression in medical settings with the Patient Health Questionnaire (PHQ): A diagnostic meta-analysis. *Journal of General Internal Medicine, 22*(11), 1596-1602. https://doi.org/10.1007/s11606-007-0333-y

Goossens, L. (2006). Adolescent development: Putting Europe on the map. In Jackson. S., & Goossens. L. (Eds.) *Handbook of Adolescent Development*. New York.

Hames, A., Matcham, F., Joshi, D., Heneghan, M. A., Dhawan, A., Heaton, N., & Samyn, M. (2016). Liver transplantation and adolescence: the role of mental health. *Liver Transplantation*, *22*(11), 1544-1553. https://doi.org/10.1002/lt.24629

Hames, A., Matcham, F., Makin, I., Day, J., Joshi, D., & Samyn, M. (2021). Adherence, Mental Health and Illness Perceptions in Autoimmune Liver Disease: Looking Beyond Liver Function Tests. *Journal of Pediatric Gastroenterology and Nutrition*, *73*(3), 376-384. https://doi.org/10.1097/MPG.0000000000003119

Hanghøj, S., & Boisen, K. A. (2014). Self-reported barriers to medication adherence among chronically ill adolescents: a systematic review. *Journal of Adolescent Health*, *54*(2), 121-138. https://doi.org/10.1016/j.jadohealth.2013.08.009

Högler, W., Baumann, U., & Kelly, D. (2012). Endocrine and bone metabolic complications in chronic liver disease and after liver transplantation in children. *Journal of Pediatric Gastroenterology and Nutrition*, *54*(3), 313-321. http://doi.org/10.1097/MPG.0b013e31823e9412

Hong, J. C., Yersiz, H., Farmer, D. G., Duffy, J. P., Ghobrial, R. M., Nonthasoot, B., Collins, T., Hiatt, J., & Busuttil, R. W. (2009). Longterm outcomes for whole and segmental

liver grafts in adult and pediatric liver transplant recipients: a 10-year comparative analysis of 2,988 cases. *Journal of the American College of Surgeons*, *208*(5), 682-689. https://doi.org/10.1016/j.jamcollsurg.2009.01.023

Jacobson, N. S., & Truax, P. (1992). Clinical significance: A statistical approach to defining meaningful change in psychotherapy research. In A. E. Kazdin (Ed.), *Methodological Issues & Strategies in Clinical Research* (p. 631–648). American Psychological Association. https://doi.org/10.1037/10109-042

Jakubowska-Winecka, A., & Biernacka, M. (2018). Parental attitudes and medication adherence in groups of adolescents after liver and kidney transplantations. In *Transplantation Proceedings* (Vol. 50, No. 7, pp. 2145-2149). Elsevier. https://doi.org/10.1016/j.transproceed.2018.05.007

Jerson, B., D'Urso, C., Arnon, R., Miloh, T., Iyer, K., Kerkar, N., & Annunziato, R. A. (2013). Adolescent transplant recipients as peer mentors: A program to improve self-management and health-related quality of life. *Pediatric Transplantation*, *17*(7), 612-620. https://doi.org/10.1111/petr.12127

Joanna Briggs Institute (2020). JBI Critical Appraisal Tools. https://jbi.global/critical-appraisal-tools

Kaller, T., Langguth, N., Petermann, F., Ganschow, R., Nashan, B., & Schulz, K. H. (2013). Cognitive performance in pediatric liver transplant recipients. *American Journal of Transplantation*, *13*(11), 2956-2965. https://doi.org/10.1111/ajt.12408

Kaptein, A. A., Hughes, B. M., Scharloo, M., Fischer, M. J., Snoei, L., Weinman, J., & Rabe, K. F. (2008). Illness perceptions about asthma are determinants of outcome. *Journal of Asthma*, *45*(6), 459-464. https://doi.org/10.1080/02770900802040043

Kroenke, K. & Spitzer, R.L. (2002). The PHQ-9: A new depression and diagnostic severity measure. *Psychiatric Annals, 32*, 509-521. https://doi.org/10.3928/0048-5713-20020901-06

Kroenke, K., Spitzer, R. L., Williams, J. B., Monahan, P. O., & Löwe, B. (2007). Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. *Annals of Internal Medicine*, *146*(5), 317-325. https://doi.org/10.7326/0003-4819-146-5-200703060-00004

KyngÄs, H. A., Kroll, T., & Duffy, M. E. (2000). Compliance in adolescents with chronic diseases: a review1. *Journal of Adolescent Health*, *26*(6), 379-388. https://doi.org/10.1016/S1054-139X(99)00042-7

La Greca, A.M., &,Bearman, K.J. (2003). Adherence to pediatric treatment regimens. In Roberts, M.C. (Eds.), *Handbook of Pediatric Psychology* (pp. 119–140). New York: The Guilford Press..

Landgraf, J. M., Abetz, L., & Ware, J. E. (1999). The CHQ user's manual. Second printing. *Boston, MA: HealthAct*.

Laederach-Hofmann, K., & Bunzel, B. (2000). Noncompliance in organ transplant recipients: a literature review. *General Hospital Psychiatry*, *22*(6), 412-424. https://doi.org/10.1016/S0163-8343(00)00098-0

Leventhal, H., Nerenz, D.R. & Steele, D.J. (1984). Illness representations and coping with health threats. In: Baum, A., Taylor, S.E. and Singer, J.E. (Eds.), Handbook of psychology and health: social psychological aspects of health, Vol. 4. (pp. 219–252). Earlbaum, Hillsdale, NJ.

L eventhal, H., Meyer, D. and Nerenz, D. (1980). The common sense model of illness danger. In: Rachman, S. (Ed.), Medical psychology, Vol. 2. (pp. 7–30). Pergamon, New York.

Löwe, B., Decker, O., Müller, S., Brähler, E., Schellberg, D., Herzog, W., & Herzberg, P. Y. (2008). Validation and standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the general population. *Medical care*, 266-274. https://www.jstor.org/stable/40221654

Lurie, S., Shemesh, E., Sheiner, P. A., Emre, S., Tindle, H. L., Melchionna, L., & Shneider, B. L. (2000). Non-adherence in pediatric liver transplant recipients− an assessment of risk factors and natural history. *Pediatric Transplantation*, *4*(3), 200-206. https://doi.org/10.1034/j.1399-3046.2000.00110.x

Molmenti, E., Mazariegos, G., Bueno, J., Cacciarelli, T., Alasio, T., Khanna, A., Kosmach, A., Jain. J., & Reyes, J. (1999). Noncompliance after pediatric liver transplantation. In *Transplantation Proceedings* (Vol. 31, No. 1-2, p. 408). Elsevier. https://doi.org/10.1016/S0041-1345(98)01682-0

Morisky, D. E., Ang, A., Krousel-Wood, M., & Ward, H. J. (2008). Predictive validity of a medication adherence measure in an outpatient setting. *The Journal of Clinical Hypertension*, *10*(5), 348-354. https://doi.org/10.1111/j.1751-7176.2008.07572.x

Nazroo, J. Y. (2003). The structuring of ethnic inequalities in health: economic position, racial discrimination, and racism. *American Journal of Public Health*, *93*(2), 277-284. https://doi.org/10.2105/AJPH.93.2.277

O'Carroll, R. E., McGregor, L. M., Swanson, V., Masterton, G., & Hayes, P. C. (2006). Adherence to medication after liver transplantation in Scotland: a pilot study. *Liver Transplantation*, *12*(12), 1862-1868. https://doi.org/10.1002/lt.20828

Pai, A. L., & Ostendorf, H. M. (2011). Treatment adherence in adolescents and young adults affected by chronic illness during the health care transition from pediatric to adult health care: A literature review. *Children's Health Care*, *40*(1), 16-33. https://doi.org/10.1080/02739615.2011.537934

Pinquart, M., & Shen, Y. (2011). Depressive symptoms in children and adolescents with chronic physical illness: an updated meta-analysis. *Journal of Pediatric Psychology*, *36*(4), 375-384. https://doi.org/10.1093/jpepsy/jsq104

Resnick, M. D., Catalano, R. F., Sawyer, S. M., Viner, R., & Patton, G. C. (2012). Seizing the opportunities of adolescent health. *The Lancet*, *379*(9826), 1564-1567. https://doi.org/10.1016/S0140-6736(12)60472-3

Sawyer, S. M., Azzopardi, P. S., Wickremarathne, D., & Patton, G. C. (2018). The age of adolescence. *The Lancet Child & Adolescent Health*, *2*(3), 223-228. https://doi.org/10.1016/S2352-4642(18)30022-1

Sharif, K., & Millar, A. J. W. (2009). Paediatric liver transplantation. In P. Puri & M. Hollwarth (Eds.), *Pediatric Surgery* (pp. 603–615). Berlin: Springer.

Shemesh, E. (2004). Non-adherence to medications following pediatric liver transplantation. *Pediatric Transplantation*, *8*(6), 600-605. https://doi.org/10.1111/j.1399-3046.2004.00238.x

Sockalingam, S., Blank, D., Abdelhamid, N., Abbey, S. E., & Hirschfield, G. M. (2012). Identifying opportunities to improve management of autoimmune hepatitis: evaluation of drug adherence and psychosocial factors. *Journal of Hepatology*, *57*(6), 1299-1304. https://doi.org/10.1016/j.jhep.2012.07.032

Suris, J. C., Michaud, P. A., & Viner, R. (2004). The adolescent with a chronic condition. Part I: developmental issues. *Archives of Disease in Childhood*, *89*(10), 938-942. http://dx.doi.org/10.1136/adc.2003.045369

Tucker, C. M., Fennell, R. S., Pedersen, T., Higley, B. P., Wallack, C. E., & Peterson, S. (2002). Associations with medication adherence among ethnically different pediatric patients with renal transplants. *Pediatric Nephrology*, *17*(4), 251-256. https://doi.org/10.1007/s00467-001-0806-x

Varni, J. W., Seid, M., & Kurtin, P. S. (2001). PedsQL™ 4.0: Reliability and validity of the Pediatric Quality of Life Inventory™ Version 4.0 Generic Core Scales in healthy and patient populations. *Medical care*, 800-812. https://www.jstor.org/stable/3767969

Venkat, V. L., Nick, T. G., Wang, Y., & Bucuvalas, J. C. (2008). An objective measure to identify pediatric liver transplant recipients at risk for late allograft rejection related to non-adherence. *Pediatric Transplantation*, *12*(1), 67-72. https://doi.org/10.1111/j.1399-3046.2007.00794.x

Vik, S. A., Maxwell, C. J., & Hogan, D. B. (2004). Measurement, correlates, and health outcomes of medication adherence among seniors. *Annals of Pharmacotherapy*, *38*(2), 303-312. https://doi.org/10.1345%2Faph.1D252

Ware, J. E. (1993). SF-36 health survey: manual and interpretation guide. *Health Institute*.

Weigard, A., Chein, J., Albert, D., Smith, A., & Steinberg, L. (2014). Effects of anonymous peer observation on adolescents' preference for immediate rewards. *Developmental science*, *17*(1), 71-78. https://doi.org/10.1111/desc.12099

World Health Organization. (2003). *Adherence to long-term therapies: evidence for action*. World Health Organization.

Wright, J., Elwell, L., McDonagh, J. E., Kelly, D. A., & Wray, J. (2015). 'It's hard but you've just gotta get on with it'–The experiences of growing-up with a liver transplant. *Psychology & Health*, *30*(10), 1129-1145. https://doi.org/10.1080/08870446.2015.1024245

Wu, H., Zhao, X., Fritzsche, K., Salm, F., Leonhart, R., Jing, W., ... & Schaefert, R. (2014). Negative illness perceptions associated with low mental and physical health status in general hospital outpatients in China. *Psychology, health & medicine*, *19*(3), 273-285. https://doi.org/10.1080/13548506.2013.802358

Zelikovsky, N., & Schast, A. P. (2008). Eliciting accurate reports of adherence in a clinical interview: development of the Medical Adherence Measure. *Pediatric Nursing, 34*

Section B: What Variables Are Associated with and Predictive of Medication Adherence in Adolescents and Young Adults with Chronic Liver Disease? An Empirical Study

Word Count: 8603

Abstract

Purpose: There is little understanding of the poorer medication adherence observed in adolescents and young adults, which can result in significantly worse clinical outcomes compared to both adults and children with chronic liver disease. This project aimed to investigate the relationships between demographic factors, clinical variables, mood and illness beliefs and medication adherence including testing a predictive model informed by empirical literature, the Common Sense and Health Belief Models.

Methods: Retrospective cross-sectional (n=292) and longitudinal (n=73) clinical and self-report data from service users (16-25 years) receiving treatment at a Young Adult Liver Service for a range of chronic liver diseases were used. Correlational and categorical analyses was conducted to assess relationships with medication adherence, and structural equation modelling used to investigate the fit of a hypothesised model before this was refined in exploratory analyses.

Results: In line with the hypotheses and previous literature, adolescents and young adults who were older, older at time of transplant / diagnosis and who reported a greater emotional impact of their condition appeared to be at a higher risk of not adhering to medication. Other factors were also potentially associated with adherence, although results were mixed; other hypotheses and the original proposed model were either not supported or only tentatively so.

Conclusions: Future research is needed to validate findings, further investigate the appropriateness of the theories applied and refine the predictive model, given overall fit indices of the revised version were just short of specified thresholds and this analysis was exploratory. However, there are considerations clinicians working with this population should be aware of that may help improve adherence and associated clinical outcomes.

Keywords: Liver disease, liver transplant, adherence, adolescence, young adult

Introduction

The aetiologies of paediatric liver diseases are typically different to those diagnosed in adulthood (D'Agata & Balistrei, 1999). Managing a liver disease diagnosed in childhood or adolescence (such as auto-immune liver disease [AILD], biliary atresia, non-alcoholic fatty liver disease, metabolic conditions and/or a liver transplant) requires lifelong monitoring with hospital visits and blood tests, daily medications and/or lifestyle changes (Arya & Balistreri, 2008).

Unfortunately, outcomes for adolescents and young adults (A&YAs) with chronic liver disease are poorer than those for children and adults with similar clinical prognoses (Dharnidharka et al., 2015; Ebel et al., 2017). This may include relapse or exacerbation of their condition (e.g. in AILD) and complications such as organ rejection and death (after liver transplantation); thought associated with the greater prevalence of medication non-adherence at this age (Berquist et al., 2006, Sudan et al., 1998). Medication non-adherence has also been associated with lower health-related quality of life, greater parental emotional distress, reduced family cohesion and restrictions in school and education activities (Fredericks et al., 2007). Furthermore, increased medical care utilisation results in heightened costs to health systems and wider economy (Cleemput et al., 2002).

Adherence refers to the level a service user's behaviour follows recommended medical advice (World Health Organisation [WHO], 2003), and is recognised as complex and multi-faceted (Sabate´ & Sabate´, 2003). In this study, it refers to the extent service users take their medications as prescribed (Haynes et al., 2005); selected due to the reliance on medication to keep many liver diseases in remission, with non-adherence to treatment having significant consequences on service user outcomes.

The WHO (2003) emphasised the need to move away from the term "compliance" towards "adherence" to avoid the suggestion that blame lies with the service user for their

behaviour and that they are simply required to passively obey medical instructions, yet it still appears to be used clinically in some circumstances. It is acknowledged that "adherence" still does not necessarily reflect a person-centred approach and from a psychological perspective may be perceived to infer a paternalistic undertone (Christensen, 2004) and power imbalance between clinician and service user (Bissonnette, 2008). However, it is used throughout this paper to remain consistent with existing literature and ensure it speaks to the wide audience for whom it is hoped the findings will be beneficial (psychologists, hepatologists, other allied health professionals and researchers).

Developmental theory and empirical research have demonstrated adolescence is associated with significant physical, social, emotional and cognitive changes, culminating in the assumption of adult responsibilities and roles (Choudhury, 2010). It is a period that more recently is considered to stretch into the mid-twenties (Sawyer et al., 2018), associated with increased risk-taking (Dahl, 2004), greater social sensitivity (Blakemore & Mills, 2014), concerns around body image (Friedman & Litt., 1987) and wider (specifically social) influences on decision-making (Weigard et al., 2014). Experiencing a chronic illness during adolescence may therefore understandably introduce additional social restriction, pain and worry relative to healthy peers (Suris et al., 2004), perhaps explaining the higher levels of anxiety and depression seen in this group (Hames et al., 2016; Pinquart & Shen, 2011). Symptoms, restricted functioning and complex treatment regimens may interfere with numerous facets of adolescent life and cause frustration during this transitional stage of psychosocial development and rapid growth (Suris et al., 2004). The inherent challenges associated with this period mean it is not surprising adherence rates are poor (Litt & Cuskey, 1980); non-adherence being four times higher in adolescents than adults following liver transplant, for example (Shemesh, 2004). Prevalence estimates vary depending on age range

and measurement tools but appear to be around 17-40% from self-reports (Berquist et al., 2006; 2008; Bilhartz et al., 2015; Fredericks et al., 2008; Hames et al., 2021).

Research into approaches to increase adherence in A&YAs with liver or other chronic diseases has included education, counselling, medication dose adjustments and/or simplification, yet this has been limited and interventions have not yet yielded significant improvements (Burra et al., 2011). This indicates the need for a greater understanding of adherence behaviour and more multi-faceted approach, although it is acknowledged this is complicated by the inconsistency of adherence measurement approaches and range of what constitutes "non-adherence" (Dobbels et al., 2005). Furthermore, the finding that mental health difficulties associated with chronic diagnoses can vary depending on disease type (Pinquart & Shen, 2011) means research from different clinical populations is not necessarily transferrable. Enhanced medical interventions for paediatric liver diseases have only recently resulted in improved survival rates (Vajro et al., 2014), which also may explain why this population has received comparatively less research attention than A&YAs with other chronic diseases (e.g. diabetes).

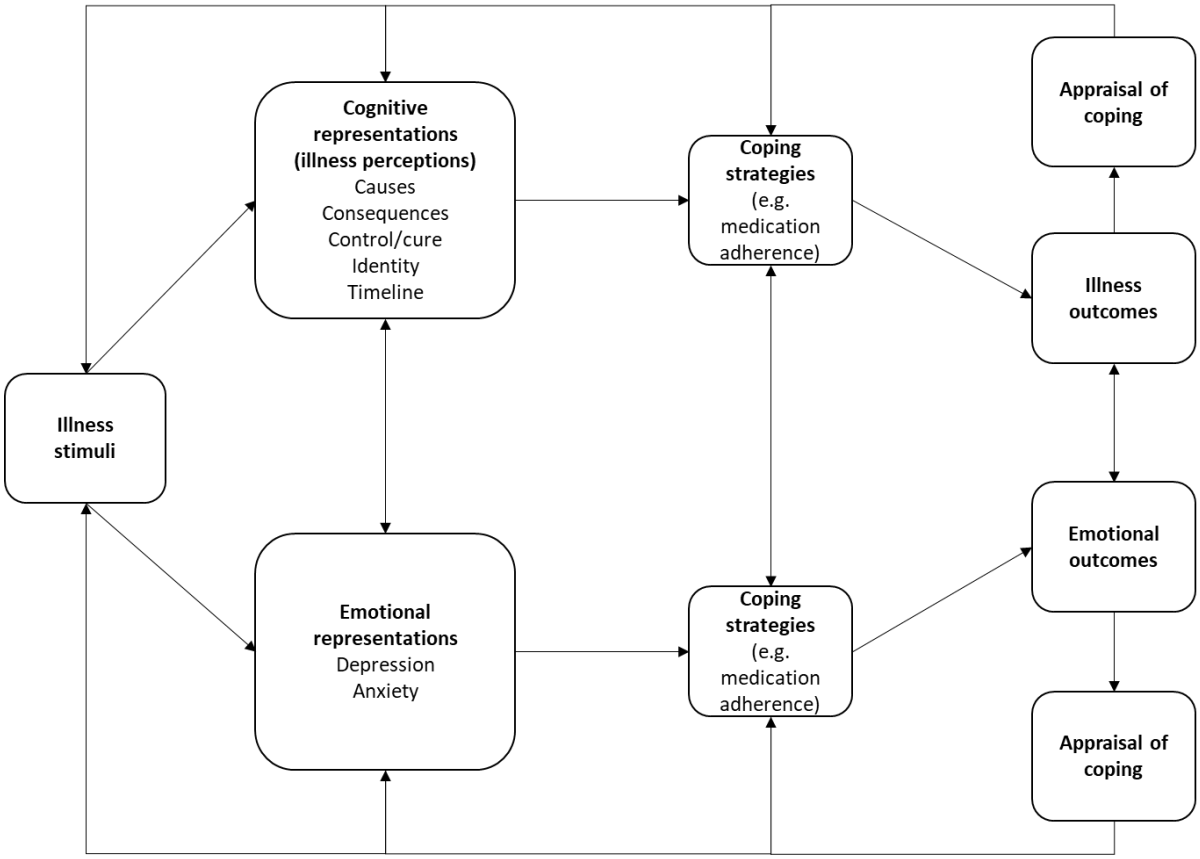
There have been attempts to conceptualise the factors underlying medication adherence, although a common limitation in A&YA research is the lack of explicit reference to a theoretical framework (McGrady et al., 2015). Health behaviour theories that appear to have been applied most in this or similar populations are the Common-Sense Model of Self-Regulation [CSM] (Leventhal et al., 1980, Leventhal et al., 1984) and Health Belief Model (Becker, 1974).

The CSM (Figure 1) suggests individuals develop cognitive representations (or perceptions), to make sense of their health threat (Leventhal et al., 1980). It is proposed individuals process these through: interpretation (forming perceptions based on factors such

as understanding of the disease/treatment and experience of symptoms); coping procedures to reduce the threat (medication adherence has been identified as a problem-focused strategy [Brandes & Mullan, 2014]); and, appraisal (analysis of the subsequent outcome) (Hagger & Orbell., 2003). In parallel are the emotional representations one makes, which may be associated with anxiety or depression elicited by the disease (Diefenbach & Leventhal, 1996).

Figure 1

The Common-Sense Model of Self-regulation (Adapted from Hagger & Orbell, 2003)



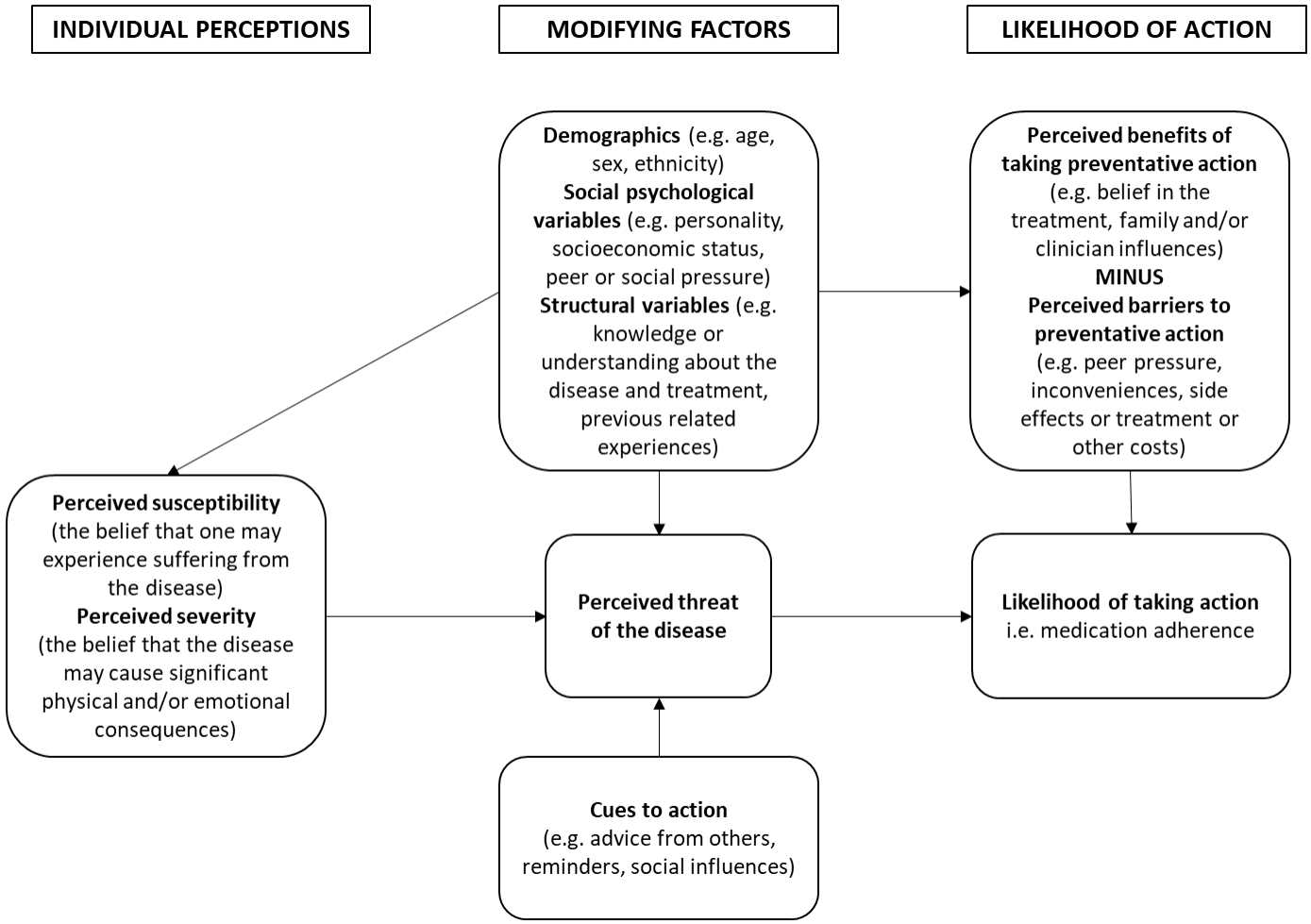
Research is limited but the application of the CSM in other conditions within A&YA has been beneficial, for example diabetes (Edgar & Skinner, 2003) and cystic fibrosis (Bucks et al., 2009). These often require a high level of treatment adherence (like liver disease) and for the latter also has cosmetic implications, making them of particular relevance. Furthermore, Hames et al. (2016) conducted one of the first studies into illness perceptions, a critical component to the CSM, in A&YAs with liver disease. Although they did not investigate adherence, they found significant correlations between depression and anxiety, and specific illness perceptions. A later publication by Hames et al. (2021) found an association between adherence and one illness perception (regarding treatment control), although this was in a relatively small sample (n=68) and included only those with AILD.

