Exploring the psychological and physiological issues associated with X-linked ichthyosis

Georgina Wren

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Summary

This thesis investigates the psychological and physiological issues associated with congenital skin conditions, with a particular focus on X-linked ichthyosis (XLI), a rare dermatological disorder stemming from genetic variations proximal to the steroid sulfatase (STS) gene. Prior work by our research group has previously identified higher susceptibility to various physical and psychological conditions in males with XLI (and female carriers of XLI-linked genetic variants). Notably, higher incidences of mood and neurodevelopmental disorders and atrial fibrillation have been observed. Nevertheless, the extant literature offers only preliminary insights in this area, warranting further exploration into a) potential interactions among these extracutaneous manifestations, b) comparative analysis with other dermatological conditions, and c) possible comorbid factors influencing various functional domains.

To address these gaps in knowledge and to provide a comprehensive understanding of the experiences of those living with XLI, this thesis adopted a mixed-methods approach through online survey methodologies spanning four distinct research studies. Outcomes detailed in Chapters 3 and 4 highlighted increased prevalence rates of mood and neurodevelopmental disorders and related traits due to skin-specific factors, alongside negative effects on memory and executive functioning. Furthermore, findings discussed in Chapter 5 reveal higher susceptibility to cardiac arrhythmias among XLI cohorts, frequently precipitated by stress and concomitantly linked with gastrointestinal complications, asthma, and anaemia. The concluding feasibility trial in Chapter 6, asserts the suitability and efficacy of smartwatch technology for early detection of cardiac arrhythmias in XLI populations.

These novel findings underscore the importance of providing comprehensive long-term care strategies for individuals with XLI, encompassing various risk mitigation measures. Subsequent interventions may focus on developing effective coping strategies and stress reduction to enhance overall wellbeing, and potentially reduce both physiological and psychological burden.

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List of Acronyms

AD	Atopic Dermatitis
AD	Alzheimer's Disease
ADHD	Attention Deficit Hyperactivity Disorder
AE	Atopic Eczema
AF	Atrial Fibrillation
APPG	All Party Parliamentary Group on Skin
ASD	Autism Spectrum Disorder
AQ10	Autism Quotient 10
ASRS	Adult ADHD Self-Report Scale
AVN	Atrioventricular node
BAD	British Association of Dermatologists
BITe	Brief Irritability Test
BMI	Body Mass Index
CISI	Congenital Ichthyosis Skin Index
CSM	Common Sense Model of Self-Regulation
DALY	Disability Adjusted Life Year
DHEA/S	Dehydroepiandrosterone/ sulfate
DLQI	Dermatology Life Quality Index
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
FIRST	Foundation for Ichthyosis & Related Skin Types
FSQ	Feelings of Stigmatisation Questionnaire
GDB	Global Disease Burden
GI	Gastrointestinal
GP	General Practitioner
GPwERs	GP with an Extended Role in Dermatology'

HCP	Healthcare Professionals
HR	Heart rate
HRA	Heart rhythm abnormality
HRQoL	Health-related quality of life
HS	Hidradenitis Suppurativa
IBS	Irritable bowel syndrome
ISG	Ichthyosis Support Group
IV	Ichthyosis Vulgaris
K10	Kessler Psychological Distress Scale
MDD	Major Depressive Disorder
MDT	Multi-disciplinary team
MMQ	Multifactorial Memory Questionnaire
NDD	Neurodevelopmental disorder
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSC	National Screening Committee
NTS	Neurodevelopmental trait score
OCD	Obsessive Compulsive Disorder
OR	Odds Ratio
PASI	Psoriasis Area and Severity Index
PVB	Premature Ventricular Beats
QoL	Quality of Life
RAVLT	Rey Auditory Verbal Learning Test
RDAP	Rare Disease Action Plan
SAN	Sinoatrial node
SD	Standard deviation
SOC	Skin of Colour

STS	Steroid Sulfatase
TMB	TestMyBrain
UK	United Kingdom
UKBB	UK Biobank
US	United States
VE	Ventricular Ectopic Beats
VPB	Ventricular Premature Beats
XLI	X-linked ichthyosis

Preface

Over the course of the doctoral studentship, I have authored and co-authored a number of papers. These are listed below (those with direct relevance to the research presented in this thesis are marked with an asterisk). Where relevant, these papers are also noted at the start of related chapters.

Publications

Wren GH., O'Callaghan P., Zaidi A., Thompson AT., Humby T., Davies W. – Monitoring heart rhythms in adult males with X-linked ichthyosis using wearable technology: a feasibility study. (*Submitted for publication)*

Wren GH, Davies W. Cardiac arrhythmia in individuals with steroid sulfatase deficiency (X-linked ichthyosis): candidate anatomical and biochemical pathways. Essays in Biochemistry. 2024 Apr 4:EBC20230098.

*Wren G, Flanagan J, Underwood J, Thompson A, Humby T, Davies W. Memory, mood and associated neuroanatomy in individuals with steroid sulfatase deficiency (X-linked ichthyosis). Genes, Brain and Behavior. 2024.

*Wren G, Baker E, Underwood J, Humby T, Thompson A, Kirov G, Escott-Price V, Davies W. Characterising heart rhythm abnormalities associated with Xp22. 31 deletion. Journal of Medical Genetics. 2023 Jul 1;60(7):636-43.

Wren GH, Davies W. X-linked ichthyosis: New insights into a multi-system disorder. Skin Health and Disease. 2022 Dec;2(4):e179.

Brcic L, Wren GH, Underwood JF, Kirov G, Davies W. Comorbid medical issues in X-linked ichthyosis. JID Innovations. 2022 May 1;2(3).

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Hewitt RM, Ploszajski M, Purcell C, Pattinson R, Jones B, Wren GH, Hughes O, Ridd MJ, Thompson AR, Bundy C. A mixed methods systematic review of digital interventions to support the psychological health and well-being of people living with dermatological conditions. Frontiers in Medicine. 2022 Nov 3;9:1024879.

*Wren GH, Humby T, Thompson AR, Davies W. Mood symptoms, neurodevelopmental traits, and their contributory factors in X-linked ichthyosis, ichthyosis vulgaris and psoriasis. Clinical and Experimental Dermatology. 2022 Jun 1;47(6):1097-108.

Wren G, Mercer J. Dismissal, distrust, and dismay: A phenomenological exploration of young women's diagnostic experiences with endometriosis and subsequent support. Journal of Health Psychology. 2022 Sep;27(11):2549-65.

Conference Presentations

Throughout my PhD, I have also presented my work at a number of conferences, workshops and voluntary talks, as listed below. Those with direct relevance to the research presented in this thesis are marked with an asterisk.

Wren G, Davies W & Elgie T. (3rd-6th September 2024 – Estoril, Portugal) *'A mixed methods approach to characterising the ichthyoses across the lifespan'* (38th Annual Conference of the European Health Psychology Society – Oral Presentation)

*Wren G. (7th June 2024 – Cardiff, Wales) *'Exploring the psychological and physiological issues associated with X-linked ichthyosis'* (Three Minute Thesis/3MT)

*Wren G, Flanagan J, Underwood J, Thompson A, Humby T, Davies W. (24-27th February 2024 - Turin, Italy) *'Memory and associated cognitive functioning in individuals with steroid sulfatase deficiency'* (12th Congress, Steroids and Nervous System - Young Researcher's Symposium)

Davies W., & Wren G. (9th September 2023 – Shropshire, UK) '*X-linked ichthyosis (XLI) and ichthyosis vulgaris (IV): mental and physical health'* (ISG Family Day - Workshop)

*Wren GH, Humby T, Thompson AR, Davies W. (17th March 2023 – Cardiff, UK) *A rare skin disorder, impaired memory abilities, and depression – what is the (X)link?* (PGR Medicine and Dentistry Symposium – Oral Presentation)

*Wren GH, Humby T, Thompson AR, Davies W. (27th July 2022) *'An investigation into heart-related symptoms and attitudes towards heart screening in X-linked ichthyosis (XLI)'* (BPS PsyPAG Annual Conference – Oral Presentation)

*Wren GH, Humby T, Thompson AR, Davies W. (27th June 2022) *'An investigation into heart-related symptoms and attitudes towards heart screening in X-linked ichthyosis (XLI)'* (11th European Conference on Rare Diseases & Orphan Products – Poster Presentation)

*Wren GH, Humby T, Thompson AR, Davies W. (18th May 2022 – Cardiff, UK) *'An investigation into heart-related symptoms and attitudes towards heart screening in X-linked ichthyosis (XLI)'* (Speaking of Science Conference – Oral Presentation)

Wren G., & Mercer J. (13th April 2022 – Online) *'Supporting staff with endometriosis'* (EY Gibraltar - International Women's Day Office Talk Series)

*Wren GH, Humby T, Thompson AR, Davies W. (18th November 2021– Cardiff, UK) *'An investigation into heart-related symptoms and attitudes towards heart screening in X-linked ichthyosis (XLI)'* (School of Psychology Conference – Oral Presentation)

Wren G., & Mercer J. (25th August 2021 – Online) *'Dismissal, distrust and dismay: a phenomenological exploration of young women's diagnostic experiences with endometriosis and subsequent support'* (EHPS Virtual Conference – Oral Presentation)

*Wren GH, Humby T, Thompson AR, Davies W. (14th July 2021 – Cardiff, UK) *'An investigation into mood and neurodevelopmental disorder-associated traits in X-linked ichthyosis, Ichthyosis Vulgaris and psoriasis'* (School of Psychology Conference – Poster Presentation)

*Wren GH, Humby T, Thompson AR, Davies W. (12th June 2021 – Online) *'An investigation into mood and neurodevelopmental disorder-associated traits in XLI, IV and psoriasis'* (European Society for Dermatology & Psychiatry Conference– Oral Presentation)

Awards

ThreeMinuteThesis (3MT) Institutional Round Winner, June 2024

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To my incredible friends and family for listening to me talk about this PhD for the last four years, I promise this is definitely my last degree! You've been there through thick and thin, and I can't thank you all enough…and I owe you all a drink.

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All glory to God.

Chapter 1: GENERAL INTRODUCTION

**Note: some of the material included in this Chapter relates to the following published work, for which I am listed as the first author:*

Wren GH, Davies W. X-linked ichthyosis: New insights into a multi-system disorder. Skin Health and Disease. 2022;2(4):e179.

1.1 Dermatological Conditions

1.1.1 What is a dermatological condition?

Dermatological (skin) conditions affect a wide range of individuals across all countries, genders, and ages, and can be genetic in origin, infectious, inflammatory, degenerative, and in some cases, cancerous [1-3]. The most commonly reported skin disorders globally are psoriasis, skin cancer, eczema, and acne [4, 5]. Individual cases are treated based on the potential for spontaneous resolution, regular relapse/remission cycles, or improvements due to weather changes (heat), and common treatment methods include pharmaceutical drugs, topical treatments, and self-management techniques such as dietary restrictions [6].

1.1.2 The economic and societal burden of skin conditions

Skin diseases affect almost one third of the global population [1, 7] and are the fourth most common global health complaint [5], thus presenting a pressing challenge for the global economy. The global financial burden of skin complaints was estimated at $35.9 billion in 1997 [8], increasing to $39.3 billion in 2004 [7], with the current cost likely to be significantly higher again. Hospitalisations due to dermatological conditions alone produced an annual cost of $5.04 billion in the US in 2014, and although modern treatments including laser therapy and targeted biologicals are highly effective, they are also associated with higher costs [9]. Across Europe, up to 20% of visits to primary care are due to skin complaints [10], and in the UK specifically, >50% of individuals will experience a skin condition in their lifetime [11]. In 2013, over 25% of Americans visited a

primary care clinician due to skin complaints. In a one-month period studied in 2020, over 10% of consultations with a General Practitioner [GP] in the UK were dermatological in nature [12]. Early and more accurate identification of skin disorders may reduce this economic and societal burden, by utilising preventative measures and prioritizing effective and timely treatment.

1.1.3 How do UK healthcare professionals manage dermatological conditions?

To effectively and efficiently manage the high number of individuals affected by common skin complaints such as psoriasis and eczema, primary care clinicians such as GPs can utilise clinical guidelines created by the British Association of Dermatologists [BAD] and accredited by the National Institute for Health and Care Excellence [NICE]. Designed for healthcare providers, commissioners, patients, and carers, the 43 guidelines currently available provide recommendations for the management of common and rare diseases, as well as details on treatment methods such as pharmacological therapeutics [13]. Referral pathways for outpatient care are largely dependent on the availability of regional services within the UK, with some NHS Trusts offering specialist clinics for dermatology patients [14]. In other areas of the UK, specially designed web-based resources are available to assist primary care clinicians in the diagnosis, management and referral procedures for patients presenting with suspected skin conditions [15, 16]. Other resources freely available to GPs include webinars and e-learning courses via the Royal College of General Practitioners [17], and 'Essential Dermatology' events via the Primary Care Dermatology Society [18]. To support the psychological needs of patients presenting with skin complaints, all NHS healthcare practitioners have free access to a set of e-learning resources to guide the psychosocial management of common disorders [19]. Furthermore, GPs with a special interest in dermatology can apply with the BAD to be recognized as a 'GP with an Extended Role in Dermatology' [GPwERs]; this allows GPs to undertake tasks beyond the normal scope of their role, including receiving referrals for dermatology patients outside of their immediate practice [20].

Online learning resources and training pathways for primary care clinicians interested in dermatology provide an excellent opportunity to upskill healthcare professionals to meet the urgent and unmet needs of this patient population. However, current research suggests that most skin conditions are still regularly untreated and underdiagnosed, due to insufficient access to care, limited knowledge about dermatology amongst primary care clinicians, and high treatment costs [21, 22]. A recent assessment of dermatology-specific facilities and staffing across the UK exposed large variations in how BAD guidelines were utilised, with a widespread shortage of appropriately trained nurses and a distinct lack of psychodermatology services reported [23]. Patients experiencing moderate-severe psychological or emotional distress as a result of their skin condition are rarely referred to an appropriate specialist, and these challenges are often underestimated by healthcare professionals [24, 25]. As such, the most recent report published by the All Party Parliamentary Group on Skin [APPG] emphasised the urgent need for improved, accessible psychological care for individuals with a skin condition [26].

1.1.4 Crisis in Dermatology

Issues surrounding understaffing, underdiagnosis and a lack of specialist services, have recently cumulated in a 'crisis in dermatology' [23]. Within the UK healthcare system, in particular, these issues stem from two key areas of concern: a) a shortfall in the number of practising dermatologists and b) the availability of service provisions. Suggestions for how to address this crisis largely focus on service restructuring, specifically prioritising the following areas:

- Increase time allocated to dermatology training on undergraduate medical programmes (current provision <20 hours per course [27, 28 29, 30]).
- Improve access to high-quality training provisions for HCPs [26, 31].
- Improve diagnosis, understanding and management of skin complaints on black and brown skin (also known as 'non-white skin', or 'skin of colour' [SOC]) to reflect societal ethnic diversity [32 33].
- Increase the number of dermatology training posts for junior doctors [23 34].

- Enhance the focus on multi-disciplinary teams (MDTs) including primary care clinicians, dermatologists and psychologists to manage dermatologic disease [26, 35].

Tackling these systemic issues, will in all likelihood, subsequently address the current poor care provisions for patients, dissatisfaction with available support from clinicians [36-39], and improve diagnostic accuracy [35 76]. This 'bottom-up' approach is a crucial first step to improving awareness, knowledge, resources and understanding amongst HCPs. These targets are especially relevant for rare skin disorders, which are often misdiagnosed [40] and can require extensive genetic and clinical examination on first presentation [41]. The work from this thesis aims to improve understanding of rare skin disorders (predominantly X-linked ichthyosis), and long-term, to enhance patient care.

1.2 Comorbid medical conditions with skin disorders

Some skin disorders are also associated with comorbid medical conditions. For example, individuals with psoriasis and atopic dermatitis are significantly more likely to develop cardiovascular issues such as hypertension [42, 43], chronic pulmonary disease [44], myocardial infarction [44, 45], and coronary artery disease [45, 46]. Other conditions commonly associated with psoriasis and dermatitis include diabetes mellitus [44, 47], autoimmune conditions [48] such as Crohn's disease [43] and psoriatic or rheumatoid arthritis [48-51]. There is also an established link between obesity and psoriasis/atopic dermatitis [47, 52, 53], and in psoriasis specifically, comorbidities appear to be more common in those with more severe skin phenotypes [44]. Individuals with acne are also at increased risk of comorbid conditions, including asthma, sinus infection, food/digestive allergy [54], as well as changes to gut microbial diversity [55].

There are various potential explanatory mechanisms to explain the link between skin disorders and extracutaneous conditions. One potential explanation is the heritable nature of these conditions; genetic predisposition to skin disorders such as psoriasis, AD and acne may also predispose individuals to comorbid disorders [56, 57]. Well-studied genes responsible for this heritability include *PSORS1* (psoriasis) [57], *TNF* (acne) [58] and

filaggrin (*FLG*) null gene mutations (atopic dermatitis) [59]. The extent to which these suggested genes impact upon comorbid disorder risk is likely dependent on the type/size of genetic variant. However, whole-genome analysis remains a developing area of research, and thus these links are not fully established, requiring further analysis of rare genetic variants and additional candidate gene studies [56, 59, 60].

Alternatively, environmental influences such as diet, or extracutaneous conditions may impact skin health and the reverse may also be true, with skin conditions having downstream impacts upon other biological systems. For example, disturbances in the gut microbiota can negatively impact the skin [61 62 63], while improving gastrointestinal functioning can positively affect the skin [64, 65]. Some gastrointestinal conditions have been associated with cutaneous manifestations such as redness and skin ulcers, specifically inflammatory bowel disease (IBS) [66, 67] and intestinal bacterial overgrowth [61]. The key pathways between the skin and gut are a topic of debate; suggestions include a) the modulatory role of the gut microbiota via immune responses and metabolic capacity, subsequently impacting the skin, b) the gut bacteria may travel to the skin via a damaged gut barrier, and/or c) changes or disturbances in the diet which may impact both skin and gut [68, 69].

Other explanations largely focus on the wider causal role of inflammation across both skin disorders and related medical issues as discussed. Some skin conditions such as psoriasis and acne often begin as a result of an abnormal immune response, triggering systematic inflammation across the body [42, 70]. Environmental triggers such as smoking, changes in weather or infection can also exacerbate skin responses [57, 71, 72], and stressful life events have been seen to induce psoriasis [71, 73]. Alternatively, patients with preexisting conditions such as obesity [42, 52], may be more likely to develop skin conditions due to adipocytes and inflammatory-type macrophages which play a causal role in both disease processes [17 74]. The exact mechanisms and direction of this relationship is another topic of contemporary debate [57, 75], but this remains an exciting opportunity to improve patient outcomes using personalized medicine [75, 76].

1.2.1 Psychological comorbidities

The impact of living with a dermatological condition can be extensive and may affect many aspects of physical and psychological well-being, as well as daily functioning. To quantifiably measure this effect, various frameworks and scales are utilised to gauge the impact on 'Quality of Life' (QoL), or more specifically in this field, 'Health-Related Quality of Life' (HRQoL). Although the two terms are similar in reported outcomes, there are some key distinctions; measures of QoL typically refer to all known factors impacting on an individual's life whereas HRQoL relates only to health-based factors [77]. Measurements of QoL alone, are typically focused on a satisfaction judgement, concerning a sense of general wellbeing, specifically physical, social and emotional functioning, [78, 79]. In contrast, measures of HRQoL reflect measures of functioning relating to particular physical, mental, emotional and social aspects of health, as well as general well-being [80, 81]. To better explain these concepts, a conceptual model was proposed by Wilson & Cleary; this model combined biomedical and psychosocial approaches to health to better measure HRQoL [82, 83]. As depicted in Figure 1 (revised version), this model focuses on the causal relationship and interactions between contributory factors, both from the individual and environment [82, 84]. A comprehensive systematic review of the Wilson & Cleary model recommended that these factors could be equivocally applied to "all individuals, irrespective of age, health and disease conditions as well as culture" [83].

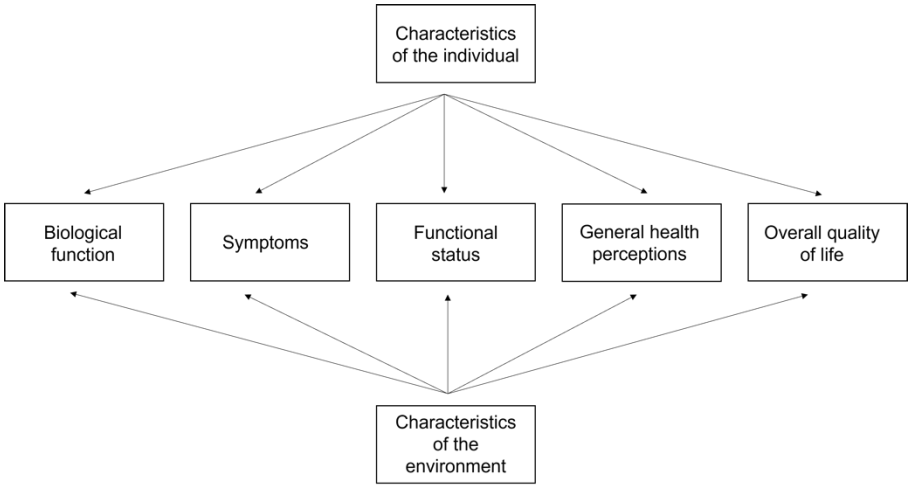


Figure 1: Revised version of Wilson & Cleary's conceptual model of HRQoL

QoL and HRQoL-based measures are both commonly used to understand patients' lived experiences of a condition, guide treatment decisions in a healthcare setting, and measure impact as part of clinical research [77, 85, 86]. In the field of dermatology, researchers and clinicians have expanded these measures by developing specific scales for patients with skin complaints; these include the Dermatology Quality of Life Index (DLQI) [87], EQ5D [88] and Skindex [89]. To understand how dermatological conditions can affect patients, it is important to explore the outcomes of these QoL and HRQoL measures.

1.2.2 Impact of dermatological conditions on QoL

Balieva, Kupfer (2017) measured HRQoL in a large-scale study of adults in dermatology settings across Europe and reported a substantially worse self-reported health status compared to controls (EQ5D) [88]. Individuals with a diagnosis of hidradenitis suppurativa (HS), blistering conditions, leg ulcers, psoriasis, and eczemas, produced the highest risk for a reduction in self-rated health status. This risk was reportedly similar to individuals with cardiovascular disease, cancer, and chronic obstructive pulmonary disease (COPD), thus demonstrating the significant impact of skin disorders on health [88]. Another large-scale study reported lower DLQI scores and reduced physical functioning in dermatology patients compared to controls [90]. Studies exploring the experiences of individuals with a skin condition have reported significantly reduced HRQoL in adults with atopic dermatitis (AD) [91], acne [92] and hidradenitis suppurativa (HS) [93]. Much of this research highlights the relationship between higher impairments in HRQoL and worse disease severity, including increased visibility of lesions [94-96]. However, very few studies provide additional information about any factors contributing towards reduced HRQoL, with some citing 'soreness of skin' and 'difficulty sleeping' [97, 98].

Although the many QoL and HRQoL measures are designed for widespread use across patient populations, recent research suggests that these scales may not be fit for use, unless key variable differences such as ethnic and social backgrounds are taken into account [99]. One example of these distinctions is sex-based measurements; in many cases, worse HRQoL and QoL are associated with female sex, due to genetic, physical and social factors [100, 101]. Furthermore, when segregating by ethnicity and skin colour, research has also highlighted some prominent differences; Indian and Malaysian patients with psoriasis reported significantly worse QoL scores compared to Chinese individuals [102]. Individuals with darker skin consistently report worse QoL and emotional well-being scores compared to White participants, even when controlling for skin severity [103, 104]. Research investigating the link between ethnicity/skin colour and QoL remains limited, although contemporary work has begun to explore potential associations. Disparities in socioeconomic status, education and employment levels between different ethnic groups may contribute to this relationship [102, 105], as well as cultural differences in perceived stigma and awareness surrounding visible skin conditions [106]. Furthermore, delays in diagnosis due to skin colour, and clinical bias may conceivably affect QoL. However, sex and skin colour-based segregated data are rarely reported in current research and thus explanations behind these differences remain challenging to establish.

1.2.3 Impact of dermatological conditions on daily functioning

Measures of QoL and HRQoL are not the only ways in which the impact of a dermatological condition can be assessed; Disability Adjusted Life Years, more commonly known as 'DALYs' measure the burden of a disease, specifically the number of years lost due to the absence of full health [107, 108]. DALYs are most prominently used to measure the 'Global Disease Burden' (GDB) across several skin conditions, and this burden is steadily increasing. Between 1990 and 2017, the burden of skin and subcutaneous diseases increased by >45%, and is now rated fourth for incidence of disease [109]. Much like QoL, there is some variation in recorded measurements of

burden, based on geographical location, age and sex and preliminary work suggests that burden scores may often be undervalued [107], particularly due to complex ICD diagnosis criteria and underreporting of skin disorders due to stigma [107].

The burden of skin disease as measured by DALYs also negates to account for the significant and often underappreciated burden on financial wellbeing and employment for individuals living with a skin condition. Additional costs to an individual can range from $880-$930 per annum, with 95% of patients reporting extra necessary spending [110, 111]. These added expenses are a result of visits to clinicians or specialist centres, cost of treatments, washing products and clothing/bedding [3, 111]. This economic burden is not limited to purchases and expenditure; across a sample of patients with atopic dermatitis (AD), an average of 52 working days per annum were lost due to their condition [98]. A similar study of individuals with AD in the Netherlands showed that 64% of individuals had lost one or more working days due to their condition in the last year, compared to 50% of controls [112]. Furthermore, nearly 60% of patients with atopic eczema (AE) and psoriasis attributed time off work in the last year to their condition [3, 111].

Thus, the physical and financial burden on the well-being of individuals living with a skin condition, in addition to the impact on daily functioning and productivity is clear, yet possibly still underestimated.

1.2.4 Impact of dermatological conditions on psychological wellbeing

The emotional, psychological and mental impact of living with a skin condition cannot be overlooked; on average, more than 30% of dermatology patients in specialist clinics present with a concern for their psychological well-being [113], with an overall prevalence of psychiatric comorbidity estimated at more than 40% [114]. Compared to the general population, as well as individuals with other long-term medical conditions such as diabetes and hypertension, patients presenting with a dermatological condition are typically at increased risk of developing depression and/or anxiety. Across a sample of adults with visible skin conditions, 43% of patients presented with symptoms above the

cut-off for clinical depression, compared to 18% of the general population controls [115]. In adults with psoriasis, the risks of depression, anxiety and in some cases, suicidal ideation are significantly higher than individuals without a dermatological condition [4, 116], even after controlling for factors such as age, BMI, alcohol use and physical activity levels [117]. One study estimated that more than 10,000 cases of depression and 7000 cases of anxiety are attributable to psoriasis in the UK on an annual basis [118]. These increased rates of depression and anxiety are also similar for individuals suffering from acne vulgaris [119], with nearly 25% of adolescents in New Zealand presenting with depressive symptoms [120]. Other dermatological conditions in which the risk of depression and anxiety are elevated compared to general population controls, including atopic dermatitis (AD) [121, 122], and hidradenitis suppurativa (HS) [123, 124].

Other measures of psychological well-being for individuals living with skin conditions include self-esteem, social isolation, burden on relationships and embarrassment. In a large assessment of individuals with a skin disorder in the UK, more than 50% reported 'social challenges', including issues surrounding social appearance, and stigma [97]. Individuals also commonly report feelings of worry about their skin and how it will be received by peers [125], with people under the age of 18 more likely to report increased bullying and social isolation [126]. Research has revealed significantly lower self-esteem and body satisfaction in individuals suffering from acne, due to the visible nature of the condition largely on the face [92, 127]. Patients with psoriasis and/or psoriatic arthritis have reported diminished self-esteem due to their condition [128, 129], as well as reduced social functioning, and increased social isolation in individuals with AD or HS [91, 130]. The impact of living with a skin condition is not only felt by the individual but also by family members and friends; due to the time-consuming nature of skin treatments, parents of young children may experience sleep disturbance and exhaustion [131], with adult partners reporting a negative impact on sex life [132].

To summarise, it is important to understand the impact of living with a dermatological condition on emotional and mental wellbeing, as well as the physical impact on individuals. Treatment plans should also take into account further environmental factors

which may place individuals at increased risk of not only exacerbating the skin condition but also developing comorbid physiological and psychological conditions. These factors include smoking, quality of life, and airborne contaminants [133, 134 135]. Inflammation associated with skin conditions can also increase later disease risk and lead to early mortality [136], and thus effective long-term management is essential [137, 138].

1.3. Managing a dermatological condition

The physical, financial, and psychological burdens of living with a dermatological condition are clear, with individuals across a range of disorders describing reduced QoL, economic struggle, and reduced self-esteem compared to the general population. To manage these impacts, individuals may employ a range of coping and management strategies to support themselves, as well as other affected parties including family and friends. The Common Sense Model of Self-Regulation suggests that individuals may manage their diagnosis on both a cognitive and an emotional level, using five main dimensions of illness: illness representations: cause, consequence, identity, duration, and controllability [139, 140]. A small-scale review by Rocholl, Ludewig (2021) using the CSM framework identified key coping procedures used by individuals with eczematous skin diseases; these included workplace changes (time off work, changing professions), skin protection, and diagnostic procedures and treatment (e.g., regular health checks, self-medication) [141]. Thus, coping strategies sitting within the CSM dimensions may offer an adaptable approach to managing a complex, long-term illness such as a skin condition.

1.3.1 How do patients manage/support themselves?

The use of structured coping and self-management can play a key role in an individual's experience of living with a long-term skin condition, if effective. However, Kent (2000) suggests that avoidance and concealment are two of the most common negative coping strategies employed by individuals with visible differences such as skin disorders [142], which in turn maintain distress [143, 144] and reduce QoL [145, 146]. Furthermore, other

adverse coping skills such as denial and catastrophising are also associated with increased stress and anxiety, more intense itch severity and reduced physical functioning [145, 147-150]. Thus, it is important that individuals are empowered and supported in managing their skin condition effectively, to reduce distress and promote resilience [148, 151].

Effective coping and self-management is largely focused on reducing the physical effects. An investigation by Fisher, Ellen (2020) revealed that individuals suffering from HS or psoriasis tried to avoid recurrent outbreaks by avoiding certain foods, adhering to strict treatment regimens and following self-care rituals [152]. To cope with any outbreaks, individuals tended to focus heavily on self-care including taking multiple showers and staying in bed due to fatigue and feelings of embarrassment. These active coping methods are also employed by individuals with other common skin conditions, with methods such as dietary restrictions [153] and adherence to treatment plans [154] frequently cited. Furthermore, mothers of children suffering from eczema describe a need to control the pain as a shared problem between them and the child, with the responsibility for treatment adherence thus typically resting on the mother [155].

Another key element of self-management and coping for individuals suffering from a skin condition could be described as the ability to be psychologically flexible, sufficiently enough to support healthy emotional regulation [156]. Psoriasis patients on a specialist dermatological ward who exhibited a 'fight spirit strategy', focused on encouragement and positive reframing, experienced less severe itch intensity, fewer itch episodes and overall better social functioning [148]. Some individuals with highly visible conditions such as facial acne or HS, describe ways in which they compensate for their condition by the use of humour and enhanced personality traits [154, 157]. The coping skills utilised by parents, partners and friends seem to focus more closely on support and acceptance; recent work by Amaro (2020) depicts how mothers of children with eczema focus on communal coping in an attempt to normalize and accept the condition as part of everyday life [155].

To manage the emotional and physical burden of living with a skin condition, individuals often rely on various forms of social support, including family and friends, as well as online groups. More specifically, this can include disclosing symptoms to friends and family, obtaining information from specialist medical staff, as well as sharing experiences and feeling empathy from online patient support groups or forums [152, 154, 158]. These coping skills can play a key role in an individual's long-term management plan as high perceived social support levels can significantly reduce the risk of depression and improve quality of life [159-161]. However, some individuals choose to avoid socialising or limit their interactions with others due to perceived stigmatization, potential for 'othering' amongst friends, thus prompting withdrawal from social activities [157, 162]. A lack of social interactions can be associated with feelings of loneliness [163], reduced resilience [164], as well as the potential for bullying and discrimination from peers and teachers for children of school age [165].

Structuring an appropriate and effective plan for managing a skin condition long-term is an essential element of coping for many individuals. Strategies to successfully manage a dermatological diagnosis may include changes to daily habits such as diet or physical activity, emotion regulation such as positive reframing, and reliance on social support including peers, family, and online channels.

1.3.2 How do the healthcare system/clinicians support individuals?

Although structured self-management techniques are a key component of coping for individuals living with a skin condition, specialist clinics designed to deliver targeted psychological interventions and guidance are also a crucial pillar of support. Psychodermatological clinics, also known as 'psychoneurocutaneous services' in the US, provide care for individuals suffering from psychiatric comorbidities commonly associated with many skin conditions or mental health components such as low self-esteem or reduced resilience. Interventions can include the identification of coping strategies, positive restructuring, and a focus on taking control of life whilst managing a skin condition [166, 167]. The recent introduction of psychodermatology in the UK and US,

has largely focused on the creation of MDTs, typically made up of dermatologists, psychologists, and psychiatrists [167]. There has also been an expansion of skin specific services and clinician expertise within general mental health service provision for people living with a long-term condition. This includes self-referral to psychological care such as cognitive behavioural therapy (CBT) through Improving Access to Psychological Therapies (IAPT), and strengthened primary care management [168].

However, there continues to be a significant dearth of interventions (and trials of these) offered/delivered within dermatology or psychological therapy services, designed for individuals with skin conditions. Thus, it is difficult to evaluate the effectiveness of these provisions due to being sparse in nature. Furthermore, amongst existing interventions, there is significant variability across countries, clinics, and HCPs, as well as differences between types of skin conditions, condition severity and biological mechanisms associated with certain disorders. Thus, the following review largely focuses on interventions delivered outside of psychodermatology clinics.

A large-scale meta-analysis of the effectiveness of psychological interventions for adults with skin conditions reported a medium-large effect on outcomes related to itch/scratch, skin severity and psychosocial well-being [169]. Effect sizes differed between the types of intervention, with habit reversal offering the largest effect [169]. Furthermore, condition-specific interventions have produced variable results; for individuals suffering from AD, interventions targeting physical health outcomes including itch intensity, skin severity and scratching have proven highly effective [170, 171]. Psychosocial-focused interventions designed for AD patients also show significant improvements in QoL, understanding of the disease, and positive coping behaviours [170, 172]. Similar psychological therapies designed for patients with psoriasis revealed that >70% of individuals found mindfulness and compassion-based interventions helpful [173], but there was no difference in skin severity for individuals completing an emotional disclosure programme [174]. Based on these outcomes, it is clear that psychosocial interventions may be effective for skin condition patients, but there is no 'one size fits all' approach.

Based on these findings, it is clear that further evaluations and audits of existing psychodermatology services are necessary to establish the efficacy of current interventions. Although some provisions may be effective in reducing the physical and psychological burden of living with a skin condition, these resources are not widely available, as discussed previously. Reports from clinical staff suggest that <25% of dermatology-based HCPs have access to a localised psychodermatology clinic, with 90% of staff deeming existing services as 'poor' due to a lack of funding, referral challenges and high demand [175]. The importance of providing targeted and readily accessible psychological therapies cannot be ignored; >75% of adults living with a skin condition felt that they would benefit from more support [125], with individuals emphasizing the need for greater understanding from clinicians [176]. In the recent APPG report, >50% of patients were unaware that they could seek psychological help, and only 18% of respondents had received some form of mental health support [26]. This report outlined a series of urgent recommendations to improve access to psychological support for patients, and to develop timely referral pathways for clinicians; these include suggestions for specialist paediatric services, training for HCPs and increased staffing [26]. The 'psychodermatological research priorities' outlined by Thompson, Guterres and Bewley (2020) reiterate the need for an improved understanding of the how effective psychological interventions can be in supporting individuals with a wide range of skin conditions, specifically related to QoL and psychosocial outcomes [178]. As such, informed, effective psychosocial care for individuals living with a skin condition is of paramount importance for the future of dermatology.

1.4 The ichthyoses

The ichthyoses, also known as disorders of keratinization (DOK) [179] represent a heterogeneous group of dermatological conditions, arising from abnormal cornification and desquamation processes [180]. These conditions are characterised by dry, thickened scales, and typically affect the face, extensor surfaces and trunk [181]. Other changes to the skin include erythroderma (redness), palmoplantar keratoderma (thickening of the palms and soles), hypohidrosis (diminished sweating), and recurrent infections [179].

These cutaneous manifestations are caused by abnormal barrier function in the epidermis, leading to abnormally rapid cell growth, known as hyperproliferation [179, 181]. Although all types of ichthyosis are caused by impaired barrier function, different classifications of ichthyosis involve variable affected layers and corresponding keratinocytes of the epidermis, including cholesterol, ceramides, and filaggrin [179, 181]. Ichthyosis can also occur either in an exclusively cutaneous manner (in the skin, known as non-syndromic), or with additional extracutaneous manifestations (syndromic) [180], and are known as either inherited (genetic basis) or acquired (secondary to other causes such as cancer, infectious diseases and nutritional deficiencies) [181]. Characteristics and epidemiology of some of the main types of ichthyoses are presented in Table 1 below:

TYPE	**SUBTYPE**	**PREVALENCE**	**CLINICAL FEAUTURES**	**GENETIC PATHWAYS**
Ichthyosis Vulgaris (IV)		1 in 100-250 adults [182]	Xerosis, keratosis pilaris, palmar hyperlinearity [183, 184]	Loss of function mutations in the filaggrin gene [182]
X-linked ichthyosis (XLI)		1 in 3000-6000 males [185]	Polygonal brown scaling and erythema [185]	Genetic deletion at Xp22.31 (*STS*) [185-187]
Autosomal recessive congenital ichthyosis (ARCI)	Congenital ichthyosiform erythroderma	2.18 per million [188]	Generalized severe scaling and erythroderma without blister formation [189]	(Not yet clearly established) Mutations at *ABCA12* [190], *TGM1* [191], *ALOXE3* or *ALOX12B* [192]
	Lamellar ichthyosis	4.5 per million [193]	Grey/brown thick scaling across body [194, 195]	(Not yet clearly established) Mutations at *TGM1* [196] [197],

				ALOXE3 or *ALOX12B* [192]
	Harlequin ichthyosis	0.12 per million[198]	Thick scale plates separated by deep fissures	Mutations at *ABCA12* [199] [200]
	Epidermolytic ichthyosis (also known as bullous ichthyosiform erythroderma)	1 in 100,000–300,000 [201, 202]	Erythroderma and blistering at birth, later development of hyperkeratosis	Mutations at *KRT1*/*KRT10* [202-205]
	Netherton's syndrome	0.80 per million [193]	Pruritic polycyclic erythematous patches with a double-edged circinate or serpiginous scale and hair shaft abnormalities [206, 207]	Mutations at *SPINK5* [204, 205]

Table 1: Types of ichthyosis and characteristics

1.4.1 Ichthyosis Vulgaris

The most common type of inherited ichthyosis is ichthyosis vulgaris (IV), characterised by xerosis, scaling, keratosis pilaris, as well as palmar and plantar hyperlinearity [182]. IV is the most common type of ichthyosis, affecting 1 in 100 to 1 in 250 individuals [41], and appears to be more common in European populations compared to Asian populations based on ancestral genetic components [208]. Recent genotyping identified that loss of function mutations at the filaggrin gene (*FLG)* are likely responsible for IV [209]. This mutation results in a deficiency or total loss of filaggrin, thus causing disruption to the epidermal barrier [208]. These loss of function mutations are also a predisposing factor in the development of atopic dermatitis (AD), with 2.5%–37% of patients with AD also displaying evidence of IV [210].

Individuals with IV are also at increased risk of developing several other conditions: due to the disrupted skin barrier, vitamin D deficiency appears to be more common in children with IV compared to healthy individuals [211]. Other complications include ocular abnormalities, namely ectropion [212], as well as hearing loss [211]. In addition, similar to other dermatological conditions discussed in 1.2.3, individuals with IV commonly present with a lower QoL [211, 213, 214], worsened by skin severity [215].

1.4.2 X-linked (recessive) ichthyosis

In the early 20th century, a new subtype of ichthyosis was identified, known as X-linked recessive ichthyosis (XLI) [216], which was later found to be caused, in most cases, by a genetic deletion at the Xp22.31 area of the genome. The majority of affected males inherit the genetic deletion from a heterozygous carrier mother (see Figure 2); this deletion is typically 1.5-1.7Mb in size and either completely or partially encompasses the *STS* gene, as well as its immediate neighbours (the protein-coding genes *PUDP*(*HDHD1*), *VCX*, and *PNPLA4* and the non-coding microRNA *MIR4767*) [185-187, 217]. In a small number of XLI cases, the causal variant is an *STS* point mutation or, rarely, a larger deletion covering many contiguous genes [185-187, 217]. Individuals with these extensive deletions frequently present with issues affecting multiple organ systems, known as syndromic XLI, on which this thesis will focus, compared to non-syndromic versions of XLI where only the skin is affected [186].

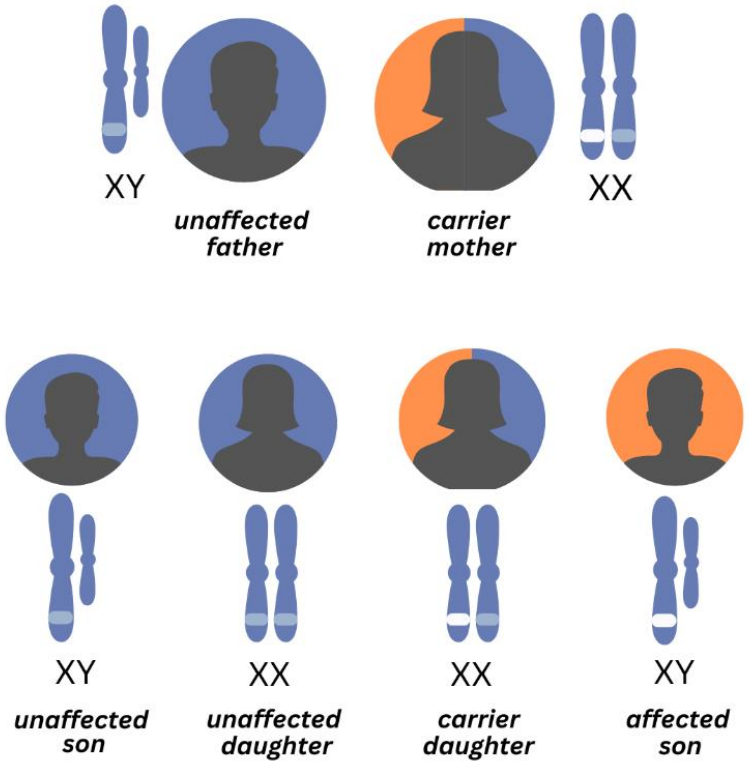


Figure 2: Depiction of X-linked recessive inheritance. Here, the white band represents XLI genetic risk variant.

Prenatal screening studies estimate typical Xp22.31 deletions to be present in 1 in 1500 general population males [218, 219] yet XLI is diagnosed in as few as 1 in 6000 males [185]. This difference in rates of diagnosis implies that many individuals with a resulting STS deficiency are either not receiving an XLI diagnosis (perhaps because they exhibit subclinical skin symptoms) or are being misdiagnosed. Consequently, individuals diagnosed in dermatology clinics tend to have a more severe skin phenotype than those diagnosed genetically in the initial instance [220]. The enzyme STS cleaves sulfate groups from multiple different steroid hormones, affecting their water-solubility, bioavailability, and activity [221]. This mechanism is responsible for the skin phenotype in XLI, due to an accumulation of cholesterol sulfate (and a deficit of cholesterol) in the stratum corneum (see Figure 3) [222, 223].

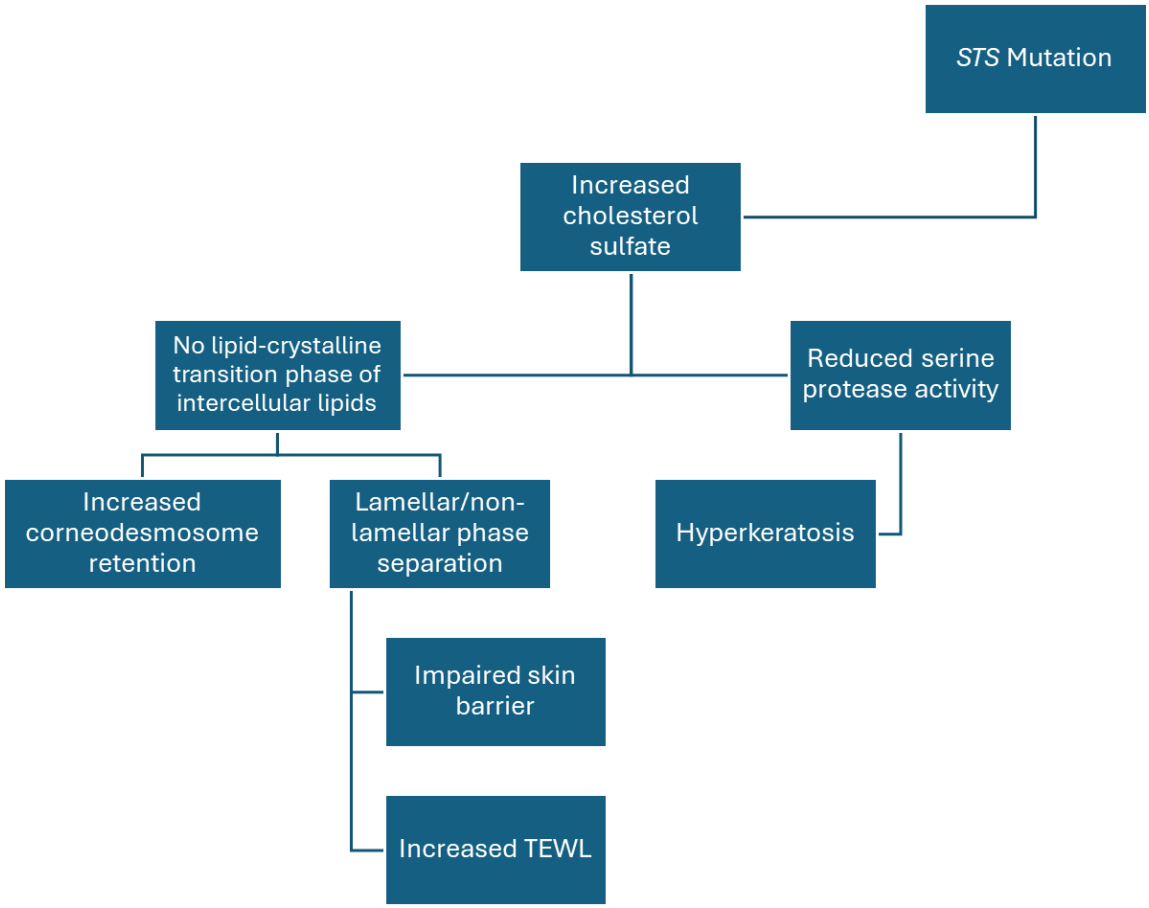


Figure 3: Pathogenesis of XLI [224, 225] (Note: TEWL: transepidermal water loss)

The skin phenotype typically presents at birth as widely distributed polygonal, translucent scales, which are gradually replaced with large, darker brown-grey scales occurring primarily on the neck, trunk, and lower extremities, and on extensor surfaces [226].

Due to the widespread expression of STS across the body, individuals with XLI can also present with one or more extracutaneous manifestations, as discussed below.

1.4.3 Physical conditions associated with XLI

Cryptorchidism

In the late 1970s and early 1980s, initial case reports highlighted a connection between XLI and the occurrence of bilateral or unilateral cryptorchidism, where one or both testicles fail to descend into the scrotum during development, observed in 10-40% of affected individuals [227]. These instances were notably more frequent in cases involving obstetric complications, notably due to delayed or prolonged labour occurring in over 60% of carrier mothers, attributed to placental STS deficiency [228]. More recent case series [229, 230], and data from the DECIPHER XLI-relevant cohort [231] suggest a lower prevalence rate of 10-15% in XLI populations, which still surpasses the prevalence rate of 2-8% seen in the general paediatric population [232].

Despite the presence of these structural abnormalities in the gonads, most individuals with XLI maintain their fertility and undergo normal sexual development [226]. In boys, serum testosterone levels appear comparable to those of unaffected boys, albeit lower post-puberty [233].

Cardiac rhythm abnormalities

Work from our research group based on data within the UK Biobank, recently revealed that middle-aged males with typical Xp22.31 deletions are around four times more likely to be diagnosed with atrial fibrillation/flutter (AF), compared to their non-carrier counterparts (10.3% vs. 2.7%) [187]. Downstream consequences of cardiac arrhythmia such as AF, include stroke, heart failure, and cognitive decline/dementia [234], and thus this finding is of particular clinical relevance for XLI populations.

A new paper by McGeoghan, Camera (2023), used a knockdown model of STS to investigate the phenotype of patients with XLI [235]. A finding of particular interest to cardiac function emerged when examining genes that were downregulated following STS knockdown. It was observed that a significant number of these genes are associated with 'cardiac/ventricular septum morphogenesis', the process of septum wall

development. Despite the investigation being conducted in skin cells rather than cardiac cells, this intriguing finding raises the possibility that STS deficiency could potentially increase the susceptibility to cardiac septal defects [236, 237] and subsequently to arrhythmias [238-240]. Furthermore, case series of individuals with Xp22.31 deletions has reported a few instances of septal defects [241] [242] [243]. To further explore the link between Xp22.31 deletions and cardiac structural defects, we produced a review paper [244], but this relationship requires further investigation, specifically using cardiac traces in affected individuals.

It is important to acknowledge that most of this most has been conducted in the last 5 years, and this is a growing area of research, amongst the field of genetics, cardiology, and medicine. Thus, to date, the prevalence of cardiac arrhythmias (including AF), their nature/precipitants, their response to intervention and their association with other medical conditions within XLI populations has not been investigated and will be a key focus of this thesis.

Corneal Opacities

In the late 1960s, initial research identified the presence of 'deep corneal opacities' in a small case series of males with XLI, while female carriers exhibited a less severe phenotype [245]. These opacities, dispersed throughout the entire cornea, were initially described as grey-white and resembled commas or dots [245]. Subsequent investigations from the 1980s onwards revealed that this 'frosted layer' typically resides deep within the posterior corneal stroma, near or within the Descemet basement membrane [246, 247], likely stemming from elevated levels of cholesterol sulfate in the area [248].

Recent prevalence estimates suggest that 10-15% of individuals with XLI may develop corneal opacities [185], compared to less than 7.5% of the general population [249]. These opacities typically emerge during adolescence or early adulthood and generally do not affect vision directly [245], though they have occasionally been associated with corneal erosion [185]. Copy number analysis in individuals with corneal opacities has shown deletions ranging from 1.7Mb [250] to 4.4Mb [251], all of which involve the *STS* gene. This

suggests that individuals with larger deletions may have a higher likelihood of experiencing extracutaneous symptoms like corneal opacities.

Dupuytren's Contracture

A newly identified comorbid condition is Dupuytren's contracture, in which one or more fingers progressively become permanently flexed [252]. This typically onsets in middle age due to fibrosis of the palmar fascia [251]. In a UK Biobank (UKBB) sample, 3.5% male deletion carriers reported a diagnosis (compared to 0.6% non-carriers) [187], and the DECIPHER database describes one patient with a pathogenic point mutation within *STS* and contracture of the 5th finger [231].

Bleeding conditions

In the UKBB dataset researchers identified a specific phenotype related to bleeding issues (termed 'haemorrhage or hematoma complicating a procedure'), which appears to be more prevalent (3.5%) in males carrying deletions compared to male non-carriers (0.5%) [253]. Additionally, recent findings from a knockdown model [235] indicate that the knockdown of *STS* gene expression in skin cells can influence the expression of genes associated with blood clotting, thus consistent with these results. This finding may be attributed to several factors: a) deletion carriers might undergo more frequent or invasive medical procedures due to the likelihood of experiencing extracutaneous symptoms, and/or b) deletion carriers may be more prone to receiving retinoid-derived pharmacotherapy for their skin, which can negatively impact blood clotting [254]. Alternatively, and perhaps more likely given that no deletion carriers reported being prescribed such medications, it could have a biological explanation, as *STS* is most highly expressed in adult arterial vasculature [255, 256].

1.4.4 Psychological and psychiatric conditions associated with XLI.

Cognition in XLI

An initial case report of an 11-year-old boy with XLI revealed a non-verbal intelligence quotient (IQ) of 57 (TONI-2), consistent with a mild intellectual disability [257]. More

recent case studies also report intellectual disabilities such as global developmental delay and 'cognitive impairment' in both male and female children with XLI [258]. This work was followed up using data from the UK Biobank, identifying impaired performance on the Fluid Intelligence Test in a large sample of male and female deletion carriers [187]. However, IQ is typically within the normal range, and academic attainment appears unaffected [187, 259], and thus the exact impact of *STS loss* on cognition is not yet fully understood.

Neurodevelopmental disorders and traits

Childhood-onset epilepsy appears to be more prevalent in individuals with typical XLI deletions (10-15%) [230, 257, 260], compared to the general male population (<1%) [261], often presenting as focal epilepsy with centrotemporal spikes [230, 257, 260]. This condition is frequently accompanied by other neurodevelopmental conditions such as ADHD [262, 263]. STS deficiency is implicated as a key causal factor in epilepsy susceptibility due to its role in neurotransmitter receptor modulation [264]. However, epilepsy-related symptoms have not been observed in STS-deficient rodents, suggesting that other factors within the Xp22.31 region or co-segregating factors may contribute to the risk [260], or these findings may be specific to humans.

Xp22.31 deletion may increase the risk of schizophrenia, especially in the presence of other neurodevelopmental conditions. Reported cases include a young boy with a typical deletion exhibiting symptoms consistent with early-onset schizophrenia [257], and two females with paranoid schizophrenia [265]. Furthermore, female carriers tend to display more schizotypal personality traits compared to non-carriers [228]. This may be due to increased DHEAS levels in individuals deficient in STS, as this enzyme is responsible for de-sulphating DHEAS to DHEA. Lifetime psychotic symptoms have been associated with higher DHEAS levels [266], and thus STS deficiency appears a plausible mechanism [267].

Although attention deficits and hyperactivity were occasionally noted in rare cases of *STS* deficiency with chromosomal rearrangements in the early 2000s [268, 269], it was not

until 2008 that the first case series exploring attention deficit hyperactivity disorder (ADHD) in X-linked ichthyosis (XLI) was documented [270]. This series found that 40% of assessed boys with XLI met diagnostic criteria for ADHD, with 80% exhibiting the inattentive subtype, contrasting with a general population prevalence of ≤5% [271]. Subsequent case series confirmed that approximately 30% of boys with XLI fulfil ADHD diagnostic criteria, often alongside other neurodevelopmental conditions like Tourette syndrome, dyspraxia, and epilepsy [229, 230]. A worldwide online survey comparing ADHD diagnoses/related traits in males with XLI to those in matched controls confirmed an excess of most traits (excluding 'motor impulsivity') in the former group [272], a pattern also observed in female carriers [228]. Independent mouse models further support these ADHD-related traits, demonstrating that impaired STS leads to attention deficits [273, 274], and reduced motor impulsivity [275].

Autism spectrum disorder (ASD) also appears to be more prevalent in XLI deletion carriers; research suggests that 20% of adult males met the DSM-IV criteria for ASD diagnosis or 'related language/communication difficulty' [270], significantly higher than the <5% prevalence in the male general population [276]. This affected group often had larger genetic deletions, including the *VCX3A* and *NLGN4X* genes, potentially contributing to ASD-related behavioural phenotypes. This trend was consistent across studies involving smaller deletions/mutations affecting the STS gene, including case studies [263] and surveys of self-reported ASD-related traits [272], and in female carriers [228], suggesting that gene loss within the typical deletion interval predisposes individuals to autism-related traits.

Mood disorders and traits

Research suggests that individuals with XLI are also significantly more likely to present with a mood disorder, compared to the general population. A preliminary online survey from our research group revealed that a higher proportion of the adult males with XLI reported a previous mood disorder diagnosis (20%), as well as higher levels of impulsiveness and recent psychological distress compared to general population

estimates [272]. A follow-up survey for female carriers of XLI-associated genetic variants corroborated these results, with 29% of individuals reporting a previous mood disorder diagnosis, in addition to higher impulsiveness, psychological distress and schizotypal personality scores [228]. Using the UK Biobank resource (UKBB), further work within our research group later identified higher levels of mental distress ($p=0.003$), irritability ($p<0.001$) and depressive anxiety traits ($p<0.05$) in male deletion carriers relative to male controls [187]. This pattern of depressive/anxious and impulsive mood traits suggests that loss of STS function may play a prominent role in the development of these disorders and associated traits.

However, beyond the initial studies, there remains a gap in understanding the specific nature and magnitude of depression, anxiety, ASD, and ADHD traits and subtypes in deletion carriers, particularly in adults, in comparison to unaffected samples. Moreover, it's unclear whether these mood/NDD symptoms vary between male and female carriers as they have not been directly compared. Additionally, there is a lack of comparison between the prevalence of mood and NDD disorders/symptoms with other dermatological conditions, such as IV or psoriasis. Although reduced Quality of Life (QoL) seems prevalent among individuals with skin conditions (see 1.2.3), this hasn't been quantified in XLI individuals, nor in comparison with different skin conditions.

Furthermore, there is little understanding of factors which may contribute towards neurodevelopmental and mood disorders, such as poor sleep quality [277, 278], side-effects of retinoid-derived medications, and stigmatisation due to the skin condition. It is important to note that there may be an interaction between NDD/mood disorder-associated traits, due to common shared environmental (and some genetic) influences [279] [280], but this has not yet been explored with reference to XLI.

To date, there has been no exploration of risk mechanisms or causal components in the development of mood and neurodevelopmental disorders and related traits. Quantifying and exploring NDD and mood disorders and associated traits, as well as effects on cognition, in individuals with XLI, could enhance understanding of the condition, leading

to more targeted treatment advice and a more holistic approach to multidisciplinary care.

1.4.5 Current guidelines and support for XLI individuals

Within the UK NHS and in the US healthcare system, there are no existing treatment frameworks or formal guidelines to assist clinicians and HCPs following an initial diagnosis of XLI, or for long-term management of the condition. Instead, HCPs may rely on a variety of ichthyosis-wide resources to support patient care; these include information from the British Association of Dermatologists (BAD) [281], BMJ Best Practice [282] and FIRST (Foundation for Ichthyosis & Related Skin Types) [283]. Patients often rely on similar information and guides from relevant charities such as the Ichthyosis Support Group (ISG) [284], FIRST and relevant medical advisory boards. In addition, a new 'practical clinical guide' was recently published by researchers, aiming to support the longitudinal care of patients with ichthyosis which may support clinicians and patients in shared decision-making processes [285].

Since 2021, all four UK nations have published their first 'Rare Disease Action Plan' (RDAP) which outlines plans to 'improve the lives of the 3.5 million people in the UK living with a rare disease' [286-289]. The main principles of the RDAPs focus on ensuring a faster diagnosis, improving awareness amongst HCPs, improving coordination of care for patients, and improving access to specialist care [286-289]. Progress made since the earliest publication of the England Framework in 2021 offers encouraging outcomes, including the updated design of newborn screening programs, expansion of digital resources and creation of a toolkit for virtual healthcare consultations. As a rare disease, it is hoped that patients with XLI will directly benefit from these advancements. However, as a precursor to these interventional strategies, it is important to understand the full range and severity of conditions associated with XLI. To date, research involving individuals with XLI has been predominantly clinically focused on case series and individual cases. These types of clinical studies are restricted in their application, as they are often expensive and small scale by nature. In addition, patients taking part in

this type of research may be more severely affected than typical individuals with the condition, and likely restricted in terms of geographical distribution. Although clinical work can offer detailed and important phenotyping in some areas (e.g. skin condition), there is often little available information on comorbid conditions and how these may manifest. Understanding more about the experiences of individuals with XLI through open ended research questions, drawing upon the views of many affected individuals from geographically disparate areas and backgrounds, is also essential.

1.5 Epistemological Position and Paradigm

Pragmatism is a relatively new but commonly used paradigm for conducting research across mixed methods, qualitative and quantitative approaches [290, 291] . Pragmatism focuses on the consequences and meanings of an action or event [292], and the ways in which we interpret these experiences [293]. This paradigm avoids the constraints of other approaches such as positivism which largely focuses on the objective nature of experiences and the validity of knowledge. Instead, pragmatism focuses on a process-based approach to knowledge and the way in which this knowledge can be applied and utilised in a real-world setting [294, 295]. When applying this paradigm to the research process, there is also an emphasis on the importance of the research question (with less focus on research methodology) and how different forms of data collection can address the topic under study [295].