There are mixed results as to the predictive ability of components of CSM on adherence. Jones et al's (2016) review found six of nine studies demonstrated improvements in adherence through interventions based on the CSM. However, in their 2013 meta-analyses, Brandes and Mullan found only small effects for the ability of illness perceptions to predict adherence in chronically ill patients (although there were no studies on those with liver disease included). This highlights the potential limitations of the CSM and need to include other variables found to be associated with adherence in any future predictive models.

This leads to the importance of considering a second theory. The HBM (Figure 2), is similar in that it proposes health perceptions (such as perceived severity of the threat, benefits and barriers to the behaviour in question) underly an individual's willingness to engage in a certain behaviour. Whilst the literature behind specific illness perceptions within the CSM appears more developed, the HBM more explicitly details the role other variables may play that the CSM does not (such as demographics; found to be associated with adherence within this project's population; see Table 2). The HBM has been successfully used to support the explanation or prediction of medication adherence in research in A&YAs with other conditions such as diabetes (Bond et al., 1992) and cystic fibrosis (Dempster et al., 2017).

Figure 2

The Health Belief Model (adapted from Rosenstock et al., 1988)



Purpose of this Study

The limited literature within this population combined with a lack of explicit reference to theoretical models demonstrates the need for further research into the interaction between liver disease, treatment, adherence and the complex cognitive, social and emotional changes occurring during adolescence. This study will build on existing research that uses some of the same data (Hames et al., 2016, 2021), taken from a UK young adult liver service (16-25 years) to investigate the relationships between demographic, clinical, mood and illness perception variables and adherence. It is distinct from previous research due to its larger sample, inclusion of a wider selection of liver disease diagnoses, investigation of more variables, use of longitudinal data and development of a predictive model.

It will also draw more explicitly upon theory; it is not unreasonable to assume that the unique experiences during A&YA development may contribute to the development of illness perceptions and thus shape that individual's behaviour. However, the CSM's lack of explicit reference to additional factors found to be relevant within this study's population justifies the need to be informed by both the CSM and HBM theoretical models (although at this stage, only some of the main theorised pathways), in addition to empirical findings that have not explicitly referenced a theoretical framework.

The selected approach for the predictive element of this study is a structural equation model (SEM) where multiple factors can be included in parallel (given there is insufficient empirical evidence as this stage to justify a moderated mediation model, for example), and the model subsequently refined in a more exploratory nature (Byrne, 2016). Helpful methodological SEM examples in the context of adherence, which influenced the approach taken in the current study, included Knowles et al. (2017) in adults with irritable bowel disease and De Las Cuevas (2017) in adult psychiatric outpatients.

The age group (16-25 years) is in line with recent definitions of adolescence and evidence that the neurological developments associated with this period stretch into the mid-twenties (Casey et al., 2008; Sawyer et al., 2018), together with literature suggesting older A&YAs are most vulnerable to non-adherence and poorer clinical outcomes (Ebel et al., 2017).

It is hoped this research will be beneficial clinically and academically. Specifically, findings will inform service provision in young adult liver services (and potentially services for A&YA with other chronic conditions) in the hope of improving care and subsequent physical health outcomes in line with NHS values 'commitment to quality of care' and 'improving lives'. It is also hoped findings will help fill research gaps regarding adherence in this population and contribute to existing literature surrounding the application of theoretical frameworks (specifically the CSM and HBM) to this unique period of development.

Hypotheses

Hypotheses are grouped into four sections, detailed along with their empirical and/or theoretical justification in Table 1. The first section regards prevalence of mental health difficulties; that is, A&YAs with chronic liver disease will present with higher rates of anxiety and depression than the general A&YA population (1a).

The second concerns the associations between a range of demographic, clinical and mood variables and adherence. Specifically, it hypothesises that greater symptoms of anxiety and depression will be associated with specific perceptions about illness (2a) and poorer adherence (2b). Other variables hypothesised to be associated with poorer adherence include worse liver function blood tests (2c), specific illness perceptions (2d), older age at diagnosis or transplant (2e), older age (2f), lower socioeconomic status (2g) "supportive" as opposed to "treatment" medication (2h), and female gender (2i). Females are also hypothesised to report

greater symptoms of depression, anxiety and more maladaptive illness perceptions than male service users (2j).

Section 3 includes the hypothesis that Model A (Figure 3), which contains variables detailed in Hypotheses 2b-i, will be predictive of adherence. Finally, section 4 concerns a smaller subset of longitudinal data where it is anticipated specific illness perceptions and greater symptoms of depression and anxiety at timepoint 1 will be associated with lower adherence scores (4a) and poorer physical health markers (4b) at timepoint 2.

Table 1

Hypotheses and Their Theoretical and/or Empirical Justification

No.	Hypothesis	Theoretical and/or Empirical Justification
Section 1: Adherence Prevalence		
1a	Adolescents and young adults (A&YAs) with chronic liver disease will present with higher rates of anxiety and depression than the general A&YA population (the latter being taken from existing literature).	This will be a replication of Hames et al's (2016) analyses, with a larger and broader sample, who found that 17.7% participants screened positive for anxiety and/or depression. They compared this to Green et al. (2004) who found between 4-6% of the general A&YA population in the UK screened positive (note different methodologies were used). Higher rates of anxiety and depression have also been demonstrated in young people with other chronic health conditions (see Pinquart & Shen, 2011 for a meta-analysis).
Section 2: Relationships between Adherence, Demographic, Clinical, Mood and Illness Perception Variables		
2a	Symptoms of depression and anxiety will be positively correlated with specific perceptions about illness, including 'impact of the illness on their life' (Brief Illness Perception Questionnaire; BIPQ, Broadbent et al., 2006; Question 1), 'how much are symptoms experienced' (BIPQ Question 5), 'level of concern about the illness' (BIPQ Question 6) and the 'emotional impact of the illness' (BIPQ Question 8), and negatively correlated with 'level of perceived personal control' (BIPQ Question 3). Anxiety may additionally be positively correlated with 'how long you think your condition will continue' (BIPQ question 2) *(note that correlational analyses will be undertaken for all eight illness perceptions within the BIPQ but significant results are only anticipated for those specified).*	The Common-Sense Model of Self-Regulation (CSM, Leventhal et al., 1980, Leventhal et al., 1984) suggests illness perceptions can influence emotional problems. It also suggests coping skills can mediate some of these relationships, although this is not examined within this study. This will be a replication of Hames et al's (2016) study with a larger and broader sample, who found that higher levels of depression were associated with increased scores in questions 1, 5, 6 and 8 on the BIPQ and reduced scores on question 3. Higher levels of anxiety had the same associations with BIPQ questions as depression, in addition to higher anxiety scores also being positively correlated with higher scores in question 2. Literature into other chronic health conditions have found similar patterns of results using the BIPQ and measures of anxiety and depression. For example, Blanco & Weinman (2018) in adults with a chronic skin condition and Wu et al. (2014) in adult hospital outpatients. Muscat et al. (2020) found illness beliefs (specifically questions 2,3,5 and 8) were the strongest predictors of distress in adults with chronic kidney disease.

No.	Hypothesis	Theoretical and/or Empirical Justification
2b	Higher rates of depression and anxiety will be correlated with poorer self-reported medication adherence. This will be supported by categorical analyses, with the non-adherent group (reportedly taking their medication <80%) having significantly higher (worse) scores for depression and anxiety than the adherent group (≥80%).	The CSM suggests illness beliefs, emotional problems and behaviour (such as medication adherence) can impact and interact with each other. In A&YAs with AILD, Hames et al. (2021) found those with higher depression scores were less punctual in taking medication but found no other associations between other aspects of adherence with either depression or anxiety. However, Sockalingham et al. (2012) did find adults with AILD experiencing depression or anxiety were less likely to be adherent to medication and psychological distress was also identified as a risk factor for non-adherence in A&YA liver transplant recipients in Burra et al's (2011) literature review. Similar results have been found in other chronic conditions, for example: Bautista et al. (2012) found that in adults with hypertension, those with at least mild depression and anxiety were 2.48 and 1.59 times respectively more likely to become non-adherent in the following 3 months. Annunziato et al. (2018) has suggested that those experiencing mental health difficulties can find it difficult to engage with health services and adhere to treatment, which can impact their quality of life and result in poorer physical health outcomes
2c	Higher self-reported medication adherence will be correlated with better physical health markers (liver function blood tests). This will be supported by categorical analyses, with the non-adherent group (<80%) having significantly (worse) liver function results than the adherent group (≥80%).	Poorer physical health and clinical outcomes have consistently been found to be associated with non-adherence to medication in A&YAs with liver disease and/or post liver transplant. For example, Annunziato et al. (2018) and Bilhartz et al. (2015) found an association with episodes of rejection (evidenced by biopsy), and Fredericks et al. (2010) and Hames et al. (2021) with liver function blood tests.
2d	Illness perceptions identified in Hypothesis 2a will be correlated with poorer self-reported medication adherence in the same direction as 2a. That is, higher scores in BIPQ questions 1,5,6,8 and lower scores in question 3 will be associated with poorer self-reported adherence.	The CSM suggests illness beliefs, emotional problems and behaviour (such as medication adherence) can impact and interact with each other. The Health Belief Model (HBM, Becker, 1974) also recognises the role individual perceptions may have on the perceived threat of an illness and subsequent likelihood of taking action. Hames et al. (2021) found only the level of perceived "treatment control" was associated with adherence, although their sample only included A&YAs with AILD. In other populations, illness perceptions have been associated with adherence but the specific questions reaching significance varied. In adults

No.	Hypothesis	Theoretical and/or Empirical Justification
	This will be supported by categorical analyses, with the non-adherent group (<80%) having significantly higher scores in BIPQ questions 1,5,6 and 8 and lower score in BIPQ question 3, than the adherent group (≥80%).	following liver transplant, for example, O'Carroll (2006) found beliefs about consequences (BIPQ question 1), emotional effect (8) and medication (4) were associated with adherence. In Kaptein's (2008) meta-analyses in people with asthma, they found illness perceptions were correlated with and/or could predict adherence. Results supported Mc Sharry et al's (2011) meta-analyses who found that in people with diabetes, various illness perceptions were associated with and/or could predict adherence, particularly Identity (5), Personal Control (3) and Concern (6). The five illness perceptions specified were selected (out of the potential eight) as these were the ones found to be associated with depression and/or anxiety by Hames et al. (2016) within a comparable population and most consistently associated with adherence in other studies, albeit in different populations. However, this is speculative given the limited literature within this population.
2e	Age at diagnosis / transplant will be negatively correlated with self-reported adherence. This will be supported by categorical analyses, with the non-adherent group (<80%) having a significantly older mean age of diagnosis / transplant than the adherent group.	Berquist et al. (2006) found an older age at liver transplant in A&YAs was associated with poorer adherence, but this was not supported by Hames et al. (2021) who found no significant association between adherence and age at diagnosis in A&YAs with AILD. Yazigi et al. (2017), do however suggest age at transplant is important to understand adherence behaviour as transplantation may cause an increased level of 'uncertainty and vulnerability' at this more sensitive age.
2f	Age will be negatively correlated with self-reported adherence. This will be supported by categorical analyses, with the non-adherent group (<80%) having a significantly older mean age than adherent group.	Older age has consistently been found to be associated with poorer adherence in A&YAs with liver disease and/or after transplant (Annunziato et al., 2018; Berquist et al., 2006, Bilhartz et al., 2015; Fredericks et al., 2010). However, Shemesh et al. (2011) found age did not impact whether A&YA transplant recipients were more likely to be adherent and Berquist et al. (2006) and Fredericks et al. (2010) found non-significant associations for age. Using some of the same data that will be included within this study (only those with AILD), Hames et al. (2021) found age was inversely associated with adherence. It would be helpful to ratify this within a larger population and across other liver disease types.
2g	Service users with a lower socioeconomic status will be less likely to be adherent than those with a higher socioeconomic status.	Berquist et al. (2006) found A&YAs of a lower socioeconomic status post liver transplant were less likely to be adherent, with similar (yet statistically non-significant) results in their 2008 study. Dobbels et al. (2005) similarly found A&YA transplant recipients with a lower socioeconomic status were

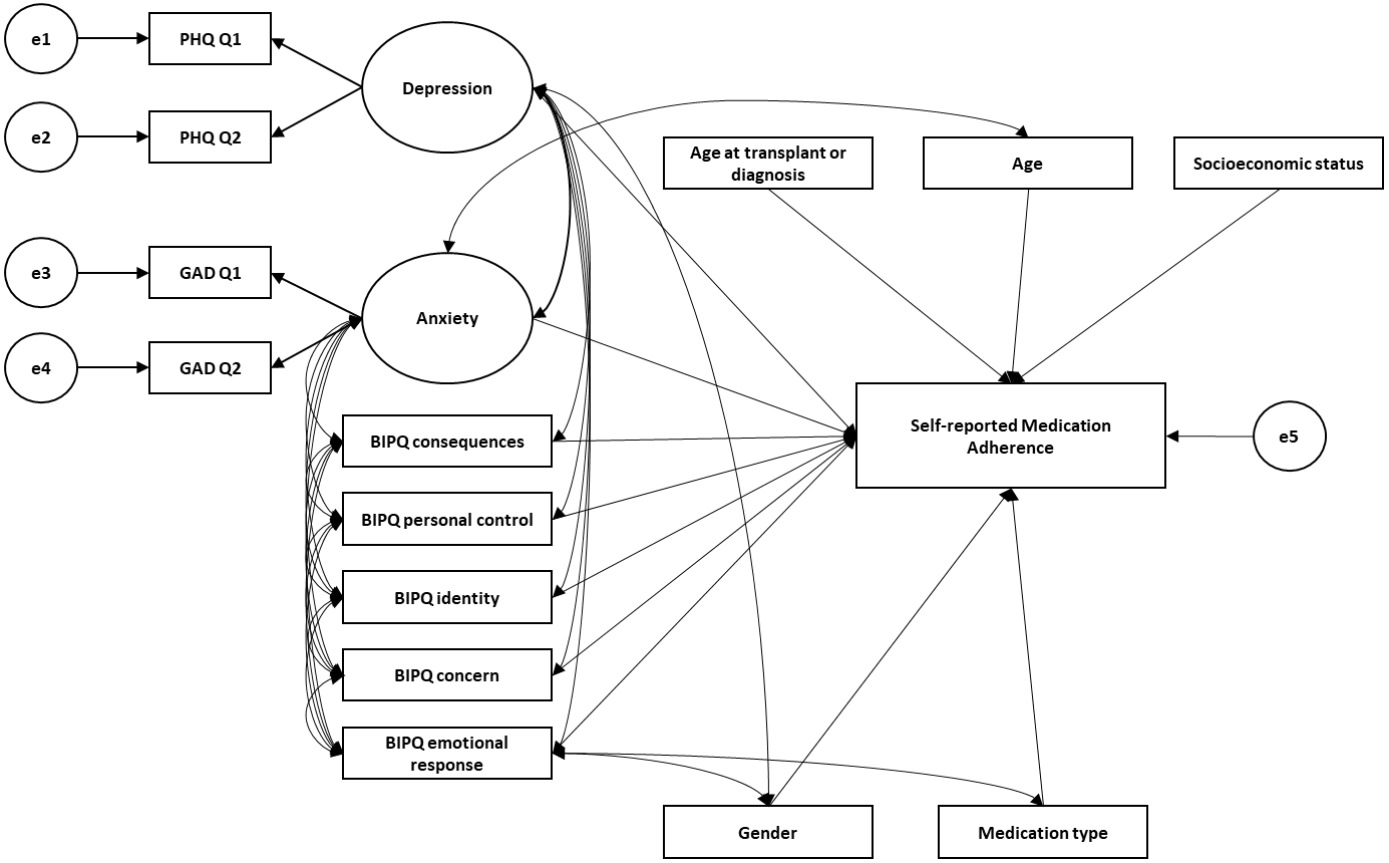
No.	Hypothesis	Theoretical and/or Empirical Justification
		significantly less likely to be adherent (although indicators used across studies vary, and in the latter included whether the: family received benefits; parents didn't have a college degree or the A&YA lived with only one parent). A&YAs post liver transplant living in single-parent families were also found to be less adherent by Berquist et al. (2008, and similarly in 2006 yet this result was not statistically significant). Whilst not necessarily a reflection of socioeconomic status, other psychosocial factors have also been associated with a greater chance of non-adherent behaviour in A&YAs with AILD (Hames et al., 2021).
2h	Service users prescribed "Treatment" will be more likely to be adherent than those prescribed "Supportive" medication, in categorical analyses.	Immunosuppressant (classified as a "treatment" medication) side effects, which can include weight gain, hirsutism and mood changes have been associated with non-adherence (Fredericks et al., 2008). However, theoretically, the CSM and HBM would suggest a greater perceived threat of the disease (i.e. more likely in those prescribed "treatment" rather than "supportive" medication) would increase the likelihood of engaging in protective health behaviours, such as medication adherence.
2i	Female service users will report lower adherence than male service users in categorical analyses.	Sex and gender have been found to be associated with adherence in some studies in other populations (e.g. female adult renal transplant recipients; Frazier et al.,1994). It was suggested that this may have been due to side effects of immunosuppressants on physical appearance having more of an impact on female service users. However, other studies in A&YAs with liver disease and/or post liver transplant found no association between sex or gender and adherence (Berquist et al., 2008, Bilhartz et al., 2015, Fredericks et al., 2008). Berquist et al. (2006) found female adolescents were more likely to be nonadherent than males following liver transplant, but this result was non-significant.
2j	Female service users will report greater symptoms of depression, anxiety and more maladaptive illness perceptions than male service users.	Hames et al. (2021) found female service users were more likely to be worried, anxious and emotionally impacted by their diagnosis than male service users, using some of the data within this study. Greater mental health difficulties are generally reported by female A&YAs throughout the general population (Sen, 2004).

No.	Hypothesis	Theoretical and/or Empirical Justification
Section 3: Predictors of Adherence using Structural Equation Modelling		
3a	A model (A; Figure 3) involving multiple variables (specifically illness perceptions, anxiety, depression, socioeconomic status, age of diagnosis or transplant, age, medication type and gender) will be predictive of self-reported medication adherence (in the directions specified in Section 2 hypotheses).	The CSM suggests illness stimuli (such as clinical variables) and subsequent illness beliefs and emotional problems may impact that individual's behaviour (i.e. medication adherence). The HBM also recognises the importance of individual perceptions on that individual's level of perceived threat and subsequent likelihood of taking action (such as adhering to medication), in addition to the potential role demographic variables may play in modifying this relationship. Berquist et al. (2006) identified the need for future research in this population to include the creation and testing of a model to predict non-adherence. It would be helpful to develop this informed by theory (specifically the CSM and HBM) and other empirical evidence.
Section 4: Associations Between Mood and Illness Perceptions at Timepoint 1 with Adherence and Physical Health at Timepoint 2		
4a	Higher scores for certain illness perceptions (BIPQ questions 1,5,6,8), depression (PHQ) and anxiety (GAD) and lower scores for BIPQ question 3 at timepoint 1 will be associated with lower adherence scores.	Whilst literature in this population is limited, illness perceptions specified within the CSM have been found to have a predictive role of adherence in various populations (Kucukarslan, 2012)
4b	Higher scores for certain illness perceptions (BIPQ questions 1,5,6,8), depression and anxiety and lower scores for BIPQ question 3 at timepoint 1 will be associated with worse liver function blood tests at timepoint 2.	Whilst literature in this population is limited, illness perceptions specified within the CSM have been found to predict health outcomes in other disease types, such as those with pre-dialysis chronic kidney disease (Muscat et al., 2020) and diabetes (Vedhara et al., 2016).

Notes. Full details of all measures used are described in the Methods section.

Figure 3

Model A: Model Developed to Test Whether the Specified Variables can Predict Medication Adherence in A&YAs with Liver Disease



Note. e = error. PHQ = *Patient Health Questionnaire (PHQ-9; Spitzer et al., 1999) GAD = Generalized Anxiety Disorder Questionnaire (GAD-7; Spitzer et al., 2006), BIPQ = Brief Illness Perception Questionnaire (Broadbent et al., 2006).* Full details are included in the Method section.

Method

Setting

This study used data from a young adult liver service, which looks after A&YA (16-25 years) under the care of paediatric and adult liver specialists, including for liver transplantation. This multidisciplinary service (consisting of medical, psychological and social workers) takes a therapeutic approach to support the bespoke needs of this age group in managing their condition.

The service routinely uses an electronic screening platform; IMPARTS (Integrating Mental and Physical healthcare: Research Training and Services), an initiative funded by King's Health Partners aiming to improve mental healthcare provision across their medical settings through the collection and analyses of patient data. Service users completed a battery of questionnaires at the time of their appointment, using iPads.

Sample

All service users who attended an outpatient clinic on days when a volunteer was available to administer the iPad between 2013 and 2019 were asked to participate (note no new data was collected since 2020 due to a lack of volunteers and the coronavirus pandemic).

For service users who had data for more than one appointment, only the first appointment with the most complete data was included in cross-sectional analyses (Hypotheses 1a-3a) (n=292). For longitudinal analyses (hypotheses 4a&b), data were included if service users had attended more than one appointment with a gap of at least six months between them (as IMPARTS automatically does not request certain questionnaires if they attended more recently than this). Where a service user had complete data for three or more appointments, two were selected that had a gap closest to one year. This resulted in a sample size of 73 (range=6-58, mean=18.8, standard deviation (SD)=16.6 months between

timepoint 1 and 2). There were no additional exclusion criteria; service users with all types and severity of liver disease were included.

A priori power analyses using G*Power (Faul et al., 2009) indicated the cross-sectional and longitudinal sample sizes were sufficient to detect small and medium correlations, respectively. For SEM analyses, the sample size was also sufficient considering its ratio with the number of variables and parameters to be estimated (Kyriazos, 2008).

The mean age within the cross-sectional and longitudinal samples was 18.3 (SD=1.9) and 17.9 years (SD=1.7), respectively. The mean age at transplant or diagnosis (see "Measures of Variables" section below for definition) was 9.3 (SD=5.7) and 10 years (SD=5.9) within the cross-sectional and longitudinal samples respectively. Further demographic and clinical characteristics are included in Table 2. Note that it was not possible to include ethnicity data due to poor quality in the retrospective data set.

Table 2

Demographics and Disease Characteristics within the Samples

Characteristic	n (%) in Cross-sectional Sample	n (%) in Longitudinal Sample (at timepoint 1)
Gender (in medical records)		
Male	138 (47.3)	38 (52.1)
Female	154 (52.7)	35 (47.9)
Index of Multiple Deprivation*		
1	15 (5.1)	2 (2.7)
2	32 (11.0)	7 (9.6)
3	44 (15.1)	15 (20.5)
4	27 (9.2)	3 (4.1)
5	33 (11.3)	8 (11.0)
6	34 (11.6)	7 (9.6)
7	25 (8.6)	5 (6.8)
8	26 (8.9)	8 (11.0)
9	27 (9.2)	9 (12.3)
10	23 (7.9)	9 (12.3)
Age		
16-18 years	185 (63.3)	50 (68.5)
19-21 years	87 (27.7)	19 (26.0)
22-25 years	20 (6.8)	4 (5.5)
Liver Disease Type		
A1AT deficiency	13 (4.5)	1 (1.4)
Acute Liver Failure	8 (2.7)	2 (2.7)
AILD**	83 (28.4)	24 (32.9)
AISC**	32 (11)	11 (15.1)
Alagille Syndrome	7 (2.4)	1 (1.4)
Biliary Atresia	58 (19.9)	14 (19.2)
Gilbert's Syndrome	4 (1.4)	1(1.4)
NAFLD**	16 (5.5)	0
Wilson's Disease	13 (4.5)	4 (5.5)
Other	58 (19.9)	15 (20.5)
Medication Type		
Treatment	199 (67.9)	60 (82.2)
Supportive	94 (32.1)	13 (17.8)
Transplant (at time of appointment)		
Yes	81 (27.7)	26 (35.6)
No	211 (72.3)	47 (64.3)

Note. See "Measures of Variables" section for definitions of characteristics, where relevant.

* Taken from the 2019 English Indices of Deprivation using postcode data

(https://www.gov.uk/government/statistics/english-indices-of-deprivation-2019)

**A1AT = Alpha-1 antitrypsin deficiency, AILD = Autoimmune Liver Disease, AISC =

Autoimmune Sclerosing Cholangitis, NAFLD = Non-alcoholic Fatty Liver Disease

Design and Data Collection

This study predominantly used archival self-report data, collected using IMPARTS whilst service users waited for their appointment. The battery included the measures detailed below, and others not included within this study (for example regarding smoking, alcohol use and worries).

Data were supplemented by demographic and disease variables gathered manually from electronic patient records, resulting in two quantitative data-sets (cross-sectional and longitudinal).

Ethical Considerations and Consent

Generalised NHS ethics approval has been granted for IMPARTS data to be used in research, which therefore covers this project. A formal application was approved by the IMPARTS Research Database Oversight Committee (details of both in Appendix B).

As data was collected routinely as part of clinics, there were no significant risks to participants associated with data collection that had not already been accounted for by the clinical team. For example, IMPARTS provides clinicians with real-time feedback and any indication of mental or physical health difficulties were identified and discussed with the service user that day.

Service users were provided with an IMPARTS information sheet (Appendix C) and provided consent for data (including self-report measures and medical information from patient records) to be used for research purposes. When gathering data from patient records, all IMPARTS protocols were followed, including accessing and recording data only required as part of the study, and anonymising and storing data. No paper records were used.

Measures of Variables

Patient Health Questionnaire (PHQ-9) (Spitzer et al., 1999) (Appendix D)

The PHQ-9 is a brief, self-administered screening tool for depression, whereby participants are asked to rate nine items based on the last two weeks, using a scale of "not at all", "several days", "more than half the days" or "nearly every day". The National Institute for Health and Care Excellence (NICE) advises using the PHQ-9 to measure symptoms of depression in people with chronic physical health conditions given its recognised validity and reliability (NICE, 2009). Although initially designed for adults, Allgaier et al. (2012) demonstrated similar sensitivity and specificity in A&YAs.

Generalized Anxiety Disorder Questionnaire (GAD-7) (Spitzer et al., 2006) (Appendix D)

The GAD-7 is a similar brief, self-administered screening tool for anxiety, sharing the same four response Likert scale with the PHQ-9. Spitzer et al. (2006) recognised it has good reliability as well as criterion, construct, factorial and procedural validity. Mossman et al. (2017) demonstrated it an efficient tool for use in A&YAs, with acceptable specificity and sensitivity.

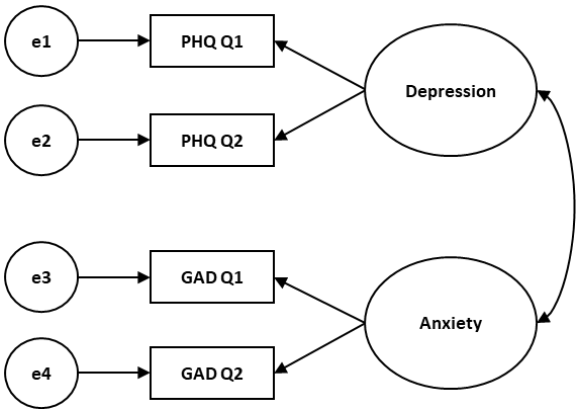
PHQ-2 and GAD-2. The approach taken by IMPARTS, with the aim of reducing load for service users, was to stop requesting responses to the PHQ-9 and GAD-7 if the participant scored zero or one for both of the first two questions. This followed the screening approach (PHQ-2 and GAD-2) demonstrated by Richardson et al. (2010) and Plummer et al. (2016) respectively as having good-acceptable quality of identifying major depression and GAD, and has been used in similar publications (Hames et al., 2021). However, this approach resulted in large amounts of missing responses for questions three-nine (PHQ-9) and three-seven (GAD-7); 77% and 78% respectively within the cross-sectional sample. To establish the reliability of using only questions one and two within this sample, the total

scores (where available) for the PHQ-9 and GAD-7 were correlated against their respective sum of questions one and two. These were statistically significant and strongly positive ($r(69)=0.73$, $p<.001$ for the PHQ and $r(63)=0.58$, $p<.001$ for the GAD), so it was deemed appropriate to conduct subsequent correlation analyses between the sum of questions one and two with other variables (Section 2).

In SEM (Section 3), scores for questions one and two in the PHQ-9 and GAD-7 were used as continuous observed variables for the latent constructs of depression and anxiety (respectively). Confirmatory Factor Analysis (CFA) was used to examine their reliability, validity and uni-dimensionality (Figure 4) using the approach advised by Byrne (2016). This achieved good model fit indices ($\chi 2(1, N=292) = 1.521$, $p=.218$; CFI =.999; NFI=.997; RMSEA=.042 [90%CI, 0.000-0.169]) and parameter estimates (Byrne, 2016). This indicated the latent variables of both depression and anxiety could be used within subsequent analyses using an SEM framework. Note that interpretation details are included within the Results section, as part of the SEM analyses (including definitions and thresholds for good model fit; Table 10).

Figure 4

Confirmatory Factor Analyses to Test the Latent Variables of Depression and Anxiety



A categorical approach was also taken for Section 1 and relevant analyses in Section 2, classifying participants according to the criteria detailed in Table 3. Lowe et al. (2004) found this approach had an 83% (95% confidence interval, 72-91%) sensitivity and 90% (95% confidence interval, 87-93%) specificity for identifying probable major depression disorder (MDD) cases. With regards to the GAD, this approach followed that used by Hames et al. (2016).

Table 3

Criteria applied for Depression and Anxiety Symptom Categorisations

Classification (code)	Depression Criteria	Anxiety Criteria
No symptoms	Scoring zero or one for both of the first two questions (and thus not meeting the criteria to complete the full questionnaire)	Score of less than 5
Some symptoms (PHQ) / Mild anxiety (GAD)	Meeting the criteria to complete the full questionnaire but not meeting the threshold for Probable MDD	Score of 5-9
Probable MDD / Probable GAD	Scoring two or three on at least one of the first two questions and on at least five out of all nine symptoms within the last two weeks	Score of 10 or more

Brief Illness Perception Questionnaire (BIPQ) (Broadbent et al., 2006) (Appendix D)

The BIPQ consists of eight single-item questions (thus no total score is obtained), designed to capture cognitive and emotional representations of illness (Table 4). This brief version was developed from the original Illness Perception Questionnaire (IPQ, Weinman et al., 1996) and later IPQ-R (revised; Moss-Morris et al., 2002), all of which draw on the five dimensions of the cognitive representation of illness (identity, cause, consequences, timeline and cure or control) identified by Leventhal et al. (1984). For each question in the BIPQ, participants mark their responses using a 0-10 Likert scale to assess how far an illness belief

corresponds with their views. Zugelj et al. (2010) demonstrated the BIPQ predicted health behaviours (specifically adherence to medication) in young people. Whilst responses to all eight items were requested from respondents, only scores from five questions were included in the model, in line with literature described in Table 1.

Table 4

Brief Illness Perception Questionnaire; Questions, Summary Terms and Scoring Direction (reproduced from Broadbent et al., 2006)

No – Summary Term	Question (0-10 scale labels)	Positive /Negative Scoring
1 - Consequences	How much does your condition affect your life? (No affect at all – Severely affects my life)	Negative
2 - Timeline	How long do you think your condition will continue? (A very short time – Forever)	Negative
3 – Personal Control	How much control do you feel you have over your condition? (Absolutely no control – Extreme amount of control)	Positive
4 – Treatment control	How much do you think your treatment can help your condition? (Not at all – Extremely Helpful)	Positive
5 – Identity	How much do you experience symptoms from your condition? (No symptoms at all – Many severe symptoms)	Negative
6 - Concern	How concerned are you about your condition? (Not at all concerned – Extremely concerned)	Negative
7 - Understanding	How well do you feel you understand your condition? (Don't understand it at all – Understand very clearly)	Positive
8 – Emotional Response	How much does your condition affect you emotionally? (e.g. does it make you angry, scared, upset or depressed?) (Not at all affected emotionally – Extremely affected emotionally)	Negative

Note. Summary terms are used within the Results section so are important for analyses interpretation. Positive scoring is where a selection of ten from the Likert scale indicates a more positive belief. Negative scoring is where a score of ten indicates a more negative belief.

Medication Adherence

Scaled responses to the question, *"In general, what percentage of the time do you take your medication?"* were used. Justification for this includes a small but significant correlation between responses and two liver function blood tests (indicative of adherence); aspartate aminotransferase (AST) and alanine aminotransferase (ALT), within a small subset of the same data (Hames et al., 2021). A categorical classification (≥80% = "adherent") was used to examine group differences, in line with Hames et al's (2021) approach.

Physical Health Markers

Blood tests, specifically AST, Bilirubin and GGT (Gamma-glutamyl transpeptidase) were selected as an indication of liver function/health within analyses (Lala et al., 2021). These were obtained from patient records following advice from the Consultant Hepatologist.

Socioeconomic Status (SES)

The Index of Multiple Deprivation (IMD) taken from the 2019 English Indices of Deprivation (https://www.gov.uk/government/statistics/english-indices-of-deprivation-2019) was used as an indication of socioeconomic status, using postcodes obtained from patient records. The IMD is the official measure of relative deprivation in England, obtained by weighting and then combining individual scores for seven deprivation domains (such as income, crime and employment). Once a combined rank is obtained for the IMD (1st being the most and 32844th the least deprived area), areas are grouped into deciles (1 being the most and 10 the least deprived).

Gender

Gender (as listed on medical records) was coded for the purposes of statistical analyses into 1 (male) and 2 (female).

Age at Transplant or Diagnosis

As a transplant is such a significant undertaking and the main determinant of treatment someone receives, age at transplant was used where this was relevant (similar to the approach by Berquist et al., 2006). For those who had not received a transplant, age at diagnosis was used (as in Hames et al., 2021). Where the latter was not explicit, the date of the service user's first appointment with the service was taken as date of diagnosis.

Medication Type

Medications were categorised by the function they served into "treatment" (for example, those that can actively alter the individual's immune system; coded 1), or "supportive" (those with a milder impact on the body or serve a more supportive function, such as vitamins; coded 2). Medications within "treatment" included immunosuppressants and steroids (for example Advagraf, Prograf, Prednisone and Mycophenolate Mofetil) and for supportive, Ursodeoxycholic Acid, Tranexamic Acid and Phenobarbitone. "Supportive" medications are generally less likely to carry significant side effects (Di Maira et al., 2020).

Data Analyses

Extensive data checks, cleaning and coding were undertaken before analyses, which included manual identification and combination of data from the appropriate appointments within the longitudinal sample.

Preliminary data analyses were conducted using IBM SPSS Statistics Version 27 and SEM analyses using IBM SPSS AMOS Version 26. SEM was selected due to its capacity to examine complex models and the relationships between multiple exogenous (independent, including latent) and endogenous (dependent) variables simultaneously (Hair et al., 2006), allowing for the predictive effect of multiple variables on medication adherence to be investigated.

All variables were screened for missing entries and outliers. Pair-wise deletion was used within correlation analyses and regression imputation (in line with recommendations from Byrne, 2016) within SEM. There was <1% of missing data across all variables within the final cross-sectional sample, which is within limits that would yield reliable SEM results (<5%, Olinsky et al., 2003). Model fit indices were compared between analyses that included and excluded imputation and, as there did not appear to be any notable differences, only output that included data imputation is presented within the results.

Non-normality can lead to an underestimation of fit indices and/or increase in the chi-square value within SEM (Hair et al., 2006). Data were within the suggested range of -2 to +2 indicating skewness was not an issue (Hair et al., 2006), univariate kurtosis values were under the threshold of seven indicating normality (West et al., 1995) except for adherence, and multivariate kurtosis was above the threshold of five advised by Bentler and Wu (2005), indicating a non-normal multivariate distribution. Kurtosis is known to severely impact tests of variances and covariances (DeCarlo, 1997), thus recommendations by Byrne (2016) were followed to address this. A log10(constant[101]-x) transformation of adherence score and removal of four outliers (using mahalanobis distance; observations furthest from the centroid), brought the adherence univariate score within and the multivariate kurtosis score closer to, but not within, the recommended thresholds. Given the latter, SEM results for Model A should be treated with caution.

Descriptive statistics were employed to obtain a better understanding of the data. Further details regarding the analytic approach, grouped by hypotheses, are provided within the results to aid ease of reading and interpretation. Apart from in cases where more detail was informative, statistics are reported to two decimal places.

Results

Section 1: Prevalence of Depression and Anxiety (Hypothesis 1a)

Percentages of those meeting criteria for depression and anxiety (Table 3) were calculated to establish prevalence. This indicated 11.6% met criteria for probable MDD and 16.1% for probable GAD (Table 5) with a further 12.7% and 6.2% presenting with mild symptoms respectively. This, as hypothesised, was greater than the most comparable figures detailed by de la Torre et al. (2021) (2.4% for probable depressive disorder in 16–29 year-olds), Thapar et al. (2012) (>4% one year prevalence of unipolar depressive disorder by the end of adolescence) and Green et al. (2004) (4-6% for males and females respectively screening positive for either depression or anxiety). However, it is acknowledged that somewhat different ages and measures were used, so this comparison should be treated with caution. For example, de la Torre et al. (2021) assessed depression prevalence using a full, earlier version of the PHQ in a large, representative UK sample (their closest comparable category was 16-29 years).

Table 5

Distribution of Depression and Anxiety Symptoms Within the Cross-sectional Sample (n=292)

Categorisation	Depression n (%)	Anxiety n (%)
No symptoms	221 (75.7)	226 (77.4)
Some symptoms (PHQ) / Mild anxiety (GAD)	37 (12.7)	18 (6.2)
Probable MDD / Probable GAD	34 (11.6)	47 (16.1)
Missing score	0	1 (0.3)

Section 2: Relationships between Adherence, Demographic, Clinical, Mood and Illness Perception Variables (Hypotheses 2a-j)

To address Hypotheses 2a-j, correlational (Table 6) and categorical analyses (Tables 7-9) were conducted. As data did not meet normality assumptions, Spearman's correlations were used.

Table 6

Correlational Analyses between Continuous Variables within the Cross-Sectional Sample (n=292)

		BIPQ															
		Cons	Time	PC	TC	Iden	Conc	Und	ER	PHQ	GAD	SES	Age	Age at t/d	Adhe-rence	AST	GGT	Bili-rubin
BIPQ	Cons		**.13***	**-.31*****	-.08	**.58*****	**.64*****	-.04	**.69*****	**.35*****	**.38*****	-.06	.05	**.17****	**-.16***	.09	**.13***	.06
	Time			-.03	**.14***	.09	.07	-.04	**.15***	.07	**.15***	**.13***	.03	**-.15***	.03	.06	.03	-.03
	PC				**.25*****	**-.17****	**-.26*****	**.21*****	**-.18****	-.09	-.11	**-.13***	.03	.06	-.03	-.03	-.02	-.11
	TC					-.05	**-.13***	**.25*****	-.06	**-.12***	**-.12***	-.02	-.05	.01	**.18****	-.02	-.06	.00
	Iden						**.56*****	-.06	**.61*****	**.36*****	**.37*****	-.09	.04	**.31*****	**-.23*****	.12	**.15***	.10
	Conc							**-.14***	**.68*****	**.35*****	**.42*****	**-.14***	**.13***	**.17****	**-.15***	**.14***	**.15***	.02
	Und								-.01	.06	-.11	-.06	.05	**.17****	.06	.11	.11	.11
	ER									**.47*****	**.49*****	**-.19****	**.14***	**.25*****	**-.24*****	.05	.10	-.07
PHQ											**.55*****	-.06	.09	**.20****	**-.14***	.05	**.14***	-.09
GAD												-.02	.11	.09	**-.17****	.01	.07	.03
SES													**-.13***	-.09	.08	-.10	-.11	-.11
Age														-.01	**-.18****	.08	.11	.05
Age at t/d															**-.13***	.06	.09	-.05
Adherence																**-.20****	**-.18***	-.04
AST																	**.78***	**.44****
GGT																		**.39****

Note. BIPQ Cons (1-Consequences), Time (2-Timeline), PC, (3-Personal Control), TC (4-Treatment Control), Iden (5-Identity), Conc (6-Concern), Und (7-Understanding), ER (8-Emotional Response), age at t/d (transplant or diagnosis), AST (aspartate aminotransferase), GGT (Gamma-glutamyl transpeptidase).

*p<.05. **p<.01. *** p remains significant when multiple comparisons (Bonferroni correction) are adjusted for (p<.0004)

For categorical analyses (Tables 7-9), independent sample t-tests were selected despite data not meeting the necessary normality assumptions, in line with recommendations for large samples (Fagerland, 2012). Levene's test was used to test whether equal variances were assumed, and the appropriate result used.

When using the categorical definition of adherence (self-rated score ≥80%), 72.6% of the cross-sectional sample (who completed the adherence questionnaire) were classified as adherent.

Table 7

Differences in Illness Perceptions, Anxiety, Depression, Relevant Demographic and Clinical Variables Between the Adherent and Non-adherent Group

Variable	Adherent (≥80%, n=180) mean (SD)	Non-adherent (<80%, n=68) mean (SD)	t	df	p-value
BIPQ 1 - consequences	**3.79 (2.75)**	**4.62 (2.90)**	**-2.07**	**246**	**.04***
BIPQ 2 - timeline	8.63 (2.50)	8.91 (2.11)	-0.83	246	.41
BIPQ 3 - personal control	5.38 (3.17)	5.63 (3.00)	-0.56	246	.58
BIPQ 4 - treatment control	7.25 (2.94)	6.65 (2.69)	1.47	246	.14
BIPQ 5 – identity	**3.12 (2.80)**	**4.43 (3.21)**	**-3.15**	**246**	**.002*****
BIPQ 6 – concern	**4.15 (3.14)**	**5.15 (3.42)**	**-2.18**	**246**	**.03****
BIPQ 7 – understanding	7.24 (2.55)	7.09 (2.37)	0.42	246	.67
BIPQ 8 - emotional response	**3.82 (3.39)**	**5.29 (3.44)**	**-3.04**	**246**	**.003*****
PHQ	1.31 (1.65)	1.57 (1.62)	-1.15	246	.25
GAD	1.33 (1.75)	1.63 (1.64)	-1.21	245	.23
Age	18.12 (1.83)	18.57 (1.72)	-1.78	246	.08
Age at transplant or diagnosis	**9.09 (6.05)**	**10.84 (4.66)**	**-2.42**	**246**	**.02****
Socioeconomic status	5.42 (2.71)	5.10 (2.62)	0.83	242	.41
AST	**47.55 (42.06)**	**71.54 (82.49)**	**-2.45**	**75**	**.03***
GGT	100.04 (158.66)	112.70 (146.06)	-.55	221	.58
Bilirubin	19.81 (28.63)	17.28 (18.31)	.66	222	.51

Note. SD (standard deviation), df (degrees of freedom), AST (aspartate aminotransferase), GGT (Gamma-glutamyl transpeptidase).

*p<.05. **p<.01. *** p remains significant when multiple comparisons (using Bonferroni correction) are adjusted for (p<.003).

In line with Hypothesis 2a, symptoms of depression (PHQ) and anxiety (GAD) were weakly-moderately positively correlated with BIPQ questions 1 (consequences), 5 (identity), 6 (concern) and 8 (emotional response) (Table 6). There was no negative correlation, contrary to Hypothesis 2a, between PHQ and GAD scores and BIPQ question 3 (personal control), although there was an association for question 4 (treatment control). Only GAD scores were positively correlated with BIPQ question 2 (timeline), as anticipated, although for the latter two, their associations were weak and not significant using the adjusted p-value.

Hypothesis 2b was only tentatively met, as while higher depression (PHQ) and anxiety (GAD) scores were associated with poorer self-reported medication adherence (Table 6), these correlations were weak and not significant using the adjusted p-value, nor were the relationships sustained in categorical analysis (Table 7).

Mixed results were also found regarding Hypothesis 2c. Lower self-reported adherence scores were weakly associated with higher (worse) physical health markers (AST and GGT), although not using the adjusted p-value, and not at all for bilirubin (Table 6). In categorical analysis, those classified as "non-adherent" had higher (worse) AST results, but there was no significant difference for GGT or bilirubin (Table 7). Note that AST results are more relevant than bilirubin and GGT in the context of non-adherence, as they are the clinical markers used to define remission in AILD and normal graft function in those post liver transplant.

BIPQ questions 1 (consequences), 5 (identity), 6 (concern) and 8 (emotional response) were weakly-moderately correlated with adherence in the anticipated directions specified in Hypothesis 2d (Table 6), supported by group differences in categorical analyses (Table 7). There was also a weak unpredicted correlation with question 4 (treatment control).

However, only the relationships between adherence and BIPQ questions 5 and 8 remained significant once multiple comparisons were adjusted for.

Poorer adherence was significantly correlated with (older) age at transplant or diagnosis and (older) age, as predicted in Hypotheses 2e and f respectively (Table 6), although these did not remain significant using the adjusted p-value and a significant categorical difference was only found for the former (Table 7). There was no association between adherence and socioeconomic status, contrary to Hypothesis 2g.

Table 8

Medication Type Differences in Illness Perceptions, Anxiety, Depression and Adherence

Variable	Treatment (n=198) mean (SD)	Supportive (n=94) mean, (SD)	t	df	p-value
BIPQ 1 - consequences	4.1 (2.68)	3.29 (2.98)	2.34	290	.20
BIPQ 2 - timeline	8.69 (2.30)	8.07 (3.21)	1.66	140	.10
BIPQ 3 - personal control	5.58 (3.02)	5.21 (3.41)	0.88	165	.38
BIPQ 4 - treatment control	**7.49 (2.61)**	**5.50 (3.50)**	**4.90**	**144**	**<.001*** **
BIPQ 5 - identity	**3.59 (2.89)**	**2.53 (3.02)**	**2.87**	**290**	**.004*** **
BIPQ 6 - concern	**4.50 (3.13)**	**3.66 (3.29)**	**2.11**	**290**	**.04** **
BIPQ 7 - understanding	7.25 (2.39)	6.95 (2.86)	0.90	157	.37
BIPQ 8 - emotional response	**4.43 (3.41)**	**2.95 (3.24)**	**3.52**	**290**	**<.001*** **
PHQ	1.36 (1.59)	1.26 (1.73)			.61
GAD	1.38 (1.66)	1.28 (1.76)	0.50	290	.63
Adherence	85.75 (19.36)	78.44 (27.91)	1.81	67.82	.08

Note. SD (standard deviation), df (degrees of freedom)

*p<.05. **p<.01. *** p remains significant when multiple comparisons (using Bonferroni correction) are adjusted for (p<.003).

Contrary to Hypothesis 2h, there was no difference in adherence between the two medication types (although it was close to significance) (Table 8). However, service users prescribed medication classified as “Treatment” rated their treatment as more “helpful”

(BIPQ question 4) and reported greater symptoms (5), concern (6) and significant emotional impact (8) of their condition.

Table 9

Gender Differences in Illness Perceptions, Anxiety, Depression and Adherence

Variable	Male n=138 mean (SD)	Female n=154 mean (SD)	t	df	P value
BIPQ 1 - consequences	**3.46 (2.79)**	**4.18 (2.77)**	**-2.23**	**290**	**.03***
BIPQ 2 - timeline	8.43 (2.70)	8.53 (2.58)	-0.34	290	.74
BIPQ 3 - personal control	5.44 (3.18)	5.47 (3.15)	-0.09	290	.93
BIPQ 4 - treatment control	6.76 (3.14)	6.93 (3.00)	-0.47	290	.64
BIPQ 5 - identity	**2.74 (2.76)**	**3.70 (3.09)**	**-2.82**	**290**	**.005*****
BIPQ 6 - concern	**3.71 (3.20)**	**4.70 (3.14)**	**-2.66**	**290**	**.009****
BIPQ 7 - understanding	7.24 (2.44)	7.08 (2.64)	0.54	290	.59
BIPQ 8 - emotional response	**3.10 (3.27)**	**4.71 (3.39)**	**-4.13**	**290**	**<.001*****
PHQ	**0.90 (1.34)**	**1.71 (1.77)**	**-4.43**	**282**	**<.001*****
GAD	**1.05 (1.52)**	**1.61 (1.80)**	**-2.87**	**288**	**.004*****
Adherence	85.03 (22.36)	83.37 (21.06)	0.60	246	.55

Note. SD (standard deviation), df (degrees of freedom).