This paradigm appears to be the most appropriate approach for this thesis as it uses a hierarchy of evidence, in which different types of evidence can serve different purposes [295, 296]. This is particularly important for this thesis, considering the multi-component approach to understanding XLI, and the mixed methods used. Furthermore, pragmatism recognises that individual experiences are both limited by the nature of the world and that our understanding of the different realms is limited to our own interpretation of experience [295, 296]. This is important for this thesis as participants were recruited globally and thus experiences between healthcare systems may vary. Crucially, pragmatism also allows for flexibility in the data collection and analysis

process, and places experiences at the centre of the research [293, 295, 296], an important aspect of this work in a rare disease group.

It is also important to consider how pragmatism interacts with and impacts reflexivity: at its very core, a pragmatic worldview encompasses a flexible, reflective approach to research design [297]. Reflexivity is complementary to this, as an act of discussion and curiosity around one's own assumptions and experiences, and the way in which these may influence the research process [298]. There is scope for reflexivity at all stages of the research process: this may include discussions with the research team about potential assumptions about participants, the use of visual methods to challenge the way in which hypotheses are being interpreted, and a wider consideration of how the evidence may reflect our own biases [298, 299]. In particular, a critical realist stance was adopted to reflexivity throughout this thesis; this was to account for the breadth of studies addressing one key aim, to understand more about the physiological and psychological issues associated with XLI. This perspective includes an open approach to invisible barriers to research participation, with a focus on interacting factors at different levels to address the research question/s [300, 301].

Using Dewey's pragmatic theory of social inquiry, it was clear that overcoming problems as this research progressed, was to be a careful process, focused on how the problem is situated in society [302, 303]. Some potential issues that were anticipated in this thesis included the representation of complex medical history, recruitment of a rare disease patient group, and the researcher's standing as an individual without XLI. Based on pragmatic underpinnings, these topics should be approached carefully and with a strong understanding of the experiences of both the participants (and the wider sample) and the researcher [303]. To ensure the experiences of individuals with XLI were accurately represented, a strong relationship was forged with a leading individual from the Ichthyosis Support Group, as well as provisional discussion of materials with patients from the group. This supported our paradigm, allowing for a closer focus on the research question and ensuring that accurate interpretation of experiences was central to the research process.

Furthermore, pragmatism raises some concerns about the research methods employed, especially as the research topic under study is multi-layer [297]. As such, it was important to establish some level of crossover between studies (e.g. assessment of depressive-anxiety traits in both Chapters 3 and 4) to robustly answer the wider research questions and begin to establish reliability in these findings [304]. Pursuing a holistic view of the data and outcomes from each study, with a focus on individuals' experiences was a key reflexive practice across this thesis. The use of a mixed methods approach speaks more to this approach.

1.6 Mixed Methods

Defining 'mixed methods' presents particular challenges, namely the distinction of method vs. methodology, but most agree that there should be at least one component of quantitative and qualitative work [294, 305]. Mixed methods can relate to all aspects of the research process [294], and offers a novel approach to addressing complex research problems [305], by utilising different components of each (quant/qual) to most effectively and appropriately tackle the research question [306, 307]. Creswell and Clark (2017) summarise the multidimensional role of the researcher in this process:

- Collection of both quantitative and qualitative data in response to the research question and hypotheses
- Integration of both forms of data and respective results
- Organisation of research protocols and procedures to provide a logical design for conducting the study.
- Frame these procedures within theory and philosophy.

One important benefit of using a mixed methods approach is the way in which the limitations of one method can be offset or managed by the strengths of the other. This approach can offer new insights into research questions that cannot be fully explored by simply applying either quantitative or qualitative methods [294 308]. Mixed methods also offer readers and fellow researchers more confidence and insight into the results and conclusions drawn from these e.g. allowing participants to expand on their answers in a

qualitative manner may minimise bias in researcher interpretation [309]. Other rationale for using this approach include exploration (needed to develop an instrument or review a protocol), completeness (provide a more holistic account of a phenomenon), or to answer different research questions within the same study [308].

Within the overarching approach of mixed methods, three distinct designs have emerged from theoretical discussions amongst the literature [294]:

a) Convergent design:

In using convergent design, equal priority is assigned to both quantitative and qualitative data collection, but the results of each remain separate [308]. By discussing both sets of data in relation to the other, this approach aims to better understand a phenomenon, efficiently addressing a single research question. Convergent design also allows for comparison and contrast of quantitative and qualitative findings, thus improving the depth of the data and encouraging interpretation [294, 308].

This was the approach applied throughout this project; in most cases, qualitative responses took the form of the 'free text' boxes which allowed participants to expand on their quantitative survey responses. This data allowed for more accurate analysis of results (e.g. more information about specific medication used) and offered participants an important opportunity to share their experiences, which is particularly important in rare disease patient groups due to limited opportunities for patients to get involved in research.

b) Explanatory sequential

This design is similar to convergent, with the exception that the quantitative phase of data collection must be completed before the qualitative phase can commence. Thus, the qualitative phase aims to follow up on results from prior quantitative data, requiring a longer timeframe but often a more focused qualitative approach [294 308].

c) Exploratory sequential

In contrast to explanatory sequential design, this approach utilises an initial investigative qualitative phase which develops into a later quantitative phase [308]. Often used in the absence of existing theory or instruments, this approach is led by the results of the qualitative phase to test the application of results to a wider population [294].

Content Analysis

For the relevance of Chapter 3,4 & 5, a mixed inductive and deductive content analysis approach to qualitative free-text responses was used. Krippendorff (2004) defines content analysis as "a research technique for making replicable and valid inferences from texts". Broadly, this approach allows for flexibility in the analysis process, based on features in the data[311, 312]. Frameworks for conducting content analysis can vary between theoretical approaches, but the key stages involve a) condensing the data into smaller parts (units), b) coding the data to succinctly represent what is being discussed, and c) identifying patterns in the data, to categorise these codes [313, 314]. It is worth noting that this is a non-linear, flexible process, and thus content analysis is conducted in a reflective manner, involving multiple adjustments at all stages [313, 314]. For the purpose of this thesis, the results of each section of content analysis are discussed with reference to the quantitative data and thus defined categories are not deliberated independently.

1.7 Rationale

The work reported in this thesis is focussed on online survey methods. For use in a rare disease patient group, this method of data collection has many advantages over traditional clinical assessments; due to the widespread location of individuals with XLI based on the rare nature of the condition, online methods offer access to large groups of socially and geographically diverse participants [315] [316] [317]. Individuals from rare disease patient groups are also usually under-studied and thus keen to engage with

research [317]. Although this research was restricted by the English-language nature of the work, this online approach allowed for international recruitment and thus aim for a sample that represented the wider community in terms of demographic factors such as ethnicity [318]. Utilising online methods also allowed for a direct insight into how participants feel and their own opinions, rather than relying second-hand information via a clinician. This is essential when adopting a pragmatic worldview (see 1.5) and a patient-centred outcomes approach, as it ensures that the data collected and questions asked within the research, are of meaning and importance to participants [319, 320].

The structure of online surveys can include a combination of custom-designed components and existing measures, which was particularly important for this work e.g. the need for well-validated measures of mood to be used and compared across multiple studies. For the research team, the process of collecting-analysing-distributing results from online surveys can be quick, thus resulting in more timely usage of results in a clinical setting to improve patient outcomes [321] [322] [323]. This form of data collection also presents few ethical implications, as the data is completely anonymous and thus poses no issues with confidentiality or data security, and minimal risk of harm to the participant [321, 323].

For individuals with XLI, completing an online survey also presented minimal time commitment (all surveys designed to take less than 25 minutes to complete) [316] [323], and could be completed at a time/place convenient to them [322] [317]. By removing the need to speak to a member of the research team or a clinician face-to-face, online methods also minimise social stigma and subsequent desirability effects in these results [316] [321] [323]. In combination with open-ended, qualitative response options offered in the surveys, this method allows patients to share their experiences without fear of judgement [316] [321] [323], whilst also allowing researchers to gain a richer insight into their lives [324].

Responses from these online surveys can also be triangulated with other sources of data, for example from clinical/animal studies, to order to examine the reliability of the

data. Converging evidence from multiple approaches is likely to provide convincing evidence of a genuine effect.

However, it should be recognised there are some potential limitations and challenges associated with using an online survey, which must be considered. This approach heavily relies on self-reported data, and the honesty of participants, thus lacking any element of objective clinical assessment. There is also the potential for participants to (often unknowingly) misreport their circumstances, especially without the ability to clarify the question with a member of the research team at the time [317]. Thus, it is particularly important to apply results from this type of work in conjunction with clinical measures such as genetic information, biomarker data and controlled neuropsychological tests, when designing future interventions or care improvements.

Another potential issue is response bias; individuals who identify more with the topic under study e.g. those with concerns about their memory, may be more likely to take part [316, 323]. However, this issue is not specific to online research and thus the current approach was focused on designing an inclusive advert that encouraged all eligible individuals to take part. Furthermore, the use of online platforms may exclude those with limited technological proficiency or access to an electronic device which is a difficult problem to address, but which may be attenuated through the development of accessible and intuitive surveys [317].

It is also important to consider the importance of building a rapport with potential participants to encourage honesty in their responses, which would usually occur in the pre-study assessment when conducting in-person research [322]. Participants may be sceptical of the research when conducted online and thus may be less inclined to take part or be honest/open in their responses [322]. To address this issue, extensive information was provided in the study advert and information sheet about the research aims, what the data will be used for and how it may benefit patients [323]. As social media patient support groups were used as a key opportunity for recruitment, this also prompted some (infrequent) previous concerns from the patient group, from those who

were sceptical about the work. However, due to established links between our research group and several patient groups, the advert was well received.

1.8 Significance of Research

This chapter has reviewed key literature surrounding the experiences of patients within a dermatology setting, suggesting that the current 'crisis in dermatology' has a detrimental effect on patient care, and diagnostic/treatment accuracy. It has also discussed the impact of living with a dermatological condition, and the negative effects on emotional/mental health, including quality of life, and a variety of coping strategies employed by patients on a day-to-day basis. Finally, this chapter has explored the literature surrounding the cutaneous and extracutaneous manifestations of the genetic skin disorder, X-linked ichthyosis, on which this thesis will focus.

From this literature review, it is clear that dermatology patients as a collective, are in many cases receiving sub-standard care, yet HCPs are not receiving the appropriate training, provisions, or information to support these individuals. The APPG report truly reveals the scope of this issue from a psychosocial perspective, and more specifically, the Rare Disease Action Plans highlight opportunities for improvement in care for rare disease patient groups such as XLI individuals. Representing and engaging underrepresented groups is of crucial importance, as highlighted by the RDAPs, in the development of best clinical practices [325] improved health outcomes [326], and increased awareness/destigmatisation [327, 328].

To develop these wider aims, it is first necessary to develop a better understanding of the characteristics, risk factors, and comorbid conditions associated with rare disorders such as XLI. This chapter has explored the lack of formal guidance for both patients and clinicians when it comes to standardised, long-term care plans for individuals with XLI. As the condition is predominantly diagnosed in the first year of life [283], it appears essential to adopt a preventative approach to managing potential comorbid conditions and traits related to the Xp22.31 deletion.

1.9 Scope

The overarching objective of this thesis is to develop a better understanding of the psychological and physiological issues associated with XLI, to understand how these issues may interact and to enable earlier identification of, and intervention for, XLI-associated symptoms. This thesis comprises four empirical chapters, focusing on three common comorbid issues, the design of which are described below:

- Chapter 3: Using established online survey methodology and measures, this study investigated the nature and magnitude of mood and neurodevelopmental disorders and associated traits, and self-reported factors which may contribute to mood phenotypes in male and female participants carrying XLI-associated genetic variants; males and females affected by IV, and males and females affected by psoriasis were used as comparator groups. A key aim of this study was to identify potential targets for effective interventions/therapies, to minimise mood problems and psychological distress, associated with ichthyoses and psoriasis.
- Chapter 4: This study used online measures to compare self-reported memory performance, word-picture recall, and mood in male and female carriers of XLI-associated genetic variants, to a control group of males and females with IV.
- Chapter 5: This study aimed to improve understanding of how heart rhythm abnormalities (HRAs) may develop, how they may be best addressed clinically, and to improve the prediction of AF in individuals with an Xp22.31 deletion. The purpose of this study was two-fold:
    a) To characterise heart rhythm abnormality (HRA)-related phenotypes and comorbidities in men, male children with XLI (parental reports), and female carriers, using an established online survey methodology. These initial analyses aimed to i) investigate the onset, treatment, and severity of any cardiac abnormalities ii) identify risk factors that commonly precipitate arrhythmic episodes iii) identify common comorbid disorders associated with HRAs.

b) This study also explored attitudes towards preventative screening for cardiac abnormalities in adults with XLI or female carriers.

- Chapter 6 Given an association between elevated abnormal heart rhythm risk in males with XLI (previous published work and Chapter 5), a feasibility study was conducted to monitor the heart rhythms of a small group of males with XLI over 8 weeks using wearable technology. The wider goal was to understand whether the use of wearable technology such as smart watches may be an acceptable form of screening for this population and, if so, to determine the optimal study procedures for a larger-scale trial.

1.10 Chapter Summary

This chapter introduced the wider topic within the field of dermatology, identified opportunities for further research in XLI specifically, outlined the significance and scope of this thesis and provided an overview of the thesis structure.

Chapter 2: METHODS

This chapter focuses on the specific methods used to sample, recruit and work with the data obtained, whereas the methodology and paradigmatic approach to the work have been described in Chapter 1.

2.1 Sampling and Recruitment

2.1.1 Recruitment Channels

Due to the nature of XLI and IV as rare diseases (and psoriasis as a comparative condition but to a lesser extent), recruitment for these studies presented particular challenges, namely the lack of a central database of patients and the widespread nature of individuals worldwide. Thus, to reach as many potential participants as possible, a solely online approach to recruitment was adopted, via several established channels utilised in previous studies from our research group [228, 272]. This approach also allowed for the management of response bias, as participants from a range of cultures could take part. Adverts for each study were initially posted on social media sites such as Twitter, using relevant hashtags and 'tagging' relevant charities and organisations for maximum reach. These charities and representative individuals directly were subsequently contacted, across the UK (Psoriasis UK, Ichthyosis Support Group (ISG)), Netherlands, and the US (Foundation for Ichthyosis & Related Skin Types (FIRST)) with information about the studies, and this was often distributed amongst patients through newsletters or direct correspondence. Through previous research studies, there was a pre-established mailing list of individuals who had consented to be contacted about upcoming research studies. Thus, information about each study was sent to this list using the anonymous 'Bcc' email function. Study adverts were also published on existing online social media support groups, specifically Facebook, for which specific permission from the site moderators had been given.

When recruiting participants, a distinct difference in responses between males and females (defined by sex at birth) was observed, with females more likely to respond.

Thus, many of the 'reminder' posts and adverts following the initial recruitment launch targeted males and emphasised the need for a representative sample.

2.1.2 Inclusion Criteria

For all four studies, only individuals >18 years of age (except for parents reporting on behalf of their children <18 years in Chapter 5), with a diagnosis of XLI (or IV/psoriasis) from a medical professional were recruited. Proof of diagnosis was not required (only the basis of their diagnosis e.g. genetic testing) as it is often unlikely that patients could provide written evidence and thus this may have deterred certain valid individuals from participating.

All aspects of the studies were conducted in English, and thus participants were required to have a good understanding of the English language, but there were no restrictions on country of residence. When completing the demographic sections of each survey, participants were required to state both their sex at birth (for the purpose of sex-based analysis and genetic information) and/or their self-described gender where relevant to the study (Chapter 3 only) [324].

Further specific inclusion criteria for each study are detailed in the relevant chapters and summarised below in Table 2.

CHAPTER	INCLUSION
CHAPTER 3	>18 years old
	One of the following: a) male with a clinical diagnosis of XLI, b) confirmed female carrier of a genetic change related to XLI, c) person with a clinical diagnosis of IV, d) person with a clinical diagnosis of psoriasis
CHAPTER 4	>18 years old
	One of the following: a) male with a clinical diagnosis of XLI, b) confirmed female carrier of a genetic change related to XLI, c) person with a clinical diagnosis of IV.

CHAPTER 5	>18 years old (and/or a parent of a child < 18 years)
	One or more of the following: a) male with a clinical diagnosis of XLI, b) confirmed female carrier of a genetic change related to XLI, c) parent of a male child (<18 years) with a clinical diagnosis of XLI
CHAPTER 6	Aged 18-80 years
	Male at birth (sex)
	Clinical diagnosis of XLI
	Owns an iPhone and willing to download and use applications
	Willing to wear an Apple Watch for up to 8 weeks
	Willing to submit data from watch about heart rhythm

Table 2: Inclusion criteria for each Chapter

2.1.3 Power Analyses

To identify the optimal minimum number of participants for each study, power analyses were conducted using G*Power. Parameters were set at 80% power with α=0.05 to reliably detect at least a moderately sized effect. The sample sizes identified are discussed within the relevant chapters.

2.2 Design

I used a mixed methods design throughout this thesis, as detailed in Table 3. Demographic information and carrier status were both represented by descriptive statistics.

CHAPTER	QUANTITATIVE ANALYSIS	QUALITATIVE ANALYSIS
CHAPTER 3	Congenital Ichthyosis Skin Index (CISI)	

	Kessler Psychological Distress Scale (K10)	Underlying factors in mood disorders
	Adult ADHD Self-Report Scale (ASRS)	
	Autism Quotient (AQ10)	
	Brief Irritability Test (BITe)	
	Dermatology Life Quality Index (DLQI)	
	Feelings of Stigmatisation Questionnaire (FSQ)	
CHAPTER 4	Word/picture recall scores	None
	Congenital Ichthyosis Skin Index (CISI)	
	Kessler Psychological Distress Scale (K10)	
	Multifactorial Memory Questionnaire (MMQ)	
CHAPTER 5	Congenital Ichthyosis Skin Index (CISI)	None
	Medical diagnoses	
	Heart rhythm factors	
	Vignette statement ratings	
CHAPTER 6	Feedback on ECGs from cardiologists	
	Perceived stress level at each ECG reading	Circumstances surrounding individual ECG readings
	Post-trial acceptability ratings	Post-trial feedback for the research team

Table 3: Outline of quantitative and qualitative aspects of individual chapters

2.2.1 Online survey measures

For Chapters 3,4 & 5 (survey-based), participants responded to study adverts via an anonymous URL and were directed to a custom-designed survey hosted by Qualtrics [329]. Each survey included an information sheet, consent form, and debrief form with links to further information, support post-study if necessary, and contact details for the research team.

2.2.2 Feasibility trial

For this phase of the research, participants completed an online screening questionnaire to assess suitability for the study, followed by an outline of the trial, completion of the consent form, and data collection for eight weeks. Following the trial, participants completed an online 'post-trial feedback form' and received extensive debrief information.

2.3 Data Analysis

In cases where participants had not answered specific questions within a measure or section (<3% of all responses), their response for the relevant analyses was omitted. Summary data are reported as percentages, mean±SD (normally distributed data) or median with 95% CI (non-normally distributed data). Boxplots were produced using BoxPlotR software. $P < 0.05$ was considered statistically significant.

Across this project, a range of methods for the quantitative sections of the analysis were used. The decision-making grid is shown in Table 4 below, alongside the chapters in which was utilised each test. More details about the application of each test can be found in the respective chapters.

	Type of test	Independent Variable	Dependent Variable	Chapter
Independent t-test	• Comparison of means • Parametric	• Categorical • One predictor	• Grouped by different population	3&5
Mann Whitney U	• Comparison of means • Non-parametric	• Categorical • One predictor	• Grouped by different population	5
ANOVA	• Comparison of means • Parametric	• Categorical • One or more predictor	• Single outcome	3&4
ANCOVA	• Comparison of means • Parametric	• Categorical • One or more predictor • One or more covariates	• Single outcome	3&4
Kruskal-Wallis	• Correlation • Nonparametric	• Categorical • Three or more groups	• Continuous	3
Pearson	• Correlation	• Two continuous variables • Normally distributed data		3&4
Spearman	• Correlation	• Two continuous variables • Not normally distributed data		3&4
Chi-squared	• Correlation	• Categorical	• Categorical	4&5
Fishers Exact Test	• Correlation	• Categorical • Two categories	• Categorical • Two categories	4&5
Hierarchical linear regression	• Regression	• Categorical • Two or more	• Continuous	3

Table 4: Outline of decision-making for statistical tests used

In regards to qualitative analysis, a mixed deductive and inductive content analysis approach was used to assess the 'free text' responses in Chapters 3, 5 & 6. This allows for analysis of both latent and semantic content and offers more opportunity for researcher interpretation with relevant context to the data [330].

2.4 Research Ethics & Governance

Ethical approval was obtained by the Cardiff University School of Psychology (individual EC numbers and amendments listed in relevant chapter appendices).

Prior to engaging with the study, all participants were fully informed about the background of the study, as well as the rationale and aims, right to withdrawal (without reason or penalty), data anonymity, distribution of results, and data storage policies. All participants signed an informed consent form before beginning the study.

Following the completion of the study, participants were provided with details for support services such as telephone helplines and online guidance in the case of distress or concern following their participation. Participants were also provided with a link to a separate survey if they wanted to provide their contact details (name and email address) to get involved in future studies. This information was stored separately from the survey data and could not be linked to their survey responses in any way.

All data was anonymised (no IP address saved by Qualtrics and no personal data e.g. name or email address requested) and stored in line with Cardiff University policy.

For the feasibility trial (Chapter 6), the ECGs were uploaded in PDF format by the participant on a Qualtrics survey, accessed using their individual participant number. Due to the process of storing and retrieving these readings via the Apple Health app on the individuals' iPhones, each PDF contained their name, date of birth (DOB) and age, as well as details about when the reading was taken. Before distribution to the cardiologists to assess the ECGs, these PDFs were cropped to remove all identifiable

data and then resaved using their participant number for reference. All other aspects of the weekly and post-trial submissions from this trial were anonymous, and no IP address was saved.

2.5 Summary

This chapter provides an overview of the sampling and recruitment methods used across this thesis, the design and data analysis approach, and details about research ethics and governance.

Chapter 3: MOOD AND NEURODEVELOPMENTAL DISORDERS AND ASSOCIATED TRAITS IN X-LINKED ICHTHYOSIS (XLI), ICHTHYOSIS VULGARIS (IV) AND PSORIASIS

**Note: some of the material included in this Chapter and relevant appendices relates to the following published work, for which I am listed as the first author:*

Wren GH, Humby T, Thompson AR, Davies W. Mood symptoms, neurodevelopmental traits, and their contributory factors in X-linked ichthyosis, ichthyosis vulgaris and psoriasis. Clinical and Experimental Dermatology. 2022 Jun 1;47(6):1097-108.

3.1 INTRODUCTION

Dermatological conditions are strongly associated with increased rates of mental health conditions, including mood disorders and associated traits [4, 26]. However, current work offers a limited explanation towards potential causal factors and limited comparisons of clinical samples to general population controls. The study reported in this Chapter investigated mood and neurodevelopmental disorders and associated traits in three skin conditions (XLI, IV and psoriasis), with the aim of identifying how these compare to prevalence and magnitude in general population control subjects, how their prevalence and magnitude compare with one another and to identify key targets for future interventions/therapies to minimise associated psychological issues.

3.1.1 Mood/neurodevelopmental disorders, and psychological wellbeing in individuals with common and rare dermatological conditions

The link between skin disease and mental health is well established, with over 98% of individuals diagnosed with a skin condition experiencing a negative impact of their condition on psychological/emotional wellbeing [26]. This negative impact includes feelings of stigmatisation, issues with self-esteem, and the impact of the skin condition upon work/social activities [26, 331]. Such factors may play a significant contributory role in

negative mental health outcomes including major depressive disorder (MDD) and anxiety, as discussed in Chapter 1 (1.2.4). Negative psychological outcomes, and associated mood disorders such as these, can also subsequently affect quality of life (QoL) [9, 88]. Identification of key causal/contributory factors in these negative mood/behaviour-related outcomes is a crucial step to developing effective targeted therapies within psychodermatology.

However, thus far, psychodermatological research has largely focused on comparing mental health outcomes in specific conditions to unaffected members of the general population, in particular using small samples from limited demographic regions. Current work has also only employed a small range of measures to assess psychological functioning and emotional wellbeing, with little continuity across different studies, thus making comparison between samples difficult. One key study which significantly contributes to understanding in this field was conducted by Dalgard, Gieler (2015), examining the psychological burden of living with a skin condition, across various dermatological diagnoses [4]. Depression, anxiety and suicidal ideation were significantly more common across the sample as a whole, compared to controls. This work was later developed within the research group, with new findings in a similar sample suggesting that body dysmorphic disorder (BDD) is also significantly more common in patient with dermatological conditions [332].

However, these are two of the only large-scale studies in this area, yet to be replicated outside of the EU, or using different measures. Furthermore, this work did not include rarer skin disorders such as ichthyosis and thus are limited in their application to this work. As such, there is a need to compare wider psychological symptoms between a geographically diverse sample of dermatological patients to general population controls, as well as across a range of different skin conditions (including rare disorders). Due to sex differences in the prevalence of many skin conditions [333], and psychological phenomena [334], a range of reliable measurement tools might arguably also be employed to stratify psychodermatological outcomes by sex.

One previously well-studied dermatological condition with reference to psychological outcomes is psoriasis; a chronic inflammatory multi-organ disease, characterised by demarcated salmon-coloured plaques and extracutaneous manifestations including arthritis and diabetes [44, 335]. Psoriasis has previously been strongly associated with increased risk of depression and anxiety disorders, and psychological distress [336-338].

Increased rates of mood disorders also occur across the inherited ichthyoses, linked to negative emotional functioning and diminished QoL [214, 339]. Qualitative data suggests that this may be due to a combination of factors, including concerns around physical health, daily life issues, and relationships with oneself and others [340]. However, as the aetiology, severity, and epidemiology can vary between types of ichthyoses, it is important to examine each condition separately.

In individuals with ichthyosis vulgaris (IV), the most common type of inherited ichthyosis, new research indicates elevated rates of mood disorders/symptoms, in addition to moderately decreased QoL and increased social rejection [214]. However, very little further research has been carried out to investigate this link with a larger sample of individuals with IV, and thus the results of this work are difficult to interpret. Recent studies have also identified similar elevated rates of mood disorders (and associated symptoms), in males with XLI-associated genetic variants, compared to sex-matched controls [187, 228, 272].

More recent work by Cavenagh (2019) developed these findings, using similar survey-based measures to collect self-report information for adult female carriers of genetic variants associated with XLI. Compared to normative data from female general population controls, carrier females exhibited increased rates of mood disorders and psychological distress [228]. This research was extended using the UK Biobank resource, to examine mood-related phenotypes in adult males and females carrying genetic deletions spanning the *STS* gene. Similar patterns of behaviour and mood associated traits were identified; adult males carrying XLI-associated genetic deletions presented with increased rates of depressive-anxiety traits and mental distress compared to male

non-carriers. Both male and female deletion carriers also showed significantly elevated rates of irritability [187]. It is important to recognise that such data from the UK Biobank is less likely to be prone to response bias, compared to survey-based approaches which rely more heavily on self-reported data, thus suggesting these findings are reliable.

Current work also presents increased risk of neurodevelopmental disorders such as autism spectrum disorder (ASD) and attention deficit (hyperactivity) disorder (ADHD), amongst these groups. Compared to unaffected controls, adult males with XLI exhibit significantly more traits consistent with neurodevelopmental disorders [272], as well as female XLI carriers [228]. Initial work suggests that individuals with psoriasis are also more likely to present with neurodevelopmental conditions [341, 342], often suggested to link to the autoimmune nature of the condition.

These initial findings suggest significantly elevated rates of mood and neurodevelopmental disorders and associated traits, in individuals with inherited ichthyoses, specifically XLI and IV, as well as some findings in individuals with psoriasis. However, this research area is notably sparse, with limited comparative literature available and no understanding the prevalence of neurodevelopmental disorders in individuals with IV. Thus, current research offers a) no comparison between affected individuals, and different skin conditions, b) limited samples, concerning demographic and geographical factors, c) restricted analysis of these phenotypes as stratified by sex, and finally d) little insight into potential contributory factors in these mood/developmental disorders and associated traits. Furthermore, previous research has yet to separate mood-related traits into distinct aspects of mood (depression, anxiety, and irritability) which may vary greatly in frequency, severity and underlying neurobiology both within and across conditions.

3.1.2 Use of online survey measures

Online survey methods were used in this study as a simple, time-efficient way in which to collect data from a rare disease patient group. Using online surveys, distributed mainly via social media channels, enables a wide geographical and demographic spread

of participants, as well as simple dissemination to reach a large number of individuals [321, 343]. The online, anonymous nature of these surveys is designed is limit social desirability and encourage honesty from participants about their experiences [323, 343], which may be particularly important when discussing mental health. The inclusion of open-ended qualitative responses, in conjunction with other question types such as multiple choice and rating scales, allows participants to elaborate on their answers and produces a rich dataset [323]. Furthermore, online surveys are of particular benefit when studying unique populations such as rare disease populations like XLI, as these individuals are typically more motivated to engage in research in comparison to over-studied groups [323], and this method allows participants to respond at their own convenience [343].

3.1.3 Psoriasis as a comparative group

To provide a suitable comparative condition in this study, a sample of individuals with a clinical diagnosis of psoriasis was recruited. Psoriasis is notably more common than rarer skin conditions such as IV and XLI [44, 182, 185], and it is typically well-studied in terms of mood and NDD disorders and associated traits, unlike IV and XLI [337, 338, 341, 342]. Furthermore, psoriasis has a very different aetiology compared to the ichthyoses; it is thought to manifest as a result of an immune response of various origins [344], although some linkage studies suggest that various loci may play a role in the case of inherited versions of the condition [345, 346]. However, these loci are distinct from the genetic aetiology of IV and XLI, thus offering a strong comparative condition irrelevant of genetic underpinnings. In addition, all three conditions manifest across the body and look similar in appearance of the skin, reducing any differences in effects related to stigma or body image. As a common disorder, recruiting individuals with psoriasis also posed significantly less of a challenge compared to a rarer condition, and this would allow for a sample more closely matched in terms of gender and age for contrast.

3.1.4 Aims and Hypotheses

The present study aimed to investigate and compare mood and neurodevelopmental disorders and associated traits, as well as self-reported factors which may contribute to depressive, anxious and irritable phenotypes in male and female participants carrying XLI-associated genetic variants, males and females affected by IV, and males and females affected by psoriasis. Specifically, this study aimed to investigate (i) mood/neurodevelopmental disorders and associated traits in the six groups compared with the best-available matched general population samples, (ii) mood/neurodevelopmental disorders and associated traits, as well as quality of life and stigmatisation measures, compared across the six experimental groups and (iii) factors self-reported to contribute most substantially towards mood (depressive, anxiety, and irritability) symptoms across the six groups. A key aim of this study was to identify potential targets for effective interventions/therapies, to minimise mood problems and psychological distress, associated with ichthyoses and psoriasis.

Based on the recent work in adult males and females with XLI, IV and psoriasis as outlined in this Chapter and Chapter 1, the following was hypothesised:

a) Increased rates of mood and neurodevelopmental disorder diagnoses, disorder-associated traits, and irritability in all conditions, compared to general population controls.

b) An inverse relationship between adverse mood traits and quality of life in all skin conditions.

c) An inverse relationship between stigmatisation and quality of life in all skin conditions

d) Moderate-severe levels of stigmatisation across all skin conditions, with significant correlations between skin severity and degree of stigmatisation.

3.1.5 Summary

- Previous work suggests that individuals with a dermatological condition are more likely to present with a mood disorder such as depression or anxiety, as well as a reduced quality of life (QoL) and neurodevelopmental disorders such as autism.
- Recent findings from our research group corroborate these findings in individuals with X-linked ichthyosis, but research is sparse and lacks comparison between conditions.
- Current literature also offers little insight into potential factors contributing to these mood and neurodevelopmental conditions and the relationship between these.
- To address these limitations, this study aims to use online survey methods to investigate these disorders and associated traits in more detail in individuals with XLI, IV and psoriasis, allowing for an in depth cross-comparison between groups.

3.2 METHODS

3.2.1 Ethics

This study was given ethical approval by Cardiff University School of Psychology Ethics Committee (EC.20.12.08.6184)

3.2.2 Design

This study used an online survey via Qualtrics, using a combination of custom-designed questions with a series of well-validated self-report questionnaires. This method focused primarily on quantitative data collection, using Likert scales and self-rating methods, in addition to qualitative data through the use of 'free text' boxes for participants to elaborate on their prior responses.

3.2.3 Sampling and Recruitment

Convenience sampling was used to recruit adults (>18 years) with a past clinical diagnosis of XLI, IV or psoriasis, or with confirmed carrier status for an XLI-associated genetic variant. Participants were recruited globally, via past contact/participation in previous research, social media patient support groups, charities, and other social media sites (e.g., Twitter), and directed to the online survey using an anonymous URL. Responses were returned to the research team between 8th January and 27th April 2021.

3.2.4 Survey Structure

In the initial stages of the survey, participants provided the following general demographic information: age, country of residence, ethnicity and higher level of education obtained. Participants then provided information based on their dermatological diagnosis, or how their carrier status was determined. They then provided information regarding any previous neurodevelopmental/mood disorder diagnosis. Participants were then asked to rate their skin condition, on average throughout their life and across the whole body (excluding female XLI carriers) using sample clinical images from the Congenital Ichthyosis Severity Index (CISI) (scores range 2-8) [347] or the Psoriasis Area and Severity Index (PASI) (score range 3–15) [348].

Following this, participants completed the following well-characterised psychological measures: K10, ASRS, AQ10, BITe, DLQI and FSQ.

a) Kessler Psychological Distress Scale (K10): a well-validated self-report measure, to assess depression/anxiety-related traits in the last 30 days [349]. A five-point 10-item Likert-scale measure; each item scored from 1-5 (total score range 10-50). Higher score = higher psychological distress.

b) Adult Attention Deficit Hyperactivity Disorder (ADHD) Self-Report Scale (ASRS) V1.1: a short self-report measure of both attention and impulsivity ADHD-related

traits [350]. A five-point 18-item Likert-scale measure; each item scored from 0-4 (total score range 0-72). Higher score = more ADHD related traits.

c) Short Autism Spectrum Quotient (AQ10): a short self-report measure to assess traits commonly associated with autism spectrum disorder [351]. A four-point 10-item Likert-scale measure; items endorsed as being consistent with autism-related traits were scored with 1 point (total score range 0-10). Higher score = more ASD related traits.

d) Brief Irritability Test (BITe): a short self-report measure of irritability-related traits in the last two weeks [352]. A six-point 5-item Likert-scale measure; each item scored from 1-6 (total score range 5-30). Higher score = more irritable.

e) Dermatology Life Quality Index (DLQI): a brief self-assessment of the extent to which the skin problem has impacted daily functioning in the last 7 days [87]. A four-point 10-item Likert-scale measure; each item scored from 0-3 (total score range 0-30). Higher score = higher impact on QoL.

f) Feelings of Stigmatization Questionnaire (FSQ): a self-report measure to assess levels of lifetime skin-disease-related stigmatisation [353]. A six-point 33-item Likert-scale measure; each item scored from 1-6 (total score range 33-198). Lower score = higher perceived stigma.

Part A of the ASRS offers a brief investigation of symptoms highly consistent with ADHD. A composite 'neurodevelopmental trait score' (NTS) was also created: ASRS and AQ10 scores contributed equally to the NTS, with a score range of 0-144.

To explore potential contributory factors in individuals' psychological/emotional distress and well-being, a custom-designed short measure was created in which participants rated a series of factors known, or suspected, to be associated with elevated adverse mood symptoms, on a sliding scale, based on the perceived impact on depressive, anxious and irritability traits. This comprised of 19 differently themed factors, including neurodevelopmental disorder-specific components, skin-specific frustrations, and other

physical/mental health concerns. Participants were also able to input their own suggestions, via a free text comment box to ensure all possible factors were considered. This sliding response scale was the final item in this questionnaire: participants rated each factor on a scale from 'not at all' (0) to 'very much' (10). The factors presented in this section are listed below:

1. Embarrassment of social interaction because of your skin condition
2. Pain, discomfort or itching associated with your skin condition.
3. Stigma or bullying associated with your skin condition.
4. Difficulties or frustration associated with treating your skin condition (e.g., regularly having to source and apply moisturizer)
5. Educational, work, or social challenges due to finding it hard to pay attention e.g., getting distracted, not finishing work on time, not listening to instructions.
6. Educational, work, or social challenges due to being impulsive e.g., making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
7. Educational, work, or social challenges due to difficulties with social interaction e.g., not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humor or sarcasm etc.
8. Stigma or bullying due to finding it hard to pay attention e.g., getting distracted, not finishing work on time, not listening to instructions.
9. Stigma or bullying due to being impulsive e.g., making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
10. Stigma or bullying due to difficulties with social interaction e.g., not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humor or sarcasm etc.

11. Severe adverse life events (bereavement, life-threatening illness etc.)
12. Moderate chronic life events (relationship difficulties/divorce, chronic illness, work-related stress etc.)
13. Medical issues (non-skin related)
14. Sleep problems related to your skin condition e.g., due to excessive itchiness, night-time sweating etc.
15. Sleep problems unrelated to your skin condition
16. Allergies
17. Low quality/quantity of friendships and relationships
18. Difficulty regulating body temperature/sweating.
19. Stress due to having a child with a long-term medical (skin) condition.

The following items in this survey were omitted for female XLI carriers due to the absence of dermatological manifestations: CISI, DLQI, FSQ and skin-specific mood factors. This group were the only group to be presented with the mood factor 'Stress due to having a child with a long-term medical (skin) condition' in the final section of the questionnaire due to the genetic basis of XLI. Participants completed the questionnaire in an average time of 30 minutes. Scoring information for each of these measures can be found in Appendix 3.1.

3.2.5 Data Analysis

All data was exported from Qualtrics into Excel. Quantitative data was uploaded to SPSS V.28 for analysis, and qualitative data was exported to a separate Excel file. Summary data are reported as percentages, mean±SD (normally distributed data) or median with 95% CI (non-normally distributed data).

Decision making details for the type of statistical tests used are described in Chapter 2.3. For two-tailed analyses with $\alpha = 0.05$ and a general population sample > 10 times

that of the experimental group, ≥ 35 participants per group provided > 80% power to reliably detect a medium-sized effect (Cohen d = 0.5). Subsequently, experimental groups were directly compared using unpaired t-test or ANOVA with main factors of sex (men/women) and condition (XLI, IV, psoriasis). An overall sample of ≥ 235 participants enabled reliable detection of main and interaction effects of small–medium effect size (partial η2 = 0.04) with > 80% power (α = 0.05).

When rating the factors relating to mood at the end of the survey, participants could assign a value from 0 (not at all) to 10 (very much), depending on the perceived impact on feelings of depression, anxiety and irritability across the lifespan. Once data collection was complete, the mean score for each factor was calculated for each experimental group. The three factors with the highest mean scores for each aspect of mood for each experimental group were highlighted as being particularly important self-rated contributors.

To analyse the qualitative data from the free text responses at the end of the survey, a mixed inductive and deductive approach to content analysis was chosen (see Chapter 1.6). The subjective nature of this analysis allowed for an individual interpretation of the qualitative data, to understand the meaning of participants' responses based on a broad research question [354]. The research question for this content analysis was: *'What additional underlying factors do males with XLI, female carriers of XLI, and males/females with IV or psoriasis, believe have influenced aspects of their mood (depression, anxiety, irritability) across the lifespan?'*. Following a process of interpretation, coding and categorizing, a series of themes and subthemes were created to represent responses [354].

3.3 RESULTS

3.3.1 Participants

A total of 371 participants were recruited for this study; 54 males with XLI, 83 female carriers of XLI-associated genetic variants, 23 males with IV, 59 females with IV, 30

males with psoriasis, and 122 females with psoriasis. One individual self-described as non-binary but selected the descriptor 'female carriers of XLI associated mutations' and thus has been included in the analyses for this group. Participants were diagnosed by a medical professional, based on skin condition, family history, and confirmatory genetic/biochemical testing where necessary. All groups were closely matched for age (medians 40-50 years, $H_{(5)} = 5.11$, $P = 0.40$), country of residence (74%–87% UK/North America), ethnicity (74-91% White European) and highest level of education obtained (63-85% college/university, or postgraduate education). Self-reported skin severity using the CISI or PASI scoring system was considered 'moderate' across all groups (40-53% maximum score). Detailed participant demographic information can be found below Table 5.

Demographic Feature		Males diagnosed with XLI (n=54)	Female carriers for XLI associated mutations (n=83)	Males diagnosed with IV (n=23)	Females diagnosed with IV (n= 59)	Males diagnosed with psoriasis (n= 30)	Females diagnosed with psoriasis (n= 122)
Age (yrs.)		45.13 (95%CI: 40.6-49.7)	43.8 (95%CI: 41.4-46.2)	45.96 (95%CI: 39.2-52.8)	43.29 (95%CI: 39.5-47)	46.2 (95%CI: 41.1-51.3)	41.41 (95%CI: 39.2-43.6)
Country of residence	United Kingdom	31%	34%	43%	36%	73%	83%
	United States of America	43%	37%	26%	29%	3%	2%
	Europe (excluding UK)	9%	5%	4%	10%	0%	1%
	Canada	7%	8%	9%	5%	23%	0%
	Rest of world	4%	12%	17%	20%	0%	14%
	No response	6%	4%	0%	0%	0%	0%
Gender	Male	89%	0%	100%	100%	100%	0%
	Female	7%	94%	0%	0%	0%	100%
	Non-binary	0%	1%	0%	0%	0%	0%
	Other	0%	0%	0%	0%	0%	0%
	Prefer not to say/no answer	4%	5%	0%	0%	0%	0%
Ethnicity	White	78%	87%	74%	75%	80%	91%
	Black, African, Caribbean or Black British	0%	1%	0%	2%	0%	1%
	Asian or Asian British	6%	0%	9%	2%	13%	4%
	Mixed or Multiple ethic groups	4%	1%	4%	7%	0%	2%
	Other or no response	13%	11%	13%	15%	7%	2%
Highest level of education	No formal education	0%	0%	0%	0%	3%	1%
	High school education	28%	23%	22%	15%	33%	24%
	College or university education	54%	43%	43%	61%	37%	46%

	Postgraduate education	15%	30%	35%	24%	27%	28%
	No response	4%	4%	0%	0%	0%	0%
Basis of diagnosis	Assessment by medical professional alone	19%	4%	43%	59%	80%	80%
	Assessment by medical professional and self-diagnosis/family history alone, or with genetic/biochemical test	52%	7%	30%	24%	10%	16%
	Self diagnosis/family history and genetic/biochemical test	2%	13%	-	-	-	-
	Self diagnosis and/or family history alone	25%	46%	26%	14%		2%
	Genetic/biochemical test alone	2%	28%	-	3%	-	2%
	Don't know	0%	-	-	-	10%	-
	No response	-	2%	-	-	-	-

Table 5: Demographic Features

3.3.2 Data Preparation

The complete data set was prepared for analysis, by removing the responses in the following categories: a) did not agree to consent form and thus no completion of the survey or b) completion of consent form but no further response. Where participants had not completed sections of the survey, or individual questions with a specific measure, their response was omitted from relevant analyses.

3.3.3 Psychological Diagnoses

Nearly 50% of the overall sample reported a previous diagnosis of a mood or neurodevelopmental condition. The prevalence of these previous diagnoses across the six groups, compared with data available on lifetime diagnostic prevalence in the general population is shown below in Table 6.

Prevalence %	Depression	Anxiety Disorder (incl. OCD)	ASD	ADHD/ADD	Dyslexia	Bipolar Disorder
General Population						
Males	19 [355]	14 [356]	1 [357]	5 [358]	-	-
Females	27 [355]	23 [356]	0.1 [357]	4 [358]	-	-
Both sexes	-	-	-	-	2-11 [359]	2 [360]
XLI						
Males	31	31	`10	19	6	2
Females	45	30	1	10	3	1
IV						
Males	35	22	0	4	0	4
Females	37	19	0	7	3	7
Psoriasis						
Males	40	10	0	0	0	0
Females	33	25	0	2	0	1

Table 6: Prevalence of psychological diagnoses

The prevalence of depression in all groups was higher than in the general population, with a substantial difference most notable in XLI females, although this is the only group to present with consistently mild if any, skin symptoms. The prevalence of anxiety disorder (including OCD) was substantially higher in males and females in the XLI and IV conditions, but not for individuals with psoriasis, compared to the general population estimates [356]. The prevalence of dyslexia across all groups was relatively low and thus matched estimates within the general population [359]. Females with IV were the only group with a marked increased prevalence of bipolar disorder, compared to the general population [360]. The prevalence of neurodevelopmental diagnoses, specifically ADHD and ASD, were similarly low among individuals with IV and psoriasis, whereas male and female carriers of XLI exhibited a substantially higher prevalence than the general population [357, 358].

3.3.4 Comparison of mood/neurodevelopmental traits

Kessler Psychological Distress Scale (K10)

Average scores for the K10, indicated moderate levels of depressive-anxiety-related traits in all groups, thus consistent with having a mild to moderate level of psychological distress (Figure 4/Appendix 3.3). K10 scores did not significantly differ between condition ($F_{(2,345)} = 0.56$, $P = 0.57$) or by sex ($F_{(1,345)} = 0.49$, $P = 0.49$). Although the interaction between condition x sex was significant ($F_{(2,345)} = 3.28$, $P = 0.033$, *post hoc* pairwise comparisons were not. Males with XLI presented with the highest K10 scores of any group, and these were notably higher than males with IV and psoriasis. Females with IV and psoriasis also scored notably higher than their male counterparts.

Most notably, K10 scores were significantly higher in all groups compared to general population figures (Cohen $d = 0.95–1.28$, $P < 0.001$) (unscreened community-recruited Australian adult women, n=882, 35-44yrs; and men, n=566, 45-54yrs) [361] (Appendix 3.3). K10 scores were also compared to previously collected data in males with XLI and female XLI carriers, to distinguish any potential impact of the current data set being collected during the COVID-19 pandemic. Scores in these experimental groups did not significantly differ and were slightly lower on average,

compared to the data from previous work (25.2±9.8 vs. 28.4±9.3 respectively, $U = 886.5$, $P = 0.11$; women: 23.3±7.2 vs. 23.6±8.6 respectively, $U = 3531.5$, $P = 0.96$). This comparison suggests a lack of effect of COVID-19 on psychological wellbeing for individuals with dermatological conditions such as XLI, and thus these elevated K10 scores are unlikely to be directly related to pandemic-specific issues.

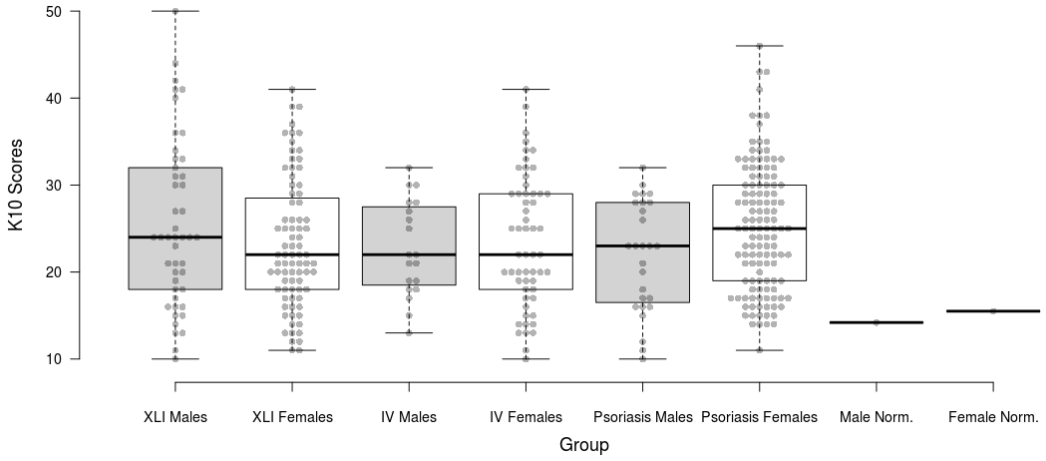
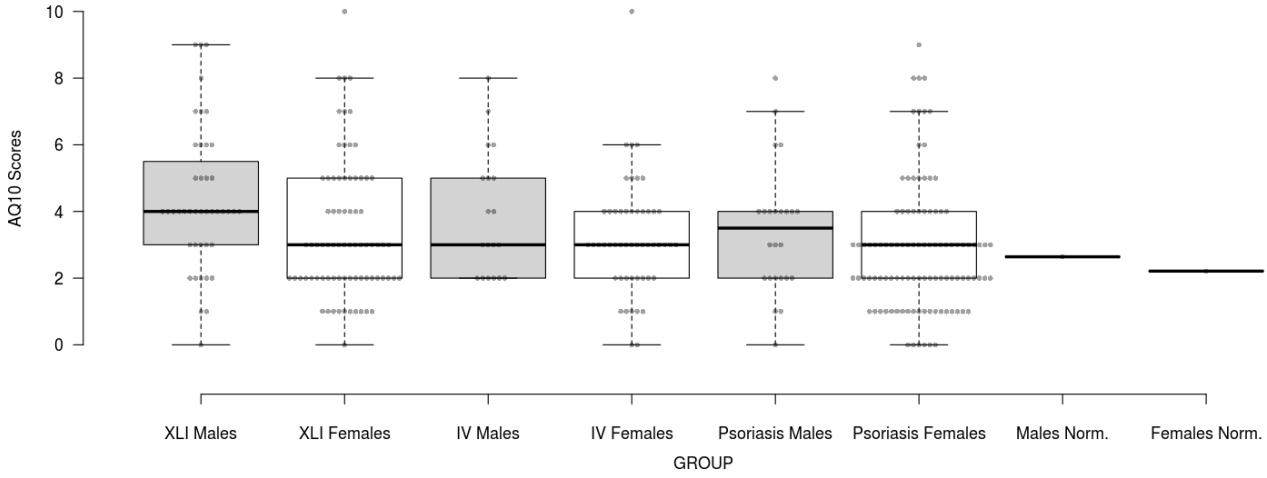


Figure 4: Boxplot of K10 scores in experimental groups compared to normative data

Autism Quotient 10 (AQ10)

AQ10 scores in all six groups were significantly higher than scores from an unscreened population of healthy, general population adults (45-64 years) from Sweden (10,796 women and 7904 men) (Cohen $d = 0.31–0.70$, $P < 0.05$) (Figure 5/Appendix 3.3). The most substantial difference in scores was identified in XLI males (Cohen's $d = 0.70$), with nearly 25% of participants in this experimental group reaching the threshold for a referral for a comprehensive autism assessment [351]. As expected, AQ10 scores were significantly higher in males compared to females when comparing all skin conditions (effect of sex: $F_{(1,319)} = 7.44$, $P < 0.01$). No overall effect of condition however was observed ($F_{(2,319} = 2.86$, $P = 0.059$), and no significant interaction between condition x sex was found ($F_{(2,319)} = 0.37$, $P = 0.69$).



Adult ADHD Self-Report Scale (ASRS) (Part A and inattentive/hyperactive traits)

Part A scores in the ASRS measure were also significantly higher in all groups (Cohen $d = 0.31–0.70$, $P < 0.05$), compared to an adult general population sample (unscreened community-recruited Australian adults; 1098 women and 993 men, aged 47-54 years) (Figure 6/Appendix 3.3). Across all groups, inattentive symptom scores were higher than hyperactive-impulsive symptom scores (significant in all groups apart from psoriasis males - Appendix 3.4). Males with XLI presented with the highest ASRS score overall, although ASRS scores did not differ by condition ($F_{(2,334)} = 0.79$, $P = 0.46$) or sex ($F_{(1,334)} = 1.84$, $P = 0.18$) or as a function of condition × sex ($F_{(2,334)} = 0.51$, $P = 0.60$) (Figure 6).

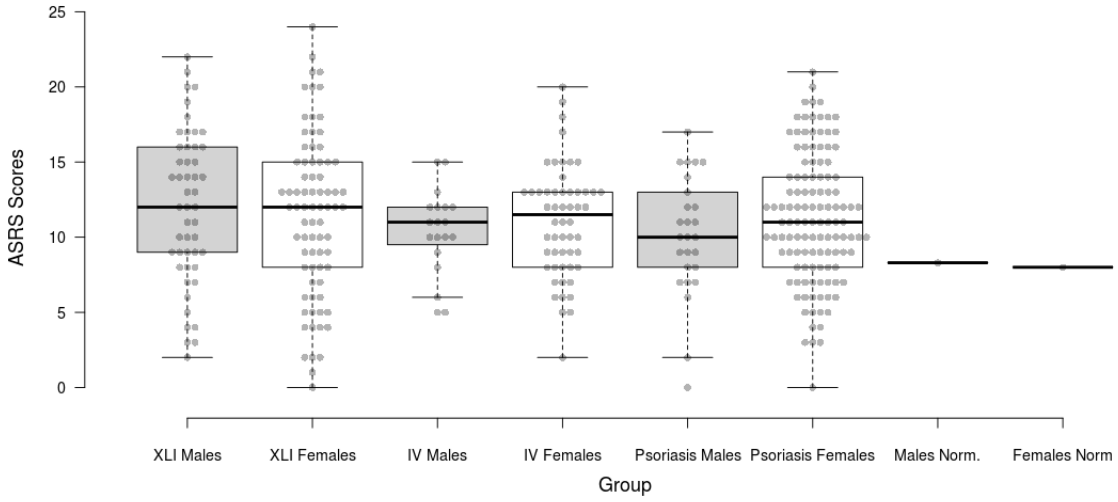


Figure 6: Boxplot of ASRS scores in experimental groups compared to normative data

The Brief Irritability Test (BITe)

Compared to a previously reported combined sample of undergraduate students and outpatient clinic-recruited chronic pain patients (711 women, 405 men, mean age 28 years) [352], all experimental groups scored higher on the BITe measure on average. Formal statistical analysis with this comparative sample was not possible due to the absence of a complete dataset from this work. Males with XLI scored notably higher compared to all other experimental groups (Figure 7/Appendix 3.3) and compared to females in each experimental group (XLI, IV and psoriasis), all males scored higher on this measure. However, there was no significant effect of condition ($F_{(2,319)} = 0.62$, $P = 0.54$) or sex ($F_{(1,319)} = 2.78$, $P = 0.10$), and no interaction between condition x sex ($F_{(2,319)} = 1.36$, $P = 0.26$).

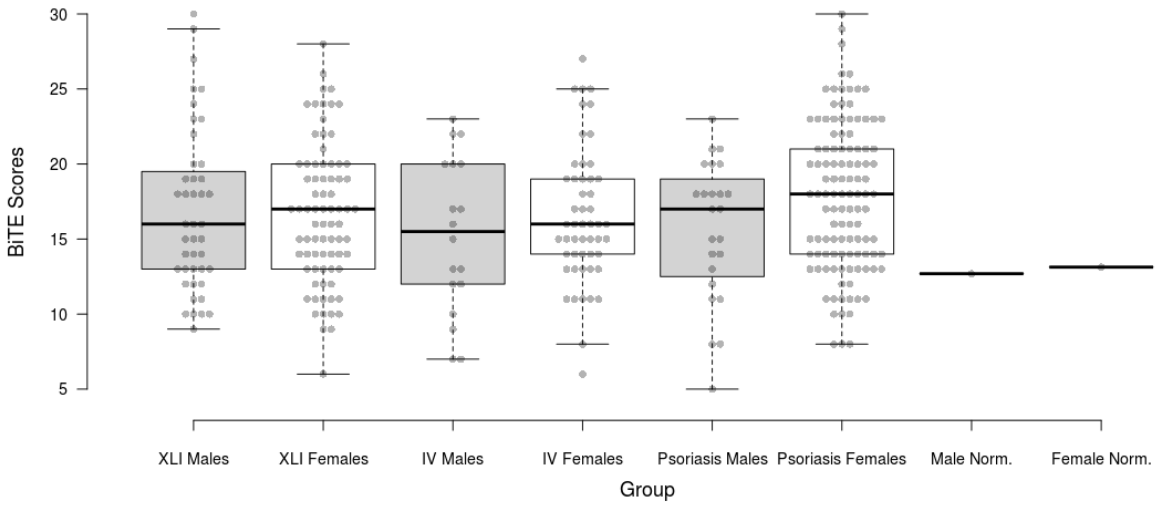


Figure 7: Boxplot of BITe scores in experimental groups compared to normative data

3.3.5 Quality of life and feeling of stigmatisation in individuals with skin conditions

Females with IV or psoriasis presented with similar scores on the DLQI (median ~10) ($t_{(1,161)} = 0.13$, $P = 0.72$), indicating moderate to large effects of the skin condition on QoL (Figures 8&9). Compared to the female experimental groups, males with XLI, IV or psoriasis exhibited lower, equivalent scores on the DLQI (median ~5-10), thus consistent with lower but still moderate effects on QoL.

Between the three groups of males, there was no significant difference in DLQI scores ($F_{(2,85)} = 0.876$, $P = 0.42$).

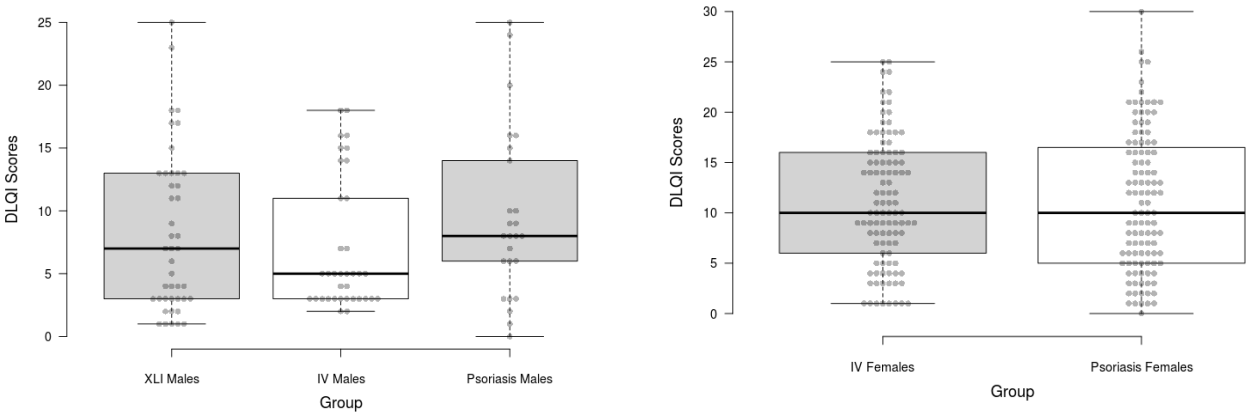


Figure 8 & 9: Boxplots of DLQI scores in experimental groups compared to normative data

Males with XLI, IV or psoriasis exhibited similar median scores (~125) for the FSQ ($F_{(2,79)} = 0.45$, $P = 0.64$), whereas females with IV or psoriasis exhibited notably lower median scores (100-120) on this measure ($t_{(1,157)} = 0.035$, $P = 0.85$), thus indicating higher levels of perceived stigmatisation in females (Figures 10&11).

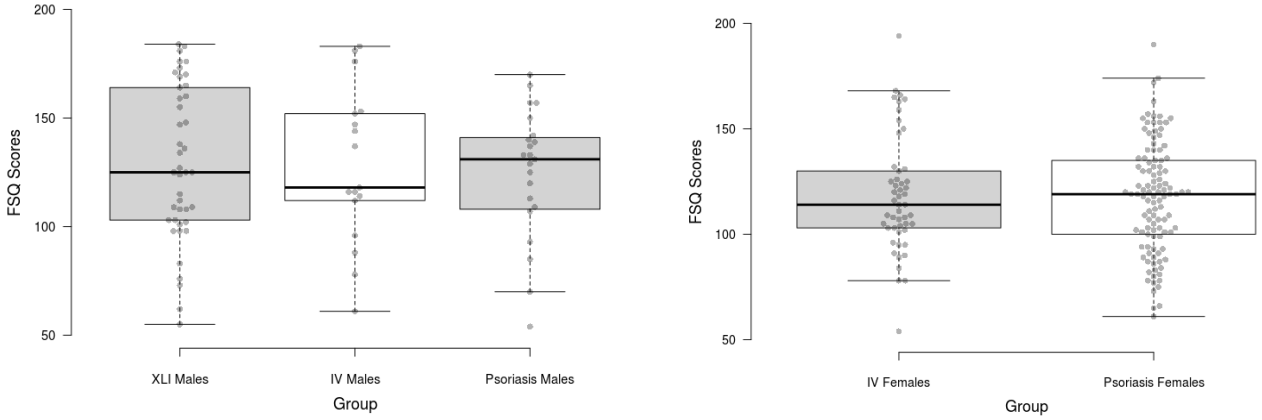


Figure 10 & 11: Boxplots of FSQ scores in experimental groups compared to normative data

3.3.6 Relationships between skin severity and psychological measures

Although it was predicted that worse skin severity would be positively correlated with a history of depression and mood-related traits, no association between

CISI/PASI scores and a previous diagnosis of depression was found for any experimental group (Appendix 3.2). However, females with IV ($r_s = 0.30$, $P = 0.026$) and psoriasis ($r_s = 0.34$, $P < 0.001$) both showed weak positive correlations between skin severity (CISI/PASI) and recent adverse mood symptoms (K10). This correlation was not evident in males with XLI ($r_s = 0.04$, $P = 0.80$), IV ($r_s = 0.21$, $P = 0.40$) nor in males with psoriasis ($r_s = 0.26$, $P = 0.19$).