*p<.05. **p<.01. *** p remains significant when multiple comparisons (using Bonferroni correction) are adjusted for (p<.003).

There was no significant adherence difference between male and female service users, contrary to Hypothesis 2i (Table 9). However, as predicted in Hypothesis 2j, female service users reported greater symptoms of depression (PHQ) and anxiety (GAD) and rated themselves more severely affected (BIPQ question 1), with greater symptoms (5), concern (6) and emotional impacts (8) of their condition.

Section 3: Predictors of Adherence using SEM

The SEM used cross-sectional data from sample 1 (n=292) to establish the predictive statistical effect of illness perceptions, mood (anxiety and depression), demographic factors (gender, age, SES) and clinical factors (medication type, age at diagnosis or transplant) on

adherence (Model A). Note that categorical variables (gender, medication type) were treated as continuous for these analyses, as per Byrne (2016).

Table 10 details the fit indices used in this study, selected using recommendations from Byrne (2016).

Table 10

Structural Equation Model Fit Indices used in this Study

Index	Category	Threshold (reference)
Likelihood Ratio Chi-Square (x2)	Absolute	p>.05 (Barrett, 2007)
Root Mean Square of Approximation (RMSEA)	Absolute	<.06 good (Hu & Bentler, 1999)
Comparative Fit Index (CFI)	Incremental	≥.95 good (Hu & Bentler, 1999)
Normed Fit Index (NFI)	Incremental	≥.90 (Bentler & Bonnet, 1980)

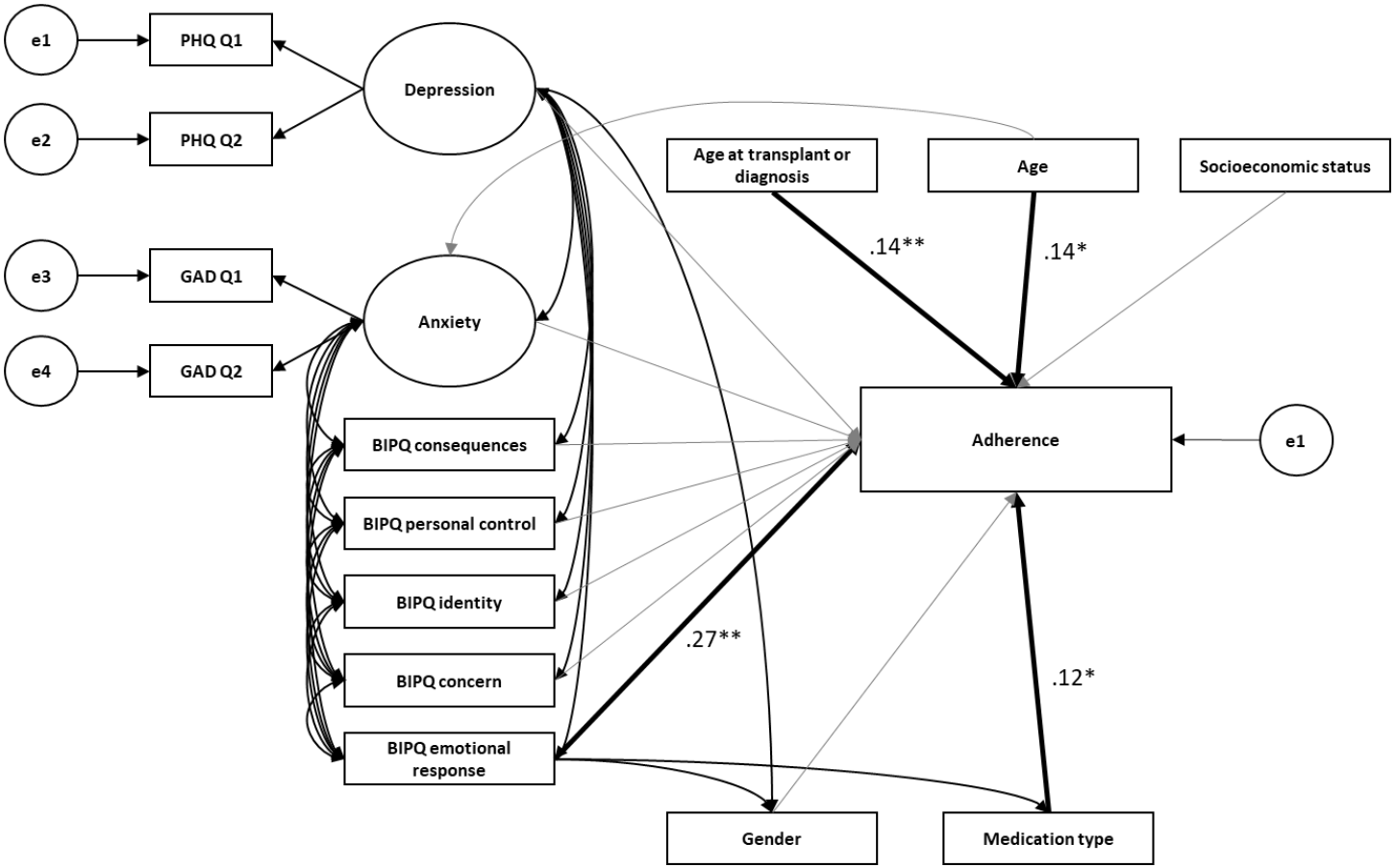
With regards to Hypothesis 3a, the chi-square test suggested poor model fit ($\chi 2(63) = 136.9$, $p<.001$), however this is thought an unreliable indication in larger sample sizes (Bentler & Bonnet, 1980) and is also sensitive to deviations from multivariate normality (McIntosh, 2006). Other indices demonstrated satisfactory or close to acceptable model fit (CFI=.94, NFI=.90, RMSEA=.06 [90%CI, .05-.08]).

However, examination of variable estimates indicated that factor loadings for only four variables onto adherence were statistically significant (Figure 5 and Table 11). These were BIPQ emotional response, age, age at transplant or diagnosis and medication type, with two further illness perceptions (personal control and identity) close to significance.

These results do need to be treated with caution considering the deviation from the multivariate assumption advised by Byrne (2016), described in the Method.

Figure 5:

Indication of Statistically Significant Factor Loadings Between Predictor Variables and Adherence



Note. Bold lines indicate significant associations, but only weightings for predictor variables are provided (not correlations between predictor variables), to aid readability and avoid duplication of earlier analyses.

Table 11

Standardised Regression Weights from Proposed Predictors to Adherence for Model A

Variable	Standardised Regression Weight	p-value
Depression	-.12	.20
Anxiety	.07	.48
BIPQ Consequences	-.07	.42
BIPQ Personal Control	.11	.06
BIPQ Identity	.13	.08
BIPQ Concern	-.02	.78
BIPQ Emotional Response	**.27**	**.005****
Age	**.14**	**.01***
Gender	.01	.82
Socioeconomic status	.001	.99
Age at transplant or diagnosis	**.14**	**.009****
Medication type	**.12**	**.04***

Note. *p<.05. **p<.01.

Exploratory Model Development

Once analyses on Model A was complete, revisions were made to attempt to identify and test a new model that was a better fit to the data (Model B). This section of post hoc analyses is exploratory and would need confirmation by replication using subsequent data. However, the univariate and multivariate normality assumptions were met for Model B and as such there can be more confidence in the statistical findings.

The approach to model revision followed Byrne (2016). This initially included removal of variables where factor loadings onto adherence were not significant or close to that. Secondly, modification indices were examined to establish further improvements such as additional bivariate correlations between predictors, which were only added if consistent with existing theory or empirical literature.

The resulting Model B demonstrated an improved chi-squared model fit index that was closer to the desired non-significance, ($\chi 2(3)=10.32$, p=.02). Other indices fell just short of the recommended thresholds (CFI=.90, NFI=.87, RMSEA=.09, 90%CI=.04-0.16).

However, all regression weights between predictors and adherence were now significant or close to significant (Figure 6, Table 12).

Figure 6

Model B; Predictors of Adherence

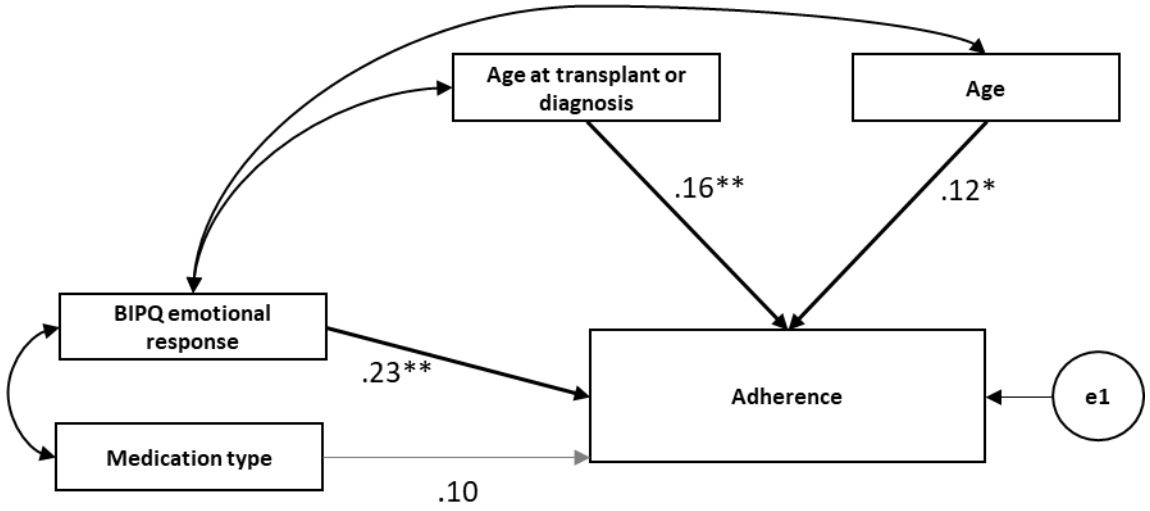


Table 12

Standardised Regression Weights from Proposed Predictors to Adherence for Model B

Variable	Standardised Regression weight	p-value
BIPQ Emotional Response	**.23**	**<.001**
Age	**.12**	**.01***
Age at transplant or diagnosis	**.16**	**.004****
Medication type	.10	.07

Note. *p<.05. **p<.01.

Section 4: Associations Between Timepoint 1 and 2

As data did not meet normality assumptions, Spearman's correlations were conducted on all variables to test Hypotheses 4a and b.

Table 13

Spearman Correlations Between Variables at Timepoints 1 and 2

		Timepoint 1									
		BIPQ								PHQ	GAD
		Cons	Time	PC	TC	Iden	Conc	Und	ER		
Timepoint 2	Adherence	-.14	.05	.08	.07	**-.30***	**-.38****	.12	-.18	-.04	-.09
	AST	-.03	.18	-.06	-.11	-.12	.01	.16	-.05	.07	-.05
	GGT	.14	**.28***	-.07	-.09	.05	.09	.15	.11	.14	.07
	Bilirubin	-.10	-.03	.10	.04	.06	-.05	.09	-.12	-.11	-.23

Note. BIPQ Cons (1-Consequences), Time (2-Timeline), PC, (3-Personal Control), TC (4-Treatment Control), Iden (5-Identity), Conc (6-Concern), Und (7-Understanding), ER (8-Emotional Response), AST (aspartate aminotransferase), GGT (Gamma-glutamyl transpeptidase).

*p<.05. **p<.01. *** p remains significant when multiple comparisons (Bonferroni correction) are adjusted for ($p<0.001$).

Those who rated themselves as experiencing more severe symptoms (BIPQ question 5) greater concern (6) about their condition at timepoint 1 were less likely to be adherent at timepoint 2. Associations between other illness perceptions, depression and anxiety predicted as part of Hypothesis 4a were not significant. With regards to Hypothesis 4b, only one significant association was found; those who perceived their condition would continue for longer were more likely to have higher (worse) later GGT scores. However, significant correlations for both hypotheses were all weak and none remained significant when multiple comparisons were adjusted for.

A summary of whether hypotheses were met is detailed in Table 14.

Table 14

Summary of Whether Hypotheses were Met

No	Hypothesis	Hypothesis met – Yes, No, Partially, Tentatively
Section 1: Adherence Prevalence		
1a	Adolescents and young adults (A&YAs) with chronic liver disease will present with higher rates of anxiety and depression than the general A&YA population (the latter being taken from existing literature).	Yes
Section 2: Relationships between Adherence, Demographic, Clinical, Mood and Illness Perception variables		
2a	Symptoms of depression and anxiety will be positively correlated with specific perceptions about illness, including 'impact of the illness on their life' (Brief Illness Perception Questionnaire; BIPQ, Broadbent et al., 2006; Question 1), 'how much are symptoms experienced' (BIPQ Question 5), 'level of concern about the illness' (BIPQ Question 6) and the 'emotional impact of the illness' (BIPQ Question 8), and negatively correlated with 'level of perceived personal control' (BIPQ Question 3). Anxiety may additionally be positively correlated with 'how long you think your condition will continue' (BIPQ question 2).	Partially (yes for BIPQ questions 1, 5, 8 with depression and anxiety, yes for BIPQ question 2 with anxiety but not for BIPQ question 3 with depression or anxiety).
2b	Higher rates of depression and anxiety will be correlated with poorer self-reported medication adherence. This will be supported by categorical analyses, with the non-adherent group (reportedly taking their medication <80%) having significantly higher (worse) scores for depression and anxiety than the adherent group (≥80%).	Tentatively (only in correlational analyses, although not using the adjusted p-value)

No	Hypothesis	Hypothesis met – Yes, No, Partially, Tentatively
2c	Higher self-reported medication adherence will be correlated with better physical health markers (liver function blood tests). This will be supported by categorical analyses, with the non-adherent group (<80%) having significantly (worse) liver function results than the adherent group (≥80%).	Partially and tentatively (in correlational analyses - yes for aspartate aminotransferase [AST] and Gamma-glutamyl transpeptidase [GGT], but not using the adjusted p-value, no for bilirubin. In categorical analyses - yes for AST only, although again not significant using the adjusted p-value)
2d	Illness perceptions identified in Hypothesis 2a will be correlated with poorer self-reported medication adherence in the same direction as 2a. That is, higher scores in BIPQ questions 1,5,6,8 and lower scores in question 3 will be associated with poorer self-reported adherence. This will be supported by categorical analyses, with the non-adherent group (<80%) having significantly higher scores in BIPQ questions 1,5,6 and 8 and lower score in BIPQ question 3, than the adherent group (≥80%).	Tentatively (Yes for BIPQ questions 1, 5, 6 and 8 in both correlational and categorical analyses, although only the correlations for questions 5 and 8 remained significant using the adjusted p-value)
2e	Age at diagnosis / transplant will be negatively correlated with self-reported adherence. This will be supported by categorical analyses, with the non-adherent group (<80%) having a significantly older mean age of diagnosis / transplant than the adherent group.	Tentatively (yes in both correlational and categorical analyses, although this did not remain significant using the adjusted p-value.
2f	Age will be negatively correlated with self-reported adherence. This will be supported by categorical analyses, with the non-adherent group (<80%) having a significantly older mean age than adherent group.	Partially and tentatively (yes in correlational, although not using the adjusted p-value, but not in categorical analyses)
2g	Service users with a lower socioeconomic status will be less likely to be adherent than those with a higher socioeconomic status.	No
2h	Service users prescribed “Treatment” will be more likely to be adherent than those prescribed “Supportive” medication, in categorical analyses.	No

No	Hypothesis	Hypothesis met – Yes, No, Partially, Tentatively
2i	Female service users will report lower adherence than male service users in categorical analyses.	No
2j	Female service users will report greater symptoms of depression, anxiety and more maladaptive illness perceptions than male service users.	Yes
Section 3: Predictors of Adherence using SEM Modelling		
3a	A model (A; Figure 3) involving multiple variables (specifically illness perceptions, anxiety, depression, socioeconomic status, age of diagnosis or transplant, age, medication type and gender) will be predictive of self-reported medication adherence (in the directions specified in Section 2 hypotheses).	Partially and tentatively (not for all hypothesised predictors - see revised model B, although note this did not meet all specified model fit thresholds).
Section 4: Associations Between Mood and Illness Perceptions at Timepoint 1 with Adherence and Physical Health at Timepoint 2		
4a	Higher scores for certain illness perceptions (BIPQ questions 1,5,6,8), depression (PHQ) and anxiety (GAD) and lower scores for BIPQ question 3 at timepoint 1 will be associated with lower adherence scores.	Partially and tentatively (only for two BIPQ question scores, 5 and 6, although not using the adjusted p-value)
4b	Higher scores for certain illness perceptions (BIPQ questions 1,5,6,8), depression and anxiety and lower scores for BIPQ question 3 at timepoint 1 will be associated with worse liver function blood tests at timepoint 2.	Partially and tentatively (only for GGT and not AST or bilirubin, although not using the adjusted p-value)

Discussion

This study used cross-sectional and longitudinal data from service users (16-25 years) attending a multidisciplinary young adult liver service to identify variables associated with and predictive of self-reported medication adherence. 72.6% of participants were classified as adherent, in line with literature using other self-report measures (Berquist et al., 2006; 2008; Bilhartz et al., 2015; Fredericks et al., 2008; Hames et al., 2021).

As per Hypothesis 1a, A&YAs with chronic liver disease appear to experience greater mood difficulties than healthy peers (although comparison data included different measurement approaches and sample characteristics). This supports previous literature (Hames et al., 2016; some of the data from which was also included in this study) and research in A&YAs with other chronic diseases (Pinquart and Shen, 2011). It is perhaps reflective of the breadth and severity of consequences of managing a chronic liver disease during this complex developmental period, including on school, work, sports, social activities, relationships, sex and family (Burra, 2012).

Relationships between Adherence, Demographic, Clinical, Mood and Illness Perception Variables

As predicted (Hypothesis 2a), A&YAs with higher reported symptoms of anxiety and depression reported their condition had a greater impact on their life, worse symptoms, greater concern and more extreme effects of their condition. These findings validate those by Hames et al. (2016), together with results from samples of other ages and diagnoses type (Blanco & Weinman, 2018, Wu et al. 2014). It is also consistent with (though doesn't prove) the CSM suggestion that illness perceptions can influence emotional problems.

In line with predictions, poorer adherence was associated with greater anxiety and depression (Hypothesis 2b) and two (AST and GGT) of the three liver function blood tests

(Hypothesis 2c). The significant associations support Fredericks et al. (2010) and Hames et al. (2021). However, associations were weak, did not survive Bonferroni correction and only the one with AST was sustained using categorical analysis. However, this is perhaps not surprising given AST is typically most relevant in monitoring disease activity (specifically in those with AILD, AISC, Wilson's disease and those post liver transplant). The weak associations may be due to the sensitivity of physical health markers used, as stronger associations with adherence have been identified using other clinical outcome measures, such as episodes of rejection (Annunziato et al., 2018; Bilhartz et al., 2015).

Both categorical and continuous analyses indicated those who reported poorer adherence were more likely to rate their condition as having a greater impact on their life, experience more extreme effects, experience worse symptoms and express greater concern, although only associations with the latter two remained significant after Bonferroni correction. These, albeit weak, relationships were as predicted in Hypothesis 2d and are consistent with the CSM (and HBM) suggestion that illness perceptions are critical in shaping health behaviours, such as adherence. It also supports literature in other populations (Kaptein, 2008; O'Carroll, 2006) and highlights the need for further research to validate the specific illness perceptions most relevant to this group.

In line with existing research (e.g. Bilhartz et al., 2015) and predictions, those who were older at transplant or diagnosis were less likely to be adherent (Hypothesis 2e). Although this did not remain significant after Bonferroni correction, this tentative finding contradicts Hames et al. (2021) despite some of the data within their study (those with AILD) being used. However, they looked at age of diagnosis only, perhaps suggesting age of transplant may be more associated with adherence and thus should be investigated separately. This is supported by Yazigi et al. (2017), who argued transplantation may cause increased 'uncertainty and vulnerability' at this sensitive age.

Older age was associated with poorer adherence in correlational but not categorical analyses, tentatively supporting Hypothesis 2f. Although this did not survive Bonferroni correction, it supports compelling evidence from previous literature (Annunziato et al., 2018, Berquist et al., 2008, Hames et al., 2021). The weaker association may be reflective of the slightly older sample than some of those above (e.g. 9-17 years; Annunziato et al., 2018 and 12-21 years; Berquist et al., 2008), perhaps indicative of less developmental variability and subsequent increased homogeneity in adherence behaviours. However, the finding does raise concerns for those over 18 years supported by adult services without multidisciplinary support and less focus on the difficulty many this age experience with non-adherence.

The lack of significant association between poorer adherence and lower socioeconomic status (Hypothesis 2g), "supportive" medication type (2h) or female gender (2j) may be due to a variety of reasons. Previous literature that identified a relationship with socioeconomic status and/or home environment used different measures, suggesting it is more likely complex psychosocial factors (e.g. Hames et al., 2016) or single-parent status (e.g. Berquist et al., 2008) that may contribute to an environment with less resources to support adherence. There might also be geographical variations; related to private insurance in other countries where medical and medication costs are significant and more likely to be a causative factor than in the UK.

Service users prescribed "treatment" rated their medication as more "helpful" than those prescribed "supportive". However, they also reported more symptoms, concern and significant emotional impact of their condition. If the (currently close to significant) effect between treatment type and adherence was found to be significant in a subsequent study with larger sample size, it could be understood in terms of the HBM. That is, a greater perceived threat (perhaps represented by increased symptoms and concern) together with increased perceived benefit (perhaps reflected by the more "helpful" medication rating) increase the

likelihood of adherence. However, the lack of significance may be attributable to the developmental suggestion that perception of threat is suppressed in adolescence, thought associated with the evolutionary need to leave home (Darcy & Samyn, 2017), thus lowering the likelihood of adherence compared to adults (regarding whom the HBM was initially designed).

The lack of association between adherence and gender contradicts evidence from other populations that females are less likely to be adherent (Frazier et al., 1994), although does support literature from adolescents with liver disease (Berquist et al., 2006, 2008, Bilhartz et al., 2015, Fredericks et al., 2008, Hames et al., 2021). This suggests gender differences in adherence are less apparent in this population, although female service users did rate themselves as more anxious, depressed, severely affected, with more severe symptoms, increased concern and experiencing greater emotional impacts of their condition than male service users. This appears reflective of gender patterns in the general population (Sen, 2004) and validates findings by Hames et al. (2021) in a comparable population. It also demonstrates the need to consider the complexity and potential interaction between variables; specifically, that despite female service users being more likely to hold certain beliefs associated with non-adherence, this will not necessarily translate to that behaviour.

Predictors of Adherence Using SEM Analyses

The satisfactory fit indices for Model A were likely due to the significant correlations between predictor variables rather than its ability to predict adherence itself, given most regression weights to adherence were non-significant. The presence of multicollinearity between predictor variables may also help explain why some of the directions within regression analyses contradicted correlations. When predictors were narrowed down for Model B, overall fit indices were just short of specified thresholds. However, more

confidence can be had in the predictors themselves as three met and one was close to significance, plus Model B now met all univariate and multivariate assumptions.

A greater reported emotional response to their condition (BIPQ 8), age (older) and age at transplant or diagnosis (older) had a predictive effect for adherence, with medication type (supportive) close to significance (although regression weights for the first three contradicted the directions found in correlations). Furthermore, standardised SEM regression weights were small (in line with Brandes and Mullan; 2013), which raises questions about how clinically meaningful some results are. Whilst this analysis has highlighted potential vulnerabilities, it is unlikely clinicians can rely on a handful of variables to predict adherence, particularly as this does not appear to account for the complex relationship and potential interactions between other factors (e.g. gender and beliefs).

It was surprising that only one illness perception was a significant predictor in the final model despite other question scores being significantly associated with adherence in correlational and categorical analyses. However, questions regarding Identity, Personal Control and Treatment Control were close to significance in exploratory SEM analyses. These were also the same illness perceptions associated with mood (PHQ and GAD scores), yet mood was not a predictor of adherence itself. Similar findings regarding a relationship between specific illness perceptions and adherence being stronger than between mood and adherence include Broadbent et al. (2015), Kaptein et al. (2008) and McSharry et al. (2011) albeit in different clinical populations.

More research is therefore needed to further test and develop this model, which may not have met the specified overall fit indices for various reasons. It is likely other variables need to be considered, for example, coping strategies (CSM) and disease/treatment knowledge (HBM) and relationships between variables need to be better understood. The

self-report adherence measure used may also have been sensitive to under-reporting, so future research may benefit from additional measures, such as immunosuppressant SD (for transplant recipients) used by Annunziato et al. (2018) and Bilhartz et al. (2015).