To further analyse this relationship between K10 and CISI/PASI scores, a linear regression was conducted whilst controlling for certain factors as covariates. After adjusting for skin severity as the covariate, the NTS explained 34-40% of the variance within K10 scores, in males with XLI, IV or psoriasis. In females with IV or psoriasis, this rate was substantially lower (7-12%). After adjusting for NTS score as the covariate across all five experimental groups, skin severity scores explained only 1-9% of the variance within K10 scores.

ASRS scores ($r_s = 0.45$-0.73, $P < 0.04$) were moderately-strongly correlated with K10 scores in all experimental groups. AQ10 scores were also moderately correlated with K10 scores in males with XLI ($r_s = 0.34$, $P = 0.02$) and female XLI carriers ($r_s = 0.45$, $P < 0.001$), males with IV ($r_s = 0.62$, $P = 0.004$), females with psoriasis ($r_s = 0.45$, $P < 0.001$), but not in females with IV ($r_s = 0.26$, $P = 0.11$) or males with psoriasis ($r_s = 0.36$, $P = 0.09$). After adjusting for skin severity, AQ10 scores explained 16-19% of the variance in K10 scores in males with XLI, females with IV and females with psoriasis. This rate was notably higher in males with IV (29%) and males with psoriasis (43%), suggesting that autistic traits may precede mood issues in these groups. ASRS scores also explained a marked rate of variance in K10 scored in all groups after adjusting for skin severity (20-55%). These analyses demonstrate a strong positive relationship between neurodevelopmental disorder-associated traits, and depressive-anxiety traits, after controlling for skin severity.

Skin severity, however, did not correlate with FSQ scores in any group apart from a weak correlation observed in females with psoriasis ($r = -0.21$, $P = 0.030$; all other groups, $r = -0.17$ to 0.35, $P > 0.12$). As predicted, DLQI scores were significantly negatively correlated with FSQ scores in all five experimental groups ($r_s = 0.456$-

0.758, $P < 0.03$) (female XLI carriers omitted from this analysis), demonstrating a relationship between QoL and feelings of stigmatisation.

After adjusting for both NTS and skin severity scores, FSQ scores explained 14-18% of the variance in K10 scores in male and female individuals with psoriasis, as well as 10% in males with XLI and 3% in males and females with IV. After adjusting for NTS and skin severity scores, FSQ scores explained 32–40% of the variance in DLQI scores in men with XLI, IV or psoriasis, and slightly less (17–25%) in women with IV or psoriasis. These correlations demonstrate a moderate-strong positive relationship between dermatology-related QoL, and feelings of stigmatisation, after controlling for neurodevelopmental traits and skin severity in all experimental groups (correlations between psychological measures reported in Appendix 5 & Appendix 6).

3.3.7 Contributory factors towards aspects of mood

Participants in this study rated each of the 19 factors contributing to aspects of mood (depression, anxiety, and irritability), and the top three factors for each aspect and group are illustrated in Figures 12 & 13 (complete dataset separated by group reported in Appendix 3.7-3.12). Free-text responses were analysed using content analysis and these results can be found in Figure 14 (complete analysis can be found in Appendix 3.13).

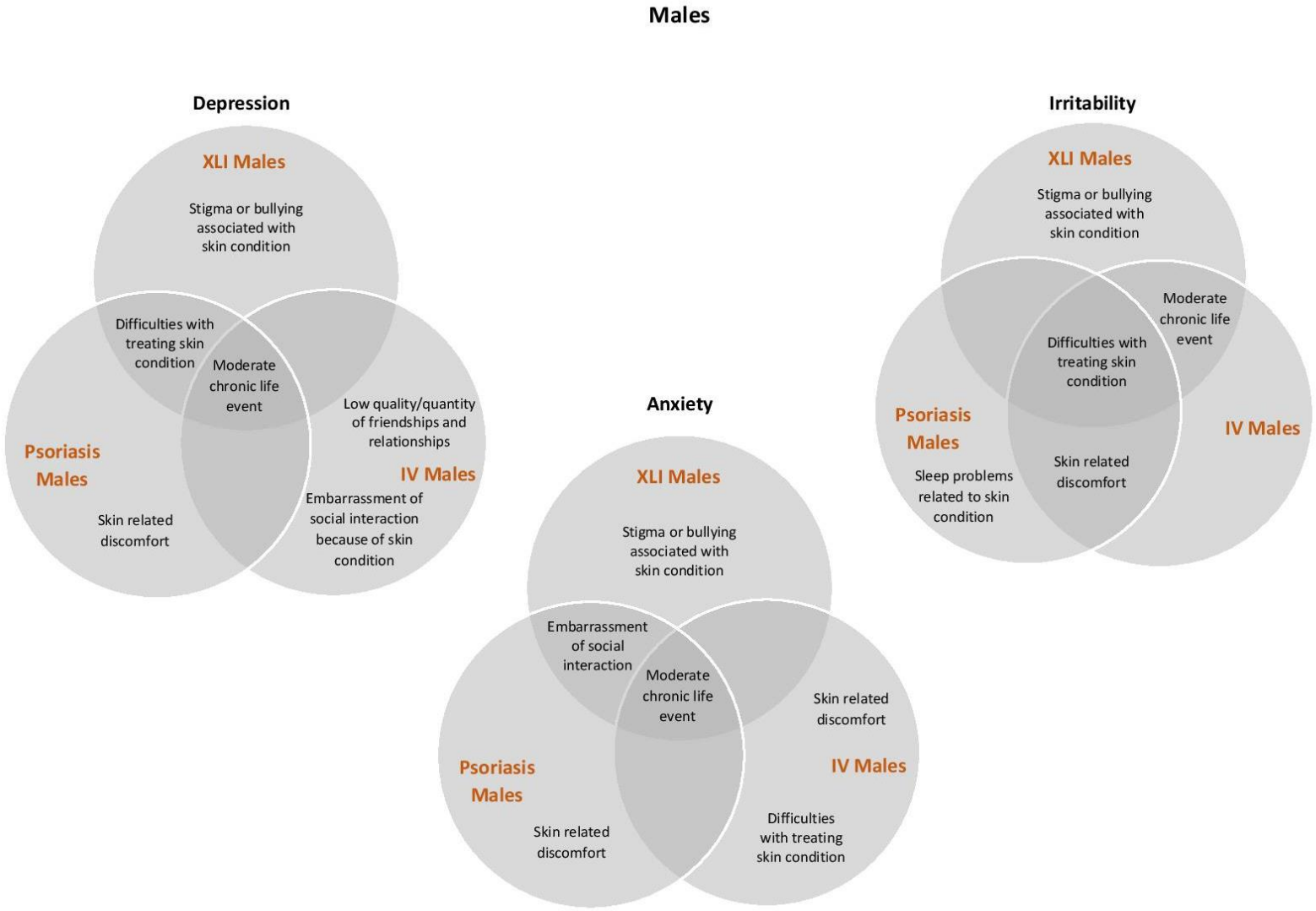


Figure 12: Venn diagrams illustrating the three factors self-reported to be most strongly associated with aspects of mood (depression, anxiety, irritability) across the male experimental groups

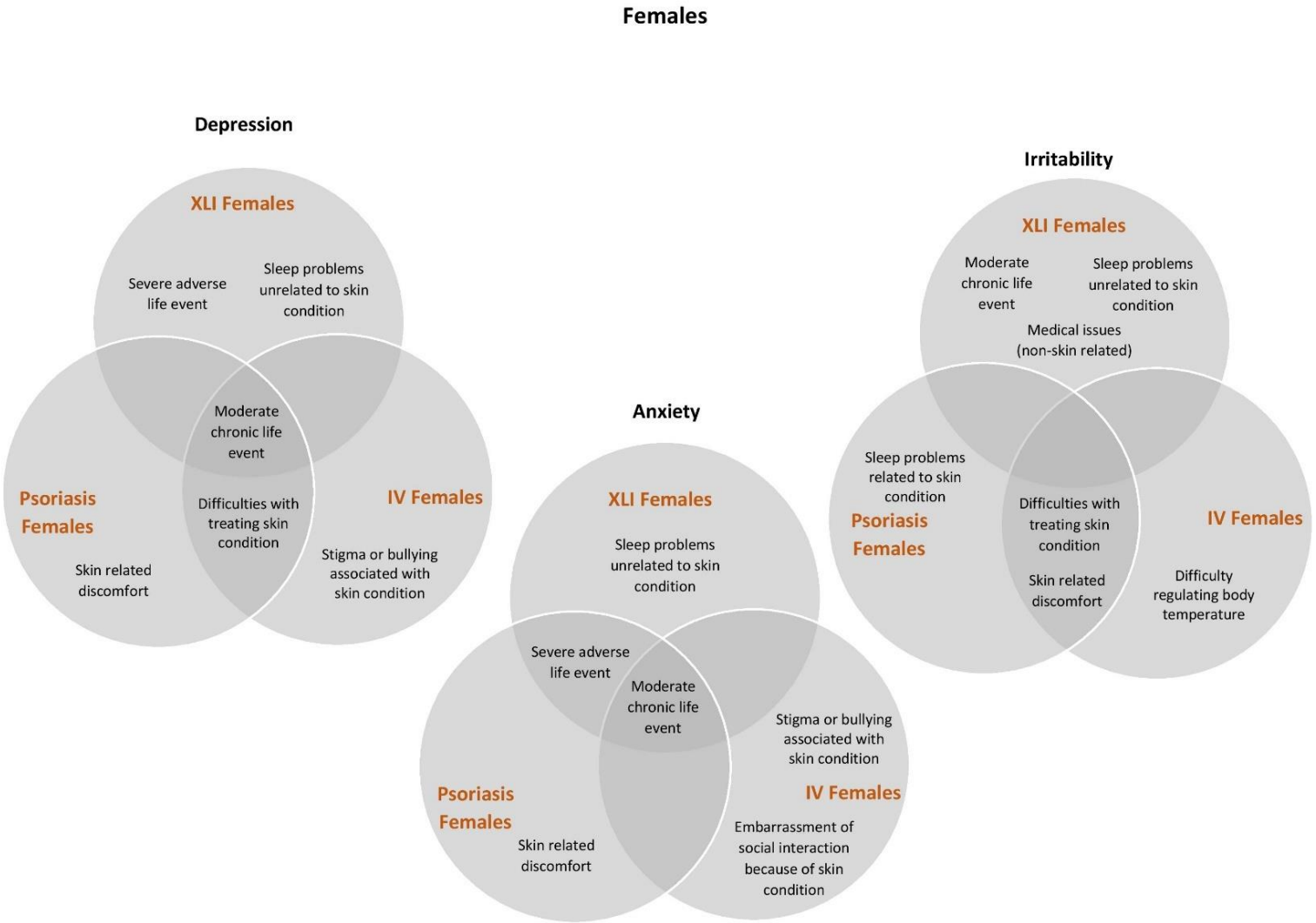


Figure 13: Venn diagrams illustrating the three factors self-reported to be most strongly associated with aspects of mood (depression, anxiety, irritability) across the female experimental groups

Across all-male groups, 'moderate life event' was the most common contributory factor across depression, anxiety, and irritability-related mood factors. 'Difficulties treating skin condition' was also a key contributory factor towards feelings of irritability in all male experimental groups. 'Stigma and bullying associated with skin condition' was the highest ranked factor contributing to overall mood for males with XLI only. Males with IV perceived 'low quality/quantity of friendships or relationships', and males with psoriasis 'sleep problems due to the skin condition' to be some of the strongest factors contributing to feelings of irritability. Discomfort associated with the skin condition was also rated highly as a contributory factor towards mood symptoms in males with psoriasis, and specifically towards irritability in males with IV.

Across all female groups, the most commonly reported factor contributing to all three aspects of mood, was 'moderate chronic life event', referring to instances such as relationship difficulties/divorce, chronic illness or work-related stress etc. Due to the mild or absent nature of any skin issues for female XLI carriers, the most common factors in this group focused on sleep problems unrelated to skin problems, and life events. Skin-related factors, specifically 'difficulties with treating skin condition' and 'skin-related discomfort' were the most common concerns reported by females with IV or psoriasis. Factors surrounding the impact of skin conditions on social functioning, including 'skin-related stigma or bullying' and 'embarrassment of social interaction' were only highlighted by females with IV, as well as 'difficulty regulating body temperature'.

After rating each of the 19 factors, participants were also provided with an optional 'free text' box to provide any additional comments, specifically about any other aspects not discussed that they believe to have influenced their mood (depression, anxiety, irritability) across the lifespan. 101 participants responded to this free text box, and responses were analysed using inductive content analysis as discussed in 3.2.4. The themes identified during this analysis are presented in Figure 14 below (see Appendix 3.13 for full outline):

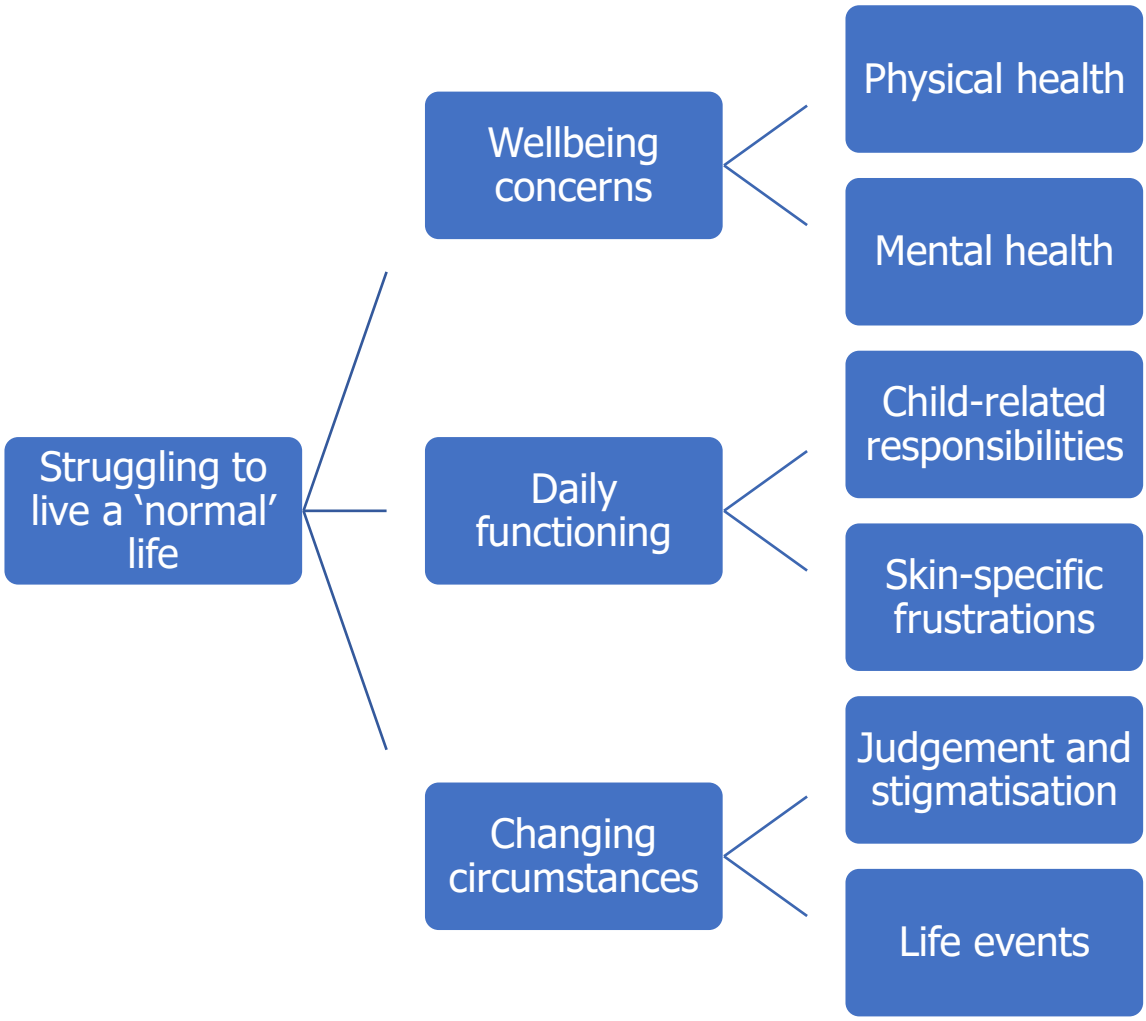


Figure 14: Summary of themes identified in content analysis

Although some themes were not identified in certain experimental groups (e.g., no discussion of skin-specific frustrations by female XLI carriers), participants' experiences were mostly similar in nature and mirrored the previous top-rated factors. The subtheme 'wellbeing concerns' largely focused on comorbid conditions or other health-based anxieties, in addition to mental health concerns such as repetitive thoughts, frustration and worry about the future. The subtheme 'daily functioning' depicted skin-specific concerns, such as a lack of public understanding about the skin condition, the burden of managing the condition, and the inability to engage in social activities due to skin-related embarrassment and worry. This subtheme also represented responsibilities relating to caring for a child or dependent, as well as concerns around raising a child with the same skin condition.

The final subtheme, 'changing circumstances' represented significant life events including abuse and bereavement, in addition to differing levels of judgement and stigmatisation from others; notably, this was dependent on life stages e.g., bullying specifically during childhood.

3.4 DISCUSSION

3.4.1 Summary

This study investigated mood and neurodevelopmental disorders and associated traits, as well as potential causes and consequences, in two rare skin conditions (XLI and IV), compared to a better-studied comparative condition (psoriasis). Using a well-established online survey method, measures of depressive, anxiety, and irritability-related traits were compared across conditions and to general population controls, in addition to investigating self-rated contributory factors relating to aspects of mood over the lifespan. Participants across all experimental groups were closely matched for demographic factors, and skin severity and thus these findings are unlikely to be attributable to such variables.

3.4.2 Mood and Neurodevelopmental Disorders and Associated Traits

Our first key finding in this study was an increase in diagnoses of both depression and anxiety in all experimental groups, compared to matched general population controls. This finding was mirrored in the significantly elevated depressive-anxiety trait across all experimental groups compared to controls, thus indicating a mild-moderate psychological disorder. Previous work using similar online survey methodology, in addition to data from the UK Biobank, reported similarly elevated rates of depression and anxiety in both males with XLI and female XLI carriers [228, 272]. Similar findings around psychological distress have also been reproduced in work in adults with IV [214] and psoriasis [337, 338], but these three conditions have yet to be directly compared. Participants in all experimental groups also presented with notably higher irritability scores, compared to a comparative population; this finding replicates previous work in carriers of XLI-associated genetic deletions [187] but irritability has not yet been investigated in individuals with IV or psoriasis. Elevated

rates of mood disorders in the XLI experimental group specifically illustrate the role of STS or adjacent genes in neurobehavioral function; as female XLI carriers do not present with skin pathology, mood-related outcomes are more likely to arise from a deficiency of STS and thus are independent of the skin condition. Crucially, this study compares similar rates of mood disorder diagnoses and associated traits in the under-studied conditions of XLI and IV, compared to the well-studied condition of psoriasis.

Another key finding in this study, was the moderately elevated ASD and ADHD (particularly inattentive) related traits in all experimental groups, compared to age/gender matched general population adults. Most notably, males with XLI and female carriers of XLI-associated genetic variants also exhibited significantly higher rates of ASD and ADHD diagnoses, in addition to the NDD-related traits compared to general population controls. These results mirror previous work in XLI males and female XLI carriers, thus corroborating higher rates of neurodevelopmental disorders in this condition [187, 228, 272]. Rates of ASD diagnoses were notably higher in males with XLI compared to female XLI carriers (10% vs. 1%), however, this disparity mirrors current and historical trends in underdiagnoses of this disorder in females [362], as well as general population patterns [357]. These elevated rates of NDD-related traits also mirror previous work in individuals with psoriasis, which reported elevated rates of ASD in particular [341, 342]. This result is, however, a new finding in adults with IV, perhaps suggesting a lack of appropriate and timely diagnoses of conditions such as ASD and ADHD for this group. Nevertheless, this work contributes to a growing body of literature proposing a link between NDD conditions and multiple skin conditions [363].

To better understand the relationship between these skin conditions, and mood disorders/related traits, it is important to explore potential causal factors. Contrary to the original hypotheses, no difference in skin severity scores was found between individuals with a diagnosis of depression and those without. Weak associations between skin severity and recent adverse mood symptoms/feelings of stigmatisation were discovered in females only. These findings suggest that worse skin severity confers only a small risk in the risk of exhibiting adverse mood symptoms or feelings

of stigmatisation. However, a strong positive relationship between NTS and adverse mood symptoms was identified, particularly in men, and this pattern mirrors findings in general population samples [364]. Importantly, NTS scores explained a high proportion of the variance between K10 scores, after adjusting for skin severity. To explain this relationship, we have identified three possible explanations: (i) high levels of neurodevelopmental traits confer a later risk of mood problems, (ii) high levels of mood problems confer high levels of neurodevelopmental disorder-associated traits e.g. sleep impairments, and subsequent executive functioning, and (iii) biological mechanisms related to the skin conditions (e.g. genetic factors, skin permeability, inflammation) affects neurodevelopment and mood-related processes via dissociable mechanisms. However, neurodevelopmental disorder-associated traits e.g., difficulties with social interaction, and potential life challenges associated with these, were not reported as a major contributory factor towards mood symptoms in any group. Thus, options (ii) and/or (iii) seem more likely explanations for this observed relationship.

One potential explanation relating to suggestion (iii), is the role of inflammation in mood and neurodevelopment which has been a focus of psychiatry in recent years [365, 366]. In his most recent book, Edward Bullmore explores new scientific breakthroughs which indicate a clear link between inflammation and depression [367]. Bullmore poses an important question: "How can inflammatory changes in the body's immune system cause changes in the way the brain works so as to make people feel depressed?" [367]. A growing base of evidence in the last 10 years has strongly implicated the role of inflammation as a mediator in the development of mood disorders such as major depressive disorder and bipolar disorder [365, 368, 369]. The exact causal link between inflammation and mood has not yet been determined in its entirety, yet anti-inflammatory-based clinical treatments remain key targets for treatments [365, 368].

With specific reference to inflammation via the skin, the most widely accepted and researched explanation involves the (gut)-brain-skin axis. Here, a bidirectional relationship is proposed between psychological distress, and inflammatory physiological responses [370]. Inflammatory cytokines (a signalling molecule able to

cross the blood-brain barrier), are released via one or more of the following mechanisms: a) a skin condition-related inflammation e.g., psoriasis, triggers the HPA axis, and/or b) a response to psychological stress [371]. Thus, either psychological stress is a trigger for inflammatory physiological responses, thus playing a causal role in the development of certain skin conditions, or alternatively, these inflammatory conditions may elicit a stress response in the brain, thus playing a causal role in mood disorders such as depression [371, 372]. New work in this area has suggested an immunomodulatory role of the gut, acting in parallel to, and combination with, the brain-skin axis. Alterations in the gut microbiota can induce inflammation across the body, including the skin and brain, although the certain mechanism behind this relationship remains unclear [373, 374]. Alternatively, inflammation as a result of the skin condition, or mood disorder may affect dysregulation of the gut microbiota [373, 374].

The inflammatory component of the brain-gut-skin axis may also partially explain the apparent relationship between neurodevelopmental disorders such as autism (and associated traits) and dermatological conditions. Recent work suggests that certain brain areas implicated in autism, including the fusiform gyrus and amygdala, are also more likely to be affected by inflammatory cytokines such as IL-37 and IL-8, compared to other subcortical areas [375, 376]. More generally, proinflammatory cytokines are significantly elevated in individuals with autism [377], with further suggestions of increased permeability in the gut microbiome in individuals with ASD [378, 379]. Regarding ADHD, the link to inflammation is less clear; higher levels of inflammatory cytokines have been found in children with ADHD, most frequently IL-6, compared to children without the condition [380-382]. However, a large cohort study of adults with ADHD found no association between the condition and several inflammatory markers, including IL-6 [383]. Furthermore, some measures of inflammation, including cortisol, may differ depending on the subtype of ADHD, and in some cases, potential sex-based differences [384, 385]. However, this work requires further development to investigate the precise nature of any relationship between neurodevelopmental disorders such as ASD and ADHD and inflammation. Little work has directly compared levels of inflammatory markers in individuals with/without

specific skin conditions, in addition to those with/without mood or neurodevelopmental disorders. A key area for future work will be to better understand the role of the (gut)-brain-skin axis in mediating the relationship between skin/mood/NDD disorders.

However, unlike the established link between psoriasis and inflammation [75, 386], current work has not evidenced inflammatory processes in most types of ichthyoses, specifically XLI and IV. Psoriasis, as an immune-mediated disorder, is associated with key inflammatory processes contributing to comorbid outcomes including cardiovascular disease and myocardial infarction (MI), psoriatic arthritis and obesity [75, 387-389]. Inflammatory markers including IL-6, and C-reactive protein (CRP) are typically elevated in individuals with psoriasis compared to healthy controls [389, 390]. Evidence of increased levels of inflammatory cytokines and proinflammatory molecules including IL-17 and IL-2 have also been reported in some types of ichthyoses such as Netherton's and Harlequin's ichthyosis [391] [392] [393]. However, although the brain-gut-skin axis may play a key role in explaining the relationship between mood and neurodevelopmental disorders, and other inflammation-related skin conditions such as psoriasis, there is no current evidence to suggest that this explanation is relevant for ichthyoses, specifically XLI and IV.

Thus, it is more likely that a combination of biological factors (inflammation in case of psoriasis, effects of genetic variants on neurodevelopment in the case of IV and XLI), social factors (stigma/bullying, social isolation) and psychological factors (self-esteem, coping) that play a cumulative role in the development of mood disorders. It is important not to understate the impact of any of these physiological or social contributory factors, as adverse mood in these groups is clearly a complex topic.

3.4.3 Quality of Life and Feelings of Stigmatisation

Feelings of stigmatisation and quality of life were significantly correlated across all groups, thus suggesting that those individuals with increased perceived stigmatisation, also experienced a worse QoL. However, compared to males in this study, females in all experimental groups presented with considerably larger effects of their skin condition on QoL, as well as notably higher feelings of stigmatisation.

Greater negative effects on QoL in females specifically are commonly reported across other skin conditions, including chronic pruritus, psoriasis and acne [394-396]. One potential explanation may be that skin-related issues such as painful skin on hands, regular application of ointment and exposure to heat/cold, may be more impactful due to the type of roles most commonly undertaken by women e.g., care/health-based professions, retail, and teaching [397, 398]. However, the greater effect of skin condition on feelings of stigmatisation in females across all skin conditions appears to be relatively specific to this study. Relevant work across other skin conditions, including eczema, acne and vitiligo, report equivalent or similar levels of perceived stigma between males and females [331, 399, 400]. However, more generally, research suggests that females are more dissatisfied with their appearance, and thus more self-critical compared to males [401, 402]. Compared to age-matched males, women tend to place a greater value on their appearance and body and attribute more negative values when compared to others [401-403]. Thus, this novel work in males and females with ichthyosis specifically demonstrates the negative impact of the skin condition on QoL and feelings of stigmatisation, similar to negative body esteem in general population females [402].

However, although stigmatisation and QoL were significantly correlated, there was no relationship between stigmatisation and mood. This may be due to the short time point assessed by the K10 (mood) measure, compared to the lifetime nature of the FSQ (stigmatisation) measure.

3.4.4 Factors self-reported to affect participants' mood

For the first time, this study highlights condition-specific and general factors which individuals with XLI, IV or psoriasis perceive as contributing significantly towards their mood symptoms (depression, anxiety, irritability). These factors may be targeted by clinicians and Healthcare Professionals (HCPs) to minimise the adverse psychological effects of living with a skin condition long-term. Some of the main factors contributing to mood across all groups focused on patients' discomfort and frustrations in managing their skin on a regular basis. Thus, patients should be supported and advised by clinicians on sourcing and applying treatments, with a

primary focus on minimising both pain and inconvenience. Skin management in the evening/night was of particular concern to individuals with psoriasis, suggesting that this group requires additional support to improve their experiences at this time.

Stigmatisation, experiences of bullying and embarrassment also appeared to be particular issues of concern, for males with XLI and females with IV, as well as low quality or quantity of friendships in males with IV. Due to the rare nature of these conditions, education and improving awareness amongst the general population about medical conditions which may affect appearance should be a key priority. Psychological therapies may focus on coping strategies and self-management techniques to improve psychological wellbeing, and support groups should be available for individuals to share experiences. Support groups specifically for people who identify as male, may be particularly useful to provide emotional support and to provide an opportunity to help alleviate loneliness.

One potential explanation for the issues reported by particularly patients with XLI and psoriasis regarding their sleep may be due to the increased rates of mood disorders in these groups compared to the general population. Research suggests that 80-90% of individuals diagnosed with major depressive disorder (MDD) also experience sleep disturbances [404, 405]. The relationship between mood disorders and sleep is likely to be complex and multifaceted, and sleep-related issues may also stem from lifestyle factors such as medication or stress [406], or via mechanisms related to inflammation as previously discussed [407]. Supporting individuals with sleep issues should be another key focus for clinicians in the management of dermatological conditions such as XLI and psoriasis.

3.4.5 Strengths and Limitations

This study collected detailed self-report data on mood and neurodevelopmental traits from a relatively large (in terms of rare disease), geographically diverse cohort of individuals, much of which is consistent with previous findings from our group and others. One key strength of this study is the direct comparison between three skin conditions; this type of analysis is rarely performed in this research field, and thus novel relationships both between and within groups have been identified in this

work. Recruitment of participants within these experimental groups stemmed from multiple sources, largely focused on social media, and thus participants' self-reported dermatological and psychiatric/behavioural diagnoses could not be objectively confirmed. Due to the rare nature of ichthyosis, however, this was a necessary tactic to recruit a sufficient number of participants. Internal consistency across questionnaires as indexed by Cronbach α was generally high (> 0.8) and comparable across groups.

The online survey method used in this study ensured all participants' responses were anonymized; it is anticipated that this allowed participants to respond more honestly [408]. Furthermore, the use of free-text responses throughout the survey, also provided participants with a chance to elaborate on their answers, thus delivering a richer dataset for qualitative analysis and a greater understanding of factors contributing to mood, some specific to each condition.

To aid understanding of sex-based factors, the question about participants' gender could be changed to 'sex at birth'. This question did not lead to many difficulties in analysing the data as only one participant self-identified as non-binary, however, it is not known whether participants' genders were the same as their sex at birth.

Due to the nature of this online survey approach, some limitations to this study must be considered. Firstly, the self-report nature of this survey may introduce some inaccuracies to the data: participants may misrepresent or exaggerate their diagnoses or symptoms, either consciously or subconsciously. However, this study has demonstrated high consistency between diagnostic questions e.g., depression, and established questionnaires e.g., K10 measuring depressive-anxiety traits. Furthermore, these self-report measures are beneficial, especially for rare disease communities, as they allow the researchers direct access to participants' perceptions of their conditions. Using objective measures would likely remove the subjective, personal nature of data collection. The use of self-report data is highly contested and commonly perceived as a limitation in health-based research in particular [409, 410]; however, there are very limited solutions and alternatives. Asking participants to describe or report on their experiences is a core component of clinical work, yet the issues that arise such as recall bias and social desirability are equally likely when

using clinician-reported data if the onus is on participants to recall their experiences [409, 410]. Managing these issues should remain a prominent focus, as opposed to eliminating self-report data.

For example, to manage and minimise recall error, the length of the recall period should be as short as possible, and the characteristics of both the disease (acute/chronic) and the individual (age) should be accounted for [409]. To assess the likelihood of social desirability, it is important to consider how likely it is that a participant may fake or exaggerate their responses; is the context of the study a 'high-stake' environment or are they motivated to do so? Is there a clear, desirable norm or expectation of the participant when completing a measure? Accounting for these types of factors may reduce potential self-report bias in the data, and improve confidence in participants' response [410].

Secondly, this study also introduces the possibility of response bias; participants with worse/more prominent symptoms, or those who related more to the title or description of the study, may have been more likely to take part. To minimise this bias, open, welcoming language was used in the study advert to encourage participants from all backgrounds to apply. This type of response bias is difficult to avoid; however, this study did find very similar patterns of results to previous work in the UK Biobank which used a different analysis strategy and participant response characteristics [187]. This suggests that participants from varying backgrounds, experiences and comorbid diagnoses are taking part in our work. However, consistency with previous work in XLI populations [187, 228, 272] may potentially be due to the non-independence of samples, due to the rare nature of ichthyoses. Significant effort has been made to address this by recruiting through a diverse range of channels and consistently expanding recruitment avenues compared to previous work.

Another potential limitation of this work is the matching of samples to general population controls; samples were matched as closely as possible, based on age and gender and available literature. However, this was not perfect and thus there is potential for inflation of actual effect sizes. The effect of this matching was

minimized by using the best available published samples regarding size and participant characteristics.

3.4.6 Summary

This study found similar elevated rates of mood disorders, and associated traits across three dermatological conditions, compared to the general population. Results also showed elevated rates of neurodevelopmental traits, and irritability, as well as a greater impact on QoL and increased feelings of stigmatisation across all three skin conditions, compared to the general population. To support future psychological therapies and educational strategies, some key factors contributing to negative mood in individuals with XLI, IV and psoriasis were also identified. Future work should focus on developing appropriate interventions to support the development of individual adjustment, as well as support for HCPs to improve long term management of the condition. In addition, further research is required to understand the mechanisms linking skin and mood disorders.

Chapter 4: MEMORY AND MOOD FUNCTIONING IN X-LINKED ICHTHYOSIS (XLI) AND ICHTHYOSIS VULGARIS (IV)

**Note: some of the material included in this Chapter and relevant appendices relates to the following published work, for which I am listed as the first author:*

Wren G, Flanagan J, Underwood J, Thompson A, Humby T, Davies W. Memory, mood and associated neuroanatomy in individuals with steroid sulfatase deficiency (X-linked ichthyosis). Genes, Brain and Behavior. 2024.

4.1 INTRODUCTION

4.1.1 The role of STS in cognitive functioning

The enzyme steroid sulfatase (STS) cleaves sulfate groups from a number of steroid hormones, thus altering their solubility and/or activity. One such steroid hormone is dehydroepiandrosterone (DHEA), and its more stable, soluble sulfate conjugate dehydroepiandrosterone sulfate (DHEAS). These hormones are thought to play a role in neural activity via the regulation of neuroactive steroids, and modulation of both neurodevelopmental and neurodegenerative processes [411-413].

There is some evidence from animal studies that STS deficiency might impact specific aspects of cognition, including memory. Early work in adult rats initially identified a beneficial effect of STS inhibition on memory and hippocampal function, possibly through initial elevated peripheral DHEAS levels [414] and/or downstream effects on local acetylcholine levels [415]. Furthermore, more recent rodent work identified that intra-hippocampal and peripheral infusion of STS inhibitor reversed deficits in spatial and working memory in a rat model of dementia-related pathology [416]. Long-term administration of STX64, a similar STS inhibitor, also alleviated memory impairments in hippocampal and cortical neuropathology in a genetic mouse model of relevance to Alzheimer's Disease (AD) [417]. Interestingly, deletion of the closest worm orthologue of *STS* appeared to increase longevity and offer some degree of protection against AD-associated pathology [417].

X-linked ichthyosis allows for clarification on the relationship between loss of STS function and memory, and to examine the impact on memory in humans as suggested in the animal work [185]. In contrast to findings in rodents, preliminary data from deletion carriers in the large UK Biobank sample generally performed worse than non-carrier individuals across tasks indexing general executive function, processing speed, reaction time, short-term memory, and attention [187]. Furthermore, this work also identified a mild impairment in a measure of Fluid Intelligence [187]. The impact of the loss of STS function can also be seen in negative effects on mood: recent work from our group has identified a higher rate of mood and neurodevelopmental disorders and associated traits in adults with XLI [228, 418, 419], as well as the findings from Chapter 3. As systemic DHEA(S) levels may influence both mood [420] and memory [187] and as the two are often comorbid [421], potentially there may be an interaction between mood and any memory findings in individuals with XLI. [422].

These data clearly suggest that varying levels of DHEA(S) in the brain, dependent on the presence or absence of STS, may affect aspects of memory and neurodegenerative processes in man. However, notwithstanding the early data in UKBB, to date, there has been no further exploration of specific aspects of cognition/memory in individuals with XLI, or their relationship with mood symptoms. This study examined a variety of memory-related measures in males with a clinical diagnosis of XLI, and in female carriers.

4.1.2 Use of objective online recall measures

To test the relationship between STS deficiency and memory in man, a custom designed online memory measure was used to objectively assess recall. Online survey methods were employed in this study as a time-efficient way in which to assess short-term recall from a comparatively large, widely dispersed rare patient group [321]. Although in-person assessments may offer more control of external variables [423] such as environmental distractions [424-426] or emotional interference [427], previous work suggests that online memory test measures demonstrate similar performance outcomes in adults [428-430] and young people [431, 432], even when auditory

distraction is introduced [423]. Furthermore, online testing offers a more naturalistic approach as participants are completing the tests in their usual environment and thus can proceed at their own pace without the stress of being observed, compared to an artificial lab-based setting. A short list of phonologically short neutral words were used (n=15), and a short set of neutral pictures (n=20) in the recall task, adapted from the Rey Auditory Verbal Learning Test (RAVLT) [433, 434].

4.1.3 Use of subjective self-reported memory and mood measures

To understand more about how participants perceived their own memory abilities, it was important to include a subjective measure of memory in this study. In adults, research suggests that higher self-efficacy is typically moderately associated with better performance on objective memory tests [435, 436], although subjective self-assessment of memory may only be weakly correlated with objective memory in individuals with poor memory test performance [437]. Co-presentation of objective and subjective (self-report) measures of memory in the survey would allow for testing of the relationship between them.

The Multifactorial Memory Questionnaire is designed to assess metamemory in middle-aged and older adults using three different scales; satisfaction with memory functioning, self-appraisal of memory ability, and self-reported use of memory aids/strategies [438]. A recent meta-analysis revealed high-quality evidence for 'internal consistency, stability, measurement error, convergent validity, and known-groups validity' for all three MMQ scales [439]. Scale measurement properties were also consistent across different participant sample characteristics and study designs [439], and further factor analyses support the validity of the MMQ as a subjective memory measure [440].

To objectively assess recent mood symptoms the Kessler Psychological Distress Scale (K10) was used as a well-validated self-report measure of depression/anxiety-related traits in the last 30 days [349]. This measure has been used in our previous studies, and thus it is reliable in this population and easy to administer.

4.1.4 Use of TestMyBrain (TMB)

In Phase 2 of this study, participants were given the opportunity to complete a series of six neuropsychological tests assessing individual components of memory and cognitive functioning from the 'TestMyBrain' online battery (https://testmybrain.org/) as additional objective measures. This free platform allows researchers to test different aspects of cognition, including processing speed, attention, and episodic memory across a series of short online tests. These are designed for use in English-speaking samples but are otherwise culturally neutral.

4.1.5 Ichthyosis Vulgaris as a comparative condition

In this study, a sample of adults with a clinical diagnosis of ichthyosis vulgaris (IV) were recruited as a control group . IV is a dermatological condition similar in presentation to XLI and with consistent evidence of similarly-sized effects on mood [214, 419], but has not previously been associated with effects on memory.

4.1.6 Aims and Hypotheses

The present study aimed to compare self-reported memory performance, word-picture recall, and mood in male and female carriers of XLI-associated genetic variants, to a control group of males and females with IV using an online survey. This study was exploratory in nature, as it was difficult to predict whether STS deficiency would be associated with enhanced memory (as suggested by the animal model data) or with impaired memory (as suggested by limited pre-existing human data). It was anticipated that both XLI and IV groups would display high levels of adverse mood symptoms as in previous work in these populations. Finally, it was hypothesised that there would be a relationship between mood symptoms and memory-related measures overall and that this relationship may differ by group.

4.1.7 Summary

- Based on existing animal work, it appears that steroid sulfatase (STS) plays a crucial role in cognition and neurodegeneration.

- There is a current lack of work in man investigating the effects of STS loss. Individuals with XLI who suffer complete loss of STS are ideal candidates for comparison.
- To assess memory performance and executive functions, this study employed a series of objective and subjective online measures in individuals with XLI or IV as a control group.

4.2 METHODS

4.2.1 Ethics

This study was given ethical approval by the Cardiff University School of Psychology Ethics Committee (Phase 1: EC.22.04.26.6565, Phase 2: EC.22.08.09.6610).

4.2.2 Sampling and Recruitment

To recruit for Phase 1 (and subsequently Phase 2) of this study, convenience sampling was used to recruit adults (>18 years) with a self-reported clinical diagnosis of XLI (n=41 males) or IV (n=30 males, n=68 females), or those with a self-reported confirmed carrier status for an XLI-associated genetic variant. (n=79 females). Participants were recruited globally, via past contact/participation in previous research, social media patient support groups, charities, and other social media sites (e.g., Twitter), and directed to the Phase 1 survey URL via which they could respond anonymously. Once participants had completed Phase 1, they were given the opportunity to provide their contact details if they were interested in taking part in the next phase of this study. Using this information, interested participants were recruited for Phase 2 of this study via email.

4.2.3 Design

This study consisted of two main phases. In the first phase, a custom-designed basic word/picture recall test was created in Qualtrics, accompanied by three brief questionnaires about participants' self-rated memory abilities. The second phase of this study, using the same participant group, consisted of a series of more specific and well-validated memory tests, administered online via the platform 'TestMyBrain'.

4.2.4 Qualtrics Test Structure (Phase 1)

The initial survey was created using Qualtrics software and accessed by participants via an anonymous URL or QR code. After completing the consent form, participants were immediately instructed that they were about to be shown a list of 15 neutral words (e.g. *moon, colour, coffee*) (Appendix 4.3) for a period of 30 seconds, followed by a selection of 20 randomly selected neutral pictures (e.g., *aeroplane, candle, guitar*) (Appendix 4.4) for 45 seconds and these must be retained without the use of any memory aids.

To avoid potential negative effects of boredom on performance [441] and avoid a floor effect [442], a short list of phonologically short neutral words was used and a small set of neutral pictures in the recall tasks. All items were selected from a list of culturally neutral words from the Rey Auditory Verbal Learning Test (RAVLT), typically used as a neuropsychological assessment to evaluate verbal memory in adults [433, 434]. To appropriately adapt this test for online application, a selection of words was randomly assigned to either the word condition (15 items) or picture condition (20 items). Using these words, simple stock images were selected. Both word and picture lists comprised of 'neutral' items, to avoid biased differences in recall ability based on the emotional status of the word [443], e.g., negative words such as 'coffin' [444], or images with potentially positive or negative connotations such as 'baby' [445, 446]. The potential cultural significance of some items was also accounted for in both the word and picture lists to avoid social bias [447, 448].

Following this, several demographic measures pertinent to memory and mood were collected, including participant age, country of residence (UK/USA, elsewhere), assigned sex at birth (male/female), and highest level of education (up to high school, greater than high school). Participants were then asked whether they had a parent, grandparent, or sibling who had been diagnosed with a condition affecting memory (and, if so, to specify which relative), followed by self-rated lifetime severity of skin redness and skin scaling (if relevant) (based upon Congenital Ichthyoses Severity Index [347], scale range 2-8). In the next section of the survey, participants completed the Kessler Psychological Distress Scale (K10), a 10-item five-point response questionnaire to assess recent depression/anxiety-related traits (possible

score range 10-50, with a score of ≥20 being consistent with significant psychological distress) [449]. Following this, participants completed the Multifactorial Memory Questionnaire (MMQ), comprised of three sections to assess a) recent satisfaction with memory functioning (18 items each scored 0-4, higher scores indicating greater satisfaction), b) perceived memory abilities (20 items each scored 0-4, higher scores indicating better subjective memory ability), and c) the use of strategies to aid memory (19 items, each scored 0-4 with higher scores indicating greater memory aid usage) [438]. In the final stage of this survey, participants were presented with a list of 30 words and asked to select which of these they had been presented with at the start of the survey (maximum 15 choices permitted), followed by the same task based on a montage of 40 pictures (maximum 20 choices permitted). To generate a 'word-picture-recall index', the number of correctly identified words was multiplied by four, and the number of correctly identified pictures was multiplied by three, with possible overall index scores ranging from 0-120. The duration of survey completion was recorded (excluding participants where this was >5400s indicating failure to end the survey) to control for the length of time between the stimulus presentation and recall phases.

4.2.5 TMB Test Structure (Phase 2)

Participants from Phase 1 who indicated that they were interested in Phase 2 of this study were asked via email to complete a short screening questionnaire, and once completed, participants were sent a personalised link to the test battery.

To assess individual components of memory and cognitive functioning, a series of six neuropsychological tests from the 'TestMyBrain' online battery were chosen (https://testmybrain.org/). These consisted of the following: Forward Digit Span, Backward Digit Span, Digit Symbol Matching, Verbal Paired Associates, and Visual Paired Associates, and tested skills including Auditory Span, Processing Speed, Short Term Memory, Episodic Memory, and Attention. Scoring for each of these tests was as follows:

1. TMB Forward Digit Span: higher score = greater digit span recalled
2. TMB Backward Digit Span: higher score = greater digit span recalled

3. TMB Digit Symbol Matching: higher score = more symbols matched
4. TMB Verbal Paired Associates: higher score = more pairs recalled
5. TMB Visual Paired Associates: higher score = more pairs recalled

To create a single measure of memory, scores from each of these tests were combined for use in subsequent analyses. There was no upper or lower limit for these scores as it was dependent on participant performance.

If participants were interested in the results of these tests, they were encouraged to contact a member of the research team for a summary of their outcomes with comparisons to normative scores provided by TMB. All participants who completed the TMB battery had the opportunity to enter a random prize draw to win a £50/$60 online shopping voucher.

4.2.6 Data Analysis

All data from Qualtrics was exported to Excel after data collection had finished, and then uploaded to SPSS V.28 for subsequent analysis. Individual results from the TMB Test Battery were downloaded from the online platform as an Excel file, and subsequently merged into a centralised dataset.

Decision making details for the type of statistical tests used are described in Chapter 2.3. Following a chi-squared or Fishers Exact Test for categorical data across groups, post hoc analyses were performed using adjusted residuals with Bonferroni correction. Continuous data were analysed by ANOVA/ANCOVA with factors of GROUP (XLI, IV) and SEX (male or female) and covariates of age, K10 score and/or highest level of education. Significant effects for an ANOVA were followed up with Tukey's Least Significant Difference (LSD) and for ANCOVA, followed up with simple contrasts. Correlations were performed using one or two-tailed Pearson's test or Spearman's test depending upon normality of the data, as determined by Shapiro-Wilk test, and by directionality of the predicted effect.

Summary data are reported as percentages, mean±SD (normally distributed data) or median with 95% CI (non-normally distributed data). The sample size was sufficient

to reliably detect a weak-moderately-sized effect (f>0.20) of GROUP (XLI, IV) at 80% power with α=0.05.

4.3 RESULTS

4.3.1 Demographic and Clinical Variables

Specific details about the demographic and relevant clinical variables for each group are available in Appendix 4.1. The mean ages when comparing across the four groups were very similar (42-49 years), although individuals in the IV group were significantly older than the XLI group (p=0.007). The majority of participants self-identified as 'White British' (76-90%) and resided in the UK or US (>70%). Across both XLI and IV, a greater number of females reported an education level greater than high school, although post hoc analysis revealed no significant differences from the null distribution for either condition. There was a significant difference effect of group (4) on the frequency of self-reported family history of memory disorders, with males with XLI reporting the highest proportion of affected relatives (55%) (p=0.028) (Figure 15) Male participants in the XLI and IV groups and female participants with IV did not differ in terms of self-reported skin severity (moderate), whilst female carriers of XLI-associated genetic variants exhibited no-mild skin phenotypes as expected.

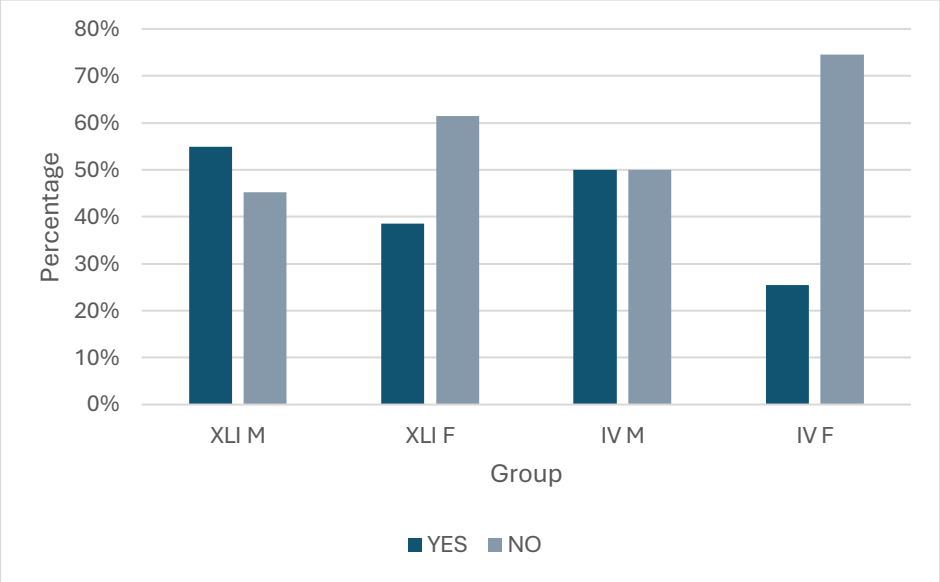


Figure 15: Family history across each XLI and IV group

4.3.2 Recent mood symptoms (K10)

After covarying for age, K10 scores did not differ significantly by GROUP ($F[1,210]=1.70$, $p=0.194$), nor by SEX ($F[1,210]=0.449$, $p=0.504$), and there was no GROUP x SEX interaction ($F[1,210]=3.61$, $p=0.059$) (Appendix 4.2). Across all four groups, mean K10 scores indicated mild-moderate psychological distress (>20) (Figure 16).

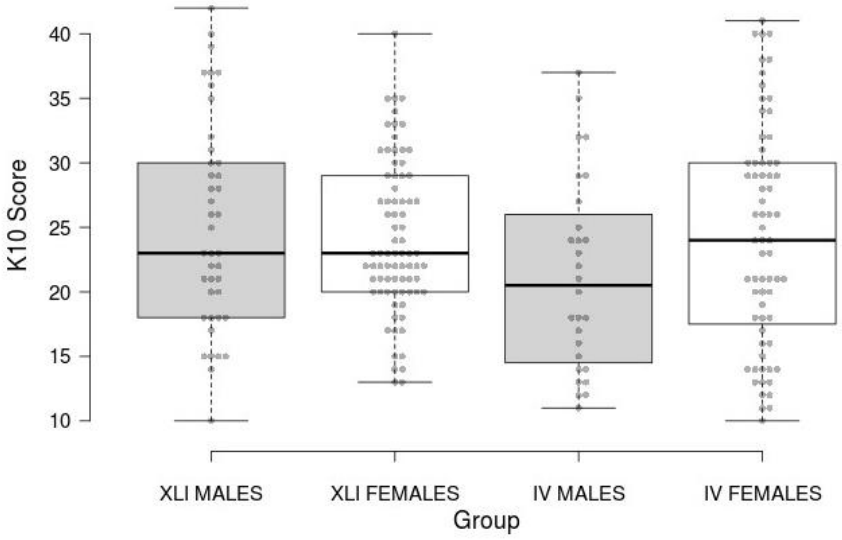


Figure 16: K10 scores across each XLI and IV group

There was a weak positive correlation across the four groups between CISI score and K10 scores ($r_s[208]=0.12$, one-tailed $p=0.045$), which was primarily determined by an association in female XLI carriers ($r_s[72]=0.25$, $p=0.016$) (all other within-group correlations $r_s \leq 0.1$, $p>0.2$).

There was a weak negative significant partial correlation between K10 scores and MMQ2 scores, whilst controlling for age, in both the XLI group ($r(113)=-0.223$, $p=0.016$), and a moderate negative correlation in the IV group ($r(91)=-0.440$, $p<0.001$).

4.3.3 Self-reported memory function (MMQ)

After covarying for age, there was no significant effect of group ($F[1,212]=2.35$, $p=0.127$) or sex ($F[1,212]=0.062$, $p=0.803$) on 'satisfaction with memory' (MMQ1), nor any group x sex interaction ($F[1,212]=0.316$, $p=0.574$) (Appendix 4.2).

Covarying for age and K10 score (recent mood), or for age, K10 score, and the highest level of education combined, offered a very similar pattern of findings.

With regards to 'perceived memory ability' (MMQ2), after covarying for age, there was a significant effect of group ($F[1,209]=4.442$, $p=0.036$), but no effect of sex ($F[1,209]=0.510$, $p=0.476$), nor any group x sex interaction ($F[1,209]=0.512$, $p=0.475$) (Appendix 4.2). Post hoc analyses revealed that scores in the IV group were significantly higher than the XLI group, indicating a better subjective impression of memory capabilities. However, after covarying for age and K10 scores, there was no significant difference in MMQ2 scores between the two groups ($p=0.086$); additional adjustment for highest education level did not change the pattern in results ($p=0.141$).

Covariation for age alone on the 'use of strategies to aid memory' measure (MMQ3), revealed no significant effect of group ($F[1,200]=2.762$, $p=0.098$), nor any effect of sex ($F[1,200]=1.892$, $p=0.171$), nor any group x sex interaction ($F[1,200]=0.071$, $p=0.790$) (Appendix 4.2). Covarying for age and K10 score, or for three measures (age, K10 score, and highest level of education), produced an identical null pattern of findings.

4.3.4 Word-picture recall index

Across the whole sample, there was a moderate positive correlation between word recall and picture recall scores ($r_s[198]=0.37$, one-tailed $p<0.001$). When comparing composite 'word-picture recall' scores, after covarying for age, there was a significant effect of group ($F[1,195]=16.558$, $p<0.001$), and a significant interaction between group x sex ($F[1,195]=10.384$, $p=0.001$), but no significant effect of sex alone ($F[1,195]=3.109$, $p=0.079$) (Appendix 4.2). Post hoc analyses revealed that scores in the IV group were significantly higher than in the XLI group. LSD post hoc test results revealed that males in the XLI group had significantly lower 'word-picture recall' scores compared to males in the IV group, females in the IV group, and females in the XLI group. Covarying for age and K10 combined, produced identical results, but when covarying for three measures (age, K10 score, and highest level of

education), there was a significant effect of SEX not found previously (F[1,195]=3.909, p=0.049), with females performing better than males.

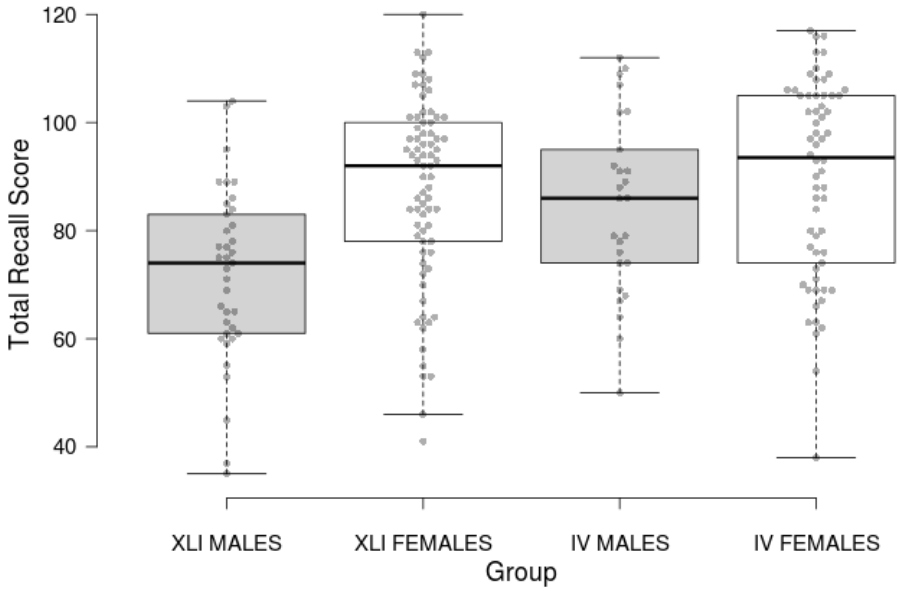


Figure 17: Total recall scores across each XLI and IV group

Across the whole sample, there was a weak positive correlation between composite 'word-picture recall score' and 'perceived memory ability' score (MMQ2) (r_s[197]=0.234, one-tailed p<0.001).

Word-picture recall scores for males and females in the XLI group with a family history of a memory problem did not differ from those without a family history (males t(27)=-1.105, p=0.279); females t(62)=-0.631, p=0.530), nor in the IV group (males t(21)=-0.293, p=0.772; females t(51)=-0.844, p=0.402).

Complete sets of word-picture recall scores and TestMyBrain (TMB) cognitive scores were available for 10 individuals (two males with XLI, three female carriers of XLI-associated variants, two males with IV, and three females with IV). Despite low power, a moderately significant positive correlation between word-picture recall score and score on the TMB Visual Paired Associates task was found (r_s[8]=0.56, one-tailed p=0.046); there were no other significant correlations (r_s<0.33, p>0.18). These data indicate that the objective memory ability measures of 'word-picture recall' and TMB tests, and the self-reported MMQ measure, are consistent with each other, and thus these cognitive skills may be functionally related; these relationships

appeared particularly consistent within the larger XLI group, potentially due to higher power.

4.4 DISCUSSION

4.4.1 Summary

Using an online survey approach, this study compared objective memory (recall) measures and subjective self-reported memory abilities between males with XLI (and female carriers) and individuals with IV (males and females); in addition, it investigated whether any effects on memory were likely to be related to established effects on mood within these groups.

4.4.2 Word-picture recall

The results of the 'word-picture recall' test in this study, indicate that genetic variants associated with XLI are associated with lower memory performance, with a particularly notable effect in males, compared to female carriers of XLI-associated variants and males and females with IV. This effect appeared to be somewhat independent of effects on mood symptoms. A more severe effect in hemizygous males (with complete Xp22.31 gene loss) than in heterozygous females (with loss of only one copy of Xp22.31 genes) is perhaps unsurprising. These findings contrast with previous animal model work suggesting a memory-enhancing/neuroprotective effect of STS deficiency [415-417]. Such differences in findings between humans and rodents may be due to a) species differences in cognitive processes, b) genetic variants in man result in complete STS loss whereas STS inhibition only results in partial deficiency, c) compounds used as STS inhibitors can have off-target and estrogenic effects [450], d) XLI-associated genetic variants may delete adjacent brain-expressed genes, in addition to STS. Crucially, these findings are consistent with previous work in the UK Biobank sample, in which carriers of deletions around the STS gene performed worse compared to non-affected individuals on a number of memory and executive functioning tests [187]. More specifically, carrier individuals (n=398) exhibited significantly poorer performance on the 'Pairs Matching' memory test than non-carriers (n=97,141) [187]. The consistency of these results suggests a

robust and generalizable effect beyond this sample, based on two differentially recruited genotyped, and cognitively tested samples. It should also be noted that memory deficits in this group could be secondary to attentional impairments during the original encoding of the stimuli. Our previous work shows significantly higher rates of ADHD diagnoses and related traits compared to general population controls [451], and thus inattention may have played a role (although this link requires closer exploration).

Outcomes from the 'word-picture recall' test demonstrated an overall effect of sex on memory performance, with males performing significantly worse in both groups, after covarying for age, mood symptoms, and highest level of education (combined). Here, sex-based differences in memory performance in this study are unlikely due to adverse mood symptoms, as these did not differ by group or sex, and recall scores were largely unchanged after controlling for K10 scores. This effect of sex is consistent with recent findings which suggest a simple negative relationship between memory performance and male sex, as well as older age, and lower levels of education [452, 453]. Positive effects of female sex on recall may be due to sex-biased factors in memory and executive functioning; research suggests a potential beneficial effect of oestrogen on cortical areas associated with memory function [454], including the hippocampus [455] and temporal lobe [456]. Thus females may produce better recall abilities for words and pictures compared to males [457, 458], including for neutral stimuli [459]. However, females have not shown better memory abilities in all human studies [460, 461], and thus alternative explanations such as neuroanatomical differences should be considered. Initial work suggested that relative to brain size, females typically may have increased hippocampal [462] and prefrontal cortex volume [463]; however more recent work reveals some inconsistencies in these findings [464], thus suggesting cortical volumes in these areas may not necessarily be sexually dimorphic [465, 466]. Thus, other explanations for this sex difference in recall include a potential lower frequency of distraction in females compared to males [467], particularly during acquisition phase [468].

There was no difference in recall between individuals with/without a family history of a memory problem in either group, thus suggesting that the nature of the Xp22.31

deletion as a hereditary genetic variant cannot explain memory deficits in individuals with XLI compared to IV. Furthermore, of the 16 participants who reported a first or second-degree relative as being affected by a memory disorder, there is no clear evidence for an X-linked genetic effect; a greater number of fathers > mothers were reported to be affected (n=2 vs. n=1), equal numbers of grandfathers and grandmothers were affected (n=6 per group) and similar numbers of brothers and sisters were affected (n=1 and n=0).