Associations between Timepoint 1 and 2

Only two illness perceptions (identity and consequences) were associated with later adherence and one (timeline) with GGT in longitudinal analyses. This is contrary to Hypotheses 4a and 4b, which predicted relationships with additional illness perceptions, depression, anxiety and blood tests. The lack of findings for depression and anxiety are not surprising given only weak associations were identified in cross-sectional analyses. However, it is unclear why relationships with other illness perceptions were not sustained longitudinally. Variability in time between data points may have limited the potential to identify longitudinal relationships. With regards to 4b, liver function blood tests may not be sensitive enough to identify an effect given illness perceptions were found to be predictive of different clinical outcomes in other populations e.g. Muscat et al. (2020). However, it is also possible that developmental factors mean longitudinal relationships are less apparent in this population and the three weak associations are indicative of Type I errors.

Strengths and Limitations

This project benefited from a relatively large sample, however, additional participants may have been beneficial for SEM (Brown, 2018) and allowed certain variables (such as medication type and other illness perceptions) to reach significance. The sample size was possible due to the retrospective design, although this also introduced limitations such as variability between timepoints in longitudinal data. The use of largely cross-sectional data limited the ability to make causal interpretations and difficulty meeting all SEM assumptions introduced the need for caution in interpretation. There were limitations in some measurement approaches that may have introduced potential noise, such as the use of only

the first two questions of the PHQ and GAD and reliance on self-reports, particularly for adherence where there is evidence of under-reporting (Vik et al., 2004). However, the use of both categorical and continuous adherence measures was a strength. The application of Bonferroni to account for multiple comparisons was conservative, which is why p-values both with and without this correction are included.

Other strengths include addressing existing literature gaps (such as investigation of relationships between illness perceptions and adherence in this population), inclusion of a wide spectrum of liver diseases and generalisability of the cohort due to representative demographics. However, a potential opportunity was missed in investigating demographics such as ethnicity (not possible given the way this was recorded in data collection) given some indication that factors associated with ethnicity are associated with adherence (e.g. Tucker et al., 2002). Finally, the approach taken within this young adult liver service is unique and it is not possible to rule out the potential impact the team's therapeutic approach and open discussion about adherence may have had on a service user's mood, illness perceptions and adherence, together with their willingness to report these. This may limit generalisability and the comparability of findings to other studies.

Clinical Implications

The project has highlighted certain demographic and clinical variables that may be associated with a higher risk of medication non-adherence, which clinicians working with this age group should be aware of (specifically older age, older age at transplant or diagnosis and more "supportive" medication types). It is reassuring that A&YAs prescribed medication including steroids and immunosuppressants (more critical than "supportive" medications, in terms of prognosis and chance of liver failure) were more likely to be adherent. This finding may also demonstrate A&YAs are better able to understand and weigh up risks associated with non-adherence than previous developmental arguments might suggest. The finding that

illness perceptions appear more associated with adherence than mood is also important, although it should be noted effect sizes were small, so recommendations are tentative. The identification of BIPQ questions that appear most relevant (emotional response, and to a lesser extent consequences, identity and concern) may be of benefit in informing where clinicians could focus discussions during medical and clinical psychology appointments, particularly given the broad amount of data currently collected from service users and routine questions only on mood.

Clinicians should also be aware of the complex network of factors likely associated with adherence, suggestive of a subtle and nuanced interaction that may be difficult to replicate in a statistical model. This acknowledgement may help avoid potentially misleading clinical assumptions, such as the likelihood of female service users being less adherent simply based on their increased scores on the identified illness perceptions. The development of tailored support packages for those diagnosed or transplanted later, including more frequent psychosocial monitoring, may also be beneficial.

Research Implications

There are outstanding questions regarding the role a service user's emotional response to their condition may play in subsequent adherence behaviours, as BIPQ question 8 is phrased to include a range of negative emotions including "anger" and "upset". Qualitative research (like Wright et al., 2015, for example) may help supplement findings with a greater understanding of service user's experiences.

To the best of the author's knowledge, this is the first attempt at predicting adherence using SEM within this population. Whilst the final model (B) did not meet specified fit indices, it has provided an initial indication of factors most associated with. However, given Model B was exploratory and not predicted in advance, it requires replication. It would also be beneficial use the findings to develop a model with specified moderators and mediators,

rather than predictors operating in parallel. This would help unpick underling mechanisms behind the relationships identified, particularly given the anticipated multicollinearity between variables that may explain the contradictory directions between some correlation coefficients and regression weights.

Future (ideally prospective) longitudinal research would also be beneficial, where confounding variables (such as time between measures) could be standardised and/or accounted for, to track relative changes over time. This would also allow for additional elements of the CSM (e.g. additional coping strategies) and HBM (e.g. illness and treatment knowledge and peer influences, the latter known to be heightened during adolescence; Darcy & Samyn, 2017) to be captured, in order that these theoretical constructs can be tested more comprehensively. Inclusion of a broader range of demographics (specifically ethnicity) and clinical outcomes (such as biopsies, graft failures and mortality) in future designs would also be helpful.

Finally, adaptations to existing models of health behaviours are needed to account for the unique developmental challenges within adolescence that may exacerbate difficulties with adherence. This has in part been addressed by Hagger and Orbell (2021) following their development of an extended CSM that includes greater detail on coping strategies, behavioural and treatment beliefs and other potential moderators (e.g. optimism and perfectionism). However, there still appears scope to incorporate social and peer factors that are covered within the HBM, for example, together with a better reflection of the complex interaction between variables suggested by the results within this study.

Conclusion

A&YAs who were older, older at time of transplant or diagnosis and who reported a greater emotional impact of their condition appeared at higher risk of not adhering to medication. Other factors such as medication type (more “supportive” medications such as

vitamins) and other illness perceptions (specifically reporting: their condition had a greater impact on their life; worse symptoms; and greater concern about their diagnosis) also appear associated with non-adherence, to a lesser extent. Whilst the theoretical frameworks selected (CSM and HBM) appear to in part explain some of the relationships identified, their use is limited by their lack of acknowledgement of A&YA developmental differences, such as increased risk-taking. This study highlights the need for greater consideration within clinical practice of characteristics that may leave service users vulnerable to non-adherence and provides indications for future research to help further understand the complex interaction between adherence, illness perceptions, mood, demographic and disease variables within this unique period of development.

References

Allgaier, A. K., Pietsch, K., Frühe, B., Sigl-Glöckner, J., & Schulte-Körne, G. (2012). Screening for depression in adolescents: validity of the patient health questionnaire in pediatric care. *Depression and anxiety*, *29*(10), 906-913. https://doi.org/10.1002/da.21971

Annunziato, R. A., Bucuvalas, J. C., Yin, W., Arnand, R., Alonso, E. M., Mazariegos, G. V., Venick, R. S., Stuber, M. L., Schneider, B.L., & Shemesh, E. (2018). Self-management measurement and prediction of clinical outcomes in pediatric transplant. *The Journal of Pediatrics*, *193*, 128-133. https://doi.org/10.1016/j.jpeds.2017.09.069

Arya, G., & Balistreri, W. F. (2002). Pediatric liver disease in the United States: epidemiology and impact. *Journal of gastroenterology and hepatology*, *17*(5), 521-525. https://doi.org/10.1046/j.1440-1746.2002.02678.x

Barrett, P. (2007). Structural equation modelling: Adjudging model fit. *Personality and Individual differences*, *42*(5), 815-824. https://doi.org/10.1016/j.paid.2006.09.018

Bautista, L. E., Vera-Cala, L. M., Colombo, C., & Smith, P. (2012). Symptoms of depression and anxiety and adherence to antihypertensive medication. *American journal of Hypertension*, *25*(4), 505-511. https://doi.org/10.1038/ajh.2011.256

Becker, M. H. (1974). The health belief model and sick role behavior. *Health Education Monographs*, *2*(4), 409-419. https://doi.org/10.1177%2F109019817400200407

Bentler, P. M., & Bonett, D. G. (1980). Significance tests and goodness of fit in the analysis of covariance structures. *Psychological bulletin*, *88*(3), 588. https://psycnet.apa.org/doi/10.1037/0033-2909.88.3.588

Bentler, P. M., & Wu, E. J. (2005). EQS 6.1 for Windows. *Structural equations program manual. Encino, CA: Multivariate Software*. https://www.mvsoft.com/wp-content/uploads/2021/04/EQS_6_User_Guide_R8.pdf

Berquist, R., Berquist, W. E., Esquivel, C. O., Cox, K. L., Wayman, K. I., & Litt, I. F. (2006). Adolescent non-adherence: prevalence and consequences in liver transplant recipients. *Pediatric Transplantation, 10*(3), 304-310. https://doi.org/10.1111/j.1399-3046.2005.00451.x

Berquist, R. K., Berquist, W. E., Esquivel, C. O., Cox, K. L., Wayman, K. I., & Litt, I. F. (2008). Non-adherence to post-transplant care: prevalence, risk factors and outcomes in adolescent liver transplant recipients. *Pediatric Transplantation, 12*(2), 194-200. https://doi.org/10.1111/j.1399-3046.2007.00809.x

Bilhartz, J. L., Lopez, M. J., Magee, J. C., Shieck, V. L., Eder, S. J., & Fredericks, E. M. (2015). Assessing allocation of responsibility for health management in pediatric liver transplant recipients. *Pediatric Transplantation*, *19*(5), 538-546. https://doi.org/10.1111/petr.12466

Bissonnette, J. M. (2008). Adherence: a concept analysis. *Journal of Advanced Nursing*, *63*(6), 634-643. https://doi.org/10.1111/j.1365-2648.2008.04745.x

Blakemore, S. J., & Mills, K. L. (2014). Is adolescence a sensitive period for sociocultural processing?. *Annual review of psychology*, *65*, 187-207. https://doi.org/10.1146/annurev-psych-010213-115202

Bond, G. G., Aiken, L. S., & Somerville, S. C. (1992). The health belief model and adolescents with insulin-dependent diabetes mellitus. *Health Psychology*, *11*(3), 190. https://psycnet.apa.org/doi/10.1037/0278-6133.11.3.190

Brandes, K., & Mullan, B. (2013). Is the common sense model of illness representations a valid model to predict adherence?. *Psychology & Health*, *28*(S1), 181-182. https://doi.org/10.1080/08870446.2013.810851

Brandes, K., & Mullan, B. (2014). Can the common-sense model predict adherence in chronically ill patients? A meta-analysis. *Health psychology review*, *8*(2), 129-153. https://doi.org/10.1080/17437199.2013.820986

Broadbent, E., Petrie, K. J., Main, J., & Weinman, J. (2006). The brief illness perception questionnaire. *Journal of Psychosomatic Research*, *60*(6), 631-637. https://doi.org/10.1016/j.jpsychores.2005.10.020

Broadbent, E., Wilkes, C., Koschwanez, H., Weinman, J., Norton, S., & Petrie, K. J. (2015). A systematic review and meta-analysis of the Brief Illness Perception Questionnaire. *Psychology & health*, *30*(11), 1361-1385. https://doi.org/10.1080/08870446.2015.1070851

Brown, T. A. (2015). *Confirmatory factor analysis for applied research*. Guilford publications.

Bucks, R. S., Hawkins, K., Skinner, T. C., Horn, S., Seddon, P., & Horne, R. (2009). Adherence to treatment in adolescents with cystic fibrosis: the role of illness perceptions and treatment beliefs. *Journal of pediatric psychology*, *34*(8), 893-902. https://doi.org/10.1093/jpepsy/jsn135

Burra, P. (2012). The adolescent and liver transplantation. *Journal of hepatology*, *56*(3), 714-722. https://doi.org/10.1016/j.jhep.2011.07.032

Burra, P., Germani, G., Gnoato, F., Lazzaro, S., Russo, F. P., Cillo, U., & Senzolo, M. (2011). Adherence in liver transplant recipients. *Liver Transplantation*, *17*(7), 760-770. https://doi.org/10.1002/lt.22294

Byrne, B. 2016. *Structural equation modeling with Amos: basic concepts, applications, and programming*. (3rd eds.). Routledge

Casey, B. J., Getz, S., & Galvan, A. (2008). The adolescent brain. *Developmental review*, *28*(1), 62-77. https://doi.org/10.1016/j.dr.2007.08.003

Choudhury, S. (2010). Culturing the adolescent brain: what can neuroscience learn from anthropology?. *Social cognitive and affective neuroscience*, *5*(2-3), 159-167. https://doi.org/10.1093/scan/nsp030

Christensen, A. J. (2004). *Patient adherence to medical treatment regimens: Bridging the gap between behavioral science and biomedicine*. Yale University Press.

Cleemput, I., Kesteloot, K., & DeGeest, S. (2002). A review of the literature on the economics of noncompliance. Room for methodological improvement. *Health policy*, *59*(1), 65-94. https://doi.org/10.1016/S0168-8510(01)00178-6

D'Agata, I. D., & Balistreri, W. F. (1999). Evaluation of liver disease in the pediatric patient. *Pediatrics in Review*, *20*(11), 376-390. https://doi.org/10.1542/pir.20.11.376

Dahl, R. E. (2004). Adolescent brain development: a period of vulnerabilities and opportunities. Keynote address. *Annals of the New York Academy of Sciences*, *1021*(1), 1-22. https://doi.org/10.1196/annals.1308.001

Darcy, A., & Samyn, M. (2017). Looking after young people with liver conditions: understanding chronic illness management in the context of adolescent development. *Clinical Liver Disease*, *9*(5), 103. https://dx.doi.org/10.1002%2Fcld.637

DeCarlo, L. T. (1997). On the meaning and use of kurtosis. *Psychological methods*, *2*(3), 292. https://psycnet.apa.org/doi/10.1037/1082-989X.2.3.292

de la Torre, J. A., Vilagut, G., Ronaldson, A., Dregan, A., Ricci-Cabello, I., Hatch, S. L., ... & Alonso, J. (2021). Prevalence and age patterns of depression in the United Kingdom.

A population-based study. *Journal of Affective Disorders*, *279*, 164-172. https://doi.org/10.1016/j.jad.2020.09.129

De las Cuevas, C., De Leon, J., Penate, W., & Betancort, M. (2017). Factors influencing adherence to psychopharmacological medications in psychiatric patients: a structural equation modeling approach. *Patient preference and adherence*, *11*, 681. https://doi.org/10.2147/PPA.S133513

Dempster, N. R., Wildman, B. G., Masterson, T. L., & Omlor, G. J. (2018). Understanding treatment adherence with the health belief model in children with cystic fibrosis. *Health Education & Behavior*, *45*(3), 435-443. https://doi.org/10.1177%2F1090198117736346

Dharnidharka, V. R., Lamb, K. E., Zheng, J., Schechtman, K. B., & Meier-Kriesche, H. U. (2015). Across all solid organs, adolescent age recipients have worse transplant organ survival than younger age children: a US national registry analysis. *Pediatric Transplantation*, *19*(5), 471-476. https://doi.org/10.1111/petr.12464

Di Maira, T., Little, E. C., & Berenguer, M. (2020). Immunosuppression in liver transplant. *Best Practice & Research Clinical Gastroenterology*, *46*, 101681. https://doi.org/10.1016/j.bpg.2020.101681

Diefenbach, M. A., & Leventhal, H. (1996). The common-sense model of illness representation: Theoretical and practical considerations. *Journal of social distress and the homeless*, *5*(1), 11-38. https://doi.org/10.1007/BF02090456

Dobbels, F., Damme-Lombaert, R. V., Vanhaecke, J., & Geest, S. D. (2005). Growing pains: Non-adherence with the immunosuppressive regimen in adolescent transplant recipients. *Pediatric transplantation*, *9*(3), 381-390. https://doi.org/10.1111/j.1399-3046.2005.00356.x

Ebel, N. H., Hsu, E. K., Berry, K., Horslen, S. P., & Ioannou, G. N. (2017). Disparities in waitlist and posttransplantation outcomes in liver transplant registrants and recipients 18–24 years old: analysis of the UNOS database. *Transplantation*, *101*(7), 1616. https://dx.doi.org/10.1097%2FTP.0000000000001689

Edgar, K. A., & Skinner, T. C. (2003). Illness representations and coping as predictors of emotional well-being in adolescents with type 1 diabetes. *Journal of pediatric psychology*, *28*(7), 485-493. https://doi.org/10.1093/jpepsy/jsg039

Fagerland, M. W. (2012). t-tests, non-parametric tests, and large studies—a paradox of statistical practice?. *BMC medical research methodology*, *12*(1), 1-7. https://doi.org/10.1186/1471-2288-12-78

Faul, F., Erdfelder, E., Buchner, A., & Lang, A. G. (2009). Statistical power analyses using G* Power 3.1: Tests for correlation and regression analyses. *Behavior research methods*, *41*(4), 1149-1160. https://doi.org/10.3758/BRM.41.4.1149

Frazier, P. A., Davis-Ali, S. H., & Dahl, K. E. (1994). Correlates of noncompliance among renal transplant recipients. *Clinical transplantation*, *8*(6), 550-557. https://europepmc.org/article/med/7865918

Fredericks, E. M., Dore-Stites, D., Well, A., Magee, J. C., Freed, G. L., Shieck, V., & James Lopez, M. (2010). Assessment of transition readiness skills and adherence in pediatric liver transplant recipients. *Pediatric Transplantation*, *14*(8), 944-953. https://doi.org/10.1111/j.1399-3046.2010.01349.x

Friedman, I. M., & Litt, I. F. (1987). Adolescents' compliance with therapeutic regimens: Psychological and social aspects and intervention. *Journal of Adolescent Health Care*, *8*(1), 52-67. https://doi.org/10.1016/0197-0070(87)90246-4

Fredericks, E. M., Lopez, M. J., Magee, J. C., Shieck, V., & Opipari-Arrigan, L. (2007). Psychological functioning, nonadherence and health outcomes after pediatric liver

transplantation. *American Journal of Transplantation, 7*(8), 1974-1983. https://doi.org/10.1111/j.1600-6143.2007.01878.x

Fredericks, E. M., Magee, J. C., Opipari-Arrigan, L., Shieck, V., Well, A., & Lopez, M. J. (2008). Adherence and health-related quality of life in adolescent liver transplant recipients. *Pediatric Transplantation, 12*(3), 289-299. https://doi.org/10.1111/j.1399-3046.2008.00901.x

Green. H., McGinnity, Á., Meltzer, H., Ford, T., & Goodman, R. (2004). *Mental health of children and young people in Great Britain* (p. 2005). H. Green (Ed.). Basingstoke: Palgrave macmillan.

Hagger, M. S., & Orbell, S. (2003). A meta-analytic review of the common-sense model of illness representations. *Psychology and health, 18*(2), 141-184. https://doi.org/10.1080/0887044031000813 21

Hagger, M. S., & Orbell, S. (2021). The common sense model of illness self-regulation: a conceptual review and proposed extended model. *Health psychology review*, 1-31. https://doi.org/10.1080/17437199.2021.1878050

Hair, J. F., Black, W. C., Babin, B. J., Anderson, R. E., & Tatham, R. L. (2006). Multivariate data analysis 6th Edition. *Pearson Prentice Hall. New Jersey. humans: Critique and reformulation. Journal of Abnormal Psychology, 87*, 49-74.

Hames, A., Matcham, F., Joshi, D., Heneghan, M. A., Dhawan, A., Heaton, N., & Samyn, M. (2016). Liver transplantation and adolescence: the role of mental health. *Liver Transplantation, 22*(11), 1544-1553. https://doi.org/10.1002/lt.24629

Hames, A., Matcham, F., Makin, I., Day, J., Joshi, D., & Samyn, M. (2021). Adherence, Mental Health and Illness Perceptions in Autoimmune Liver Disease: Looking Beyond Liver Function Tests. *Journal of Pediatric Gastroenterology and Nutrition, 73*(3), 376-384. https://doi.org/10.1097/MPG.0000000000003119

Haynes R.B., Yoa X., Degani A., Kripalani S., Garg A. & McDonald H.P. (2005) Interventions to enhance medication adherence (Review). Cochrane Database of Systematic Reviews, Issue 4,1–77. http://doi.org/10.1002/14651858.CD000011.pub2

Hu, L. T., & Bentler, P. M. (1999). Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Structural equation modeling: a multidisciplinary journal*, *6*(1), 1-55. https://doi.org/10.1080/10705519909540118

Jones, C. J., Smith, H. E., & Llewellyn, C. D. (2016). A systematic review of the effectiveness of interventions using the Common Sense Self-Regulatory Model to improve adherence behaviours. *Journal of Health Psychology*, *21*(11), 2709-2724. https://doi.org/10.1177%2F1359105315583372

Kaptein, A. A., Hughes, B. M., Scharloo, M., Fischer, M. J., Snoei, L., Weinman, J., & Rabe, K. F. (2008). Illness perceptions about asthma are determinants of outcome. *Journal of Asthma*, *45*(6), 459-464. https://doi.org/10.1080/02770900802040043

Knowles, S. R., Austin, D. W., Sivanesan, S., Tye-Din, J., Leung, C., Wilson, J., Castle, D., Kamm, M.A., Macrae, F., & Hebbard, G. (2017). Relations between symptom severity, illness perceptions, visceral sensitivity, coping strategies and well-being in irritable bowel syndrome guided by the common sense model of illness. *Psychology, health & medicine*, *22*(5), 524-534. https://doi.org/10.1080/13548506.2016.1168932

Kucukarslan, S. N. (2012). A review of published studies of patients' illness perceptions and medication adherence: lessons learned and future directions. *Research in social and administrative pharmacy*, *8*(5), 371-382. https://doi.org/10.1016/j.sapharm.2011.09.002

Kyriazos, T. A. (2018). Applied psychometrics: sample size and sample power considerations in factor analysis (EFA, CFA) and SEM in general. *Psychology, 9*(08), 2207. https://doi.org/10.4236/psych.2018.98126

Lala, V., Goyal, A., & Minter, D. A. (2021). Liver function tests. In *StatPearls [Internet]*. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK482489/

Leventhal, H., Meyer, D. and Nerenz, D. (1980). The common sense model of illness danger. In: Rachman, S. (Ed.), Medical psychology, Vol. 2. (pp. 7–30). Pergamon, New York.

Leventhal, H., Nerenz, D.R. & Steele, D.J. (1984). Illness representations and coping with health threats. In: Baum, A., Taylor, S.E. and Singer, J.E. (Eds.), Handbook of psychology and health: social psychological aspects of health, Vol. 4. (pp. 219–252). Earlbaum, Hillsdale, NJ.

Litt, I. F., & Cuskey, W. R. (1980). Compliance with medical regimens during adolescence. *Pediatric Clinics of North America*, *27*(1), 3-15. https://doi.org/10.1016/s0031-3955(16)33815-9

Löwe, B., Kroenke, K., Herzog, W., & Gräfe, K. (2004). Measuring depression outcome with a brief self-report instrument: sensitivity to change of the Patient Health Questionnaire (PHQ-9). *Journal of affective disorders*, *81*(1), 61-66. https://doi.org/10.1016/S0165-0327(03)00198-8

McGrady, M. E., Ryan, J. L., Gutiérrez-Colina, A. M., Fredericks, E. M., Towner, E. K., & Pai, A. L. (2015). The impact of effective paediatric adherence promotion interventions: Systematic review and meta-analysis. *Child: care, health and development*, *41*(6), 789-802. https://doi.org/10.1111/cch.12271

Mc Sharry, J., Moss-Morris, R., & Kendrick, T. (2011). Illness perceptions and glycaemic control in diabetes: a systematic review with meta-analysis. *Diabetic Medicine*, *28*(11), 1300-1310. https://doi.org/10.1111/j.1464-5491.2011.03298.x

Mossman, S. A., Luft, M. J., Schroeder, H. K., Varney, S. T., Fleck, D. E., Barzman, D. H., Gilman. R., Delbello. M. P., & Strawn, J. R. (2017). The Generalized Anxiety Disorder 7-item (GAD-7) scale in adolescents with generalized anxiety disorder: signal detection and validation. *Annals of clinical psychiatry: official journal of the American Academy of Clinical Psychiatrists*, *29*(4), 227. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5765270/

Moss-Morris, R., Weinman, J., Petrie, K., Horne, R., Cameron, L., & Buick, D. (2002). The revised illness perception questionnaire (IPQ-R). *Psychology and health*, *17*(1), 1-16. https://doi.org/10.1080/08870440290001494

Muscat, P., Weinman, J., Farrugia, E., Camilleri, L., & Chilcot, J. (2020). Illness perceptions predict mortality in patients with predialysis chronic kidney disease: a prospective observational study. *BMC nephrology*, *21*(1), 1-8. https://doi.org/10.1186/s12882-020-02189-7

National Institute for Health and Care Excellence (2009). *Depression in adults with a chronic physical health problem: recognition and management* [CG91]. https://www.nice.org.uk/guidance/cg91.