It is important to consider the possible causal mechanism for negative effect of Xp22.31 deletion on memory, which appears to act largely independently of mood symptoms. An XLI deletion of typical size covers not only the *STS* gene, but also *PUDP, VCX,* and *PNPLA4* genes, and *MIR4767* microRNA [187]. Some of these may be likely ruled out from impacting on cognition; *VCX* expression is testis specific and *MIR4767* expression in the brain is very low (https://www.gtexportal.org/home/). Conversely, the other three proteins (*PUDP*, *STS,* and *PNPLA4*) are all expressed in the brain at low-moderate levels and thus it seems likely that deficiency of one or more of these is the most plausible biological mechanism in impaired mood functioning. However, if this was the case then it would be expected that individuals with a large deletion to experience both impaired mood functioning and impaired memory and by our estimates, this does not seem to be the case. Thus, future studies investigating the effects of similar deletions in this area of the genome, or null alleles of these individual genes, on cognition in both human and animal subjects may help to further define causal processes.

Other potential causal mechanisms in explaining poorer recall may include memory components of early onset dementia/Alzheimer's Disease which is often largely genetically determined [469-471]. However, in this study participants were not asked to detail any current or previous memory problems and thus it could be suggested that poor memory performance is predominantly attributed to the genetic variants resulting in the constitutive absence of functional STS protein. Another potential contributory causal factor is disrupted sleep, which often occurs as a result of night-time itching or pain associated with the skin for individuals with ichthyosis [278, 472]. Sleep disturbances resulting from skin discomfort were rated one of the most

impactful contributory factors in adverse mood symptoms in our previous work [419]; however, an effect in both XLI and IV individuals would be expected due to the nature of the skin conditions, and thus the explanatory power of sleep disturbance on memory in XLI is unlikely.

4.4.3 Multifactorial Memory Questionnaire (MMQ)

Individuals in the XLI group both objectively and subjectively scored worse for the recall and MMQ2 measures respectively. Individuals in the XLI group reported a poorer impression of their memory abilities compared to IV individuals when assessed using the MMQ2. This suggests that XLI participants aware of deficits in their memory may also perform worse when tested using objective recall measures. However, after introducing adverse mood symptoms (K10) as a covariate, this effect was attenuated, thus suggesting that mood may mediate perceived memory abilities to some extent, but not objective recall scores as above.

However, individuals in the XLI group did not differ in self-reported satisfaction with memory abilities (MMQ1), or use of memory aids (MMQ3). These ratings also did not differ by sex, suggesting that contentment and use of memory aids are similar across males vs. females, as well as in XLI individuals vs. individuals in the IV group. Internal consistency of the MMQ is consistently rated highly [439] and thus this data suggested that although individuals in the XLI group perceive their memory abilities to be poorer than those in the IV groups, they are not significantly less satisfied with their memory, and not do not tend to use more memory aids.

4.4.4 Strengths and Limitations

This work provides a novel exploration of the effects of genetic variants resulting in complete STS loss in humans on memory functioning; it is believed that this study is one of the first to investigate these effects and has different attributes to a conceptually similar study in UKBB reported previously.

Due to the nature of this study as an investigation into memory, it is possible that XLI and IV individuals with memory concerns or existing deficits may have been more likely to respond to the study advert. This may partially explain the larger

effect sizes found compared to the UK Biobank study [187]. However, participants were not asked about any existing or previous memory problems and thus, although this is hard to establish, a general moderate effect appears likely. To understand more about the magnitude of the negative effects on recall, this data was later compared in XLI and IV samples to an unaffected general population sample. Inclusion of a general population sample removed any skin-related general effects on results e.g., sleep disturbances due to skin irritation [472], and wider effects of skin-related inflammation on mood/cognitive functioning [473, 474]. Key findings from this work indicated a significant effect of group on 'word-picture recall' scores, by which both XLI groups performed significantly worse than both general population groups ($p<0.001$) [451]. These results also revealed significantly worse self-rated memory abilities, memory satisfaction mood symptoms in the XLI and IV groups compared to the general population samples, as well as greater use of memory aids. This comparison corroborates that Xp22.31 genetic variants are associated with lower memory performance, likely independent of mood factors. This data also suggests that IV may be associated with self-perceived memory issues, but not necessarily with true memory deficits.

The novel creation of the word and picture recall tests used neutral stimuli originating from the Rey Auditory Verbal Learning Test (RAVLT), which is more typically used to assess verbal memory in adults [433, 434]. Due to the nature of the online survey methods used to conduct this study, a relatively quick way was required to objectively measure recall across participants from varying education levels, demographics, and familiarity with cognitive testing. Thus, although the novel memory test is not well validated, this appeared to be the most effective and efficient option. The significant correlations between objective and subjective memory outcomes (word recall, picture recall, perceived memory abilities, and a memory-based task from TMB) indicate that this new measure genuinely indexed relevant aspects of memory. The concordance across memory-related measures provides evidence that participants were self-reporting any memory issues accurately.

Due to the unmonitored nature of the word and picture recall tests at the end of the survey, there was potential for participants to use memory aids or record the items to improve their performance on these tests. To minimise the likelihood of these aids, it was stipulated that participants were not to use any assistance or tools to aid their performance, before starting the recall measures. Most participants scored well below the maximum possible scores, suggesting that they were unlikely to be making use of such aids.

To provide a more in-depth assessment of memory and cognitive functioning, TestMyBrain (TMB) was used as a second-stage assessment. Participants were asked to complete a short online screening questionnaire, after which they would receive an individualised link to the test battery. However, only 53 people completed their screening stage, and only 10 individuals finished the complete test battery. To encourage eligible individuals to take part, a financial incentive was offered in the form of a shopping voucher, however, there was still a low uptake for this stage of the study. To improve this stage, the engagement process could have been simplified, as well as utilising a more user-friendly interface.

4.4.5 Conclusion

This study used online survey methods to examine objective and subjective memory abilities in individuals with XLI compared to a control group of individuals with a clinical diagnosis of IV. Genetic deletions at Xp22.31 are associated with impaired objective memory performance, and worse perceived memory abilities, which appear to be largely unrelated to mood factors, however this requires replication to establish the reliability of results. Future studies in deletion carriers may investigate biological and cognitive causal processes contributing to these negative effects on memory.

Chapter 5: CARDIAC PHENOTYPES AND ATTITUDES TOWARDS CARDIAC SCREENING IN X-LINKED ICHTHYOSIS (XLI)

**Note: some of the material included in this Chapter and relevant appendices relates to the following published work, for which I am listed as the first author:*

Wren G, Baker E, Underwood J, Humby T, Thompson A, Kirov G, Escott-Price V, Davies W. Characterising heart rhythm abnormalities associated with Xp22. 31 deletion. Journal of Medical Genetics. 2023 Jul 1;60(7):636-43.

Wren G, Davies W. Sex-linked genetic mechanisms and atrial fibrillation risk. European Journal of Medical Genetics. 2022 Apr 1;65(4):104459.

5.1 INTRODUCTION

Previous work in adult males from the UK Biobank carrying the Xp22.31 deletion revealed a substantially increased risk of being diagnosed with the cardiac arrhythmia atrial fibrillation/flutter (AF) compared to controls without the deletion. This new finding could explain up to 1 in 300 cases of AF in middle-aged men [187]. Effective management and early diagnosis of AF are crucial in minimizing downstream effects such as thrombosis, embolism, and stroke, as well as dementia [475]. It is possible that Xp22.31 deletion increases the risk for heart rhythm abnormalities (HRA) more generally. Further exploration of how HRA present in both adult XLI males and female carriers to help identify high-risk individuals is essential, in addition to more in-depth characterization and understanding of patients' perceptions of the condition. This study aimed to address these gaps in current research, through the use of online survey methodology to examine the characteristics and risk factors/comorbidities associated with Xp22.31 deletion associated HRA and to explore attitudes towards heart screening in deletion carriers.

5.1.1 Atrial Fibrillation

What is AF?

Atrial fibrillation (AF) is the most common supraventricular tachycardia and is characterised by chaotic twitching, or quivering, of the atrial myocardium [476]. Occurring in an estimated 2.5% of adults worldwide [477], AF is typically diagnosed through a combination of electro- and echocardiograms, chest x-rays, and blood tests [476]. The condition is commonly associated with the sensation of an irregular or very fast heartbeat, even when resting, often accompanied by chest pain, breathlessness, fatigue, and feelings of dizziness or faintness [478]. In some cases, AF can remain asymptomatic and only discovered during routine medical examinations [478]. The severity of AF can vary from a single, rapidly resolving incident, to recurrent episodes resolving quickly (within seven days, 'paroxysmal AF'), resolving more slowly ('persistent AF'), or not resolving at all ('permanent AF') [234]. To effectively manage AF, treatment methods aim to regulate heart rate and rhythm, to limit possible future consequences. These treatments include medication such as beta-blockers, anti-arrhythmic drugs, anti-coagulants, breathing exercises to manage acute episodes, cardioversion, and surgical techniques such as ablation or pacemaker implantation [479]. Lifestyle management is also advised, such as reduced smoking and limiting alcohol consumption [478]

General risk factors in AF

Lifetime risk for developing AF typically increases with age, with an estimated 5% of individuals >65 years and 10% of individuals >80 years, suffering from AF [478, 480]. Key risk factors include heart tissue pathology (e.g., arising due to hypertension, valvular or congenital heart disease, pericarditis, cardiomyopathy, and diabetes), and the condition may be secondary to pulmonary conditions such as asthma [481]. Other modifiable risk factors in developing AF and subsequent cardiac complications include high BMI, smoking, and psychological stress [478, 482, 483]. More specifically, recent case reports in adult males with XLI have identified other comorbid complications including paroxysmal supraventricular tachycardia with anaemia [484], in

addition to AF with kidney disease, type 2 diabetes mellitus, hypertension, and dyslipidaemia [485].

Effects of AF on physical health and QoL

Downstream consequences of AF include stroke, heart failure, and cognitive decline/dementia [234]. Most notably, women typically present with a larger risk of AF-associated adverse outcomes, including mortality and stroke due to mechanisms related to female-specific factors such as pregnancy and menopause [486]. In recent years, awareness of these key diagnostic and risk markers has greatly improved, and thus diagnosis and optimal treatment strategies are more advanced [482, 487]. However, precision medicine approaches are crucial to identify those individuals at a higher risk of AF and associated complications, and thus target these groups for preventative therapeutic management [482].

The impact of persistent or permanent AF on daily functioning is clear; QoL is significantly worse in adults with an AF diagnosis compared to general population controls [488], and compared to individuals with hypertension [489]. Worse QoL was also correlated with symptoms of depression and anxiety in adults with AF, compared to adults with hypertension [489]. Key factors, most notably female sex, more severe symptoms, and increasing age, also frequently resulted in poorer QoL [489] [490] [491]. Use of rate and/or rhythm control medication strategies often resulted in notable improvements in symptoms, and QoL [488] [490]. Hence, there is a need to identify and treat individuals with AF as early as possible to mitigate the effects on QoL.

5.1.2 Candidate genes for increased AF risk

The genetic profile of AF originated from linkage studies, examining familial risk. Initial work suggests that mutations at *KCNQ1* (11p15.5) are likely to initiate and maintain AF, through the reduction of action potential duration and effective refractory period in atrial myocytes [492]. Later linkage studies also reported gain-of-function mutations at the genes *TBX5* [493] and *NPPA* [494], *MYL4* (early-onset AF) [495], and loss of function variant at *KCN5A* [496]. Genome-wide association studies (GWAS), allowing for a wider analysis of AF in the general population, initially identified two sequence variants near the *PITX2* gene in strong association with AF [497]. Further

work corroborated this link, based on structural and biochemical cardiac abnormalities in both rodents [498, 499] and humans [500, 501] with reduced *PITX2* expression (although the exact mechanisms explaining the involvement of *PITX2* in AF are not fully understood [502]). Other large GWASs have identified other loci, including *NEURL* [503, 504], *ZFHX3* [503, 505] and *KCNN3* [503, 505], but *PITX2* remains most strongly associated with AF [502 505].

Recent epidemiological work has identified that male sex is also a major risk factor in the development of AF (rates 1.2–2.7 times higher in males vs. females) [506-509], although females typically present with more severe symptoms and worse QoL [483, 510]. To investigate possible mechanisms contributing to this bias, we conducted a review of sex-linked genetic mechanisms and atrial fibrillation risk [511]. In this review, we consider four potential sex-linked genetic mechanisms that may influence sex-biased phenotypes related to AF; X-linked gene dosage, X-linked genomic imprinting, sex-biased autosomal gene expression, and male-limited Y-linked gene expression.

For the attention of this Chapter, it is important to focus specifically on the dosage of genes that escape X-inactivation, which largely differ by sex when expressed in the heart. In comparison to typical sex chromosomes, both under- and over-dosage of one or more X-escapees may predispose individuals to risk factors contributing to, or the occurrence of, AF [512]. Crucially, recent work has identified that genes associated with AF are completely or partially subject to X-inactivation and can explain a large proportion of X-linked heritability in adult heart tissue [512-514]. The Xp22.31 region deleted in XLI typically escapes X-inactivation, and thus gene(s) within it may contribute towards sex differences in AF risk. Our work examining common genetic variants across the deleted region in idiopathic cases of AF from UK Biobank only showed enrichment for risk variants within STS, implicating this gene specifically in AF risk [515]. STS deficiency may confer risk via several potential mechanisms including established links between AF and circulating DHEAS levels [233, 516], reduced triadin expression [517, 518] and/or fibrosis [519], but this relationship requires further exploration.

However, beyond this initial UKBB work, there is little to no further research exploring the implications of total loss of STS on AF risk in man. Furthermore, there is no existing work to explore other contributory components in AF risk relating to STS loss such as age and sex, nor precipitating factors or common comorbid conditions in this group. As such, it is difficult to accurately characterise and predict AF in individuals with complete STS loss.

5.1.3 Purpose and Aims

Initial work suggests that males carrying Xp22.31 deletions incur a significantly increased risk of AF, compared to non-carrier and duplication control males [187]. However, the characteristics and risk factors associated with heart rhythm arrhythmias (HRAs) such as AF, remain unclear. Thus, the purpose of the present study was two-fold. Firstly, to characterise HRA-related phenotypes and comorbidities in men, male children with XLI (parental reports), and female carriers, using an established online survey methodology. These initial analyses aimed to i) investigate the onset, treatment, and severity of any cardiac abnormalities ii) identify risk factors that commonly precipitate arrhythmic episodes iii) identify common comorbid disorders associated with HRAs. The second aspect of this study aimed to explore attitudes towards screening for cardiac abnormalities in individuals with a confirmed Xp22.31 deletion.

More broadly, this study aimed to improve understanding of how HRAs may develop, how they may be best addressed clinically, and to improve the prediction of AF in individuals with an Xp22.31 deletion. To do this, an online survey design was adopted as a timely and effective way to recruit an international sample for this rare disease group, no input or time from clinicians required.

5.1.4 Summary

- Atrial fibrillation is a common type of cardiac arrhythmia, associated with several downstream consequences including stroke, dementia/cognitive decline, and heart failure.

- Various candidate genes contributing to AF risk have been identified, most notably *STS* in the Xp22.31 region under study, which escapes X-inactivation, thus contributing to sex differences in AF risk.
- This study aims to better understand and characterise heart rhythm abnormalities such as AF in individuals with a deletion at Xp22.31, as well as attitudes towards preventative screening measures, using an established online survey methodology.

5.2 METHODS

5.2.1 Design

An online survey was conducted via Qualtrics, using a series of questions to explore participants' history of HRAs and associated factors. This work was largely quantitative, although there were 'free text' comment boxes for participants to elaborate on certain answers e.g. type of medication used.

5.2.2 Sampling and Recruitment

To recruit participants convenience sampling was used to establish recruitment channels including past contact/participation in previous research, social media patient support groups, charities, and other social media sites (e.g., Twitter). The sample was comprised of adult (>18 years) males with a confirmed clinical diagnosis of XLI, adult female carriers of an XLI-associated genetic variant, and parents reporting on behalf of their male children with a confirmed clinical diagnosis of XLI (0-18 years). The survey was accessed via a URL or QR code, and anonymous responses were returned to the research team during the period 2nd September to 22nd December 2021.

5.2.3 Survey Structure

Participants initially provided the following basic demographic information about themselves and/or their child: age, country of residence, ethnic group, and assigned sex at birth, followed by information based on their skin diagnosis, or how their carrier status was confirmed. Participants then rated their skin condition on average

throughout their life, using sample clinical images from the Congenital Ichthyosis Severity Index (CISI) (range 2-8) [347]. Participants then provided information on any current/previous medical or psychiatric conditions common in individuals with STS loss (including neurodevelopmental/mood disorders, testicular maldescent, and prolonged labour in females), as well as any family history of heart or cardiovascular issues (see Appendix 5.2).

If participants did not self-report a history of HRAs, they continued to the final section of the survey (vignette). If participants self-reported an HRA (see Appendix 5.1), they continued to a series of questions to investigate the specific characteristics of their condition/s. These included age of identification, any known cause/s, previous/ongoing treatments, perceived treatment success, any known risk factors, specific onset periods, diagnostic tests, and management strategies if applicable. Participants who stated that they had a diagnosis of a heart murmur, completed a different section using questions more specific and applicable to this condition (cause/treatment/type).

Following these questions, all participants (both with and without HRAs) were presented with the following short vignette (see below) which outlined the risk of AF for individuals with an Xp22.31 deletion, potential downstream consequences, and a brief description of potential screening procedures for early identification of AF. Based on this vignette, participants were asked to rate a series of statements from strongly agree to strongly disagree on a 10- or 5-point scale (see Appendix 5.3 for list of statements).

Vignette:

Atrial fibrillation/flutter (AF) is a medical condition characterised by an irregularly irregular heart rhythm resulting from disorganised signals to the atria (upper chambers of the heart). The latest evidence suggests that in middle-aged males with XLI, the risk of AF is approximately 4 times greater than in males without XLI (affecting around 10% of males with XLI compared to 2.5% of unaffected males). The scientific literature also describes rare cases of abnormal heart rhythm in young boys with XLI. Individuals with AF are at increased risk of blood clots, and associated

disorders including stroke (5x more likely), dementia/cognitive decline (1.5x more likely) and heart failure (3.5x more likely). Stroke, dementia and heart failure can be associated with long-term impairments in mobility and cognitive function, and increased care needs. If identified early, AF can be effectively treated via rate control medication (to lower the heart rate), rhythm control medication (to restore a regular heart rhythm), and/or anti-coagulation (blood clot/stroke prevention) medication, both on a short- and long-term basis.

Individuals may be monitored for AF via an electrocardiogram (ECG) (wires attached to the chest, routinely undertaken at local doctors), blood pressure monitoring (using a cuff placed around the arm) and cardiovascular examinations (examining any external physical indicators e.g. skin discolouration, eyes) via hospital appointments from early life, and appropriate interventions administered.

5.2.4 Data Analysis

All data from Qualtrics was exported to Excel after data collection had finished, and then uploaded to SPSS V.28 for subsequent analysis.

Decision making details for the type of statistical tests used are described in Chapter 2.3. For each group, participants were split by 'HRA' and 'non-HRA' groups depending on the medical conditions reported. These two groups were subsequently compared across demographic measures and medical phenotypes to identify factors co- segregating with heart arrhythmias within these populations. Continuous variables were compared between groups with unpaired t- test or Mann- Whitney U test depending on normality of the data, and categorical data were analysed by X^2 or Fisher's exact test; ORs are presented as a measure of effect size. Where multiple medical phenotypes were assessed, Benjamini- Hochberg False Discovery Rate correction was applied.

Where participants had provided written responses in the free-text boxes provided e.g., description of medication or risk factor, these were collated, and similar responses were grouped per question for descriptive results.

Participants' responses to the vignette-related statement were scored from 'strongly disagree' (0) to 'strongly agree' (5 or 10 depending on the rating scale). Means ± SD for each statement from each group were calculated: the higher the score, the more participants agreed with the statement.

5.3 RESULTS

5.3.1 Data Preparation

The complete data set was prepared for analysis, by removing the responses in the following categories: a) did not agree to consent form and thus no completion of survey or b) completion of consent form but no further response. Where participants had not completed complete sections of the survey, or individual questions with a specific measure, their response was omitted from relevant analyses.

5.3.2 Participants

A total of 191 participants were recruited in this study; 43 males with XLI, 79 female carriers of XLI-associated genetic variants, and 69 male children with XLI (males reporting on behalf of their children). These groups were split based on whether participants did or did not report a clinical diagnosis of one of the following HRAs: Atrial Fibrillation, Atrial Flutter, Supraventricular Tachycardia, Ventricular Tachycardia, Bradycardia, Tachycardia. A total of 15 males (35%), 20 females (28%), and 15 male children (28%) carrying Xp22.31 deletions self-reported, or were reported by parents, to have a clinical diagnosis of a heart rhythm abnormality (HRA) (Figure 18).

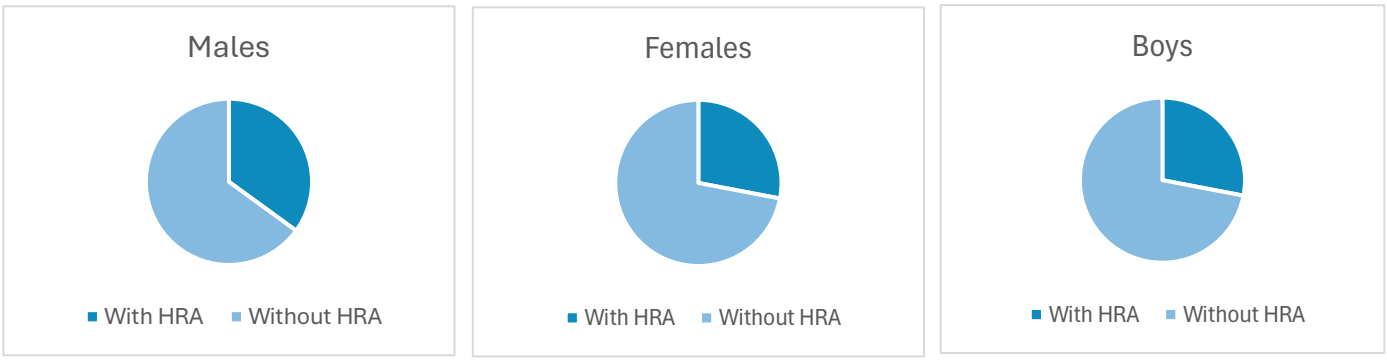


Figure 18: *Percentage of individuals with XLI (or female carriers) reporting HRA*

Adult female carriers with HRA and without HRA were closely matched for age and were significantly younger than both groups of adult males (with/without HRA) who were also closely matched for age. Both groups of male children were also closely matched in age. Across the three groups, individuals affected by HRAs and those unaffected were also matched closely for country of residence and ethnicity (Appendix 5.4).

Self-reported skin severity using the CISI scoring system was considered 'moderate' across all groups (44-59% maximum score). There was no consistent pattern of association between severity of the skin condition in XLI and HRA (Figure 19). In adult males, individuals without HRA reported significantly worse skin severity, compared to those with HRA (*4.58±1.40 vs. 3.53±1.89, U=93.00, p=0.011*). Conversely, boys with HRA present with significantly higher scores and thus worse severity, compared to boys without HRA *(4.73±1.39 vs. 3.27±1.30, U=209.00, p=0.008).* This finding was replicated in adult females with vs. without HRA *(3.60±2.14 vs. 2.56±0.95, U=304.00, p=0.009).* There was no significant difference between skin severity scores in adult males and boys (combined) with vs. without HRA (*4.13±1.74 vs. 3.696±1.43, U=1092.00, p=0.895*).

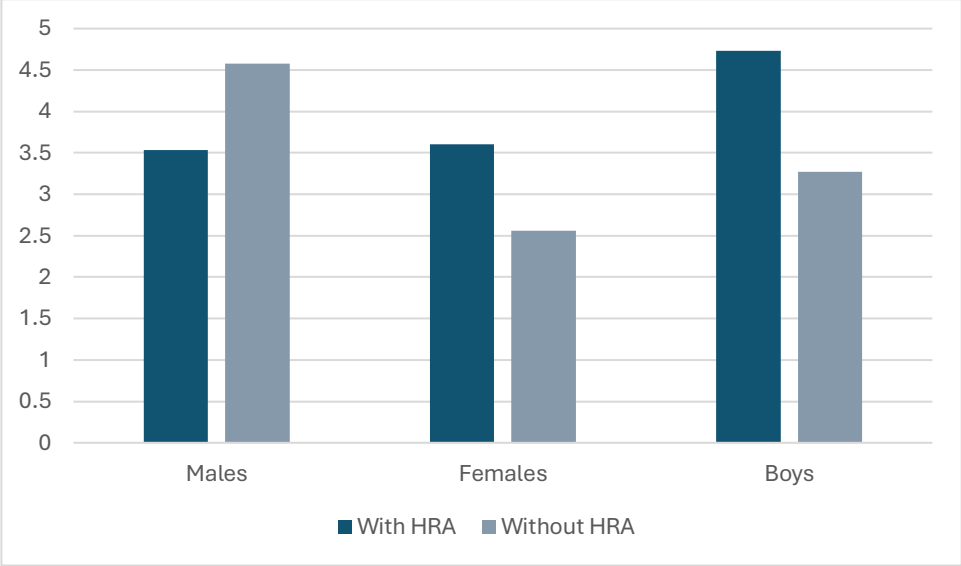
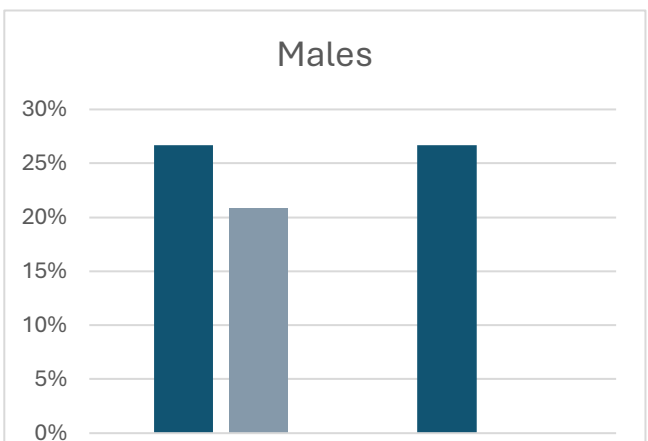


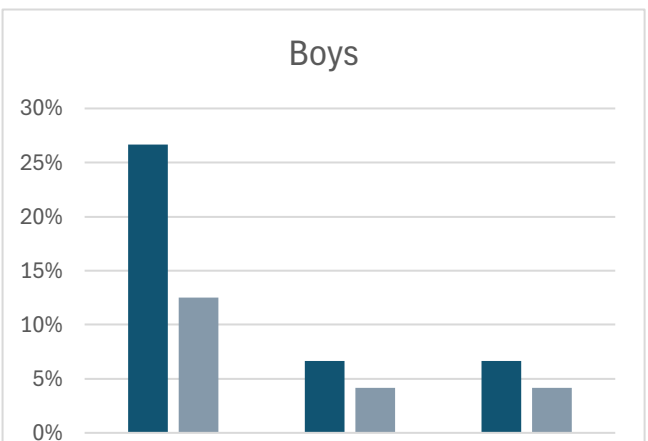
Figure 19: *Skin severity (CISI) between individuals with vs. without HRA*

5.3.3 Medical History

Boys with HRA exhibited higher, but not significantly more developmental conditions compared to those without HRA (testicular maldescent: 20% vs 10%, respectively, p=0.09; neurodevelopmental disorder: 27% vs 27%, respectively, p=1.0). Female XLI carriers with HRA exhibited notably, but not significantly higher rates of prolonged labour compared to females without HRA (67% vs 46%, respectively, $\chi 2$ (1) = 1.28, p=0.259). Consistent with a possible genetic influence on arrhythmia risk, males with HRA were more likely to endorse a family history of cardiovascular issues than males not reporting HRA (77% vs 46%, respectively, p=0.005); this pattern of results was maintained when female carriers were also included in the analysis (74% vs 49%, respectively, $\chi 2$ (1) =8.88, p=0.003).

After assessing several medical conditions that can co-occur with HRA, only 'gut problem' was significantly more common in males with HRA compared to males without (OR: 7.0; 95% CI: 1.3 to 38.4, p=0.022) (Figure 17). In females, 'heart murmur' (OR >10, p=0.005), anaemia (OR: 5.0; 95% CI: 1.5 to 17.2, p=0.011) and asthma (OR: 5.0; 95% CI: 1.3 to 18.2, p=0.017) were all significantly more common in those with HRA compared to those without (Figure 20). After combining adult/child males, and female deletion carrier group, four medical conditions were identified as significantly more common in HRA compared to non-HRA groups: 'heart valve disease or malformation' (OR: 10.6 (95% CI: 1.2 to 97.4), p=0.025), 'anaemia' (OR: 3.2 (95% CI: 1.1 to 8.7), p=0.027), 'asthma' (OR: 2.9 (95% CI: 1.3 to 6.4), p=0.010) and 'gut problem' (OR: 4.9 (95% CI: 1.7 to 14.3), p=0.004); of these, only 'gut problem' survived Benjamini- Hochberg False Discovery Rate correction (adjusted p=0.1). Rates of hypertension, obesity (BMI>30), and high cholesterol were all equivalent across groups when categorizing individuals based on HRA (Appendix 5.5A/B).





Anaemia

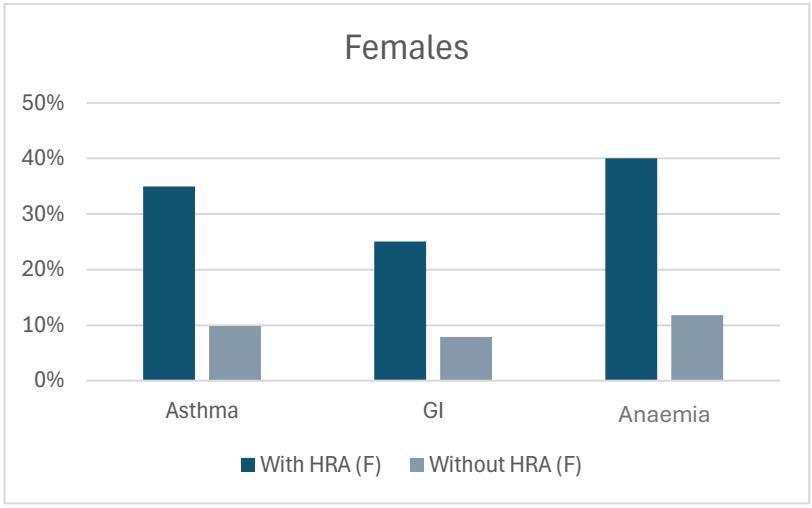


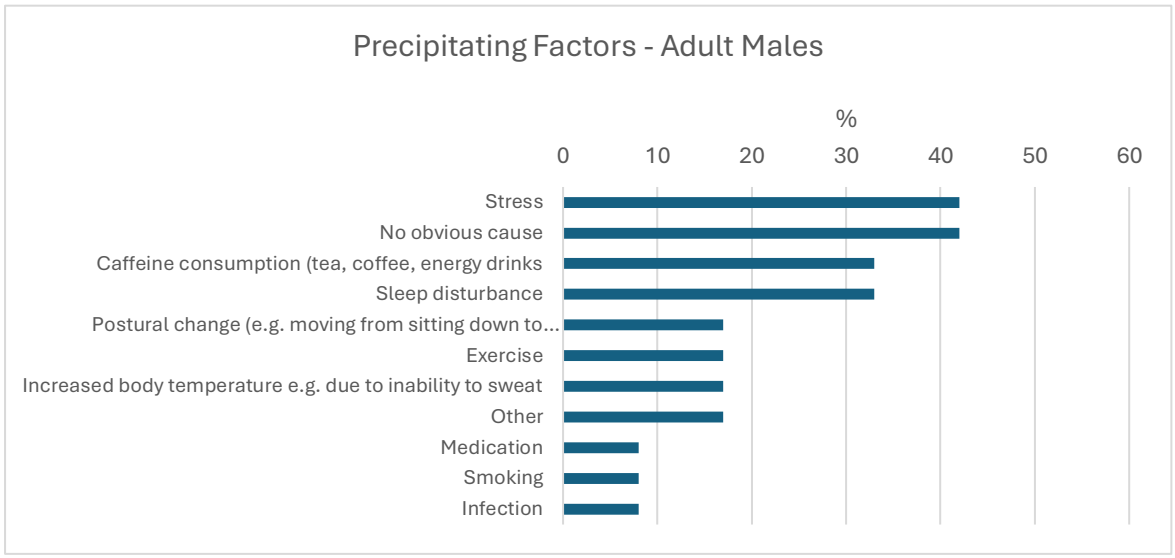
Figure 20: *Prevalence of asthma, gastrointestinal issues (GI) and anaemia between individuals with vs. without HRA*

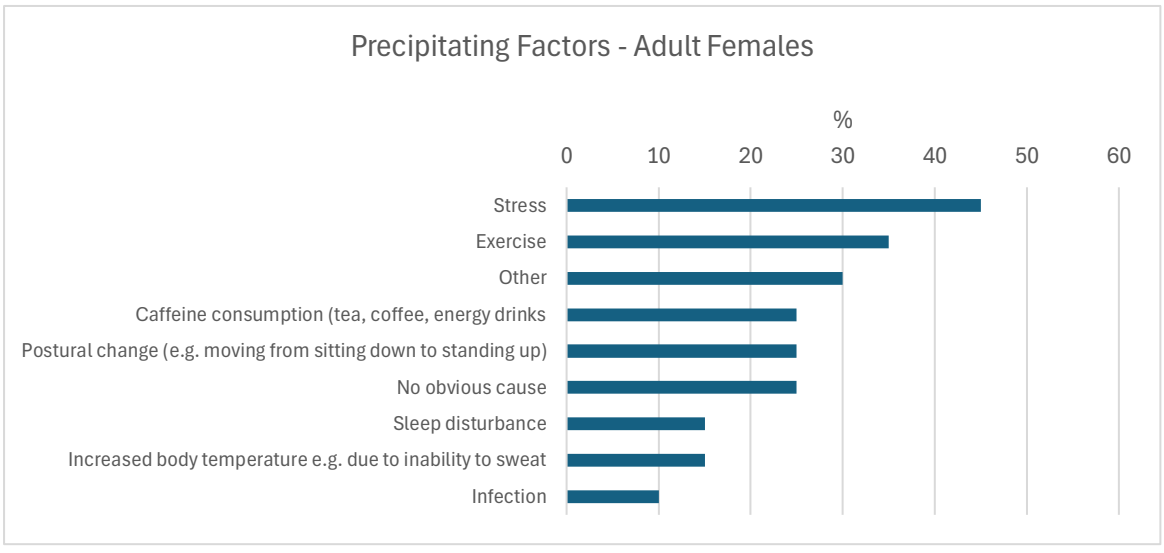
5.3.4 HRA Characteristics

Across individuals with a self-reported HRA diagnosis from a medical professional, atrial fibrillation/flutter (AF) was the most common arrhythmia in adult males (33%), closely followed by tachycardia (27%) It is important to note that when specifying the type of HRA, participants could endorse multiple conditions and thus there is potential for crossover as AF is a type of tachycardia. In adult females, tachycardia was the most commonly reported HRA (55%), followed by AF (35%). In male children, tachycardia and bradycardia were the most commonly reported (both 33%), with 20% reporting AF. Methods used by clinicians to diagnose these conditions most commonly included a combination approach of ECGs, echocardiograms, chest x-rays, and blood tests.

Stress was cited in the top three most commonly reported precipitating factors contributing to the onset of HRA episodes across all three groups (cited as a

precipitant in 42% of XLI males, 45% of female carriers, and 14% of parents of male children with XLI). Other common precipitating factors across individual groups included 'exercise' (female XLI carriers) and 'increased body temperature due to inability to sweat' (boys with XLI) (Figure 21/Appendix 5.6).





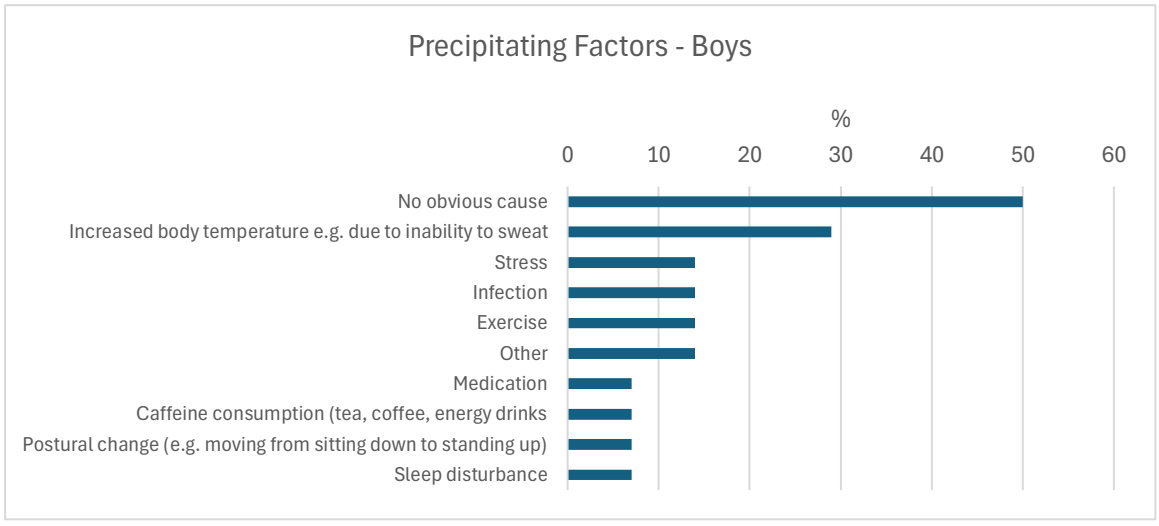


Figure 21: *Percentage of individuals with XLI (or female carriers) reporting involvement of precipitating factor in onset of AHR episodes*

Across all three groups, there was no clear pattern across time periods for the onset of HRA episodes (Appendix 5.7). Spontaneous resolution of HRA episodes was most common within 12 hours of the incident commencing across all three groups (82% of males with XLI, 85% of female carriers, and 82% of male children), if not within 1 hour (36%, 61%, and 55%, respectively). A small number of individuals experienced no spontaneous resolution and thus medical intervention was required (18% of males with XLI, 15% female carriers, and 18% male children). Where intervention strategies were required to control the heart rhythm, breathing exercises were most commonly cited across all three groups (33% of affected males with XLI, 67% of female carriers, and 75% of male children). Perceived intervention success was generally reported as being good (>5 out of 10) in 61% of males with XLI, 100% of female carriers, and 86% of male children with XLI.

5.3.5 Response to vignette

Across adult males with XLI (Figure 22) and female carriers (Figure 23), >80% agreed or strongly agreed that i) risk of AF in XLI was a significant health concern, ii) cardiac screening should be routinely performed following confirmation of XLI, iii) screening for heart problems in XLI is a good use of healthcare funding, iv) they would be happy attending, or bringing their child to attend, heart screening appointments, v) they would prefer to be made aware of potentially adverse medical conditions than not know, and vi) the potential benefits of heart screening outweighed the risks. Fewer than 50% of individuals stated that they would require further information about the link between heart arrhythmias and XLI to decide on potential screening.

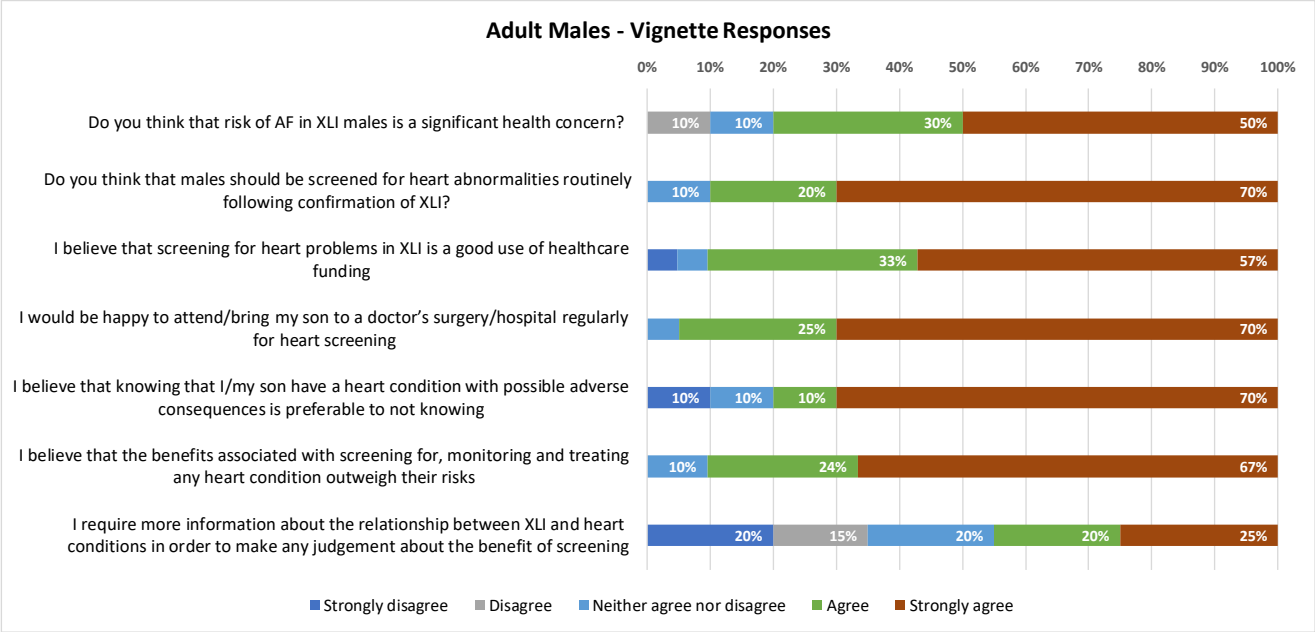


Figure 22: *Adult males' responses to vignette statements by percentage*

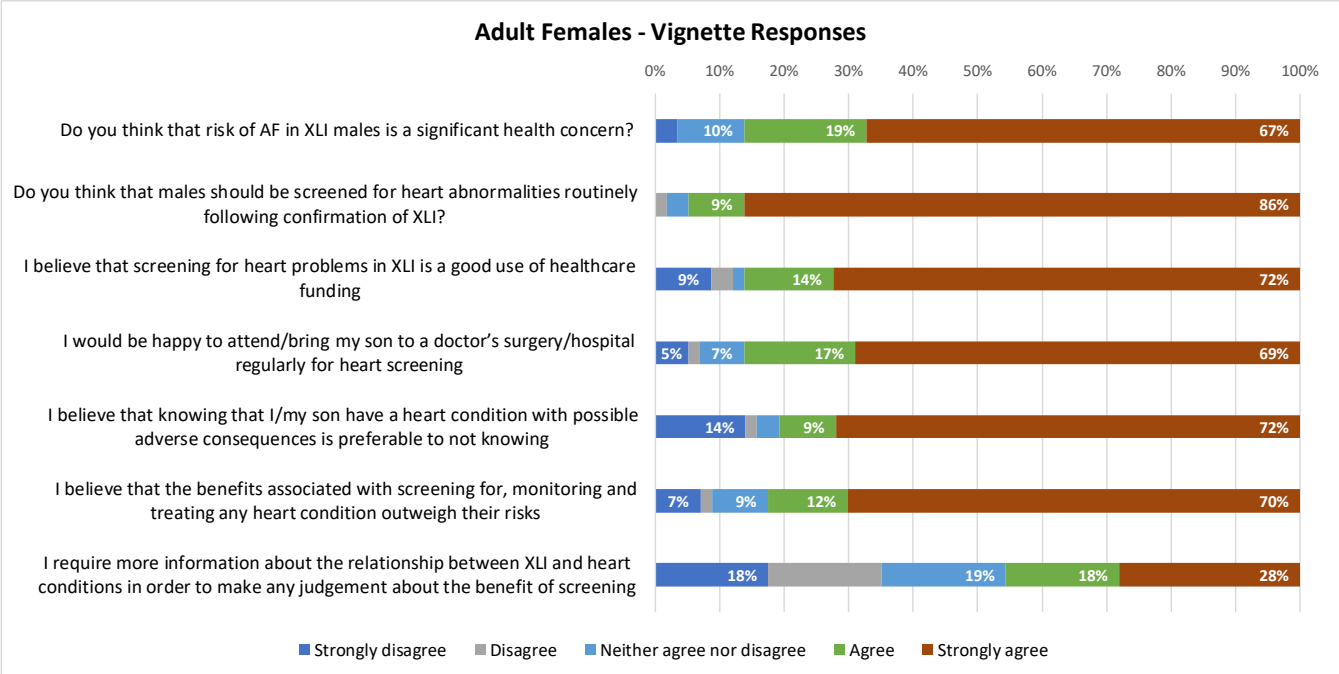


Figure 23: *Adult females' responses to vignette statements by percentage*

5.4 DISCUSSION

5.4.1 Summary

This study investigated the characteristics and prevalence of heart rhythm abnormalities and comorbid medical conditions, in addition to attitudes towards heart screening procedures in adult males with XLI (n=43), female XLI carriers (n=79), and parents reporting on behalf of their male children (n=69). Responses from each group were compared, based on the self-reported presence (or absence) of a HRA diagnosed by a medical professional. These HRA/non-HRA groups were closely matched for demographic factors including age and ethnicity.

5.4.2 Summary of HRA characteristics

This study showed that around 1/3 of individuals carrying Xp22.31 deletions had been clinically diagnosed (based upon self-report) with a heart rhythm abnormality (HRA). Across the three experimental groups, atrial fibrillation (AF) was the most common HRA in adult males, whereas tachycardia was the most common in adult females and male children. These figures are higher than previous work in the UK Biobank which only indicated a mildly elevated rate of AF in deletion carriers (10%). Elevated prevalence in this study may be due to the inclusion of multiple HRAs, including AF, as well as response bias by which participants with an HRA were more likely to respond to the study advert. The prevalence of HRAs in deletion carriers is higher than in the general population; arrhythmia was self-reported in 13.3% of men and 21.9% of women aged 40-49 years from the general population [520] and cardiac arrhythmias of any type were objectively detected in 17.2% of >10,000 general dentistry patients [521]. Furthermore, rates of atrial fibrillation specifically were substantially higher in male deletion carriers compared to a general adult population (15.4% vs. ~2.5%) [522]. Rates of tachycardia are difficult to establish in a normative population due to the term commonly used as an 'umbrella diagnosis' for more specific cardiac conditions; however, a study of Norwegian infants reported that 0.02% of live births were diagnosed with a cardiac arrhythmia, compared to the 28% boys with XLI in the current study [523].

To explain the increased risk of HRAs in Xp22.31 deletion carriers, it appears that STS deficiency is the strongest functional candidate. STS is highly expressed in adult arterial vasculature [524], and the enzyme is known to affect valve function [525] and fibrotic pathways [511, 526]. Furthermore, STS plays a crucial role in balancing sulfated and non-sulfated steroids such as DHEA/S. Higher levels of DHEA(S) can correlate with AF risk in older men [187], and the levels of these hormones (and the DHEA:DHEAS ratio) increase upon acute psychosocial stress, with the increase in levels correlating with the stress-induced increase in heart rate [527].

The likelihood of presenting with a cardiac arrhythmia was significantly higher in individuals with a family history of heart or cardiovascular problems, highlighting a key genetic risk component in the development of HRA. This is a common finding in the general population, as cardiac arrhythmia such as atrial fibrillation can be partly attributed to genetic and epigenetic risk factors [528, 529]. In addition, environmental risk factors such as obesity, alcohol consumption, and poor diet have also been linked to a family history of HRA [530]. Thus, although inherited genetic deletions across the XLI region are the most likely explanation, hereditary links to cardiac arrhythmia may be strongly influenced by other genetic, epigenetic, and environmental risk factors.

These are novel findings, and apart from recent UKBB findings in our research group, high rates of HRAs within the XLI population have not been recognised previously. This may be due to the seemingly non-impairing, sporadic nature of HRAs in individuals with XLI/female carriers, and/or the lack of cardiology-specific support/expertise for primary care clinicians typically responsible for managing individuals with XLI.

The onset of HRA was most commonly reported as being precipitated by stress in both male and female deletion carriers. Research suggests that stress can have an adverse effect on cardiovascular health, in both a short- and long-term manner; periods of psychological stress can trigger electrical instability in the heart, with chronic stress increasing the risk of future arrhythmic events [531, 532]. Furthermore, negative emotions and symptoms of depression (common in individuals with XLI, as shown in Chapter 3) [419], are strongly associated with triggering cardiac events and

increasing future arrhythmic risk [533, 534]. This suggests that a stress management-based intervention may be useful for individuals with XLI, to reduce the frequency and likelihood of arrhythmic events, and to promote self-management.

Our data further suggests that the prevalence of HRAs within the Xp22.31 population increases with age and that these typically resolve quickly and respond well to intervention where this is required. Across all groups, there were no clear patterns or common factors used to manage, treat, or resolve the HRAs, suggesting that these characteristics may differ greatly depending on the type and severity. The perceived success of treatment methods was consistently rated above 'average' by >80% of participants. The perceived success of common treatment methods for HRAs can vary significantly between individuals; the single procedure success rate in individuals treated for AF using radiofrequency catheter ablation (RFA) ranged from 50-64% [535].

There was no clear relationship between HRAs, and the severity or presence of features commonly associated with XLI (skin condition in adults, testicular maldescent, neurodevelopmental disorders) implying some dissociable causes.

5.4.3 Medical and Comorbid Conditions

Our results suggest that gastrointestinal problems, asthma, and anaemia are the comorbidities most closely associated with HRA in deletion carriers, with GI issues more prominent in male carriers with HRA, asthma, and anaemia more strongly comorbid in female deletion carriers, as well as a heart murmur. Based on a recent association study, it has been speculated that the *PNPLA4* gene (adjacent to *STS*), which may also be absent in deletion carriers, may be responsible for these comorbid issues, and that these medical vulnerabilities may exacerbate any HRA risk incurred as a consequence of STS deficiency [515]. Briefly, in gene-based analyses, significant associations were found between *PNPLA4* and asthma (p=0.040) and anaemia (p=0.013) in females, and between *PNPLA4* and gastrointestinal issues in males (p=0.022) [515]. Furthermore, PNPLA4 deficiency could feasibly contribute to the lipid metabolism and mitochondrial abnormalities associated with asthma [536, 537], anaemia [538, 539], and gastrointestinal disorders [540, 541]. Thus, we suggest that loss of

PNPLA4 function may likely predispose to anaemia and asthma in females and GI issues in males.

Another potential explanation for increased GI issues in this population is the 'gut-skin' axis as described in Chapter 1.1; disturbances in the gut microbiome have been associated with cutaneous manifestations such as redness [66, 67], and common skin disorders such as rosacea [61]. The mechanisms by which this association occurs are not yet clear, and these findings in an XLI population are novel. Thus, this presents are interesting area for future research and development, with improving gut bacteria as a therapeutic target.

Other potential contributing factors in the development of GI issues in adult males include older age [542], long-term use of therapeutic agents such as anticoagulants used to manage conditions such as AF [543, 544], in addition to obesity, hypertension, and diabetes through various dissociable mechanisms including inflammation [526, 545]. This study, however, did not find a difference in rates of obesity, hypertension, and diabetes between individuals with HRA and those without, and thus the most likely principal mechanism between GI issues and HRA remains *PNPLA4* deficiency, potentially covariate by age (although no significant differences in age between males with HRA compared to those without were identified).

Increased risk of asthma is also generally more common in general population individuals with atrial fibrillation [546]; a recent Norway-based longitudinal study reported that adults with asthma had a 38% higher risk of developing atrial fibrillation [547]. General population individuals with tachycardia are also at increased risk of developing asthma [548]. Current findings suggested that female deletion carriers were more at risk of developing anaemia, which mirrors trends in the general population [549, 550]. Anaemia is commonly associated with abnormal cardiac function, specifically increased atrial stress and a higher risk of heart failure [551, 552], thus perhaps explaining this link.

Potentially, if GI issues and atopic conditions/anaemia exacerbate HRA in deletion carriers, effective treatment of them could have clinical benefits. Identification and awareness of the potential consequences of these conditions are crucial when

developing prevention strategies. Crucially, no significant differences in the frequency of downstream consequences of AF were identified when comparing individuals with/without HRA, including stroke, acute myocardial infarction, and dementia. this may be because common variants within Xp22.31 contribute marginally towards AF risk, and AF in turn only contributes to the pathogenesis of a relatively small fraction of stroke, acute MI, and dementia cases.

5.4.4 Attitudes towards heart screening

Participants' responses to the vignette and statements about preventative heart screening procedures in a primary care setting were largely positive. More than 80% of participants stated that, based on their statistically likely increased risk of AF, they would be willing to attend screening. Current data indicates that individuals with XLI (or female carriers) presenting with GI issues, asthma or anaemia might be prioritized. Current treatment frameworks for individuals with XLI, both in the UK and the US, do not refer to increased risk of HRAs [282] [283, 285], and thus it may be difficult to establish or introduce early prevention strategies. The use of a specialist multidisciplinary team, as well as comprehensive guidance for patients, is a crucial step in improving care for individuals with XLI in a clinical setting. Diagnosis and treatment pathways are pre-existing in the NHS for the short- and long-term management of cardiac arrhythmia such as AF and thus these could be incorporated into the care package for deletion carriers [553]. However, almost half of the participants in this study stated that they would require further information about heart screening procedures, thus illustrating the need for greater awareness and support from within primary care to support individuals with XLI in their treatment-based decision-making.

5.4.5 Strengths and Limitations

The approach used in this study allowed for gathering essential information about HRA frequency, precipitating factors, and willingness to attend future preventative screening. The use of self-reported data provides information on HRAs occurring at time points across the lifespan as opposed to temporally restricted clinical monitoring via, for example, ECG. However, limitations of this method of data

collection include possible misreporting by participants in the absence of objective clinical measures as well as additional challenges associated with parental reporting on their sons' experiences. Furthermore, individuals with an HRA may be more likely to have responded to the advert, presenting a potential response bias.

Using an extensive list of common medical conditions, a basic medical background was established, and any related family history. However, the results of this survey offer limited information about participants' complete medical history and thus it may be difficult to establish direct causation between cardiac arrhythmia, STS deficiency, and other comorbid conditions.

Although the majority of participants agreed that AF provides cause for concern for individuals with XLI, the reasoning why ~20% of participants would not feel comfortable attending screening procedures was not investigated. Thus, it is important to a) understand and explore these concerns with patients and b) provide comprehensive guidance and information to individuals or parents of children with XLI when diagnosed, to promote increased awareness and self-management.

Future work in our research group aims to utilise a newly developed STS-deficient mouse model to investigate biological mechanisms in HRA. Other avenues for further research based on the results of this work include investigation of heart structure/function (e.g. ECG), molecular biomarkers and steroid hormone levels in Xp22.31 deletion carriers, relating to HRA. Future work may also explore the relationship between HRA and key precipitating factors (e.g. stress), comorbid conditions (e.g. GI issues) and responses to medication.

5.4.6 Conclusion

This study provides preliminary results to suggest that genetic deletion at Xp22.31 increased the risk of HRA and three comorbid medical conditions; anaemia, asthma, and GI issues. This work reveals stress to be a key precipitating factor in the onset of HRAs and suggests treatment success is moderate for most individuals. Future work using *in vitro* and *in vivo* models, as well as more detailed clinical analyses, may improve understanding of the physiological, cellular, and molecular mechanism(s) through which genetic variants at Xp22.31 affect the risk of HRA. This

may improve both clinical guidelines and support for deletion carriers, as well as contribute to better-informed genetic counselling.

This study also showed that deletion carriers (including parents reporting on behalf of their children) are strongly in favour of preventative cardiac screening measures to avoid potential downstream consequences associated with HRAs. As such, investigating the utility and viability of screening within these populations, particularly in individuals with comorbid gastrointestinal disorders, asthma, or anaemia, is of particular interest.

Chapter 6: ASSESSING THE FEASIBILITY OF USING SMART WEARABLE TECHNOLOGY TO RECORD HEART RHYTHMS IN MALES WITH XLI

6.1 INTRODUCTION

In the previous chapter, high rates of self-reported cardiac abnormalities were identified in males with XLI and female deletion carriers. Stress was identified as the most common precipitating factor in the onset of arrhythmic episodes, and participants were strongly in favour of preventative screening procedures. Early identification of HRA may prevent downstream consequences such as stroke, cognitive decline and dementia, thus reducing the long-term health burden for patients and the healthcare system. Where possible, non-invasive methods should be used to effectively and efficiently identify HRA, to allow for early monitoring and necessary interventions. This study assessed the feasibility of using wearable technology as a novel form of heart rhythm monitoring for males with XLI.

6.1.1 Cardiac arrhythmias and atrial fibrillation

Abnormal cardiac rhythm occurs when the heart's normal sinus rhythm is disrupted in some way [554]. In normal sinus rhythm, the sinoatrial node (SAN) in the right atrium produces an electrical wave through the four chambers of the heart, to the atrioventricular node (AVN), subsequently triggering the contraction of the heart muscles to pump blood to organs in the body [554-556]. In regular sinus rhythm, the heart typically beats around 70-75 beats per minute [554], distributing blood containing necessary nutrients, immune receptors, and regulatory molecules around the body [554-556]. Disruption of this process, also known as cardiac arrhythmia, can result in adverse or no heart rhythm, thus affecting the essential flow of blood to the body [557]. The development of cardiac arrhythmias has three basic mechanisms:

A) Enhanced or suppressed automaticity: impaired SAN functioning can result in the misfiring of pacemaker cells in the absence of external stimuli [558], often due to disease, drugs, or changes in the automatic nervous system [559-561].

    a. Enhanced automaticity: causes tachycardia (fast heart rate)

b. Suppressed automaticity: causes bradycardia (slow heart rate) [562]

B) Triggered activity: this describes an abnormal impulse initiation in the cardiac fibres, either midway through or shortly after the passage of electrical current through the myocardium [560] [563]. A triggered response usually precipitates tachycardic arrhythmias [560, 564], such as atrial fibrillation (AF) [560, 565, 566].

C) Re-entry: at its simplest form, this mechanism occurs when a cell impulse fails to cease at its origin site within the myocardium, thus re-exciting the heart and forming a secondary 're-entry' circuit [560, 562, 567]. Re-entry can be caused by an anatomical abnormality (usually relating to the AVN), dysfunctional circuits, or diseased cells [560, 562, 567], and is responsible for the majority of clinically relevant cardiac arrhythmias.

Symptoms of cardiac arrhythmia, caused by one of these three mechanisms, typically include dizziness, chest pain, shortness of breath, palpitations, and feelings of weakness or fatigue [561]. Diagnostic procedures for symptomatic arrhythmias typically include a combination of blood pressure and ECG and observation of any abnormal symptoms [561]. Arrhythmias are typically split into two categories: a) tachycardia, characterised by an abnormally fast heart rate (>100 bpm), or b) bradycardia, characterised by an abnormally slow heart rate (<60 bpm). Common forms of tachycardia include supraventricular tachycardias (originating from the AVN) such as atrial fibrillation or flutter (AF) and ventricular tachycardia (originating below the AVN) such as premature ventricular beats (PVC) [561, 568]. Bradycardic disorders include atrioventricular blocks (usually asymptomatic) and sinus node dysfunctions such as sinus arrest or sinus pause (failure or delayed impulse generation/transmission) [561, 568]. Treatment of arrhythmias is largely dependent on the severity of the perceived risk to the individual and may include 'shock' therapy (defibrillation or cardioversion), implantation of a pacemaker, antiarrhythmic drugs, or cardiac ablation [561, 568].

As described in the previous chapter, atrial fibrillation (AF) is the most common supraventricular tachycardia [476] (re-entry mechanism) and occurs in an estimated 2.5% of adults worldwide [477]. AF can be classified into three distinct categories:

paroxysmal (terminating within seven days), persistent (longer than seven days, and requires cardioversion for termination), or permanent (cannot be terminated by cardioversion) [569]. The condition is commonly precipitated by older age [478, 480], and modifiable risk factors such as high BMI, smoking, and psychological stress [478, 482, 483], and is estimated to affect 5% of individuals >65 years and 10% of individuals >80 years [478, 480]. Downstream consequences of living with AF, if untreated or not effectively managed, include increased risk of stroke, heart failure, and cognitive decline [234], as well as worse quality of life (QoL) [488 489] and increased symptoms of depression and anxiety [489]. Following a diagnosis of AF, individuals are usually referred to a specialist cardiac team for further tests including imaging, blood tests, and additional cardiac screening [570].

In addition to long-term effects on health for patients, HRAs such as AF also pose a significant economic burden to society and global healthcare systems: the national incremental cost of AF was $6 billion in the US [571], and the cost burden of undiagnosed AF is estimated at $3.1 billion [572]. This is especially relevant when referring to individuals with multimorbidity; the cost of AF-related stroke alone was estimated to be 8-45% higher than the cost of stroke in patients without AF [573-575], at an average cost of €362 million a year [576]. These costs are predominantly attributed to healthcare costs such as longer hospital stays (69% of acute care costs were attributed to comorbidity [577]), in addition to productivity losses and recurrence of stroke [574 578]. To reduce stroke risk and improve long-term health outcomes for individuals with AF, the condition must be identified and monitored as early as possible, and if necessary, appropriately managed using medication [579].