O'Carroll, R. E., McGregor, L. M., Swanson, V., Masterton, G., & Hayes, P. C. (2006). Adherence to medication after liver transplantation in Scotland: a pilot study. *Liver Transplantation*, *12*(12), 1862-1868. https://doi.org/10.1002/lt.20828

Olinsky, A., Chen, S., & Harlow, L. (2003). The comparative efficacy of imputation methods for missing data in structural equation modeling. *European Journal of Operational Research*, *151*(1), 53-79. https://doi.org/10.1016/S0377-2217(02)00578-7

Pavon Blanco, A., Turner, M. A., Petrof, G., & Weinman, J. (2019). To what extent do disease severity and illness perceptions explain depression, anxiety and quality of life

in hidradenitis suppurativa?. *British Journal of Dermatology*, *180*(2), 338-345. https://doi.org/10.1111/bjd.17123

Pinquart, M., & Shen, Y. (2011). Depressive symptoms in children and adolescents with chronic physical illness: an updated meta-analysis. *Journal of Pediatric Psychology*, *36*(4), 375-384. https://doi.org/10.1093/jpepsy/jsq104

Plummer, F., Manea, L., Trepel, D., & McMillan, D. (2016). Screening for anxiety disorders with the GAD-7 and GAD-2: a systematic review and diagnostic metaanalysis. *General hospital psychiatry*, *39*, 24-31. https://doi.org/10.1016/j.genhosppsych.2015.11.005

Richardson, L. P., Rockhill, C., Russo, J. E., Grossman, D. C., Richards, J., McCarty, C., & Katon, W. (2010). Evaluation of the PHQ-2 as a brief screen for detecting major depression among adolescents. *Pediatrics*, *125*(5), e1097-e1103. https://doi.org/10.1542/peds.2009-2712

Rosenstock, I. M., Strecher, V. J., & Becker, M. H. (1988). Social learning theory and the health belief model. *Health education quarterly*, *15*(2), 175-183. https://doi.org/10.1177%2F109019818801500203

Sabaté, E., & Sabaté, E. (Eds.). (2003). *Adherence to long-term therapies: evidence for action*. World Health Organization.

Sawyer, S. M., Azzopardi, P. S., Wickremarathne, D., & Patton, G. C. (2018). The age of adolescence. *The Lancet Child & Adolescent Health*, *2*(3), 223-228. https://doi.org/10.1016/S2352-4642(18)30022-1

Sen, B. (2004). Adolescent propensity for depressed mood and help seeking: race and gender differences. *Journal of Mental Health Policy and Economics*, *7*(3), 133-145.

Shemesh, E., Bucuvalas, J. C., Anand, R., Mazariegos, G. V., Alonso, E. M., Venick, R. S., & Shneider, B. L. (2017). The Medication Level Variability Index (MLVI) predicts

poor liver transplant outcomes: a prospective multi-site study. *American Journal of Transplantation*, *17*(10), 2668-2678. https://doi.org/10.1111/ajt.14276

Sockalingam, S., Blank, D., Abdelhamid, N., Abbey, S. E., & Hirschfield, G. M. (2012). Identifying opportunities to improve management of autoimmune hepatitis: evaluation of drug adherence and psychosocial factors. *Journal of Hepatology*, *57*(6), 1299-1304. https://doi.org/10.1016/j.jhep.2012.07.032

Spitzer, R. L., Kroenke, K., Williams, J. B., & Löwe, B. (2006). A brief measure for assessing generalized anxiety disorder: the GAD-7. *Archives of internal medicine*, *166*(10), 1092-1097. http://doi.org/10.1001/archinte.166.10.1092

Spitzer, R. L., Kroenke, K., & Williams, J. B. (1999). Patient Health Questionnaire Primary Care Study Group, & Patient Health Questionnaire Primary Care Study Group. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. *Jama*, *282*(18), 1737-1744. http://doi.org/10.1001/jama.282.18.1737

Sudan, D. L., Shaw Jr, B. W., & Langnas, A. N. (1998). Causes of late mortality in pediatric liver transplant recipients. *Annals of surgery*, *227*(2), 289. https://dx.doi.org/10.1097%2F00000658-199802000-00020

Suris, J. C., Michaud, P. A., & Viner, R. (2004). The adolescent with a chronic condition. Part I: developmental issues. *Archives of Disease in Childhood*, *89*(10), 938-942. http://dx.doi.org/10.1136/adc.2003.045369

Thapar, A., Collishaw, S., Pine, D. S., & Thapar, A. K. (2012). Depression in adolescence. *The Lancet*, *379*(9820), 1056-1067.

Tucker, C. M., Fennell, R. S., Pedersen, T., Higley, B. P., Wallack, C. E., & Peterson, S. (2002). Associations with medication adherence among ethnically different pediatric patients with renal transplants. *Pediatric Nephrology*, *17*(4), 251-256. https://doi.org/10.1007/s00467-001-0806-x

Vajro, P., Ferrante, L., Lenta, S., Mandato, C., & Persico, M. (2014). Management of adults with paediatric-onset chronic liver disease: strategic issues for transition care. *Digestive and Liver Disease*, *46*(4), 295-301. https://doi.org/10.1016/j.dld.2013.10.018

Vedhara, K., Dawe, K., Miles, J. N., Wetherell, M. A., Cullum, N., Dayan, C., Drake. N., Price. P., Tarlton. J., Weinman. J., Day. A., Campbell. R., Reps. J., & Soria, D. (2016). Illness beliefs predict mortality in patients with diabetic foot ulcers. *PloS one*, *11*(4). https://doi.org/10.1371/journal.pone.0153315

Weigard, A., Chein, J., Albert, D., Smith, A., & Steinberg, L. (2014). Effects of anonymous peer observation on adolescents' preference for immediate rewards. *Developmental science*, *17*(1), 71-78. https://doi.org/10.1111/desc.12099

Weinman, J., Petrie, K. J., Moss-Morris, R., & Horne, R. (1996). The illness perception questionnaire: a new method for assessing the cognitive representation of illness. *Psychology and health*, *11*(3), 431-445. https://doi.org/10.1080/08870449608400270

West, S. G., Finch, J. F., & Curran, P. J. (1995). Structural equation models with nonnormal variables: Problems and remedies. In R. H. Hoyle (Ed.), *Structural equation modeling: Concepts, issues, and applications* (pp. 56–75). Sage Publications, Inc.

World Health Organization. (2003). *Adherence to long-term therapies: evidence for action*. World Health Organization.

Wright, J., Elwell, L., McDonagh, J. E., Kelly, D. A., & Wray, J. (2015). 'It's hard but you've just gotta get on with it'–The experiences of growing-up with a liver transplant. *Psychology & Health*, *30*(10), 1129-1145. https://doi.org/10.1080/08870446.2015.1024245

Wu, H., Zhao, X., Fritzsche, K., Salm, F., Leonhart, R., Jing, W., & Schaefert, R. (2014). Negative illness perceptions associated with low mental and physical health status in general hospital outpatients in China. *Psychology, health & medicine*, *19*(3), 273-285. https://doi.org/10.1080/13548506.2013.802358

Yazigi, N. A. (2017, August). Adherence and the pediatric transplant patient. In *Seminars in pediatric surgery* (Vol. 26, No. 4, pp. 267-271). WB Saunders.

Žugelj, U., Zupančič, M., Komidar, L., Kenda, R., Varda, N. M., & Gregorič, A. (2010). Self-reported adherence behavior in adolescent hypertensive patients: the role of illness representations and personality. *Journal of pediatric psychology*, *35*(9), 1049-1060. https://doi.org/10.1093/jpepsy/jsq027

Section C: Appendices of Supporting Material

Appendix A: Assessment Against Joanna Briggs Criteria (JBI, 2020)

Table A.1

Assessment Against Joanna Briggs Criteria (JBI, 2020) for Analytical Cross-Sectional Designs

Question	Berquist et al. (2008)	Bilhartz et al. (2015)	Fredericks et al. (2008)	Fredericks et al. (2010)	Hames et al. (2021)	Jakubowska-Winecka and Biernecka (2018)
Were the criteria for inclusion in the sample clearly defined?	Yes – inclusion criteria were clearly specified.	Yes – inclusion criteria were clearly specified	Yes – inclusion criteria are clearly specified.	Yes – inclusion criteria were clearly defined.	Yes – inclusion criteria were clearly defined.	Yes – inclusion criteria were clearly specified. Note that this is the only study that gathered data from a broader range of participants (other transplant / disease types).
Were the study subjects and the setting described in detail?	Yes – full details of subjects were described (including disease, transplant and demographic variables), and setting and timeframes were clearly specified.	Partly – study subjects were described, although there was scope for further demographic variables to be included, such as ethnicity and socioeconomic status. Some basic information was given about the setting, with again scope for further details. However, timeframes were described.	Yes – study subjects were described in detail, although lacked socioeconomic status within the demographic data. Timeframe details were comprehensive and some information on clinic setting was provided.	No – only limited demographic details about the subjects were included. The setting was defined but not described in detail. Study start month/year is specified but ongoing timelines are less explicit than their previous publication.	Yes – detailed demographic information was provided, including employment/education and family circumstances (single parent families etc), together with clinical outcomes data.	No – limited demographic information was provided (other than age and gender).

Question	Berquist et al. (2008)	Bilhartz et al. (2015)	Fredericks et al. (2008)	Fredericks et al. (2010)	Hames et al. (2021)	Jakubowska-Winecka and Biernecka (2018)
Was the exposure measured in a valid and reliable way?	Yes – exposure variables in this study were demographic and disease variables, taken from medical records.	Partly – the exposure variable was Assessment of Responsibility (AoR) using a bespoke questionnaire. Whilst PCA analyses determined two primary components and Cronbach's alpha calculations suggested good internal consistency, further details and conclusions about the reliability and validity of the measure were not provided.	Yes – at the time of writing, there were no validated transplant-specific Health Related Quality of Life (HRQOL) measures and as such the authors used two tools. Details were provided for the two measures used, and their psychometric properties (indicating they are valid within broader relevant populations).	Partly – Assessment of Responsibility (AoR) was measured using an adapted (and thus unvalidated) survey. Psychometric properties (specifically construct and content validity) of the bespoke Transition Readiness Survey were investigated as part of the study (indicating these were "good"). However, this was done retrospectively to survey administration.	Yes – the majority of tools used were well-known and validated (e.g. PHQ9, GAD7 and BIPQ), although psychometric properties were not provided within the study. Other exposure factors included demographics, taken from medical records.	Partly – the Parental Attitudes Scale (PAS) was used to assess parental attitudes, but no details were provided of the tool's validity. Data was collected by self-report, which appears reliable.
Were objective, standard criteria used for measurement of the condition?	No – non-adherence was defined as any service user admission over a one-year period of non-adherence or not having attended a clinic visit in the same period. There is therefore a risk of	Yes – specified criteria were used to determine eligibility for inclusion and medication non-adherence was measured using immunosuppressant standard deviation (a	Yes – specified criteria regarding the participants' medical conditions were used to determine eligibility for inclusion and medication non-adherence was assessed	Yes – specified criteria regarding the participants' medical conditions were used to determine eligibility for inclusion and medication non-adherence was assessed	Unclear – specified criteria regarding the participants' medical conditions were used to determine eligibility for inclusion. Medication non-adherence was assessed used a non-	Unclear – no information was provided as to how details of the participants' medical conditions were defined and identified. The tool used to assess medication

Question	Berquist et al. (2008)	Bilhartz et al. (2015)	Fredericks et al. (2008)	Fredericks et al. (2010)	Hames et al. (2021)	Jakubowska-Winecka and Biernecka (2018)
	subjectivity in this measure.	choice that was well justified).	comprehensively, using a multi-method approach.	comprehensively, using a multi-method approach (using clinic attendance and immunosuppressant SD, although not the clinician interview included in their earlier publication).	validated self-report tool.	adherence (the Morisky Medication Adherence Scale; MMAS-8) was a self-report measure (and thus may have been subjective), for which no psychometric properties were provided.
Were confounding factors identified?	No – confounding variables were not explicitly identified.	Yes – the authors identified that as the study period was different for each participant (six months, over a three-year period), there was the potential for confounding clinical factors such as variability in personnel and clinical practices or other environmental considerations. Other demographic variables such as gender and age were included within the main analyses, although not	No – confounding variables were not identified nor referenced. However, they did establish that certain demographic variables (specifically time since transplantation, age at transplantation, race and "other demographic variables") were not significantly associated with outcome measures.	No – confounding variables were not identified nor referenced. However, they did look at the relationships between demographic variables with both the exposure and outcome measures.	No – no confounding variables were identified nor referenced. However, age, gender and other demographics were included as part of the main correlation analyses.	No – no confounding variables were identified nor referenced. However, age and gender were included as part of the main correlation analyses.

Question	Berquist et al. (2008)	Bilhartz et al. (2015)	Fredericks et al. (2008)	Fredericks et al. (2010)	Hames et al. (2021)	Jakubowska-Winecka and Biernecka (2018)
		specifically named as confounding variables.				
Were strategies to deal with confounding factors stated?	No – as above.	No – there was no way to address the potential clinical and environmental confounding variables identified, as mentioned above. However, differences by gender were investigated and partial correlations were used, but only to control for the effects of non-adherence on the relationship between age and AoR.	No – confounding variables were not mentioned.	No – confounding variables were not mentioned. Relationships with demographic variables were not then controlled for in later analyses between exposure and outcome variables.	No – confounding variables were not mentioned. Relationships with demographic variables were not controlled for in analyses.	No – confounding variables were not mentioned. Relationships with demographic variables were not controlled for in analyses between parental attitudes and adherence.
Were the outcomes measured in a valid and reliable way?	No – as above, their measure of non-adherence was not measured in a valid way. However, the additional clinical outcome measure of late acute rejection was well-defined and appeared objective.	Yes – despite its limitations, using immunosuppressant SD as a measure of medication non-adherence is well documented and accepted as a valid measure. Data was collected from service user records	Yes – although their approach to measuring medication non-adherence included a clinician-conducted interview using an unvalidated tool, they also used clinic attendance and immunosuppressant	Partly – they also used clinic attendance and immunosuppressant levels (for which predictive and concurrent validity have been suggested previously).	No – the tool used to assess adherence was a bespoke (and thus non-validated) self-report measure. However, the authors do discuss the benefit and potential validity of the tool given significant	No – the tool used to assess medication adherence (the Morisky Medication Adherence Scale; MMAS-8) was a self-report measure (and thus may have been subjective), for which no psychometric

Question	Berquist et al. (2008)	Bilhartz et al. (2015)	Fredericks et al. (2008)	Fredericks et al. (2010)	Hames et al. (2021)	Jakubowska-Winecka and Biernecka (2018)
		by research assistants not directly involved with the study, to reduce bias and improve reliability.	levels (for which predictive and concurrent validity have been suggested previously).		correlations were identified between scores and blood tests (indicative of liver function and thus most likely, medication adherence).	properties were provided.
Was appropriate statistical analysis used?	Yes – descriptive statistics, group differences and univariate and multivariate logistic regression were used. This appears comprehensive, with the latter allowing the probability of non-adherence to be modelled. However, no details were provided for statistical assumption testing prior to analyses.	Yes – appropriate analyses appears to have been used to both identify the psychometric properties of the AoR measure and explore relationships between the specified factors. However, there appears to have been scope for more predictive analyses, such as multiple regression. Due to its exploratory nature, the authors did not adjust for multiple comparisons (which may have increased the risk of type I errors).	Partly – both correlational and two-tailed t-tests were used (looking at adherence data both as a continuous and categorical construct). However, tests for statistical assumptions were not referenced and there was again scope for more predictive analyses.	Yes – appropriate analyses appears to have been used including CFA to establish the factorial structure of the TRS, descriptive statistics and correlations. Skewed data was identified, justifying the use for non-parametric tests. Adherence data was not also split categorically for additional analyses in the same way as their previous publication, however.	Yes – tests appear to be appropriate, although there was scope for more predictive analyses. Non-parametric tests were used, although details of how data were non-normal were not provided.	Partly – descriptive and correlation analyses were used.

Table A.2

Assessment Against Joanna Briggs Criteria (JBI, 2020) for Cohort Designs

Question	Annunziato et al. (2018)	Berquist et al. (2006)
Were the two groups similar and recruited from the same population?	n/a	n/a
Were the exposures measured similarly to assign people to both exposed and unexposed groups?	n/a	n/a
Was the exposure measured in a valid and reliable way?	Yes – reliability and validity of the measurement tools (e.g. REFILS) used was described where available and preliminary analyses (Cronbach alpha for internal consistency, Kappa coefficients and intraclass correlations for inter-rater reliability, and factor analysis for validity) was also conducted.	Yes – exposure variables in this study were demographic and disease variables, taken from medical records.
Were confounding factors identified?	No – these were not identified, nor was this recognised as a limitation.	No – these were not identified, nor was this recognised as a limitation.
Were strategies to deal with confounding factors stated?	No - potential confounding variables were not controlled for in analyses.	No - potential confounding variables were not controlled for in analyses.
Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	n/a	n/a
Were the outcomes measured in a valid and reliable way?	Yes – the use of the Medication Level Variability Index as an indication of medication non-adherence was well-detailed. Whilst limitations of using immunosuppressant SD do exist, this is generally accepted as a valid measurement. Data collection appeared reliability, through the use of a secure web-based interface to a data-coordinating centre.	Partly – medication non-adherence was defined prior to data collection as any documented report in medical records (by service user, parent or clinician). However, this is a subjective measure and may also have been subject to reviewer bias.
Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Partly – participants were followed for only two years, which may not have been sufficient time for non-adherence and/or poor clinical outcomes to present themselves.	Yes – the retrospective chart review was over a 15-year period (although note that participants may have had their liver transplant at any point during this time).

Question	Annunziato et al. (2018)	Berquist et al. (2006)
Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Partly – all data was gathered from the review period specified above. Details were not provided of those lost to follow up.	Partly - all data was gathered from the review period specified above. Details were not provided of those lost to follow up.
Were strategies to address incomplete follow up utilized?	Unclear – whilst 98% of participants recruited within the specified age range completed the REFILS, no details were provided regarding if anyone was lost to follow up subsequently.	n/a – this study involved retrospective data collection of participants being seen in routine clinic.
Was appropriate statistical analysis used?	Yes – tests appear to be appropriate (including for the assessment of reliability and validity of the REFILS), although there was scope for more predictive analyses. Non-parametric tests were used, although details of how data were non-normal were not provided.	Yes – tests appear to be appropriate, although there was scope for more predictive analyses. Non-parametric tests were used, although details of how data were non-normal were not provided.

Table A.3

Assessment Against Joanna Briggs Criteria (JBI, 2020) for Quasi-experimental Designs

Question	Jerson et al. (2013)
Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	Yes – it was clear that the causal variable being manipulated was being a peer mentor "now" or "later" and the effect (tacrolimus SD, as a measure of medication adherence) was measured pre and post this intervention.
Were the participants included in any comparisons similar?	Yes – chi-square and one-way ANOVA analyses showed no significant baseline demographic or measure score differences between the two groups. However, a waitlist control design was utilised (to make the programme available to all eligible and interested) and as such allocation was based on the date the service user consented to participation rather than random assignment. Justification of why this approach was taken together with potential limitations were explored within the paper.
Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Partly – it was inferred that this was the case given all participants were being treated at the same clinic for similar diagnoses. However, any variations in clinician, medication type etc were not made explicit. It is known, however, that the "now" group attended a clinic appointment from May to August and the "later" group September to December of that year.
Was there a control group?	Yes – the control was the "later" group, who were on the waitlist to become a peer mentor during the period the "now" (experimental) group were receiving this intervention. Thus results could be compared between those who had and had not had the intervention, without anyone missing out on receiving it.
Were there multiple measurements of the outcome both pre and post the intervention/exposure?	Yes – the same measures were completed both pre and post the intervention. However, there was only one measure of medication adherence used (tacrolimus SD), although the authors do provide justification for this over other options. Similarly, one measure was used for each of the healthcare management skills and health related quality of life (HRQOL) variables being assessed.
Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	No – post-intervention outcome measures were captured three months following completion of the peer mentor programme and there was no subsequent follow-up included within the design. However, eight/nine and all (13) participants in the experimental and waitlist control groups respectively completed both pre and post measures, providing comprehensive data, albeit with a small sample size.
Were the outcomes of participants included in any comparisons measured in the same way?	Yes – outcomes for both the "now" (experimental) and "later" (waitlist control) group were measured and analysed in the same way.

Question	Jerson et al. (2013)
Were outcomes measured in a reliable way?	Partly – medication adherence was measured in a reliable way using tacrolimus SD from clinic records. However, the authors did not specify how or by whom this data was collected, which thus introduces the potential for bias. The other measures (for healthcare management skills and HRQOL) were measured using self-report questionnaires.
Was appropriate statistical analysis used?	Partly – whilst the specific statistical tests used for both between and within group analyses appeared appropriate, details were not included on whether testing of necessary assumptions was undertaken. Furthermore, the sample size was small and thus it was assumed the study had low power. However, the authors did not include details of any power calculation nor effect sizes.

Table A.4

Assessment Against Joanna Briggs Criteria (JBI, 2020) for Qualitative Research

Question	Wright et al. (2015)
Is there congruity between the stated philosophical perspective and the research methodology?	Partly – Justification was provided for the use of IPA and broader methodology. Specifically, the need to explore the views of A&YAs who had experienced liver transplant was clear and described within the context of previous literature and associated gaps.
Is there congruity between the research methodology and the research question or objectives?	Yes – the aim (detailed above) and methodology appeared congruent i.e. the use of IPA to support the exploration of participants' experiences.
Is there congruity between the research methodology and the methods used to collect data?	Yes – the study took a phenomenological approach and the detailed description of the interview process appears to fit with this. Specifically, that whilst an interview schedule was available as a guide, this was not prescriptive, and interviews were flexible and guided by the interviewee. However, one limitation was that the interviews took place when participants were at the hospital for their routine appointments and thus a few were cut short prematurely.
Is there congruity between the research methodology and the representation and analysis of data?	Yes – a detailed description of the data analyses process was provided which appeared congruent with the stated phenomenological approach. Specifically, the principles of IPA (Smith, 1996) were followed, based on the four-step process specified by Smith and Osborn (2003).
Is there congruity between the research methodology and the interpretation of results?	Yes – it was stated that the aim of the results was to help design and develop tailored interventions for A&YAs who have had a liver transplants (potentials for which are detailed in their 'Implications for clinical practice and suggestions for further research section'), which appears congruent with the stated phenomenological approach.
Is there a statement locating the researcher culturally or theoretically?	No – whilst there was a comprehensive section on reflexivity, including the gender and professional background of the lead authors, more specific details on beliefs, values and their potential influence on the study were not detailed. However, there was a recognition that the authors personal narratives contributed to the interpretative process.
Is the influence of the researcher on the research, and vice-versa, addressed?	Yes – as above, the section on reflexivity included recognition of the authors/researchers' influence on the study. However, there was no recognition that the study would in turn influence the author/researchers and/or how they responded to events arising during the study.
Are participants, and their voices, adequately represented?	Yes – illustrations from the data through the use of quotes was provided.
Is the research ethical according to current criteria or, for recent studies, and is there evidence of ethical approval by an appropriate body?	Yes – appropriate ethical approval was sought, and best practice followed.

Do the conclusions drawn in the research report flow from the analysis, or interpretation, of the data?	Yes – conclusions drawn (including future clinical and research implications) flowed from the themes identified through data analyses.

Appendix B: Ethics approval and details regarding end of study

This has been removed from the electronic copy.

This has been removed from the electronic copy.

This has been removed from the electronic copy.

Appendix C: Participant Information Sheet

This has been removed from the electronic copy.

Appendix D: Copies of Measures Used

The PHQ-9 (Patient Health Questionnaire-9) (Spitzer et al., 1999)

This has been removed from the electronic copy.

The GAD-7 (Generalised Anxiety Disorder Scale) (Spitzer et al., 2006)

This has been removed from the electronic copy.

The BIPQ (The Brief Illness Perceptions Questionnaire) (Broadbent et al., 2006)

This has been removed from the electronic copy.

Appendix E: End of Study Report for the Service User Group

As this was an archival data project (and in line with IMPARTS guidelines), individual feedback will not be provided to each service user included in the study. However, the following information sheet was drafted for the Service User Group at the Young Adult Liver Service, at which results from this study will also be presented.

……..

A study investigating factors that are associated with how likely someone is to take their medication for a chronic liver disease
Overview for Service User Group

This document is a summary of research undertaken recently that has used data from some of the service users who have attended this clinic. The purpose of this project was to see if we could identify any factors that might make it more or less likely for service users to take their medication as prescribed.

Why did we investigate this?
Previous research and discussions with service users in clinic has indicated that some adolescents and young adults are less likely to take medication as prescribed, compared to children and adults. We think this is why some adolescents and young adults might be more likely to experience complications following a diagnosis or transplant, such as liver failure or transplant rejection.

For many service users receiving care from our clinic, medications can include immunosuppressants such as steroids which are important to stop liver diseases progressing or maintain a transplanted liver. However, we also know many of these medications can have significant side effects and implications on day-to-day life, such as weight gain, having to remember multiple tablets at specific times of day and not drinking alcohol.

Other studies have also shown that having to manage a chronic health condition at any time of life, but particularly during adolescence can impact one's quality of life and mood. Each person will also develop beliefs about their illness, which may depend on their previous experience of health difficulties, level of support they receive, impact of symptoms etc. These factors have also been shown to potentially be associated with whether someone is likely to take their medications.

We therefore decided to use the data we have been collecting in our clinic, to investigate what factors might be associated with how likely someone is to take their medication in the population we treat; adolescents and young adults (16-25 years) with chronic liver disease. These factors included demographic and clinical variables (such as age, age at diagnosis/transplant, sex, medication type) mood (scores for depression and anxiety) and illness perceptions (such as the level of concern one has about their illness or how much it impacts them emotionally).

What was our approach?
Data from the questionnaires that service users are asked to undertake prior to clinic appointments were used, supplemented by information from clinical records. All data were anonymised before analyses took place. Different statistical approaches were used, which allowed us to see if there were any relationships between different factors with medication adherence (answers to the question "*In general, what percentage of the time do you take your medication?"*) and if any factors could predict how likely someone was to take their medication.

We included 292 service users in the main sample and 73 in a smaller subset, the latter of whom we used data from over two appointments at least six months apart to see if there were any longer-term relationships between the factors specified above at appointment 1 and how likely it was for someone to take their medication and their liver function (from blood tests) at appointment 2.

What were the main findings and what might this mean?
We found that service users who were older, older at time of transplant or diagnosis and who reported a greater emotional impact of their condition appeared to be at a higher risk of not taking their medication. This fits with other research and demonstrates the difficulties that regular medication requirements may pose to older adolescents, who are more likely to be at an age when they are taking increased personal responsibility for their health in addition to naturally seeking more independence in other aspects of their life. It also importantly highlights how those who may be feeling particularly worried or angry about their health condition might need greater support in their treatment.

We also found that female service users were more likely to report difficulties with mood and more negative illness beliefs than male service users, although this did not mean they were less likely to take medication. This finding might be reflective of patterns we see in the general population; that girls and women are more likely to experience mental health difficulties such as low mood and anxiety compared to boys and men.

What will we do next?
We will share the outcome of this research with clinicians and researchers, to contribute to the understanding we have about adolescents and young adults with chronic liver disease.

Compared to other research already undertaken in this group, some of the approaches taken in this project were new. It will therefore be important to repeat some of the analyses with more data to see if we get the same results. Whilst we have identified some factors that might make a service user less likely to take their medication, we have also shown that it is probably not possible to reliably "predict" this using different pieces of data. Instead, there are likely to be multiple factors that are specific to that individual, many of which will interact with each other.

As a clinic, we will therefore continue to provide the opportunity in clinic appointments for service users to explore how they are feeling about their treatment, but we may also pay more attention to responses to the particular questions identified in this study that appear important with regards to whether someone is likely to take their medication. We will also continue to ensure we aim to provide care and support for service users that is specific to the needs of that individual and their family.

We hope this overview has been of interest, but if you have any questions or concerns about the findings then please do raise these within the Service User Group or with any of the

clinicians that are involved with your care. Thank you for completing the questionnaires at your appointments – this data allows us to conduct important research that we hope will improve the experience you have throughout treatment and the overall health of our service users.

Appendix F: Author Guideline Notes for the Journal of Adolescent Health

GUIDE FOR AUTHORS

"Submission Checklist"

Types of articles

The *Journal of Adolescent Health* publishes the following types of articles. Word count limits apply only to the main body of the manuscript and do not include the title, references, or figure and table captions.

Original Articles
Original Articles are full-length scientific reports on the results of original research. Text is limited to 3500 words with a 250-word structured abstract, 5 tables/figures, and 40 references. Original articles should include a 50-word Implications and Contribution summary statement.

Adolescent Health Briefs
Adolescent Health Briefs are brief scientific reports of original research that represent preliminary findings, small samples, and newly described associations in unique populations. Briefs are limited to 1000 words, with a structured abstract of 150 words or less. A combined total of 2 figures and/or tables and a maximum of 20 references will be accepted. Briefs should include a 50-word Implications and Contribution summary statement.

Review Articles
Review Articles provide a high-quality summary of existing science in a specific area. Systematic reviews and meta-analyses are preferred, though strong, evidence-based integrative will be considered for publication. All review articles are subject to a rigorous peer-review process. The format of the review article should include the introduction, review of the relevant literature, discussion, summary and implications section. Each review article must have a 200-word summary abstract. Review articles are limited to 4500 words, 5 tables/figures, and an unlimited number of references. Review articles should include a 50-word Implications and Contribution summary statement.

Clinical Case Reports
Case Reports represent rare and new observations in the clinical arena. Papers in this format are limited to 1000 words and should include an introduction, concise discussion of the clinical observation, and discussion. Clinical observations should include a 200-word summary abstract. A combined total of 1 figure, table, or illustration and 10 references will be accepted.

Letters to the Editor
Letters to the Editor typically represent correspondence regarding articles published in the Journal within the preceding 6 months. The author(s) of the article that is the subject of the correspondence will be invited to respond. Letters to the Editor may also be utilized to notify the Journal audience about reports, events, organizations, or other announcements that may be relevant to the international adolescent and young adult health community. Letters should not exceed 400 words. If appropriate, Letters can be accompanied with up to 5 references. This correspondence is published at the discretion of the Editor-in-Chief and the Associate Editors.

Commentaries
Commentaries serve as a forum for thoughtful discussions of critical issues in adolescent and young adult health, placed within the context of the scientific literature. Topics may include changes in relevant healthcare training and guidelines, governmental health policies and reports, international health, medical/scientific ethics, and meeting reports. Commentaries should not exceed 1,000 words and 10 references. Commentaries are published at the discretion of the Editor-in-Chief and the Associate Editors.

Editorials
Editorials are invited by the Editor-in-Chief and are linked to an original research article published in the same Journal issue. Editorials aim is to highlight important research findings and to place findings within a broader context for a wide audience. Editorials should not exceed 1,000 words and 20 references. Editorials are published at the discretion of the Editor-in-Chief and the Associate Editors.

JAH Intersection
JAH Intersection Section is a platform for sharing creative and artistic work by young people, family and community members, and health professionals. *JAH Intersection* intends to deepen our insights into the health and well-being of adolescents and young adults that can augment scientific peer-reviewed research. *JAH Intersection* amplifies the intersection of childhood with adulthood, and art with science. Submitted work may take the form of written word (e.g., poetry, personal narratives), or images (e.g., photographs or two-dimensional artwork). Submissions from persons under the age of 18 years must be accompanied by written permission to submit from a legal guardian. If the submission involves a true patient story or image, the patient must be adequately de-identified or the author/artist must obtain the patient's written permission for publication and current contact information. This should be provided in a cover letter to the editorial team upon submission. Items accepted for publication in *JAH Intersection* Section may also be used by the Society for Adolescent Health and Medicine for professional educational and awareness purposes, and the person who submitted the work will always be acknowledged. Submissions are reviewed and selected by the *JAH Intersection* Section Committee, and published at the discretion of *The Intersection* Section Editor(s), Editor-in-Chief, and Associate Editors.

The editorial process

Acceptance for review
Manuscripts submitted to the *Journal of Adolescent Health* are reviewed internally for interest and relevance. Approximately two thirds of all submitted manuscripts are returned to the authors following this internal review by the Editors; the remaining one-third are subjected to full peer-review. This decision is made quickly, within 10 days of submission.

Peer review and decision
Manuscripts accepted for peer review are sent to three external reviewers. Reviewers are anonymous; authors' names are revealed. The Journal's goal is to complete peer review and reach a decision within six weeks of submission.

Manuscripts will either be declined based on reviewer comments or referred back to the authors for revision.

Revisions requested

A Revise and Resubmit decision is an invitation to present a carefully revised draft for further peer review; it is not an acceptance.

Authors are asked to complete revisions within 30 days. If the authors do not respond within 30 days, the editors may decline to consider the revision. The editors reciprocate by providing a final decision quickly upon receipt of the revision.

Revised manuscripts should highlight changes to the text. Please include a response letter that describes how the authors have responded to each of the reviewer critiques. A response organized in a table format is preferred. The editors of the *Journal of Graduate Medical Education* have written an excellent guide to writing response letters.

Appeal process
Authors may appeal decisions. All appeals are reviewed by the Editor-in-Chief, on a case-by-case basis, or a designated Associate Editor if the Editor-in-Chief is recused from the review. This appeal must: (1) be submitted by the primary author in writing, (2) rebut the negative decision, and (3) be submitted within 30 days after the decision is rendered. Consideration of the appeal will be based on the appeal letter and the version of the manuscript that was peer reviewed. The decision of an appeal is final.

Acceptance for publication
All manuscripts accepted for publication will require a written assignment of the copyright from the author(s) to the Society for Adolescent Health and Medicine. Elsevier Inc. will maintain all records of the copyright for the Society for Adolescent Health and Medicine. No part of the published material may be reproduced elsewhere without written permission from the publisher.

Authors will receive typeset galley proofs via e-mail from the Journal Manager at Elsevier. Proofs should arrive approximately four to six weeks following acceptance. It is the corresponding author's responsibility to carefully review typeset galley proofs for accuracy.

Articles Online First
The *Journal of Adolescent Health* publishes articles online ahead of print publication in the Articles Online First section of our web site. Articles are published online approximately six to eight weeks following the galley proofs. The online article is identical to the version subsequently published in the print journal and is citable by the digital object identifier (DOI) assigned at the time of online publication.

Fast-tracking for critical issues in adolescent health and medicine
Manuscripts accepted for a fast-track review will receive a two-week expedited review. The Journal will notify authors of the outcome of the review within three weeks of submission. If the review is favorable, fast-track authors will be asked to complete any necessary revisions within two weeks.

Upon acceptance, fast-track manuscripts are prioritized for publication and should appear in print within two months.

Fast tracking is a rare event intended for high-priority findings and should not be viewed simply as a mechanism for an expedited review. The article should be prepared in the same manner as an Original Article.

Release to media
Until the time of publication on the *Journal of Adolescent Health*'s website, it is a violation of the copyright agreement to disclose the findings of an accepted manuscript to the media or the public. If you require an embargo date for your article, please contact the editorial office.

Supplements
The *Journal of Adolescent Health* publishes funded supplements containing peer-reviewed articles. Initial inquiries and proposals for supplements should be directed to the JAH Managing Editor, JAH Supplement Editor, and/or to Elsevier's Senior Supplements Editor:
Craig Smith
Elsevier Supplements Department
230 Park Avenue
Suite 800
New York, NY 10169-0901
Tel: (212) 462-1933
Fax: (212) 462-1935
E-mail: c.smith@elsevier.com

Contact details for submission

Editor
Carol A. Ford, M.D., Editor-in-Chief
Tor D. Berg, Managing Editor
Phone: 415-502-1373
E-mail: tor.berg@ucsf.edu
Editorial Office, Journal of Adolescent Health
University of California, San Francisco
Research and Policy Center for Childhood & Adolescence
3333 California Street, Suite 245
San Francisco, CA 94118-6210

Publisher
Luke Verrillo, Publisher
Phone: 215-239-3712
E-mail: l.verrillo@elsevier.com
Elsevier
1600 John F. Kennedy Blvd, Suite 1600
Philadelphia, PA 19103

http://www.jahonline.org/
https://www.editorialmanager.com/jah/default.aspx

BEFORE YOU BEGIN

Ethics in publishing

Please see our information on Ethics in publishing.

Human and animal rights

Studies of human subjects must document that approval was received from the appropriate institutional review board. When reporting experiments utilizing human subjects, it must be stated in writing, in the Methods section, that the Institution's Committee on Human Subjects or its equivalent has approved the protocol. Secondary data analyses require formal exemption from review by the Committee on Human Subjects or its equivalent. The protocol for obtaining informed consent should be briefly stated in the manuscript. The Editor-in-Chief may require additional information to clarify the safeguards about the procedures used to obtain informed consent. Within the United States, the authors should verify compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) prior to submission. When reporting experiments on animal subjects, it must be stated that the institution's animal care and use committee has approved the protocol.

Authors must immediately disclose to the *Journal of Adolescent Health* in writing the existence of any investigation or claim related to the manuscript with respect to the use of human or animal subjects that may be initiated by an institutional, regulatory, or official body at any time, including investigations or claims arising subsequent to manuscript submission, approval, or publication.

Conflict of interest

According to the World Association of Medical Editors (WAME):

"...a conflict of interest (competing interest) is some fact known to a participant in the publication process that if revealed later, would make a reasonable reader feel misled or deceived (or an author, reviewer, or editor feel defensive). Conflicts of interest may influence the judgment of authors, reviewers, and editors; these conflicts often are not immediately apparent to others. They may be personal, commercial, political, academic, or financial. Financial interests may include employment, research funding (received or pending), stock or share ownership, patents, payment for lectures or travel, consultancies, nonfinancial support, or any fiduciary interest in the company. The perception of a conflict of interest is nearly as important as an actual conflict, since both erode trust."

Authors are required to disclose on the title page of the initial manuscript any potential, perceived, or real conflict of interest. All accepted manuscripts, commentaries, and letters to the editor will be published with a conflict of interest statement as a footnote on the first page of the article. If no conflict is reported, the footnote will state that no conflict has been reported. Authors must describe the role of the study sponsor(s), if any, in (1) study design; (2) the collection, analysis, and interpretation of data; (3) the writing of the report; and (4) the decision to submit the manuscript for publication. Authors should include statements even when the sponsor had no involvement in the above matters. Authors should also state who wrote the first draft of the manuscript and whether an honorarium, grant, or other form of payment was given to anyone to produce the manuscript. If the manuscript is accepted for publication, the disclosure statements may be published. See also https://www.elsevier.com/conflictsofinterest. Further information and an example of a Conflict of Interest form can be found at: https://service.elsevier.com/app/answers/detail/a_id/286/supporthub/publishing.

Submission declaration

Submission of an article implies that the work described has not been published previously (except in the form of an abstract or as part of a published lecture or academic thesis; poster and platform presentations and abstracts are not considered duplicate publications but should be noted in the manuscript's cover letter and Acknowledgements section of the manuscript); that it is not under consideration for publication elsewhere; that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out; and that, if accepted, it will not be published elsewhere including electronically in the same form, in English or in any other language, without the written consent of the copyright-holder.

If the submitted manuscript contains data that have been previously published in print or online, is in press, or is currently under review by another publication in any format, the authors are required to submit a reprint of the published article or a copy of the other manuscript to the Editor-in-Chief with a clarification of the overlap and a justification for consideration of the current submitted manuscript.

The editors encourage authors to report fully the complete findings of their studies. The editors recognize that large and longitudinal datasets often result in multiple publications both on different topics and on the same topics across the span of development. Therefore, it is the authors' strict responsibility both to notify the editors of the existence of multiple manuscripts arising from the same study and to cross-reference all those that are relevant.

Manuscripts accepted for peer review may be submitted to the iThenticate plagiarism checker. iThenticate compares a given manuscript to a broad range of published and in-press materials, returning a similarity report, which the editors will then examine for potential instances of plagiarism and self-plagiarism.

Failure to disclose multiple or duplicate manuscripts may result in censure by the relevant journals and written notification of the appropriate officials at the authors' academic institutions.

Use of inclusive language

Inclusive language acknowledges diversity, conveys respect to all people, is sensitive to differences, and promotes equal opportunities. Content should make no assumptions about the beliefs or commitments of any reader; contain nothing which might imply that one individual is superior to another on the grounds of age, gender, race, ethnicity, culture, sexual orientation, disability or health condition; and use inclusive language throughout. Authors should ensure that writing is free from bias, stereotypes, slang, reference to dominant culture and/or cultural assumptions. We advise to seek gender neutrality by using plural nouns ("clinicians, patients/clients") as default/wherever possible to avoid using "he, she," or "he/she." We recommend avoiding the use of descriptors that refer to personal attributes such as age, gender, race, ethnicity, culture, sexual orientation, disability or health condition unless they are relevant and valid. When coding terminology is used, we recommend to avoid offensive or exclusionary terms such as "master", "slave", "blacklist" and "whitelist". We suggest using alternatives that are more appropriate and (self-) explanatory such as "primary", "secondary", "blocklist" and "allowlist". These guidelines are meant as a point of reference to help identify appropriate language but are by no means exhaustive or definitive.

Changes to authorship

Authors are expected to consider carefully the list and order of authors **before** submitting their manuscript and provide the definitive list of authors at the time of the original submission. Any addition, deletion or rearrangement of author names in the authorship list should be made only **before** the manuscript has been accepted and only if approved by the journal Editor. To request such a change, the Editor must receive the following from the **corresponding author**: (a) the reason for the change in author list and (b) written confirmation (e-mail, letter) from all authors that they agree with the addition, removal or rearrangement. In the case of addition or removal of authors, this includes confirmation from the author being added or removed.
Only in exceptional circumstances will the Editor consider the addition, deletion or rearrangement of authors **after** the manuscript has been accepted. While the Editor considers the request, publication of the manuscript will be suspended. If the manuscript has already been published in an online issue, any requests approved by the Editor will result in a corrigendum.

Registration of clinical trials

Clinical trials are studies that prospectively assign human subjects to an intervention or comparison group to test cause-and-effect relationships. Assignments are generally, but not necessarily, randomized. Interventions include behavioral treatments, process-of-care changes, nutritional programs, surgical procedures, drug regimens, medical and other devices, and the like.

Authors reporting results of a clinical trial must affirm that the study has been registered at www.clinicaltrials.gov or another WHO-approved national or international registry prior to the enrollment of the first subject. A list of registries can be found at http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/. The trial registration number must be listed on the title page of the manuscript submission packet.

Authors are strongly encouraged to include the CONSORT Flow Chart Diagram and a CONSORT Checklist (MSWord document) with their manuscript submission.

Copyright

Upon acceptance of an article, authors will be asked to complete a 'Journal Publishing Agreement' (see more information on this). An e-mail will be sent to the corresponding author confirming receipt of the manuscript together with a 'Journal Publishing Agreement' form or a link to the online version of this agreement.

Subscribers may reproduce tables of contents or prepare lists of articles including abstracts for internal circulation within their institutions. Permission of the Publisher is required for resale or distribution outside the institution and for all other derivative works, including compilations and translations. If excerpts from other copyrighted works are included, the author(s) must obtain written permission from the copyright owners and credit the source(s) in the article. Elsevier has preprinted forms for use by authors in these cases.

Author rights

As an author you (or your employer or institution) have certain rights to reuse your work. More information.

Elsevier supports responsible sharing
Find out how you can share your research published in Elsevier journals.

Role of the funding source

You are requested to identify who provided financial support for the conduct of the research and/or preparation of the article and to briefly describe the role of the sponsor(s), if any, in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. If the funding source(s) had no such involvement, it is recommended to state this.

Open access

Please visit our Open Access page for more information.

Language (usage and editing services)
Please write your text in good English (American or British usage is accepted, but not a mixture of these). Authors who feel their English language manuscript may require editing to eliminate possible grammatical or spelling errors and to conform to correct scientific English may wish to use the English Language Editing service available from Elsevier's Author Services.

Submission

Manuscript Preparation

General information
Submission to this journal proceeds totally online, and you will be guided stepwise through the creation and uploading of your files. The system automatically converts source files to a single PDF file of the article, which is used in the peer-review process. Please note that even though manuscript source files are converted to PDF files at submission for the review process, these source files are needed for further processing after acceptance. Please do not submit PDF documents as source files. All correspondence, including notification of the Editor's decision and requests for revision, takes place by e-mail, removing the need for a paper trail.

Manuscript documents must comply with layout and length requirements outlined below. All accepted manuscripts may be subject to editing and revision by the editors and their agents. Authors should take care to avoid redundancy within the text and between the tables, figures, and text. Due to page limitations, the editors may decide that figures, appendices, tables, acknowledgments, and other materials be published online only and referenced in the print edition of the *Journal*.

Online submission
Manuscripts must be submitted online via Editorial Manager (EM). To access EM, go to https://www.editorialmanager.com/jah/default.aspx and register as a new user. You will be guided stepwise through the creation and uploading of the various files and data. Once the uploading is done, the system automatically generates an electronic (PDF) proof, which is then used for reviewing. All correspondence regarding submitted manuscripts will be handled via e-mail through EM.

For the purposes of EM, a manuscript submission consists of a minimum of four distinct files: a Cover Letter, Manuscript, Title Page (with any Acknowledgments), and at least one Author Statement. EM accepts files from a broad range of word processing applications. Files should be set in 12-point double-spaced type. The manuscript file should follow the general instructions on style/arrangement, and, in particular, the reference style. Pages in the manuscript file should be numbered consecutively.

In addition, Tables and Figures should be included as separate and individual files.

If electronic submission is not possible, please contact Tor Berg, the Managing Editor, at tor.berg@ucsf.edu, or by phone at 415-502-1373 or by mail at: Editorial Office, *Journal of Adolescent Health*, University of California, San Francisco, Research and Policy Center for Childhood and Adolescence, 3333 California Street, Suite 245, San Francisco, CA 94118.

Cover Letter

A Cover Letter must accompany all submissions. The Cover Letter should describe the manuscript's unique contribution and provide the following information in accordance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication available at http://www.icmje.org:

- Disclosure of any prior publications or submissions with any overlapping information, including Methods, or a statement that there are no prior publications or submissions with any overlapping information;
- A statement that the work is not and will not be submitted to any other journal while under consideration by the *Journal of Adolescent Health*;
- A statement of any potential conflict of interest, real or perceived, the role of the study sponsor, and additional disclosures, if any; potential conflicts must also appear on the Title Page

Submit your article

Referees

To assist with a prompt, fair review process, authors are asked to provide the names, institutional affiliations, and e-mail addresses of 5 potential reviewers who have the appropriate expertise to evaluate the manuscript. Failure to provide at least 3 potential reviewers may result in delays in the processing of your manuscript. Do not refer potential reviewers with whom you have a current or past personal or professional relationship. Do not recommend members of the *Journal*'s editorial board. Authors may also provide the names of persons who should not be asked to review the manuscript. Ultimately, the editors reserve the right to choose reviewers.

Proprietary products

Authors should use nonproprietary names of drugs or devices unless mention of a manufacturer is pertinent to the discussion. If a proprietary product is cited, the name and location of the manufacturer must also be included.

Use of word processing software

It is important that the file be saved in the native format of the word processor used. The text should be in single-column format. Keep the layout of the text as simple as possible. Most formatting codes will be removed and replaced on processing the article. In particular, do not use the word processor's options to justify text or to hyphenate words. However, do use bold face, italics, subscripts, superscripts etc. Turn on page numbering in your manuscript file. When preparing tables, if you are using a table grid, use only one grid for each individual table and not a grid for each row. If no grid is used, use tabs, not spaces, to align columns. The electronic text should be prepared in a way very similar to that of conventional manuscripts (see also the Guide to Publishing with Elsevier). Note that source files of figures, tables and text graphics will be required whether or not you embed your figures in the text. Please do not submit PDF documents as source files. See also the section on Electronic artwork. To avoid unnecessary errors you are strongly advised to use the 'spell-check' and 'grammar-check' functions of your word processor.

PREPARATION

Use of word processing software

It is important that the file be saved in the native format of the word processor used. The text should be in single-column format. Keep the layout of the text as simple as possible. Most formatting codes will be removed and replaced on processing the article. In particular, do not use the word processor's options to justify text or to hyphenate words. However, do use bold face, italics, subscripts, superscripts etc. When preparing tables, if you are using a table grid, use only one grid for each individual table and not a grid for each row. If no grid is used, use tabs, not spaces, to align columns. The electronic text should be prepared in a way very similar to that of conventional manuscripts (see also the Guide to Publishing with Elsevier). Note that source files of figures, tables and text graphics will be required whether or not you embed your figures in the text. See also the section on Electronic artwork.
To avoid unnecessary errors you are strongly advised to use the 'spell-check' and 'grammar-check' functions of your word processor.

Article structure

Subdivision

Divide your article into clearly defined sections. Each subsection is given a brief heading. Each heading should appear on its own separate line. Subsections should be used as much as possible when cross-referencing text: refer to the subsection by heading as opposed to simply 'the text.'

The text of Original Articles and Briefs should usually, but not necessarily, be divided into the following sections: **Introduction**, **Methods**, **Results**, and **Discussion**. Additionally, the *Journal* requests an **Implications and Contribution** summary statement.

Implications and Contribution: In addition to the abstract, please include a summary statement at the beginning of your manuscript. This summary should be no more than 50 words in length and should describe the significance of your study's findings and its contribution to the literature in plain language. These summaries appear on the published articles and in various digests and newsletters.