6.1.2 Asymptomatic arrhythmias

However, not all incidences of arrhythmia are symptomatic or preceded by known risk factors; the prevalence of asymptomatic ventricular pre-excitation is estimated to be around 0.1-0.3% of all cases but this is often particularly hard to determine [580, 581]. The prevalence of asymptomatic ventricular tachycardia ranges from 1-3% (healthy adult population) [582, 583] to 10% (elderly population) [584], and >30% in patients with ischaemic heart disease [585]. Diagnosis of asymptomatic bradycardias is

difficult due to slow disease progression and commonly lower heart rates in young athletes and adults older than 65 [586, 587].

Most notably, research suggests that during routine screening or monitoring, between 10-40% of adult cases of AF were asymptomatic by nature [588-592]. Risk factors associated with asymptomatic AF include older age, male sex, and limited physical activity [591, 593], thus mirroring known general risk factors in the development of cardiac arrhythmia in adult populations [478, 480, 21, 22]. The prognosis of asymptomatic AF compared to symptomatic AF is difficult to determine; some work suggests an increased risk of mortality for patients with asymptomatic AF [593, 594], yet others suggest that stroke frequency is similar across the two groups [591, 595]. Crucially, AF is initially diagnosed in 11-24% of patients following a stroke [596, 597], and thus early preventative screening for asymptomatic AF in at-risk populations is essential [598].

6.1.3 Preventative Cardiac Screening

However, there is currently no systematic screening for AF in place in the UK. Outcomes from the 2019 UK National Screening Committee (NSC) suggested that although targeted and opportunistic screening is cost-effective, a widespread screening programme is not recommended [599]. This decision is based on the following criteria: variable types of AF and thus stroke risk profiles, limited evidence for the effectiveness of treatment of asymptomatic AF, and a lack of understanding as to whether screening is more beneficial than the current approach to detection and management [599]. However, an ongoing feasibility trial at Cambridge University ('SAFER' Trial), was recently welcomed by the NSC [600]; in collaboration with GP practices across England, this trial is using a "non-invasive hand-held ECG recording device" across a 3-week period to establish whether AF screening is "effective and cost-effective in reducing stroke and other key outcomes compared to current practice" [601]. However, this trial is only recruiting individuals over 70 years of age, due to justified age-related risk factors and is currently in Phase 4 out of 6. Following the conclusion of this trial, the NSC recommendations surrounding the effectiveness of AF screening will be reviewed in 2023/4 [599]; but meanwhile, there is

limited provision for widespread AF screening for the general population through primary care in the UK [599]. Recommendations from the US Preventive Services Task Force (USPSTF) led to similar conclusions; following a review of the evidence surrounding the benefits of AF screening for adults >50 years old, the task force concluded that "current evidence is insufficient to assess the balance of benefits and harms of screening for AF" [602].

A population-based systematic screening program may take various forms in the UK [603-605]:

a) General population screening for a defined group e.g. age-based (>65 years)

b) Targeted screening for those at a higher known risk of AF (hypertension, diabetes, sleep apnoea, etc.)

c) Opportunistic screening during consultations with health-care professionals e.g. GP, flu clinics, community pharmacy

As a population more at risk of AF [187, 511], adults with an Xp22.31 deletion would likely be eligible for a systematic targeted form of screening. Current treatment guidelines for XLI individuals largely focus on topical therapies, specifically emollient use [285], with more recent considerations for psychosocial implications [606] and ocular abnormalities [607]. However, to date, there are no clear guidelines for the management or prevention of cardiac arrhythmia following the diagnosis of XLI, for both patients and healthcare professionals, neither in the UK nor the US. This presents an issue for clear referral pathways from primary care to specialist cardiac care providers, thus relying on patient advocacy and knowledge.

6.1.4 The use of wearable technology

A possible new opportunity and advancement in health monitoring, particularly relevant to the field of cardiovascular care, is the use of wearable technology. According to Godfrey, Hetherington (2018), wearable technology can be defined as "a plethora of devices worn directly on or loosely attached to a person" and can be divided into two distinct categories: a) primary: devices operating independently (e.g. smart watch, smartphone), and b) secondary: devices which offload specific

data to a primary device for analysis (e.g. chest heart rate monitor) [608]. These devices can measure or track a number of physiological/biochemical parameters, as well as certain behaviours, including heart rate, blood pressure, and posture [609]. The market for wearable devices is rapidly growing, with the global market expected to reach over $70 billion by 2025 [610], and over 20% of US residents owning a smart wearable device [611].

Wearable technologies can offer novel solutions for current issues in healthcare, particularly around the prevention of disease and maintenance of health, as well as encouraging patient disease management [609]. Examples include fall identification and prevention (particularly in elderly populations), sports medicine, increasing physical activity in sedentary populations, hypertension detection, and diabetes management [609].

User acceptance is crucial when designing and implementing wearable devices both in a clinical and home setting. Adults with persistent medical conditions consistently report finding smartwatches useful and convenient [612, 613], and a large-scale review found that over 60% of elderly individuals were interested in the future use of a wearable device [614]. Furthermore, these devices are often more cost-effective compared in the long term, compared to clinical assessments [615, 616], and offer a non-invasive, regular monitoring tool which emphasises patient adherence and inclusion in the decision-making process [615, 617, 618]. However, patient confidentiality and security of data is a prominent concern for many users [613, 619, 620], and thus the element of data encryption, privacy, and 'opt-out' options within the user interface are of critical importance.

6.1.5 The use of wearable technology in cardiovascular care

The use of wearable technology is particularly pertinent to cardiovascular monitoring; primary and secondary devices such as smart watches can contain ECG and heart rate variability (HRV) monitoring systems [621, 622], in addition to the use of photoplethysmography (PPG) sensors in devices such as smart rings [622, 623]. Although this is a new technology, a chest-worn HR monitor offers a very high agreeability with the 'gold standard' 12-lead ECG, closely followed by a smartwatch

(mean agreement of 91-5% depending on the brand) [624, 625]. Due to the asymptomatic/'clinically silent' nature of >1/3 incidences of AF, continuous monitoring through the use of wearable technology has the capability to transform cardiovascular care [623]. Following detection of these instances of AF, individuals can share the ECG and/or PPG readings with their healthcare providers, to determine a clinical diagnosis and to develop a long-term treatment plan if appropriate.

Previous work suggests that screening for cardiac arrhythmia such as AF using wearable technologies may be highly effective, and feasible for varying populations. Screening for undiagnosed AF in high-risk individuals via an ECG patch was effective in more timely identification of AF onset and thus initiation of drug treatment, as well as health care resource utilisation following the trial [626]. A large-scale trial using an ECG patch in adults with no known history of AF, identified 0.52% of individuals with an irregular pulse, with a positive predictive value of 0.84 for AF detection via the patch, paired with an irregular pulse notification via a smartphone [627]. Furthermore, another study utilising the 'Huawei Band 2 PRO' showed a positive predictive value of 99.6% in identifying AF [628].

An ongoing large-scale randomized controlled 'HEARTLINE' study, in collaboration with Apple, is exploring how the Apple Watch (Series 4 and later) may be used as an early detection device for AF in adults over the age of 65 in the US population [623, 629]. Data collection for this study is still ongoing, but this trial is the first of its kind to evaluate the effectiveness of a commercially available wearable device to detect irregular heart rhythms in the general population.

6.1.6 Purpose and Aims

Previous work suggests that wearable technology such as smartwatches, may offer an effective, reliable way in which to identify and monitor cardiovascular health in the general population, specifically cardiac arrhythmia such as AF. The previous study identified an elevated rate of atrial fibrillation/flutter (AF) in adult males with X-linked ichthyosis (XLI), and increased rates of tachycardia in adult female carriers of XLI-associated genetic deletions [511, 515]. However, this work relies on a) a formal clinical diagnosis of AF via a healthcare professional, and b) reliable self-reporting

from participants. It also depends on an individual's awareness of the increased risk of cardiac arrhythmia, as well as an understanding of the severity of potential downstream consequences of poorly managed or untreated AF. Improving understanding of how wearable technology may be used in this population as a targeted screening tool, may inform future long-term monitoring both in a clinical and a home-based setting.

Moreover, >80% of males with XLI in our recent survey were amenable to and appreciated the potential benefits of, cardiac screening. Thus, it is important to test whether heart rhythm screening in XLI males using wearable technology may be an appropriate method for the timely identification of HRAs, and the prevention of downstream consequences. If this approach is effective on a large scale, this may be rolled out to newly diagnosed cases of XLI as a focused screening programme.

As a precursor to the pathway above, in collaboration with local consultant cardiologists, a feasibility study was conducted to monitor the heart rhythms of a small group of UK-based adult males with XLI over 8 weeks using the Apple Watch Series 8 as an FDA-approved ECG device [630]. Crucially, this study aimed to understand whether the use of an Apple Watch is an acceptable form of screening for this population and determine the optimal study procedures for any subsequent larger-scale trial. The main outcome measures from this study were participant ECGs and feedback from participants and clinicians. The goals of the feasibility study were as follows:

- To assess participant engagement with the study.
- To test whether the device/app technology can be used effectively by patient group members and to identify any issues with using the device on ichthyotic skin.
- To streamline procedures: for delivery/return of monitoring device, for return of relevant data from participant to researchers/clinicians, and for clinician advice to participants.
- To gather initial data and to identify the prevalence/occurrence, nature, and precipitants of any arrhythmic episodes.

- To determine the optimal time/frequency for participants to take ECG readings.

6.1.7 Summary

- Cardiac arrhythmia and the associated downstream consequences are a significant economic and societal burden but can be prevented and managed if detected early.
- The use of wearable technology is growing in healthcare systems across the world, and new research indicates that this may be a beneficial approach in cardiovascular care.
- This study aimed to assess the appropriateness of the Apple Watch as a form of wearable technology, for individuals with XLI who have previously been identified as being at increased risk of HRAs.

6.2 METHODS

6.2.1 Design

This study used a feasibility trial to monitor the heart rhythms of a small group of UK-based adult males with XLI over 8 weeks using the Apple Watch Series 8. Recent feasibility trials using smartwatch technology to assess cardiovascular function, have employed larger samples (40-50 participants) [631] [632] [633]; however, these studies used general population groups with minimal inclusion criteria. Recruiting individuals from a rare disorder group, with strict inclusion criteria, as well as high demands on participants and funding limitations, reduced the intended sample size to <10. Participants provided a weekly set of three ECG readings via an online form, and these were independently reviewed by two experienced NHS consultant cardiologists. Following the trial, participants completed a feedback form about their experiences.

6.2.2 Sampling and Recruitment

A short advert was sent to an established mailing list of participants who had previously taken part in our research, with inclusion criteria and contact details for

the team if they were interested in taking part. The Ichthyosis Support Group (ISG) newsletter was also utilised, using the same advert, and advertised via social media patient support groups. The following inclusion criteria were applied:

- Adult (18-80yrs) male with clinical diagnosis of XLI
- Own an iPhone (Series XS or later) and willing to download and use applications.
- Willing to complete a series of very short online questionnaires.
- Willing to wear an Apple Watch Series 8 for up to 8 weeks.
- Willing to submit data from the watch about heart rhythm to the research team at regular intervals.

There were no exclusion criteria.

6.2.3 Procedure

Before starting the study, participants completed a short screening questionnaire to ensure that they understood all the parameters of the trial and that they met the inclusion criteria. Once they had read the information sheet and completed the consent form, each participant provided their contact details (email address and postal address). Participants were then informed if they had been approved for the trial, and subsequently sent an Apple Watch Series 8, charging equipment and printed instructions for setting up the watch, ECG readings and troubleshooting information. The instructions also included contact details for the research team, and any queries were managed within 48 hours to avoid delay.

Participants were asked to wear the Apple Watch continuously for 8 weeks starting on the closest upcoming Monday to when they received the watch to ensure continuity of readings. Using the instructions provided, participants used the watch to take routine ECG readings once a day, every Tuesday, Friday, and Sunday. This was a simple process; using the ECG function on the Apple Watch, participants placed their finger over the sensor on the watch for one minute and the ECG was automatically saved into the Apple Health app on their iPhone. There was no set

time period for these readings, as participants were encouraged to take readings at variable time points throughout the day at their discretion depending on their daily schedule (e.g. night shifts, caring responsibilities). If the watch independently detected any irregular heart rhythm and notified the participant, this reading would automatically be saved in the app, and participants were also asked to report this to the research team via the weekly form.

At the end of each week (Monday morning), participants were sent an automatic reminder email to complete a weekly Qualtrics form, accessed using their participant number. Here, participants would upload each of their ECG readings from the week, in addition to the time and date that the reading was taken, circumstances of this ECG reading (i.e. what they were doing at the time of the reading, how they were feeling, etc.) and, given the potential association between stress and heart rhythm abnormalities identified in Chapter 5, a stress/anxiety rating at the time of the reading was also requested (scale 1-9, 1 = not stressed at all, 9 = very stressed). If the participant had received any irregular HR notifications, the same information was also inputted for their occasions. On this form, participants were also asked to report any new heart-related symptoms e.g. heart palpitations, pain in the chest, breathlessness, etc.

Following the submission of these ECGs, each reading was manually anonymized and grouped, then sent to two experienced NHS cardiology consultants at University Hospital Wales, Cardiff, with whose expertise, this study was collaboratively planned. Each consultant independently provided feedback on each ECG reading to one member of the research team (identification of any abnormal rhythms), to avoid bias and this was recorded. This process was repeated for each week of the trial for each participant.

Once the participants had completed all eight weeks of the trial, they were asked to wipe the data stored on the Apple Watch, return it to factory settings, and then return it to the research team. If any irregular heart rhythms were identified by the cardiology team, the participant would receive feedback and advice about the next steps, and information to take to their primary care provider (typically a GP). However, no tailored medical advice was offered as part of this study.

Participants were also asked to complete a short post-trial feedback form to gauge their satisfaction with a) the practicalities of screening for cardiac arrhythmias using the Apple Watch, b) a combination usage of the Apple Watch and the iPhone 'Health' app to download ECG outputs, as well as any suggested improvements or concerns with the trial. Participants were also asked to rate several statements relating to how using the Apple Watch affected/was affected by their skin (Appendix 6.1).

Participants were each awarded a £50 Love2Shop voucher for their time and dedication to this study.

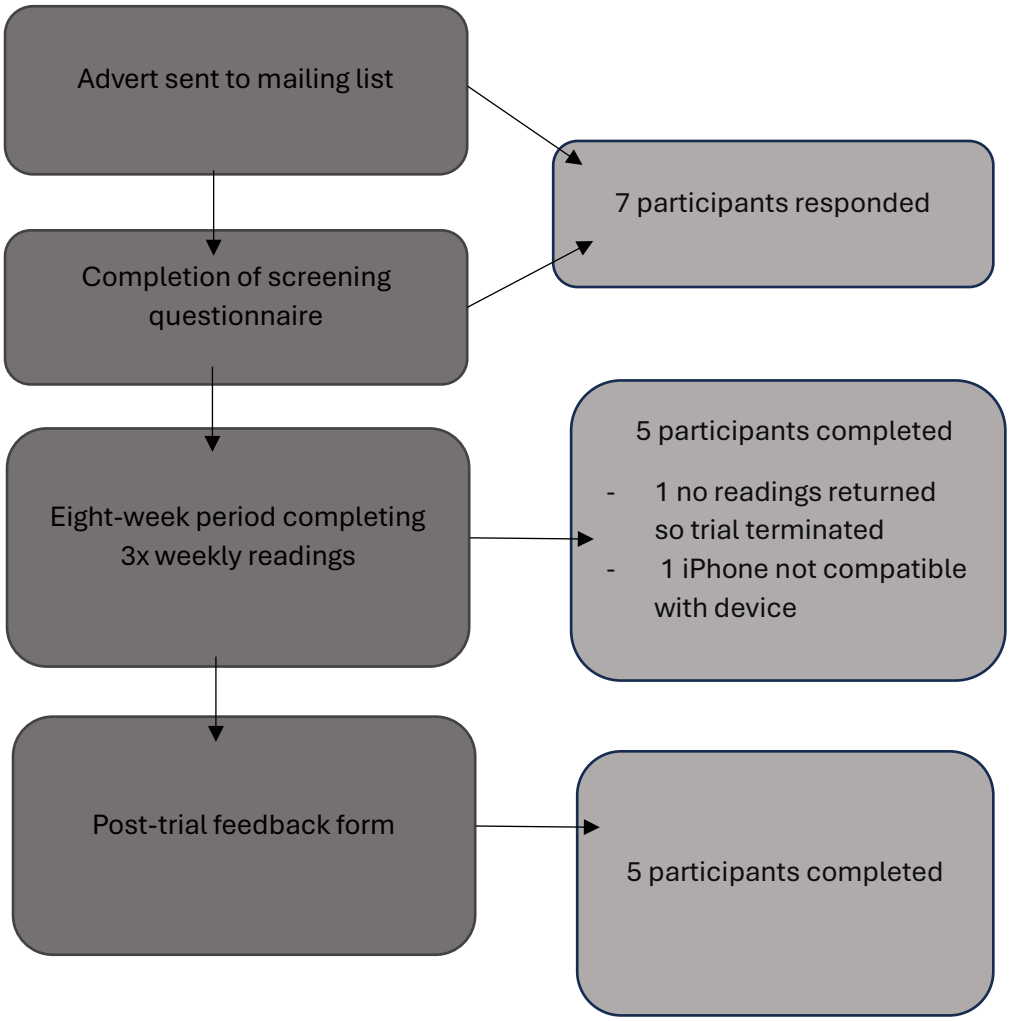
6.2.4 Data Analysis

Following each set of ECG uploads, the PDF file and associated data (stress, precipitating factors, etc.) were downloaded from Qualtrics as an Excel file, and the ECGs were anonymised and sent to the cardiologists for review. Feedback from the cardiology team was submitted into the central database and appropriately coded e.g. 'Normal sinus rhythm', 'Single VPB'. Following completion of the trial, these readings were marked as 'normal' or 'abnormal' based on guidance from the cardiologists. The proportion of abnormal readings per participant was recorded. Stress ratings were measured on fixed scale of 1-9, and the overall difference between stress ratings related to normal vs. abnormal measures was assessed using an independent t-test. All other data is reported as percentages or mean±SD.

6.3 RESULTS

6.3.1 Participant Recruitment

Overview of the recruitment process



6.3.2 Participant Demographics

Five adult males between the ages of 27-69yrs were recruited, with a confirmed clinical diagnosis of XLI. The specific demographic factors of each participant are listed in Table 7 below. All the participants reported a preexisting cardiac condition (including atrial fibrillation/flutter, AF) although this was not part of the inclusion criteria. 3/5 of the participants reported a preexisting medical/psychological condition.

Participant Number	Age	Pre existing cardiac conditions	Pre-existing medical or psychological conditions
2	45	Hypertension (managed by medication)	-
3	63	Three previous episodes of AF (managed by daily medication). Previous experiences of 'missed beats'.	Diabetes (managed by medication)
5	49	Three previous episodes of AF.	-
6	27	Paroxysymal AF	Underactive thyroid, hayfever, depression (all managed by medication).
7	69	Hypertension (managed by medication). Supraventricular ectopic beats - associated with dizziness and pain (managed by medication). Cardiac cauterisation aged 21 for heart murmur.	Reflux, hiatus hernia (both managed by single medication), glaucoma (managed by medication). Dyslexia.

Table 7: individual participant demographics (age, preexisting conditions)

6.3.3 Response Details

From a total of 123 possible ECG readings (one participant produced an extra week of readings, hence three extra 3 readings), 5% were not uploaded where the participant forgot to take a reading. As shown in Figure 24, participants were most likely to take their ECG readings in the morning, between 9am and 12pm, but the time distribution was similar at all other grouped periods.

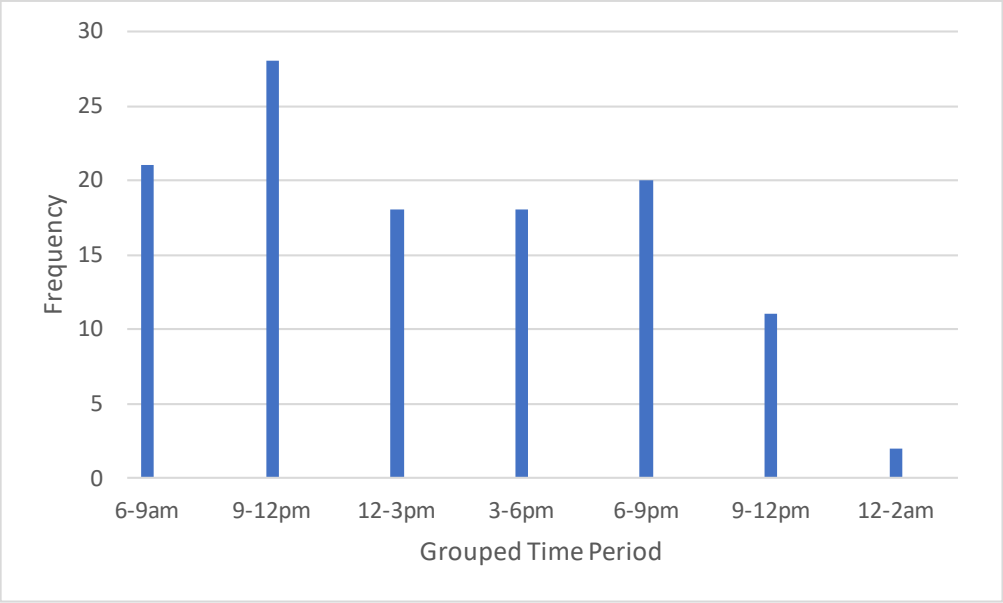


Figure 24: frequency of time periods for ECG recordings

Across the trial, 3/5 participants reported experiencing 'heart-related symptoms' (survey description: 'heart palpitations, pain in chest, breathlessness, etc.') as

summarised in Table 8. Out of a total of 7 incidences across 3 participants, only one of these triggered an 'alert' on the Apple Watch, followed by an automatic ECG at this time. This alert was later rated as 'normal sinus rhythm' by both cardiologists.

Participant ID	Week (per participant)	Summary	ECG Feedback
2	2	Positive COVID test and cold	NO ALERT
3	1	Breathlessness	NO ALERT
3	2	Infrequent palpitations	NO ALERT
3	3	Irregular abnormal beats	NO ALERT
3	4	Palpitations and lightheadedness	NO ALERT
7	3	Palpitations	NO ALERT
7	4	Increased HR unable to settle	ALERT - SR

Table 8: summary of participant descriptions of 'heart-related symptoms'

6.3.4 Nature of Readings

100% of the ECGs submitted by participants were interpretable by the cardiologists. There was a 98% agreement rate between the two cardiologists. All ECG readings submitted by Participants 5,6 & 7 were interpreted as 'normal sinus rhythm' (56% of the total readings from this trial). For Participant 2, 5/23 readings were considered abnormal by Cardiologist 1 and 3/23 readings by Cardiologist 2 respectively; two readings were labelled as VPBs by Cardiologist 1 but labelled as 'sinus rhythm' by Cardiologist 2. Finally, for Participant 3, a total of 21/26 (80%) readings were considered abnormal (i.e. not normal sinus rhythm). From those readings rated abnormal, the classification of each is shown in Table 9 below, separated by participant, with Unifocal Ventricular Premature Beats (VPB – as described by Cardiologist 1) or Ventricular Ectopic Beats (VE as described by Cardiologist 2) being the most common. VPB/VEs are a type of premature ventricular contraction; this occurs when the electrical signal originates in the ventricles, not in the atrium as usual [634].

Participant	Reading Number	Classification	
		Cardiologist 1	*Cardiologist 2*
2	5	Frequent unifocal VPBs	Normal sinus rhythm
2	6	Frequent unifocal VPBs	Normal sinus rhythm
2	7	Frequent unifocal VPBs	Frequent VEs
2	8	Frequent unifocal VPBs	Frequent VEs
3	9	Single VPB	One VE
3	7	Frequent unifocal VPBs	Frequent VEs
3	8	Frequent unifocal VPBs	Frequent VEs
3	9	Single VPB	One VE
3	7	Frequent unifocal VPBs	Frequent VEs
3	8	Frequent unifocal VPBs	Frequent VEs
3	9	Frequent unifocal VPBs	Frequent VEs
3	10	Frequent unifocal VPBs	Frequent VEs
3	11	Frequent unifocal VPBs	Frequent VEs
3	12	Frequent unifocal VPBs	Frequent VEs
3	13	Frequent unifocal VPBs	Frequent VEs
3	14	Frequent unifocal VPBs	Frequent VEs
3	15	Frequent unifocal VPBs	Frequent VEs
3	16	Frequent unifocal VPBs	Frequent VEs
3	17	Frequent unifocal VPBs	Frequent VEs
3	18	Frequent unifocal VPBs	Frequent VEs
3	19	VPB	Frequent VEs
3	20	Unifocal VPBs	Frequent VEs
3	21	Unifocal VPBs	Frequent VEs
3	22	Frequent unifocal VPBs	Frequent VEs
3	23	Frequent unifocal VPBs	Frequent VEs
3	24	Frequent unifocal VPBs	Frequent VEs

Table 9: Classification of abnormal ECGs by cardiologists

From a total of 26 abnormally rated readings (24 from Cardiologist 2), none of these triggered an alert on the Apple Watch. Across all participants in the trial, there was only one alert reported which both cardiologists rated as 'normal sinus rhythm'.

Stress

Following each reading, participants provided a stress rating from 1 (not stressed at all) to 9 (very stressed). There were 11 missing stress values, excluding the ECG readings that were not taken. Previous work showed that stress was the most commonly reported precipitant for heart rhythm disturbances in Xp22.31 deletion carriers [515] (Chapter 5). The mean stress rating for readings classified as 'abnormal'

was slightly (but not significantly) higher than those rated as 'normal' (2.96±1.78 vs. 2.49±1.79, t(106)=1.18, p=0.12).

6.3.5 Referral

Following completion of the feasibility trial, the cardiologists involved in this study recommended that Participant 3 should discuss the results of his ECGs (frequent VPBs) with his GP, with the potential for a formal referral to cardiology. Following the referral, this individual was fitted with a 24-hour Holter heart monitor. The results of this monitoring period identified a mean HR of 86bpm, with 87% of beats classified as 'normal', 13% as 'VE (ventricular ectopic) beats' and <1% as 'SVE (supraventricular ectopic) beats'. The individual reported one event of "fluttering in the heart" (similar to the experiences described by the participant in the screening survey), which was identified as sinus rhythm with frequent isolated VEs. These results will be fed back to the individuals' GP to establish an appropriate treatment plan.

6.3.6 Participant Feedback

Across all the domains included in the post-trial feedback form, participants were highly satisfied and offered several suggestions for how their experience could be improved.

Trial Engagement

Participants were all 'very satisfied' with the conduct of the overall trial, with a mean satisfaction rate of 9.0±1.4 out of 10; participants were satisfied with the frequency of monitoring, the mechanism of data return, and with study engagement (Figure 25). Suggested improvements to the trial included a larger watch strap, clearer guidance about the type of iPhone required to take part and clearer visual scales for stress ratings.

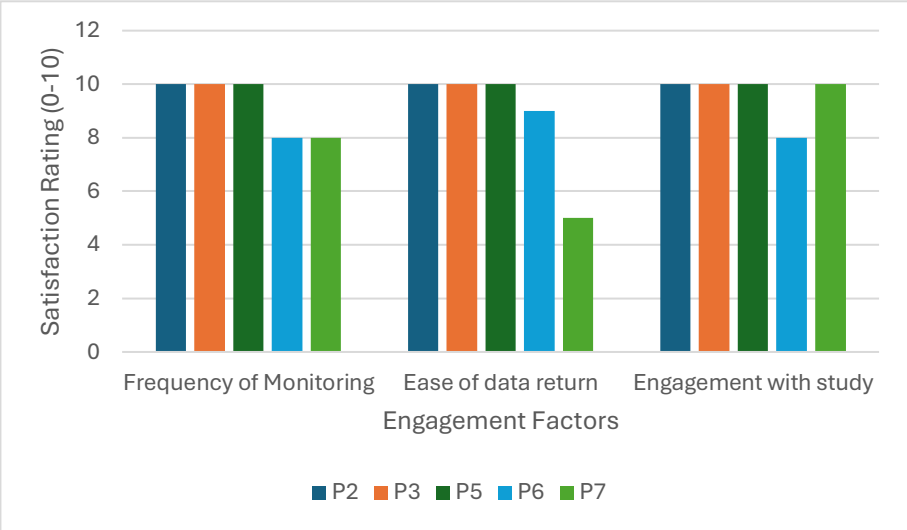


Figure 25: Participant satisfaction with survey engagement

Use of ECG tool in the Apple Health app

Participants were also highly satisfied with their use of the ECG tool with the Apple Health app, with an average satisfaction rating of 9.5±1.1 (Figure 26). One participant stated that using the app took some time to comprehend but they quickly understood the process.

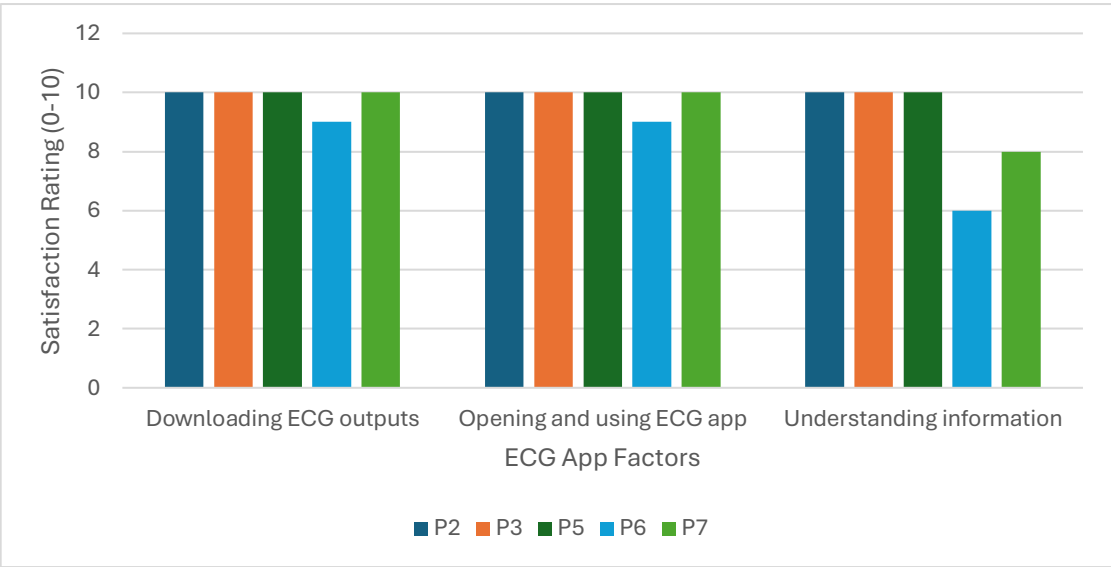


Figure 26: Participant satisfaction with ECG tool

Using watch functions

Participants reported that the Apple Watch was 'very easy to use' (mean 9.5±1.1) (Figure 27). One participant commented that the battery life of the watch could be better.

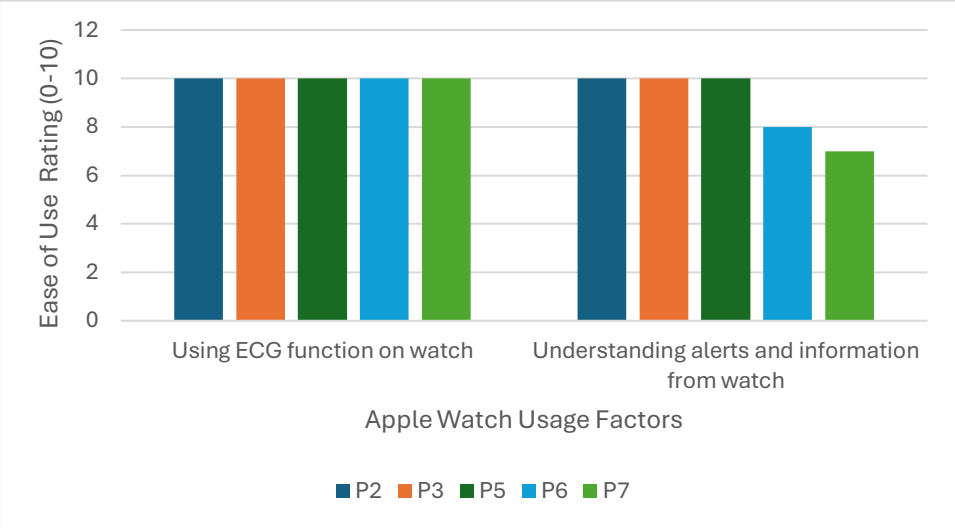


Figure 27: Ease of use of Apple Watch functions

Wearability of watch

Participants found the watch comfortable to wear on a daily basis (mean agreement 9.4±0.9) and reported little to no discomfort on their skin. Figure 28 below shows the number of participants who agree/disagree with each of the statements presented. One participant reported that the sensation of wearing the watch every day was overwhelming.

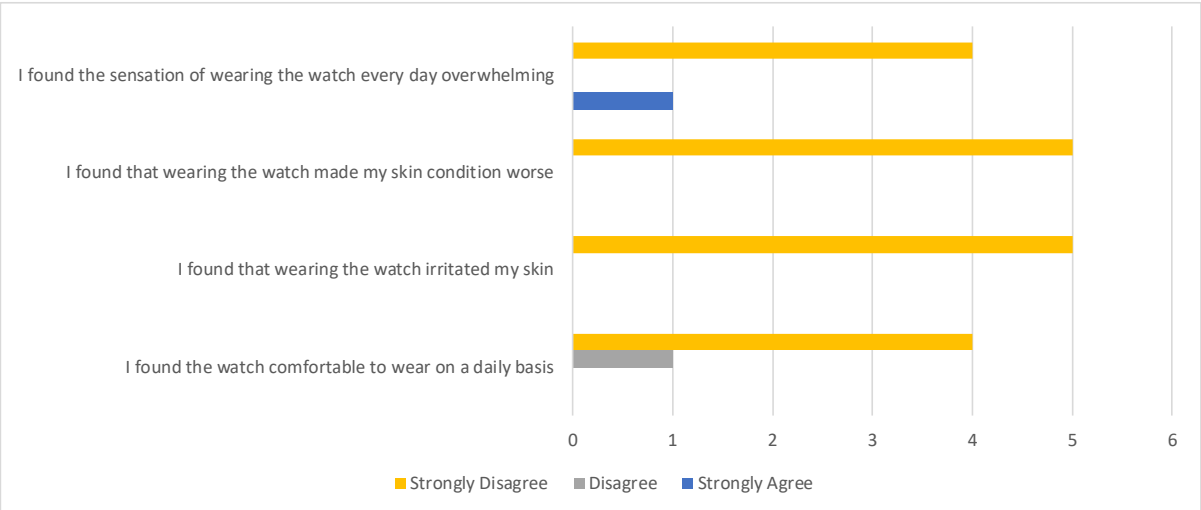


Figure 28: Wearability of Apple Watch

Qualitative feedback

Participants also answered a series of questions about their thoughts on the use of wearable technology as a preventative screening measure. The overall response was extremely positive, with participants describing their enthusiasm towards the new technology:

> *"I think it's a fantastic idea… if the tech is reliable, I think it should be encouraged and could help alleviate pressure on services"* (P6)

> "…*from my experiences hospital staff and some GPs are not yet open to this technology, maybe within the next decade"* (P3)

However, participant 7 described their preference for other forms of ECG monitoring systems as they expressed concern with the lack of alerts from their Apple Watch:

> *"I think wearing ECG mentor might work better. I wore a Holter Monitor that picked up discrepancies in my heartbeat"* (P7)

> *"I was never notified by the watch or iPhone even though I could feel them [irregular beats]"* (P7)

Some participants also provided suggestions for changes and greater transparency in the process, including the regular feedback of ECGs even if rated 'normal':

> *"I would like some feedback from yourselves, as we are not experts in reading ECGs"* (P3)

> *"Although taking ECGs three times a week was manageable, I don't know whether monitoring for a set time period would provide more accurate data"* (P5)

Overall, the trial was generally received well by participants.

> *"Very easy, seamless and professional"* (P6)

> *"I found the monitoring easy and I was pleased to join your study"* (P7)

6.4 DISCUSSION

This feasibility trial monitored the heart rhythms of five adult males with *STS* deficiency (X-linked ichthyosis) over an 8-week period using the Apple Watch Series 8. The trial assessed the suitability of the Apple Watch as a form of wearable technology to monitor heart rhythms in this group, as well as determining the most effective procedures. Overall, this study was highly successful in recruiting the intended number of participants, with a high engagement and response rate over the trial and minimal procedural issues. Abnormal heart rhythms, specifically VPB/VEs, were identified in two participants, one of whom was subsequently referred for formal cardiac monitoring. There was no significant association between stress and abnormal readings, although consistent with our previous work, on average, abnormal heart rhythms were associated with slightly higher self-reported stress levels. This form of monitoring was positively received by all participants, and there were no reported issues with the use of the watch on ichthyotic skin (i.e. all readings were reliable and interpretable by the cardiologists, and reports of skin irritation were limited).

6.4.1 Positive Outcomes

As intended, five individuals were recruited across a range of ages to take part in this trial. One individual was not able to take part in the trial, as a change in the iPhone hardware requirements midway through the trial in order to use an Apple Watch in conjunction with the Apple Health app, was not anticipated. This was an unavoidable issue, but larger studies in the long term may need to take the potential for these changes into consideration.

Across participants who did take part in the trial, there was a high engagement and response rate, specifically in submitting the ECGs on a weekly basis, and in providing post-trial feedback. Compared to other web-based cardiovascular trials [635, 636], and longer-term wearable technology trials [637], consistent engagement levels were considerably higher in this study.

The ECG readings taken on the Apple Watch were all interpretable by the cardiologists, and participants were highly satisfied with the ease of use of the watch, the associated Apple Health app, and the process of submitting readings. This high satisfaction rate mirrors the research discussed in 6.1, concerning the importance of user acceptance when implementing wearable devices to improve health outcomes [612, 613].

Another positive outcome of this trial, is the detection/identification of multiple VPB/VEs in two participants, allowing onward referral in one case to formal cardiac monitoring. The watch data from this trial was consistent with data from the subsequent 24hour Holter monitoring, demonstrating high reliability of results.

Research also emphasises the importance of data protection and security within the data infrastructure for patients [613, 619, 620], with concerns around data interception, spyware and software vulnerabilities [638]. However, these issues were comprehensively addressed in the information provided pre-trial, as well as in the printed information pack that participants received alongside the watch. Post-trial feedback from participants did not reveal any concerns or issues with data security, and participants were encouraged about the potential for future implementation of wearable technologies in healthcare.

6.4.2 Potential issues to address in larger trials

One potential cause for concern in this trial is the lack of alerts from the Apple Watch, even where participants perceived heart rhythm disturbances. Over a total of 119 readings, 26 readings were rated abnormal by Cardiologist 1 (24 by Cardiologist 2). This was made up of 5 readings from Participant 2 and 21 readings from Participant 3. However, none of these triggered an alert on the Apple Watch. It is important to note that VPB/VEs are not necessarily harmful and occur in 40-75% of healthy individuals undergoing a 24-hour ambulatory ECG monitoring [639-641]. However, VPB/VEs were rated as abnormal by cardiologists in this trial based on the prediction that individuals with >200 premature ventricular complexes (PVCs, also known as VPB/VE are a type of ventricular tachycardia) per 24 hours are statistically more likely to develop a supraventricular tachycardia [642, 643], thus presenting

potential future cause for concern. As this study only required participants to take three ECG readings per week, it is not possible to ascertain whether Participants 2/3 were experiencing >200 PVCs per 24 hours. However, following formal referral to cardiologists outside of the trial, the results of the 24-hour heart rhythm monitoring from Participant 3 marked 16,709 beats as 'VE' over this period, thus far surpassing the 200-beat threshold for concern. The lack of alert from the Apple Watch for any of these VPBs during the trial raises concerns about the effectiveness of the device in detecting HRAs beyond clear supraventricular tachycardias such as AF [623, 629].

In this trial, participants were asked to record ECGs 3x per week, and therefore arrhythmic episodes may have been missed. Other ECG device trials have requested 4x readings per day, over a shorter trial period (e.g. SAFER trial: https://www.safer.phpc.cam.ac.uk). Thus, this is a practical component that may be considered in follow-up trials.

Another potential limitation of this trial is the stress rating provided with every ECG upload. These were uploaded to the Qualtrics platform at the end of each week, and thus unless the participant had made an accurate record at the time of taking the ECG reading, this score may not be accurate. To overcome this issue, a tracking sheet or template could be offered for participants to record their stress scores and concurrent behaviours, at the same point as the ECG.

In the post-trial feedback, one participant also requested more feedback about their ECG ratings. In the information sheet and debrief form, participants were reminded that none of the information for the trial was sufficient to make a clinical diagnosis and that the cardiologists would be responsible for providing information (via the research team to maintain anonymity) to any participants who may require further testing/examination from their GP. However, to improve transparency and communication with participants in future trials, it may be necessary to provide a comprehensive written outline of the outcomes from each ECG reading.

6.4.3 Long Term Implications

The referral of Participant 3 to formal cardiac investigation via their GP is a significant success of this trial and highlights the potential benefits of using

affordable wearable technologies to identify (symptomatic or asymptomatic) rhythm abnormalities of potential clinical significance in individuals at genetically elevated risk. These findings build on the published results from the previous Chapter [515], to provide an effective monitoring measure for these at-risk individuals. Furthermore, the ongoing HEARTLINE study, as discussed in 6.1, will hopefully aid in understanding how the Apple Watch can be used to identify AF in older populations, which may also apply to individuals with an *STS* deficiency.

Crucially, the results of this study suggest that individuals with an *STS* deficiency may not only be at risk of AF as previously suggested [187, 511, 515], but also at risk of other cardiac rhythm abnormalities including VPB/VE. VPB/VEs are predisposing factors in the development of AF, and thus early identification may prevent downstream consequences such as stroke, cognitive decline and heart failure [234], as well as negative psychosocial outcomes [488] [489]. This offers a potential therapeutic target and an avenue for future research to establish successful intervention strategies to develop this monitoring. Furthermore, recent work in our group has recently suggested that increased arrhythmia risk in XLI may be a consequence of structural heart issues, notably septal defects [244]; VPB/VEs are associated with such defects [644]. Thus, monitoring should include screening for anatomical differences, as well as heart rhythm abnormalities.

Monitoring methods which involve one or more components of collaboration with the individual may be more likely to improve patient adherence and satisfaction with care, especially for long-term conditions [645, 646]. Monitoring processes such as the Apple Watch require heavy reliance on patients and their consistent feedback in the trial. The high levels of participant engagement and the positive feedback received in this trial, highlight the importance of an efficient and open discourse with patients when utilising monitoring technology.

For larger scale, future monitoring, the results of this study suggest that clear, visual instructions about how to use wearable technologies and associated devices e.g. Apple Watch and iPhone, are crucial in obtaining reliable, time-efficient results. Future trials should also allow time for participants to 'test-run' the equipment before formally starting the trial, to become familiar with the procedures. Weekly

reminders also proved effective in this trial to encourage participants to submit their readings, and as a way to maintain an open dialogue for any concerns or questions throughout the 8-week period.

6.4.4 Conclusion

This study assessed the feasibility of using Apple Watches as a form of wearable technology to monitor heart rhythms in five adult males with XLI. The results of this study indicate that this approach is effective at recording ECGs for formal review, and these results are reliable when compared to commonly used Holter monitoring. The lack of watch alerts for VPB/VEs experienced by some participants (precursory factors in the development of HRAs), suggests that involvement and close review by cardiologists is a necessary component of this trial. Participants were highly committed to this trial, and minimal issues with the procedure adopted were encountered. Larger trials of such wearable technologies may employ more frequent monitoring over a shorter period of time, and more specialist, accessible software for uploading ECG readings and relevant contextual details.

Chapter 7: GENERAL DISCUSSION

**Note: some of the material included in this Chapter and relevant appendices relates to the following published work, for which I am listed as the first author:*

Wren GH, Davies W. Cardiac arrhythmia in individuals with steroid sulfatase deficiency (X-linked ichthyosis): candidate anatomical and biochemical pathways. Essays in Biochemistry. 2024 Apr 4:EBC20230098.

Wren G, Baker E, Underwood J, Humby T, Thompson A, Kirov G, Escott-Price V, Davies W. Characterising heart rhythm abnormalities associated with Xp22. 31 deletion. Journal of Medical Genetics. 2023 Jul 1;60(7):636-43.

7.1 Strengths of the research approach and a summary of key findings

Using an established online survey methodology in conjunction with a feasibility trial, this thesis aimed to develop a greater understanding of the psychological and physiological issues associated with the rare congenital skin condition, X-linked ichthyosis (XLI), caused by deletions at *STS*. The design and implementation of this research allowed for an in-depth exploration of physiological and psychological factors associated with loss of *STS* function. This directly relates to the biopsychosocial model as discussed in Chapter 3: by examining the interconnections between all three components (biology, psychology and socio-environmental), this research has improved our holistic understanding of XLI as a condition.

A key strength of this thesis is the high levels of participant engagement achieved; through a range of recruitment channels, the intended sample sizes (determined by G*Power) were met for every study. This produced reliable results across a wide range of participants. The online nature of the study allowed for a geographically, and socially diverse sample that may not have been studied otherwise. Furthermore, patients with XLI may be limited in time due to the intense nature of their condition, and thus online surveys involve minimal time commitment at a time/location that suits the individual [323]. Although participants experienced high levels of stigma, they

may have been more comfortable answering questions online without the pressure or presence of a researcher which may have yielded more valid results [323].

Another key strength of this work was the strong working relationship developed with the ISG, which greatly aided recruitment and participation levels across all four studies. The research adverts were posted online on the ISG website, social media and via the regular newsletter, in addition to other international organisations such as FIRST, which increased the reach to a wide sample of potential participants. Through our collaboration with the ISG, we were able to develop trust with individuals and thus hopefully promoting an honesty in their responses and a better representation of their experiences. In addition, as members of Facebook-based patient support groups, we were able to build community in our research group, involve participants in decision making, and stay up to date with new concerns discussed amongst patient which greatly aided the research process as a whole.

The results of this work (Chapter 3) provide substantial evidence of a higher risk of mood and neurodevelopmental disorders and associated traits in both males and females with XLI compared to matched dermatological (IV) and general population samples, thus corroborating and extending previous results from our research group [187, 228, 272, 418]. Contributory factors towards mood symptoms in XLI were investigated for the first time, as indexed by self-reporting; this analysis indicated that chronic life events, stigma and bullying, and skin-related frustrations were perceived as the most important contributors which may be targeted through behavioural and/or societal interventions.

Chapter 4 investigated memory and associated executive functioning in individuals with XLI and female deletion carriers compared to matched IV/general population controls and tested whether any effects on memory might be related to altered mood. The main finding, that XLI (or carrier) status was associated with poorer self-reported and objectively-ascertained memory performance independently of current mood, contrasted with previous rodent work indicating a beneficial neurocognitive effect of STS deficiency [416, 417].

This thesis also presents initial evidence for a considerably increased risk of abnormal cardiac function, specifically ventricular tachycardias, in individuals with XLI and female carriers (Chapter 5). The onset of arrhythmias was most often self-reported to be precipitated by stress, and individuals with heart rhythm abnormalities were also found to be more likely to present with several comorbid conditions (anaemia, asthma, and gastrointestinal issues). Given the potentially serious and long-term consequences, identifying heart rhythm abnormalities early in high-risk populations (such as XLI) is important. Therefore, Chapter 6 discussed a feasibility trial which assessed the effectiveness and acceptability of the Apple Watch as a form of non-invasive wearable technology to monitor heart rhythms in adult males with XLI. Results from this trial indicate that this is an acceptable and streamlined form of monitoring for patients with XLI. However, the sensitivity and specificity of this method for detecting an irregular heartbeat remain to be fully explored.

Overall, these findings provide new evidence for the effects of *STS* loss on emotional, cognitive and physiological functions in man, across a large and diverse mixed-sex sample. The mixed methods approach adopted for this thesis allowed for an in-depth, focused investigation of relevant factors that may be relevant in the long-term care of individuals with XLI. Providing opportunities for participants to share their experiences and offer additional detail to support their quantitative response, created a rich dataset and aided our understanding of the patient experience.

I hope that the long-term management of XLI improves as a consequence of the new findings described within this thesis. The increased risk of emotional, cognitive, and cardiac phenotypes in the XLI population may be attenuated through a combination of early identification and ongoing monitoring with pharmacological, psychological and societal intervention where required. To facilitate this, I have published/aim to publish all of my findings open access in respected journals for patients, family members, clinicians and other relevant stakeholders to access. Additionally, by sharing this work at relevant dissemination events, and through collaborating with relevant charities, I am optimistic that awareness of XLI and its

comorbidities will improve. To aid this cause, I am currently working with Ichthyosis Support Group UK to develop information leaflets providing the most up to date information for sharing with its members and other interested parties worldwide.

7.2 Interpretation of Findings

In the following section, the nature of these findings, and the possible biological mechanisms, are discussed in greater detail.

7.2.1 Effects on Mood and Cognition

The study outlined in Chapter 3 identified increased rates of both formal diagnoses of depression and higher levels of psychological distress across adult XLI, IV and psoriasis patients, compared to age/sex-matched general population samples. These findings corroborate extensive work in previous dermatological samples [115, 119, 121-124], suggesting that individuals living with a skin condition are significantly more likely to develop adverse mood symptoms. However, this is one of the first studies to directly compare these symptoms across skin conditions, each of which has a distinct aetiology.

Unexpectedly, the results presented in Chapter 3 show no link between stigmatisation and mood, although all participants exhibited moderate levels of perceived stigma. This contrasts to existing work which suggests that negative mood in individuals with a skin condition is often linked to lower self-esteem [92, 127], increased social isolation and diminished social functioning [91, 130]. The general impact of stigmatisation cannot be underestimated: effects on health include increased likelihood of other psychological problems, neurological issues, and adverse physiological responses [647], all of which have negative downstream consequences. [648]. This presents a unique biopsychosocial challenge which can seemingly only be remedied with improvements in the appearance of the skin [649].

However, in this study it may be possible that age may play a substantial role in mitigating this relationship, with younger people more likely to be concerned about their appearance [91, 130] and thus more likely to experience psychological distress. This was not directly analysed in Chapter 3, especially as only participants over 18

years old were recruited, and thus understanding the psychological impact of XLI in adolescents may be of particular interest in future research. This is of particular importance as adolescent depression and anxiety are strong predictors of mental health problems and poor health and social outcomes in adulthood [650, 651]. Furthermore, low self-esteem in adolescence is a strong predictor of adult depression [652, 653]. Thus, although this has not yet been directly explored in this field, mediating psychological distress at the earliest stage may have beneficial effects on future health outcomes in this group.

Chapter 3 also explored general and condition-specific factors that patients have associated with contributing towards their adverse mood symptoms. General factors included skin-related discomfort and difficulties with treating the skin condition, and thus patients with XLI/IV/psoriasis should receive adequate guidance and support for the sourcing and application of topical treatments with the view to minimize pain/inconvenience. Stigma and bullying appeared to be a major contributory factor for males with XLI, whereas female carriers (little to no cutaneous manifestations) were more affected by chronic life events. Education at a societal level about medical conditions that affect appearance should be a priority, such as charities like Changing Faces which provide support and promote respect for individuals with a visible difference [654]. Such organisations also prioritise building community and challenging loneliness, which can be a key factor in acceptance and improving self-esteem. Another approach to avoid or effectively manage adverse mood symptoms may include promoting resilience and developing coping strategies as discussed in 1.3.1. Emotion regulation and cognitive restructuring have proved effective in improving both physical and psychological factors in other dermatological conditions [148, 154, 157]. However, this has yet to be explored concerning more rare skin conditions such as IV or XLI and thus this offers an exciting opportunity for developing effective psychological support structures for these groups.

The results from Chapter 3 also indicate that individuals with XLI, IV and psoriasis all experience reduced QoL, as measured by the dermatology-specific tool, the DLQI. This mirrors existing literature from several other dermatological groups; individuals living with a skin condition are more likely to report a significantly lower health

status [88] [90], compared to healthy controls (see 1.2.3). Interestingly, this study found that females in particular exhibited worse DQLI scores compared to males in both the IV and psoriasis groups. This supports recent literature, suggesting that female sex is often associated with worse HRQoL and QoL [655], due to several genetic, physical and social factors [100, 101]. More specifically, this may be due to historical neglect of women's health [656], lower personal income [655, 657], marital status [655], or complex living arrangements e.g. caring for an older relative which are more common for females [657]. Although none of these factors were explored in this study, it is clear that these sex-based (or gender depending on the definition used) effects on QoL can be generalised beyond XLI as a dermatological condition.

It is important to acknowledge that as discussed in Chapter 3, QoL outcomes were strongly influenced by feelings of stigmatisation in males, and moderately influenced in females. Thus, targeting factors such as self-esteem and stigmatisation as a possible avenue for intervention is likely to subsequently improve QoL. As discussed with reference to contributory mood factors, methods to reduce stigmatisation may include increased public awareness and information about rare diseases and visible differences, as well as increased knowledge within clinical care. Public dissemination events and campaigns may also be effective in raising awareness of conditions such as XLI. Strategies and interventions to develop resilience for both young people and adults with XLI may also be particularly effective [658-660], but there is little research surrounding the effectiveness of resilience in mediating long-term emotional health outcomes.

The findings presented in Chapter 4 offers novel findings regarding the effects of *STS* loss on memory and executive functioning, which has not yet been explored in humans. These results provide further evidence for prominent effects on cognition in individuals with XLI. Before conducting the study reported in Chapter 4, it was expected that individuals with memory deficits would exhibit more adverse mood symptoms. However, findings suggest that impaired memory is independent of mood in both males and females with XLI. Thus, it may be the case that the mood effects of STS deficiency do not adversely affect memory (or that the memory effects do not adversely affect mood). It may also be the case that individuals with a

larger deletion may be more at risk of developing certain deficits compared to individuals with a smaller deletion, but this is a developing area of genomic research. To help define this causal process, future work may investigate the relationship between deletion size and effects on mood and cognition (memory).

One biological explanation to explain the link between XLI (as well as IV and psoriasis) and adverse mood symptoms, is the effects of inflammation. Recent research has suggested that inflammation may play crucial role in the development of impaired psychological function, including negative mood [365, 368, 369] (as discussed in 3.4.2). In regards to executive functioning, markers of systemic inflammation have previously been associated with reduced memory [661, 662] and cognitive deficits [663], independent of depression, and cardiovascular or metabolic risk factors [663]. This initially suggests that inflammation, as a result of the cutaneous manifestations of XLI, may play a causal role in the deficits in memory and mood. However, although female carriers of XLI-associated genetic deletions rarely exhibit cutaneous manifestations (thus unlikely to exhibit increased inflammatory markers although this has not been tested as of yet), they do experience deficits in mood, memory, and increased neurodevelopmental associated traits. Thus, it is unlikely that inflammation offers the best explanation for the development/absence of deficits in mood/memory unless inflammation markers independent of the skin were significantly higher in the female group (but this is not something that has been assessed).

Alternate biological mechanisms which may have important implications for mood regulation and cognitive functioning include modified lipid metabolism which is perturbed in XLI as a result of STS deficiency [225, 664 235 665]; altering lipid composition of the brain may cause small changes to cell membrane structure [666, 667] and potentially subsequent effects on memory. Further explanations include findings from neuroimaging in deletion carriers which identified smaller right globus pallidus [451], previously been associated with neurodevelopmental disorders [668, 669], and disruption of which has previously been implicated in ADHD-related traits and motor response inhibition [670]. Thus, altered global pallidus structure or function may contribute towards impaired mood and memory function in individuals with XLI.

Another potential explanation is altered serotonin levels in the hippocampus; recent findings in mouse models revealed elevated levels of 5-HT (5-hydroxytryptamine, more commonly known as serotonin) in mice lacking STS in both the hippocampus and the striatum [671]. In the striatum, this directly correlated with increased hyperactive and aggressive behaviours, as corroborated by further research into the effects of differing 5-HT levels of ADHD [672, 673] and depression [674]. This work offers another potential biological explanation for this behavioural phenotype following STS loss; however, this mechanism may be limited to mood symptoms, as findings are not robust for whether levels of 5-HT have sustained effects on memory or other executive functioning skills [675-677].

Altered levels of other circulating steroid hormones, specifically DHEA/S, may also have effects on mood [420]; the administration of DHEA in man led to improved mood [678] and reduced depressive symptoms [679] (which is the opposite of XLI as loss of STS function results in higher levels of un-sulfated DHEAS > DHEA). Thus, although the biological mechanism is not yet clear, higher levels of DHEAS>DHEA in individuals with STS loss may be key in explaining higher adverse mood symptoms. However, the effects of elevated DHEAS on memory are not so clear: initial rodent models suggest that elevated DHEAS levels have a positive effect on memory (see 4.1.1), but other work suggests negative impact on cognitive function [680]. Work from our research group using a UKBB sample corroborated this mouse work, in which Xp22.31 carriers (with higher levels of DHEAS) performed worse on general executive function and intelligence tests [187]. Thus, the exact relationship between DHEA/DHEAS levels and cognitive function remains unclear, although results from Chapter 3 and 4 lend weight to the negative effects of elevated DHEAS in man.

7.2.2 Effects on physiology

In addition to the adverse effects on mood and memory, this thesis also showed that individuals with a loss of *STS* are significantly more likely to develop heart rhythm abnormalities (HRA) (Chapter 5). This work was based on recent findings from our research group where we showed Xp22.31 deletion (including *STS* loss) acted as a strong risk variant for the development of AF [515]. The Xp22.31 region

deleted in XLI typically escapes X-inactivation, and thus gene(s) within it, including *STS*, may contribute towards sex differences in AF risk (male sex is a significant risk factor in the development of the most common form of tachycardia, atrial fibrillation (AF)) [506-509]. Using online self-report methods, a significantly higher prevalence of HRAs, specifically tachycardic HRAs, was identified in adult males with XLI, female carriers of XLI-associated genetic deletions, and boys under 18 years, compared to general population figures (see 5.3). These findings corroborate original findings from previous work [515] and, in combination with gene association analyses carried out in parallel, suggest that STS deficiency specifically is a strong functional candidate in the development of HRAs such as AF [515]. This is a novel discovery and provides important evidence pertaining to the long-term management of XLI for patients. Early identification and management of HRAs and precipitating factors, is crucial in the prevention of adverse downstream effects such as morbidity, stroke, cognitive decline, and heart failure [234]. This is of particular importance for females, as they typically present with a larger risk of AF-associated adverse outcomes, including mortality and stroke due to female-specific factors such as pregnancy and menopause [486].

Biochemical and anatomical explanations for the increased HRA risk in individuals with STS loss are not yet certain, but we recently published a paper proposing a potential mechanism [244]. STS is highly expressed in arterial vasculature and cardiac tissue [524, 681] and although these findings suggest that STS may influence cardiac function, this may be as a result of direct effects on cardiac tissue, or indirect effects on cardiac tissue via mediating effects on the endocrine system [244]. The first suggested anatomical risk mechanism is a predisposition to abnormal septal development. This idea was stimulated by findings presented in a new paper by McGeoghan, Camera (2023) in which the authors explored the effects of knocking down *STS* expression in human skin cells, and found significant enrichment for genes involved in ventricular septum morphogenesis. Septal defects, although only present in around 0.5% live or stillbirths [682], can lead to impaired cardiac function, including tachycardia, and are associated with later risk of arrhythmia in adults, even where the defect has been repaired in early-life [236, 237]. The prevalence of septal

defects in individuals with the typical XLI-related deletion at Xp22.31 was 4.4% in a comprehensive analysis of the DECIPHER database [683]; in addition a small number of case studies of children [241, 684] [243] and fetuses carrying such deletions have implicated structural heart abnormalities [242]. Thus, despite the limited data and possible reporting bias, rates of septal defects in Xp22.31 deletion carriers appear notably higher compared to estimates from the general population and thus this may be one possible biological explanation for increased rates of HRA in this population.

Our recent review proposed a cellular and molecular pathway by which steroid sulfatase deficiency leads to increased vulnerability to septal defects and thereafter to HRAs [244] (Figure 29). Research suggests that the proliferation of cardiac fibroblasts and levels of laminin proteins are dependent on DHEAS, levels of which are impacted by loss of STS [685-687]. Moreover, loss of STS may also cause impaired basement membrane function [259], thus partially explaining the cutaneous and extracutaneous phenotypes associated with XLI. Matricellular Cellular Communication Network (CCN) factor proteins are also particularly sensitive to loss of STS [259, 688] and are key components of healthy cardiac and septal development [689]; when their expression is dysregulated, CCNs are associated with an increased risk of fibrosis. Thus, although the exact mechanisms and role of each of these cellular components is not yet clear, our model suggests that loss of STS, via effects on systemic steroid sulfatase levels, may affect a) cardiac fibroblast proliferation [235], b) laminin secretion [690, 691] and, c) interactions between CCNs and basement membrane [692]. These endocrinological and cellular processes may cumulatively affect vulnerability to septal defects, ventricular hypertrophy, and increased arrhythmia risk (Figure 29).

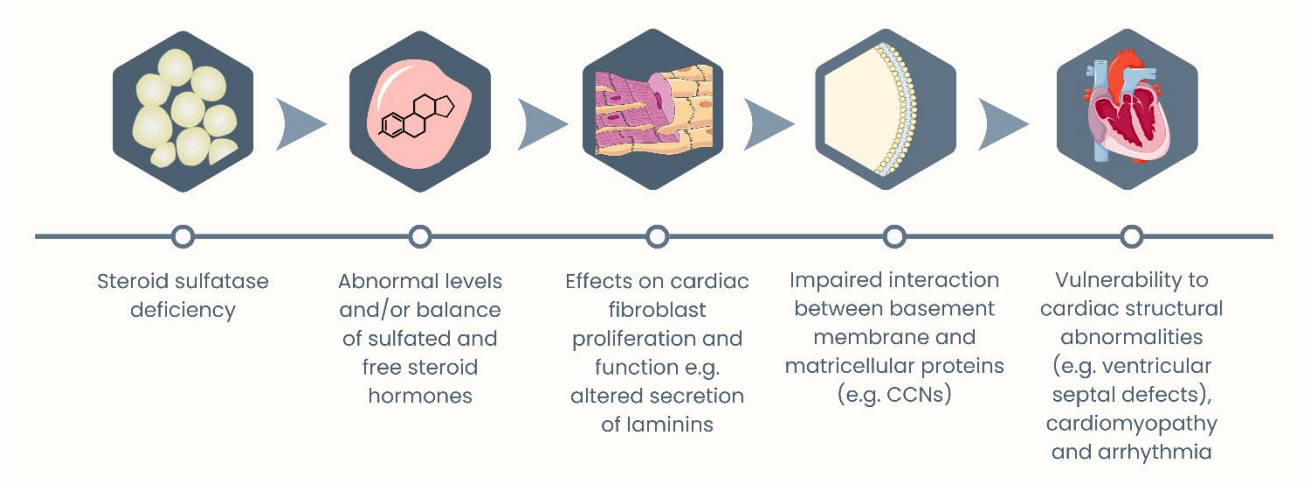


Figure 29: Theoretical model linking STS deficiency to increased vulnerability to cardiac arrhythmias (from Wren and Davies (2024))

To further investigate the relationship between Xp22.31 deletions, steroid hormone levels and cardiac morphology/function, more work is required in human participants. Analyses may utilise resources such as the UKBB, with maximum experimental power in large samples, to explore and compare septum morphology and ECG readings. Performing a comprehensive series of clinical investigations such as auscultation, echocardiography, and electrocardiography in individuals presenting with XLI may be of particular importance for determining the consequences of Xp22.31 deletions with respect to cardiac function. Furthermore, supporting research may utilise mammalian models such as mice to further explore the effects of *Sts*-deletion or inhibition on cardiac pathways and signaling [693].

In this study, three different conditions which were frequently comorbid in individuals with an HRA were also identified: asthma and anaemia in females, and gastrointestinal issues (GI) in males; patients with these comorbidities may be prioritised for cardiac screening. It is suggested that loss of function of *PNPLA4* is the most likely candidate for these comorbidities, as research suggests this gene plays a prominent role in their development and this is supported by gene association analysis (see 5.4.3) [515] [515]. Typically sized XLI deletions are likely to encompass *PNPLA4*, and thus individuals experiencing loss of *STS* and HRA, are likely to have a deletion spanning this area. Other explanations for these comorbid conditions are discussed in 5.4.3, as it is important to recognise the potentially beneficial effects of effectively treating asthma and anaemia in reducing HRA burden [547] [551, 552]. There is little current evidence for the relationship between GI issues and HRA [694], but dissociable mechanisms include obesity, hypertension, and diabetes [526, 545], although no relationship with these variables was found in this work. The putative bidirectional relationship between HRA and the comorbid conditions reported in Chapter 5, might be investigated further; effective management of both components may mitigate future adverse health outcomes [547, 695, 696].

7.3 Managing disorder risk in XLI

It is important to recognise that at the time of writing, there is no known cure or treatment for loss of STS in man. Thus, although cutaneous manifestations can be managed to an extent using topical treatments and self-management strategies [697], the risk of developing XLI and these comorbid conditions cannot yet be directly managed through biological manipulation of the causal mechanism i.e. through gene therapy. Thus, early identification of, and monitoring of/intervention for comorbidities and managing other known risk or precipitating factors should be the focus of interventions for individuals with XLI.

7.3.1 Clinical Care

The findings presented in this thesis offer compelling insights into the physiological and psychological issues associated with loss of *STS* function, which warrant careful consideration. These results have the potential to significantly inform the advancement of care structures and future interventions tailored to individuals with XLI.

As discussed in 1.4.6, there is currently no central treatment framework or formalised assigned guidelines following a diagnosis of XLI. The new 'practical clinical guide' published in 2023 [285], and the 2019 'European Guidelines of Care' [606], are both designed to cover all types of congenital ichthyoses, and thus offer a brief, limited overview of treatment recommendations. In particular, current guidelines lack information about extracutaneous manifestations associated with the ichthyoses which, as this thesis has shown, are both common and significantly impact daily functioning. One important example of this is the impact of stimulant medications used to treat ADHD which can initiate/exacerbate cardiac arrhythmias [698]. This is an important consideration in a group at risk of both ADHD and arrhythmia and might suggest the need for close monitoring of medication, or alternative non-stimulant medications considered to treat ADHD. Thus, current guidelines should be appropriately updated to include all the possible comorbid conditions, to primarily educate and inform clinicians when making a diagnosis, and for long-term management of XLI. To improve care standards for this population, clearer referral

pathways should also be established to promote more timely identification of comorbid conditions, and for patients to receive the necessary specialist support.

An outline of relevant guidelines and clinical pathways should also be freely available to patients if requested or required, to improve understanding of their condition, and to promote a collaborative approach to care with the clinician [699, 700]. Collaborative practice may include connecting with MDTs, active engagement in care practices, regular review and follow-up, and 'looking beyond the condition' [701, 702]. Research suggests that this type of approach is effective in producing positive perceptions of clinicians, reducing reliance on healthcare services, and helping patients to feel more involved in their care [702, 703].

A potential avenue for future research and development in patient care based on this thesis, is the creation of a comprehensive information guide such as booklets or leaflets, to be offered to patients (or parents if relevant) when diagnosed with XLI. As this thesis has shown, individuals with the condition are at significantly increased risk of developing several comorbid conditions, but this may not be conveyed to patients when diagnosed due to the lack of formalised guidelines. Thus, a thorough physical and/or online resource explaining the condition, aetiology, treatment options and success rates, risk factors in the development of comorbid conditions and how to manage these, and signposting to other resources such as charities, may be effective in improving patient care, particularly long term.

7.3.2 Psychosocial Support

The results from Chapter 3 clearly showed the impact of living with XLI on mood, self-esteem, irritability, QoL and perceived stigmatisation, and thus more must be done to support the psychosocial wellbeing of this population. Supporting individuals to effectively cope with their condition long-term should be a priority in psychodermatology care and also dermatology patients need parity of esteem in terms of access to existing psychological services developed to provide intervention and support to people living with long-term conditions. Based on these findings, interventions should focus on the following key factors:

A) Coping strategies for stigmatisation and bullying.
    a. *Note: this is not solely the responsibility of the individual, as more should be done to improve awareness of ichthyoses on a societal level.
B) Self-management techniques and long-term planning for the management of the skin condition e.g. applying ointment.
C) Access to specialist mental health and wellbeing services to support ongoing and new mood diagnoses.
D) Improved access to timely neurodevelopmental disorder diagnoses and specialist NDD support services and provisions
E) Improved access and signposting to government-level benefits e.g. caring responsibilities, disability, and workplace accommodations.

As discussed in Chapter 1, access to these types of services may vary greatly depending on location and healthcare provisions, but reviews of current care structures may take these suggestions into account. Comprehensive psychosocial interventions (as discussed in 1.3.2) may lead to significant improvements in QoL and mood symptoms, through creating individualised support packages for individuals with XLI. It is important to note that individuals with a neurodevelopmental disorder such as ASD or ADHD (applying to >10% of males and females with XLI in particular), may require additional accommodations. For example, successful practices in other fields such as dentistry and healthcare include the use of visual aids (pre-, peri and post-treatment) [704, 705], 'tell-show-do' approaches [704], avoiding over-sensitisation [704 706], soft lighting when being examined [706], and longer duration appointments [707]. More clinician-focused suggestions include management guides for optimising care for autistic patients, online training modules to improve understanding, and access to autism-specific care plan structures [708]. These suggestions could be implemented into BAD resources and existing treatment/management guidelines. Thus, to enhance accessibility and maximise the effectiveness of newly developed psychodermatological interventions for a broad range of individuals, it is advisable to consider implanting accommodations such as these.

7.3.3 Screening and Monitoring

Another important implication as a result of these findings, is the potential for future development of preventative screening and monitoring procedures for HRAs and cognitive decline. As shown in the feasibility study (Chapter 6), wearable technology may offer an accessible and effective way to monitor for cardiac arrhythmia. This approach may work best in partnership with regular monitoring and assessment in a clinical setting, particularly for those individuals most at risk (as discussed in 6.1.1 – older age, high BMI, etc.). Encouragingly, responses discussed in Chapter 5 demonstrated that individuals with XLI understood the elevated risk of AF and were optimistic about preventative screening in primary care for HRAs.

Based on the results from Chapter 4, it might also be important to monitor and screen individuals with XLI who are particularly at risk of cognitive decline or memory issues. Early screening measures are designed to identify key hallmarks of a neurodegenerative condition, and can include cognitive assessments, imaging and a clinical evaluation [709, 710]. Research suggests if identified early, treatment may be more effective in slowing down disease progression [709] and may allow patients to come to terms with the diagnosis [711]. However, some scholars suggest early identification is associated with risks such as stigmatisation, loss of status and employment, and low mood [711]. Furthermore, current healthcare systems are unlikely to have the resources to undertake large sets of assessments due to the cost and time burden [712]. Cost and time-effective monitoring measures may take into account general risk factors such as older age [713]. Thus, screening may not be applicable or appropriate for all adults with XLI, but the opportunity to take part should be available, especially for more at-risk individuals.

7.3.4 Managing risk via modifiable environmental risk factors

Stress

The results from Chapters 3,4 and 5 crucially highlight the importance of effectively managing key factors which may contribute to increased HRA (and GI), mood and memory risk. One key example of risk mitigation is stress reduction: findings from Chapter 5 suggest that stress is a common precipitating factor in the onset of HRA

periods. This is of particular interest, given that levels of DHEA/S (and the ratio of these hormones) which are regulated by STS, also typically increase with psychological stress, with this increase also correlating with heart rate [525]. Research widely suggests that psychological and physiological stressors have a significant direct and indirect impact on cardiovascular functioning, and increase the immediate and long-term likelihood of arrhythmia such as AF [714, 715]. Through direct neuronal, endocrine, autonomic, and immune processes and indirect behaviours, research indicates that stress plays a key modulatory role in AF initiation and potentiation [715-717]. As discussed in 3.4.2, stress can also play a role in the (gut)-brain-skin axis; psychological stress can trigger inflammatory physiological responses [371, 372] and subsequently dysregulate gut microbiota [373, 374]. Furthermore, research suggests that exposure to stress can result in the development of inflammatory gut responses, as well as gastrointestinal disorders including inflammatory bowel disease (IBD), and irritable bowel syndrome (IBS) [718, 719].

Moreover, stress is also highly correlated with adverse mood symptoms (particularly depression and anxiety) [720-722], and chronic stress following adverse life events often precede depressive symptoms in adults and children [723-725]. More valuably for future interventions, prolonged periods of 'regular' stress (i.e. not related to life events), are known to increase the likelihood of presenting with adverse mood symptoms, including depressive and anxiety-related traits [726 727]. It is important to note that adverse (childhood) life events are often not avoidable, and thus effective guidelines should focus on adult, everyday stressors to reduce mood disorder risk.

Evidence suggests that stress management is effective in reducing psychological distress, depression, and anxiety, and improving coping in healthy individuals [728, 729]. However, it is important to recognise that given the persistent nature of XLI as a skin condition, minimising stress, anxiety and irritability may present a challenge for both patients and clinicians. Thus, techniques which have proven effective in improving coping, improved well-being and quality of life, and better health outcomes for other long-term health conditions should be prioritised. These include mindfulness-based stress reduction (MBSR) [730-732], and stress management training [733, 734] (also effective in reducing mortality for cardiovascular-related deaths [735]).

Although there is currently no evidence for the effectiveness of such approaches for individuals with XLI, there is no reason why these methods may lead to positive changes in this population. To further reduce the burden of the condition and associated distress, clinicians should also aim to establish a clear, long-term treatment and management plan in collaboration with patients, including opportunities for regular reviews.

Sleep

Another modifiable risk factor which may be a crucial component in long-term patient care plans is sleep quality and time. Current research offers a clear evidence base for the detrimental impact of sleep deprivation (including interrupted sleep) on mood, specifically increased depressive and anxiety-related traits [736] [737], worse adaptive emotion regulation [738], and decreased positive mood [739]. Furthermore, research suggests that impaired sleep may also have negative effects on memory and cognition; individuals experiencing sleep deprivation in a lab setting produced worse working memory scores [740] [739], impaired attention [739], worse reaction times [737] and degraded quality of items stored in memory [740]. These effects are not limited to cognition; unhealthy sleep duration (>8 hours or <6 hours) [741] and insomnia [742] are associated with increased risk of AF in general population adults. Healthy sleep patterns in contrast, characterised by factors such as no snoring, no daytime sleepiness, and adequate sleep duration, are also associated with lower AF risk [743]. One explanation for this association suggests that reduced REM sleep leads to increased vagal tone [744], which can trigger AF episodes [745]. Other suggestions include metabolic changes as a result of deprived sleep which contribute to adverse cardiovascular functioning [743], as well as a disrupted balance between the sympathetic nervous system and vagal outflows which is associated with arrhythmias [743]. However, it is important to note that the relationship between healthy sleep and cardiac arrhythmias is complex and thus multifaceted [742].

Individuals with XLI commonly experience impaired or disrupted sleep [257, 278], often as a result of skin discomfort, as shown in Chapter 3. It is possible adverse mood and neurobehavioral features including high irritability, as well as executive functioning deficits may be exacerbated by these sleep issues [277, 278]. Furthermore,

as the evidence suggests, an increased risk of HRA in individuals with XLI may also be linked to poor sleep quality. Thus, targeted intervention for this population should include sleep-based interventions such as CBT-based approaches [746, 747], relaxation/mindfulness and hypnotherapy [748, 749], and skin discomfort should be minimised to aid this objective.

Obesity

Another key way in which the risk of HRA, GI, and impaired mood/cognitive functioning may be managed for individuals with XLI, is through reducing body mass. Obesity is a key factor in the development of the associated physiological and psychological issues associated with XLI and thus appears to be a key target for risk management.

Evidence suggests a strong relationship between high BMI and cardiac arrhythmias such as AF [750-752], through suggested mechanisms such as cardiac remodelling [753, 754 755], reduced left atrial volume [750 756, 757] and increased epicardial adipose tissue [758-760]. Thus, weight management may reduce HRA risk in individuals with XLI, although the influence of other conditions related to obesity and HRA risk such as hypertension, sleep apnoea and generally increased inflammation [695, 761] should not be overlooked in clinical care recommendations.

As may be predicted, obesity is also highly correlated with several gastrointestinal issues, likely due to its effects on GI motility [762, 763]. These symptoms include upper abdominal pain [763], gastroesophageal reflux [763, 764], diarrhoea [763 764, 765], and heartburn [763]. Thus, management of body mass may potentially alleviate some of the GI issues reported by participants in Chapter 5.

Obesity has also been correlated with adverse mood in both general population adults [766] and adolescents [767], however, this is often a bidirectional relationship [768, 769]. Depressive symptoms and higher body mass are linked via several direct and indirect physiological and psychosocial pathways, including elevated inflammation [770, 771], immunological dysfunction [772], and negative cognitions [773]. Other mediating components include increased stigma, poor body image and level of physical activity [774]. When considering appropriate targets for interventions to reduce adverse mood

risk, individuals with XLI should play a central role in their clinical care, as these components may be more challenging and complex compared to the general population e.g. difficulty exercising due to skin discomfort.

Long-term care plans for individuals with XLI may also take into account the effects of obesity on memory; overweight individuals are significantly more likely to develop Alzheimer's Disease (AD) [775, 776], as well as deficits in verbal learning [777, 778], visual episodic memory [779], working memory [780] and attention issues [781]. Suggested causal mechanisms include the systemic effects of inflammation [782], decreased brain volume [783], and consequences of related conditions such as hypertension [784]. However, it is important to note that this correlation is not firmly established with significant contrasting research [785, 786] [784] and individual differences may play a prominent role. It is important to recognise that although body mass index (BMI) has historically been the central measurement tool for obesity, this is a problematic assessment as it does not differentiate between muscle and fat tissue [787]. Furthermore, this tool negates to account for the sexually dimorphic nature of obesity statistics, with generally higher body fat in females compared to males [784, 788].

Thus, with specific reference to individuals with XLI or deletion carriers, weight management may play an important role in managing HRA, GI, adverse mood and impaired cognitive functioning risk. Other common general health and wellbeing advice should also apply to individuals with XLI, specifically in relation to psychological wellbeing; a reduction in fat intake, improved nutritional value in foods consumed, and reduced red meat intake can significantly improve depressive symptoms in at least 50% of individuals [789, 790] [791]. Thus, dietary and lifestyle guidance from clinicians should remain similar to the general population.

7.4 Limitations

Even though these studies had high participant engagement, the sample remained ethnically homogenous, with a maximum of 20% of individuals defining their ethnicity as a category other than 'White'. Thus, the sample may not be

representative of all individuals with XLI and there may feasibly be ethnicity/geographic specificity in the nature/magnitude of some of the findings presented here. Furthermore, the CISI measure used to self-specify skin redness and scaling is not applicable for individuals with black and brown skin as the exemplar images are of white skin. Thus, this may have deterred some individuals from completing this measure (or taking part at all), or the options selected may not have been accurate for their skin. Currently, there are no alternative measurement scales for ichthyotic skin and thus the CISI was the only option, although campaigns such as 'Mind the Gap' are aiming to improve diversity in medical education [792].

Another demographic limitation of this thesis was the English-only nature of each study. Due to time and funding limitations, it was not possible to offer alternative language translations and thus only individuals with English-language proficiency would have been able to take part. This may have played a role in recruiting a homogenous sample and may thus limit the reliability of the findings across a wider demographic.

The online survey methodology utilised in all studies also offered some benefits and several challenges. An obvious challenge when using online research methods is the lack of objective clinical assessment or tests; this may lead to the (un)intentional misreporting of clinical symptoms or results by participants which may have skewed the data [323]. To manage this, repeated measures were incorporated for the same factor where possible to check the validity of reporting e.g. ASD diagnosis reporting, and ASD-related traits assessment. Another issue with the lack of objective assessment, specifically in a traditional clinical setting, is the lack of complete phenotyping. If participants reported a certain medical condition which required more detail or clarification, there was no follow-up available (unlike face-to-face alternatives), thus providing only a snapshot of information. To tackle this, we offered follow-up text boxes after relevant questions with clear prompts, but these were not always completed.

By conducting a large proportion of the work reported within this thesis online (partly due to COVID-19 restrictions in the first 18 months), the participant sample was necessarily restricted to computer-literate individuals. This may have limited

access to the surveys by older individuals, those without access to the Internet or an appropriate device, or those concerned about data privacy online. This online approach also allowed for potential errors in the technology such as system crashes or irregular formatting which may not have been clear or obvious. Future work may utilise a combination of online and in person testing to develop a broader and more complete dataset, including individuals who may not be comfortable with certain technology.

One way in which the research methods and approach could have been improved would be to expand the involvement and role of patients in the design, data collection and dissemination process. Although strong links were formed with the ISG and other patient organisations, a deeper level of coproduction could have been considered to deepen patient involvement and create a more equitable power dynamic between researcher and participant [793, 794] . This may have improved the materials used, increased the reach of the recruitment strategies, and developed links with patients directly. Future work should prioritise patient involvement, potentially through the creation of a 'patient advisory group' to provide feedback on the research plans, and to provide an expert opinion on new strategies.

7.5 Reflexivity

As a psychologist, I am likely to lean on psychological underpinnings and theoretical components when undertaking my research. My supervisory team who have contributed to this project, although all based in the School of Psychology, may offer different perspectives due to a range of experiences and thus this may have influenced my approach. Furthermore, discussions and interactions with the Ichthyosis Support Group (ISG), both patients and organisers, may also have contributed to a more patient-centred, inclusive approach to this research.

As an individual without XLI, it is difficult for me to truly grasp the experiences of this population. However, as someone with a chronic skin condition, I can empathise and understand the experience to some degree. Throughout each study, I have undertaken a professional approach to communicating with participants, which in some cases has required a lot of patience which has been a learning opportunity for

me. Pursuing a flexible approach to research design, as described in Chapter 1, was particularly challenged at some points, due to challenges with participant recruitment and unexpected findings. Furthermore, my own biases and experiences of illness were also challenged throughout this thesis, but focusing on accurately representing patient experiences was a key development point in my reflexivity practice. This thesis has taught me that although I cannot understand some specific experiences of XLI relevant to these patients, my own understanding of chronic illness can play a profound and important role in my practice as a researcher [795, 796].

Throughout the course of this work, I have learnt a huge amount about XLI and the lived experience of those with the condition. Attending the ISG Family Day in September 2023 to deliver a workshop with patients was a highlight of my PhD, as it provided an opportunity to discuss our work and future research with those affected. These conversations and the results of my thesis have shown me the importance of awareness and information about rare diseases such as XLI, and I have been keen to advocate for this via my volunteer role within Skin Care Cymru.

One particular highlight of this project, was the referral of one participant in the feasibility trial to formal cardiac monitoring, following the identification of VPB/VEs. Without taking part in the trial, the individual may have remained unaware of these issues, thus putting him at increased risk of an HRA. Thus, it is rewarding to know the difference that our research has made.

7.6 Future Research and Conclusions

This thesis has built on previous research into the extracutaneous manifestations associated with loss of *STS* function, using an established online survey methodology, and a feasibility trial. The results of this thesis provide clear, new evidence for increased risk of mood and neurodevelopmental disorders and associated traits, cardiac arrhythmia, and impaired memory and cognitive functioning in individuals with XLI. Implications for clinical care should focus on the development of preventative HRA screening measures and holistic psychosocial care, as well as emphasising the importance of stress and lifestyle management. Future research may explore causal mechanisms in the relationship between loss of *STS*

and mood/HRA/memory, with a particular focus on the (gut)-brain-skin axis. Increased prevalence of HRAs is a novel finding in humans, and thus this requires further investigation, specifically around risk factors and precipitation of HRA onset.

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Appendices

Table of Contents

APPENDIX CHAPTER 2

Appendix 2.1: Ethical Approval – Chapter 3

Dear Will & Georgina,

The Ethics Committee has received the amendment to your PG project: *A comparison of mood symptoms and associated risk factors in X-linked ichthyosis (XLI), Ichthyosis Vulgaris (IV) and psoriasis* (**EC.20.12.08.6184A**)

The amendment has been considered, and based on the guidance disseminated in the Recommencing Human Participant Research document by the Open Research Integrity and Ethics Committee (ORIEC)/Research Integrity and Governance Team (RIGE), it is classed as non-substantial, therefore it does not require further review.

Your new Ethics Committee (EC) code is confirmed in the subject title of this e-mail.

Please note that if any further changes are made to the above project then you must notify the Ethics Committee.

Best wishes,
Sean

Appendix 2.2: Ethical Approval – Chapter 4 (Phase 1)

Dear Georgina,

The Ethics Committee has considered your PG project proposal: An investigation into memory, cognitive function and mood in ichthyosis (EC.22.04.26.6565).

Your project proposal has received a **Favourable Opinion** based on the information described in the proforma and supporting documentation.

Conditions of the favourable opinion
The favourable opinion is subject to the following conditions being met:

- You must retain a copy of this decision letter with your Research records.
- Please note that if any changes are made to the above project then you must notify the Ethics Committee.
- Please use the EC reference number on all future correspondence.
- The Committee must be informed of any unexpected ethical issues or unexpected adverse events that arise during the research project.
- The Committee must be informed when your research project has ended. This notification should be made to psychethics@cardiff.ac.uk within three months of research project completion.

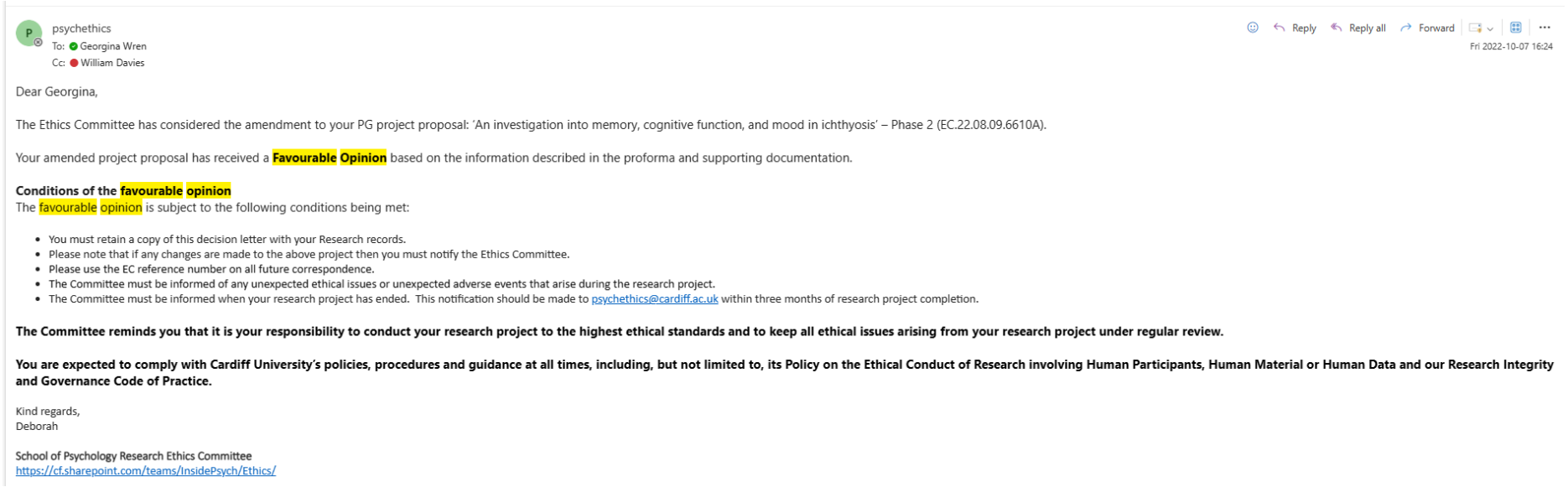
The Committee reminds you that it is your responsibility to conduct your research project to the highest ethical standards and to keep all ethical issues arising from your research project under regular review.

You are expected to comply with Cardiff University's policies, procedures and guidance at all times, including, but not limited to, its Policy on the Ethical Conduct of Research involving Human Participants, Human Material or Human Data and our Research Integrity and Governance Code of Practice.

Kind regards,
Deborah

School of Psychology Research Ethics Committee
https://cf.sharepoint.com/teams/InsidePsych/Ethics/

Appendix 2.3: Ethical Approval – Chapter 4 (Phase 2)



psychethics
To: Georgina Wren
Cc: William Davies

Reply | Reply all | Forward
Fri 2022-10-07 16:24

Dear Georgina,

The Ethics Committee has considered the amendment to your PG project proposal: 'An investigation into memory, cognitive function, and mood in ichthyosis' – Phase 2 (EC.22.08.09.6610A).

Your amended project proposal has received a **Favourable Opinion** based on the information described in the proforma and supporting documentation.

Conditions of the favourable opinion
The favourable opinion is subject to the following conditions being met:

- You must retain a copy of this decision letter with your Research records.
- Please note that if any changes are made to the above project then you must notify the Ethics Committee.
- Please use the EC reference number on all future correspondence.
- The Committee must be informed of any unexpected ethical issues or unexpected adverse events that arise during the research project.
- The Committee must be informed when your research project has ended. This notification should be made to psychethics@cardiff.ac.uk within three months of research project completion.

The Committee reminds you that it is your responsibility to conduct your research project to the highest ethical standards and to keep all ethical issues arising from your research project under regular review.

You are expected to comply with Cardiff University's policies, procedures and guidance at all times, including, but not limited to, its Policy on the Ethical Conduct of Research involving Human Participants, Human Material or Human Data and our Research Integrity and Governance Code of Practice.

Kind regards,
Deborah

School of Psychology Research Ethics Committee
https://cf.sharepoint.com/teams/InsidePsych/Ethics/

Appendix 2.4: Ethical Approval – Chapter 5

From: psychethics <psychethics@cardiff.ac.uk>
Sent: 18 August 2021 15:39
To: Georgina Wren <WrenG@cardiff.ac.uk>; William Davies <DaviesW4@cardiff.ac.uk>
Subject: Ethics Feedback - EC.21.07.13.6374R

Dear Georgina & Will,

The Ethics Committee has considered your revised PG project proposal: *An investigation into heart-related symptoms and attitudes towards heart screening in X-linked ichthyosis (XLI)* (**EC.21.07.13.6374R**).

The project has been approved.

Please note that if any changes are made to the above project then you must notify the Ethics Committee.

Best Wishes,
Sean

Appendix 2.5: Ethical Approval – Chapter 6

psychethics
To: William Davies
Cc: Georgina Wren

Reply Reply all Forward
Thu 2023-05-11 16:11

Dear Will,

The Ethics Committee has received the amendment to your PG project proposal: A feasibility trial to explore the use of wearable technology in monitoring heart rhythms in X-linked ichthyosis (XLI) (EC.22.09.20.6621RA).

The amendment has been considered and based on the guidance disseminated in the Recommencing Human Participant Research document by the Open Research Integrity and Ethics Committee (ORIEC)/Research Integrity and Governance Team (RIGE), it is classed as non-substantial, therefore it does not require further review.

Your new Ethics Committee (EC) code is confirmed in the subject line of this e-mail.

Additional approvals
This letter provides an ethical opinion only. You must not start your research project until all appropriate approvals are in place.

Conditions of this decision
The favourable opinion is subject to the following conditions being met:

- You must retain a copy of this decision letter with your Research records.
- Please note that if any changes are made to the above project then you must notify the Ethics Committee.
- Please use the EC reference number on all future correspondence.
- The Committee must be informed of any unexpected ethical issues or unexpected adverse events that arise during the research project.
- The Committee must be informed when your research project has ended. This notification should be made to psychethics@cardiff.ac.uk within three months of research project completion.
- All data will be retained/processed/destroyed in line with University policy.

Complaints/Appeals
If you are dissatisfied with the decision made by the Committee, please contact psychethics@cardiff.ac.uk in the first instance to discuss your complaint. If this discussion does not resolve the issue, you are entitled to refer the matter to the Head of School for further consideration.
The Head of School may refer the matter to the Open Research Integrity and Ethics Committee (ORIEC), where this is appropriate.
Please be advised that ORIEC will not normally interfere with a decision of the Committee and is concerned only with the general principles of natural justice, reasonableness and fairness of the decision.

The Committee reminds you that it is your responsibility to conduct your research project to the highest ethical standards and to keep all ethical issues arising from your research project under regular review.

You are expected to comply with Cardiff University's policies, procedures and guidance at all times, including, but not limited to, its Policy on the Ethical Conduct of Research involving Human Participants, Human Material or Human Data and our Research Integrity and Governance Code of Practice.

Kind regards,
Deborah

School of Psychology Research Ethics Committee
https://cf.sharepoint.com/teams/InsidePsych/Ethics/

APPENDIX CHAPTER 3

Appendix 3.1: Psychological scales and their scoring

Kessler Psychological Distress Scale (K10)

A five-point 10-item Likert-scale questionnaire assessing recent depression or anxiety-related traits. K10 items were scored from 1–5 (total score range 10–50) with a score ≥20 being consistent with significant psychological distress

Adult ADHD Self-Report Scale version 1.1 (ASRS v1.1)

A five-point response (scored 0-4) 18-item Likert-scale screening questionnaire assessing recent attentional (nine items) and hyperactive-impulsive (nine items) traits based on diagnostic criteria for ADHD; total scores from the Part A screener (0-24) and overall questionnaire (0-72) were calculated, as were hyperactive-impulsive and inattentive symptom scores (0-9)

Short Autism Spectrum Quotient (AQ10)

A four point 10-item Likert-scale questionnaire, assessing behavioural traits associated with autism spectrum disorders; items endorsed as being consistent with autism-related traits were with scored with 1 point (total score range 0-10) with a score of ≥6 being consistent with a referral for a comprehensive autism assessment

Brief Irritability Test (BITE)

A six-point 5-item Likert-scale questionnaire assessing irritability traits. BITE items were scored from 1-6 (total score range 5-30), with a greater score associated with increased irritability

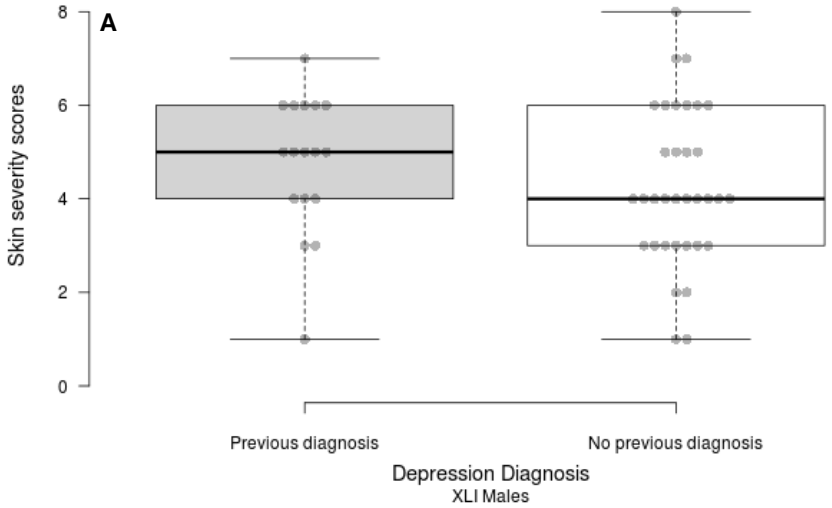
Dermatology Life Quality Index (DLQI)

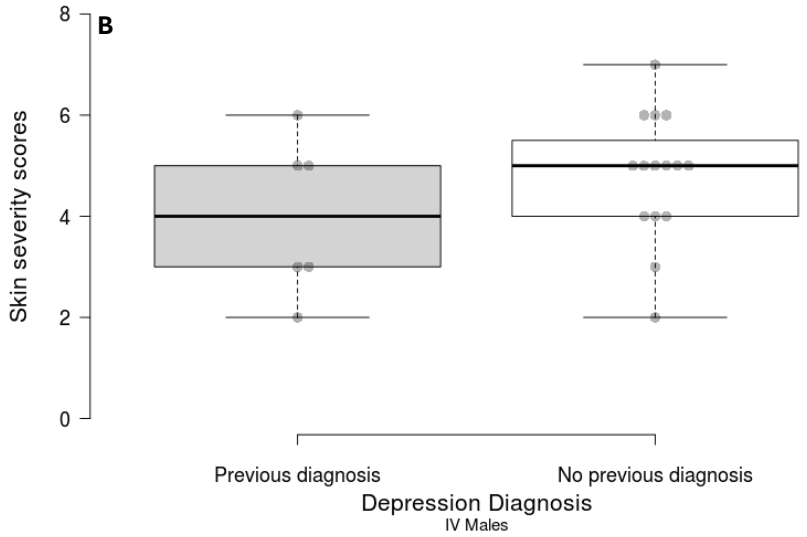
A four-point 10-item Likert-scale questionnaire assessing dermatology-specific quality of life. DLQI items were scored from 0-3 (total score range 0-30), with a higher score associated with a greater impairment on quality of life

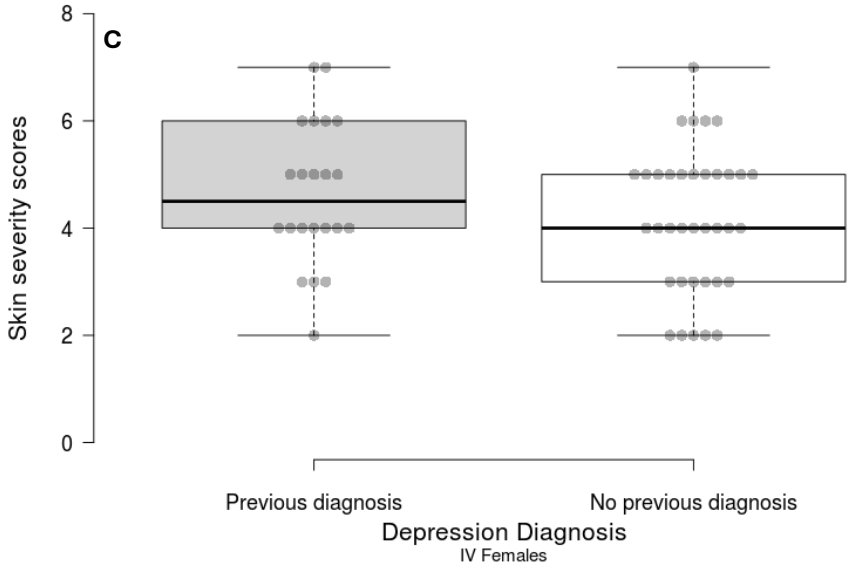
Feelings of Stigmatisation Questionnaire (FSQ)

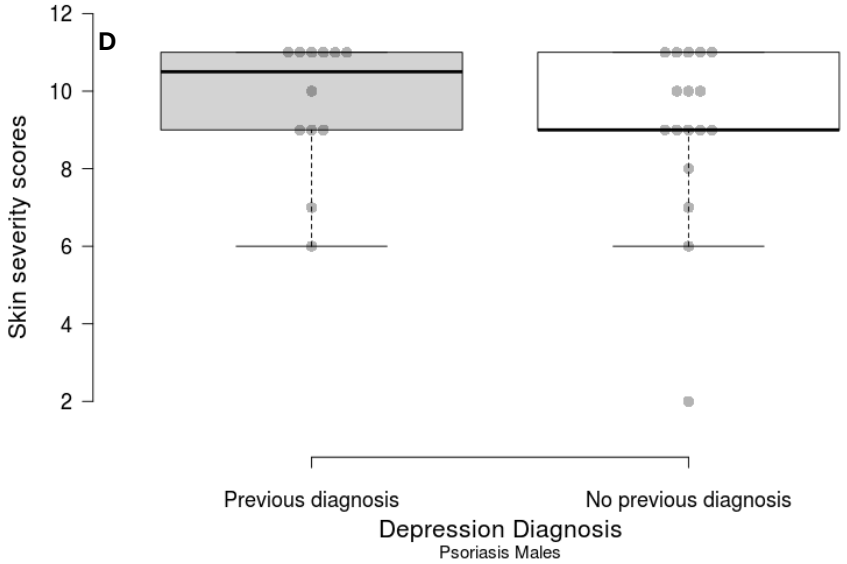
A six-point, 33-item Likert-scale questionnaire assessing levels of skin disease-related stigmatisation. FSQ items were scored from 1-6 (total score range 33-198), with lower scores indicative of higher levels of perceived stigma.

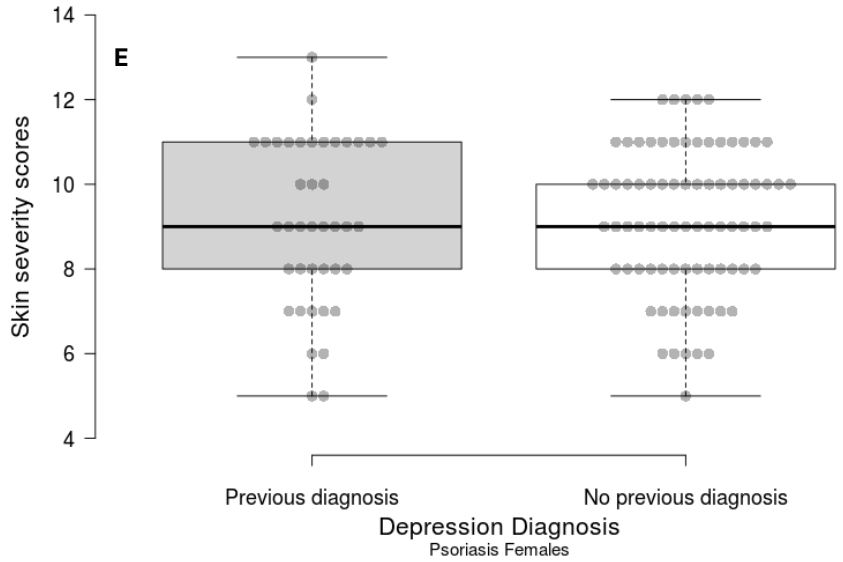
Appendix 3.2: Dot plots showing the relationship between skin severity as indexed by self-report based upon CISI (ichthyosis) or PASI (psoriasis) images and a depression diagnosis in males with XLI (A), males with IV (B), females with IV (C), males with psoriasis (D) and females with psoriasis (E).






C
Skin severity scores
0
2
4
6
8
Previous diagnosis
No previous diagnosis
Depression Diagnosis
IV Females


D
Skin severity scores
2
4
6
8
10
12
Previous diagnosis
No previous diagnosis
Depression Diagnosis
Psoriasis Males


E
Skin severity scores
14
12
10
8
6
4
Previous diagnosis
No previous diagnosis
Depression Diagnosis
Psoriasis Females

Appendix 3.3: Comparison of K10, ASRS Part A, AQ10 and BITE scores vs. normative samples across the six groups

	K10	AQ10	ASRS (Part A only)	BITE
General population sample (male)	14.2±7.1 (n=566)[1]	2.6±3.7 (n=7904)[2]	8.3±3.5 (n=993)[3]	12.69[4]
General population sample (female)	15.5±8.9 (n=882)[1]	2.2±3.1 (n=10796)[2]	8.0±3.33 (n=1098)[3]	13.13[4]
XLI male	25.2±9.8 (n=50) t[53]=7.76, p<0.001	4.3±2.1 (n=46) t[45]=5.34, p<0.001	12.1±5.1 (n=49) t[50]=5.16, p<0.001	16.6±5.5 (n=47)
XLI carrier female	23.3±7.2 (n=78) t[99]=8.98, p<0.001	3.4±2.2 (n=74) t[75]=4.62, p<0.001	11.6±5.3 (n=75) t[77]=5.81, p<0.001	16.7±4.6 (n=74)
IV male	21.5±5.5 (n=19) t[19]=5.63, p<0.001	3.9±1.9 (n=19) t[18]=2.88, p=0.010	10.4±2.9 (n=19) t[19]=3.11, p=0.006	14.5±5.2 (n=19)
IV female	23.4±7.6 (n=57) t[66]=7.52, p<0.001	3.2±1.7 (n=54) t[57]=6.04, p=0.002	11.1±3.7 (n=54) t[57]=6.04, p=0.002	16.4±4.5 (n=52)
Psoriasis male	22.7±6.4 (n=26) t[27]=6.59, p<0.001	3.6±1.9 (n=23) t[22]=2.42, p=0.024	10.5±4.0 (n=25) t[24]=2.72, p=0.012	16.3±4.7 (n=23)

Psoriasis female	25.4±7.3 (n=122) t[174]=13.64, p<0.001	3.0±1.9 (n=111) t[116]=4.32, p<0.001	11.5±4.3 (n=116) t[129]=8.51, p<0.001	18.0±5.0 (n=111)

Appendix 3.4: Inattentive vs. hyperactive-impulsive symptom counts across ASRS for all six groups

Group	Hyperactive-Impulsive Symptom Count	Inattentive Symptom Count	Statistical comparison between hyperactive-impulsive and inattentive symptom count
XLI males	2.7±2.1	4.6±2.6	t(48)=6.12, p<0.001
XLI females	2.9±2.3	3.2±2.6	t(72)=5.85 p<0.001
IV males	1.9±1.9	4.1±2.3	t(18)=5.21, p<0.001
IV females	2.6±2.1	4.1±2.5	t(53)=4.79, p<0.001
Psoriasis males	2.5±2.5	3.2±2.2	t(24)=1.48, p=0.153

Psoriasis females	3.0±2.5	4.2±2.7	t(117)=4.69, p<0.001

Appendix 3.5: Relationship between recent mood, neurodevelopmental traits and irritability across groups

Group		Neurodevelopmental Trait Score (NTS)	BITE score
XLI males	**K10 score**	r=0.615, n=47, p<0.001	r=0.647, n=47, p<0.001
	Neurodevelopmental Trait Score (NTS)	-	r=0.174, n=47, p=0.241
XLI females	**K10 score**	r=0.660, n=74, p<0.001	r=0.704, n=74, p<0.001
	Neurodevelopmental Trait Score (NTS)	-	r=0.427, n=74, p<0.001
IV males	**K10 score**	r=0.652, n=19, p=0.002	r=0.717, n=18, p=0.001
	Neurodevelopmental Trait Score (NTS)	-	r=0.753, n=18, p<0.001
IV females	**K10 score**	r=0.467, n=52, p<0.001	r=0.487, n=52, p<0.001
	Neurodevelopmental Trait Score (NTS)	-	r=0.342, n=52, p<0.013
Psoriasis males	**K10 score**	r=0.617, n=24, p<0.001	r=0.670, n=24, p<0.001

	Neurodevelopmental Trait Score (NTS)	-	r=0.569, n=24, p=0.004
Psoriasis females	**K10 score**	r=0.599, n=112, p<0.001	r=0.621, n=112, p<0.001
	Neurodevelopmental Trait Score (NTS)	-	r=0.542, n=112, p<0.001

Appendix 3.6: Relationship between recent mood, quality of life and feelings of stigmatisation across groups

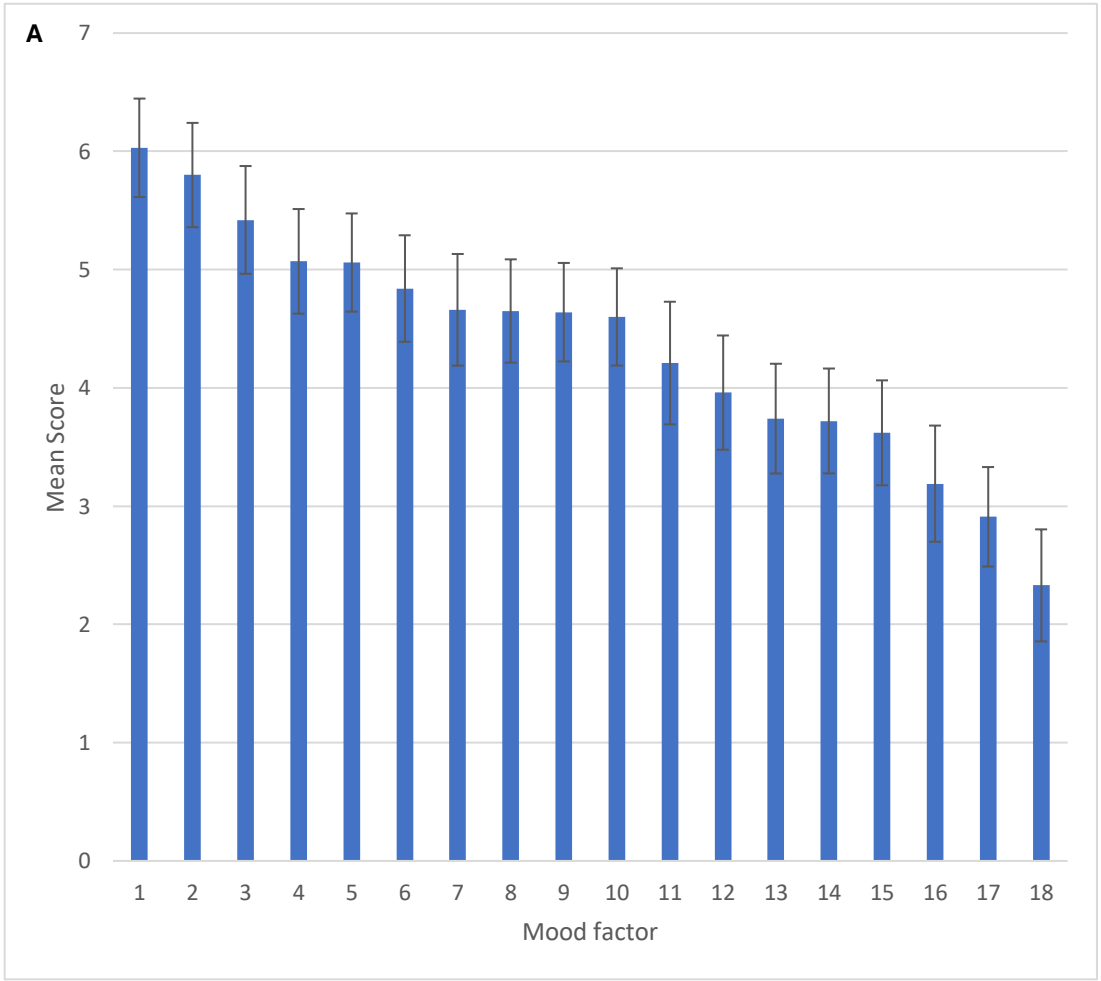
Group		**DLQI score**	**FSQ score**
XLI males	**K10 score**	r=0.548, n=47, p<0.001	r=-0.483, n=46, p=0.001
	DLQI score	-	r=-0.253, n=45, p=0.094
IV males	**K10 score**	r=0.264, n=18, p=0.290	r=-0.141, n=17, p=0.589
	DLQI score	-	r=-0.411, n=17, p=0.102
IV females	**K10 score**	r=0.220, n=52, p=0.117	r=-0.305, n=50, p=0.031
	DLQI score	-	r=-0.198, n=50, p=0.168
Psoriasis males	**K10 score**	r=0.776, n=25, p<0.001	r=-0.485, n=23, p=0.019

	DLQI score	-	r=-0.476, n=22, p=0.025
Psoriasis females	**K10 score**	r=0.464, n=112, p<0.001	r=-0.455, n=109, p<0.001
	DLQI score	-	r=-0.294, n=109, p=0.002

Appendix 3.7: Ranking of factors (scored from 0-10) potentially predisposing to adult mood symptoms (depression (A)), anxiety (B) and irritability (C) in males with XLI

Rank	Mood Factor - Depression
1	Moderate chronic life event (relationship difficulties/divorce, chronic illness, work-related stress etc.)
2	Stigma or bullying associated with your skin condition
3	Difficulties or frustration associated with treating your skin condition (e.g. regularly having to source and apply moisturizer)
4	Severe adverse life event (bereavement, life-threatening illness etc.)
5	Embarrassment of social interaction because of your skin condition
6	Sleep problems unrelated to your skin condition
7	Stigma or bullying due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions
8	Pain, discomfort or itching associated with your skin condition
9	Educational, work or social challenges due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions
10	Medical issues (non-skin related)
11	Low quality/quantity of friendships and relationships
12	Stigma or bullying due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.
13	Sleep problems related to your skin condition e.g. due to excessive itchiness, night-time sweating etc.

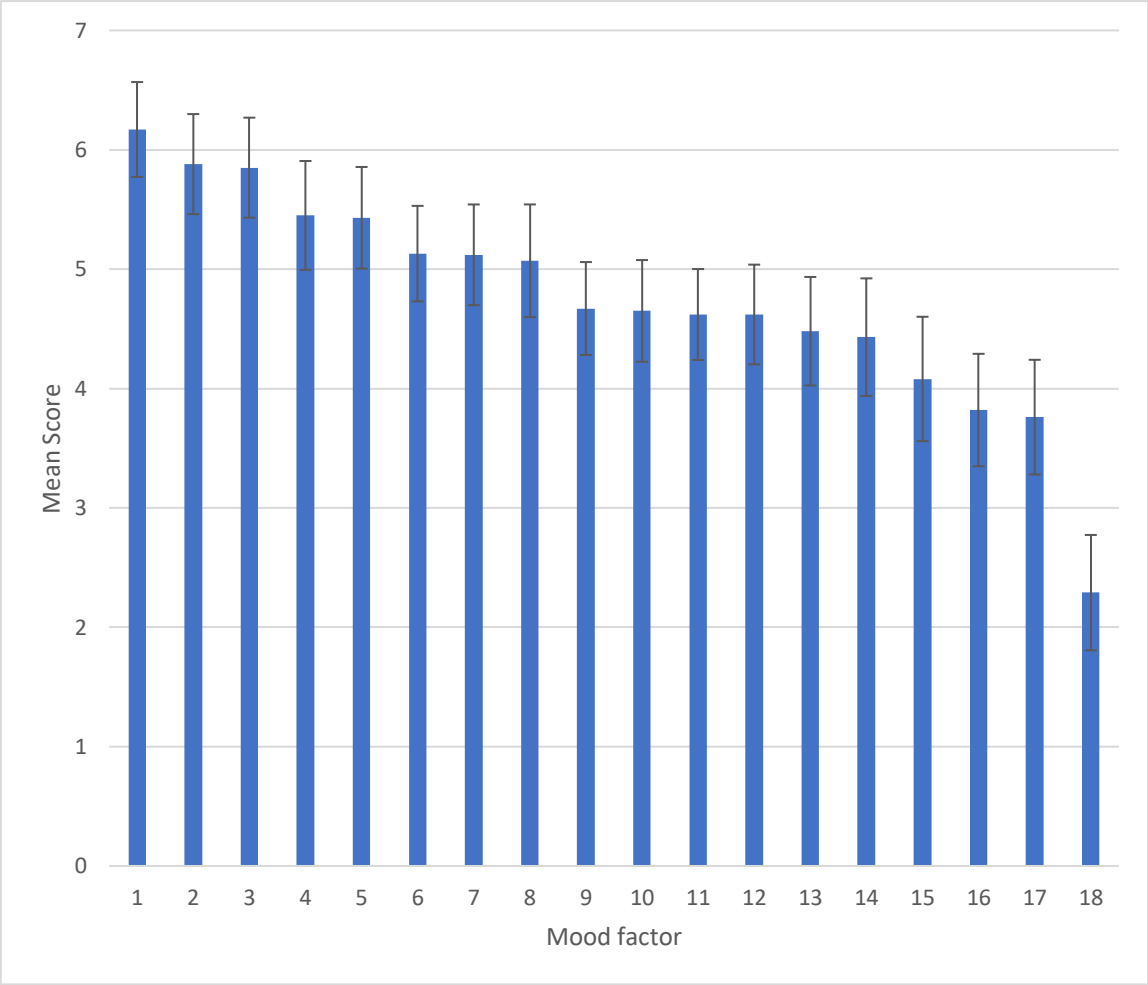
A



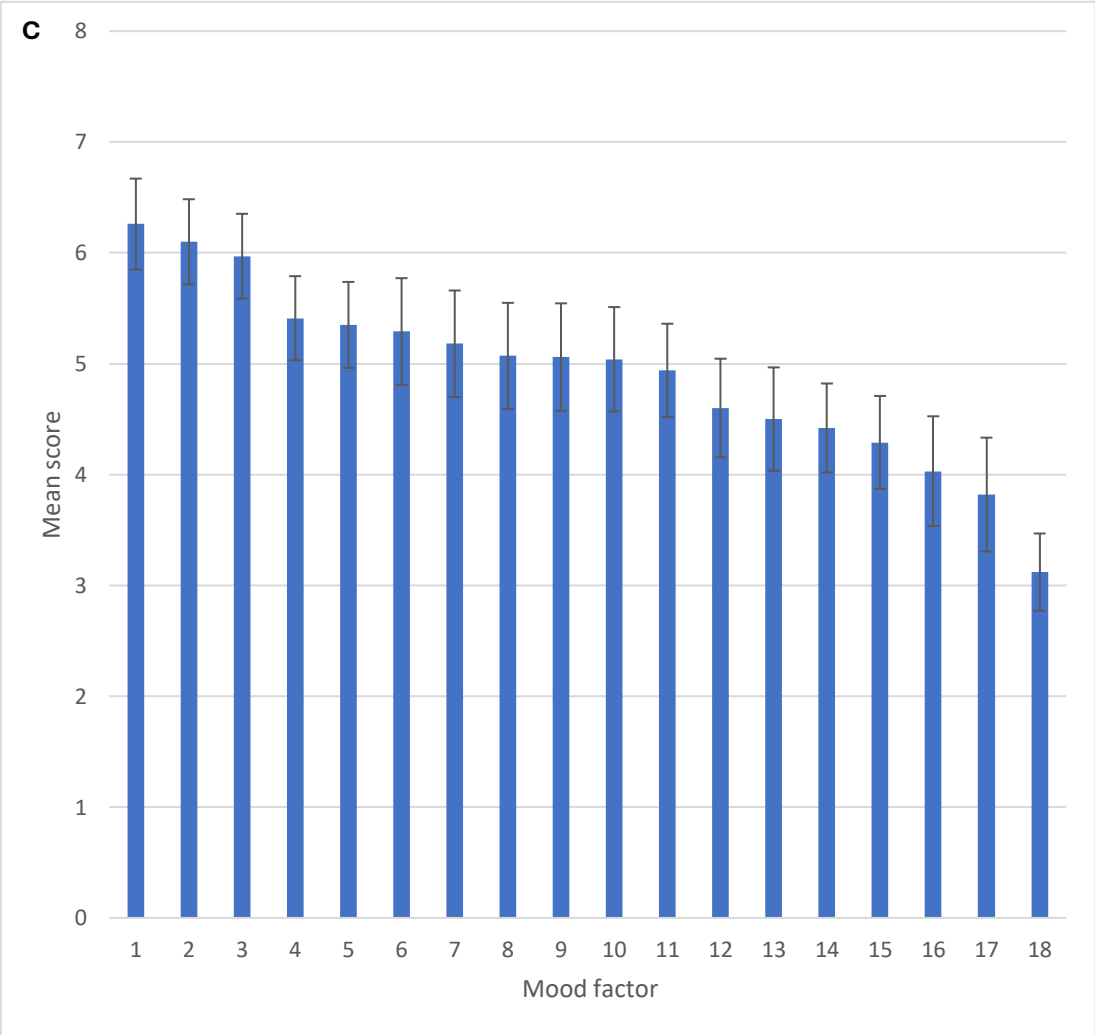
B

14	Educational, work or social challenges due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
15	Stigma or bullying due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
16	Difficulty regulating body temperature/sweating
17	Educational, work or social challenges due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.
18	Allergies

Rank	Mood Factor - Anxiety
1	Moderate chronic life event (relationship difficulties/divorce, chronic illness, work-related stress etc.)
2	Embarrassment of social interaction because of your skin condition
3	Stigma or bullying associated with your skin condition
4	Severe adverse life event (bereavement, life-threatening illness etc.)
5	Difficulties or frustration associated with treating your skin condition (e.g. regularly having to source and apply moisturizer)
6	Medical issues (non-skin related)
7	Educational, work or social challenges due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions
8	Sleep problems unrelated to your skin condition
9	Educational, work or social challenges due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
10	Stigma or bullying due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions
11	Pain, discomfort or itching associated with your skin condition
12	Stigma or bullying due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
13	Stigma or bullying due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.