Introduction: The introduction should clearly state the purpose(s) of the article and summarize the rationale for the study of observation. Please do not include an "Introduction" heading, just text. Only pertinent references should be used.

Methods: The selection of observational or experimental subjects (patients or experimental animals, including controls) should be clearly described in the Methods section. The methods, apparatus, and procedures used should be described in enough detail to allow other workers to reproduce the results. References should be provided for established methods, including statistical methods. Methods that are not well known should be concisely described with appropriate references. Any new or substantially modified method(s) should be carefully described, reasons given for its use, and an evaluation made of its known or potential limitations. All drugs and chemicals used should be identified by generic name(s), dosage(s), and route(s) of administration. The numbers of observations and the statistical significance of findings should be included when appropriate. Patients' names, initials, or hospital numbers should not be used.

*Note that when reporting experiments utilizing human subjects, approval of the protocol by the sponsoring Institution's Committee on Human Subjects or its equivalent must be stated explicitly within the Methods section of the manuscript. In addition, the protocol for obtaining informed consent should be briefly described. Secondary data analyses require formal exemption from review by a Committee on Human Subjects or its equivalent.

Results: Results should be presented in a logical sequence in the text, table(s), and illustration(s). Only critical data from the table(s) and/or illustration(s) should be repeated in the text.

Discussion: Emphasis in the Discussion section should be placed on the new and important aspects of the study and the conclusions that can be drawn. Detailed data from the results section should not be repeated in the discussion. The discussion should include the implications and limitations of the findings and should relate the observations to other relevant studies. The link between the conclusion(s) and the goal(s) of the study should be carefully stated, avoiding unqualified statements and conclusions not completely supported by the data. The author(s) should avoid claiming priority and alluding to work that has not yet been completed. New hypotheses, when stated, should be clearly identified as such. Recommendations, when appropriate, may be included.

Grammar, punctuation, and scientific writing style should follow the *AMA Manual of Style*, 10th edition.

Appendices
If there is more than one appendix, they should be identified as Appendix A, Appendix B, etc. Tables and figures in appendices should be given separate numbering: Table A1, Fig. A1, etc.

Essential title page information

• ***Title.*** Concise and informative (titles are limited to 140 characters). Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible.
• ***Author names and affiliations.*** Where the family name may be ambiguous (e.g., a double name), please indicate this clearly. Include the full names of all authors, as well as the highest academic degrees (excluding bachelor-level degrees) and the departmental and institutional affiliation of each. Please note that the *Journal* does not list fellowships of professional or certifying organizations as credentials. Relevant sources of financial support and potential conflicts of interest should be reported for all authors. Present the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lower-case superscript letter immediately after the author's name and in front of the appropriate address. Provide the full postal address of each affiliation, including the country name and, if available, the e-mail address of each author.
• ***Corresponding author.*** Clearly indicate who will handle correspondence at all stages of refereeing and publication, also post-publication. **Ensure that phone and fax numbers (with country and area code) are provided in addition to the e-mail address and the complete postal address. Contact details must be kept up to date by the corresponding author.**
• ***Present/permanent address.*** If an author has moved since the work described in the article was done, or was visiting at the time, a 'Present address' (or 'Permanent address') may be indicated as a footnote to that author's name. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes.
• ***Acknowledgments.*** The title page should also include an Acknowledgments section, listing any sources of support such as grants, equipment, or drugs; and any acknowledgments of persons who have made a substantive contribution to the study. Authors should obtain written permission from anyone that they wish to list in the Acknowledgments section. The corresponding author must also affirm that he or she has listed everyone who contributed significantly to the work in the Acknowledgments. Previous oral or poster presentations at local, regional, national or international meetings should be reported here.

Authorship Criteria
As a condition of authorship, all named authors must have seen the final draft of the manuscript, approve of its submission to the *Journal*, and be willing to take responsibility for it in its entirety.

All named authors must complete a signed Statement of Authorship. The *Journal*'s Statement can be downloaded in PDF format at https://www.elsevier.com/__data/promis_misc/jah_soa.pdf. We prefer an electronic copy of the statement: please electronically sign the PDF using Acrobat or print the PDF, sign it by hand, and scan it. Completed forms should be uploaded with your manuscript submission. We can also receive statements by email at jaheditorial@ucsf.edu or byfax at (415) 476-6106, though it may delay processing of your manuscript.

If there are concerns about how all persons listed as authors meet the criteria for authorship according to the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication* available at http://www.icmje.org, we will request further information from the corresponding author and, if necessary, request written documentation of each person's work on the report.

The *Journal* does not list corporate authors, such as research networks, professional societies, or think tanks. Only individuals meet the *Journal*'s criteria for authorship.

The names, along with any conflicts of interest, funding sources, and industry-relation, of persons who have contributed substantially to a study but who do not fulfill the criteria for authorship are to be listed in the Acknowledgments section. This section should include individuals who provided any writing, editorial, statistical assistance, etc.

Abstract

A concise and factual abstract is required. The abstract should state briefly the purpose of the research, the principal results and major conclusions. An abstract is often presented separately from the article, so it must be able to stand alone. For this reason, References should be avoided, but if essential, then cite the author(s) and year(s).

The abstract should be provided in a structured table format with the following bolded headings: **Purpose**, **Methods**, **Results**, and **Conclusions**. Emphasis should be placed on new and important aspects of the study or observations. Only common and approved abbreviations are acceptable, and they must be defined at their first mention in the abstract itself. Three to 10 key words or short phrases should be identified and placed below the abstract. These key words will be used to assist indexers in cross-indexing the article and will be published with the abstract. For this, terms from the Medical Subject Headings list in the Index Medicus should be used whenever possible.

Graphical abstract
Although a graphical abstract is optional, its use is encouraged as it draws more attention to the online article. The graphical abstract should summarize the contents of the article in a concise, pictorial form designed to capture the attention of a wide readership. Graphical abstracts should be submitted as a separate file in the online submission system. Image size: Please provide an image with a minimum of 531 × 1328 pixels (h × w) or proportionally more. The image should be readable at a size of 5 × 13 cm using a regular screen resolution of 96 dpi. Preferred file types: TIFF, EPS, PDF or MS Office files. You can view Example Graphical Abstracts on our information site.
Authors can make use of Elsevier's Illustration Services to ensure the best presentation of their images and in accordance with all technical requirements.

Abbreviations

Authors should provide a list of abbreviations on the title page. All acronyms in the text should be expanded at first mention, followed by the abbreviation in parentheses. The acronym may appear in the text thereafter. Do not use abbreviations in the title. Acronyms may be used in the abstract if they occur 3 or more times therein. Generally, abbreviations should be limited to those defined in the *AMA Manual of Style*, 10th edition.

Formatting of funding sources
List funding sources in this standard way to facilitate compliance to funder's requirements:

Funding: This work was supported by the National Institutes of Health [grant numbers xxxx, yyyy]; the Bill & Melinda Gates Foundation, Seattle, WA [grant number zzzz]; and the United States Institutes of Peace [grant number aaaa].

It is not necessary to include detailed descriptions on the program or type of grants and awards. When funding is from a block grant or other resources available to a university, college, or other research institution, submit the name of the institute or organization that provided the funding.

If no funding has been provided for the research, it is recommended to include the following sentence:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Units
Follow internationally accepted rules and conventions: use the international system of units (SI). If other units are mentioned, please give their equivalent in SI.

Math formulae
Please submit math equations as editable text and not as images. Present simple formulae in line with normal text where possible and use the solidus (/) instead of a horizontal line for small fractional terms, e.g., X/Y. In principle, variables are to be presented in italics. Powers of e are often more conveniently denoted by exp. Number consecutively any equations that have to be displayed separately from the text (if referred to explicitly in the text).

Artwork

Electronic artwork
General points
• Make sure you use uniform lettering and sizing of your original artwork.
• Embed the used fonts if the application provides that option.
• Aim to use the following fonts in your illustrations: Arial, Courier, Times New Roman, Symbol, or use fonts that look similar.
• Number the illustrations according to their sequence in the text.
• Use a logical naming convention for your artwork files.

• Provide captions to illustrations separately.
• Size the illustrations close to the desired dimensions of the printed version.
• Submit each illustration as a separate file.
A detailed guide on electronic artwork is available on our website:
https://www.elsevier.com/artworkinstructions
You are urged to visit this site; some excerpts from the detailed information are given here.
Formats
If your electronic artwork is created in a Microsoft Office application (Word, PowerPoint, Excel) then please supply 'as is' in the native document format.
Regardless of the application used other than Microsoft Office, when your electronic artwork is finalized, please 'Save as' or convert the images to one of the following formats (note the resolution requirements for line drawings, halftones, and line/halftone combinations given below):
EPS (or PDF): Vector drawings, embed all used fonts.
TIFF (or JPEG): Color or grayscale photographs (halftones), keep to a minimum of 300 dpi.
TIFF (or JPEG): Bitmapped (pure black & white pixels) line drawings, keep to a minimum of 1000 dpi.
TIFF (or JPEG): Combinations bitmapped line/half-tone (color or grayscale), keep to a minimum of 500 dpi.
Please do not:
• Supply files that are optimized for screen use (e.g., GIF, BMP, PICT, WPG); these typically have a low number of pixels and limited set of colors;
• Supply files that are too low in resolution;
• Submit graphics that are disproportionately large for the content.

Letters and symbols should be clear and even throughout and of sufficient size that when figures are reduced for publication (to approximately 3 inches wide), each item will still be legible. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, each should be identified and clearly explained in the legend.

If photomicrographs are to be submitted, the requirements for their presentation should be obtained from the Editor-in-Chief prior to submission.

If photographs of persons are used, either the subjects must not be identifiable or their pictures must be accompanied by written permission to publish the photograph.

If an illustration has been published, the original source must be acknowledged and accompanied by written permission from the copyright holder to reproduce the material. Permission is required regardless of authorship or publisher except for documents in the public domain.

Color artwork
Please make sure that artwork files are in an acceptable format (TIFF (or JPEG), EPS (or PDF), or MS Office files) and with the correct resolution. If, together with your accepted article, you submit usable color figures then Elsevier will ensure, at no additional charge, that these figures will appear in color online (e.g., ScienceDirect and other sites) regardless of whether or not these illustrations are reproduced in color in the printed version. **For color reproduction in print, you will receive information regarding the costs from Elsevier after receipt of your accepted article**. Please indicate your preference for color: in print or online only. Further information on the preparation of electronic artwork.

Illustration services
Elsevier's Author Services offers Illustration Services to authors preparing to submit a manuscript but concerned about the quality of the images accompanying their article. Elsevier's expert illustrators can produce scientific, technical and medical-style images, as well as a full range of charts, tables and graphs. Image 'polishing' is also available, where our illustrators take your image(s) and improve them to a professional standard. Please visit the website to find out more.

Figure captions
Ensure that each illustration has a caption. Supply captions separately, not attached to the figure. A caption should comprise a brief title (**not** on the figure itself) and a description of the illustration. Keep text in the illustrations themselves to a minimum but explain all symbols and abbreviations used.

Tables
Tables should be submitted as separate and individual files. Number tables consecutively in accordance with their appearance in the text. Each table should be given a brief title; explanatory matter should be placed in a table footnote. Place footnotes to tables below the table body and indicate them with superscript lowercase letters. Any nonstandard abbreviation should be explained in a table footnote. Avoid vertical rules. Be sparing in the use of tables and ensure that the data presented in tables do not duplicate results described elsewhere in the article. Statistical measures should be identified as measures of variation such as SD or SEM. If data from another published or unpublished source are used, permission must be obtained and the source fully acknowledged. EM will accept files from a wide variety of table-creation software.

References
Citation in text
Authors are responsible for the accuracy of references. References should be numbered consecutively in the order in which they are first mentioned in the text. References cited only in tables or figure captions should be numbered in accordance with the sequence established by the first identification in the text of the particular table or figure. Identify references in text, tables, and captions by Arabic numerals in brackets. Please ensure that every reference cited in the text is also present in the reference list (and vice versa). Any references cited in the abstract must be given in full. An effort should be made to avoid using abstracts as references. Unpublished observations and personal communications are not acceptable as references, although references to written, not verbal, communications may be inserted into the text in parentheses. Citation of a reference as 'in press' implies that the item has been accepted for publication. References to manuscripts accepted but not yet published should designate the journal followed by (in press) or use the DOI if assigned. All references must be verified by the authors against the original documents.

Reference links
Increased discoverability of research and high quality peer review are ensured by online links to the sources cited. In order to allow us to create links to abstracting and indexing services, such as Scopus, CrossRef and PubMed, please ensure that data provided in the references are correct. Please note that incorrect surnames, journal/book titles, publication year and pagination may prevent link creation. When copying references, please be careful as they may already contain errors. Use of the DOI is highly encouraged.

A DOI is guaranteed never to change, so you can use it as a permanent link to any electronic article. An example of a citation using DOI for an article not yet in an issue is: VanDecar J.C., Russo R.M., James D.E., Ambeh W.B., Franke M. (2003). Aseismic continuation of the Lesser Antilles slab beneath northeastern Venezuela. Journal of Geophysical Research, https://doi.org/10.1029/2001JB000884. Please note the format of such citations should be in the same style as all other references in the paper.

Data references
This journal encourages you to cite underlying or relevant datasets in your manuscript by citing them in your text and including a data reference in your Reference List. Data references should include the following elements: author name(s), dataset title, data repository, version (where available), year, and global persistent identifier. Add [dataset] immediately before the reference so we can properly identify it as a data reference. The [dataset] identifier will not appear in your published article.

Reference management software
Most Elsevier journals have their reference template available in many of the most popular reference management software products. These include all products that support Citation Style Language styles, such as Mendeley. Using citation plug-ins from these products, authors only need to select the appropriate journal template when preparing their article, after which citations and bibliographies will be automatically formatted in the journal's style. If no template is yet available for this journal, please follow the format of the sample references and citations as shown in this Guide. If you use reference management software, please ensure that you remove all field codes before submitting the electronic manuscript. More information on how to remove field codes from different reference management software.

Reference style
The titles of journals should be abbreviated according to the style used in the list of Journals Indexed for MEDLINE, posted by the NLM on the Library's web site, http://www.nlm.nih.gov/tsd/serials/lji.html. Reference style should follow that of the *AMA Manual of Style*, 10th edition, as shown in the following examples:

Journals

1. *Standard journal article*:
References should list all authors when four or fewer; when more than four, only the first three should be listed, followed by 'et al.'
Aalsma MA, Tong Y, Wiehe SE, et al. The impact of delinquency on young adult sexual risk behaviors and sexually transmitted infections. J Adolesc Health 2010;46:17-24. DOI: 10.1016/j.jadohealth.2009.05.018.

2. *Corporate Author*:
Center for Health Promotion and Education. Guidelines for effective school health education to prevent the spread of AIDS. J Sch Health 1988;58:142-8.

Books and Monographs

1. *Personal Author(s)* :
Romer D. Reducing Adolescent Risk: Toward an Integrated Approach. Thousand Oaks, CA: Sage Publications, 2003.

2. *Editor(s), Compiler(s), Chairman as Author(s)* :
Rosen DS, Rich M, eds. The adolescent male. In: Adolescent Medicine: State of the Art Reviews. vol 14. Philadelphia, PA: Hanley & Belfus, 2003.

3. *Chapter in a Book:*
Marcell AV, Irwin CE Jr. Adolescent substance use and abuse. In: Finberg L, Kleinman RE, eds. Saunders Manual of Pediatric Practice. 2nd ed. Philadelphia, PA: WB Saunders, 2002:127-139.

4. *Agency Publication:*
America's Children: Key National Indicators of Well-Being 2009. Washington, DC: Federal Interagency Forum on Child and Family Statistics, 2009.

Web sites

World Health Organization. Good information practice essential criteria for vaccine safety web sites. Available at: http://www.who.int/vaccine_safety/good_vs_sites/en. Accessed January 13, 2010.

Reference style
Text: Indicate references by number(s) in square brackets in line with the text. The actual authors can be referred to, but the reference number(s) must always be given.
List: Number the references (numbers in square brackets) in the list in the order in which they appear in the text.
Examples:
Reference to a journal publication:
[1] Van der Geer J, Hanraads JAJ, Lupton RA. The art of writing a scientific article. J Sci Commun 2010;163:51–9.
Reference to a book:
[2] Strunk Jr W, White EB. The elements of style. 4th ed. New York: Longman; 2000.
Reference to a chapter in an edited book:
[3] Mettam GR, Adams LB. How to prepare an electronic version of your article. In: Jones BS, Smith RZ, editors. Introduction to the electronic age, New York: E-Publishing Inc; 2009, p. 281–304.
Reference to a website:
[4] Cancer Research UK. Cancer statistics reports for the UK, http://www.cancerresearchuk.org/aboutcancer/statistics/cancerstatsreport/; 2003 [accessed 13.03.03].
Reference to a dataset:
[dataset][5] Oguro M, Imahiro S, Saito S, Nakashizuka T. Mortality data for Japanese oak wilt disease and surrounding forest compositions, Mendeley Data, v1; 2015. http://dx.doi.org/10.17632/xwj98nb39r.1.
Note shortened form for last page number. e.g., 51–9, and that for more than 6 authors the first 6 should be listed followed by 'et al.' For further details you are referred to 'Uniform Requirements for Manuscripts submitted to Biomedical Journals' (J Am Med Assoc 1997;277:927–34) (see also Samples of Formatted References).

Video data

The *Journal of Adolescent Health* accepts video material and animation sequences to support and enhance your scientific research. Authors who have video or animation files that they wish to submit with their article are strongly encouraged to include links to these within the body of the article. This can be done in the same way as a figure or table by referring to the video or animation content and noting in the body text where it should be placed. All submitted files should be properly labeled so that they directly relate to the video file's content. In order to ensure that your video or animation material is directly usable, please provide the files in one of our recommended file formats with a preferred maximum size of 50 MB. Video and animation files supplied will be published online in the electronic version of your article on JAHOnline.org and Elsevier's ScienceDirect: http://www.sciencedirect.com. Please supply 'stills' with your files: you can choose any frame from the video or animation or make a separate image. These will be used instead of standard icons and will personalize the link to your video data. For more detailed instructions please visit our video instruction pages at https://www.elsevier.com/artworkinstructions. Note: since video and animation cannot be embedded in the print version of the journal, please provide text for both the electronic and the print version for the portions of the article that refer to this content.

Supplementary data

The *Journal of Adolescent Health* accepts electronic supplementary material to support and enhance your scientific research. Supplementary files offer the author additional possibilities to publish supporting applications, high-resolution images, background datasets, sound clips and more. Supplementary files supplied will be published online alongside the electronic version of your article on JAHOnline.org and Elsevier's ScienceDirect: http://www.sciencedirect.com. In order to ensure that your submitted material is directly usable, please provide the data in one of our recommended file formats. Authors should submit the material in electronic format together with the article and supply a concise and descriptive caption for each file. For more detailed instructions please visit our artwork instruction pages at https://www.elsevier.com/artworkinstructions.

Research data

This journal encourages and enables you to share data that supports your research publication where appropriate, and enables you to interlink the data with your published articles. Research data refers to the results of observations or experimentation that validate research findings. To facilitate reproducibility and data reuse, this journal also encourages you to share your software, code, models, algorithms, protocols, methods and other useful materials related to the project.

Below are a number of ways in which you can associate data with your article or make a statement about the availability of your data when submitting your manuscript. If you are sharing data in one of these ways, you are encouraged to cite the data in your manuscript and reference list. Please refer to the "References" section for more information about data citation. For more information on depositing, sharing and using research data and other relevant research materials, visit the research data page.

Data linking
If you have made your research data available in a data repository, you can link your article directly to the dataset. Elsevier collaborates with a number of repositories to link articles on ScienceDirect with relevant repositories, giving readers access to underlying data that gives them a better understanding of the research described.

There are different ways to link your datasets to your article. When available, you can directly link your dataset to your article by providing the relevant information in the submission system. For more information, visit the database linking page.

For supported data repositories a repository banner will automatically appear next to your published article on ScienceDirect.

In addition, you can link to relevant data or entities through identifiers within the text of your manuscript, using the following format: Database: xxxx (e.g., TAIR: AT1G01020; CCDC: 734053; PDB: 1XFN).

Mendeley Data
This journal supports Mendeley Data, enabling you to deposit any research data (including raw and processed data, video, code, software, algorithms, protocols, and methods) associated with your manuscript in a free-to-use, open access repository. During the submission process, after uploading your manuscript, you will have the opportunity to upload your relevant datasets directly to *Mendeley Data*. The datasets will be listed and directly accessible to readers next to your published article online.

For more information, visit the Mendeley Data for journals page.

Data statement
To foster transparency, we encourage you to state the availability of your data in your submission. This may be a requirement of your funding body or institution. If your data is unavailable to access or unsuitable to post, you will have the opportunity to indicate why during the submission process, for example by stating that the research data is confidential. The statement will appear with your published article on ScienceDirect. For more information, visit the Data Statement page.

Submission checklist

checklist The following list will be useful during the final checking of an article prior to sending it to the *Journal* for review. Please consult this Guide for Authors for further details of any item.
Ensure that the following items are present:

Cover letter
- Disclosure of any prior publications or submissions with any overlapping information
- A statement that the work is not under consideration elsewhere
- Disclosure of any potential conflict of interest, real and perceived, for all named authors
- Names and contact information for 5 potential reviewers

Statements of Authorship
•Please submit a separate statement for each named author

Title page
- Article title
- Full names, academic degrees (Masters level and above), and affiliations of all authors
- Name, address, e-mail address, telephone and fax number of the corresponding author
- Sources of funding and acknowledgements of support and assistance
- Disclosure of potential conflicts, real and perceived, for all named authors
- Clinical trials registry site and number
- List of abbreviations

Manuscript
- Please double-space
- BR>• Abstract in the appropriate format: Structured for Original Articles and Briefs or Summary for Review Articles and Clinical Observations
•BR>• List of keywords
•Implications and Contributions statement
- IRB statement in the Methods section
- References should be in the correct format for this journal; all references mentioned in the Reference list are cited in the text, and vice versa
- Figure titles should be on a new page
- Manuscript has been 'spell-checked' and 'grammar-checked'

Tables
- Each saved as a separate document, including title and footnotes

Figures
- Each saved as a separate file, with captions/legends (without titles)
- Color figures are clearly marked as being intended for color reproduction on the Web (free of charge) and in print, or to be reproduced in color on the Web (free of charge) and in black-and-white in print; if only color on the Web is required, black-and-white versions of the figures are also supplied for printing purposes

- Permission has been obtained for use of copyrighted material from other sources (including the Web)
- Copies of prior and/or in press publications related to the current submission can be uploaded as separate files or e-mailed to the Managing Editor
- For any further information please visit our customer support site at https://service.elsevier.com.

AFTER ACCEPTANCE

Online proof correction

To ensure a fast publication process of the article, we kindly ask authors to provide us with their proof corrections within two days. Corresponding authors will receive an e-mail with a link to our online proofing system, allowing annotation and correction of proofs online. The environment is similar to MS Word: in addition to editing text, you can also comment on figures/tables and answer questions from the Copy Editor. Web-based proofing provides a faster and less error-prone process by allowing you to directly type your corrections, eliminating the potential introduction of errors.
If preferred, you can still choose to annotate and upload your edits on the PDF version. All instructions for proofing will be given in the e-mail we send to authors, including alternative methods to the online version and PDF.
We will do everything possible to get your article published quickly and accurately. Please use this proof only for checking the typesetting, editing, completeness and correctness of the text, tables and figures. Significant changes to the article as accepted for publication will only be considered at this stage with permission from the Editor. It is important to ensure that all corrections are sent back to us in one communication. Please check carefully before replying, as inclusion of any subsequent corrections cannot be guaranteed. Proofreading is solely your responsibility.

Offprints

The corresponding author will, at no cost, receive a customized Share Link providing 50 days free access to the final published version of the article on ScienceDirect. The Share Link can be used for sharing the article via any communication channel, including email and social media. For an extra charge, paper offprints can be ordered via the offprint order form which is sent once the article is accepted for publication. Both corresponding and co-authors may order offprints at any time via Elsevier's Author Services. Corresponding authors who have published their article gold open access do not receive a Share Link as their final published version of the article is available open access on ScienceDirect and can be shared through the article DOI link.

AUTHOR INQUIRIES

For inquiries relating to the submission of articles (including electronic submission) please send an email to jaheditorial@ucsf.edu. For detailed instructions on the preparation of electronic artwork, please visit https://www.elsevier.com/artworkinstructions. Contact details for questions arising after acceptance of an article, especially those relating to proofs, will be provided by the publisher. You can track accepted articles at https://www.elsevier.com/trackarticle. You can also check our Author FAQs at https://www.elsevier.com/authorFAQ and/or contact Customer Support via https://service.elsevier.com.