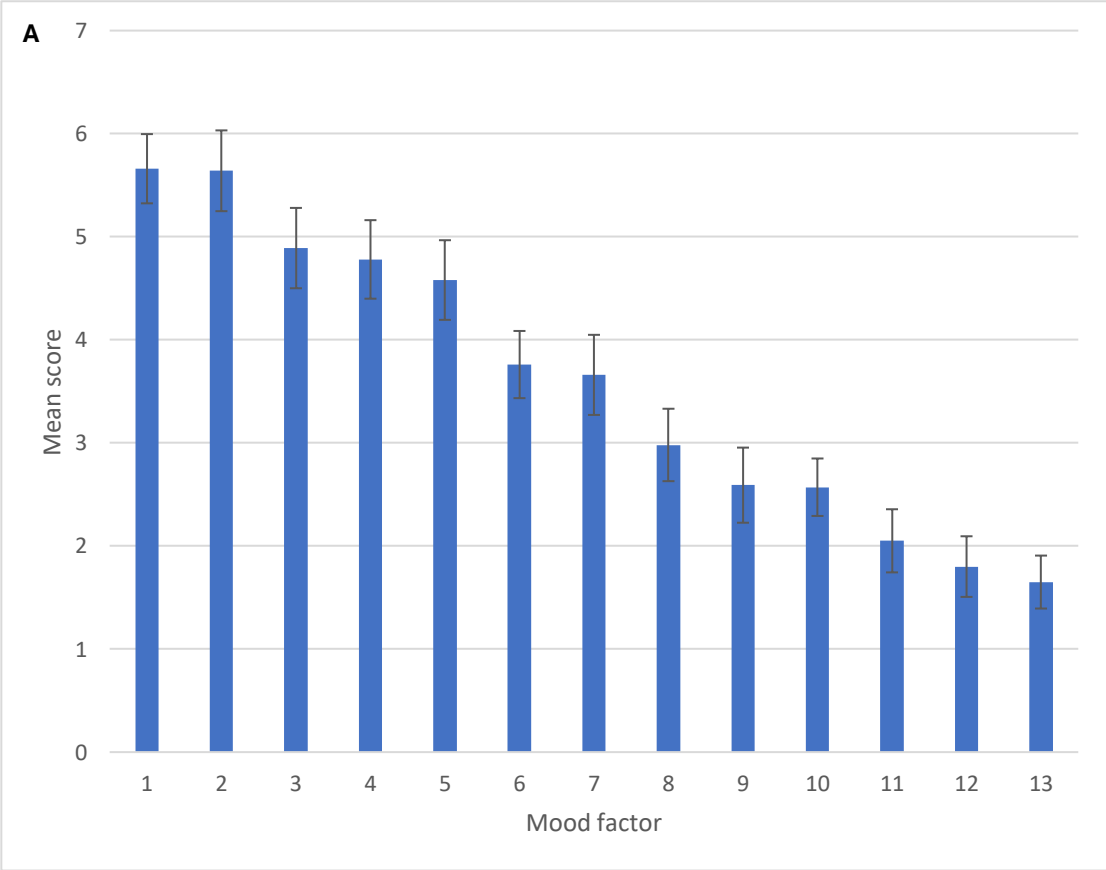


14	Sleep problems related to your skin condition e.g. due to excessive itchiness, night-time sweating etc.
15	Low quality/quantity of friendships and relationships
16	Difficulty regulating body temperature/sweating
17	Educational, work or social challenges due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.
18	Allergies

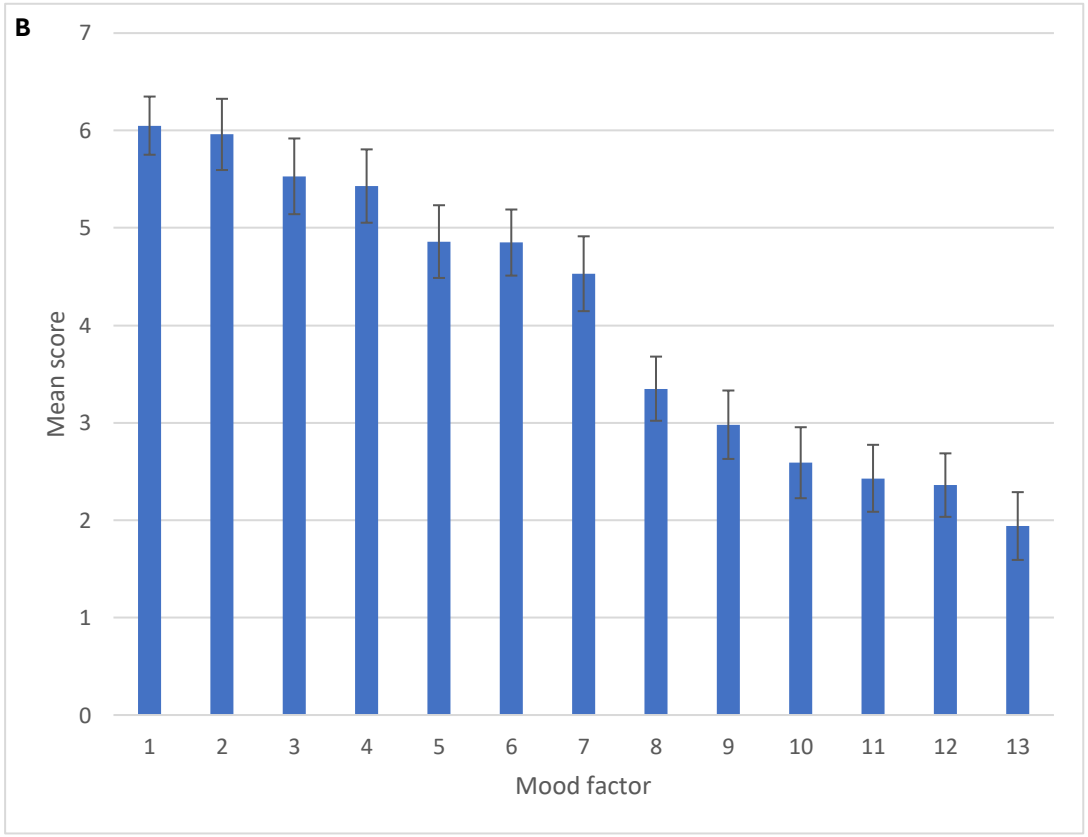


Rank	Mood Factor - Irritability
1	Stigma or bullying associated with your skin condition
2	Moderate chronic life event (relationship difficulties/divorce, chronic illness, work-related stress etc.)
3	Difficulties or frustration associated with treating your skin condition (e.g. regularly having to source and apply moisturizer)
4	Embarrassment of social interaction because of your skin condition
5	Pain, discomfort or itching associated with your skin condition
6	Sleep problems unrelated to your skin condition
7	Severe adverse life event (bereavement, life-threatening illness etc.)
8	Stigma or bullying due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions
9	Sleep problems related to your skin condition e.g. due to excessive itchiness, night-time sweating etc.
10	Difficulty regulating body temperature/sweating
11	Educational, work or social challenges due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions
12	Stigma or bullying due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
13	Stigma or bullying due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.
14	Educational, work or social challenges due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
15	Medical issues (non-skin related)
16	Educational, work or social challenges due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.
17	Low quality/quantity of friendships and relationships
18	Allergies

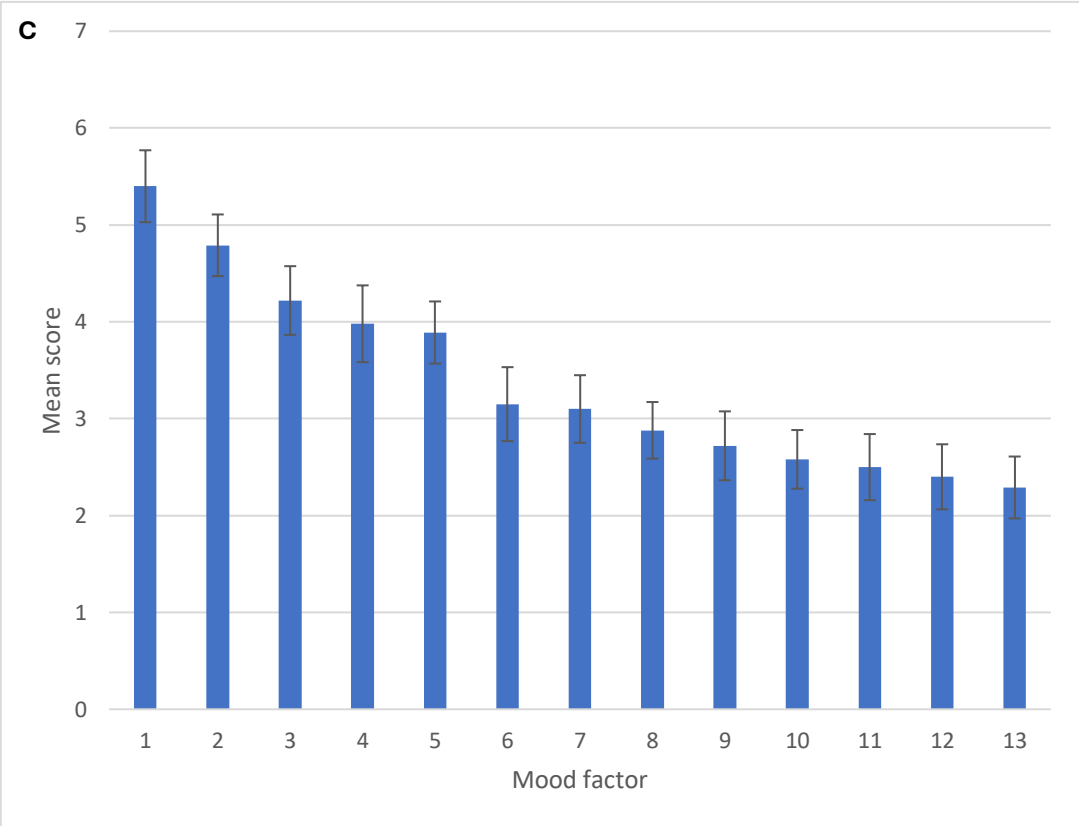
Appendix 3.8: Ranking of factors (scored from 0-10) potentially predisposing to adult mood symptoms (depression (A)), anxiety (B) and irritability (C) in female XLI carriers



Rank	Mood Factor - Depression
1	Moderate chronic life event (relationship difficulties/divorce, chronic illness, work-related stress etc.)
2	Severe adverse life event (bereavement, life-threatening illness etc.)
3	Sleep problems unrelated to your skin condition
4	Medical issues (non-skin related)
5	Low quality/quantity of friendships and relationships
6	Educational, work or social challenges due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions
7	Stress due to having a child with a long-term medical (skin) condition
8	Educational, work or social challenges due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.
9	Stigma or bullying due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions
10	Educational, work or social challenges due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
11	Stigma or bullying due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.
12	Allergies
13	Stigma or bullying due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.

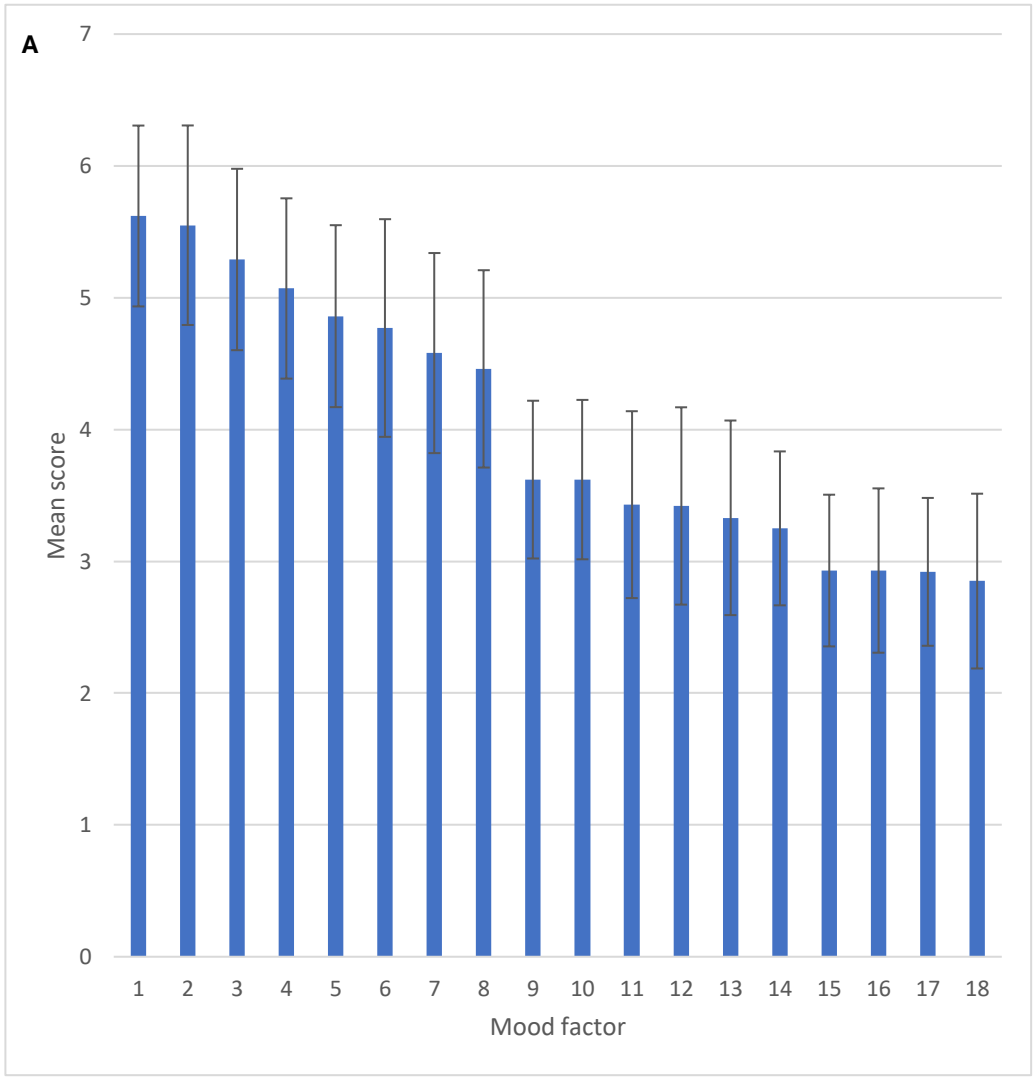


Rank	Mood Factor - Anxiety
1	Moderate chronic life event (relationship difficulties/divorce, chronic illness, work-related stress etc.)
2	Sleep problems unrelated to your skin condition
3	Severe adverse life event (bereavement, life-threatening illness etc.)
4	Medical issues (non-skin related)
5	Stress due to having a child with a long-term medical (skin) condition
6	Educational, work or social challenges due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions
7	Low quality/quantity of friendships and relationships
8	Educational, work or social challenges due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
9	Educational, work or social challenges due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.
10	Stigma or bullying due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions
11	Stigma or bullying due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.
12	Stigma or bullying due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
13	Allergies

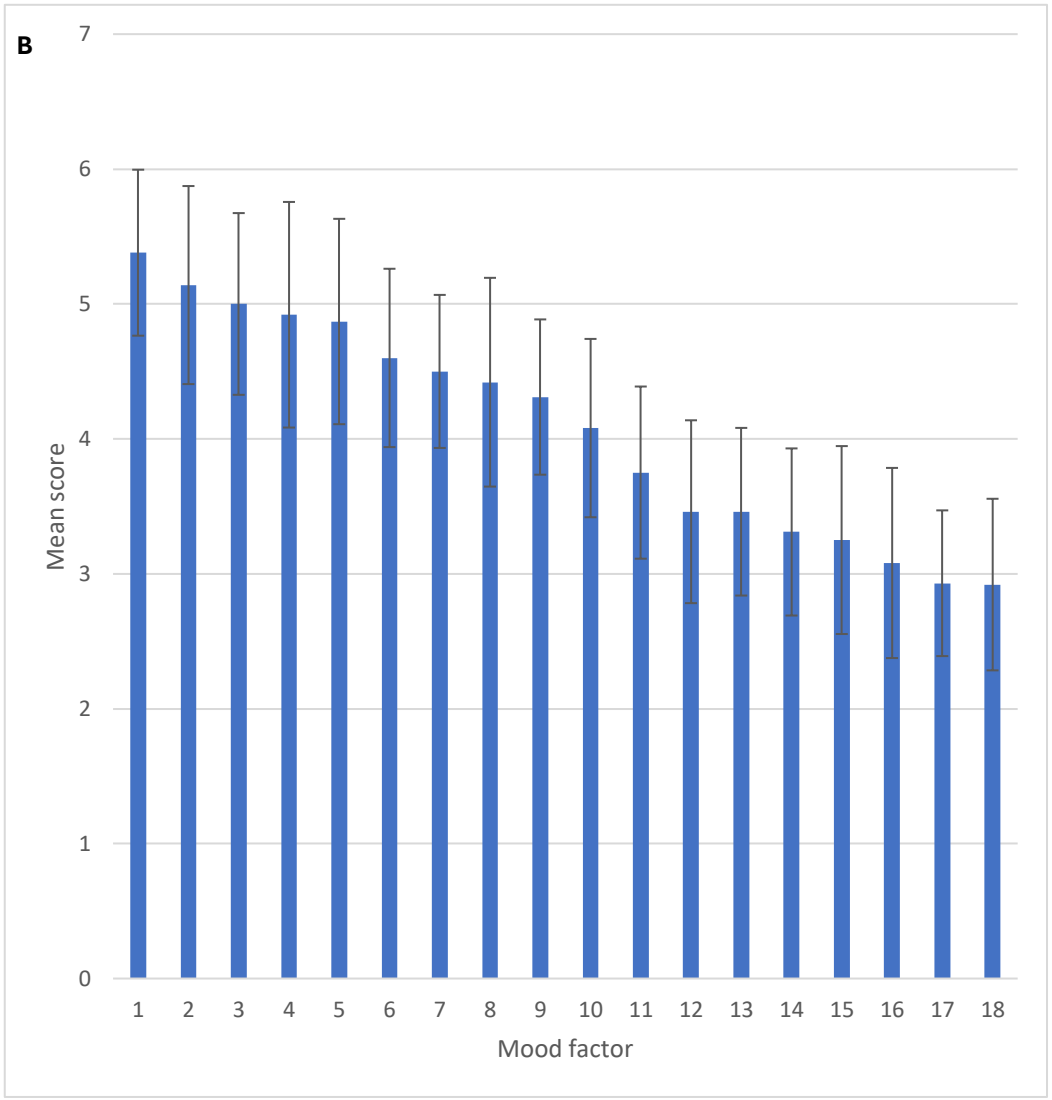


Rank	Mood Factor - Irritability
1	Sleep problems unrelated to your skin condition
2	Moderate chronic life event (relationship difficulties/divorce, chronic illness, work-related stress etc.)
3	Medical issues (non-skin related)
4	Severe adverse life event (bereavement, life-threatening illness etc.)
5	Educational, work or social challenges due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions
6	Stress due to having a child with a long-term medical (skin) condition
7	Educational, work or social challenges due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.
8	Educational, work or social challenges due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
9	Low quality/quantity of friendships and relationships
10	Stigma or bullying due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions
11	Allergies
12	Stigma or bullying due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.
13	Stigma or bullying due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.

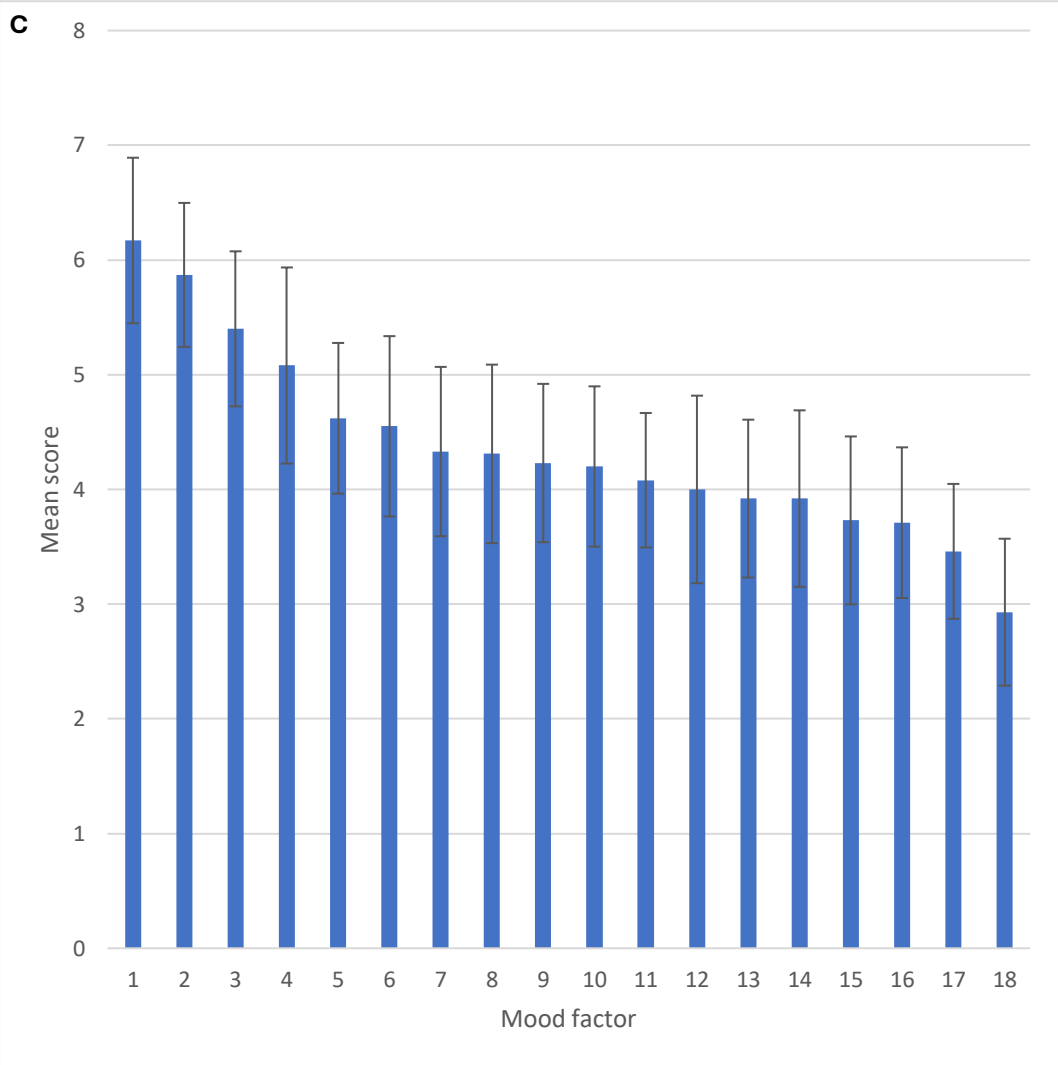
Appendix 3.9: Ranking of factors (scored from 0-10) potentially predisposing to adult mood symptoms (depression (A)), anxiety (B) and irritability (C) in males with IV



Rank	Mood Factor - Depression
1	Moderate chronic life event (relationship difficulties/divorce, chronic illness, work-related stress etc.)
2	Low quality/quantity of friendships and relationships
3	Embarrassment of social interaction because of your skin condition
4	Pain, discomfort or itching associated with your skin condition
5	Difficulties or frustration associated with treating your skin condition (e.g. regularly having to source and apply moisturizer)
6	Stigma or bullying associated with your skin condition
7	Sleep problems unrelated to your skin condition
8	Severe adverse life event (bereavement, life-threatening illness etc.)
9	Educational, work or social challenges due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions
10	Medical issues (non-skin related)
11	Stigma or bullying due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
12	Stigma or bullying due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions
13	Educational, work or social challenges due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.
14	Difficulty regulating body temperature/sweating
15	Educational, work or social challenges due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
16	Stigma or bullying due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.
17	Sleep problems related to your skin condition e.g. due to excessive itchiness, night-time sweating etc.
18	Allergies

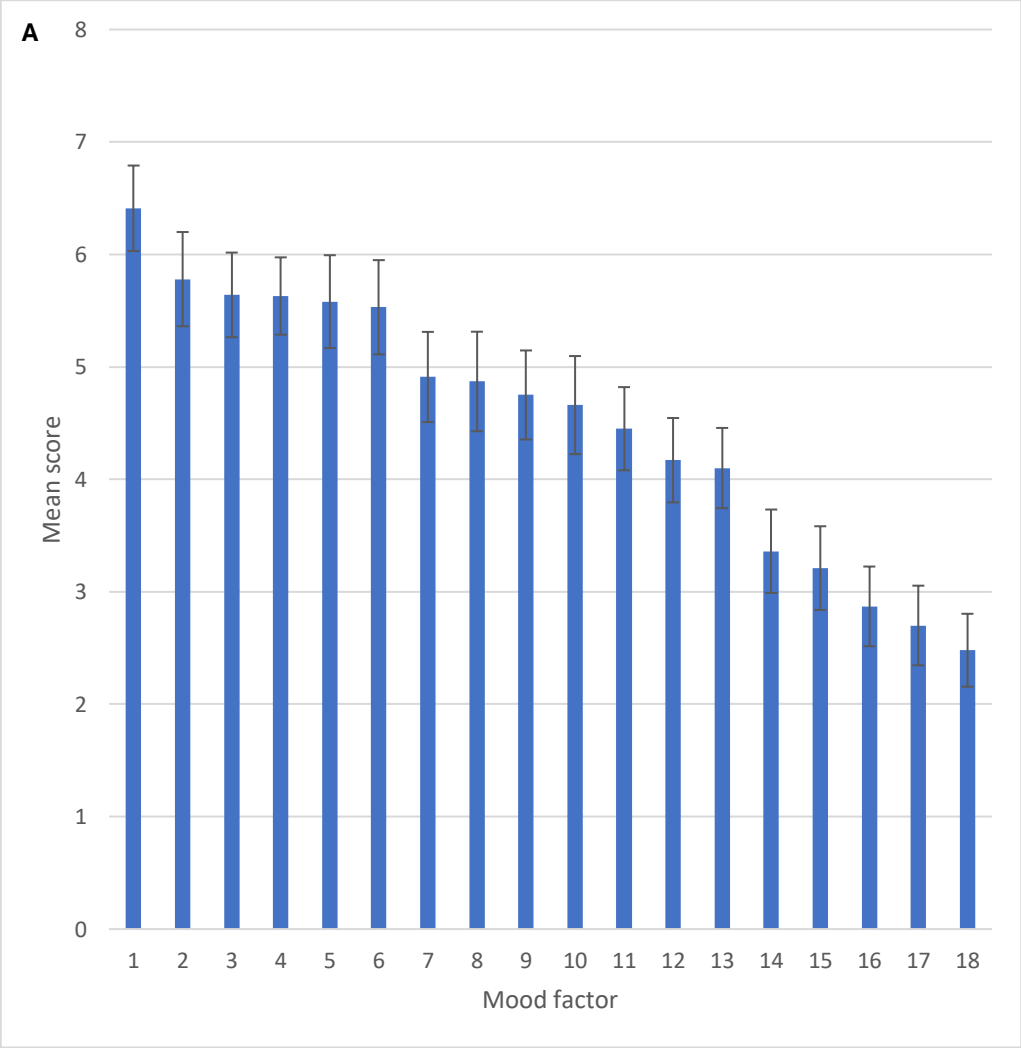


Rank	Mood Factor - Anxiety
1	Moderate chronic life event (relationship difficulties/divorce, chronic illness, work-related stress etc.)
2	Pain, discomfort or itching associated with your skin condition
3	Difficulties or frustration associated with treating your skin condition (e.g. regularly having to source and apply moisturizer)
4	Severe adverse life event (bereavement, life-threatening illness etc.)
5	Embarrassment of social interaction because of your skin condition
6	Low quality/quantity of friendships and relationships
7	Educational, work or social challenges due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions
8	Stigma or bullying associated with your skin condition
9	Medical issues (non-skin related)
10	Sleep problems unrelated to your skin condition
11	Difficulty regulating body temperature/sweating
12	Stigma or bullying due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions
13	Sleep problems related to your skin condition e.g. due to excessive itchiness, night-time sweating etc.
14	Allergies
15	Stigma or bullying due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
16	Educational, work or social challenges due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.
17	Educational, work or social challenges due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
18	Stigma or bullying due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.

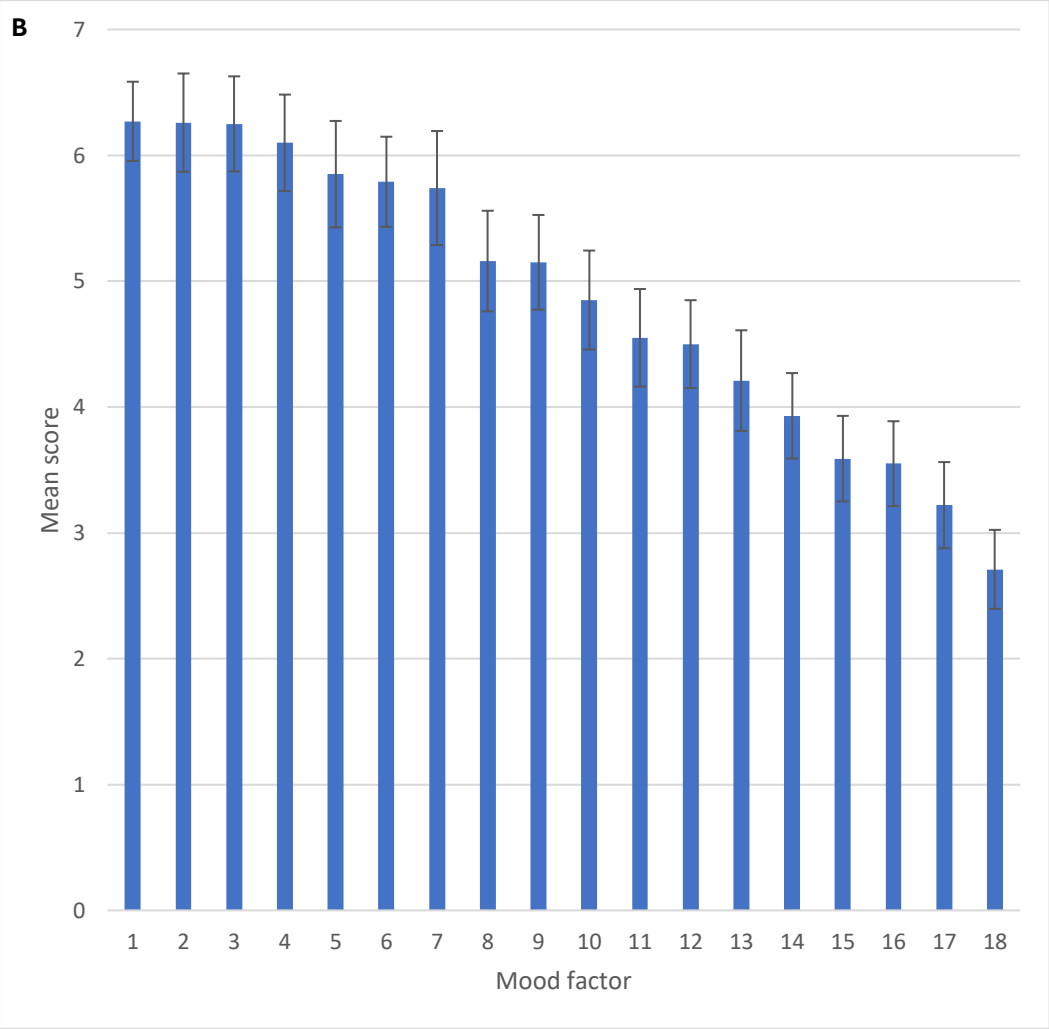


Rank	Mood Factor - Irritability
1	Moderate chronic life event (relationship difficulties/divorce, chronic illness, work-related stress etc.)
2	Pain, discomfort or itching associated with your skin condition
3	Difficulties or frustration associated with treating your skin condition (e.g. regularly having to source and apply moisturizer)
4	Stigma or bullying associated with your skin condition
5	Difficulty regulating body temperature/sweating
6	Low quality/quantity of friendships and relationships
7	Stigma or bullying due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
8	Educational, work or social challenges due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.
9	Sleep problems related to your skin condition e.g. due to excessive itchiness, night-time sweating etc.
10	Embarrassment of social interaction because of your skin condition
11	Medical issues (non-skin related)
12	Severe adverse life event (bereavement, life-threatening illness etc.)
13	Sleep problems unrelated to your skin condition
14	Stigma or bullying due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions
15	Educational, work or social challenges due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
16	Educational, work or social challenges due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions
17	Stigma or bullying due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.
18	Allergies

Appendix 3.10: Ranking of factors (scored from 0-10) potentially predisposing to adult mood symptoms (depression (A)), anxiety (B) and irritability (C) in females with IV

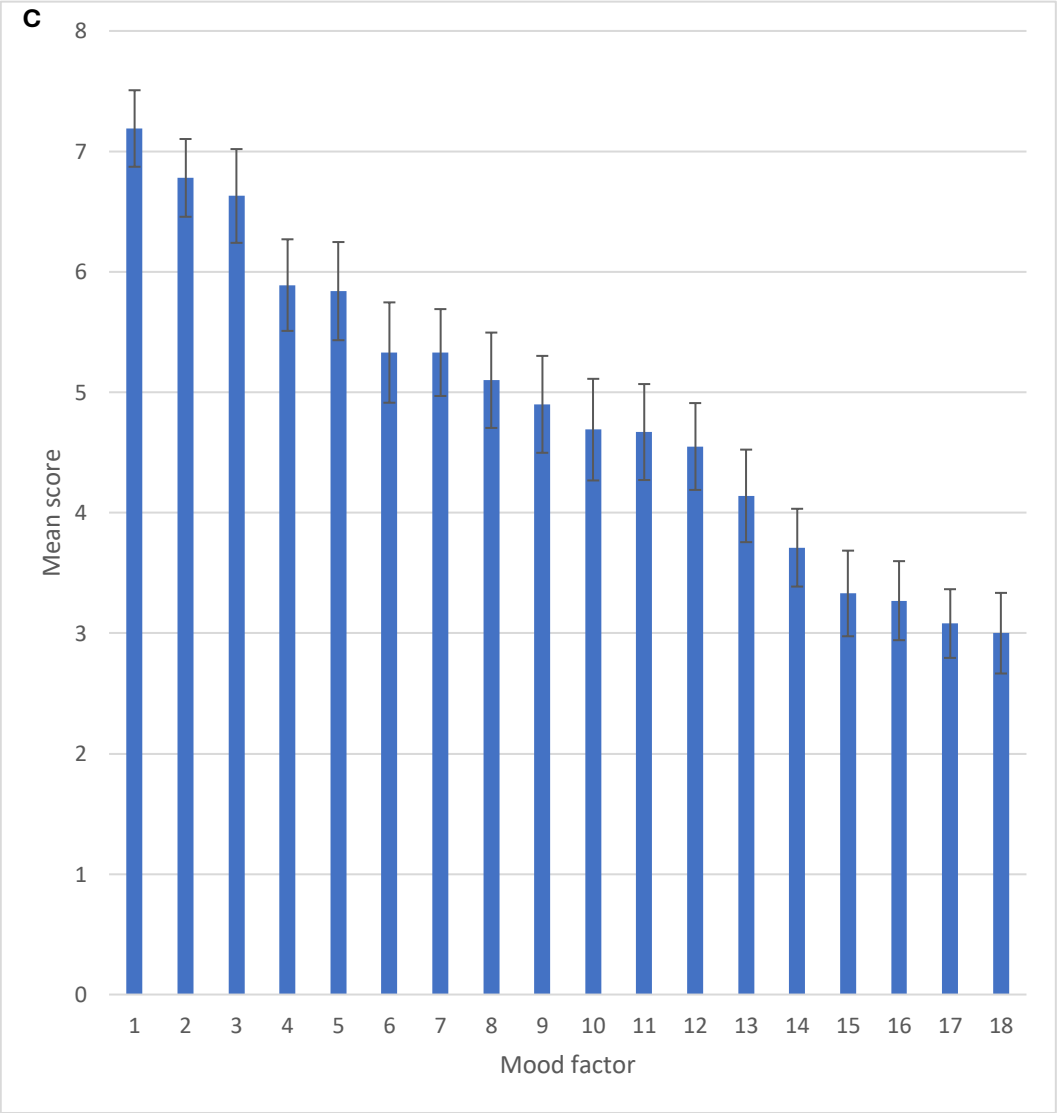


Rank	Mood Factor - Depression
1	Difficulties or frustration associated with treating your skin condition (e.g. regularly having to source and apply moisturizer)
2	Stigma or bullying associated with your skin condition
3	Moderate chronic life event (relationship difficulties/divorce, chronic illness, work-related stress etc.)
4	Embarrassment of social interaction because of your skin condition
5	Severe adverse life event (bereavement, life-threatening illness etc.)
6	Pain, discomfort or itching associated with your skin condition
7	Educational, work or social challenges due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions
8	Difficulty regulating body temperature/sweating
9	Medical issues (non-skin related)
10	Sleep problems unrelated to your skin condition
11	Sleep problems related to your skin condition e.g. due to excessive itchiness, night-time sweating etc.
12	Allergies
13	Low quality/quantity of friendships and relationships
14	Educational, work or social challenges due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
15	Stigma or bullying due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.
16	Stigma or bullying due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
17	Educational, work or social challenges due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.
18	Stigma or bullying due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions



Rank	Mood Factor - Anxiety
1	Embarrassment of social interaction because of your skin condition
2	Stigma or bullying associated with your skin condition
3	Moderate chronic life event (relationship difficulties/divorce, chronic illness, work-related stress etc.)
4	Difficulties or frustration associated with treating your skin condition (e.g. regularly having to source and apply moisturizer)
5	Severe adverse life event (bereavement, life-threatening illness etc.)
6	Pain, discomfort or itching associated with your skin condition
7	Difficulty regulating body temperature/sweating
8	Medical issues (non-skin related)
9	Sleep problems unrelated to your skin condition
10	Allergies
11	Educational, work or social challenges due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions
12	Sleep problems related to your skin condition e.g. due to excessive itchiness, night-time sweating etc.
13	Educational, work or social challenges due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
14	Low quality/quantity of friendships and relationships
15	Stigma or bullying due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.
16	Stigma or bullying due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
17	Educational, work or social challenges due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.
18	Stigma or bullying due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions

Rank	Mood Factor - Irritability
1	Difficulties or frustration associated with treating your skin condition (e.g. regularly having to source and apply moisturizer)
2	Pain, discomfort or itching associated with your skin condition
3	Difficulty regulating body temperature/sweating
4	Moderate chronic life event (relationship difficulties/divorce, chronic illness, work-related stress etc.)
5	Sleep problems related to your skin condition e.g. due to excessive itchiness, night-time sweating etc.
6	Stigma or bullying associated with your skin condition
7	Embarrassment of social interaction because of your skin condition
8	Allergies
9	Medical issues (non-skin related)
10	Sleep problems unrelated to your skin condition
11	Educational, work or social challenges due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions
12	Severe adverse life event (bereavement, life-threatening illness etc.)
13	Educational, work or social challenges due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
14	Low quality/quantity of friendships and relationships
15	Stigma or bullying due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.
16	Stigma or bullying due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
17	Stigma or bullying due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions
18	Educational, work or social challenges due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.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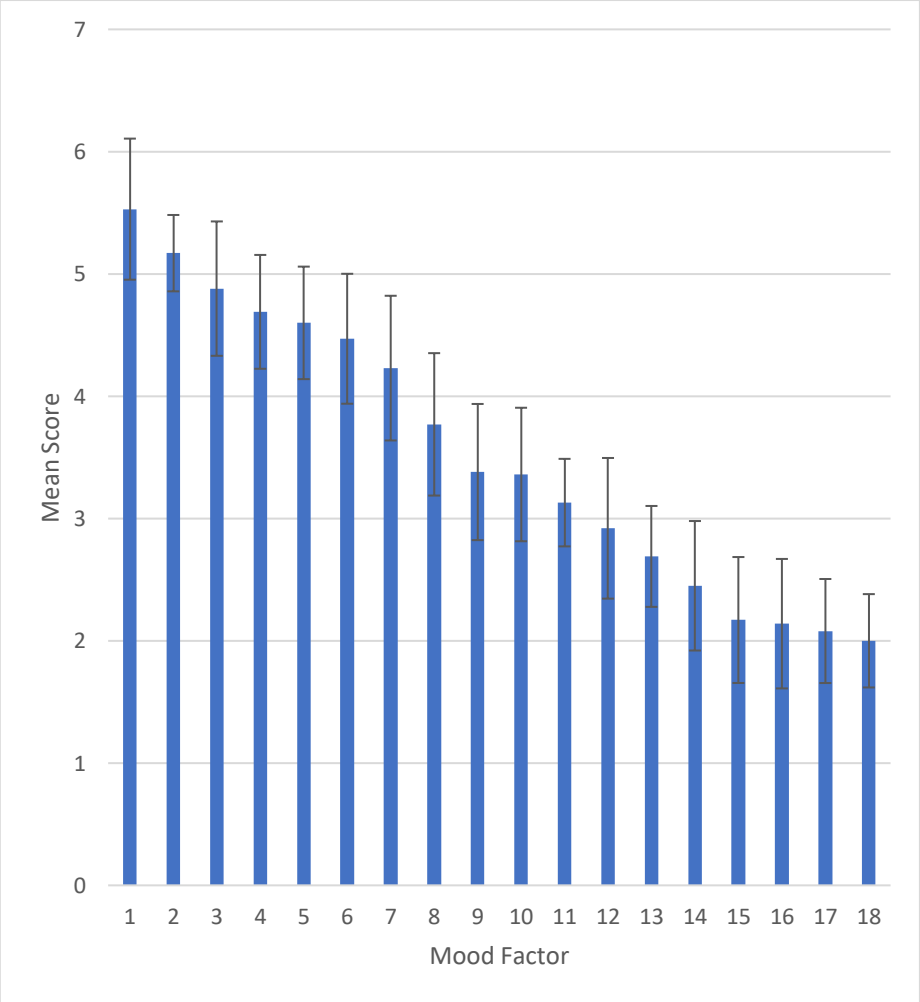
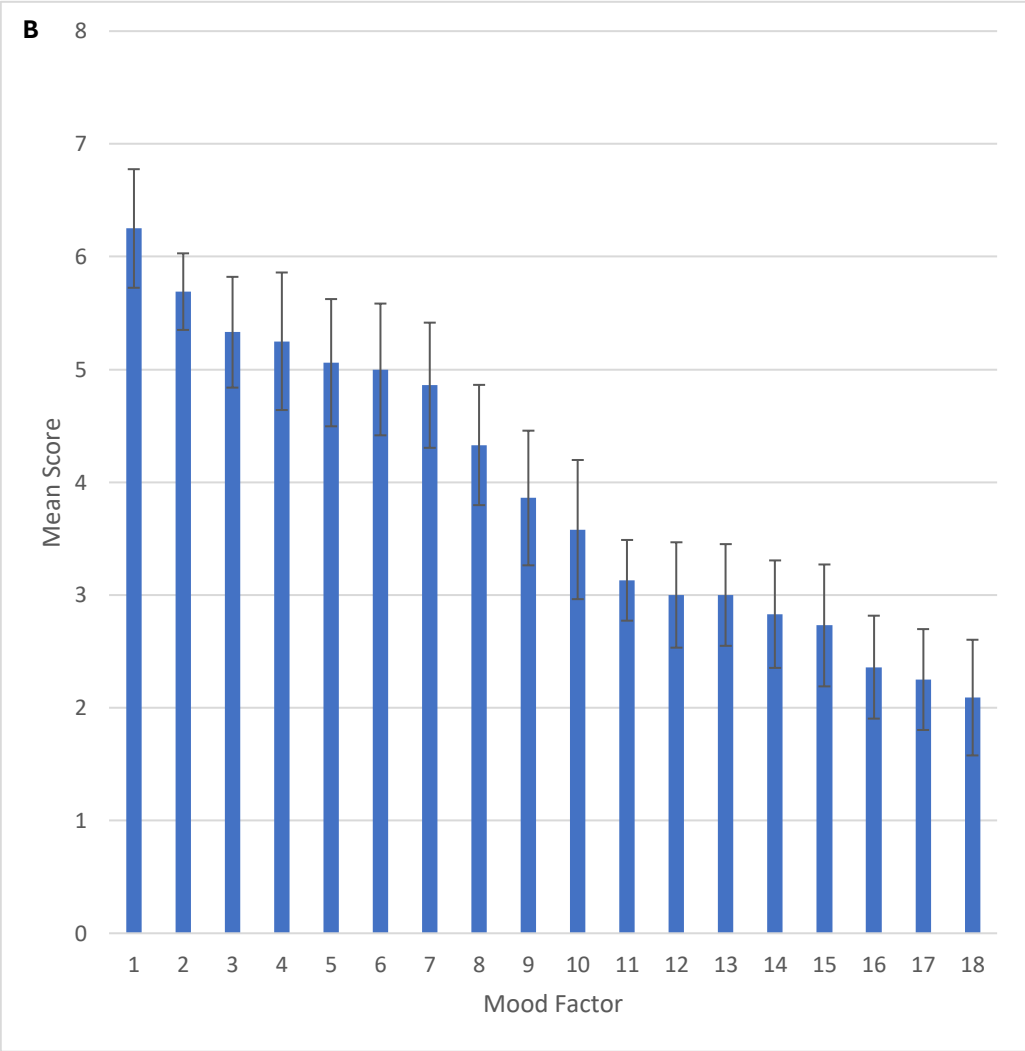
Mood factor

Appendix 3.11: Ranking of factors (scored from 0-10) potentially predisposing to adult mood symptoms (depression (A)), anxiety (B) and irritability (C) in males with psoriasis

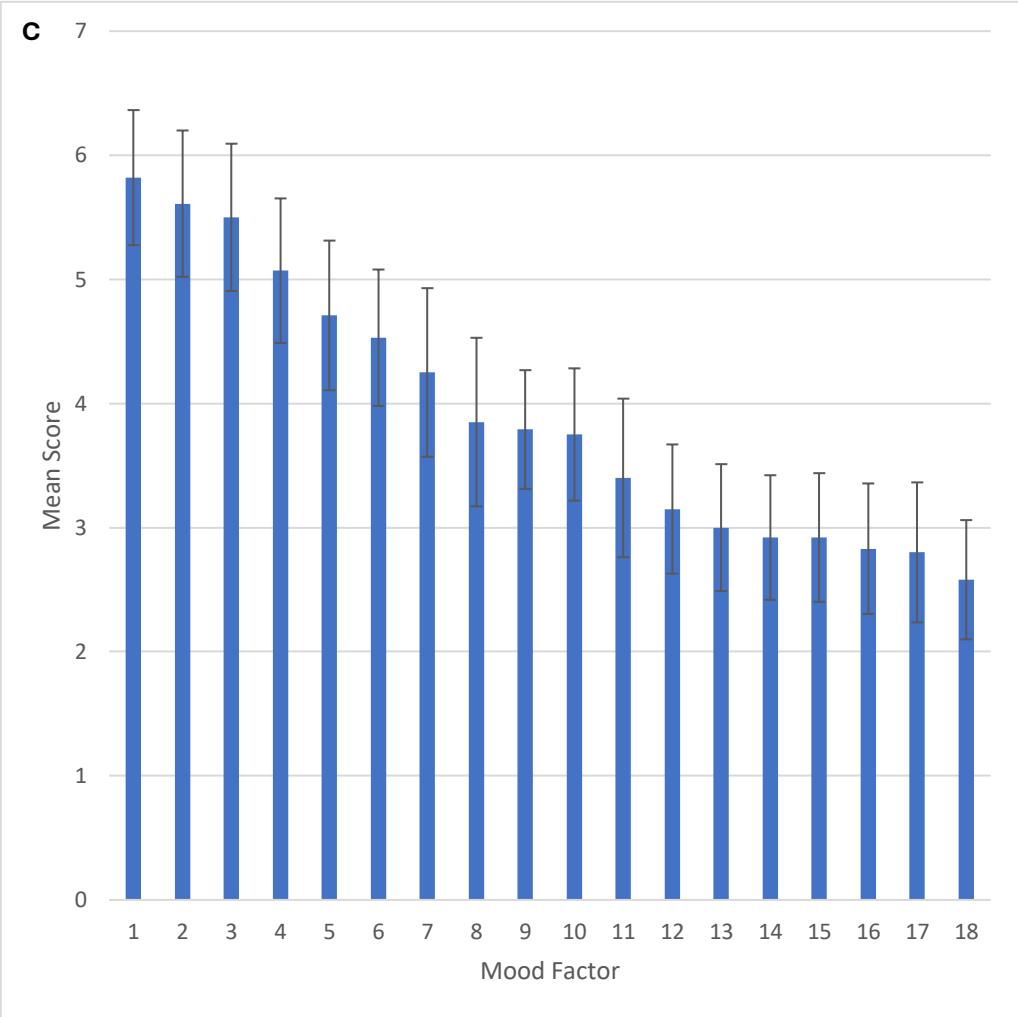
A



Rank	Mood Factor - Depression
1	Moderate chronic life event (relationship difficulties/divorce, chronic illness, work-related stress etc.)
2	Pain, discomfort or itching associated with your skin condition
3	Difficulties or frustration associated with treating your skin condition (e.g. regularly having to source and apply moisturizer)
4	Severe adverse life event (bereavement, life-threatening illness etc.)
5	Sleep problems related to your skin condition e.g. due to excessive itchiness, night-time sweating etc.
6	Embarrassment of social interaction because of your skin condition
7	Difficulty regulating body temperature/sweating
8	Medical issues (non-skin related)
9	Low quality/quantity of friendships and relationships
10	Sleep problems unrelated to your skin condition
11	Stigma or bullying associated with your skin condition
12	Stigma or bullying due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
13	Educational, work or social challenges due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions
14	Educational, work or social challenges due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.
15	Allergies
16	Educational, work or social challenges due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
17	Stigma or bullying due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.
18	Stigma or bullying due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions



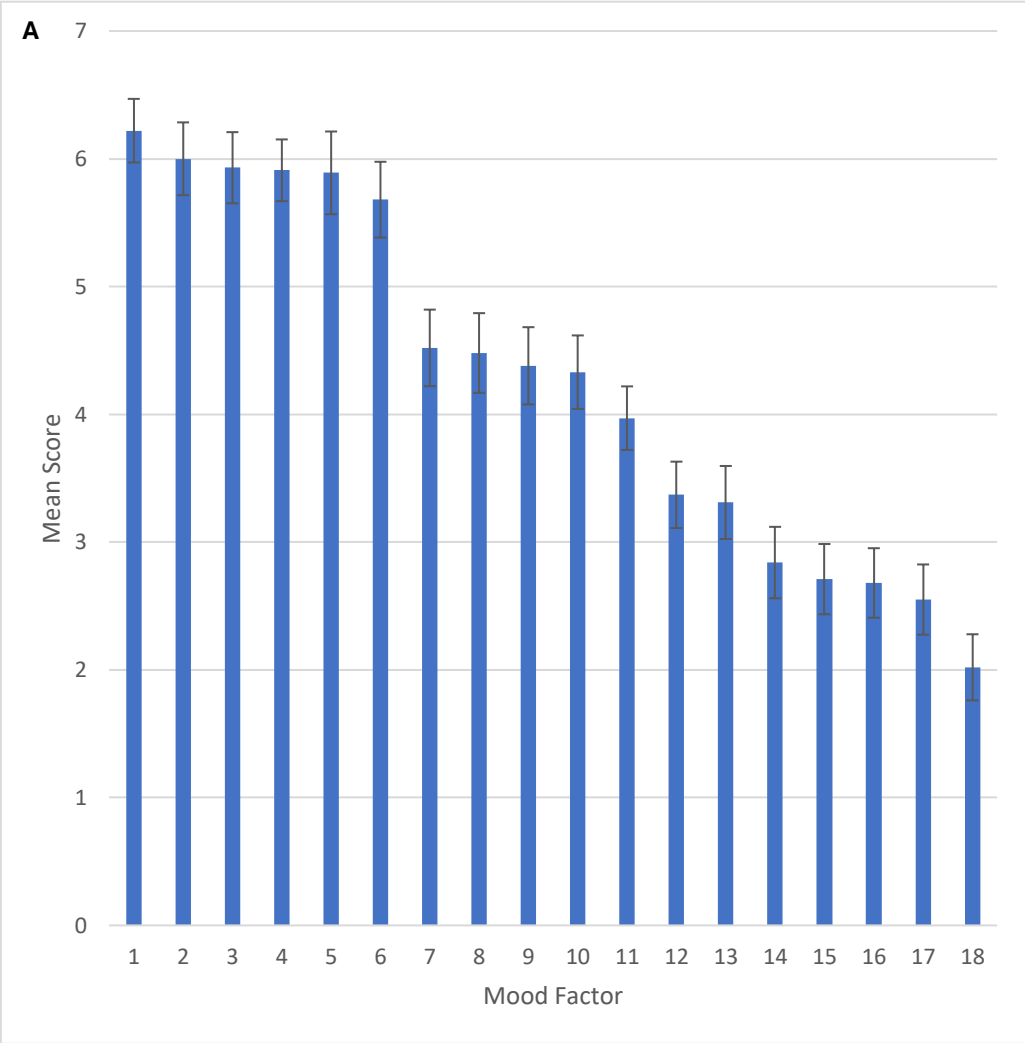
Rank	Mood Factor - Anxiety
1	Moderate chronic life event (relationship difficulties/divorce, chronic illness, work-related stress etc.)
2	Pain, discomfort or itching associated with your skin condition
3	Embarrassment of social interaction because of your skin condition
4	Medical issues (non-skin related)
5	Difficulties or frustration associated with treating your skin condition (e.g. regularly having to source and apply moisturizer)
6	Sleep problems related to your skin condition e.g. due to excessive itchiness, night-time sweating etc.
7	Severe adverse life event (bereavement, life-threatening illness etc.)
8	Sleep problems unrelated to your skin condition
9	Difficulty regulating body temperature/sweating
10	Educational, work or social challenges due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
11	Stigma or bullying associated with your skin condition
12	Educational, work or social challenges due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.
13	Educational, work or social challenges due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions
14	Low quality/quantity of friendships and relationships
15	Stigma or bullying due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
16	Stigma or bullying due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions
17	Stigma or bullying due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.
18	Allergies



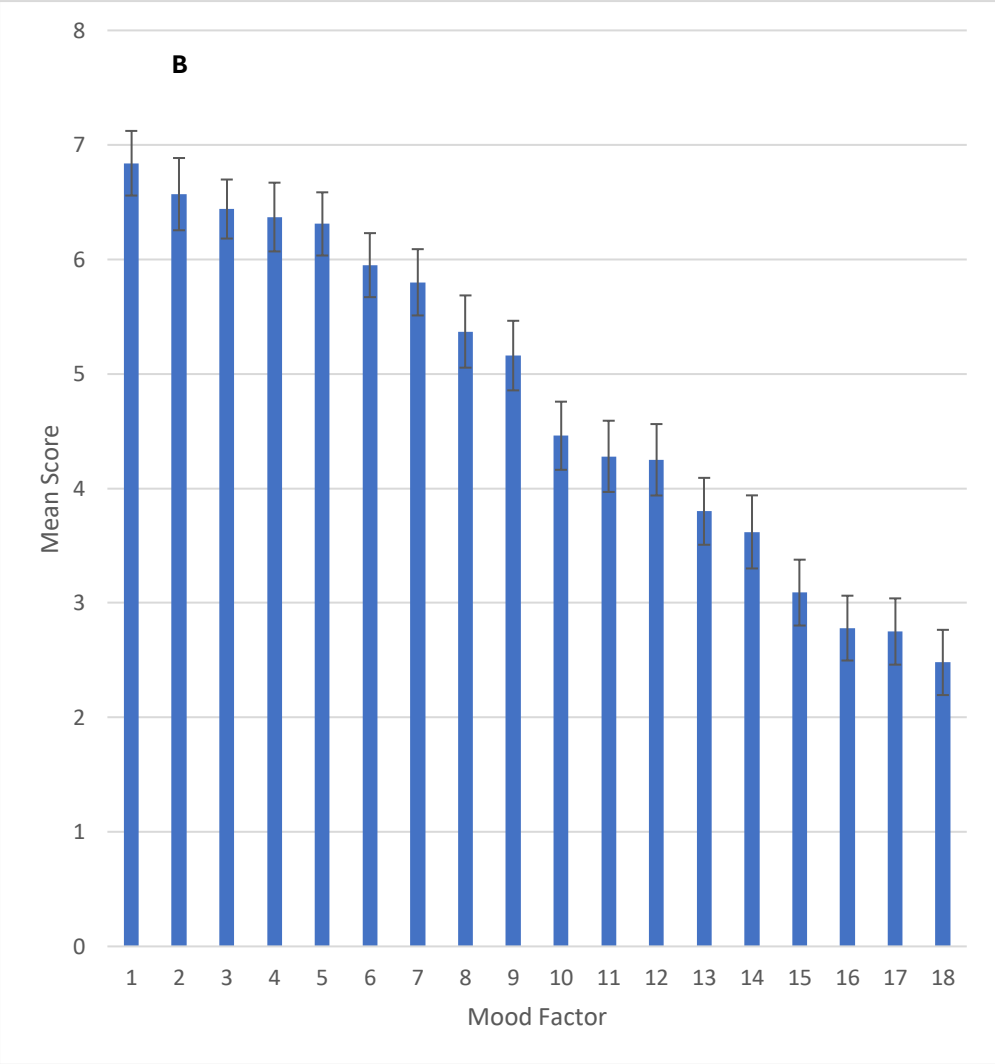
Rank	Mood Factor - Irritability
1	Difficulties or frustration associated with treating your skin condition (e.g. regularly having to source and apply moisturizer)
2	Pain, discomfort or itching associated with your skin condition
3	Sleep problems related to your skin condition e.g. due to excessive itchiness, night-time sweating etc.
4	Moderate chronic life event (relationship difficulties/divorce, chronic illness, work-related stress etc.)
5	Difficulty regulating body temperature/sweating
6	Embarrassment of social interaction because of your skin condition
7	Severe adverse life event (bereavement, life-threatening illness etc.)
8	Medical issues (non-skin related)
9	Educational, work or social challenges due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions
10	Sleep problems unrelated to your skin condition
11	Allergies
12	Stigma or bullying associated with your skin condition
13	Educational, work or social challenges due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.
14	Stigma or bullying due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions
15	Educational, work or social challenges due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
16	Low quality/quantity of friendships and relationships
17	Stigma or bullying due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
18	Stigma or bullying due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.

Appendix 3.12: Ranking of factors (scored from 0-10) potentially predisposing to adult mood symptoms (depression (A)), anxiety (B) and irritability (C) in females with psoriasis

Rank	Mood Factor - Depression
1	Pain, discomfort or itching associated with your skin condition
2	Moderate chronic life event (relationship difficulties/divorce, chronic illness, work-related stress etc.)
3	Difficulties or frustration associated with treating your skin condition (e.g. regularly having to source and apply moisturizer)
4	Embarrassment of social interaction because of your skin condition
5	Severe adverse life event (bereavement, life-threatening illness etc.)
6	Sleep problems related to your skin condition e.g. due to excessive itchiness, night-time sweating etc.
7	Sleep problems unrelated to your skin condition
8	Medical issues (non-skin related)
9	Stigma or bullying associated with your skin condition
10	Low quality/quantity of friendships and relationships
11	Educational, work or social challenges due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions
12	Educational, work or social challenges due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
13	Difficulty regulating body temperature/sweating
14	Stigma or bullying due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions
15	Educational, work or social challenges due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.
16	Stigma or bullying due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
17	Stigma or bullying due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.
18	Allergies



Rank	Mood Factor - Anxiety
1	Moderate chronic life event (relationship difficulties/divorce, chronic illness, work-related stress etc.)
2	Severe adverse life event (bereavement, life-threatening illness etc.)
3	Pain, discomfort or itching associated with your skin condition
4	Sleep problems related to your skin condition e.g. due to excessive itchiness, night-time sweating etc.
5	Embarrassment of social interaction because of your skin condition
6	Difficulties or frustration associated with treating your skin condition (e.g. regularly having to source and apply moisturizer)
7	Sleep problems unrelated to your skin condition
8	Medical issues (non-skin related)
9	Stigma or bullying associated with your skin condition
10	Educational, work or social challenges due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions
11	Low quality/quantity of friendships and relationships
12	Difficulty regulating body temperature/sweating
13	Educational, work or social challenges due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
14	Stigma or bullying due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions
15	Educational, work or social challenges due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.
16	Stigma or bullying due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
17	Stigma or bullying due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.
18	Allergies


B
Mean Score
Mood Factor
0
1
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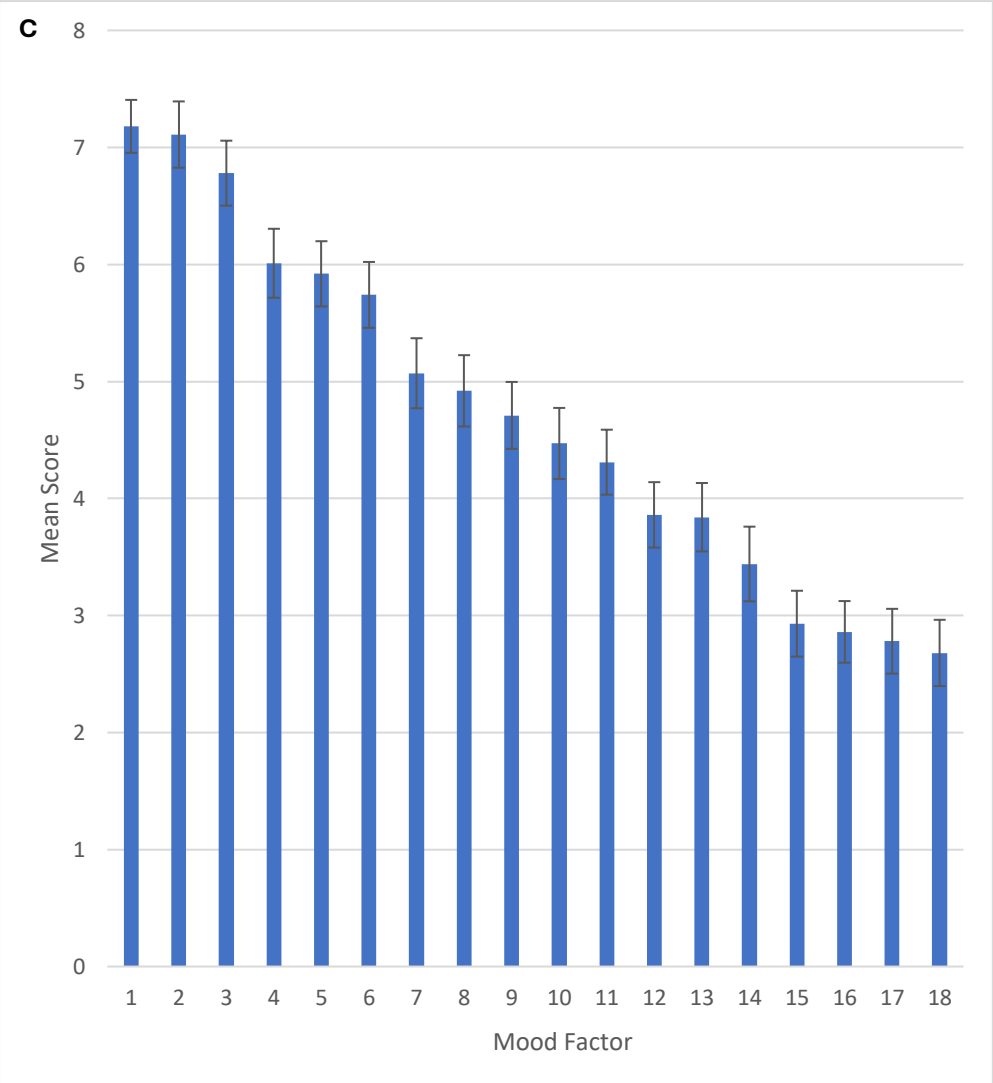


Rank	Mood Factor - Irritability
1	Pain, discomfort or itching associated with your skin condition
2	Sleep problems related to your skin condition e.g. due to excessive itchiness, night-time sweating etc.
3	Difficulties or frustration associated with treating your skin condition (e.g. regularly having to source and apply moisturizer)
4	Sleep problems unrelated to your skin condition
5	Moderate chronic life event (relationship difficulties/divorce, chronic illness, work-related stress etc.)
6	Embarrassment of social interaction because of your skin condition
7	Difficulty regulating body temperature/sweating
8	Severe adverse life event (bereavement, life-threatening illness etc.)
9	Educational, work or social challenges due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions
10	Medical issues (non-skin related)
11	Stigma or bullying associated with your skin condition
12	Low quality/quantity of friendships and relationships
13	Educational, work or social challenges due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
14	Allergies
15	Educational, work or social challenges due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.
16	Stigma or bullying due to finding it hard to pay attention e.g. getting distracted, not finishing work on time, not listening to instructions
17	Stigma or bullying due to being impulsive e.g. making rash decisions, interrupting when people are talking, doing things without thinking of the consequences etc.
18	Stigma or bullying due to difficulties with social interaction e.g. not understanding another person's point of view or social norms, finding it difficult to follow conversations. not understanding humour or sarcasm etc.

Appendix 3.13. A qualitative deductive content analysis of free-text comments relating to factors underlying mood symptoms across the lifespan across the three conditions. Inter-rater reliability across two coders was assessed by Cohen's κ and indicated substantial and significant agreement (κ=0.73, (95% CI: 0.65-0.80), p<0.001).

Group	Main Category	Categories	Sub-categories	Exemplar phrases
XLI Males	Struggling to live a 'normal' life	Wellbeing concerns	Physical health	"Diabetes, sciatica and post stroke pain", "Concern over seeping Crusty Warts, Diabetes eye jabs"
			Mental health	"Everything triggers me and makes me feel awfu", "Get angry to quickly"
		Daily functioning	Child-related responsibilities	"Having to have been a carer for most of my adult life"
			Skin-specific frustrations	"The amount of work it takes to keep my skin looking acceptable"
		Changing circumstances	Judgement and stigmatisation	"Very conscious of strangers judging my skin appearance as unsightly", "My friends nicknamed me croc"
			Life events	"Family arguments make me the most anxious and irritated", "Smothering upbringing"
XLI Females		Wellbeing concerns	Physical health	"Weight and diet and exercise", "Being unable to adequately articulate my medical needs to doctors"
			Mental health	"Inability to focus", "Health anxiety, social anxiety, repetitive and intrusive memories"
		Daily functioning	Child-related responsibilities	"Postnatal, birth trauma, child with bone tumor", "Stress having a child with ADHD/Autism"
		Changing circumstances	Judgement and stigmatisation	"Parental influence", "The pressure and struggle of feeling like I have to keep up with able bodied people"
			Life events	"Loss of both parents in teenage years", "Father with XLI mentally and physically abusive"
IV Males		Daily functioning	Skin-specific frustrations	"Unable to go to tropical destination till late 20s"
		Changing circumstances	Judgement and stigmatisation	"School bullying was pretty unrelenting", "I feel ashamed and embarrassed"
IV Females		Wellbeing concerns	Physical health	"Heavy difficult menses / period", "Inability to perspirre", "Fungal and yeast infections as a result of my skin disorder are difficult to deal with"
			Mental health	"Anxiety", "Frustration"
		Daily functioning	Skin-specific frustrations	"Embarrassment and fed up that after 50 years of managing my ichthyosis with Calmurid, I am now back to square one", "Spending so much money on creams/moisturizers", "Pain Due to Cracking"
		Changing circumstances	Judgement and stigmatisation	"Bullying in school years"
			Life events	"Child abuse, bullying, relationships"
Psoriasis Males		Wellbeing concerns	Physical health	"Deafness and wearing hearing aids"
		Daily functioning	Skin-specific frustrations	"My condition not being understood", "Psoriasis in the ears is painful and stops me from wearing my hearing aids"
		Changing circumstances	Judgement and stigmatisation	"Extreme bullying throughout primary and high school"
			Life events	"Experiencing child sex abuse, growing up in an abusive household", "Daughters growing up and getting boyfriends etc."
Psoriasis Females		Wellbeing concerns	Physical health	"Fatigue from psoriatic arthritis", "Unable to do sternous physical activity"
			Mental health	"Anxiety about progression of psoriasis", "Health anxiety"
		Daily functioning	Child-related responsibilities	"the way her skin effects her quality of life knowing you caused it all plays a larger part than my moderate life long battle with psoriasis"
			Skin-specific frustrations	"Not engaging in exercise/sports esp swimming because of comments about my skin", "Frustration with explaining what I have and that it is not contagious."
		Changing circumstances	Judgement and stigmatisation	"Being told I'm ugly, other people fearful of catching my psoriasis", "Low self esteem and embarrassed showing skin"
			Life events	"I was assaulted and as a result suffered a miscarriage", "Work issues", "Bereavement"

Appendix 3.14: Chapter 3 Advert

Advert

RESEARCHERS AT CARDIFF UNIVERSITY ARE LOOKING FOR ADULT (>18 YRS) (MALES AFFECTED BY X-LINKED ICHTHYOSIS (XLI)/FEMALE CARRIERS OF GENETIC CHANGES ASSOCIATED WITH XLI/MALES AND FEMALES AFFECTED BY ICHTHYOSIS VULGARIS (IV)/ PSORIASIS)*, TO TAKE PART IN A SHORT ONLINE SURVEY LOOKING AT MOOD SYMPTOMS AND ASSOCIATED RISK FACTORS.

***delete as appropriate depending upon recruitment avenue**

Mood problems such as depression, anxiety and irritability are commonly seen in skin conditions, including X-linked ichthyosis (XLI), ichthyosis vulgaris (IV) and psoriasis. We are undertaking a large-scale survey to better understand the frequency and severity of such problems in these three conditions, and to try and understand what might contribute to them. Our findings should lead to more targeted, and therefore more effective, clinical strategies for addressing mood issues.

If you have a diagnosis of XLI, IV or psoriasis, or if you are an adult female with confirmed carrier status of XLI-associated genetic change, we would be extremely grateful if you could complete the following short (30-40 minute) survey:

Insert survey link

Many thanks!

Georgina Wren and Dr William Davies, Cardiff University

Appendix 3.15: Chapter 3 Information Sheet

Participant Information Sheet

'A comparison of mood symptoms and associated risk factors in X-linked ichthyosis (XLI), Ichthyosis Vulgaris (IV) and psoriasis'

X-linked ichthyosis (XLI) is a skin condition caused by a particular molecule (steroid sulfatase) being absent, or not working properly. Ichthyosis vulgaris (IV) is a related skin condition, often caused by changes in the filaggrin gene (FLG). Psoriasis is a chronic, inflammatory, immune-mediated skin condition and is influenced by both genetic and environmental factors.

Previous work has shown that XLI, IV and psoriasis are associated with increased levels of mood problems (depression, anxiety and irritability). However, these analyses have been performed in relatively small samples, the relative importance of the many possible contributing factors has never been investigated systematically, and the frequency/severity of such problems across these conditions has never been examined.

We aim to recruit a large sample of adult (>18yrs) males with XLI, female carriers of genetic changes associated with XLI, and male and females diagnosed with IV or psoriasis, from around the world to complete a short (30-40mins) online survey asking about various aspects of your condition and your mental health/personality to better understand mood problems in these conditions, and to identify optimal treatment strategies.

The information you provide will be anonymous (i.e. your name will not be available to the research team and you will be identified solely with a participant number) and you will not be given feedback on your individual results. The results will not provide sufficient information to diagnose a clinical condition. Your participation in this study is voluntary, and you are free to withdraw at any time and for any reason; however, once you have submitted your answers, as they are anonymous, they will not be able to be retrieved or deleted.

If you feel uncomfortable answering any questions, please feel free to omit them.

You will be provided with further information upon completion of the questionnaire and you will have the opportunity to register to take part in future similar studies by leaving your e-mail address.

The results of the study will be disseminated by e-mail to participants, via social media, via relevant charity websites or via publication in an academic journal.

The study has been ethically reviewed by Cardiff University School of Psychology Ethical Review Panel. If you require further information on the study, please contact us: Ms Georgina Wren (wreng@cardiff.ac.uk) or Dr William Davies (daviesw4@cardiff.ac.uk) at Cardiff University, United Kingdom

Privacy Notice:

The information provided on the consent form will be held in compliance with GDPR regulations. Cardiff University is the data controller and Matt Cooper is the data protection officer (inforequest@cardiff.ac.uk). This information is being collected by Ms Georgina Wren. This information will be held securely and separately from the research information you provide. Only the researcher will have access to this form and it will be destroyed after 7 years. The lawful basis for processing this information is public interest.

Appendix 3.16: Chapter 3 Consent Form

Consent form

'A comparison of mood symptoms and associated risk factors in X-linked ichthyosis (XLI), Ichthyosis Vulgaris (IV) and psoriasis'

- I have read and understood the Participant Information Sheet for the above study and consent to take part in the survey described
- I am aged 18yrs or over and one of the following: a confirmed female carrier of a genetic change related to X-linked ichthyosis (XLI), a male with a clinical diagnosis of XLI, a male or female with a clinical diagnosis of ichthyosis vulgaris (IV), a male or female with a clinical diagnosis of psoriasis.
- I understand that study participation will take ~30-40mins, that I will be provided with further information at the end, and that I may register to take part in future similar studies by leaving my e-mail address if I wish

- I understand that the survey will not provide information sufficient for diagnosing a clinical condition, and that I am free to omit answering any questions I choose

- I understand that my responses will be anonymous (recorded solely with a participant number), that I will not be personally identifiable from my data, and that I will not receive any feedback on my individual data

- I understand that I may withdraw from the study at any point and for any reason prior to submission of my completed survey

- I understand that should I require more information before completing the survey, I am free to contact Ms Georgina Wren (wreng@cardiff.ac.uk) or Dr William Davies (daviesw4@cardiff.ac.uk)

- I understand that the information I provide may be retained indefinitely or published, and that I will not be identifiable in any publications

- I understand that this research project has been ethically reviewed by the Cardiff University School of Psychology Research Ethics Committee, and that if I have any queries about the conduct of the study I can contact the ethical review board via the following means: Secretary of Cardiff University School Ethics Board, Cardiff University School of Psychology, Tower Building, Park Place, Cardiff CF10 3AT, United Kingdom Tel: 44-(0)29-2087-0360, e-mail: psychethics@cardiff.ac.uk

Privacy Notice:

The information provided on the consent form will be held in compliance with GDPR regulations. Cardiff University is the data controller and Matt Cooper is the data protection officer (inforequest@cardiff.ac.uk). This information is being collected by Ms Georgina Wren. This information will be held securely and separately from the research information you provide. Only the researcher will have access to this form and it will be destroyed after 7 years. The lawful basis for processing this information is public interest.

Appendix 3.17: Chapter 3 Debrief Form

Debrief Form

'A comparison of mood symptoms and associated risk factors in X-linked ichthyosis (XLI), Ichthyosis Vulgaris (IV) and psoriasis'

Thank you for taking part in our study – your contribution is hugely appreciated!

Once the study is complete and the data analysed, we aim to communicate summary results to relevant organisations (e.g. charities and patient support groups), and to academic journals. If you are also interested in receiving a summary of our results, please follow the information to leave your contact e-mail address at the end of this message. All the information you have provided to us is totally anonymous and cannot be traced back to you.

X-linked ichthyosis (XLI) is a skin condition caused by a particular molecule (steroid sulfatase, STS) being absent, or not working properly; the STS molecule also normally works in the brain

and its loss is thought to be associated with behavioural and cognitive changes (including inattention, impulsivity and social function). Ichthyosis vulgaris (IV) is a related skin condition often caused by changes in the filaggrin gene (FLG). Psoriasis is a chronic, inflammatory, immune-mediated skin condition and is influenced by both genetic and environmental factors.

Our previous research has shown that on average, males with XLI and females with XLI-associated genetic changes, exhibit a different personality profile from the general population (results of these studies are freely-available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5053497/ and https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6377116/). From these studies, and those of others, it would also appear that these individuals, and those with ichthyosis vulgaris and psoriasis, are also at increased risk of developing some mental health conditions.

In the current study we want to examine these ideas further by investigating the mood symptom profile of the three disorders and how different factors may contribute. Thus, we asked about issues such as the condition of your skin (discomfort, stigmatization or inconvenience associated with being affected and managing such a condition or associated medical issues) and the behavioural or cognitive problems associated with having one of these skin conditions. We hope that by understanding which cause, or causes, contributes most to mood patterns in each condition, we can develop more effective targeted clinical interventions.

To examine the specific aspects of behaviour described above, the survey used both custom-designed and well-validated psychological questionnaires, and further details are available from the researcher team if requested. Importantly, the information you provided through these questionnaires is not sufficient to make a clinical diagnosis, and if you are worried about your physical or mental health, you should seek advice from a qualified medical professional in the usual way.

If you have any further questions about the purpose or conduct of this study, please contact the researchers or the ethical review board using the details below:

Ms Georgina Wren (PhD student), Cardiff University School of Psychology e-mail: wreng@cardiff.ac.uk

Dr William Davies (project supervisor), Cardiff University School of Psychology, Tel: 44-(0)29-2087-0152, e-mail: daviesw4@cardiff.ac.uk

Secretary of Cardiff University School Ethics Board, Cardiff University School of Psychology, Tel: 44-(0)29-2087-0360, e-mail: psychethics@cardiff.ac.uk

If you are interested in taking part in future studies related to this work, please click on the following link to leave your e-mail address: URL TBC. Your contact details will be kept separately from your responses to this questionnaire and any information you provide will only be used to feed back summary data from the current study or to contact you to see whether you would be interested in taking part in future similar studies.

Privacy Notice:

The information provided on the consent form will be held in compliance with GDPR regulations. Cardiff University is the data controller and Matt Cooper is the data protection officer (inforequest@cardiff.ac.uk). This information is being collected by Ms Georgina Wren. This information will be held securely and separately from the research information you provide. Only the researcher will have access to this form and it will be destroyed after 7 years. The lawful basis for processing this information is public interest

Appendix 3.18: Chapter 3 Direct participant invite

Direct participant invite

Dear Sir/Madam,

We are researchers at Cardiff University, UK. Following on from our previous work on mood/developmental disorders and associated traits in males with X-linked ichthyosis (XLI) and female carriers of XLI-related genetic changes, we now want to examine how these disorders/traits vary with regard to frequency, severity and cause across related skin disorders.

We saw that you were interested in XLI/ichthyosis vulgaris (IV)/psoriasis* (delete as appropriate). If you are interested in helping with our study, the link to the survey is: URL TBC

Kind regards,

Georgina Wren (PhD student) and Dr William Davies.

APPENDIX CHAPTER 4

Appendix 4.1: Demographic and clinical variables in each experimental group. Age and CISI scores are presented as mean values±standard error of the mean.

Demographic and clinical variables	Sex	Group			Statistical comparison
		XLI	IV	General population	
Age (yrs)	Male	43.8±2.8	48.6±2.5	44.1±0.6	GROUP: F[2,462]=4.62, p=0.010 SEX: F[1,462]=5.38, p=0.021 GROUP x SEX: F[2,462]=0.17, p=0.84
	Female	41.5±1.1	45.1±1.9	42.1±0.5	
Percentage of sample with highest education level greater than high school	Male	63	73	73	χ^2[5]=15.9, p=0.007
	Female	71	88	84	
Percentage of sample with positive family history (first or second-degree relative) for memory-related condition	Male	55	50	23	χ^2[5]=19.0, p=0.002
	Female	39	25	28	
CISI score indexing severity of skin condition	Male	5.1±0.2	4.5±0.2	N/A	GROUP: F[1,207]=3.31, p=0.070 SEX: F[1,207]=35.5, p<0.001 GROUP x SEX: F[1,207]=23.7, p<0.001
	Female	2.9±0.2	4.3±0.2		

Appendix 4.2: Mood and memory-related variables in each experimental group. Data are presented as mean values±standard error

Mood and memory variables	Sex	Group			Statistical comparison
		XLI	IV	General population	
K10 score	Male	25.2±1.3	21.3±1.4	19.8±0.7	GROUP: F[2,458]=21.3, p<0.001 SEX: F[1,458]=0.013, p=0.91 GROUP x SEX interaction: F[2,458]=2.27, p=0.11
	Female	24.1±0.7	24.4±1.0	18.9±0.6	
MMQ: contentment with memory	Male	34.7±2.4	39.2±2.7	46.3±1.2	GROUP: F[2,456]=22.0, p<0.001 SEX: F[1,456]=0.031, p=0.87 GROUP x SEX interaction: F[2,456]=0.25, p=0.78
	Female	36.7±1.9	38.7±1.9	46.2±1.2	
MMQ: perceived memory ability	Male	38.1±2.0	44.0±2.3	54.2±1.3	GROUP: F[2,454]=55.1, p<0.001 SEX: F[1,454]=0.42, p=0.52 GROUP x SEX interaction: F[2,454]=0.29, p=0.75
	Female	38.1±1.9	41.2±1.7	54.1±1.2	
MMQ: use of strategies to aid memory	Male	40.8±2.1	36.9±2.2	30.3±1.1	GROUP: F[2,444]=29.0, p<0.001 SEX: F[1,444]=3.32, p=0.07 GROUP x SEX interaction: F[2,444]=0.042, p=0.96
	Female	43.1±1.4	40.2±1.7	32.7±1.1	
Word-picture recall score	Male	72.6±2.6	84.5±3.2	86.0±1.8	GROUP: F[2,431]=6.88, p=0.001 SEX: F[1,431]=14.8, p<0.001 GROUP x SEX interaction: F[2,431]=1.38, p=0.25
	Female	87.4±2.0	89.7±2.3	94.0±1.7	

Appendix 4.3: List of words presented in objective recall task

Drum

Curtain

Bell

Coffee

School

Parent

Moon

Garden

Hat

Farmer

Nose

Turkey

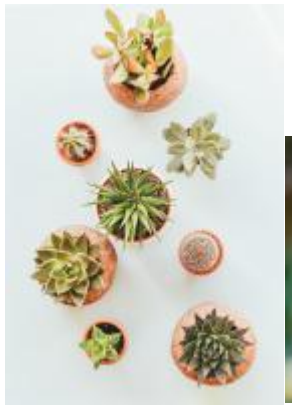
Colour

House

River

Appendix 4.4: List of pictures presented in objective recall task

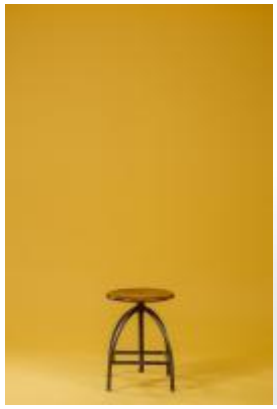


















Appendix 4.5: Chapter 4 Advert

Advert

RESEARCHERS AT CARDIFF UNIVERSITY ARE LOOKING FOR ADULT (>18 YRS) MALES AFFECTED BY X-LINKED ICHTHYOSIS (XLI)/FEMALE CARRIERS OF GENETIC CHANGES ASSOCIATED WITH XLI AND MALES AND FEMALES AFFECTED BY ICHTHYOSIS VULGARIS (IV), TO TAKE PART IN A SHORT ONLINE SURVEY LOOKING AT MEMORY

Genetic changes associated with ichthyosis-have previously been associated with effects on memory function and on brain regions important in memory. We are undertaking a study to better understand these effects, by examining different types of memory and other cognitive functions. We are also interested in how effects on memory may be related to mood (depressive and anxiety symptoms are elevated, on average, in individuals with ichthyosis). Findings from this study will help us better understand cognitive and mood function in ichthyosis.

If you have a confirmed diagnosis of XLI or IV, or if you are a confirmed adult female carrier of an XLI-associated genetic change, we would be extremely grateful if you could complete the following short (20-30 minute) survey:

Insert survey link

Many thanks

Georgina Wren and Dr William Davies, Cardiff University

Appendix 4.6: Chapter 4 Direct participant invite

Direct participant invite

To whom it may concern,

We are researchers at Cardiff University, UK. Recent research has suggested that brain changes associated with genetic differences in ichthyosis may have an impact on memory, cognitive function and mood. We want to further investigate the nature and magnitude of these possible effects in different types of memory and executive function in adult (>18 yrs.) males affected by X-linked ichthyosis (XLI), and adult female XLI carriers, and males and females affected by ichthyosis vulgaris (IV).

We saw that you were interested in taking part in ichthyosis-related research. If you are interested in taking part in our study, the link to the survey is:

If you require more details prior to completing the survey, please get in touch. We are more than happy to answer any questions or concerns that you may have.

Kind regards,

Georgina Wren (PhD student) and Dr William Davies.

Appendix 4.7: Chapter 4 Information Sheet

Participant Information Sheet

'An investigation into memory, cognitive function and mood in ichthyosis'

Recent findings in animals have indicated that biological processes associated with the skin condition ichthyosis may also be associated with effects on memory, other cognitive functions, and mood. The effects of genetic changes associated with ichthyosis on memory, cognition and mood in humans has yet to be investigated. Our study aims to address this gap in knowledge.

We are inviting you to take part in this study as part of our sample of adult (>18yrs) males with XLI, female carriers of genetic changes associated with XLI, and adults with ichthyosis vulgaris (IV) from around the world. If you take part, we will ask you to complete a short (20-30mins) online survey asking for a brief medical history, and details regarding your current mood and wellbeing. This survey will also ask about how satisfied you are with your current memory abilities, and any memory strategies you use to help. You will also take part in a short activity to test your short-term memory, in which you will be asked to recall a list of words and pictures.

Any information that you provide will be anonymous (i.e. your name will not be linked to the information and data you provide and will not be available to the research team). You will be identified solely with a unique participant code and you will not be given feedback on your individual outcomes. The results of this survey will not provide a basis from which to diagnose or treat a clinical condition or associated symptoms.

Your participation in this study is voluntary, and you are free to withdraw at any time and for any reason; however, once you have submitted your answers, as they are anonymous, they will not be able to be retrieved or deleted.

If you feel uncomfortable answering any questions, please feel free to omit them.

You will be provided with further information upon completion of this study, and you will have the opportunity to register to take part in follow-up studies examining memory using online neuropsychological tests by leaving your e-mail address. If you decide to register your interest in further work, you will be asked to generate a code unique to you so that your current and future responses can be linked.

You will not be given feedback on your individual study scores, but the results of the study (as group averages) will be disseminated by e-mail to participants, via social media and relevant charity websites, or via publication in an academic journal.

The study has been ethically reviewed by Cardiff University School of Psychology Ethical Review Panel. If you have any concerns or issues related to the study then please contact: psychethics@cardiff.ac.uk, telephone (number) or write to the Secretary of the School of Psychology Ethical Review Panel, School of Psychology, Cardiff University, Park Place, Cardiff, UK, CF10 3AT.

If you require further information about the study, please contact us: Ms Georgina Wren (wreng@cardiff.ac.uk) or the primary supervisor for this project, Dr William Davies (daviesw4@cardiff.ac.uk) at School of Psychology, Cardiff University, United Kingdom

Privacy Notice:

The information provided on the consent form will be held in compliance with UK GDPR regulations. Cardiff University is the data controller and James Merrifield is the data

protection officer (inforequest@cardiff.ac.uk). This information is being collected by Ms Georgina Wren. This information will be held securely and separately from the research information you provide. Only the researcher will have access to this form and it will be destroyed after 7 years. The lawful basis for processing this information is public interest.

Appendix 4.8: Chapter 4 Consent Form

Consent form

'An investigation into memory, cognitive function and mood in ichthyosis'

- I have read and understood the Participant Information Sheet for the above study and consent to take part in the survey described
- I am aged 18yrs or over and am one of the following: a) a confirmed female carrier of a genetic change related to X-linked ichthyosis (XLI), b) a male with a clinical diagnosis of XLI, or c) a person with a clinical diagnosis of ichthyosis vulgaris (IV).
- I understand that study participation will take ~20-30mins, that I will be provided with further information at the end, and that I may register to take part in follow-up studies by leaving my e-mail address if I wish. I understand that if I decide to register my interest in further work, I will be asked to generate a unique code to link my current and future responses.
- I understand that the survey will not provide information sufficient for clinical guidance, and that I am free to omit answering any questions I choose
- I understand that my responses will be anonymous (recorded solely with a participant code), that I will not be personally identifiable from my data, and that I will not receive any feedback on my individual data
- I understand that I may withdraw from the study at any point and for any reason prior to submission of my completed survey
- I understand that should I require more information before completing the survey, I am free to contact Ms Georgina Wren (wreng@cardiff.ac.uk) or Dr William Davies (daviesw4@cardiff.ac.uk)
- I understand that the information I provide may be retained indefinitely or published, and that I will not be identifiable in any publications
- I understand that if I choose to provide my email address and a unique self-generated code following completion of this survey to take part in subsequent studies, this information will be collected in accordance with UK GDPR i.e. stored separately from survey data, not linked to any other identifiable details (name, age etc.) and stored securely on a password-protected Cardiff University server.
- I understand that this research project has been ethically reviewed by the Cardiff University School of Psychology Research Ethics Committee, and that if I have any queries about the conduct of the study I can contact the ethical review board via the following means: Secretary of Cardiff University School Ethics Board, Cardiff University

School of Psychology, , Park Place, Cardiff CF10 3AT, United Kingdom Tel: 44-(0)29-2087-0360, e-mail: psychethics@cardiff.ac.uk

Privacy Notice:

The information provided on the consent form will be held in compliance with UKGDPR regulations. Cardiff University is the data controller and James Merrifield is the data protection officer (inforequest@cardiff.ac.uk). This information is being collected by Ms Georgina Wren. This information will be held securely and separately from the research information you provide. Only the researcher will have access to this form and it will be destroyed after 7 years. The lawful basis for processing this information is public interest.

Appendix 4.9: Chapter 4 Debrief Form

Debrief Form

'An investigation into memory, cognitive function and mood in ichthyosis'

Thank you for taking part in our study – your contribution is hugely appreciated!

Once the study is complete and all of the data has been analysed, we will communicate summary results to relevant organisations (e.g. charities and patient support groups), and to academic journals. If you are interested in receiving a summary of our results directly, please follow the links to leave your contact e-mail address at the end of this message. All the information you have provided to us in this study is totally anonymous and cannot be traced back to you.

X-linked ichthyosis (XLI) is a skin condition caused by a particular molecule (steroid sulfatase, STS) being absent, or not working properly. New research in rodents and worms has suggested that the absence of STS can increase longevity and can have neuroprotective and memory enhancing effects (https://www.tandfonline.com/doi/full/10.1080/14756366.2020.1758692; https://www.nature.com/articles/s41467-020-20269-y). In this study, and in subsequent work one of our aims is to test whether lack of STS in humans is associated with enhanced memory. Memory and mood are influenced by common brain regions; as individuals with XLI (and female carriers) appear at increased risk of adverse mood symptoms, a secondary aim of this work is to investigate the relationship between memory and mood.

Recent research by our group has suggested that individuals with ichthyosis vulgaris (IV) may present with an increased risk of mood disorders and associated traits (https://bit.ly/3qJq7i2). However, there is very little existing research exploring the impact of IV on any other areas of brain function, thus, we are also looking to compare memory, cognition and mood (and relationships between these) across individuals with XLI, IV and individuals not affected by ichthyosis.

The present study examined different types of memory ability, related executive functioning and mood in both males and females affected by XLI and IV, as well as trying to identify precipitating factors of any memory enhancing effects. Thus, we asked about your own/family history of relevant psychological conditions, as well as a basic measure of your recent mood (Kessler Psychological Distress Scale (K10) (https://www.cambridge.org/core/journals/psychological-medicine/article/abs/short-screening-scales-to-monitor-population-prevalences-and-trends-in-nonspecific-psychological-distress/F141675CCD0E08C0FB98E01C006B4E0D). To provide a baseline measure of short-term memory function, we used a short recall task involving neutral

set of words and pictures. We also asked about your satisfaction with your memory ability, your self-assessed memory capacities, and any strategies you use to aid your memory using questions taken from the Multifactorial Memory Questionnaire (MMQ) (https://bit.ly/3LWy3ET). We are interested in understanding whether these factors differ between individuals with XLI/IV and the general population. Importantly, the information you provided through these questionnaires is not sufficient to offer targeted clinical advice, and if you are worried about your physical or mental health, you should seek advice from a qualified medical professional in the usual way.

If you have any further questions about the purpose or conduct of this study, please contact the researchers or the ethical review board using the details below:

Ms Georgina Wren (PhD student), Cardiff University School of Psychology e-mail: wreng@cardiff.ac.uk

Dr William Davies (project supervisor), Cardiff University School of Psychology, Tel: 44-(0)29-2087-0152, e-mail: daviesw4@cardiff.ac.uk

Secretary of Cardiff University School Ethics Board, Cardiff University School of Psychology, Tel: 44-(0)29-2087-0360, e-mail: psychethics@cardiff.ac.uk

If you are interested in taking part in future studies related to this work, which might include neuropsychological tests, interviews, further surveys, or trying out new psychological support techniques, please click on the following link to leave your e-mail address: URL TBC. Your contact details will be kept separately from your responses to the study you have just completed and any information you provide will only be used to feed-back summary data from the current study or to contact you to see whether you would be interested in taking part in future similar studies.

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APPENDIX CHAPTER 5

Appendix 5.1: Heart rhythm abnormalities (HRA) as listed in online survey

Atrial fibrillation

Atrial flutter

Supraventricular tachycardia

Ventricular tachycardia

Bradycardia (slow heartbeat)

Tachycardia (fast heartbeat)

Appendix 5.2: Cardiovascular and metabolic conditions investigated as potential risk factors, or comorbidities, for abnormal heart rhythm in our online survey

Coronary artery/heart disease

Pericarditis

Congenital heart disease

Heart failure

Heart attack

Heart murmur

Angina

Stroke

Heart valve disease or malformation

High cholesterol

Anaemia

Hypertension

Cardiomyopathy

Type 1 diabetes

Type 2 diabetes

Rheumatoid arthritis

Inguinal hernia

Pneumonia Asthma

Gut problem

Lung cancer

Pulmonary embolism

Thyroid gland disorder

Obstructive sleep apnoea

Obesity (BMI>30)

Appendix 5.3: Statements presented following vignette for participant ratings (Strongly Disagree – Strongly Agree).

Do you think that risk of AF in XLI males is a significant health concern?

Do you think that males should be screened for heart abnormalities routinely following confirmation of XLI?

I believe that screening for heart problems in XLI is a good use of healthcare funding

I would be happy to attend/bring my son to a doctor's surgery/hospital regularly for heart screening

I believe that knowing that I/my son have a heart condition with possible adverse consequences is preferable to not knowing

I believe that the benefits associated with screening for, monitoring and treating any heart condition outweigh their risks

I require more information about the relationship between XLI and heart conditions in order to make any judgement about the benefit of screening

Appendix 5.4: Demographic variables in individuals with and without self- or parent-reported abnormal heart rhythms

Adult males with XLI (n=43)			
	Age (yrs)	**Country of residence**	**Ethnicity**
With abnormal heart rhythm	51.5 (95%CI:42.6-60.6)	UK:47% USA:27% Other:26%	White European: 100% Other: 0%

Without abnormal heart rhythm	46.2 (95%CI:41.1-51.2)	UK:54% USA:36% Other:10%	White European:86% Other: 14%
	t[40]=1.09, p=0.28	$\chi^2_{[2]}$=4.67, p=0.10	$\chi^2_{[1]}$=2.36, p=0.12
Adult female carriers (n=79)			
	Age (yrs)	**Country of residence**	**Ethnicity**
With abnormal heart rhythm	43.7 (95%CI: 39.1-48.2)	UK:35% USA:40% Other:25%	White European: 90% Other: 10%
Without abnormal heart rhythm	40.9 (95%CI: 38.2=43.6)	UK:37% USA:37% Other:26%	White European: 88% Other: 12%
	t[57]=0.57, p=0.57	$\chi^2_{[2]}$=0.51, p=0.78	$\chi^2_{[1]}$=0.77, p=0.38
Boys with XLI (n=69)			
	Age (yrs)	**Country of residence**	**Ethnicity**
With abnormal heart rhythm	8.9 (95%CI: 6.3-11.4)	UK:40% USA:40% Other:20%	White European: 80% Other: 20%

Without abnormal heart rhythm	7.5 (95%CI: 6.1-9.0)	UK:41% USA:35% Other:24%	White European: 91% Other: 9%
	t[67]=0.40, p=0.69	$\chi^2_{[2]}$=0.16, p=0.92	$\chi^2_{[1]}$=1.32, p=0.25

Appendix 5.5A: Individuals with or without abnormal heart rhythms (HRA) diagnosed with cardiovascular and metabolic conditions

Condition	Yes/No	XLI males with HRA (n=15)	XLI males without HRA (n=24)	XLI females with HRA (n=20)	XLI females without HRA (n=51)	XLI boys with HRA (n=15)	XLI boys without HRA (n=48)	All males with HRA (n=30)	All males without HRA (n=72)	All participants with HRA (n=50)	All participants without HRA (n=123)
Coronary artery/heart disease	**Yes**	0	0	1	0	0	0	0	0	1	0
	No	15	24	19	51	15	48	30	72	49	123
Pericarditis	**Yes**	0	0	0	0	0	0	0	0	0	0
	No	15	24	20	51	15	48	30	72	50	123
Congenital heart disease	**Yes**	0	0	1	0	1	0	1	0	2	0
	No	15	24	19	51	14	48	29	72	48	123
Heart failure	**Yes**	0	0	0	0	0	0	0	0	0	0
	No	15	24	20	51	15	48	30	72	50	123
Heart attack	**Yes**	0	1	0	0	0	0	0	1	0	1
	No	15	23	20	51	15	48	30	71	50	122
Heart murmur	**Yes**	0	0	4	0	2	7	2	7	6	7
	No	15	24	16	51	13	41	28	65	44	116
Angina	**Yes**	1	0	0	0	0	0	1	0	1	0
	No	14	24	20	51	15	48	29	72	49	123
Stroke	**Yes**	0	0	0	0	0	0	0	0	0	0

	No	15	24	20	51	15	48	30	72	50	123
Heart valve disease or malformation	**Yes**	1	0	2	1	1	0	2	0	4	1
	No	14	24	18	50	14	48	28	72	46	122
High cholesterol	**Yes**	4	3	3	7	0	0	4	3	7	10
	No	11	21	17	44	15	48	26	69	43	113
Anaemia	**Yes**	0	0	8	6	1	2	1	2	9	8
	No	15	24	12	45	14	46	29	70	41	115
Hypertension	**Yes**	5	4	4	10	0	0	5	4	9	14
	No	10	20	16	41	15	48	25	68	41	109
Cardiomyopathy	**Yes**	0	0	1	0	0	0	0	0	1	0
	No	15	24	19	51	15	48	30	72	49	123
Type I diabetes	**Yes**	1	0	0	0	0	0	1	0	1	0
	No	14	24	20	51	15	48	29	72	49	123
Type II diabetes	**Yes**	1	2	2	3	0	0	1	2	3	5
	No	14	22	18	48	15	48	29	70	47	118
Rheumatoid arthritis	**Yes**	1	0	1	1	0	0	1	0	2	1
	No	14	24	19	50	15	48	29	72	48	122
Inguinal hernia	**Yes**	1	0	1	3	0	0	1	0	2	3
	No	14	24	19	48	15	48	29	72	48	120

Pneumonia	**Yes**	2	3	2	3	2	2	4	5	6	8
	No	13	21	18	48	13	46	26	67	44	115
Asthma	**Yes**	4	5	7	5	4	6	8	11	15	16
	No	11	19	13	46	11	42	22	61	35	107
Gut problem	**Yes**	4	0	5	4	1	2	5	2	10	6
	No	11	24	15	47	14	46	25	70	40	117
Lung cancer	**Yes**	0	0	0	0	0	0	0	0	0	0
	No	15	24	20	51	15	48	30	72	50	123
Pulmonary embolism	**Yes**	0	0	0	2	0	0	0	0	0	2
	No	15	24	20	49	15	48	30	72	50	121
Thyroid gland disorder	**Yes**	2	1	2	6	1	0	3	1	5	7
	No	13	23	18	45	14	48	27	71	45	116
Obstructive sleep apnoea	**Yes**	1	3	3	4	0	1	1	4	4	8
	No	14	21	17	47	15	47	29	68	46	115
Obesity (BMI>30)	**Yes**	2	2	4	9	0	3	2	5	6	14
	No	13	22	16	42	15	45	28	67	44	109

Appendix 5.5B: Associated statistical analysis for Appendix 5.5A (two-tailed p-values from Fisher Exact Test) *p≤0.05, **p≤0.005

Condition	XLI adult males (HRA vs. no HRA)	Female carriers (HRA vs. no HRA)	XLI boys (HRA vs. no HRA)	All males (HRA vs. no HRA)	All participants (HRA vs. no HRA)
Coronary artery/heart disease	1.000	0.282	1.000	1.000	0.289
Pericarditis	1.000	1.000	1.000	1.000	1.000
Congenital heart disease	1.000	0.282	0.238	0.294	0.082
Heart failure	1.000	1.000	1.000	1.000	1.000
Heart attack	1.000	1.000	1.000	1.000	1.000
Heart murmur	1.000	0.005**	1.000	0.723	0.202
Angina	0.385	1.000	1.000	0.294	0.289
Stroke	1.000	1.000	1.000	1.000	1.000
Heart valve disease or malformation	0.385	0.189	0.238	0.084	0.025*
High cholesterol	0.396	1.000	1.000	0.190	0.265
Anaemia	1.000	0.011*	1.000	1.000	0.027*
Hypertension	0.266	1.000	1.000	0.119	0.322

Cardiomyopathy	1.000	0.282	1.000	1.000	0.289
Type I diabetes	0.385	1.000	1.000	0.294	0.289
Type II diabetes	1.000	0.616	1.000	1.000	0.692
Rheumatoid arthritis	0.385	1.000	1.000	0.294	0.201
Inguinal hernia	0.385	1.000	1.000	0.294	0.627
Pneumonia	1.000	0.616	0.238	0.443	0.356
Asthma	0.711	0.017*	0.231	0.263	0.010*
Gut problem	0.017*	0.105	1.000	0.022*	0.004**
Lung cancer	1.000	1.000	1.000	1.000	1.000
Pulmonary embolism	1.000	1.000	1.000	1.000	1.000
Thyroid gland disorder	0.547	1.000	0.238	0.075	0.332
Obstructive sleep apnoea	0.648	0.394	1.000	1.000	0.746
Obesity (BMI>30)	1.000	1.000	0.574	1.000	1.000

Appendix 5.6: Percentage of individuals with XLI (or female carriers) reporting involvement of precipitating factor in onset of HRA

Precipitating factor	Adults males with XLI (n=12)	Female carriers (n=20)	Boys with XLI (n=14)
Stress	42	45	14
Medication	8	0	7
Caffeine consumption (tea, coffee, energy drinks	33	25	7
Smoking	8	0	0
Postural change (e.g. moving from sitting down to standing up)	17	25	7
Sleep disturbance	33	15	7
Infection	8	10	14
Exercise	17	35	14
Increased body temperature e.g. due to inability to sweat	17	15	29
No obvious cause	42	25	50

Other	17	30	14

Appendix 5.7: Percentage of individuals with XLI (or female carriers) reporting times of onset of AHR episodes

Time of onset	Adults males with XLI (n=12)	Female carriers (n=12)	Boys with XLI (n=7)
Whilst sleeping/in the night	57	42	57
Early morning, shortly after waking	57	8	14
During the day	57	75	86
Late at night, just before sleeping	43	58	29

Appendix 5.8: Chapter 4 Advert

Advert

RESEARCHERS AT CARDIFF UNIVERSITY ARE LOOKING FOR ADULT (>18 YRS) (MALES AFFECTED BY X-LINKED ICHTHYOSIS (XLI)/FEMALE CARRIERS OF GENETIC CHANGES ASSOCIATED WITH XLI/PARENTS OF MALE CHILDREN DIAGNOSED WITH XLI)*, TO TAKE PART IN A SHORT ONLINE SURVEY LOOKING AT HEART FUNCTION

***delete as appropriate depending upon recruitment avenue**

Genetic changes associated with X-linked ichthyosis (XLI) have previously been associated with abnormal heart rhythms. We are undertaking a study to better understand the nature of these heart problems, contributing factors and treatment responses. We are also interested in attitudes towards potential heart screening for individuals affected by XLI. Our findings may help support initial diagnosis procedures and inform future cardiovascular treatment programmes.

If you have a diagnosis of XLI, if you are an adult female with confirmed carrier status of XLI-associated genetic change, or if you are a parent reporting on behalf of your male child diagnosed with XLI, we would be extremely grateful if you could complete the following short (20-30 minute) survey:

Insert survey link

Many thanks

Georgina Wren and Dr William Davies, Cardiff University

Appendix 5.9: Chapter 4 Direct participant invite

Direct participant invite

Dear Sir/Madam,

We are researchers at Cardiff University, UK. Following on from our previous research showing an increased frequency of heart arrhythmias in males with X-linked ichthyosis (XLI), we now want to further investigate the nature of, and potential risk factors associated with, heart problems in men and boys affected by XLI (and female carriers), as well as attitudes towards heart screening.

We are recruiting males with XLI, female carriers of genetic changes associated with XLI, and parents of male children diagnosed with XLI, and we saw that you were interested in XLI research. If you are interested in helping with our study, the link to the survey is: URL TBC

Kind regards,

Georgina Wren (PhD student) and Dr William Davies.

Appendix 5.11: Chapter 4 Participant Information Sheet

Participant Information Sheet

'An investigation into heart-related symptoms and attitudes towards heart screening in X-linked ichthyosis (XLI)'

X-linked ichthyosis (XLI) is a skin condition caused by a particular molecule (steroid sulfatase) being absent, or not working properly. New findings have indicated that, occasionally, XLI can be associated with heart problems, including abnormal rhythms.

Neither the nature of heart problems in males affected by XLI, or in female carriers of XLI-associated genetic changes, nor the factors which may trigger onset of symptoms, have yet been investigated in any detail. Our study aims to address this gap in our knowledge.

We aim to recruit a sample of adult (>18yrs) males with XLI, female carriers of genetic changes associated with XLI, and parents of male children diagnosed with XLI, from around the world to complete a short (20-30mins) online survey asking for a brief medical history relating to heart problems, and potential risk factors contributing to their onset. The survey also asks about attitudes and opinions related to screening for heart rhythm abnormalities in families affected by XLI; these may inform whether screening within this population is feasible and useful, and how it may be implemented.

Any information you provide will be anonymous (i.e. your name will not be available to the research team and you will be identified solely with a participant number) and you will not be given feedback on your individual outcomes. The results of this survey will not provide a basis from which to diagnose or treat a clinical condition or associated symptoms. Your participation in this study is voluntary, and you are free to withdraw at any time and for any reason; however, once you have submitted your answers, as they are anonymous, they will not be able to be retrieved or deleted.

If you feel uncomfortable answering any questions, please feel free to omit them.

You will be provided with further information upon completion of the questionnaire and you will have the opportunity to register to take part in future similar studies by leaving your e-mail address.

The results of the study will be disseminated by e-mail to participants, via social media, via relevant charity websites or via publication in an academic journal.

The study has been ethically reviewed by Cardiff University School of Psychology Ethical Review Panel. If you require further information on the study, please contact us: Ms Georgina Wren (wreng@cardiff.ac.uk) or the primary supervisor for this project, Dr William Davies (daviesw4@cardiff.ac.uk) at Cardiff University, United Kingdom

Privacy Notice:

The information provided on the consent form will be held in compliance with GDPR regulations. Cardiff University is the data controller and James Merrifield is the data protection officer (inforequest@cardiff.ac.uk). This information is being collected by Ms Georgina Wren. This information will be held securely and separately from the research information you provide. Only the researcher will have access to this form and it will be destroyed after 7 years. The lawful basis for processing this information is public interest.

Appendix 5.12: Chapter 4 Consent Form

Consent form

'An investigation into heart-related symptoms and attitudes towards heart screening in X-linked ichthyosis (XLI)'

- I have read and understood the Participant Information Sheet for the above study and consent to take part in the survey described
- I am aged 18yrs or over and am one of the following: a) a confirmed female carrier of a genetic change related to X-linked ichthyosis (XLI), b) a male with a clinical diagnosis of XLI, or c) a parent of a male child (under 18yrs) with a clinical diagnosis of XLI
- I understand that study participation will take ~20-30mins, that I will be provided with further information at the end, and that I may register to take part in future similar studies by leaving my e-mail address if I wish
- I understand that the survey will not provide information sufficient for clinical guidance, and that I am free to omit answering any questions I choose
- I understand that my responses will be anonymous (recorded solely with a participant number), that I will not be personally identifiable from my data, and that I will not receive any feedback on my individual data
- I understand that I may withdraw from the study at any point and for any reason prior to submission of my completed survey
- I understand that should I require more information before completing the survey, I am free to contact Ms Georgina Wren (wreng@cardiff.ac.uk) or Dr William Davies (daviesw4@cardiff.ac.uk)
- I understand that the information I provide may be retained indefinitely or published, and that I will not be identifiable in any publications
- I understand that if I choose to provide my email address following completion of this survey, this data will be collected in accordance with GDPR i.e. stored separately from survey data, not linked to any other identifiable details (name, age etc.) and stored securely on a password-protected Cardiff University server.
- I understand that this research project has been ethically reviewed by the Cardiff University School of Psychology Research Ethics Committee, and that if I have any queries about the conduct of the study I can contact the ethical review board via the following means: Secretary of Cardiff University School Ethics Board, Cardiff University School of Psychology, Tower Building, Park Place, Cardiff CF10 3AT, United Kingdom Tel: 44-(0)29-2087-0360, e-mail: psychethics@cardiff.ac.uk

Privacy Notice:

The information provided on the consent form will be held in compliance with GDPR regulations. Cardiff University is the data controller and James Merrifield is the data protection officer (inforequest@cardiff.ac.uk). This information is being collected by Ms Georgina Wren. This information will be held securely and separately from the research information you provide. Only the researcher will have access to this form and it will be destroyed after 7 years. The lawful basis for processing this information is public interest.

Appendix 5.13: Chapter 4 Debrief Form

Debrief Form

'An investigation into heart-related symptoms and attitudes towards heart screening in X-linked ichthyosis (XLI)'

Thank you for taking part in our study – your contribution is hugely appreciated!

Once the study is complete and the data analysed, we aim to communicate summary results to relevant organisations (e.g. charities and patient support groups), and to academic journals. If you are interested in receiving a summary of our results directly, please follow the information to leave your contact e-mail address at the end of this message. All the information you have provided to us is totally anonymous and cannot be traced back to you.

X-linked ichthyosis (XLI) is a skin condition caused by a particular molecule (steroid sulfatase, STS) being absent, or not working properly. Our previous work has indicated that middle-aged males with XLI are around four times more likely to be diagnosed with atrial fibrillation/flutter (AF, a type of irregular heart rhythm or 'arrhythmia') than males of a similar age without XLI (https://jmg.bmj.com/content/jmedgenet/57/10/692.full.pdf). AF ~~is an irregular heart rhythm which~~ can occur on a short-term or long-term basis and is associated with an increased risk of stroke, dementia/cognitive decline and heart failure (https://www.bhf.org.uk/informationsupport/conditions/atrial-fibrillation). The biological link between XLI and AF is currently unclear; it could be that loss of STS causes changes in the levels of circulating hormones which then affects heart function. Alternatively, other genes commonly deleted in XLI (besides STS) might be responsible. We are currently conducting a variety of studies to test these ideas.

The goal of the present study was to examine in detail the onset, treatment and severity of any heart problems (including arrhythmias) in both males and females affected by XLI, as well as trying to identify risk factors which commonly precipitated arrhythmic episodes. Thus, we asked about your own/family medical history with specific reference to cardiovascular conditions, as well as notable characteristics of your heart rhythm. Given the comparatively high frequency of heart issues in males with XLI and the associated severe, long-term associated effects in some cases, it may be clinically-useful to screen this population following confirmation of their skin diagnosis/genetic status. We also wish to understand participants' attitudes and opinions surrounding heart screening for AF and other arrhythmias. We hope that by understanding the characteristics, severity and potential risk factors contributing to heart arrhythmias in individuals affected by XLI, as well as attitudes towards the feasibility and usefulness of heart screenings, we can learn more about how heart issues develop in XLI, and how best they may be addressed clinically.

To examine the specific aspects of the arrhythmias described above, the survey used custom-designed questionnaires, and further details are available from the researcher team if requested. Importantly, the information you provided through these questionnaires is not sufficient to offer

targeted clinical advice, and if you are worried about your physical or mental health, you should seek advice from a qualified medical professional in the usual way.

If you have any further questions about the purpose or conduct of this study, please contact the researchers or the ethical review board using the details below:

Ms Georgina Wren (PhD student), Cardiff University School of Psychology e-mail: wreng@cardiff.ac.uk

Dr William Davies (project supervisor), Cardiff University School of Psychology, Tel: 44-(0)29-2087-0152, e-mail: daviesw4@cardiff.ac.uk

Secretary of Cardiff University School Ethics Board, Cardiff University School of Psychology, Tel: 44-(0)29-2087-0360, e-mail: psychethics@cardiff.ac.uk

If you are interested in taking part in future studies related to this work, which might include interviews or further surveys, or trying out new psychological support techniques, please click on the following link to leave your e-mail address: URL TBC. Your contact details will be kept separately from your responses to this questionnaire and any information you provide will only be used to feed-back summary data from the current study or to contact you to see whether you would be interested in taking part in future similar studies.

Privacy Notice:

The information provided on the consent form will be held in compliance with GDPR regulations. Cardiff University is the data controller and James Merrifield is the data protection officer (inforequest@cardiff.ac.uk). This information is being collected by Ms Georgina Wren. This information will be held securely and separately from the research information you provide. Only the researcher will have access to this form and it will be destroyed after 7 years. The lawful basis for processing this information is public interest.

APPENDIX CHAPTER 6

Appendix 6.1: Statements presented to participants in post trial feedback form about wearing the watch (0 = strongly disagree, 10 = strongly agree)

1. I found the watch comfortable to wear on a daily basis
2. I found that wearing the watch irritated my skin
3. I found that wearing the watch made my skin condition worse over the 8-week period
4. I found the sensation of wearing the watch every day overwhelming

Appendix 6.2: Chapter 4 Participant Information Sheet

Participant Information Sheet

'A feasibility trial to explore the use of wearable technology in monitoring heart rhythms in X-linked ichthyosis (XLI)'

X-linked ichthyosis (XLI) is a skin condition caused by a particular molecule (steroid sulfatase) being absent, or not working properly. New findings from the UK Biobank have indicated that, for adult males, occasionally, XLI can be associated with heart problems, including abnormal rhythms. Some abnormal heart rhythms are associated with an increased risk of heart failure, stroke and dementia; identifying such abnormal rhythms early using a simple non-invasive monitoring technique might allow more effective clinical intervention to maximise patient care and reduce the societal healthcare burden Our recent work has indicated that >80% of males with XLI would be willing to consider cardiac screening.

Eventually we aim to identify and characterise abnormal heart rhythms in a large sample of male individuals with a clinical diagnosis of XLI through monitoring heart rhythms using the Food and Drug Administration (FDA)-approved echocardiogram available via the Apple Watch. Before we undertake this larger study we are running a small-scale feasibility study to: a) to assess participant engagement, b) to test whether the Apple Watch device can be used effectively, c) to streamline procedures, d) to gather initial data, and e) to determine the optimal frequency for ECG readings.

We are inviting you to take part in this study as part of our small sample of adult (>18yrs) males with XLI from the UK, with an iPhone and willingness to use applications. After completing the initial screening questionnaire, you will be allocated a participant number, and will then be sent an Apple Watch to wear as much as possible (ideally continually) for a period of 8 weeks. You will be asked to send ECG outputs via a PDF (instructions on how to do this will be provided) on a regular basis to the research team (three times per week (Tues, Fri, Sun), plus any occasions where a Watch alert is sounded). These will be reviewed by an experienced cardiology consultant. Before, during and after the data collection phase, you will be sent a short questionnaire to provide feedback on your experiences with the wearable device. Following this 8-week period, you will be asked to send back the Apple Watch, and you will receive feedback about any possible arrhythmias identified by clinicians. Any participants experiencing concerning arrhythmias will be directed towards the most appropriate clinical care, and no tailored medical advice will be offered as part of this study. You will be awarded £50 for your time and dedication to this study.

All data collected and stored in the 'Apple Health' app is securely encrypted and inaccessible to third parties or Apple (https://www.apple.com/legal/privacy/data/en/health-app/). Any information and ECG outputs provided will only be accessed and available to the research team and consultants. You will not be identified by this data in any publications or data presentations. The results of this survey will not provide a basis from which to diagnose or treat a clinical condition or associated symptoms, but may indicate symptoms which warrant further investigation; if this is the case, you will be provided with information on how best to follow up these symptoms.

Your participation in this study is voluntary, and you are free to withdraw at any time and for any reason. You are free to omit answering any questions which you do not wish to answer.

You will be provided with further information upon completion of this study, and you will have the opportunity to register to take part in follow-up studies by leaving your e-mail address. You will be awarded a £50 Love2Shop or Amazon voucher for your participation.

The results of the study will be disseminated by e-mail to participants, via social media and relevant charity websites, or via publication in an academic journal.

The study has been ethically reviewed by Cardiff University School of Psychology Ethical Review Panel. If you have any concerns or issues related to the study then please contact: psychethics@cardiff.ac.uk, telephone 02920870707 or write to the Secretary of the School of Psychology Ethical Review Panel, School of Psychology, Cardiff University, Park Place, Cardiff, UK, CF10 3AT.

If you require further information about the study, please contact us: Ms Georgina Wren (wreng@cardiff.ac.uk) or the primary supervisor for this project, Dr William Davies (daviesw4@cardiff.ac.uk) at School of Psychology, Cardiff University, United Kingdom

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Appendix 6.3: Chapter 4 Consent Form

Consent form

'A feasibility trial to explore the use of wearable technology in monitoring heart rhythms in X-linked ichthyosis (XLI)'

- I have read and understood the Participant Information Sheet for the above study and consent to take part in the research described
- I am aged 18yrs or over, am a male with a clinical diagnosis of XLI, am from the UK and own an iPhone and am willing to download and use applications.
- I understand that study participation will take 8 consecutive weeks, including regular reporting to the research team and completion of regular short questionnaires.
- I understand that my participation will be recognized with a £50 voucher
- I understand that I will be provided with further information at the end of this study, and that I may register to take part in follow-up studies by leaving my e-mail address if I wish.
- I understand that the results of this study will provide basic information about any possible arrhythmias, and I will be directed to the most appropriate clinical care in this situation, thus no tailored medical advice will be offered.
- I understand that I will not be personally identifiable from any published data and only referred to using an individual participant number.

- I understand that my data is securely encrypted via the Apple Health app (https://www.apple.com/legal/privacy/data/en/health-app/) and therefore the research team will only have access to the data that I provide via PDF ECG outputs.

- I understand that I may withdraw from the study at any point and for any reason and that I can omit answering questions should I wish to do so.

- I understand that I must send the wearable technology back to the research team at the end of the data collection period (postage and packing will be provided).

- I understand that should I require more information before taking part in this study, I am free to contact Ms Georgina Wren (wreng@cardiff.ac.uk) or Dr William Davies (daviesw4@cardiff.ac.uk)

- I understand that the information I provide may be retained indefinitely or published, and that I will not be identifiable in any publications

- I understand that any personal information will be collected in accordance with UK GDPR i.e. stored separately from survey data, and stored securely on a password-protected Cardiff University server.

- I understand that this research project has been ethically reviewed by the Cardiff University School of Psychology Research Ethics Committee, and that if I have any queries about the conduct of the study I can contact the ethical review board via the following means: Secretary of Cardiff University School Ethics Board, Cardiff University School of Psychology, , Park Place, Cardiff CF10 3AT, United Kingdom Tel: 02920870707, e-mail: psychethics@cardiff.ac.uk

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Appendix 6.4: Chapter 4 Debrief Form

Debrief Form

'A feasibility trial to explore the use of wearable technology in monitoring heart rhythms in X-linked ichthyosis (XLI)'

Thank you for taking part in our study – your contribution is hugely appreciated!

Once the study is complete and all of the data has been analysed, we will communicate summary results to relevant organisations (e.g., charities and patient support groups), and to academic journals. If you are interested in receiving a summary of our results directly, please follow the links to leave your contact e-mail address at the end of this message. All the

information you have provided to us in this study cannot be traced back to you, and is only linked to your individual participant number. All data collected and stored in the 'Apple Health' app is securely encrypted and inaccessible to third parties or Apple (https://www.apple.com/legal/privacy/data/en/health-app/).
X-linked ichthyosis (XLI) is a skin condition caused by a particular molecule (steroid sulfatase, STS) being absent, or not working properly. Our previous work has indicated that middle-aged males with XLI are around four times more likely to be diagnosed with atrial fibrillation/flutter (AF, a type of irregular heart rhythm or 'arrhythmia') than males of a similar age without XLI (https://jmg.bmj.com/content/jmedgenet/57/10/692.full.pdf). AF is an irregular heart rhythm which can occur on a short-term or long-term basis and is associated with an increased risk of stroke, dementia/cognitive decline and heart failure (https://www.bhf.org.uk/informationsupport/conditions/atrial-fibrillation). The biological link between XLI and AF is currently unclear; it could be that loss of STS causes changes in the levels of circulating hormones which then affects heart function. Alternatively, other genes commonly deleted in XLI (besides STS) might be responsible. We are currently conducting a variety of studies to test these ideas.
The goal of the present study was to explore the use of wearable technology to examine heart rhythms in adult males with XLI. From our previous work, we know that >80% males with XLI are amenable to, and appreciate the potential benefits of, cardiac screening, and thus this study aimed to initiate discussion around potential for future screening processes.

Using regular ECG reports from the Apple Watch and regular screening questionnaires, we hope to: a) assess participant engagement, b) test whether the device can be used effectively, c) streamline procedures, d) gather initial data, and e) determine the optimal frequency for ECG readings. We may also identify any possible arrhythmias and their precipitants with the help of consultant cardiologists. Following this feasibility phase, we intend to conduct a larger study using a worldwide sample, to identify and characterise arrhythmias using the Apple Watch.

Importantly, you will receive feedback about any possible arrhythmias identified by the clinical team. If you are experiencing concerning arrhythmias, you will be directed towards the most appropriate clinical care, and no tailored medical advice will be offered as part of this study. In thanks for your time and dedication to this study and upon sending back the Watch, you will be sent a £50 voucher by post.

If you have any further questions about the purpose or conduct of this study, please contact the researchers or the ethical review board using the details below:

Ms Georgina Wren (PhD student), Cardiff University School of Psychology e-mail: wreng@cardiff.ac.uk

Dr William Davies (project supervisor), Cardiff University School of Psychology, Tel: 44-(0)29-2087-0152, e-mail: daviesw4@cardiff.ac.uk

Secretary of Cardiff University School Ethics Board, Cardiff University School of Psychology, Tel: 02920870707, e-mail: psychethics@cardiff.ac.uk

If you are interested in taking part in future studies related to this work, which might include interviews, further surveys, or trying out new psychological support techniques, please click on the following link to leave your e-mail address: URL TBC. Your contact details will be kept separately from your responses to the study you have just completed and any information you provide will only be used to feed-back summary data from the current study or to contact you to see whether you would be interested in taking part in future similar studies.

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